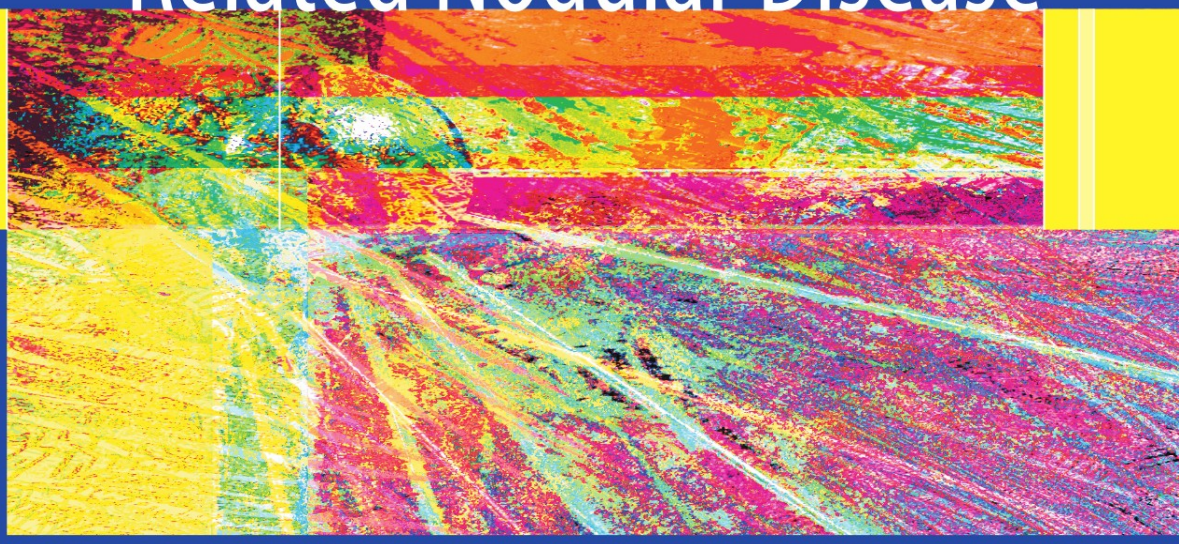
I. Ross McDougall

Management of Thyroid Cancer and Related Nodular Disease



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With 114 Figures

With contribution by

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This book is dedicated to
Liz, Shona, Stewart, Alison, and Hudson,
the greater McDougall family

Preface

After my early training in medicine, I was invited to join Professor Edward McGirr at the Royal Infirmary in Glasgow Scotland. Two of the main interests in his department were thyroid and isotopic medicine. At that time, 1969, the term isotopic medicine had been changed to Nuclear Medicine in the United States; thus, I embarked on a career in thyroidology and nuclear medicine. From 1972 to 1974, I had the opportunity to spend two years with Professor Joseph Kriss at Stanford University School of Medicine. He was an established investigator in the same subspecialities and provided inspiration, guidance, and resources for me. Both of these chiefs were role models in every regard. Although of different background and personality, they were generous, modest, insightful, ethical, innovative, and productive. Both were excellent clinicians who kept up to date with medicine in general as well as their specialities. Unfortunately, neither is alive. From 1974 to 1976, I returned to the Royal Infirmary and continued working in thyroid, nuclear medicine, and internal medicine. Since 1976, I have been at Stanford. Thus most of my experience has been in two centers with brief sabbatical leaves to a few centers in the United States and Europe. This text is a distillation of my efforts over this time.

Contents

Chapter 1

Thyroid Cancer: Epidemiology and Overview

The purpose of this textbook is to provide a single author text that covers all aspects of thyroid cancer. I requested and acknowledge the assistance of Dr Gerald Berry, a professor in Pathology at Stanford University, who adds expertise and outstanding figures to Chapter 3 on pathology of the thyroid. I hope, the text is easy to read, clinically valuable, authoritative, and enjoyable. Both or all sides of controversial issues are discussed. The final interpretation of data and their management could reflect my personal experience, but I hope not bias. The book is designed for physicians, including internal medicine and primary care doctors, endocrinologists, nuclear medicine physicians, general and head and neck surgeons, and oncologists including radiation oncologists. It is expected that a patient with a thyroid nodule or thyroid cancer would use the information as a resource. Others groups who will find an interest in the book would be trainees, including residents, medical students, and nurse practitioners, when they research a patient related problem.

In this chapter the epidemiology of thyroid cancer is presented followed by a synopsis of the educational goals of the subsequent chapters. Terminology, the use of words, abbreviations, and units of measurements are defined. The interpretation of results and statistics are discussed briefly along with evidence-based medicine and the importance of controlled studies and meta-analysis. The topics of alternative and traditional treatments are introduced briefly and are not included in the remainder of the book.

Epidemiology

In 2004 the American Cancer Society predicts there will be approximately 22,500 new cases of thyroid cancer in the United States. There is a 3:1 ratio of women to men, with estimated numbers of 16,875 cases in women versus 5,625 cases in men. Thyroid cancer accounts for about 1.1% of all cancers, and approximately 1.7% of cancers in women arise in the thyroid, compared with 0.5% of cancers in men. The prognosis is generally good, and overall 6% of patients die from the cancer, but the genders are more equally represented, with about 800 women and 600 men expected to die in the United States due to their thyroid cancers in 2004. This means that less than 0.5% of all cancer deaths are from carcinomas of the thyroid. There has been a progressive increase in the number of new cases in the United States and these have tripled over three decades. Although the total mortality numbers have also increased, they have done so only slightly, so the relative risk of dying has fallen over the same time. Figure 1.1 shows the overall number of cases and deaths in the United States over eight time periods from 1970–2003. Table 1.1 shows the number of new patients (women and men) per 100,000 people from 1973–2000. The increasing number of patients with thyroid cancer is not easily explained but could be due to a true increase that might be in part caused by radioactive fallout from atomic bomb testing, which is discussed in Chapter 5, Etiol-

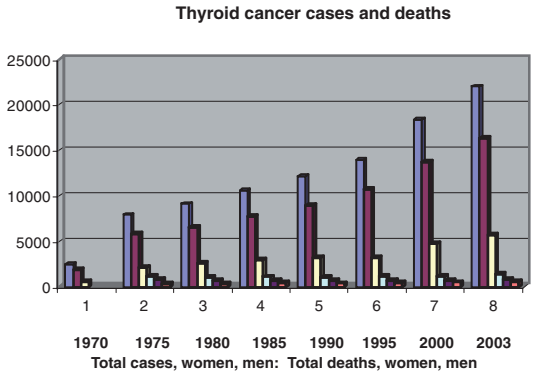

Figure 1.1. Graph shows increases in cases of thyroid cancer between 1976 and 2003 in the United States. The increases in mortality are less marked.

ogy of Thyroid Cancer. Alternatively physicians might be identifying small cancers that would have been overlooked in earlier decades, and the almost stable death rate supports this point of view. As stated above, women are more likely to develop thyroid cancer and the usual ratio is about 3:1 women to men; the only situation where the number of thyroid cancers is similar between the genders is in prepubertal children (1). Because the large majority of patients who are diagnosed with thyroid cancer have an excellent prognosis, each year there are approximately an additional 21,000 patients with this diagnosis who are expected to live for several decades. Therefore, there are several hundred thousand people in the United States who have a diagnosis of thyroid cancer.

Substantial differences in the prevalence of thyroid cancer between ethnic groups are recognized and these are hard to explain. In the United States, African Americans have a low incidence of 3.3 thyroid cancers per 100,000 women, Hawaiian women have 9.1 thyroid cancers per 100,000, Vietnamese women have 10.5 thyroid cancers per 100,000, and Filipino women have the highest incidence of thyroid cancer at 14.6 per 100,000 (1). Caucasian and Hispanic populations have similar incidences in women of 6.5 and 6.2 cancer of the thyroid per 100,000. When age is also considered Filipino women between 55 and 69 years have an incidence of 32.5 cancers per 100,000. Filipino men also have a higher incidence of thyroid cancer with 4.1 per 100,000 compared to 1.4 per 100,000 for African Americans. There would appear to be value in determining whether African Americans have a low incidence based on some protective factor or whether those populations at higher risk are exposed to an environmental or genetic factor that is hazardous. The same applies to the gender difference. Does being a man actually decrease the risk, or do female sex hormones increase it? A multi-ethnic study in the San Francisco Bay area tried to answer the environmental question, but no compelling factor was identified (2).

The incidence of thyroid cancer peaks at age 30–45 years and then levels off making this different from most malignancies, which become more common with advancing age. Hispanic men are the exception to this, having their highest incidence over the age of 70 years (9.2 per 100,000) (1).

In contrast in the United Kingdom there are 1,000 new cases annually yet the population is

Table 1.1. Incidence of thyroid cancer per 100,000 population in the United States.

	Male and female	Male	Female
1973	4.2075	2.3368	5.9243
1974	4.6620	2.9790	6.2627
1975	4.8461	3.1378	6.4344
1976	4.7977	2.9462	6.5740
1977	5.4350	3.4899	7.3072
1978	5.0885	3.1350	6.9367
1979	4.4772	2.6708	6.1617
1980	4.3205	2.3806	6.1296
1981	4.4076	2.5152	6.2171
1982	4.6203	3.0049	6.1329
1983	4.6913	2.7905	6.4705
1984	4.8407	2.6481	6.9154
1985	5.1211	3.0825	7.0859
1986	5.3105	3.0502	7.4816
1987	5.0476	2.8014	7.1354
1988	4.9462	2.9534	6.8944
1989	5.3396	2.9682	7.6179
1990	5.4602	2.8964	7.9208
1991	5.4496	3.1878	7.6181
1992	5.8518	3.5127	8.0698
1993	5.6075	3.5754	7.5896
1994	6.0576	3.3729	8.7112
1995	6.1947	3.3648	8.9393
1996	6.4426	3.4427	9.3737
1997	6.7250	3.6282	9.7197
1998	6.9075	3.6903	9.9821
1999	7.2800	3.8570	10.5671
2000	7.5069	4.0104	10.9165
2001	8.0131	4.2004	11.7265

about one fifth of that of the United States. The incidence is 2.3 thyroid cancers per 100,000 women and 0.9 per 100,000 men, which is substantially less than in the United States (3). Also in contrast 250 (25%) die annually of this cancer in the UK and the five-year survival is only 75% for women and 64% for men compared to ten-year survival rates in the United States that are better by an additional 20% (4). The basic therapies are similar in the United States and UK. The lower incidence and higher mortality in the UK might be due to delayed diagnosis until the cancer is larger and invasive, and small non-lethal lesions are not identified. The use of a staging system such as Tumor, Node, Metastasis (TNM), or a Prognostic Index (see Chapter 6) of every new case would allow this point to be proven or disproved. The survival is also dependant on race. The five-year survival for Caucasians in the United States has been 92% (1974–1976), 94% (1980–1982) and 95% (1989–1995), and over the same time intervals, the outcomes for African Americans were 88%, 94%, and 89%.

Contents of Chapters

Chapter 2 discusses clinically relevant aspects of thyroid anatomy and physiology. The fundamentals of testing thyroid function are included. These are important for understanding the results of thyroid function tests in a patient with a thyroid nodule or cancer and how to proceed with additional testing when patients are treated for these abnormalities. The anatomy of the thyroid and its lymphatics illustrate how the cancer can spread. Knowledge of the physiology of the iodide cycle and the formation of thyroid hormones illustrates how testing and treatment with radioiodine works. It also explains why false positive scans can occur due to trapping of radioiodine in non-thyroidal organs. The embryology allows an understanding of thyroid cancers in ectopic sites, such as ligual thyroid and thyroglossal duct cysts.

Chapter 3, which is on pathology, includes cytology and histology, and should aid the clinician working with a pathologist on reaching a correct decision about management. The prognosis varies depending on the type of cancer and in some cases the classification of the cancer. This is based on subtle pathological changes. Because thyroid cancer usually is diagnosed when a nodule is found in the thyroid, Chapter 4 is on management of thyroid nodules. Nodules are very common and are present in 4% to 6% of normal adults. This has to be contrasted with the 22,500 new cancers diagnosed annually in the United States. Since there are potentially 12 million to 18 million ($[4-6]/100 \times 300{,}000{,}000$ people in the United States) patients in the United States with a palpable thyroid nodule, this is a significant clinical problem. The numbers should not be interpreted as meaning that a nodule has about a one in 1,000 chance of being cancer (22,500/18,000,000), since each year there are 22,500 additional cancers and an unknown additional number of benign nodules. The numeric importance of thyroid nodules is significantly greater when it is recognized that 30% to 50% of adults have a nodule, or nodules, that can be identified by imaging, such as an ultrasound scan. Chapter 5 is devoted to the causes of thyroid nodules and more importantly of thyroid cancer. The role of radiation and genetic mutations are reviewed. The sources of radiation are medical, both diagnostic and therapeutic; occupational such as working in radiology or nuclear medicine, or a nuclear power plant and accidental release of radiation from atomic power stations; and radioactive fall-out from atomic bombs both intentional and from nuclear testing. The reader should obtain an understanding of the physics of radioactivity and the interaction of radioactive emissions with biological compounds such as deoxyribonucleic acid (DNA), plus knowledge of how mutations cause or predispose to malignant transformation.

Chapter 6 covers all aspects of differentiated thyroid cancer, which numerically is the most important cancer accounting for approximately 80% to 85% of the cases. The majority of differentiated cancers are classified as papillary cancer based on pathologic features and these along with the less common follicular cancer retain many of the functional characteristics of thyroid cells, hence the designation of differentiated thyroid cancer. All treatments in the management of differentiated thyroid cancer are addressed, including surgery, the role and logistics of radioactive iodine therapy, and long-term prescription of thyroid hormone. The methods for follow-up including scintigraphy and measurement of thyroglobulin (Tg) are presented.

Problems such as complications of thyroidectomy and radioiodine testing and treatment are described. Methods of determining the dose of iodine-131 (^{131}I) to be administered are demonstrated. Radiation safety planning for the release of radioactive patients from the hospital and the documents that can be used by medical personnel to advise and educate patients and families are provided. Controversial areas such as the need for whole-body diagnostic scans, stunning of the thyroid attributed to diagnostic ^{131}I, the role of whole-body scintigraphy with iodine-123 (^{123}I) versus ^{131}I, and the management of scan negative and Tg positive patients are debated. For each of these topics, arguments for and against are analyzed and advice of how to proceed given. The role of Positron Emission Tomography (PET and PET/CT) is included. There are several variants of differentiated cancer, such as tall cell and columnar, for which prognosis is worse, and these are discussed individually. Also included are differentiated cancers in ectopic sites such as the thyroglossal duct and the struma ovarii. Familial differentiated thyroid cancer, also called familial non-medullary cancer, is presented as a topic of increasing importance.

Chapter 7 is devoted to differentiated thyroid cancer in children. There are specific features of the disease and added emotional factors in these patients. Because thyroid cancer is predominantly a disease of women, in particular in the 20-year to 50-year age group, thyroid cancer in pregnancy, the effects of the disease and its treatment on fertility, offspring, and nursing are included in Chapter 8. The importance of not treating a pregnant patient with radioiodine is stressed, and the medical and legal literature is reviewed.

Anaplastic cancer affects the same cell as differentiated thyroid cancer and, in fact, often arises from or occurs in a pre-existing differentiated thyroid cancer. Because of its clinical course, treatment and prognosis is very different; it is discussed separately in Chapter 9. Medullary cancer and the familial syndromes of multiple endocrine neoplasia 2A and B (MEN 2A and 2B) pose different management problems and are reviewed independently. The importance of early diagnosis of familial cases by genetic screening is stressed. Lymphoma of the thyroid is also presented separately, since the treatment is very different from all other types of thyroid cancer. Most often this cancer is under the management of a medical or radiation oncologist. Finally, Chapter 12 is a brief chapter about cancers that metastasize to the thyroid. Each chapter should stand alone; therefore, there is some overlap but not excessive repetition. For example thyroid function testing is discussed in the second chapter on physiology and again in the follow-up of adult patients, children and pregnant women in Chapters 6, 7 and 8 respectively. Pathology is discussed in Chapter 3 and only the hallmarks of lesions are repeated along with each specific cancer. Genetic mutations as a cause of cancer are presented in Chapter 5 and clinically important issues reviewed in particular in Chapter 6 in the discussion of familial differentiated thyroid cancer and Chapter 10 on medullary cancer.

Words and Abbreviations

The main thyroid hormone, **thyroxine** (3,5,3′,5′ tetra-iodothyronine), can be written in many forms in addition to the two already mentioned. These include levo-thyroxine, l-thyroxine, T_4 and L-T_4. Throughout the text when thyroxine is the medication the term levo-thyroxine is used and when thyroxine, the serum level of thyroid hormone is discussed it is written as T_4 or in the case of the free hormone, FT_4.

There appears to have been the development of new languages in which only abbreviations are used. Each specialist group has its lexicon so that non-card-carrying members are left in the dark. When I read some scientific papers, the importance of the findings is lost in an alphabet soup of meaningless letters. In the book 1984, George Orwell describes a C vocabulary from which "any scientific worker or technician could find all the words he needed in the list devoted to his own speciality, but he seldom had more than a smattering of words occurring in the other lists" (5). I accept that some abbreviations are in common usage such as DNA and RNA. With regard to the thyroid there are also several in common and universal use and recognized by physicians and patients alike as shown in Table 1.2. Throughout the text when a commonly used name or term is presented the full title is given on the first occasion, followed by the shortened form and from then on the abbreviation is employed. In contrast there are enormous numbers of abbreviations that are not in common use. Table 1.3 provides a random list

Table 1.2. Abbreviations used commonly in relation to the thyroid.

Abbreviation	Full name	Possible source of confusion
T_4	Thyroxine	Thymus derived lymphocytes
	Levo-thyroxine	
	L-thyroxine	
	3,5,3′,5′ tetraiodothyronine	
FT_4	Free-Thyroxine	
	Free-Levo-thyroxine	
	Free-L-thyroxine	
	Free-3,5,3′,5′ tetraiodothyronine	
T_3	Triiodothyronine	
	3,5,3′ triiodothyronine	
FT_3	Free-Triiodothyronine	
	Free-3,5,3′triiodothyronine	
TSH	Thyroid stimulating hormone	
	Thyrotropin	
TRH	Thyrotropin releasing hormone	
	TSH releasing hormone	
Tg	Thyroglobulin	
TPO	Thyroid peroxidase	
Anti-Tg	Anti-thyroglobulin	
Anti-TPO	Anti-thyroperoxidase	
NIS	Sodium iodide symporter	
SUV	Standardized uptake value	Sports utility vehicle
CT	Computed tomography	
MRI	Magnetic resonance imaging	

Table 1.3. Examples of abbreviations not in common use.

Abbreviation	Meaning	Alternative meaning
ACZ	Acetazolamide	
ATF	Anatomic tissue fraction	
BAT	Brown adipose tissue	A flying nocturnal mammal A tool for striking a ball
BBN	Bombesin	
BETIT	Biological event targeting imaging	
BMPR 2	Bone mineral protein receptor	
Cactus	Clinical application of cellular trafficking for understanding stem cells	Desert plant
CASTLE	Carcinoma showing thymus-like differentiation	The home of a king or knight
CEA	Carcino embryonic antigen	Carotid endarterectomy
CGRP	Calcitonin gene related peptide	
DA	Diagnostic	District attorney
DCM	Dilated cardiomyopathy	
DLBCL	Diffuse lymphocytic B cell lymphoma	
EPC	Endothelial progenitor cells	
FDCS	Follicular dendritic cell sarcoma	
GBM	Glioblastoma multiforme	
GRPR	Gastrin releasing peptide receptor	
HCM	Hypercalcemia of malignancy	
IGMA	Image guided microassay analysis	
ITET	Intrathyroidal epithelial tumor	
MZBL	Marginal zone B cell lymphoma	
NAC	Non attenuation corrected	
PACAP	Pituitary adenylate cyclase activated peptide	
PDA	Poorly differentiated adenocarcinoma	Patent ductus arteriosus
PSMA	Prostate specific membrane antigen	
PTI	Perfusable tissue index	
SETTLE	Spindle epithelial tumor with thymus like differentiation	
SKA	Simplified kinetic analysis	
SMECE	Sclerosing mucoepidermoid carcinoma with eosinophilia	
VEGF	Vascular endothelial growth factor	

generated in one day from scientific papers that I was reading and a lecture I attended. The authors and speaker are not identified to protect the not so innocent. Not only are these abbreviations difficult to keep track of but also some have alternative meanings that can lead to additional confusion. In situations like those listed in Table 1.3, the full designation and not the abbreviation is repeated each time the term is used.

The word tumor is interpreted by most patients to mean cancer. In fact it is an indeterminate term that should be qualified by benign or malignant. I have tried to avoid the word and use "nodule" in place of "benign tumor" and "cancer" or "carcinoma" in place of "malignant tumor."

Units of Measurement

In many parts of the text there are descriptions and discussions of radioactivity used for diagnostic testing and for therapy. The definition of these units is presented in Chapters 5 and 6. Their use cover a very large numerical range from very small fractions to numbers that are many orders of magnitude greater. Table 1.4 provides prefixes and symbols for the range 10^{-15} (femto, f) to 10^{12} (tera, T). There are two systems for expressing the units of radiation and radioactivity. These are the *Système International* (SI) units and the standard system. There are different units for quantities of radioactivity that are administered and for radiation that is absorbed by tissues of the body. In SI the units of radioactivity that are administered are the Becquerel (Bq) or multiples of Becquerels (Megabecquerel [MBq] or Gigabecquerel [GBq]). In the standard system the Curie (Ci) is the basic unit, and usually microcuries or millicuries are administered (μCi or mCi). Absorbed radiation is expressed in units of the Gray (Gy) and the Sievert (Sv) in the SI and rad and roentgen equivalent in man (rem) in the standard system. For most forms of medical radiation Gy and Sv are equivalent as are rad and rem. These units are defined fully in Chapters 5 and 6 and how to convert from one to the other system.

Interpretation of Test Results and Statistics

A recent study found that 38% of the statistics in articles in Nature and 25% of the statistics in articles in the British Medical Journal were wrong (6). Therefore when reading an article (and this text) it is important to check the numbers and make an approximation to determine whether the conclusions of investigators are reasonable. In the interpretation of data, it is helpful to calculate sensitivity and specificity of the procedure under analysis. Sensitivity is defined as the proportion of patients with the disease who have a positive test result (7). The specificity of the test is the proportion of patients who have no disease and whose test is negative. The perfect test would have a sensitivity of 100% and a specificity of 100%, but there is no such test. Figure 1.2 provides a template for calculating these numbers.

Table 1.4. Names and numbers and their symbols.

Factor	Prefix	Symbol
10^{12}	Tera	T
10^{9}	Giga	G
10^{6}	Mega	M
10^{3}	Kilo	K
10^{-1}	Deci	d
10^{-2}	Centi	c
10^{-3}	Milli	m
10^{-6}	Micro	μ
10^{-9}	Nano	n
10^{-12}	Pico	P
10^{-15}	Femto	f

Test	Patient with disease	Patient without disease	Total
Abnormal	**True positive A**	**False positive B**	**A + B**
Normal	**False negative C**	**True negative D**	**C + D**
Total	**A + C**	**B + D**	**A + B + C + D**

Sensitivity $\frac{A}{A+C}$ Specificity $\frac{D}{B+D}$

Figure 1.2. Chart shows how to calculate sensitivity and specificity.

The equations for calculating sensitivity and specificity are:

$$\text{Sensitivity} = \frac{\text{Number of patients with disease who have a positive test [A]}}{\left(\begin{array}{c}\text{Number with disease and positive test [A]} + \\ \text{Number with disease and negative test [C]}\end{array}\right)}$$

$$\text{Specificity} = \frac{\text{Number of patients with no disease who have a negative}}{\left(\begin{array}{c}\text{Number with no disease and negative test [D]} + \text{Number with} \\ \text{no disease and positive test [B]}\end{array}\right)}$$

There is usually a reciprocal relationship between sensitivity and specificity. As the sensitivity of a test increases the specificity decreases and vice versa. When a test has a high specificity a positive result is more likely to be a true positive. Conversely a negative result from a test that has a high sensitivity has a high probability of being a true negative, which rules out disease. Although the calculation of sensitivity and specificity does not depend on the prevalence of disease, their use in managing a patient does. For example, let us assume in an investigation the sensitivity of fine needle aspiration (FNA) of a thyroid nodule for diagnosing cancer in a nodule is 80% and the specificity is 90% and we study two new and different groups of patients. The first group consists of 100 healthy, asymptomatic women with a small nodule. The second is made up of 100 patients with a thyroid nodule who had been exposed to radiation in childhood from the release of radioactive nuclides at Chernobyl. For purpose of calculation, the a priori risk of cancer in the first group is accepted to be 5% and in the second group 30%. Using the sensitivity and specificity as shown in Figures 1.3 and 1.4 the post priori risks of cancer when the FNA is positive are 31% and 77% respectively.

An additional and more useful method of handling the data is to determine the likelihood ratio (8). This is the ratio of the probability of an abnormal test in patients with the disease to the probability of an abnormal test in those who

Use of FNA in 100 patients with a thyroid nodule and 5% chance of malignancy. Sensitivity of the test is 80% and the Specificity is 90%

Test FNA	Thyroid cancer	Benign nodule	
Positive	4 A	9 B	13
Negative	1 C	86 D	87
Totals	5	95	100

Positive FNA is likely to be cancer in 4/5 (80%) [A/A + C] and there are 9 false positive results giving the specificity of 90% (86/95) [B/B + D]

Use of FNA in 100 patients with a thyroid nodule and 30% chance of malignancy Sensitivity 80%, Specificity 90%

Test FNA	Thyroid cancer	Benign nodule	
Positive	24 A	7 B	31
Negative	6 C	63 D	69
	30	70	100

Positive FNA is due to cancer in 24/30 (80%) [A/A + C]
and there are 7 false positive results and the specificity is 63/70 (90%) [B/B + D]

Figures 1.3 and 1.4. Charts demonstrate how the probability of a positive test result being a true positive depends not only on the sensitivity of a test but the prevalence of the disease in the population under investigation. Similarly the probability of a negative test being a true negative also depends on the prevalence of the disease or rather the prevalence of those who do not have the disease. These concepts are presented with a test (fine needle aspiration [FNA] of a solitary thyroid nodule) that has a sensitivity of 80% and a specificity of 90% for two populations, one with a 5% chance of disease the other with a 30% chance.

are free of the disease. When the likelihood ratio is one the result of the test is neutral and of little value. The larger the likelihood ratio is above one the more likely disease is present and conversely the lower the ratio is below one the less likely the disease. Let us return to the two groups with thyroid nodules. From the five patients in group A with thyroid cancer, four had an abnormal test (FNA), which is 80%. Nine patients without cancer had an abnormal test, 9/95 = 9.5%. The positive likelihood ratio is 80%/9.5% = 8.4. In this case the calculation can be made using the formula:

$$\text{Positive Likelihood ratio} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{The pretest possibility of cancer} = 0.05 (5 \text{ out of } 100)$$

$$\text{The pretest odds} = 0.05/0.95 = 0.053$$

$$\text{The post test odds} = \text{pretest odds} \times \text{likelihood ratio} = 0.053 \times 8.4 = 0.445$$

$$\text{The post test probability} = \text{post test odds}/(1 + \text{post test odds}) = 0.445/1.445 = 0.308(31\%).$$

Of the thirty patients in group B with thyroid cancer, twenty-four had an abnormal test (FNA), which is also 80%. Seven patients (10%) without cancer had an abnormal test. The positive likelihood ratio is 80%/10% = 8. In this case the calculation can be made using the same formula:

$$\text{Likelihood ratio} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{The pretest possibility} = 0.3$$

$$\text{The pretest odds} = 0.3/0.7 = 0.433$$

$$\text{The post test odds} = \text{pretest odds} \times \text{likelihood ratio} = 0.433 \times 8 = 3.46$$

$$\text{The post test probability} = \text{post test odds}/(1 + \text{post test odds}) = 3.46/4.46 = 0.77(77\%).$$

For people who are educated on the nuances of betting on horse or dog races the use of odds is second nature. Fagan developed a nomogram that can be used to find the post test probability when the pre test probability and likelihood ratio are known.

The negative likelihood ratio is obtained from the equation

$$\frac{1 - \text{sensitivity}}{\text{specificity}}$$

Confidence Intervals

Sensitivity and specificity are calculated from a group of patients or tests however the results might not be representative for the entire population. One method to determine the precision is the Confidence Interval. Usually this is expressed as a range that lies within random samples. The most common in practice is the 95% confidence interval, meaning that only 5% of the true answer for the population would lie outside that range. For more precision the 99% confidence intervals could be employed. When the sensitivity has been calculated the 95% confidence interval is obtained from the equation:

$$\text{Sensitivity expressed as a proportion } (p) \pm 1.96 \times \sqrt{(p[1-p])}\Big/(\text{the number of subjects}).$$

Using the second group of patients with thyroid nodules described above the 95% confidence intervals are

$$0.8 \pm 1.96\sqrt{0.8(1-0.8)\Big/100} = 0.722, 0.878.$$

Factors that are not incorporated into these calculations are the reliability of the test and the reliability of the interpreter of the test. There are very few studies addressing this point with regard to imaging tests of the thyroid. How reliable are the technical aspects of the test when a patient has the test repeated under the same conditions within a short time? To answer this is difficult to justify in the case of a patient undergoing a nuclear medicine procedure, especially when thyroid hormone has to be withdrawn and the patient is symptomatically hypothyroid. However, in the case of nuclear cardiac studies a difference of up to 5% is accepted as normal. The reader can infer that the same test in different institutes using different instruments is likely to show even less reproducibility. With regard to the interpreter, the reliability can be calculated by reading the same images on two or more occasions. All identifying features have to be removed from the images to ensure a "blinded" reading. This is called intraobserver reliability. An experienced reader can usually recall that he/she is looking at the same images and might reach a concordance by recognition. Since in many departments more than one person is responsible for the interpretation of images interobserver reliability can be measured by having a set of images read by two or more people and the concordance calculated. This is not as simple as determining how many cases the observers agree on, in other words whether both interpretations are negative or positive, since concordance can occur by chance. If two readers review 100 scans and the concordance is as shown in Figure 1.5 this appears impressive at 80 out of 100 (80%). The true agreement is called the Kappa score (K) and is calculated as follows, first using the formula:

Results of double reading of 100 thyroid scans

	Observer 2 Positive	Observer 2 Negative
Observer 1 Positive	40 (A)	10 (B)
Observer 1 Negative	10 (C)	40 (D)

This would appear to result in an 80% agreement
However there could be agreement in 50% by chance

Figure 1.5. Chart illustrates the use of the double reading of studies to determine the agreement between interpreters.

$$\frac{(A+B)\times(A+C)}{n}+\frac{(B+D)\times(C+D)}{n}$$

The result of this is 0.5 or 50% and is the chance agreement. K is then obtained from a second equation:

$$K=\frac{\text{agreement (80)}-\text{chance agreement (50)}}{1-\text{chance agreement (50)}}$$
$$=0.6 \text{ or } 60\%$$

The greater the K value the better the agreement and values below 0.4 are problematic. Our group conducts a double reading of scintiscans monthly looking not only at the interpretation but the quality of the images, clarity of the report and whether the referring physician was contacted with the results. A search of the literature did not identify a single publication addressing intraobserver or interobserver reliability of reading thyroid scans.

Received Operator Characteristics

It was stated earlier that there is reciprocity between sensitivity and specificity. The more sensitive a test is the greater the number of true positives but also the number of false positives increases so that the specificity drops. In some situations the cutoff between normal and abnormal is arbitrary, and the level chosen results in variations in sensitivity and specificity. As an example, let us use the uptake of a tracer of radioiodine in the thyroid bed after treatment of thyroid cancer by thyroidectomy and ^{131}I. Some authorities accept a value <0.1% as evidence of successful therapy but others uses values as high as 1%. This is shown graphically in Figure 1.6. The low cut-off value would identify almost all patients with residual functioning tissue (high sensitivity) but could include some where the counts are due to background activity or scattered radiation from salivary activity (low specificity). The higher value would miss patients with residual tissue (low sensitivity), but there would be few false positives (high specificity). The varying relationship between sensitivity can be produced in graphic form by plotting sensitivity (true positive) on

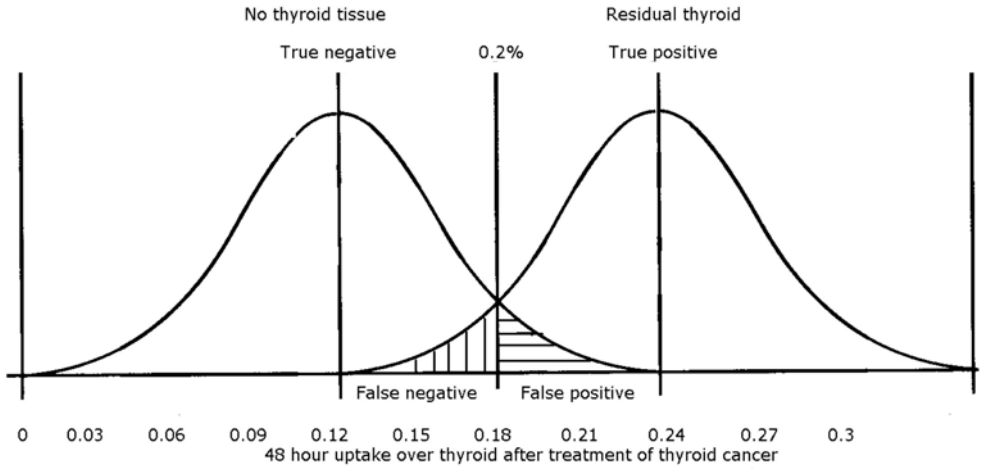

Figure 1.6. Graph demonstrates how an arbitrary decision on where to separate normal from abnormal (percent uptake over the thyroid bed after treatment of thyroid cancer) can result in different sensitivities and specificities.

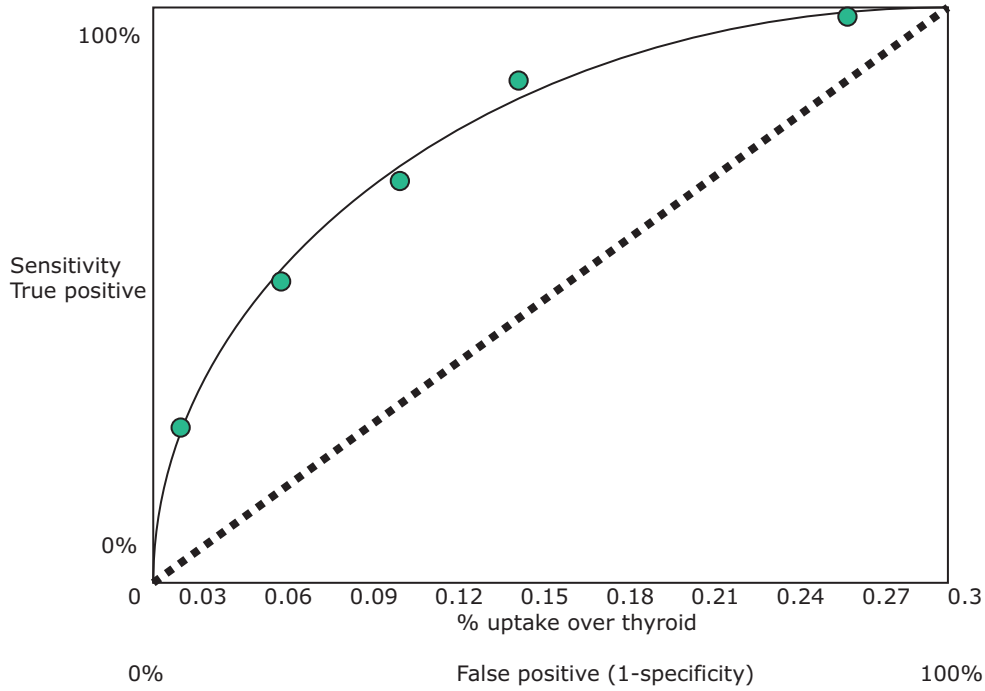

Figure 1.7. Graph shows how a receiver operator characteristic curve (ROC) is developed from pairs of sensitivities and specificities. This allows a choice of cut-off that would give the optimal choice of sensitivity coupled with specificity for the interpretation of a test.

the y-axis and one minus specificity (false positive) on the x-axis. This is the receiver operator characteristic curve (ROC). An example is shown in Figure 1.7. The goal is to identify the optimal cut-off where there is a high sensitivity and an acceptably low specificity.

Evidence-Based Medicine

An excellent definition of evidence-based medicine comes from Sackett and colleagues, who are recognized as leaders in this discipline (9). "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." External clinical evidence is based mostly on the results of randomized controlled studies and meta-analyses. These are discussed below. However, the experience of the physician is important since he or she knows the patient as a person rather than a "case" in a research investigation. There are no double blind controlled studies on any aspects of treatment of thyroid cancer; therefore, advice to use treatment A versus treatment B is not cast in stone. In spite of this limitation, some treatments can be advised with conviction. It is not correct to leave a cancer in the thyroid without any treatment. The cancer will grow and with time invade and metastasize and no controlled study of thyroidectomy versus no thyroidectomy would be justified under any circumstance. In retrospective studies total thyroidectomy appears to be superior to lobectomy, but even this is not accepted by all authorities for all patients (10, 11). Likewise, it is not ethical to compare the outcome in patients treated with thyroid hormone after thyroidectomy with those not given thyroid hormone.

Implicit in the definition of evidence-based medicine is that the treating physician has the "best available clinical evidence." This requires an enormous amount of time to read the appropriate journals, use computer searches, and

attend lectures and conferences. Sackett et al. estimated that a practitioner would need to read about twenty articles every day of the year to achieve this goal. Patients might be despondent on reading this however I am not. It appears this should be an area for potential gain. Physicians do read and make computer searches, they do attend conferences, and they do have a close understanding of the fundamentals and controversies. In addition nowadays, many patients educate themselves on their specific problems and expect to be involved actively in decisions about testing and treatment. The combination of an informed physician and patient adds power to decision making.

Randomized Controlled Studies and Randomized Double Blind Controlled Studies

Cochrane wrote, "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all randomized controlled trials." Several important aspects of the management of thyroid cancer continue to raise questions. Is it better to excise the entire gland or part of it? Is the outcome better in those treated with ^{131}I? For long-term management what is the optimal level for serum thyrotropin (thyroid stimulating hormone, TSH)? Questions such as these can be answered by randomized trials. It is unrealistic to have double blinded trials in some situations, for example the administration of ^{131}I therapy. The patients treated with ^{131}I would have symptoms, such as a change in taste, and evidence of therapy, such as a post therapy scan and measurements of emitted radiation for radiation safety requirements. Nevertheless, there would be important information from an open randomized trial comparing one group treated with ^{131}I to a control group matched for age, gender, and stage of cancer that did not receive ^{131}I. There is no data. Several reasons account for this. First and central is the excellent outcome in most patients with thyroid cancer. Physicians tend to accept that whatever treatment they administer accounts for that success, and they are, therefore, both reluctant to change that regime and also unwilling to randomize patients not to receive their therapies. Related to the overall good outcome is the number of patients and the time necessary to reach a statistically significant answer. The outcome could be recurrence of cancer or death from cancer. Let us use a hypothetical set of numbers. The chance of dying from differentiated thyroid cancer is about 5% at ten years when the disease is treated by operation and thyroid hormone. The mortality over 10 years is 4% for those treated by surgery, thyroid hormone, and ^{131}I. For those treated with ^{131}I the absolute risk reduction is 5–4 = 1%. The number needed to treat to prevent 1 death would be 100 patients followed for 10 years. The relative risk for death when ^{131}I is included is 4/5 = 0.8 or 80%. The absolute risk reduction and number to treat are more valuable than the relative risk since they incorporate the prevalence of the problem. In order to reach statistical significance, several thousand patients would need to be randomized and followed for more than twenty years.

One randomized trial concerned with ^{131}I allocated patients to one of 8 therapy groups, but all patients received ^{131}I treatment (12). Unfortunately, this trial could not answer whether ^{131}I reduced the rate of recurrence or mortality; rather it determined what administered dose would ablate residual thyroid. The lowest dose these investigators administered was 555 MBq or 15 mCi, and they increased this by 185 MBq (5 mCi) increments up to a maximum of 1.85 GBq (50 mCi). They demonstrated that doses of 925 MBq (25 mCi) or greater were superior to smaller doses. There was no difference in outcome between the subgroups treated with 0.925 MBq to 1.85 MBq (25–50 mCi). The paper includes odds ratios and confidence intervals and makes valuable reading.

There are randomized cross over placebo studies to determine the effect of levo-thyroxine on the size of thyroid nodules (13). There are randomized trials of injection of ethanol versus levo-thyroxine for thyroid nodules (14). There is no investigation comparing a supraphysiological dose of levo-thyroxine versus a physiological dose in prevention of recurrence of cancer or reduction in mortality.

Meta-Analysis

In recent years there has been a cult in the value of meta-analysis. A meta-analysis is a review combining the results or outcomes of many published studies. When each of the studies demonstrates a trend for example radioiodine therapy reducing the number of recurrences of thyroid cancer, the combined data add strength to the thesis that ^{131}I is beneficial. When the studies used for the meta-analysis show disparate results the outcome of the meta-analysis is neutral. Many meta-analyses have been used to help in development of guidelines for managing medical conditions. They also form a basis for evidence-based medicine. It is important that the basic publications are consistent in the types of patients evaluated and the therapies prescribed. If all of the patients in one study who receive ^{131}I treatment have small cancers that have been totally excised, ^{131}I will appear to be very successful because there was no residual disease to treat. If these data are combined with publications discussing patients who had metastases to distant sites, their response to ^{131}I would be substantially worse and the studies would cancel each other out. Conversely, if all of the publications analyzed contain patients with small cancers and ^{131}I appears to be consistently successful, it would be wrong to conclude that ^{131}I would be useful for metastatic disease. Therefore it is valuable to review the raw information used in a meta-analysis before making a judgement. Higgins et al. have developed a technique for measuring the degree of inconsistency in a meta-analysis (15). This has been designated I^2 and is derived from the formula $I^2 = 100 \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Cochran's Q is calculated by summing the squared deviations of each study's estimate from the overall meta-analytic estimate. The degree of freedom is the number of studies analyzed minus one.

References to Published Articles

The text is extensively referenced and includes personal published work of 35 years managing patients with thyroid disorders including thyroid nodules and thyroid cancer. I have used PUBMED and MEDLINE and on occasion Google and have tried to update each chapter as it was being revised. I had to draw the line at some empiric ending time and used December 1, 2004.

Every effort has been made to refer to key articles and I apologize for any omission. Authors who find one of their important publications has been overlooked should not take this personally; the defect is an oversight not a slight. I would be happy to receive information that has been omitted by regular mail or e-mail.

There are several very useful sources of information apart from the computer links and standard textbooks. These include medical journals and now patients in addition to physicians can usually get access to abstracts and texts through PUBMED. The search engine Google can also find information and references. Several organizations provide help for patients as well as physicians, as seen in Table 1.5. The first is reached through the web site www.thyca.org. This thyroid cancer survivor organization provides solid current information for patients and it has published an excellent

Table 1.5. Web sites of use when researching problems related to thyroid nodules or thyroid cancer.

Web site	Note
http://ebm.bmjjournals.com	Access to journals with original peer reviewed articles
http://www.clinicalevidence.com	–
http://gateway.ut.ovid.com	–
http://md.skolar.com	–
http://Pubmed.com	–
http://www.allthyroid.org/	Thyroid Foundation of America
http://www.thyroid.ca/	Thyroid Foundation of Canada
http://wwwThyCanSurv.org	Thyroid cancer survivors association
http://www.aace.com	American Association of Clinical Endocrinology
http://www.thyroid.com	American Thyroid Association

low iodine diet recipe book. This organization convenes an annual meeting with invited experts to lecture on and discuss treatment options and future developments. Other professional associations include the American Thyroid Association (ATA). The web site is www.thyroid.org. The ATA and the American Association of Clinical Endocrinologists (www.aace.com) provide medical information and can facilitate referral to specialists based on geographic requirement of the patient.

Patient-Physician Relationship

This is a complex topic to condense. The relationship of patient and physician varies greatly between doctors, from country to country. It is based on education, role models, personal characteristics of family upbringing, personal experience, of being a user rather than a giver of care, and other factors that are hard to understand. There are differences that can relate to gender, age, ethnicity, education, and interest. (16) The patient wants "a patient-physician relationship based on understanding, honesty, and trust" (17). In the United States there are two trends that are not compatible. On one hand is an educated public that wants to share in the decision-making. On the other is managed care, where the aim is to make money for shareholders of companies responsible for delivering care. Those in charge of managed care organizations state there are other aims such as providing uniform, high quality medical care and preventative medicine, but in reality these leaders would not be in position if their companies were in the red. Other countries have problems with long waiting lists for testing and therapy. I have been informed that in some European countries a patient who would benefit from ^{131}I treatment frequently has to wait for months for a designated hospital bed to become available. These events can strain the patient physician relationship. In talking to physicians from all parts of the world, there is a consensus that they are working harder and consulting on more patients than in previous years. This also strains the relationship. There are several criticisms cited by patients. First that they do not have enough time to discuss their problems and to digest and understand the protocols for testing and treatment and to ask questions. In addition, they do not have the ability to have input in their management, which is presented to them as gospel and immutable. These issues are not easy to rectify but each clinician should try within their system to provide unhurried, sensitive, empathic, and knowledgeable care and to work with rather than above the patient. Objective evaluation of empathy has demonstrated that women physicians perform better than men, and psychiatrists are significantly superior to anesthesiologists, orthopedic surgeons, neurosurgeons, radiologists, cardiovascular surgeons, obstetricians and gynecologists, and general surgeons (18). Medical schools are investing more time in development of programs to increase the communication skills of young physicians (19). Patients should be advised to bring records such as operative and pathology reports and pathology slides. The slides should be reinterpreted and where possible scintiscans and radiological studies should be reviewed. This is superior to reading the reports. On occasion the volume of information the patient brings is large and it has to be reviewed and discussed separately. I was once faced with a patient who wheeled a large suitcase full of documents into the consulting room. When a patient is referred from your own institute it is beneficial to have all the information available at the time of the consultation. Patients are also advised to develop a list of questions related to their management. Once the relationship is established small pieces of information can be discussed by a short phone call. This could include the result of a recent blood test and whether the dose of a medication should be adjusted. These interactions are usually brief. When the issue turns out to be more substantial, a clinic visit can be organized (20). A study of patients who used scripted simulated problems found that triage by telephone was erratic (21). However, the range of advice sought was diverse and when the patients and their conditions are known and the item to be discussed relates to their illness the advice should be robust. Patients appreciate this since it avoids taking time off work, parking at the hospital, registering, and waiting. All consultations, including phone messages, should be documented. Another frequent complaint is that patients say they love Dr X but he keeps them waiting three or four hours. This should not happen.

Some patients use e-mail to relay symptoms and questions. Some physicians use it to convey information. This could be the way of the future. My preference is for direct communication either in the clinic or by telephone. The new regulations concerning privacy in the United States make the use of the Internet very hazardous. The privacy requirements make it important to talk directly to the patient and only after explicit permission has been given is it acceptable to speak with a designated alternative.

Alternative Therapy

Alternative medicine applies to non-standard or unconventional treatments. Many people place great stock in these. The therapies are supported by testimonies, but usually there are no peer reviewed published data. It is difficult to argue against alternative therapy with two provisos. One, that the alternative treatment is not used in place of conventional treatment. Secondly, that the treatment is known to have no deleterious side effects. There is almost no data on the latter. I sent batches of alternative therapies used by one patient for analysis by scientists in a company that had top chemists working on identifying active ingredients of traditional Chinese and Oriental remedies. They were unable to find any known active ingredient in the patients alternative medications. This suggests the therapies would provide no benefit, but the analysis did not guarantee that the materials were non-toxic. The following are 3 examples of alternative medicines copied directly from their web sites:

If you are reading this page, you or someone you love has cancer. Dr X's goal is to provide hope and an alternative to the unsuccessful common treatments offered by the medical field. TumorX Paste & Proteolytic Enzymes. This is a web site where one can find alternative cancer treatments, using TumorX Paste and TumorX Proteolytic Enzymes. These are used in conjunction to eliminate the cancer from one's body. TumorX Paste contains the apoptotic and antiproliferative ingredient Bloodroot, (i.e., Sanguinarine canadensis.) Bloodroot's anti-cancer compounds have been known historically as Hoxsey salve, Dr. Mohs Chemosurgery salve, escharotic salve, black salve, bloodroot salve, and other names. TumorX Paste is used in conjunction with proteolytic enzymes that can, in most cases, defeat one's cancers.

Ukrain with two cycle Insulin Potentiation Therapy (IPT): We believe Ukrain/IPT is very effective. We have treated all kinds of cancers including Pancreatic, breast, colon, ovarian, thyroid, liver, lymphomas, leukemia, multiple myeloma, prostate, brain, stomach, lungs, mesothelioma, sarcoma, and so forth. Melding this modality with other therapies. Many of the cancers we treated resulted in reduction of tumor markers and shrinkage of tumor mass without any of the horrendous toxic effects we see with traditional chemotherapy.

Here are the products most useful for cancer – the top tier, foundational products:

- EOxygen Elements Plus: Four to six bottles a month are a high therapeutic amount. This would work in tandem with the oxygen utilization effects of Super Quinone.
- Ellagic Formula with Graviola: Three or four bottles is a month high therapeutic amount.
- SSR Super Quinone: A course of fourteen vials will last a month and a half and can be repeated until healthy.
- Five Elements Mineral Catalyst: One bottle lasts three months.
- U-Fn: Three bottles a month is the suggested therapeutic usage.
- MPS Gold and MPS 3X: One to three large bottles of the Gold is the therapeutic to high therapeutic level. Add on an equal amount of MPS 3X bottles to boost the immune system even more.
- Whole Cell Beta Glucan: One to three bottles a month depending on your size. This works well with MPS Gold.
- AFA Blue Green Algae: The highest therapeutic amount is about fifteen grams a

day. Try Blue Manna algae for working on emotions and mental outlook.
- Nature's Biotics: A good fundamental product to get, but you have to work into it slowly using just one bottle the first month. Three or four bottles a month would be a good high therapeutic amount.
- eTag: Several cancer clinics are successfully using the eTag to help fight cancer. Protects you from EMFs and energizes your body for better healing.

You don't have to use everything in high therapeutic amounts, but the worse your cancer is, the more you may want to use.

Readers can recognize the promoters of these are preying on the fears and hopes of patients. It is hoped that sympathetic and sensitive discussions can dissuade patients from investing a lot of hope, money, and time into these.

Traditional Herbal Therapy

The majority of herbal therapies for thyroid disorders come from Chinese sources. Most are used for goiter, thyrotoxicosis and some for hypothyroidism. Figure 1.8 shows the ingredients a patient was advised to ingest for the treatment of thyrotoxicosis. The components were to be boiled and ingested like tea. The concoction did not work. Some plant extracts are purported to have anti-tumor effects but the literature is noted for its brevity (22, 23). Some plants have been identified to have antiproliferative effect on medullary cancer cells in vitro (24). Acupuncture should be included under this heading. Acupuncture applied by experts to the right patient can be used for anesthesia (25). Acupuncture is disappointing for treatment of thyroid nodules and has no role in managing proven thyroid cancer. (26) Search of the literature did not identify an article discussing the role of acupuncture and thyroid cancer. Alternative and traditional therapies are not included further in the text.

Figure 1.8. Picture shows the ingredients for traditional medicine used to treat thyrotoxicosis.

Summary and Key Facts

The incidence of thyroid cancer is increasing in the United States. Three out of four patients are women and the average age is 30 years to 45 years. Although the treatments are established and adhered to vigorously by some authorities, there is a remarkable lack of controlled trials.

- In 2004 there are 22,500 new cases of thyroid cancer in the United States.
- Approximately 16,900 of these are in women
- There are ethnic differences with a low incidence in African Americans and high in people from the Pacific Rim in particular the Philippines.
- There is equality of genders in prepubertal patients with thyroid cancer.
- Interpretation of tests and definitions of sensitivity, specificity, positive, and negative likelihood ratios are presented.
- Methods of obtaining information through web sites are presented
- There is an increasing interest of patients to become educated about their illnesses and for them to be active and have input in discussion about management decisions.

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Appendix 1.1.

International Codes for Thyroid Diseases. ICD-9-CM Coding System.

The International Classification of Diseases is a system developed collaboratively between the World Health Organization (WHO) and ten international centers. The codes allow comparability of collection, classification, processing and presentation of health statistics.

ICD 9 code	Diagnosis
140–239	Neoplasms
193	Malignant neoplasm of the thyroid: Thyroid cancer
240.0	Simple goiter
240.9	Goiter unspecified
241.0	Non toxic uninodular goiter
241.1	Non toxic multinodular goiter
241.9	Unspecified nodular goiter
242.0	Graves' disease
–	Graves' disease with crisis
242.0	Ophthalmopathy/dermopathy
242.1	Toxic thyroid nodule
242.2	Toxic multinodular goiter
242.3	Toxic nodular goiter
242.4	Thyrotoxicosis ectopic
242.8	Thyrotoxicosis, other origin
243	Congenital hypothyroidism
244.0	Post surgical hypothyroidism
244.1	Other post ablation hypothyroidism
244.2	Iodine hypothyroidism
244.3	Other iatrogenic hypothyroidism
244.8	Specific acquired hypothyroidism
244.9	Unspecified hypothyroidism
245.0	Acute thyroiditis
245.1	Subacute thyroiditis
245.2	Chronic lymphocytic thyroiditis
245.3	Chronic fibrous thyroiditis
245.4	Iatrogenic thyroiditis
245.8	Chronic thyroiditis unspecified
246.2	Cyst of the thyroid
246.3	Hemorrhage into the thyroid

Appendix 1.2.

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Chapter 2

Thyroid Anatomy and Physiology

This chapter on thyroid anatomy and physiology is included because knowledge and understanding of the information helps with the clinical evaluation and management of the patient. It also aids in the interpretation of laboratory results, cytopathology and histopathology, the principles of surgery, and the pathophysiological changes from excess and insufficient thyroid hormones. Most readers have received basic education on the anatomy and physiology of the thyroid. The gross anatomy has not changed with time, but there are considerable advances in knowledge of molecular events. For some, including patients, there is no such grounding. The goal is to make the information clinically relevant. The chapter is not encyclopedic and references have been selected to provide reviews that include extensive bibliographies.

The thyroid is an endocrine gland that produces and secretes the thyroid hormones thyroxine and triiodothyronine. Thyroid hormones control the development of the embryo and the metabolism at all times of life. Prolonged deprivation of thyroid hormone results in slowing of the function of all systems and with time the patient becomes comatose (myxedema coma) and eventually dies. Excess thyroid hormone results in an increase in function of all systems, and this can also cause the life-threatening syndrome of thyroid crisis, which has a significant mortality.

Thyroid Anatomy: Gross Anatomy

The thyroid is a bilobed gland. The left and right lobes lie on each side of the trachea. The isthmus that joins the lobes is usually anterior to the second to fourth tracheal cartilages. The lobes extend superiorly and inferiorly from the isthmus and the shape is similar to a butterfly as shown in Figure 2.1A,B,C and Figure 2.2 in which the structures are labeled. The inferior margins of the lateral lobes in a normal gland are at the level of the sixth tracheal ring. In regions where there is adequate intake of iodine the thyroid weighs between 10 g and 20 g. Because human soft tissues are predominantly water, the gland has a volume of 10 ml to 20 ml. It is the largest endocrine gland. In an adult the dimensions of each lobe are approximately in length 5 cm, breadth 2 cm to 2.5 cm, and depth 1 cm to 1.5 cm. There is a fibrous capsule that sends septae into the gland dividing it into lobules. Branches of the arteries and veins run through the capsule with the connective tissue. The pretracheal fascia covers the gland and anterior to that are three pairs of infrahyoid strap muscles, the sternohyoids, sternothyroids and omohyoids. In front of the strap muscles the sternocleidomastoids muscles run at an angle from the mastoid superiorly and laterally to the manubrium and clavicle inferiorly and medially.

When palpating the thyroid, it is necessary to pull the sternocleidomastoid gently laterally in order to be able to feel the body and edges of the gland. There are different approaches to examination of the gland by palpation. Some prefer to sit in front of the seated patient and use the thumbs to identify anatomic landmarks, the edge of the gland, and any nodule or nodules. All authorities agree that looking at the gland with the patient seated can provide information about the size and shape of the gland, the presence of nodules and scars, and significantly enlarged lymph nodes. After inspection, most authorities, including myself, prefer to stand behind the patient and use the first and second fingers of both hands to palpate. I place my thumbs on the patient's spine at about the level of the thyroid and then position my first and second fingers gently on the trachea. The fingers are gently moved up and down to identify the isthmus, which is not covered by strap muscles. When that is felt, the examining fingers move to one lobe using the isthmus as a focal point to identify the medial border of the lobe, and the sternocleidomastoid is gently maneuvered to the side to allow the body of the lobe and its lateral margins to be felt. Then the opposite lobe is examined. When a nodule is palpated: Its size,

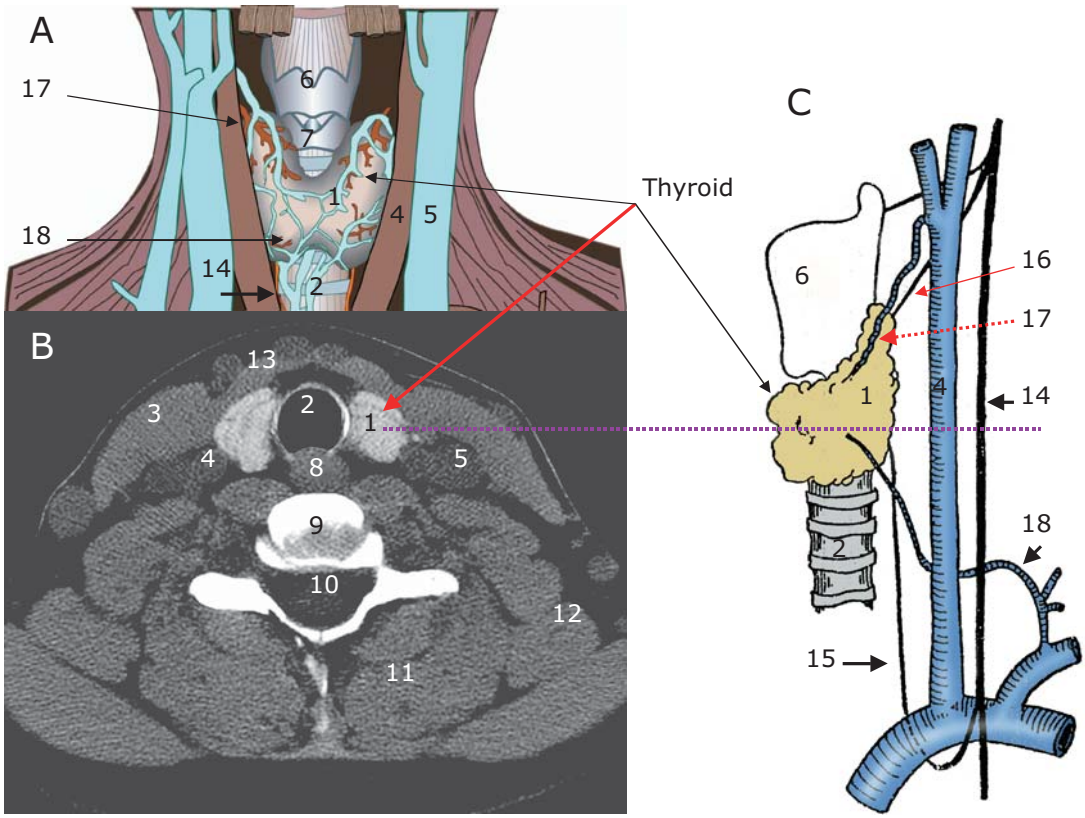


Figure 2.1. (A, B, C) Coronal, transaxial and sagittal images at the level of the thyroid. A and C are diagrams, and B is a computed tomogram. The anatomy is coded numerically. (1) is the thyroid gland, (2) the trachea, (3) the sternocleidomastoid muscles, (4) the common carotid artery, (5) the internal jugular vein, (6) the thyroid cartilage, (7) the hyoid cartilage, (8) the esophagus, (9) the body of a cervical vertebra, (10) the spinal canal and cord, (11) the erector spinae muscle, (12) the levator scapulae muscle, (13) the sternohyoid, sternothyroid muscles, (14) the vagus nerve, (15) the recurrent laryngeal nerve, (16) the external laryngeal nerve, (17) the superior thyroidal artery, and (18) the inferior thyroidal artery. In C the close proximity of the external laryngeal nerve and the superior thyroidal artery should be noted. Also of note is the close proximity of the recurrent laryngeal nerve to the inferior aspect of the thyroid.

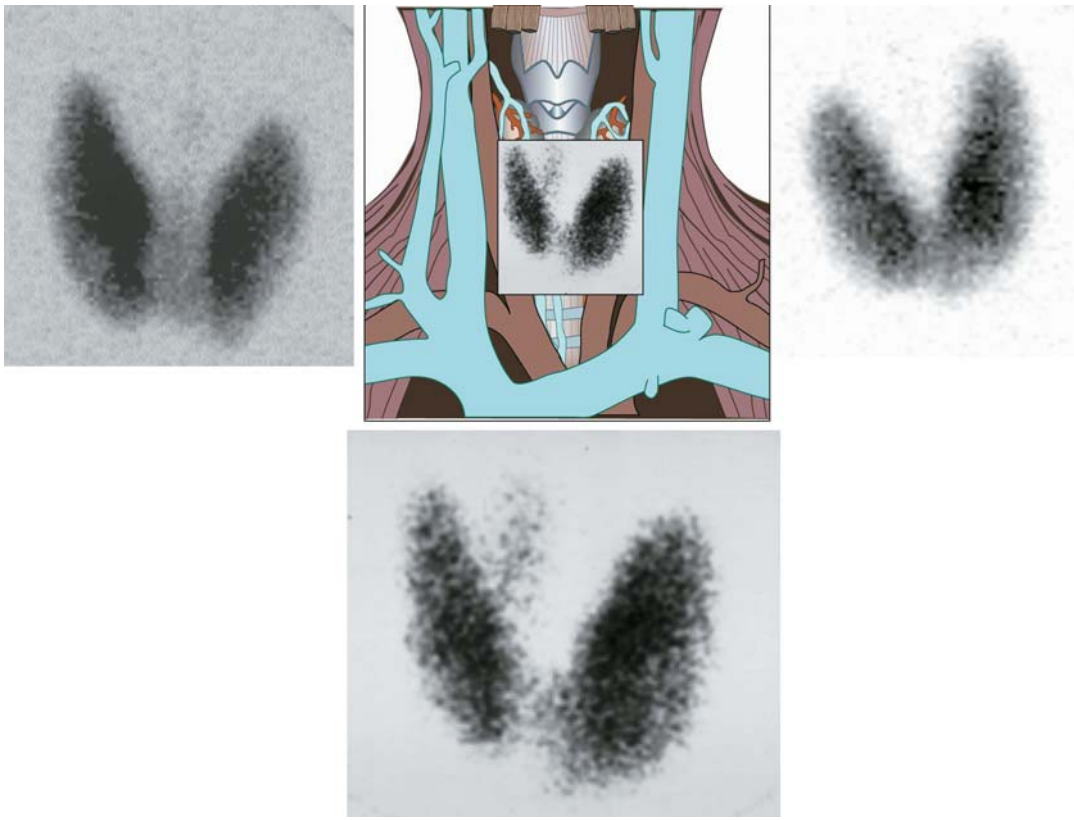


Figure 2.2. Figure shows the lobes and isthmus in three normal thyroid glands demonstrating variations in shape and the anatomic position in a coronal diagram of the neck.

consistency, movement, or fixation is documented. The thyroid moves when the patient swallows, so the examination is aided by having a glass of water available.

Then the cervical lymph nodes on each side should be examined. Although spread of cancer to the posterior cervical nodes is not common, they should be examined as part of a routine. Auscultation over an enlarged gland can identify the bruit usually associated with Graves' hyperthyroidism. A bruit over a large nodule, especially when it is pulsatile, should be a sign not to proceed to a biopsy without an ultrasound to identify the arterial flow.

In countries where the intake of dietary iodine is low, the thyroid tends to be larger. An enlarged thyroid is called a goiter. The term endemic goiter is used when 10% or more of the population have an enlarged thyroid. As the thyroid enlarges, it becomes visible and easier to feel on clinical examination. In addition when the gland enlarges, there is a tendency for nodules to form. In regions of iodine deficiency the thyroid gland in older people is almost always enlarged and nodular. This is called a multinodular goiter. In older patients as the thyroid enlarges, there is also a tendency for the inferior margin of the gland to move downwards until it enters the thoracic inlet. This movement is partly dictated by the pretracheal fascia that is denser anteriorly and superiorly, so an enlarging gland is guided inferiorly and posteriorly. Once the inferior border of the thyroid has entered the thoracic cavity the reduced pressure in the thorax caused by breathing, along with gravity, can cause the inferior migration to continue into the mediastinum. This results in a sub- or retro-sternal goiter.

Embryology

Embryologically, the thyroid forms from an invagination in the floor of the pharynx between the first and second pharyngeal pouches. That region ends up as a spot at the back of the tongue (1). At day 24 in utero the tissues migrate inferiorly to their final position in the neck, which is reached by about the eighth week in utero. Texts refer to the forming tissue as an anlage, which the dictionary defines as "the basis for later development". The thyroid is dragged by the forming heart. Three thyroid transcription factors, TTF-1, TTF-2, and PAX-8, are essential for normal development and migration of the thyroid (2). Mice that are homozygotes for a defect in the TTF-1 gene have no thyroid tissue and have severe defects of the hypothalamus, forebrain, and lungs. Similarly mice with homozygous defects in the Pax-8 gene have no thyroid (follicular) cells. In a proportion of TTF-2 knockout mice the thyroid is an ectopic position. This suggests that TTF-2 is required for migration of the forming thyroid. These three factors are also involved in the production of functional proteins by follicular cells that are essential for the formation of thyroid hormones. These include the sodium iodide symporter (NIS), thyroid peroxidase (TPO), and thyroglobulin (Tg), which are discussed individually below. The midline thyroid fuses with tissues derived from the fourth and fifth branchial clefts, which combine to form the lateral lobes. These bring neuroendocrine cells from the ultimobranchial body that forms parafollicular cells (also called C cells). C cells produce and secrete calcitonin.

Three functional stages in the development of the thyroid have been described, called precolloid, colloid, and follicular. These occur at 7 weeks to 12 weeks, 13 weeks to 14 weeks, and after 14 weeks. (3) Their appearances can be mirrored by adult pathologies that are labeled as embryonal and fetal lobulation. The thyroid can produce hormones by week 12 and some state as early as day 74.

The embryological origin of the thyroid can be seen as the foramen cecum, which is in the midline of the tongue, approximately at the junction of the anterior 2/3 and the posterior 1/3. The migratory route from the foramen cecum to the cervical position is called the thyroglossal tract. In early embryological formation this is a tube, the thyroglossal duct, but during embryologic development it usually becomes fibrotic, and after birth it is even difficult to identify at operation. Rarely the gland fails to migrate from its original site of development, resulting in a lingual thyroid, as shown in Figure 2.3. The condition presents with a mass at the base of the tongue that can cause dysphagia, dysphonia, and dyspnea (4, 5). In general a maldescended thyroid does not produce physiological quantities of thyroid hormones, and the patient is hypothyroid and has an elevated thyroid stimulating hormone (TSH). One of the reasons is because the lateral lobes have not fused with the median thyroid; therefore, the volume of cells is insufficient for adequate production of thyroid hormones. In most patients with an ectopic thyroid that is the only functioning tissue, but there are exceptions, including one report where the lingual thyroid was recognized 20 years after the patient had undergone thyroidectomy for a multinodular goiter (6). The high TSH perpetuates the growth of ectopic dysfunctional thyroids. The treatment of an uncomplicated lingual thyroid is administration of thyroid hormone for life to suppress TSH. Very occasionally the mass needs to be ablated with ^{131}I (7). Because the patients are hypothyroid it does not make sense to autotransplant the tissue since thyroid hormone will be necessary for life in any case (8). Very rarely thyroid cancer arises from follicular cells in a lingual thyroid, and its management is discussed in Chapter 6 (9, 10). The main clinical issues are to recognize that a mass in the midline at the back of the tongue can be the thyroid, and if there are any suspicious symp-

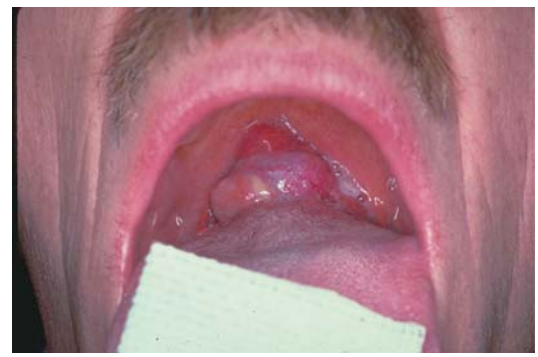


Figure 2.3. Figure shows a lingual thyroid in a middle-aged man.

toms or it has an irregular appearance or is ulcerated, it should be biopsied.

The thyroid can migrate from the base of the tongue but fail to reach its cervical position. This is a maldescended or ectopic thyroid and it usually presents as a midline swelling in the neck. The common midline swellings between the base of the tongue and above the thyroid are thyroglossal duct cysts and ectopic thyroid. The most common midline swellings in the neck are enlarged or nodular thyroids. Knowledge of the embryology is relevant in clinical practice and thyroid imaging. In some patients the inferior part of the tract can be identified using radionuclides of iodine. It appears as a thin triangle with the base on, or close to, the superior border of the isthmus, and the apex is at or near to the thyroid cartilage; hence its anatomic name, the pyramidal lobe (Figure 2.1C). The pyramidal lobe can be identified in 75% of glands at autopsy, but in most normal people there are not enough functioning cells to be seen on scintiscan. When the gland is stimulated as in Graves' hyperthyroidism the pyramidal lobe can be identified. In some patients who have had a thyroidectomy for thyroid cancer the pyramidal lobe is left, and it can be seen on scintiscan using radioactive iodine and misinterpreted as residual cancer. The pyramidal lobe usually contains normal thyroid tissue, and it is not very common for thyroid cancer to metastasize to lymph nodes in the midline superior to the isthmus. Therefore, midline tissue just cranial to the thyroid bed that traps radioiodine is usually but not necessarily benign. The clinician should review the pathology and surgical findings regarding the size and position of the primary cancer and the level of serum Tg to determine whether this is likely to be residual cancer or not.

The thyroglossal tract contains insufficient thyroid cells to be identified on scans using radioactive iodine. Very rarely these small number of thyroid cells can be the source of cancer. This usually occurs in a thyroglossal cyst. Benign thyroglossal cysts are common and said to be the most frequent congenital cervical abnormality (11). They are diagnosed most often in children and are usually identified clinically as a painless midline nodule that moves upward when the tongue is protruded. Transillumination of the cyst using a flashlight is also characteristic; however, very few physicians carry one nowadays. Less commonly the presentation can be an infection in an undiagnosed cyst, in which case the nodule is tender and inflamed. The organisms most likely gain access through a patent thyroglossal duct. The differential diagnosis of thyroglossal cyst is ectopic thyroid and an ultrasound is recommended to confirm that a cyst is present and that the thyroid is in the normal position, or alternatively, that the midline mass is solid and the thyroid is absent. Some authorities recommend fine needle aspiration (FNA) of all thyroglossal cysts to identify the rare cancer. The cost effectiveness of this has not been determined in children where the world literature indicates only seventeen cases in patients sixteen years of age or younger (11). The treatment of thyroid cancer in a thyroglossal cyst is discussed separately for the adult in Chapter 6 and for the child in Chapter 7.

In about 50% of patients undergoing thyroid surgery it is possible to identify thyroid rests situated from the inferior border of the gland to the arch of the aorta (12). These are called thyrothymic thyroid rests. Migration of thyroid tissue with the heart has been reported and is called struma cordis (13–15). There are case reports of thyroid in bizarre sites such as porta hepatis, gallbladder, and vagina, and it is hard to understand how they can migrate to those sites based on our knowledge of embryology (16). In all cases of ectopic thyroid it is important to ensure that the tissue is not a metastasis. The thyroid should be examined clinically and by ultrasound and the pathologist should look for features in the cells and their nuclei to be discussed in the next chapter that might indicate the tissue is malignant rather than ectopic.

One topic of dispute is whether there can be lateral rests of benign thyroid tissue. This used to be called lateral aberrant thyroid. The concept was that thyroid tissue could be pinched off by muscles during development. In some patients these cells have been identified within subcapsular sinuses of lymph nodes. In most cases these rests are actually well differentiated low-grade metastases from an intrathyroidal cancer. In answer to the question, "Does lateral aberrant thyroid exist?" Li Volsi states, "Here the answer must be equivocal" (3). Fortunately for patients and clinicians, this is rare. When thyroid tissue is found in the lateral neck,

efforts should be made to ensure there is no primary intrathyroidal cancer. Similarly, there are reports of normal thyroid tissue in the larynx and trachea (17). When I have encountered this, the thyroid tissue was cancer that had invaded through the trachea.

About 70% of the mass of thyroid consists of follicular cells that produce thyroid hormone and less than 1% is contributed by C cells. Embryologically, the C cells arise from the ultimobranchial body that migrate to fuse with the lateral lobes. The site is marked by the tubercle of Zukerkandl, which can contain a third cell type that appears in small nests (18). These do not appear to be clinically important. C cells are most common at the junction of the upper 1/3 and lower 2/3 of the lateral lobes. Cancers of the C cells are called medullary cancers and are discussed in Chapter 10.

Blood Supply of the Thyroid

The thyroid receives arterial blood from the superior and inferior thyroid arteries. The superior thyroid artery supplies the upper pole and is the first branch of the external carotid artery. The inferior thyroid artery enters the posterior aspect of the gland. It is a branch of the thyrocervical trunk coming from the first part of the subclavian artery. There is also an inconstant supply from the thyroidea ima artery, which arises from either the aorta or the innominate artery. The thyroid has a very rich blood supply of 4 ml/g/min to 6 ml/g/min. This is greater than the blood supply of the kidneys, brain, or heart, and even under normal physiological conditions is second only to the adrenals. When the thyroid is hyperfunctioning as in Graves' disease the increased blood flow coursing through the gland can be felt as a thrill and heard using a stethoscope as a bruit. Careful attention to these vessels is important during thyroidectomy and a small artery left unsutured can result in a post-operative hematoma, causing pressure on the airway and a post-operative emergency. There are superior, middle, and inferior thyroid veins. The superior veins drain the upper pole, and the middle veins drain the lateral aspects of the lobes. Both enter the innominate veins. There can be several inferior veins that drain the lower pole into the brachiocephalic veins.

Lymphatic Supply of the Thyroid

A rich lymphatic network drains to cervical nodes. The lymphatics follow the vasculature, those draining the upper part of the gland follow the superior thyroid artery and feed into deep cervical nodes. Lymph channels from the middle of the lateral lobes terminate in internal jugular, recurrent laryngeal, paratracheal, and paraesophageal nodes. Inferiorly, there is drainage to pretracheal and paratracheal nodes as well as inferolateral drainage to supraclavicular nodes. There is a Delphian node in the midline just above the isthmus. It is named after the Oracle of Delphi, whose predictions could be interpreted as desired by the listener. An abnormal looking Delphian node can or cannot contain cancer, and the same is true for a normal appearing node. The lymphatic drainage is important in the management of thyroid cancer since lymphatic metastases are common. Early anatomic reports of direct drainage of lymphatics into the subclavian vein could be important in systemic metastases of thyroid cancer. However, most distant metastases occur by invasion of the primary cancer into veins within the thyroid.

Some surgeons now use the technique of sentinel node imaging for management of thyroid cancer (19–21). A radioactive colloid is injected into the thyroid lesion and real time images are made of the flow of radioactivity to a node or nodes. The first node to be identified on scan is the sentinel node. The rationale is that when this node is sampled and no evidence of cancer is found by pathological examination it is unlikely that the thyroid cancer has metastasized and nodal dissection is not necessary. Sentinel node imaging is now the standard of care for breast cancer and melanoma, but not all surgeons agree with this approach for thyroid cancer, and this is expanded in Chapter 6.

Surgical Anatomy

During thyroidectomy, there are adjacent structures that are at risk and every effort should be made to preserve them. First are the recurrent laryngeal nerves. The recurrent laryngeal

nerves are branches of the vagi. The right recurrent laryngeal nerve branches from the vagus at the level of the subclavian artery and the left branches at the level of the aortic arch. They supply motor nerves to the muscles of speech and a sensory branch to the glottic larynx. The recurrent laryngeal nerves run superiorly in, or close to, the tracheoesophageal groove. They have a variable relationship to the inferior thyroid artery. The right nerve most frequently runs superficial to it, but can be inferior to or even pass between branches of that vessel. The left is more likely to run deep to the inferior thyroid artery but can also have a varied relationship to the blood vessels. In a recent study of more than 400 nerves during thyroidectomy, all were identified, and 67% on the right were superficial compared to 11% on the left (22). Knowledge of the anatomy and variations are important because damage to one nerve can cause a change in voice with a low gravelly pitch. This is due to a paralysed immovable vocal cord on the side of the nerve injury. This also causes hyperventilation when the patient gives a speech or talks for a while. The patient might also inhale when eating or drinking and have bouts of coughing and spluttering. This is more common with liquids than solids. (23) Damage to both nerves is a significantly worse complication. The voice might be reasonably preserved, but breathing is compromised, and stridor is a medical emergency. These and other complications of thyroidectomy are discussed in Chapter 6.

Secondly, the superior laryngeal nerves also arise from the vagi at the inferior vagal ganglion. As the nerves pass inferiorly, they branch, and the internal branch runs with the superior laryngeal artery. This is a sensory nerve supplying the supraglottic larynx. The external branch, also called the external laryngeal nerve, runs inferior to the superior thyroid artery and is the motor nerve to the cricothyroid muscle. This has been called "the neglected nerve" and also the "nerve of Amelita Galli-Curchi," an opera singer whose career was purported to be ended from surgical trauma to this nerve (24, 25). Damage to the external laryngeal artery results in dysphonia that can be difficult to diagnose. In 20% to 60% of patients the nerves lie within a centimeter of the superior thyroid artery and upper pole of the thyroid (26). Page et al. conducted a study to identify the nerves during 50 thyroidectomies (27). They used an electrical stimulator, and when the nerve was contacted there was contraction of the cricothyroid muscle. Only 20% of the external nerves were identified, and in only 8% of patients were both nerves visualized. Postoperatively one patient had dysphonia, not attributable to damage to the recurrent laryngeal nerve, and that patient's external laryngeal nerves had not been identified during the surgery. These investigators stress the inconsistency of anatomy and tabulate studies where attempts were made to identify the nerves and determine what percentage were at risk. This was between 12% and 78%. The recurrent and external laryngeal nerves can be damaged by transection or by stretching (neuropraxis). Management is presented in Chapter 6.

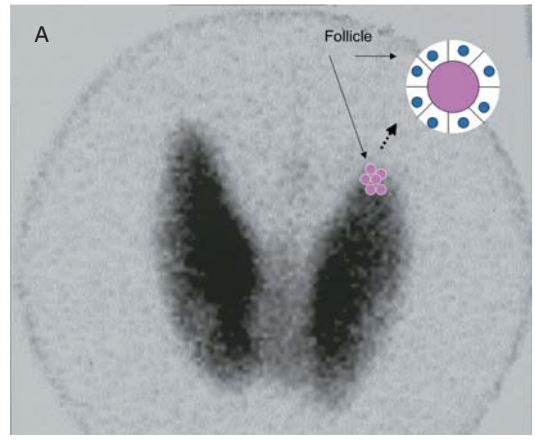
There are usually four parathyroid glands, two superior and two inferior. The superior glands arise from the fourth branchial pouch, the inferior ones from the third branchial pouch. Therefore the inferior glands migrate further and they have more chance of being in ectopic sites. About 80% of the superior glands lie approximately 1 cm above the point where the inferior thyroid artery and the recurrent laryngeal nerve come in contact. The inferior glands can lie anywhere from the angle of the jaw to the mediastinum. Those glands adjacent to the thyroid are most at risk. The glands can be accidently removed during total thyroidectomy or more commonly their function is impaired by damage to or stretching of their arteries. When all parathyroids are compromised the patient develops acute hypocalcemia, and if untreated this progresses to tetany and seizures. Temporary hypocalcemia is common after total thyroidectomy. However, in the case of certain loss of parathyroid function, one of the glands can be autotransplanted into the sternocleidomastoid or into the forearm. Some surgeons recommend this in every case of total thyroidectomy, arguing that although permanent hypoparathyroidism is uncommon, the complication rate should theoretically be zero when a transplant is undertaken (28).

During dissection of cervical nodes the cervical sympathetic nerve can be damaged. This results in a Horner's syndrome on that side (ptosis, enophthalmos, contracted pupil and reduced sweating of the face). It is uncommon, and in one review of more than 2,000 thyroid

and parathyroid operations six cases were recognized (29). The spinal accessory nerve (cranial nerve XI) is also at risk during dissection of the cervical lymph nodes, and when damaged there is weakness of the muscles of the shoulder and inability to raise the arm on the side of the injury.

Microscopic Structure of the Thyroid

Thin extensions of connective tissue of the capsule enter the substance of the thyroid and form small lobules. The lobules are made up of thirty to forty follicles. Thus, the thyroid is largely made up of follicles, as show in Figure 2.4 A and B. These are the functional as well as structural units. A follicle is spherical and consists of a single layer of thyroid cells arranged around a gelatinous core, similar to the skin of a grape around the pulp. Thyroid cells, also called follicular cells, are cuboidal and the base of the cell abuts on capillaries and lymphatics, and the apex is adjacent to the colloid (Figure 2.4B). The nucleus lies close to the base. The apex has a microvillous structure that interdigitates with the colloid. As the function of the thyroid increases, the cells enlarge and their shape becomes columnar. Causes of hypertrophy of the follicular cell include increased hormonal stimulation by the pituitary hormone TSH, iodine deficiency or thyroid stimulating immunoglobulins (TSI). The receptor for TSH is in the basal and lateral aspects of the cell. It is a seven trans-membrane protein. The extracellular component binds TSH and activates cyclic



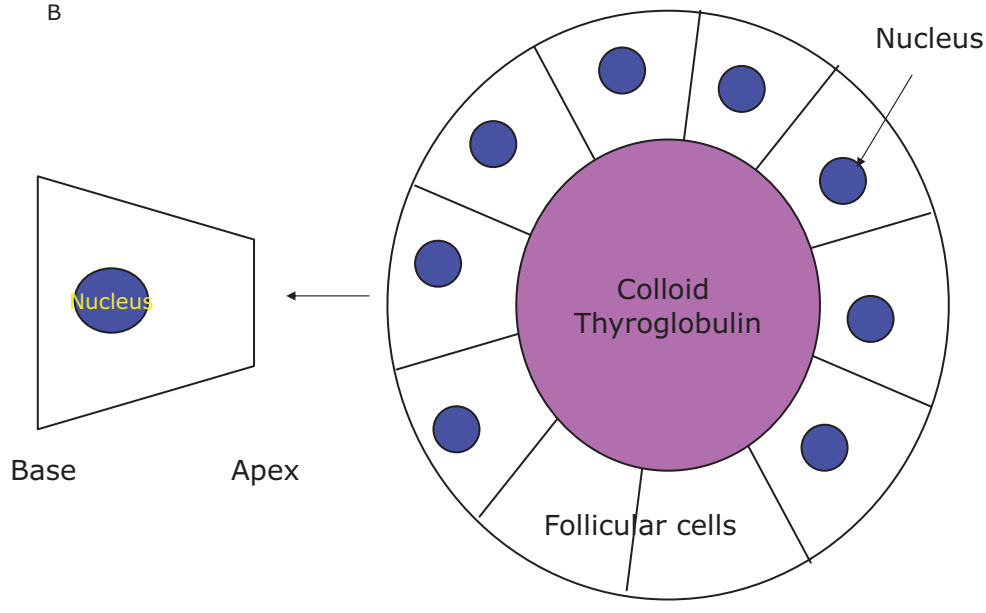


Figure 2.4. (A) This demonstrates a thyroid scan with follicles superimposed. (B) The structure of a follicle is shown with a single layer of cells surrounding the colloid that consists of thyroglobulin.

AMP and increases all aspects of function as discussed below. The sodium iodide symporter is a thirteen trans-membrane protein that transports iodide from the serum into the follicular cell. This also is present in the basal and lateral cell membrane.

The main constituent of the colloid is thyroglobulin. Thyroglobulin is a 660,000-dalton glycoprotein that is synthesized in the follicular cell and secreted into the colloid where it is the site of formation and storage of thyroid hormones. The formation of thyroid hormone, their carriage in blood, their metabolism and actions are described followed by a review of the control of thyroid function. The chapter ends with a discussion on testing thyroid function and a brief statement about calcitonin.

Formation of Thyroid Hormone

An adequate supply of dietary iodine is necessary for physiological thyroid hormone formation. Inorganic, non-radioactive, iodine is ^{127}I and the atomic number of iodine is 53. Iodine deficiency is common and it is estimated that more than 1.5 billion people are at risk. As stated above, as the intake of iodine decreases, the size of thyroid cells and the thyroid gland increase. There is an inverse linear relationship of thyroid size to urinary iodine (30). Urinary iodine measurement is a convenient method of determining iodine intake and is valuable for population studies. Inhabitants living in regions of iodine sufficiency excrete more than 100 μg iodine per liter of urine. The recommended intake for an adult is 150 μg per day and 200 μg per day during pregnancy. In regions of severe iodine deficiency less than 20 μg iodine is excreted per liter of urine. The sources of dietary iodine are fresh seafood (including fish, shrimp, crab, etc.) and kelp and vegetables grown in iodine rich soil. Populations living far from the sea in mountainous regions where glaciers have stripped the topsoil and who are also without fast transportation of fresh food are at risk. These regions include the central mountainous regions of the large landmasses of Asia, Africa, South America, Eastern Europe, and Indonesia. In more advanced countries iodination of salt has corrected the problem, and iodized salt could be included as dietary iodine. The United States was a region of iodine deficiency until the 1930s, when iodine was added to salt. The intake is approximately 500 μg per person per day. Although the intake of iodine in the United States is falling in comparison with 30 years ago, there is more than adequate iodine. Additional sources include vitamin and mineral pills, which usually contain 130 μg per pill, medical sources such as radiographic contrast, and iodine containing medications such as amiodarone. When a patient with surgically treated thyroid cancer is managed with scanning and therapy using radionuclides of iodine it is important to restrict the patient's intake of iodine so that the radioactive tracers are not diluted by non-radioactive ^{127}I. There is some evidence that chronic lymphocytic thyroiditis is more common in countries such as Japan, Iceland, and the United States where there is high dietary iodine. In contrast populations with low intake of iodine have a range of serious problems grouped together as iodine deficiency disorders. It has been estimated that 740 million have goiter, 50 million children have mental retardation or iodine deficiency brain damage, and 11 million have frank cretinism (31, 32). The importance of iodine deficiency is particularly significant in pregnancy because of adverse effects on growth and development of the central nervous system of the fetus (33–35). In regions where there is plentiful supply of iodine goiter cannot and should not be attributed to iodine deficiency and an alternative explanation should be sought. Papillary cancer is more common in areas where there is an abundance of dietary iodine and the proportion of follicular cancers increases as the intake of iodine decreases.

Iodine is rapidly absorbed in the upper gastrointestinal tract and the kidney and thyroid compete for the element, as shown in figure 2.5 A and B. When the thyroid traps 20% the kidney excretes 80%. This is a simplification because some other organs trap iodine, but that proportion is small and usually reenters the circulation and is available for trapping by the thyroid or renal excretion. Most of the iodine that is incorporated into thyroid hormone also becomes available for reuse when the hormones are metabolized. The first step in thyroid hormone formation is the trapping of iodine by the follicular cell.

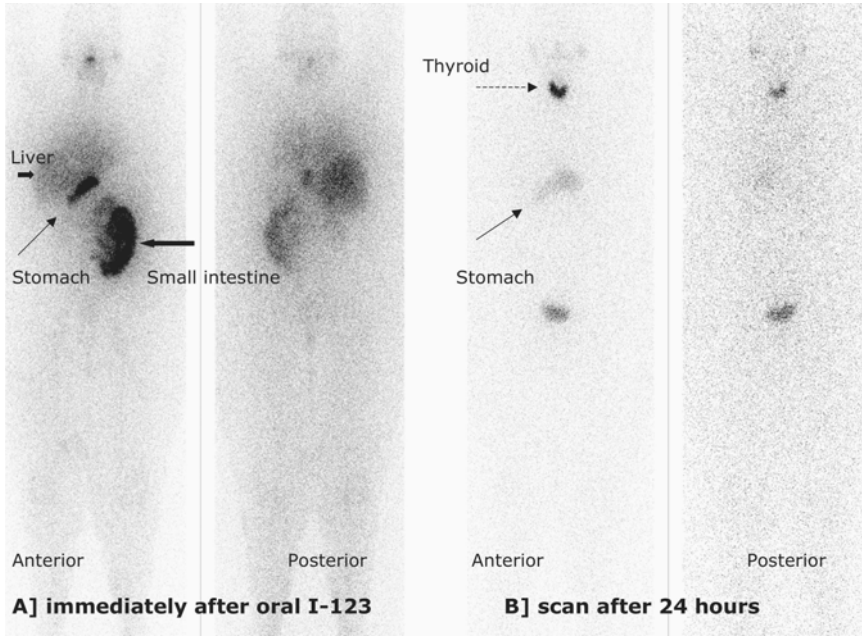


Figure 2.5. (A) The images on the left are anterior and posterior whole body scans obtained 20 minutes after ingestion of 1 mCi (37 MBq) ^{123}I. They demonstrate that radioiodine has been absorbed and distributed throughout the body. There is activity in the stomach and small intestine. The liver and heart show evidence of ^{123}I in the blood pool. (B) The images on the right were taken after twenty-four hours, showing uptake in the thyroid. There is residual uptake in the stomach, and the bladder is recognized as radioiodine is excreted in the urine. Salivary glands are faintly seen.

The Sodium Iodide Symporter

The thyroid follicular cells trap iodine and incorporate it into thyroid hormones. Iodine is an essential component of these hormones, thyroxine and triiodothyronine, that contain four and three atoms of iodine respectively, hence their designations T_4 and T_3. It has been recognized for decades that the thyroid can trap iodine and concentrate it against an electrochemical gradient. The mechanism has been clarified in recent years. The iodide trap is located on the baso-lateral membrane of follicular cells. Two atoms of sodium are transported along with one atom of iodide, and the protein transporter is called the sodium iodide symporter, designated NIS (36).

The transport can be demonstrated using a radioactive tracer of iodine, as shown in Figures 2.1, 2.2 and 2.5. Radionuclides of iodine have been employed for more than six decades for testing and treatment of thyroid disorders. The radionuclides of iodine that are clinically important are ^{123}I, ^{131}I, and ^{124}I. In the United States where the daily intake of iodine is about 500 µg approximately 20% (range 10% to 30%) of an oral dose of iodine is concentrated within the thyroid after a delay of 24 h. This is the 24-hour uptake. It can be calculated that the thyroid requires about 100 µg iodine daily (500 × 20/100). In countries where the dietary iodine intake is less, the thyroidal uptake increases to ensure there is adequate iodine (about 100 µg) for the formation of thyroid hormones. Tracers of radioiodine are clinically valuable for the diagnosis of thyroid disorders. For example, based on thyroid uptake and scan, the causes of thyrotoxicosis, such as Graves' disease, toxic nodular goiter, or silent thyroiditis can be established. In addition, patients with differentiated cancer of the thyroid (papillary or follicular cancers) who have had a thyroidectomy often are advised to have a whole-body scan using a tracer of ^{131}I or ^{123}I. This can determine whether there is residual functioning thyroid tissue, or functioning metastases, that would be amenable to therapy with a larger dose of ^{131}I. Sodium iodide symporter can be identified in specimens of normal

and abnormal thyroid by staining with labeled antibodies against the symporter (37). This could be of value in determining the aggressiveness and response of cancers to ^{131}I (38).

The uptake of radioiodine is increased by an elevated TSH and scanning in patients with thyroid cancer is undertaken either when the patient is hypothyroid or after injection of recombinant human TSH (rhTSH) (39). Other organs can be visualized on scintigraphy using radionuclides of iodine, and it is apparent that they also can trap iodine. These include the salivary glands, stomach, and occasionally the breasts in women (note: radioiodine should not be administered to women who are nursing and preferably not to those who are lactating), placenta (radioiodine should not be prescribed to pregnant patients), and the thymus (40–42). Sodium iodide symporter and mRNA for NIS have been identified in these tissues.

Structure and Function of Sodium Iodide Symporter

Human NIS is a glycoprotein containing 643 amino acids. The gene is located on chromosome IX. The rat transporter was the first to be cloned, followed by human and pig NISs (43, 44). There is considerable homology of NIS between various animals. The coding region contains fifteen exons and fourteen introns (44–46). Sodium Iodide Symporter has thirteen transmembrane segments in the basal membrane of the follicular cells. The intracellular portion of the protein has the carboxyl terminus and the extracellular segment the amino terminal. Three of the aspartate molecules in the extracellular segment have sugar molecules attached making NIS a glycoprotein (36). In addition to iodine, NIS transports the anions thiocyanate (SCN^-), perchlorate (ClO_3^-), both of which historically were antithyroid drugs acting by competition with iodine for the trapping mechanism (47). The halogens bromine and astatine are also trapped. Technetium pertechnetate (TcO_4^-), a radiopharmaceutical used to image the thyroid is trapped by this mechanism (47). Perrhenate (Rhenium ReO_4) is also trapped and there are two radionuclides ^{186}Re and ^{188}Re that could have therapeutic roles (48). ^{186}Re has a half-life of 90-hours and emits β particles (electrons) with an average energy of 349 keV. ^{188}Re has a half-life of 16.9 hours and emits β particles with a mean energy of 776 keV. The electrons could have therapeutic value. Both also emit ɤ photons that can be used for imaging. Thyroid stimulating hormone is the major physiological stimulator of NIS production. The hormone is also a major factor in targeting NIS to the plasma membrane (36). Inhibitors of NIS expression include excess iodine, thyroid hormones, interferon, tumor necrosis factor, and interleukins.

Clinical Importance of Sodium Iodide Symporter

Sodium iodide symporter is essential for trapping of iodine by the thyroid. Reduced function or improper targeting of the molecule results in reduced trapping of iodine and inadequate production of thyroid hormones. The development of antibodies in vivo leads to autoimmune thyroid disorders and is one of the rarer causes of hyperthyroidism and hypothyroidism (49, 50). The most common cause of hyperthyroidism is Graves' disease that is usually caused by an autoantibody to the TSH receptor (to be discussed below), but there are rare cases attributed to antibodies that stimulate NIS. An increase in NIS can be demonstrated in the basal membrane of thyroids of patients with Graves' disease (51). In contrast, some endogenous NIS antibodies block the trapping of iodine and cause hypothyroidism (52). One group found that the prevalence of anti-NIS antibodies was much less than reported by the above cited publications (53). For decades, it has been recognized that a rare inborn error of thyroid synthesis was the inability of the thyroid and salivary glands to trap iodine. Patients with this defect are hypothyroid and have a goiter, radionuclides of iodine are not trapped by the thyroid, and saliva does not contain any radioactive iodine. This autosomal recessive disorder has been shown to be the result of a structural alteration in the NIS, usually affecting an amino acid substitution (54, 55). At the time of this writing, ten mutations have been identified (43). As an example in one patient, substitution of proline for threonine was the cause and this was due to a base error at codon 354, with cytosine replacing adenine.

Specific anti-NIS antibodies have been developed in vitro. These will aid in knowledge of structural and functional relations.

Sodium Iodide Symporter in Patients with Thyroid Cancer

Radioiodine ^{131}I is an effective treatment for thyroid cancer. It is possible to ablate residual and locally invasive thyroid cancer, lymph node metastases, and, in some patients, distant metastases. The efficacy can be proven by demonstrating a negative follow-up scan and by having an undetectable level of Tg. In most patients these tests have concordant results, either both are abnormal or both indicate no evidence of disease. In a minority of patients, there is discordance with an elevated Tg, indicating the presence of thyroid tissue but negative whole-body iodine scan. In these patients, explanations for the inability of the cancer to trap iodine could be reduced formation, altered structure, or inappropriate targeting of NIS. Some but not all investigators have found an increase in NIS glycoprotein in thyroid cancer (43). Wapnir et al. report the NIS glycoprotein is expressed in 73% of cancers but in many cases is positioned intracellularly rather than in the plasma membrane (37). Another report indicated aberrant methylation of the NIS gene in patients with absent iodine trapping. The uptake was improved in two out of seven patients by 5-azacytidine or sodium butyrate, which resulted in demethylation of the NIS gene. Retinoic acid is used by some clinicians as an aid to stimulating uptake of ^{131}I in poorly differentiated thyroid cancer and has also been demonstrated to increase NIS (31).

Expression of Sodium Iodide Symporter in Other Tissues

Sodium iodide symporter expression has been demonstrated in functioning breast tissues including some breast cancers (40, 56). This was anticipated, because transport of iodine into milk is important for the newborn to have the raw material to synthesize thyroid hormones that are essential for physical and mental growth and development (34, 57, 58). Diffuse breast uptake of radioiodine is demonstrated occasionally on whole-body scan (59, 60). Most often this is in a patient who stopped nursing several months before but whose breasts have retained some trapping ability (59). The breast uptake can be misinterpreted as pulmonary metastases on the scan and is a potential cause of a false positive result (60). The NIS gene expression in the breast is not promoted by TSH but by estrogen and oxytocin and inhibited by prolactin. The expression of NIS in some breast cancers raises the possibility that ^{131}I, which is successful in thyroid cancer, might have a therapeutic role (40). By incorporating the NIS gene (gene transfer) into non-thyroidal cancers, it has been possible to demonstrate uptake of radioiodine into cells in vitro that would not trap under normal circumstances. A fuller review of the literature is presented in references (43, 61, 62). This has been achieved for melanoma, colon, prostate, ovarian and hepatic carcinoma, and myeloma cell lines (63, 64). There are significant obstacles to overcome if this treatment is to be clinically useful. First, how to introduce the gene selectively and consistently into solid cancer cells in vivo. Secondly, how to preserve thyroid function since the thyroid will trap more efficiently than the cancer containing the transferred NIS gene. In the case of breast cancer, the gene should be present in the malignant cells. In this situation, we used TSH suppression using triiodothyronine to reduce thyroid uptake of radioiodine in diagnostic studies of patients with breast cancer; since, the breast cancer NIS gene is not under TSH control. This might not be true for NIS gene transfer to non-thyroidal cells. Obviously large doses of iodine that are used to block thyroidal uptake of ^{131}I, when patients are treated with ^{131}I labeled antibodies or peptides for cancer, could not be used in this situation because the inorganic iodine would compete with the radioiodine. It is sad to report that the uptake of radioiodine in patients with extensive breast cancer studied by colleagues and myself was very disappointing and other methods of targeting need to be considered.

The NIS gene is also expressed in salivary glands, placenta, kidney, stomach, kidney, and thymus (41, 42, 65). These tissues can be identified on scintiscans using radioiodine and are exposed to radiation from ^{131}I treatment.

Further Metabolism of Iodine

Iodine trapped by the thyroid is transported into the colloid, as shown in Figure 2.6. One transport mechanism is the protein pendrin that is expressed in the apical membrane of the thyrocytes (66, 67). There is an autosomal recessive defect called Pendred's syndrome that causes goitrous hypothyroidism and deafness. It

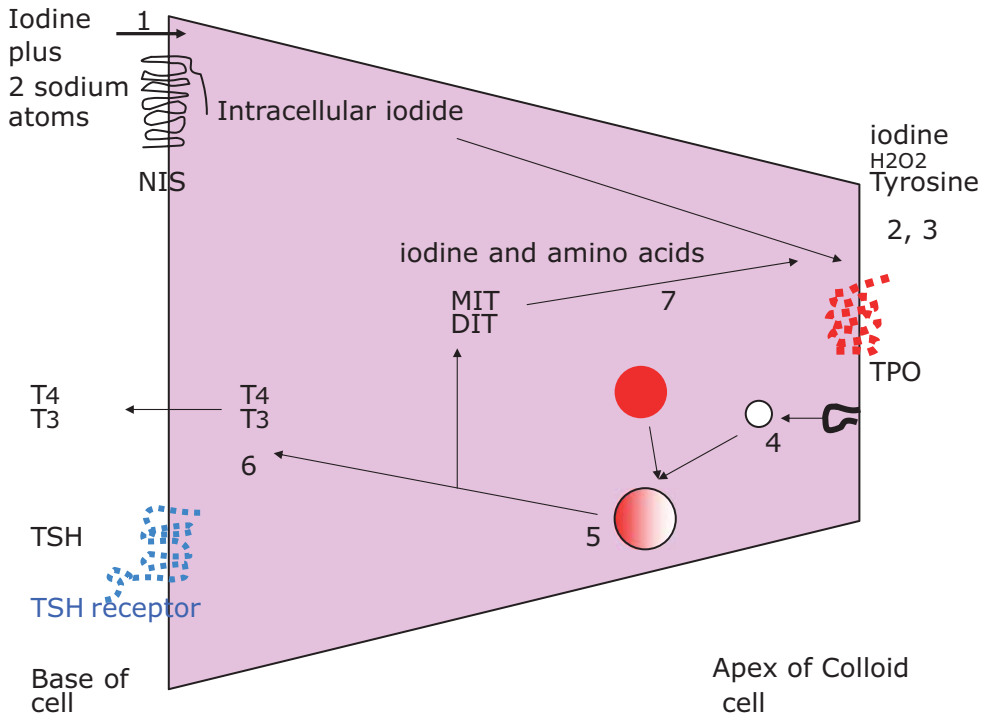


Figure 2.6. This is a diagrammatic representation of the formation of thyroid hormone in the follicular cell. (1) Trapping of iodine by NIS. (2) Iodine transported into colloid and organified with tyrosine by thyroid peroxidase and H_2O_2. (3) Coupling of MIT and DIT and storage of hormones in Tg. (4) Endocytosis of colloid droplet and fusion with lysosome. (5) Proteolytic degradation of thyroglobulin and release of T_4, T_3, MIT, and DIT. (6) T_4 and T_3 leave follicular cell to be carried in circulation by carrier proteins. (7) Deiodination of MIT and DIT. Iodine and tyrosine can be reutilized.

is attributed to a point mutation in the pendrin gene. An alternative protein called human apical iodide transporter has also been described (68). Human apical iodide transporter could not be identified in papillary thyroid cancer cells in vitro (69). One of the unresolved questions is whether an abnormality in one or both of these proteins could be a factor in cancer cells that do not retain iodine.

Transcription Factors

There are three proteins that act as thyroid transcription factors. They were discussed in the section of embryology, with regard to their importance in the development and migration of the thyroid. Thyroid transcription factor one (TTF-1, 40 kD) is a member of the NK × 2 family of transcription factors. Thyroid transcription factor one antigen is expressed in epithelial cells of the thyroid gland and the lung and cells in the midbrain. Human TTF-1 consists of 371 amino acids and there is a conserved region that binds to deoxyribonucleic acid (DNA). This is common to human, mouse, and rat TTF-1 and is encoded by two exons. Thyroid Transcription Factor interacts with regions involved in the regulation and production of mRNA of Tg and TPO.

Thyroid transcription factor two (TTF-2) is described as a fork-head protein. Its gene has a single exon. (70) In addition to its role in development of the thyroid, it has an important role in gene expression of follicular cells. (71) The protein has a DNA binding segment. Thyroid transcription factor two is the main mediator of TSH and insulin regulation of the gene for TPO. (72, 73) The gene has also been identified in developing testes and hair follicles, and this could explain the phenotype human with a germline mutation in TTF-2. (74) The patient had thyroid agenesis, choanal atresia, and spikey hair.

Standing for paired box gene, PAX-8, is a transcription factor that is expressed in follicular cells. The gene for PAX-8 is on chromosome 2q12-q14. The paired box gene interacts with

promoters of Tg and TPO production (75). Messenger ribonucleic acid (mRNA) levels and DNA binding of PAX-8 are decreased by TGF-beta 1 and this could be an explanation for reduced formation of Tg (76). Researchers have shown a synergy of TTF-1 and PAX-8 on activation of gene transcription of TPO and Tg (77). Point mutations in the PAX-8 gene are rare causes of hypothyroidism. In one child with severe hypothyroidism there was cytosine for adenine transversion in codon 119 of exon 3 that resulted in glutamine being replaced by proline (78). The PAX-8 did not bind to DNA or activate TPO gene.

Thyroperoxidase

Iodine that is transported into follicular cells is enzymatically combined to the amino acid tyrosine. This requires the presence of iodine, the enzyme thyroid peroxidase (thyroperoxidase or TPO), hydrogen peroxide and Tg. Thyroglobulin contains tyrosines at appropriate positions on the Tg molecule where they can be iodinated (79, 80). When microsomes (plasma membranes) are produced from follicular cells in vitro, TPO is a major antigenic constituent. Two forms of TPO have been identified TPO 1 and TPO 2. The DNA encoding for these are very similar and the gene is on the short arm of chromosome 2. TPO 1 is larger and contains 933 amino acids compared to TPO 2, which is constructed from 876 amino acids. The difference is due to loss of 171 base pairs in the DNA construct of TPO 2. Only TPO 1 is present in apical cell membrane and it has a longer residence time in the cells. The loss of amino acids in the smaller TPO 2 interferes with proper targeting to the apical membrane. In intact cells, specific antibodies to TPO fail to identify TPO 2 due to its intracellular position. TPO 1 does traffic to the apical cell membrane and has seven transmembrane segments. Staining of thyroid cells for TPO demonstrates that only about 2% is at the apical site (81). The functional segment of TPO is within the colloid where it catalyzes the iodination of tyrosine producing monoiodotyrosine (MIT) and then di-iodotyrosine (DIT). Iodination of tyrosine is also called organification of iodine. TPO is also the catalyst for coupling of iodotyrosines to form iodothyronines. Two molecules of DIT couple to produce the thyroid hormone thyroxine (T_4, 3,5, 3′5′ tetraiodothyronine). One molecule of DIT and one of MIT produce the other thyroid hormone triiodothyronine, (T_3, 3,5,3′ triiodothyronine). An alternative method of producing T_3 is removal of an iodine atom from T_4 by a specific 5′ de-iodinase enzyme. Thyroid hormones are stored within the colloid in quantities equal to a supply of about 100 days. There is also iodine stored in the colloid as non-hormonal compounds reverse T_3 (rT_3), MIT and DIT. From the clinical perspective the retention of iodine in Tg means that diagnostic tracers, or therapeutic doses, of radioactive iodines are retained for days or weeks and can be imaged for hours to several days depending on the half-life of the radionuclide. This allows extended measurements of retention and release of radioiodine for calculating radiation doses for treatment of thyroid cancer, and it means that therapeutic ^{131}I can deliver radiation for many days. The enzyme TPO is activated by TSH, therefore high levels of TSH increase not only the trapping of iodine but also its organification with tyrosine. Several factors suppress the TPO gene including tumor necrosis factor alpha, interferon gamma, and transforming growth factor beta one. Thyroid cancer cells express lower amounts of TPO, which could account for the reduced retention and more rapid clearance of radioiodine (81). Experiments have been undertaken using gene transfer to replace the TPO gene in anaplastic thyroid cancer cells in vitro (82). This resulted in an increase in cellular TPO but no increase in trapping and retention of radioiodine. Similar experiments inserting genes for both TPO and NIS produced an increase in both trapping and organification of iodine (83).

Autoimmune thyroid disease is common and antibodies to TPO are characteristic of Hashimoto's thyroiditis, primary hypothyroidism and Graves' disease. The original name for these antibodies was anti-microsomal antibody since an extract of thyroid cell membrane (microsome) was used as the antigen for radioimmunoassays or immuno-radiometric assays. These assays now use the pure antigen TPO. Mutations in the TPO gene are a cause of goitrous hypothyroidism (84). In this condition iodine can be trapped but is not organified and it leaks out of the gland. A defect in TPO can be demonstrated by the perchlorate discharge test (85). Most of the defects are due to a mutation in the TPO gene (86). Missense mutations resulting

in an amino acid substitution and nonsense mutations that eliminate functional domains of the protein have been identified (87).

Thyroglobulin

Thyroglobulin (Tg) is important for storage of thyroid hormone and iodine. Tg is constructed in the follicular cell. The Tg gene is located on chromosome 8q24 and contains at least forty-eight exons. The final molecule consists of two large peptides, each of molecular weight 330,000 daltons. Thyroglobulin is one of the largest active biological molecules at 660,000 daltons. It can be measured in the serum of normal people. The normal value varies depending on the assay used for measurement but is usually in the range of <0.5–50 ng/ml. Thyroglobulin values tend to be higher in patients with disorders of the thyroid, such as nodules or Graves' hyperthyroidism. It is also increased in patients with differentiated cancers of the thyroid that have metastasized. In general the values are highest in patients with metastases to the skeleton, then the lungs, and next the lymph nodes. Conversely, when a patient has been successfully treated for thyroid cancer, there should be no Tg in the circulation. Thyroglobulin measurements are very important in follow-up and management of differentiated thyroid cancer (88). There is an extensive discussion about Tg and its measurement and role in clinical practice in Chapter 6 on differentiated thyroid cancer. Antibodies to Tg are found in about 10% of the population. About 2% to 3% of the population are "patients" with clinical autoimmune thyroid diseases including chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), primary hyperthyroidism and Graves' disease. Hypothyroidism is common in certain breeds of dogs, including retrievers, and they have a high incidence of Tg antibodies (89). Antibodies to Tg are also found in 20% to 30% of patients with papillary cancer of the thyroid. These antibodies can have an effect on the accuracy of Tg measurement and their presence might have a beneficial effect on the prognosis of thyroid cancer.

There are sixty-seven tyrosine molecules per molecule of Tg but only a few at the carboxy and amino termini are available for iodination. Genetic disorders in the formation and trafficking of Tg result in goitrous hypothyroidism.

Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is produced by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Two NADPH oxidases have been identified and named THOX1 and THOX2. (90, 91) Hydrogen peroxide is a very strong oxidizing agent that is necessary for organification of iodine. It is produced at the reaction site and is under TSH control. To radioiodinate a protein in vitro it is necessary to duplicate the physiological role of the thyroid and have in the test tube the protein to be labeled, radioactive iodine, peroxidase enzyme, and H_2O_2.

Uptake of Colloid and Release of Thyroid Hormone into Blood

Thyroid stimulating hormone also increases the uptake of colloid containing Tg back into the follicular cell. This occurs by endocytosis. Endocytes are colloid droplets that have been ingested by the apical margin of the follicular cells. Endocytes fuse with intracellular lysosomes that contain proteolytic and deiodinase enzymes (also called dehalogenase). There is also a micro-endocytic pathway. (92) The colloid containing mostly Tg is digested by proteolytic enzymes and releases T_4 and T_3 that are transported into the circulation. MIT and DIT are also released and their iodine atoms are enzymatically removed from tyrosine by deiodinase. That iodine can be used again for formation of new thyroid hormones. The amino acids derived from digestion of Tg and tyrosine from MIT and DIT are also reused in the production of Tg. There are inborn autosomal defects of dehalogenase that causes goitrous hypothyroidism. The defect produces iodine deficiency through the excretion of MIT and DIT in the urine. The phenotype is more common in regions where the dietary intake of iodine is low. When radioiodinated MIT and DIT are injected into patients with these defects the radiolabeled iodotyrosines are excreted intact in the urine. In usual circumstances the radioiodine in the urine would be free, having been enzymatically released from tyrosine. This can be used as a diagnostic test.

Carriage of Thyroid Hormones in the Blood

Thyroid hormone thyroxine and T_3 are released from the follicular cells into the blood where they are largely protein bound. In the case of T_4 only 0.03% of the serum hormone is free, in other words not bound to protein. Serum T_3 is 99.7% protein bound and 0.3% free. The serum proteins that are important for binding and transport of thyroid hormones in the blood are thyroid binding globulin (TBG), transthyretin, and albumin. Although it is unnecessary to discuss the biochemical characteristics of these proteins in detail their role in physiology and in interpreting test results is important. Thyroid binding globulin, not to be confused with Tg, is produced in the liver. It is encoded by a gene on the X chromosome, so abnormalities, such as absent TBG or increased TBG, are more common in men. Estrogen increases the hepatic production of TBG and alters its structure so that its metabolism is reduced. Therefore in pregnancy or in patients taking estrogen, such as contraceptive pill or hormone replacement therapy, there is a higher TBG level. The importance of this on thyroid function testing is described below. Transthyretin is synthesized in the liver and the choroid plexus. Transthyretin is secreted into the cerebrospinal fluid by the choroid plexus and acts as a carrier of thyroid hormones, in particular T_4, into the brain via the cerebrospinal fluid (93). The transport proteins provide a buffer so that sudden changes in hormone can be modulated. They also are responsible for the long seven-day half-life of T_4 in the circulation. Because T_3 is less tightly bound it has a half-life of about one day. The long circulating time of T_4 is important after therapy of thyroid cancer with ^{131}I; because, the radionuclide is incorporated into thyroid hormones and can remain in the circulation for days and cause a prolonged radiation to all the tissues of the body. Secondly, the ^{131}I labeled thyroid hormones are metabolized in the liver and diffuse uptake in that organ is seen on post treatment scans and should not be misinterpreted as containing functioning metastases.

The active thyroid hormone is unbound or free hormone. The hypothalamic-pituitary-thyroid axis is designed to maintain normal values of free hormones. When there is too much thyroid hormone, TSH levels drop, and conversely in hypothyroidism, TSH levels increase. When there is an increase in thyroid binding proteins, in particular TBG, total thyroid hormone values are increased, but free hormones are normal provided the patient is physiologic. The values of serum total or free hormones are provided in Table 2.1.

Table 2.1. Reference ranges for thyroid function tests.

Thyroid test	Normal range non SI units	SI Units
Total T4*	4.5–12 µg/dl	58–154 mmol/l
Free T4*	0.7–1.9 ng/dl	9–24 mmol/l
Total T3*	80–180 ng/dl	1.2–2.7 mmol/l
Free T3*	0.2–4.4 ng/dl	3.5–7.7 mmol/l
TSH*	0.4–4.0 mIU/L	0.4–4.0 mIU/L
Tg*	<40 ng/ml	<40 µg/L
24 hour uptake #	10–30%	NA
Normal urinary iodine	>100 µg/L	7.9 µmol/L
Anti TPO		
Calcitonin*	<10 pg/ml	<10 ng/L

* There are small differences between laboratories.
\# Thyroid uptake results depend on dietary iodine and are higher in regions of low intake.

Metabolism of Thyroid Hormones

The majority of thyroid hormones are metabolized by de-iodination. Thyroid hormone thyroxine is the major product of the thyroid but it has considerably less function than T_3. Thyroid hormone thyroxine is de-iodinated to produce T_3, the functional hormone. Thyroid hormone thyroxine can therefore be considered a prohormone. The specific enzymes for deiodination of T_4 to T_3 are 5′ deiodinases. Two species exist, Type I 5′ deiodinase is found in liver, kidney, muscle, and white blood cells. It contains selenium as a cofactor. Type II 5′ deiodinase is present in the brain and pituitary. Figure 2.7 shows the relationship of T_4 to T_3 and the site of de-iodination at the outer phenol ring. Under normal conditions, the thyroid gland produces 100% the T_4 in the circulation and tissues and between 10% and 20% of circulating T_3. Therefore, 80% to 90% of T_3 is produced by peripheral tissues. There are other deiodinase enzymes. One is the 5 deiodinase that removes

iodine from the 5 inner ring position. 5 deiodinase converts T_4 to rT_3, which is almost devoid of thyroid action. There are several pathophysiological states that favor production of rT_3. These include fasting, ill health for any reason, including medical conditions, or surgical trauma. 5 deiodinase also removes the 5 inner ring iodine from T_3 producing 3, 3′T_2. Further deiodination of T_4, T_3 and rT_3 produces compounds with one or two iodine atoms that have less metabolical effects. The iodine released from each of these reactions enters the iodine pool and can be reused by the thyroid to form more hormones.

Deiodination of T_4 in the anterior pituitary thyrotrophs is essential for the negative feedback of thyroid hormones on TSH secretion. When serum total and free thyroid hormone values in the serum and TSH are compared in a large number of people, the closest statistical correlation is between free T_4 (FT_4) and TSH. This is paradoxical since T_3 is the active hormone. It is explained by intracellular deiodination of T_4 in the pituitary thyrotrophs. A defect in the enzyme can cause an elevated TSH when T_4 values are normal. When levo-thyroxine is prescribed based on the elevated TSH, the patient becomes hyperthyroid. However treatment with T_3 reduces TSH without causing symptoms.

Thyroid hormone can be metabolized by conjugation with glucuronide or sulfate, as shown in Figure 2.8. This occurs in the liver and can be identified on post therapy scans after a patient with thyroid cancer has been treated with a large dose of ^{131}I and is scanned several days later to demonstrate that the radioiodine had localized in residual thyroid cells. The liver shows homogeneous uptake of ^{131}I, as shown in Figure 2.9. Thyroid hormones can also be degraded by deamination and decarboxylation of the amino terminal of the molecule. These

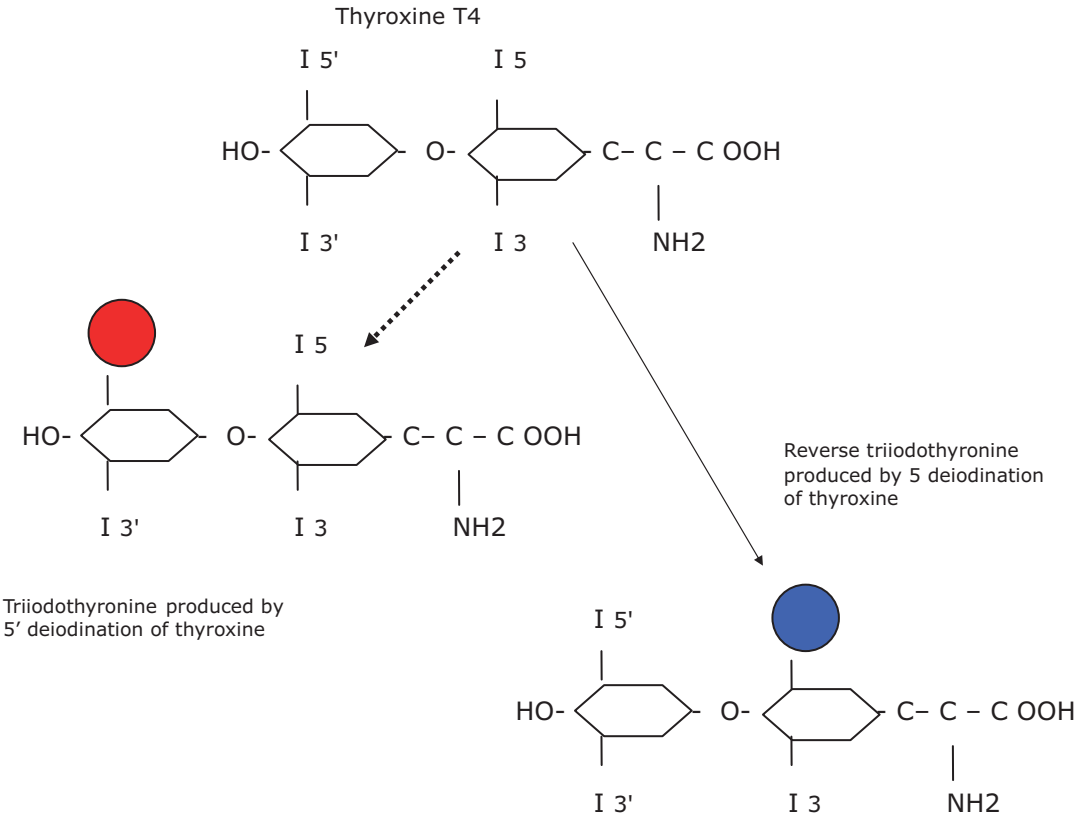


Figure 2.7. Diagram shows the structure of thyroid hormones and conversion of T_4 to T_3 by 5′ deiodinase.

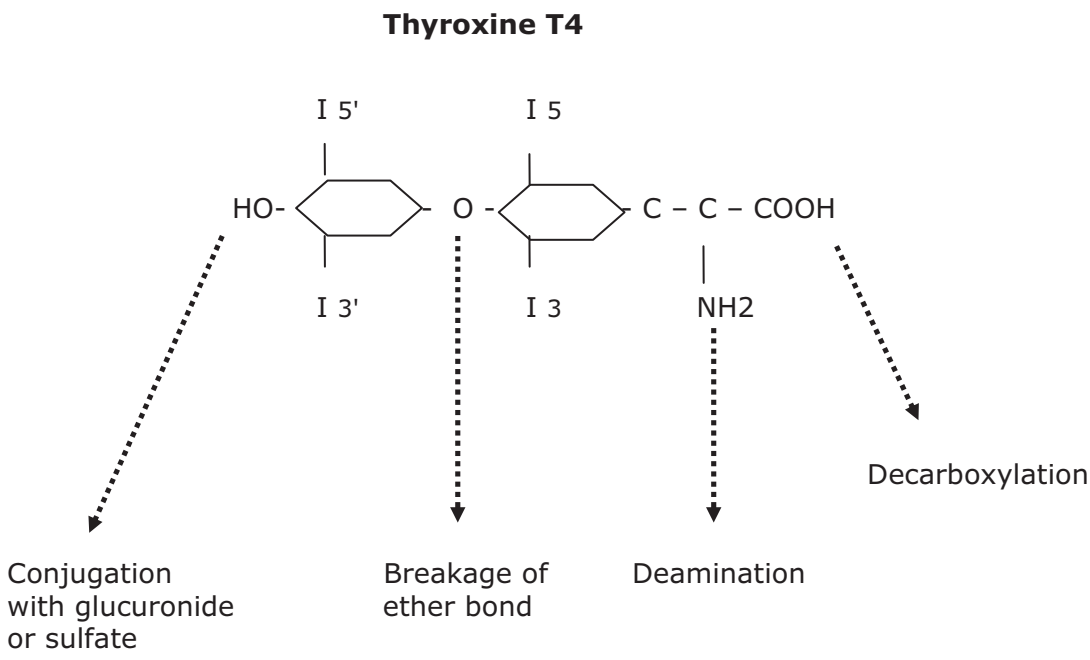


Figure 2.8. Diagram shows the metabolic pathways for degradation of T_4 by deiodination, conjugation with glucuronide and sulfate, deamination, decarboxylation, and breakage of ether bond.

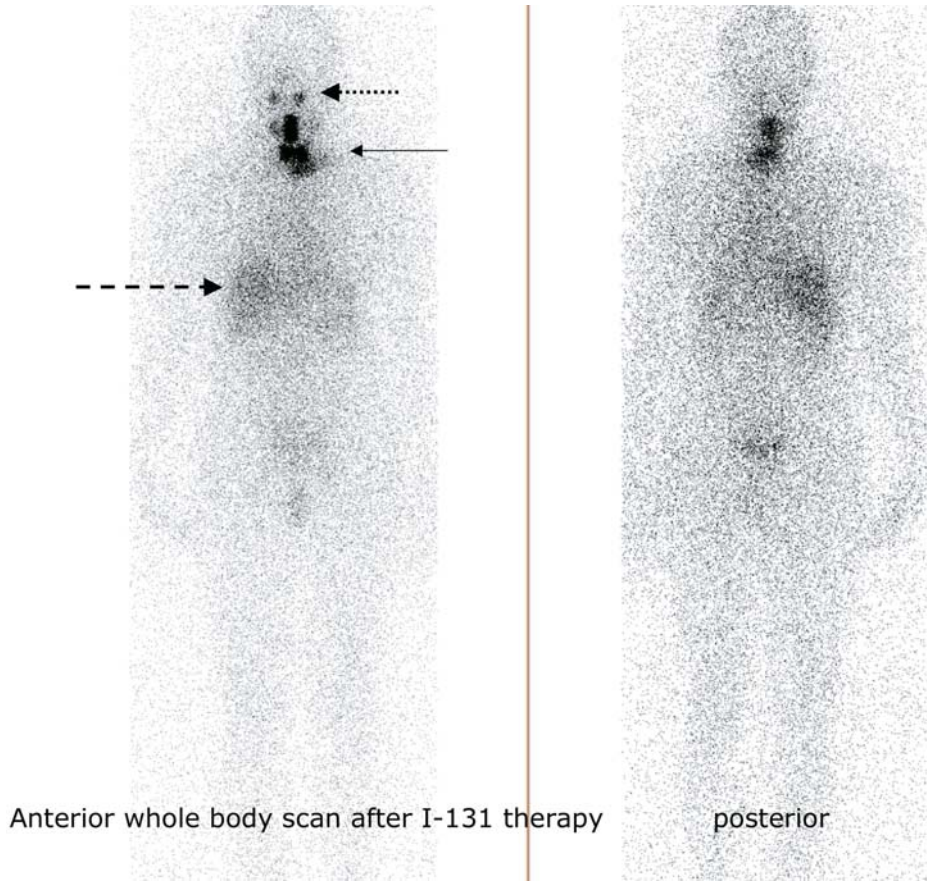


Figure 2.9. This is a whole-body scan made several days after the patient was treated with ^{131}I for thyroid cancer. There is uptake in the neck where there is residual thyroid and functioning metastases in lymph nodes after thyroidectomy. The liver is seen and is explained by metabolism of radioactive thyroid hormones in that organ. There is faint symmetric uptake in the submandibular glands.

compounds are also inert. Cleavage of the ether group between the two benzene rings can occur. These are all shown in Figure 2.8.

Action of Thyroid Hormone

There is compelling data that the main actions of thyroid hormones are within the nucleus at the level of DNA, called genomic effects. For several decades there was a bitter controversy between the nuclear proponents and the mitochondrial proponents. It is now accepted that most of the actions of thyroid hormones are nuclear, but there are also effects on mitochondria and cell membranes. Free thyroid hormones leave the circulation and enter cells. This occurs by active transport. The physicochemical characteristics of thyroid hormones indicate they would be unlikely to diffuse across lipid bi-layers but would be more likely to partition within them. Therefore active transport is required. The mechanisms have been reviewed by Abe et al. and Henneman et al. (94, 95). There are amino acid transporters, one of which belongs to the monocarboxylate transporter (MCT) family. It has been cloned and shown experimentally to increase transfer of radiolabeled T_4 and T_3 into cells and to be inhibited by cold hormones (96). A second family of transporters belong to the organic anion transporting polypeptide (OATP) family, including OATP-A, OATP-C, OAT-F, OAT-8 (97). Organic anion transporting polypeptides and other related transporters, such as liver specific transporters, LSP 1 and 2, are proteins that have 12 transmembrane domains (94, 98). Another system that transports several amino acids has been called system L (99). It is apparent that the function of thyroid hormones is very dependant on their ability to reach the site or sites of action. How the actions at the cellular levels and the rate of transportation of thyroid hormones into the cells are related is still under experimentation (99).

Within the cell T_4 is converted to T_3 by 5′ deiodinase enzymes. T_3 attaches to specific thyroid hormone receptors within the nucleus. There are several functional thyroid hormone receptors; the most important are alpha (α), Beta 1, 2 and 3 (β1, β2, β3). The α, β1, and β3 are expressed in most tissues but β2 is only present in the hypothalamus and pituitary. (100, 101) Each functional receptor has a central domain for binding to DNA, and a region at the carboxyl terminal for binding T_3 and for controlling transcription. There are compounds with similar structures that do not bind T_3 and these have inhibitory actions. The receptors are shown schematically in Figure 2.10. Thyroid hormone receptors attach to specific sites on chromosomes called thyroid response elements (TRE). The receptor can attach alone as a monomer (102). It can form homodimers with other thyroid hormone receptors, or it can form a heterodimer with another type of nuclear receptor. This is usually the 9-cis-retinoic receptor (RXR). The promoter region of most genes that are activated by thyroid hormone have two half-sites each consisting of six nucleotides with the sequence AGGTCA, or a sequence in which the adenosines can be substituted by glycosine. They are arranged as repeats with four spacers AGGTCAXXXXAGGTCA, or inverts with six spacers AGGTCAXXXXXXACTGGA or as a palindrome AGGTCAACTGGA. The combination of thyroid hormone receptor and RXR receptor appears to be the most functionally active. When this heterodimer is attached to the TRE and there is no T_3 the receptor complex has an inhibitory effect. When T_3 is attached to its receptor, the complex has a stimulatory action resulting in activation of genes, production of messenger RNA and subsequently structural and enzymatic proteins. There are both inhibitory and stimulatory coregulators that are called corepressors and coactivators. When T_3 is attached to its receptor the associated corepressor is removed and the coactivator is recruited. There is then recruitment of enzymes histone acetyl transferase and histone methyltransferase that produce a structural change in chromatin and allow ribonucleic acid (RNA) polymerase-2 to initiate transcription of mRNA for structural and functional proteins. This is shown schematically in Figures 2.11 and 2.12. Although thyroid receptor α (TRα) and thyroid receptor β (TRβ) are ubiquitous, the former is mostly expressed in skeletal muscle and brown fat and the latter in liver, kidney, and brain. Viguerie and Langin have summarized the effect of thyroid hormones on gene expression in the brain, liver, muscle, and fat (103).

Non-genomic actions of thyroid hormones have been described on the plasma membrane, mitochondria, cytoplasm, and cytoskeleton

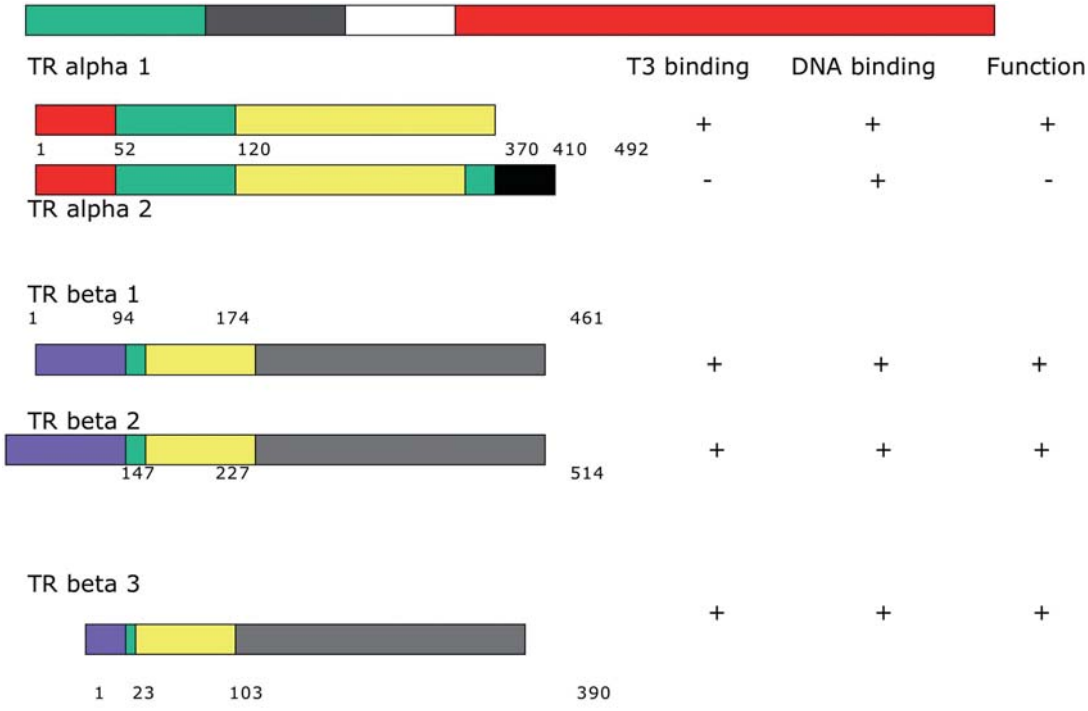


Figure 2.10. Diagrammatic representation of thyroid hormone receptors showing the DNA binding segment that attaches to the thyroid response element.

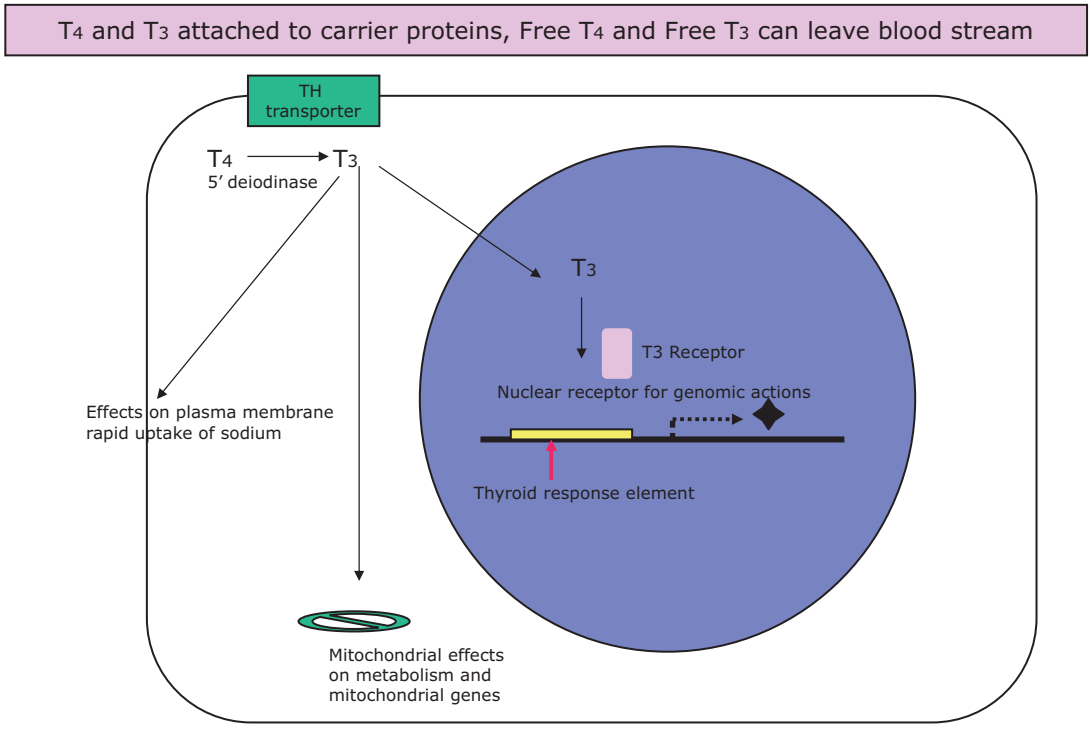


Figure 2.11. Diagram of the interaction of thyroid hormone receptor, DNA, and production of mRNA.

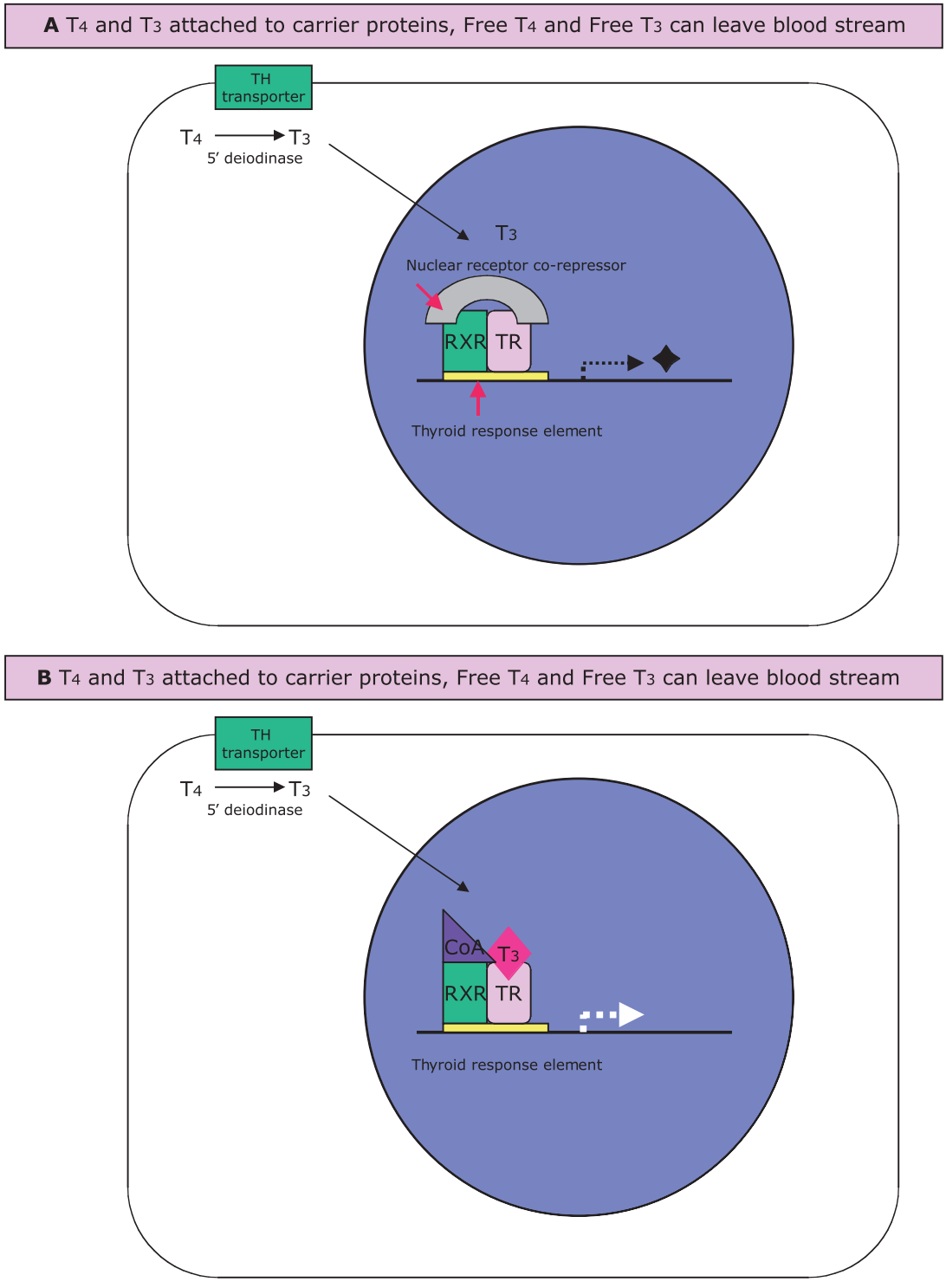


Figure 2.12. (A) Diagram of the interaction of thyroid hormone receptor and DNA and production of mRNA showing repressors. (B) The activated receptor.

(104–106). There are experimental models that demonstrate some functions of thyroid hormones in spite of the fact that their binding to DNA is inhibited (107). The pendulum is swinging in the direction of these non-genomic effects being more important than was believed over the past 3 decades. There are several actions of thyroid hormones that occur within minutes and these could not be under genomic control. Several relate to the plasma membrane including transport of Na^+, K^+, Ca^{++}, and glucose. There is a proposed seven transmembrane thyroid hormone G protein coupled receptor (101). However it is likely that the Na^+, K^+, Ca^{++} transporters themselves are under the genomic control of thyroid hormones (108).

Effects of Thyroid Hormone

Thyroid hormones have a role in proliferation and differentiation of mitochondria. Thyroid hormone triiodothyronine has an effect on mitochondrial DNA involved with cellular respiration. Historically thyroid hormones were thought to "uncouple oxidative respiration." This theory was out of favor for some time but now appears to be true. At the current level of understanding these actions are not important for clinicians treating a patient with a thyroid nodule or thyroid cancer and are not discussed further.

One of the difficult parts of the treatment of patients with thyroid cancer involves withdrawing thyroid hormone to produce clinical and biochemical hypothyroidism. Over the course of four weeks without thyroid hormones, patients gain weight, become tired and depressed, their skin dries and wrinkles, their hair loses luster, and they become constipated, cold, and miserable. Babies who are hypothyroid at birth, and are not diagnosed and treated, become irreversibly intellectually impaired, and their physical growth is retarded. The deprivation and replacement of thyroid hormone allows us to witness the many functions of thyroid hormones on virtually all the tissues of the body. In contrast at times it is necessary to prescribe a supraphysiological dose of thyroid hormone. The symptoms and signs of too little and too much thyroid hormone are shown in Table 2.2.

Resistance to thyroid hormone can be generalized or specific to the pituitary. The original description and a considerable amount of the subsequent investigations are attributed to Refetoff and colleagues (109–112). In generalized resistance there is a mutation in the gene for the β receptor. A missense mutation in the ligand binding domain or the hinge region of the β gene is the cause (113). The mutations affect amino acids in clusters between 234 and 282, 310 and 383, and 429 and 460. The receptor has reduced affinity for T_3 or there is abnormal interaction with a cofactor. The patient has high levels of free T_4 and free T_3 and an inappropriately high TSH. Rarely a patient with this syndrome develops thyroid cancer and long-term treatment aimed at maintaining a low TSH can be difficult. The control of thyroid function and the negative feedback of thyroid hormones on the hypothalamus and pituitary are discussed next.

Control of Thyroid Function: Hypothalamic Pituitary Thyroid Axis

The thyroid is under direct control of the anterior pituitary, which secretes the glycoprotein TSH. The pituitary is controlled positively by thyrotropin releasing hormone (TRH) and negatively by thyroid hormones. Thyrotropin releasing hormone is produced in the hypothalamus. Dopamine and somatostatin have a lesser negative role than thyroid hormones at the level of the pituitary. The thyroid also has internal regulating systems.

Hypothalamus and Thyrotropin Releasing Hormone (TRH)

Thyrotropin releasing hormone is the major positive stimulus for regulation of TSH. Thyrotropin is synthesized and secreted by cells in the paraventricular nuclei in the hypothalamus that lie lateral to the third ventricle. The human gene for TRH has been cloned. It has two exons and three introns and there are six repeats of the progenitor sequence, prepro-TRH. Prepro-TRH is degraded to produce TRH that is a tripeptide, glutamyl-histidyl-prolinamide. TRH was the first hypothalamic hormone to be characterized and synthesized in vitro. It is transported in neurons to the portal capillaries that supply

Table 2.2. Effects of too much and too little thyroid hormone.

System	Excess thyroid hormone	Deficient thyroid hormone
Whole body	Weight loss Increased basal metabolism Increased drug tolerance Increased need of vitamins	Weight gain Decreased basal metabolism
Cardiovascular	Tachycardia Arrythmias Atrial fibrillation Increased pulse pressure Palpitations Cardiac failure	Bradycardia Hypertension Pericardial effusion
Central nervous system	Anxiety Sleeplessness Tremor Labile mood Irritability Increased reflexes	Depression Tiredness Increased sleep Slow reflexes Psychosis Cerebellar signs Poor memory Reduced intelligence (neonatal)
Gastrointestinal	Increased appetite Increased gastric emptying Hunger Looseness of bowel and diarrhea Increased liver enzymes and alkaline phosphatase	Constipation Reduced appetite
Respiratory system	Tachypnea Breathlessness	Slow breathing
Endocrine and gynecological	Increased libido Reduced fertility Reduced menses and amenorrhea	Decreased libido Reduced fertility Increased risk of miscarriage Menorrhagia
Skin	Warm Moist Sweaty Hair loss Onycholysis	Cold Dry Puffy
Skeletal	Osteopenia Osteoporosis Bone pain Early closure of epiphysis (child)	Short stature (child) Delay closure of epiphysis (child) Stippled epiphysis (child) Delayed dentition (child)
Lymphatic	Lymphocytosis Enlarged thymus Enlarged spleen	
Features not explained by excess thyroid hormone	Goiter Infiltrative orbitopathy Pretibial dermopathy Clubbing and paraostial new bone formation	

blood to the anterior pituitary. TRH exerts its action by attaching to TRH receptors in thyrotrophs. The receptor is a G-protein coupled seven-transmembrane receptor and the presence of the ligand results in an influx of calcium into the thyrotrophs (114). This activates the phosphatidylinositol cascade. TRH increases several steps of TSH synthesis and secretion, in particular the control of the posttranslational maturation of TSH oligosaccharide chains (115). In the absence of TRH, TSH lacks its full biological activity. Thyrotropin and thyroid hormones have a complex interaction. The expression of the thyroid hormone receptor in the thyrotroph is lowered by TRH thus reducing the negative feedback of T_3. This has been identified in patients with central hypothalamic hypothyroidism, who have an elevated immunoreactive TSH with reduced biological effects (116). An additional cause of central hypothyroidism has been attributed to a mutation in the TRH receptor that causes central hypothyroidism but there is no response of the pituitary to the injection of TRH. Injection of TRH was a valuable test of pituitary function, but the production of the only FDA approved preparation in the United States has recently stopped.

Thyrotropin releasing hormone is metabolized by an enzyme called TRH-degrading ectoenzyme (117). TRH is present in other parts of the brain and has a putative role as a neurotransmitter. TRH and TRH deamidase have been identified in the liver, kidney, heart, lung, pancreas, gut, and skeletal muscle (118). TRH has been used to treat neurological conditions and epilepsy (119). It has been shown to reduce the intake of food in experimental animals (120). Hypothalamic somatostatin and dopamine have an inhibitory affect of pituitary thyrotrophs.

Pituitary and Thyroid Stimulating Hormone (TSH)

Thyroid stimulating hormone is a glycoprotein containing two peptide chains, α and β (121). The α peptide is common to luteinizing hormone (LH) and follicle stimulating hormone (FSH) and human chorionic gonadotropin (HCG). The β subunit of each of these hormones is different and confers specific biological and immunological function. In the case of TSH the β peptide is only produced in thyrotrophs that constitute about 5% of the cells in the anterior pituitary. The α chain contains ninety-two amino acids and is encoded by a gene on chromosome VI. The gene contains four exons and three introns. The β subunit has 112 amino acids and is encoded by a gene on chromosome I that has three exons and two introns. The posttranslational attachment of sugar molecules is important for full function. Glycosylation is necessary for subunit folding. Thyroid stimulating hormone lacking sugars can bind to the TRH receptor but has reduced function.

Serum TSH can be measured precisely and is the single most important test of thyroid function (see below). Thyroid stimulating hormone increases all steps of thyroid hormone production including trapping of iodine and iodination of tyrosine. An elevated TSH is important in patients who have had thyroidectomy for thyroid cancer and who are to undergo scintiscan or treatment with radionuclides of iodine or measurement of a stimulated Tg. A high level of TSH is achieved by letting the patient become hypothyroid, but patients do not like the symptoms of hypothyroidism. Scientists at the National Institute of Health cloned the α and β genes and produced recombinant human TSH (rhTSH) that can be used for testing and treating patients and is described in detail in Chapter 6 (122, 123).

Deficiency of TSH can be due to trauma to the pituitary including head injury, surgery, and radiotherapy. Structural conditions, such as a tumor, craniopharyngioma extending into the pituitary fossa, metastases, sarcoidosis, hemochromatosis, postpartum necrosis, and autoimmune hypophysitis, can cause hypopituitarism with loss of TSH secretion. Point mutations in the β gene resulting in amino acid substitutions in the subunit have a variety of effects. These include failure to produce the entire molecule because of a stop codon, formation of β subunit incapable of binding with the α peptide, and production of TSH that is detectable by immunoassays but blocks the TSH receptor. Occasionally a patient has thyroid cancer and deficiency of TSH thus making the use of rhTSH indispensable.

Pit-1 is a protein that regulates expression of genes in the thyrotroph. It is a transcription factor. Pit-1 binds to the regulatory region on chromosome I that encodes the TSH β peptide.

It also acts as a transcription factor for growth hormone and prolactin.

There is evidence that a number of proteins are local "autocrine/paracrine" regulators of TSH secretion (124). Epidermal growth factor has a positive effect and neurotensin, neuromedin B, interleukin 1 and gastrin-releasing peptide have inhibitory roles. These are considerably less important than the positive TRH action and the negative feed back of thyroid hormones. T_3 attached to its specific receptor in thyrotrophs has an inhibitory action on the gene that transcribes mRNA of TSH β. This is the key in negative feedback.

TSH Receptor

The TSH receptor is a G-protein-coupled receptor. The gene is on chromosome 14q31. The receptor has a large extracellular domain with a tertiary structure that is important for binding with TSH, as shown in Figure 2.13. In the presence of TSH there is increased production of intracellular cyclic adenosine monophosphate (cAMP). This occurs through the receptor interacting with the G_s complex and causing disassociation of the alpha subunit from the beta and gamma subunits. The alpha subunit is complexed with guanosine diphosphate (GDP) and it releases the GDP, which is replaced by guanosine triphosphate (GTP). This compound activates the enzyme adenyl cyclase converting adenosine triphosphate (ATP) to cAMP. With the increase in intracellular cAMP there is an increased uptake of iodine, production of TPO and Tg, and release of thyroid hormones. Prolonged TSH stimulation produces growth of follicular cells. When the concentration of TSH is high, the calcium phosphatidyl-inositol-phosphate protein kinase pathway is activated and this increases production of H_2O_2.

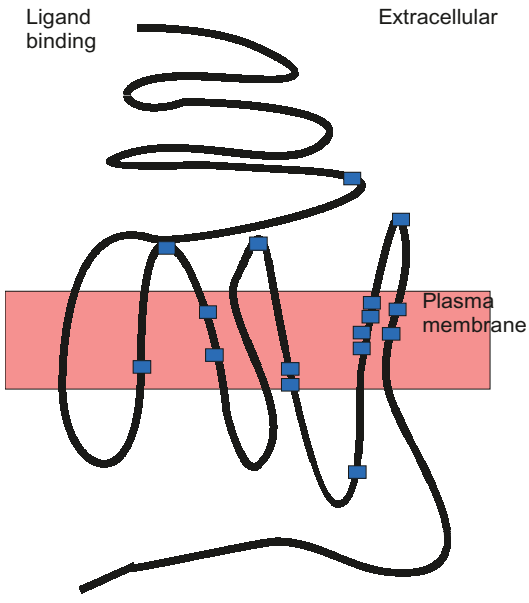


Figure 2.13. Diagram of TSH receptor with seven transmembrane segments. Sites of amino acid substitutions that result in constant activation of the receptor are shown as blue rectangles.

A number of mutations have been identified in the TSH receptor. Some of these produce a gain in function (Figure 2.13). When there is a germ line mutation and all follicular cells are affected this causes constitutive activation of all follicular cells and neonatal hyperthyroidism. The syndrome is autosomal dominant and can be confused with neonatal Graves' disease but there are no thyroid stimulating antibodies present (125, 126). When the activating mutation is on a clone of thyroid cells (a somatic mutation) this results in a functioning nodule or functioning nodular goiter (127, 128). One mutation in the TSH receptor caused gestational hyperthyroidism resulting from increased sensitivity to HCG. There is a report of metastatic follicular cancer containing activating mutations in the TSH receptor (129). Gain of function mutations is most common in the transmembrane segment of the TSH receptor from amino acids 619–661. A few are in the extracellular ligand-binding region. The cause is an amino acid substitution resulting from a base change in the TSH receptor gene. There are also mutations that inactivate the TSH receptor causing a resistance to TSH. Several are single amino acid substitutions others are due to a stop codon producing a truncated receptor. In some patients the resistance to TSH is mild, in others it is severe, resulting in neonatal hypothyroidism. There is a database maintained by researchers at the University of Leipzig. In 2003 they had compiled twenty-nine somatic activating mutations and nineteen activating germline mutations (130). The investigators have also compiled twenty-two inactivating mutations (130). The database can be accessed through www.uni-leipzig.de/innere/tshr (131).

Activating mutations in the G_s alpha subunit can produce the same effects as activating mutations of the TSH receptor. In one case, activation of the enzyme guanosine triphosphatase (GTPase) that transforms GTP to GDP resulted in continued activity of the G_s alpha subunit or GTP. A somatic mutation can result in a functioning nodule.

Antibodies to the TSH receptor (TRab also called thyroid stimulating immunoglobulins, TSI) are the cause of Graves' disease. There are reports of Graves' disease occurring after radioiodine treatment of toxic nodular goiter. These patients often have measurable TRab prior to ^{131}I treatment and after the functioning nodules are ablated the remainder of the gland is then stimulated by the autoantibodies (129).

TSH increases the formation and release of thyroid hormones resulting in a rise in free T_4 (and or free T_3) that in turn produces the negative feedback at the level of the thyrotroph and to a lesser extent the hypothalamus, as shown in Figure 2.14.

Table 2.3 provides a list of peptides and proteins that are important in thyroid physiology and gives their role and genomic information.

Autoregulation of the Thyroid

The thyroid can be subjected to large fluctuations in iodine. People living in regions of low dietary iodine have low values of plasma inorganic iodine, conversely people ingesting a diet high in iodine have high values and patients injected with intravenous contrast can have very high levels. Iodine has autoregulatory effects on the thyroid with the goal of maintaining a steady physiological state (132–136). One dramatic example is the use of inorganic iodine to reduce the thyrotoxic effects of Graves' disease. In this situation there is a rapid improvement in the symptoms and signs due mostly to reduced release of thyroid hormones from the gland. An increase in plasma, inorganic iodine produces structural alterations including a 40% increase in apical area, an 18% decrease in basilateral

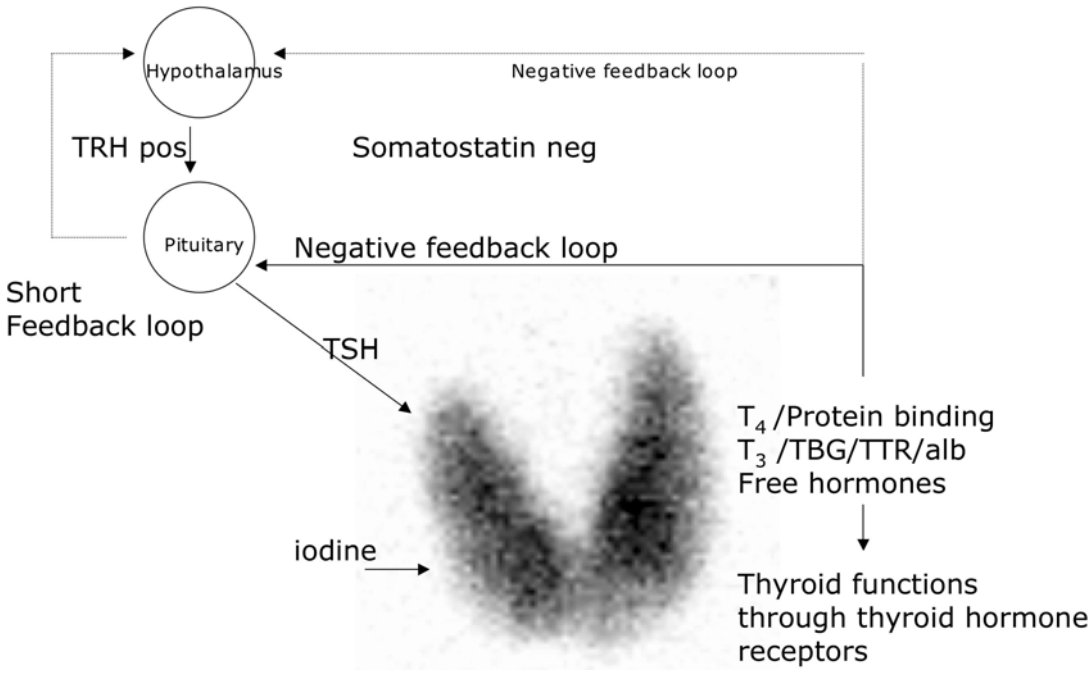


Figure 2.14. Diagrammatic representation of hypothalamic-pituitary-thyroid axis: Thyrotropin releasing hormone is secreted from the hypothalamus and attaches to receptor in thyrotrophs in the anterior pituitary. This increases formation, glycosylation and release of TSH. Thyroid stimulating hormone attaches to receptor in follicular cells that increase formation of T_4 and T_3. These hormones are released into the circulation where they are predominantly protein bound. The free hormones feedback negatively at the anterior pituitary and hypothalamus.

Table 2.3. General information on structure, function, and genetic control of important compounds related to control and production of thyroid hormones.

Protein	Function	Structure	Amino acids (Molecular Weight)	Gene
TRH	Hypothalamic hormone that stimulates production and secretion of TSH	Tripeptide	3 amino acids	Chromosome 3
TRH receptor	Stimulates production and secretion of TSH by thyrotroph	7 transmembrane protein G protein		Chromosome 8q23
TSH	Pituitary hormone that increases all steps of thyroid hormone formation	Glycoprotein with two peptides	Alpha 92 amino acids (14,700) Beta 112 amino acids (15,6000)	Alpha subunit chromosome 6Q21.1–23 Beta subunit chromosome 1p22
NIS	Transports iodine and sodium into follicular cells	Glycoprotein with 13 transmembrane segments		Chromosome 19q12–13.2
TSH receptor	G-protein-coupled receptor responsible for stimulating all aspects of thyroid hormone synthesis and release	Glycoprotein with 7 transmembrane segments	744 amino acids (~100,000)	Chromosome 14q31
Thyroperoxidase (TPO1)	Enzyme that iodinates tyrosine and couples MIT and DIT	Glycosylated hemoglobulin	933 amino acids (103,026) (64)	Short arm of chromosome 2p25
Pendrin	Possible exporter of iodine into colloid			Chromosome 7q21–34
Thyroglobulin (Tg)	Site of formation and storage of thyroid hormone	Glycoprotein	(660,000)	Chromosome 8q24
TTF-1	Morphogenesis of thyroid and pulmonary tissues and gene transcription	Peptide	371 amino acids (40,000)	Chromosome 14q12–q21
TTF-2	Morphogenesis and migration of thyroid and gene transcription	Peptide		Chromosome 9q22
PAX	Thyroid morphogenesis and gene transcription	Peptide		Chromosome 2q13–14
THOX2	Production of H2O2			Chromosome 15q21
Thyroid binding globulin (TBG)	Main transporter of thyroid hormones in the circulation	Glycoprotein	395 amino acids (54,000)	Chromosome Xq11–23
Transthyretin (TTR)	Transporter of thyroid hormone in circulation and into CSF	"Prealbumin" tetramer	127 amino acids (55,000)	Chromosome 18q11.2
Thyroid hormone receptor alpha	Nuclear receptor for T_3	Protein	410 amino acids (47,000)	Chromosome 17q11
Thyroid hormone receptor beta 1	Nuclear receptor for T_3	Protein	461 amino acids (53,000)	Chromosome 3p23
Thyroid hormone receptor beta 2	Nuclear receptor for T_3	Protein	514 amino acids (58,000)	Chromosome 3p23
Calcitonin	Hormone that reduces bone loss from bone		32 amino acids	Chromosome 11p15.3–15.5

area, and a 76% increase in cell volume (137). A high level of iodine reduces its own transport into follicular cells (138). Increased iodine also reduces its organification. This is called the Wolf-Chaikoff effect. In addition to its description in experimental animals this effect can be demonstrated in patients with autoimmune chronic lymphocytic thyroiditis where an excess of iodine induces rapid onset of hypothyroidism. Varying the amount of iodine in vitro modulates the lysosomal activity and hence the rate of degradation of Tg (139). When the intake of iodine is chronically reduced the thyroid produces a higher ratio of T_3 to T_4. This provides more of the active hormone at the expense of less iodine (T_3 has ¾ of the iodine and about 4 times the activity so there is more than a 5:1 benefit).

Testing Thyroid Function

Accurate testing of thyroid function in patients with thyroid nodules or thyroid cancer is important. Most patients with a thyroid nodule have normal thyroid function; however, when there is biochemical proof of an excess of thyroid hormone, by elevated FT_4 or FT_3 and a low TSH, the algorithm for management of the nodule changes. This is described in Chapter 4. Patients with proven thyroid cancer will be treated by surgical removal of the thyroid and are the dependant on exogenous thyroid hormone for life. The best tests to determine thyroid function are FT_4 and TSH. It is true that testing thyroid function in outpatients who have a high probability of being normal can be achieved by measurement of TSH alone (140). In patients with thyroid cancer the clinician can titrate the dose of thyroid hormone to "dial in" the desired level of TSH for each individual patient. In a patient who has no evidence of residual cancer the TSH can be maintained at the low end of the normal range. However, when the cancer cannot be cured by surgery and radioiodine there is advantage to prescribe sufficient thyroid hormone to keep TSH low. This reduces the stimulus for thyroid cells to grow and by combining both tests this can be achieved with a FT_4 that is not too high. Comparison of the TSH with FT_4 also ensures that a low TSH is not a technical error when that value is paired with a high or high normal FT_4. There have been significant technical advances in the measurement of TSH. Two decades ago it was not possible to differentiate a low normal value from a suppressed value. There have been progressive increases in sensitivity of the assays, resulting in a lowering of the level of detectability for TSH. With increasing sensitivity the assays have been termed first, second, and third generations and most can now achieve functional sensitivities <0.005 mIU/L. In the past a method for differentiating a truly low result from a normal one was to inject TRH intravenously. This causes a surge in TSH in normals, but no increase when the pituitary is suppressed by high values of thyroid hormone. The TRH test is superfluous provided that a highly sensitive TSH assay is available. Two groups of investigators still support the use of TRH stimulation when there is no third generation TSH assay (141, 142). I would recommend negotiating with the director of the clinical laboratory to implement the third generation TSH measurement. It is true that TRH testing has a role in the investigation of patients with resistance to thyroid hormone or hypopituitarism (143). As stated above, this peptide is not available in the United States.

Thyroid hormone therapy usually implies administration of levo-thyroxine. There has been an increasing interest in preparations that combine levo-thyroxine and triiodothyronine (144). This is in part based on the knowledge that the thyroid secretes both hormones although the majority of T_3 is produced by deiodination of T_3 outside of the thyroid. It is also based on some evidence that patients treated by combined therapy state that they feel better. Recently double blind trials found no evidence for this (145–147). There was no improvement in the patient's well being, cognitive function, weight, or lipid values. Thyroid function testing in a patient who is treated with a combination of thyroid hormones should include a FT_3 measurement as well.

An extensive monograph of practice guidelines for laboratory testing of thyroid function is available (148). Normal ranges for thyroid function tests are shown in Table 2.1 (149).

Thyroid scintigraphy and uptake measurement have a limited role in the management of patients with a newly diagnosed thyroid nodule but would be ordered when thyroid function is high. This is expanded in Chapter 4 on thyroid nodules. Whole-body scan with ^{131}I or ^{123}I is used

in many patients with differentiated thyroid cancer to define how much thyroid has been left after thyroidectomy and to identify functioning metastases. An uptake measurement obtained over the thyroid bed and sites of cancer at the time of scanning provides a quantification of the amount of functioning thyroid. An elevated TSH is a requisite for a technically good scintiscan. Whole-body scan is described in detail in Chapter 6, Differentiated Thyroid Cancer.

Thyroglobulin can be measured accurately by radioimmunoassays and immunoradiometric assays. This measurement is very important in the management of patients with thyroid cancer. As discussed above some investigators accept that Tg measurements are inaccurate when there are anti-Tg antibodies present. Therefore it is imperative that the anti-Tg antibodies are measured on every specimen when Tg is ordered. In spite of advances in measurement of thyroglobulin differences exist when the same specimen is measured in different laboratories or by different methods (150). There is increasing use of the same human Tg standard, CRM-457. The same conclusion about interlaboratory differences can be made when antithyroid antibodies are measured (151).

In selected patients who are undergoing whole-body scanning and therapy with radionuclides of iodine and there is concern whether they have been exposed to excess inorganic iodine. Either urinary iodine or plasma inorganic iodine can be measured. Methods for obtaining these are varied and depend on whether a rapid screening test is required or an accurate test for an individual patient (152, 153). The high-performance liquid chromatography assay is the method of choice for plasma inorganic iodine, because protein bound iodine is not measured. Historically protein bound iodine ($PB^{127}I$), which is mostly iodine in the form of circulating thyroid hormone was an indirect test of thyroid function.

Calcitonin

Calcitonin is synthesized and secreted by parafollicular C cells. The gene complex has two genes α and β. The α gene has six exons and contains transcripts for calcitonin and calcitonin gene-related peptide. The β gene produces mRNA for β calcitonin gene-related peptide. The calcitonin gene produces a 141 amino acid peptide called pre-procalcitonin. The mature hormone is the result of several enzymatic reductions that result in procalcitonin of 116 amino acids and then immature calcitonin until the mature calcitonin peptide that contains thirty-two amino acids is formed. The calcitonin receptor is a seven transmembrane protein with a large extracellular component. Bone resorption is inhibited when calcitonin attaches to its receptor. Calcitonin can be measured by radioimmunoassays and immunoradiometric assays. It is preferable to employ a two-step immunometric assay. In most assays normal people have values below 10 ng/L (10 pg/ml) but different assays have different degrees of sensitivity and the user should have knowledge of the normal values and limitations of the assay they use. Calcitonin measurement is important in the follow-up of patients who have been treated for medullary cancer. This plus the role of stimulated calcitonin measurement after injection of pentagastrin and or calcium is discussed in Chapter 10.

Summary and Key Points

This chapter provided an outline of thyroid anatomy and physiology of the production, secretion, metabolism and action of thyroid hormones. Knowledge of the precise genetics and structure of NIS has increased our understanding of its role in physiology and pathophysiology. In addition, it opens up the possibility of improving the treatment of thyroid cancers in those cases that do not trap ^{131}I. Transfer of the gene could result in treatment with radioiodine being applicable for cancers that do not normally have the ability to trap iodine. Knowledge of physiology allows an understanding of appropriate thyroid function testing.

- The thyroid is an endocrine gland that produces and secretes thyroid hormones.
- The thyroid cells are arranged in spherical structures called follicles.
- The structure of the follicular cells and follicles allows iodine to be trapped, converted into thyroid hormone, and stored.
- Iodine is essential for the formation of thyroid hormones.

- The iodide trapping mechanism, the sodium iodide symporter (NIS), is located on the basal membranes of thyroid follicular cells.
- NIS is capable of trapping all isotopes of iodine including radionuclides of iodine that can be used for diagnosis and treatment.
- Knowledge of the exact structure of NIS has led to and will continue to produce an increase in understanding of inborn errors in the function of NIS and immunological diseases.
- Treatment of selected cases of thyroid cancer could be improved by genetic engineering, for example cancers that cannot trap iodine could be made capable of this by gene transfer.
- Organification of iodine requires iodine, thyroperoxidase, hydrogen peroxide, and tyrosine.
- Tyrosine is present in thyroglobulin (Tg) that is the main component of colloid.
- Serum Tg is an important test in the follow-up of patients with treated thyroid cancer.
- Thyroid hormones are transported in the blood by thyroid binding globulin (TBG), transthyretin, and albumin.
- The majority of thyroid hormones are metabolized by deiodination.
- 5′ deiodination of T_4 produces the active hormone T_3.
- 0.03% of T_4 is unattached to carrier proteins and is free, 0.3% of T_3 is free.
- Free hormones are actively transported into cells and T_3 produces its main actions on the genome but also functions at the plasma membrane and mitochondria.
- T_3 complexes with a thyroid hormone receptor of which there are two main types, TRα and TRβ. There is one of the former and three of the latter.
- T_3 bound to the TR interacts as a homodimer or a heterodimer with retinoic acid receptor, coactivators, and corepressors at a site on the chromatid called the thyroid response element (TRE).
- In the absence of ligand the receptor has an inhibitory role in transcription of mRNA. In the presence of the ligand there is usually increased transcription.
- Thyroid function is controlled by the hypothalamic pituitary thyroid axis through TRH from the hypothalamus and TSH from the anterior pituitary.
- Thyroid hormones have a negative feedback at the pituitary and to a lesser degree at the hypothalamus.
- The thyroid incorporates several auto regulatory steps depending on the level of plasma inorganic iodine.
- The best tests of thyroid function are FT_4 and TSH.
- Calcitonin is produced by parafollicular cells (C cells) and is an important blood test in patients with medullary cancer of the thyroid.

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Chapter 3

Thyroid Pathology

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The majority of thyroid cancers arise from the thyroid follicular cell. A minority derives from parafollicular cells. Parafollicular cells produce calcitonin and are also called C cells. Cancers arising from C cells are called medullary cancers. Of the cancers that arise from follicular cells, they can be separated into a large group of cancers where the cells are well differentiated and function like thyroid cells albeit at a lesser level. The cells can trap iodine and secrete thyroglobulin (Tg). The differentiated thyroid cancers are classified as papillary or follicular, based on their histologic appearances. As each of these cancers is described in more detail, it will be recognized that in a small subset of tumors the distinct separation of the carcinomas of follicular cell origin can be blurred by histologic variants (e.g., follicular variant of papillary cancer, mixed papillary-follicular cancer and even mixed differentiated and medullary cancer). Less common types of cancers arising from follicular cells are poorly differentiated (insular) and anaplastic (undifferentiated) carcinomas. Cancers of hematolymphoid produce lymphomas and leukemias. Cancers arising in mesenchymal tissues result in sarcomas. Table 3.1 shows the cell of origin and types of cancers that arise from them with their relative frequencies. About 80% of thyroid cancers are differentiated, 90% of these are papillary, 5% to 10% are follicular, 5% to 10% are medullary, 2% to 5% anaplastic, and 2% to 5% lymphomas. For completeness, it should be recognized that metastases to the thyroid of non-thyroidal cancers can occur but are rare.

The diagnosis and classification of neoplastic and non-neoplastic lesions of the thyroid is often challenging. We strongly recommend that the clinician take the time to review the pathological slides with a pathologist. Moreover, patients coming from an outside medical facility for a consultation or second opinion should bring their pathology slides and the written report, and the slides should be officially reviewed and a pathology report produced. Occasionally the original diagnosis of cancer is overturned, and unfortunately, there are instances in our practice when an initial diagnosis of a benign neoplasm is changed to malignancy. A close working relationship with a pathologist interested in thyroid pathology is indispensable. Subtle microscopic changes that are prognostically important are identified, and important clinical details can be discussed so that each learns from the other. Pathologists at major medical centers are exposed to a large volume of thyroid pathology. In smaller hospitals this might not be the case, and the pathologist might lack sufficient cases to maintain proficiency in diagnosing subtle issues, such as distinguishing Hürthle cell adenoma from minimally invasive Hürthle cell carcinoma or identifying variants of papillary carcinoma that are associated with a more aggressive clinical course. The use of an expert consultant can be both helpful and educational. Clinicians should provide relevant information about the patient

Table 3.1. Classification of cancers of the thyroid.

Cell of origin	Type of cancer
Follicular cell	Papillary cancer (70–80%), Variants (Table 3.6)
	Follicular cancer (10%)
	Clear cell variant
	Hürthle cell
	Mixed papillary/follicular cancer
	Anaplastic (undifferentiated) cancer (2–5%)
Parafollicular cell	Medullary cancer (5–10%)
	Non familial
	Familial
	Isolated medullary cancer
Lymphoid	Lymphomas (3–5%)
Connective tissue	Sarcomas
Metastases	Melanoma
	Kidney
	Breast
	Lung
	Gastrointestinal

and clinical findings, including age, gender, family history, size of thyroid mass, the degree of concern for cancer, the presence of suspicious lymph nodes, prior surgery, and radiation treatments. In particular, radiation can produce changes in cells that make interpretation of cytology and histology more difficult (1).

The chapter discusses both cytology with specimens obtained by fine needle aspiration (FNA) and histology.

The Role of the Pathologist

As we have already alluded to in the discussion above, the pathologist plays a pivotal role in the diagnosis and management of these patients. Specific items are outlined in Table 3.2. The most important goal is the accurate classification of pathological alterations into inflammatory, neoplastic, and less commonly infectious categories. As treatment and prognosis are determined in large part by the type of neoplasm, it is essential that follicular adenomas be carefully distinguished from minimally invasive or widely invasive follicular carcinomas. The liberal use of leveled sections from the paraffin blocks and examination of the entire capsular edge of the lesion are helpful in making these distinctions. The identification of the variants of papillary carcinoma has prognostic importance, as some are associated with a more aggressive behavior. Immunohistochemistry and flow cytometry aid in the diagnosis and classification of hematolymphoid neoplasms. Immunohistochemistry is often helpful in the classification of sarcomas. The Association of Directors of Anatomic and Surgical Pathology recently provided a summary of key macroscopic and microscopic features that should be included in the reporting of thyroid carcinomas to provide clinicians with essential staging and prognostic information (2). Currently, FNA, frozen section evaluation, standard histopathological examination, and immunohistochemistry or flow cytometry serve as the cornerstones for the pathological diagnosis and classification of thyroid lesions. A significant change in the approach to the diagnostic evaluation of thyroid lesions and in particular solitary thyroid nodules has occurred over the last two decades. Moreover, the incidence of the different types of thyroiditis has also changed. Molecular advances in thyroid neoplasia have expanded from a research tool to now providing insights into biological mechanisms and tumor behavior. In the future, they will likely play a prominent role in patient management.

The purpose of FNA is to render an accurate diagnosis and aid the clinician in determining important management decisions. Common clinical issues include: (1) Is the nodule likely to be a cancer, and therefore, it should be treated by surgical excision? (2) Is the lesion unequivo-

Table 3.2. The role of the pathologist.

1. Classification of inflammatory and Infectious thyroiditis
2. Distinction of follicular adenoma from follicular carcinoma
3. Identification of histologic variants of papillary carcinoma associated with more aggressive clinical behavior
4. Enumeration of key histopathological findings for accurate staging, prognosis and management of neoplasms
5. Procurement of tissue for flow cytometry, microbiology, etc.
6. Distinguish disease recurrences from therapy effects
7. Preserve tissue for research purposes (e.g., molecular studies)

cally benign and of no risk to the patient? Most cytopathologists use five diagnostic categories: malignant, suspicious, atypical or indeterminate, benign, and inadequate in reporting the morphologic interpretation. The term "suspicious" is used when the findings share some but not all of the diagnostic features of malignancy. In general, the first three categories warrant a surgical biopsy for histopathological confirmation. The criteria utilized to determine the adequacy of a sample are controversial. Some cytopathologists require the presence of at least six clusters of ten cells to twenty cells on each of one or two slides (3). Others define an adequate sample as one that provides a morphological explanation when the clinical and pathological information are correlated. The report should include the cellularity of the epithelial component and their nuclear and staining characteristics. For this purpose we prefer both air-dried slides stained with May-Grunwald Giemsa (MGG) stain and alcohol-fixed slides stain with the Papanicolaou stain. Nayar and Frost emphasize three steps in the analysis of FNA (4): (1) the arrangement of cells with respect to one another, (2) the cytological features of individual cells, and (3) the composition of background elements. The amount and type of colloid should be included. The size of follicles should be described and whether they are monotonous and microfollicular in arrangement. Nuclear features including size, grooves, and intranuclear pseudoinclusions are important for the diagnosis of papillary cancer. The presence of lymphocytes and psammoma bodies should also be noted. Clinicians should communicate with their pathologist and ensure that there is a common language so that miscommunication does not occur. The techniques for FNA including ultrasound-guided FNA, uses and clinical results of cytology are presented in Chapter 4, Thyroid Nodule. The management of differentiated thyroid cancer and variants is presented in detail in Chapter 6. Special groups of patients such as children and pregnant women are discussed in Chapters 7 and 8 respectively.

The issue occasionally arises of a discrepancy between the FNA diagnosis and the histopathological diagnosis in the surgical specimen. Ylagan and colleagues reported a discordance rate of 18% in a group of 255 patients who underwent surgery out of total of 1,253 who had an FNA (5). Of these, close to half had an inadequate FNA. The false negative rate was 11/255 (4%) but five of these were papillary cancers smaller than 1 cm, and three of the five were 1 mm in diameter. Two other patients had cytology findings that would have prompted referral for surgery in any case. Therefore a more realistic false negative rate is 1.7% to 2.4%. The false positive rate was 14/255 (6%). In a similar comparison of 240 patients the false negative rate was 2% and false positive 4% (6). Castro and Gharib state the false negative ranges from 1% to 5% (7). Overall, the published literature suggests that in experienced hands (combining technical and diagnostic expertise) the false negative rate should be less than 5%. Carcinoma is more likely to be missed in cystic lesions than solid tumors. The false positive rate is also low, around 1% to 3%.

The indications and limitations of intraoperative evaluation are discussed in detail by Ranchod (8). The main indications are: (1) determination of malignancy in a subtotal thyroidectomy to determine the need for completion thyroidectomy, (2) examination of cervical lymph nodes to determine the indication for and extent of nodal dissection, and (3) obtaining diagnostic material for histopathological classification and ancillary studies in the setting of hematolymphoid neoplasms. We discourage intraoperative examinations for the sole purposes of satisfying the curiosity of the surgeon. Inking of the lobectomy specimen is recommended prior to sectioning. A small piece of tissue containing the interface of the lesion with the adjacent normal thyroid parenchyma permits the comparison of the cytological and architectural components from both these areas. Nodules that are predominantly cystic are usually benign adenomatous nodules that have undergone degenerative change but the possibility of cystic papillary carcinoma must also be considered. Encapsulated solid or colloid-poor nodules render a different set of diagnostic possibilities that include follicular adenoma or carcinoma, Hürthle cell neoplasms, encapsulated papillary carcinoma and rarely medullary carcinoma. It must be emphasized that the distinction between follicular adenoma and well-differentiated carcinoma, and its variants is rarely resolved on frozen section and is deferred to the examination of the permanent section slides. Other limitations of intraoperative diag-

nosis include the difficulty in providing a confident distinction between Hürthle cell adenoma and minimally or capsular invasive Hürthle cell carcinoma, identifying the numerous variants of papillary carcinoma and providing an unequivocal distinction between hyalinizing trabecular adenoma and encapsulated papillary carcinoma. In the majority of these cases the diagnosis should be deferred to the permanent sections when the multiple tissue slides and the liberal use of leveled sections can be obtained.

The decision for intraoperative consultation varies in different institutions and amongst surgeons. Some surgeons opt for frozen section confirmation of papillary carcinoma, which was previously diagnosed on FNA prior to total thyroidectomy. Others will accept the FNA results and proceed with definitive therapy. On occasion there is a discrepancy between the two modalities. Some consider FNA to be more sensitive than frozen section but not as specific (8). When the FNA result indicates papillary cancer and frozen section does not support the diagnosis most clinicians think the result of the FNA be accepted for intraoperative management issues. The guidelines of the British Society of Endocrine Surgeons accept this philosophy. Conversely, when the FNA reports an unequivocally benign diagnosis the question of whether a frozen section report of a suspicious lesion should alter the nature of the surgery arises on occasion. Generally the answer is no. It is our practice that when the FNA provides an unequivocal report of benign or malignant that it should dictate the management. Another issue that arises on occasion is the problem of an indeterminate or atypical FNA result. When the true pathological nature of the nodule is not known, and when there is approximately 80% chance that the nodule is benign, many surgeons are reluctant to advise total thyroidectomy, and many patients are reluctant to consent for the procedure. An unambiguous frozen section report stating this lesion is or is not a cancer allows the decision for complete thyroidectomy versus a lesser procedure. This would have been discussed prior to surgery and agreed upon by the patient and surgeon. In our experience, these problems are avoided by utilizing the combined techniques of frozen section examination and cytological touch/scrape preparations to enhance the diagnostic yield.

Immunohistochemistry and Recent Molecular Advances

The use of specific labeled antibodies to stain tissue sections has increased the accuracy of histologic diagnosis (9). These include Tg, galectin-3, calcitonin, cytokeratin-19 (CK19), thyroid transcription factor-1 (TTF-1), anti-mesothelial cell monoclonal antibody derived from human mesothelioma cells (HBME-1), estrogen receptor, cell adhesion molecule alpha and beta integrins, CD44, CA125, alpha1-antitrysin, and S100 (10–14). Galectin-3 has also been found to be helpful by some investigators in the cytological interpretation of thyroid lesions (15). In the case of a small cell neoplasm, lymphoma, medullary cancer, insular carcinoma, and metastasis can be confidently distinguished. Medullary cancers stain positively for calcitonin and other neuroendocrine markers (16,17). In contrast TTF-1 is positive in medullary cancers but not other neuroendocrine lesions with the exception of lung neuroendocrine neoplasms (16). Thyroid transcription factor-1 stains the majority of well-differentiated carcinomas and insular carcinomas but not anaplastic carcinomas. Immunohistochemical testing of fifty-five papillary cancers (30 classic and 25 follicular variant) was compared to thirty adenomas, twenty benign nodular lesions, and five follicular cancers (18). The authors accepted a positive result when more than 10% of the cells stained positively. A panel of markers, CK-19, EMA, HBME-1, CD57, and CD15 showed the highest sensitivity and specificity for papillary cancer (18). In a similar study the goal was to differentiate papillary cancer and its variants from pure follicular cancer (19). Immunostains for high molecular weight keratin were positive in 91% of papillary cancer and 20% of follicular cancers. More than half of the papillary cancer cells stained positively. Immunostaining for involucrin was positive in 72.5% of papillary cancers versus 29% follicular malignancies (19). The staining of follicular lesions was diffuse but faint, whereas papillary cancers showed focal intense positivity. Table 3.3 lists some of the immunohistochemistry tests of value in various thyroid cancers. No single immunochemical marker has sufficient specificity or sensitivity to permit their utility beyond that of an adjunct to cytopathology and histology (20). In each and

Table 3.3. Immunohistochemistry profiles in differential diagnosis of thyroid cancer.

Chemistry	Follicular adenoma	Papillary cancer	Follicular cancer	Medullary cancer	Anaplastic cancer	Lymphoma
Thyroglobulin	+	+	+	−	usually −	−
Calcitonin	−	−	−	+	−	−
CEA	−	−	−	+	+/−	−
CK19	−	+	−	−	+/−	−
Galectin-3	−	+	+	−	−	−
CD20 (B cell marker)	−	−	−	−	−	+
TTF-1	+	+	+	+	−	−

every case the cytological and architectural features of a neoplasm must be used as the primary discriminator of benign and malignant neoplasms.

Over the last two decades, different types of genetic abnormalities have been identified in thyroid neoplasia ranging from chromosomal rearrangements to point mutations and genomic instability. The role of oncogenes in the initiation and progression of well-differentiated thyroid malignancies has been the subject of recent investigation. Rearrangement of the RET protooncogene, normally located on chromosome 10q11.2, is now recognized as an integral molecular event in papillary carcinoma (Chapters 5 and 10). In cell culture studies and transgenic animal experiments using targeted expression of rearranged RET genes thyroid neoplasms resembling papillary carcinoma in humans can be produced (21, 22). The RET gene encodes a cell membrane–receptor tyrosine kinase. To date more than ten different RET/PTC rearrangements have been characterized reflecting the different genes that fuse with the tyrosine kinase domain (23). RET/PTC1 and RET/PTC3 are the most common rearrangements and account for 90% of those identified in papillary carcinomas in humans. The prevalence of RET/PTC varies in different age groups and geographic locations with a range of 11% to 43% (24). The RET/PTC1 rearrangement is the most common type found in sporadic conventional papillary carcinoma in adults and children and in microcarcinoma while RET/PTC3 is more frequent in solid and tall cell variants of papillary carcinoma and in children exposed to radiation leakage in the Chernobyl nuclear reactor accident (25–27). Interestingly, RET/PTC rearrangements have recently been identified in cases of hyalinizing trabecular adenoma, of which it shares similarities with papillary carcinoma but not other types of follicular adenomas and carcinomas (28). Another chromosomal rearrangement that has been identified in cases of papillary carcinoma involves a different tyrosine kinase gene called TRK. It is reported in 10% to 15% of cases and has been identified in classic papillary carcinoma and variants, such as microcarcinoma, follicular, and tall cell variants and may predict clinical behavior (29). Recently, Nikiforova and colleagues identified the translocation t(2;3) (q13;p25) in follicular carcinoma (30). The translocation produces a fusion of the transcription factor PAX-8 gene with the peroxisome proliferator-activated receptor-gene PPARgamma. The overexpression of the chimeric fusion gene PAX-8-PPARgamma is detectable by RT-PCR and immunohistochemical analyses (31).

Activating point mutations of the RAS protooncogene occur in follicular adenomas and carcinomas and anaplastic carcinomas but are uncommon in papillary carcinomas and Hürthle cell tumors. Inactivating point mutations of the p53 tumor suppressor gene are very common in anaplastic thyroid carcinoma and have been reported with less frequency in poorly differentiated (insular) carcinoma (23). Point mutations of RET protooncogene have recently been identified in both the sporadic and familial (non-MEN, MEN-2A & 2B) forms of medullary carcinoma. The discovery of the molecular defect in over 90% of families with MEN-2 led to the development of genetic screening tests for RET mutations. Currently, prophylactic total thyroidectomy is offered to asymptomatic family members as young as five years of age with positive screening results, in an attempt to detect and cure medullary carcinoma at an early stage or preferably at the premalignant phase of diffuse C cell hyperplasia.

Benign Thyroid Tumors and Tumor-Like Nodules

There are approximately 23,000 new thyroid cancers in the United States annually. By comparison 4% to 5% of adults have a palpable thyroid nodule, and 30% to 50% have a nodule that can be detected by ultrasound (7). Therefore, the vast majority of thyroid nodules are not malignant. The pathological findings in benign nodules are discussed first followed by cancers.

There are many causes of clinical nodules in the thyroid, as shown in Table 3.4. These include adenomatous (nodular) hyperplasia, adenoma, chronic lymphocytic thyroiditis, subacute thyroiditis, and colloid cyst. The normal thyroid gland is composed of central colloid rimmed by small round follicle cells. Twenty to forty follicles are arranged into a lobule surrounded by delicate fibrous septa. Admixed with the follicles are C cells, which can only be identified by immunohistochemical staining, and solid cell nests are found in the midregion of the lateral thyroid lobe. The latter represent embryological remnants of the ultimobranchial body. In FNA preparations the follicular cells are uniform in size and shape, their nuclei are central and similar in size to those of a lymphocyte. In addition there is often an admixture of groups of follicular cells and cells stripped of their cytoplasm (naked nuclei) and colloid that ranges from a "watery" appearance to "cracked glass" or the more classic tenacious material. So-called "endocrine anaplasia" refers to the nuclear enlargement and pleomorphism that occur as normal variation in single follicular cells or small clusters.

Nontoxic Multinodular Goiter and Adenomatous Hyperplasia

Goiter is a descriptive term that refers to enlargement of the thyroid gland as defined by a weight greater than 30 gm. It arises from a variety of causes including inherited enzyme deficiency, neoplasia, inflammation, or nutrient deficiency. In regions of iodine deficiency, multinodular or "endemic" goiters occur and are the most common global cause of thyroid enlargement. Women are more likely to be affected and multiparty and older age increases the prevalence. In developed countries the condition is called "sporadic goiter" (32). One explanation for this condition is that low iodine results in biochemical hypothyroidism with a chronically elevated thyroid stimulating hormone (TSH) that causes the thyroid to enlarge. That plus other growth factors such as insulin-like growth factor or fibroblast growth factor cause nodule formation. Bleeding into a nodule produces scarring that aggravates the tendency for sites of growth to form nodular structures. Recurrent hemorrhage can leave regions of calcification. In some patients one nodule can be dominant and a diagnosis of solitary nodule might be made unless there is an ultrasound showing multiple smaller nodules. One of the cells might develop a mutation in the TSH receptor that produces a constant "on" signal and in time this develops into a functioning nodule that can eventually produce

Table 3.4. Benign lesions that produce thyroid nodules.

Clinical condition	Comment
Multinodular goiter	Common in elderly and in regions of iodine deficiency.
Adenomatous hyperplasia	Nodules can develop autonomous function and cause hyperthyroidism
Follicular adenoma	There is a spectrum from benign adenoma to atypical adenoma to minimally invasive follicular carcinoma. Occasionally can develop autonomous function and cause hyperthyroidism
Hashimoto's thyroiditis	More common in women and can produce a nodular goiter
Subacute thyroiditis	Rapid onset of a painful nodule plus systemic viral symptoms and features of thyrotoxicosis
Riedel's thyroiditis	Slow onset of very hard nodular goiter that can be confused with anaplastic cancer or lymphoma
Hemorrhage in goiter	Sudden onset of painful nodule usually without thyrotoxicosis or systemic symptoms
Graves' disease	The goiter is usually not nodular however a nodule can coexist. There is a nodular variety of Graves' disease called Marine-Lenhart syndrome

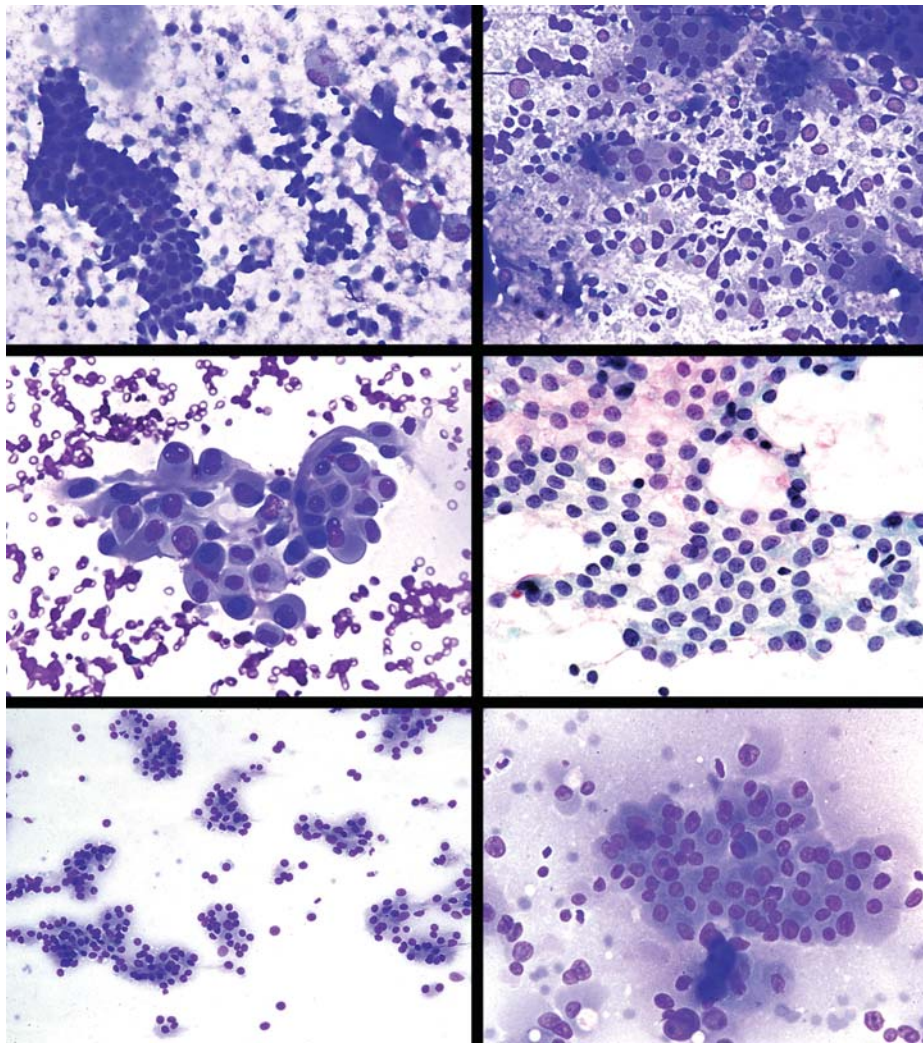

Figure 3.1. Fine Needle Aspiration Cytology of Thyroid Lesions. Top Left: Benign thyroid nodule (nodular hyperplasia) showing colloid admixed with follicular cells and scattered Hürthle cells. Top Right: Chronic lymphocytic (Hashimoto's) thyroiditis with Hürthle cells and lymphocytes. Middle Left: Papillary carcinoma showing avascular papillary group composed of large cells with metaplastic squamoid cytoplasm and occasional intranuclear pseudoinclusions. Middle Right: Follicular variant of papillary carcinoma with 2 distinct follicular spaces and papillary carcinoma cells with nuclear grooves. Bottom Left: Follicular neoplasm showing cellular repetitive microfollicular pattern in the absence of colloid. Bottom Right: Hürthle cell neoplasm with characteristic cells showing abundant fine granular cytoplasm, central nucleoli and anisocytosis.

hyperthyroidism. When several nodules are hyperactive it is called a toxic multinodular goiter. Both toxic and nontoxic multinodular goiters share similar histopathological features and must be distinguished by clinical and biochemical findings.

The histopathological terms that are most often used for sporadic goiters are adenomatous or nodular hyperplasia, hyperplastic colloid nodule or adenomatoid goiter (33). Patients have normal thyroid function studies and usually present with a slowly enlarging neck mass. Rapid enlargement and pain are caused by hemorrhage within the nodules. Fine needle aspiration displays the same constituents as the normal thyroid gland including abundant colloid and follicular cells of involuted and hyperplastic types, and there can be Hürthle cells and macrophages containing hemosiderin, as show in Figure 3.1. In surgical specimens the

gland is enlarged and there are usually many nodules of varying size, as shown in Figure 3.2. There is no evidence of invasion. Scarring and sites of hemorrhage with cystic regions and calcified areas are seen in long-standing cases. The cut surface displays abundant colloid. Histologically the follicles are large with abundant colloid, but tremendous variation in size and shape is usually present. At scanning magnification, there is a notable absence of a

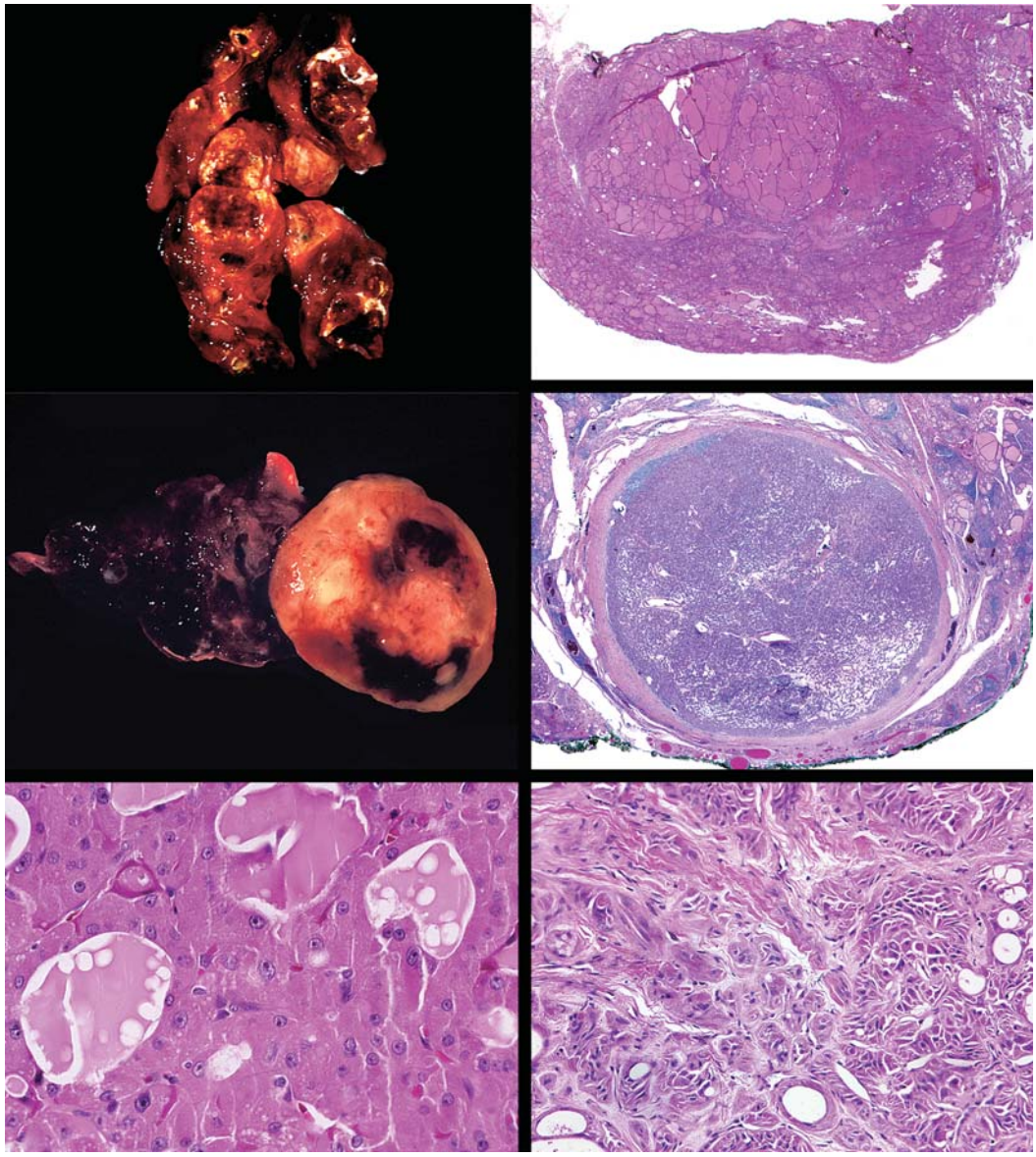

Figure 3.2. Adenomatous Hyperplasia and Follicular Adenoma of the Thyroid. Top Left: Adenomatous (Nodular) Hyperplasia showing multiple nodules of variable size. Top Right: Microscopic sections of nodular hyperplasia showing absence of capsule and follicles of different size and shape. Middle Left: Follicular Adenoma demonstrating sharply delineated margins from adjacent thyroid tissue. Middle Right: Microscopic section of follicular adenoma showing prominent continuous fibrous capsule and compression of adjacent thyroid tissue. Bottom Left: Hürthle cell adenoma with bright eosinophilic granular cytoplasm and prominent central nucleoli. Bottom Right: Hyalinizing trabecular adenoma with nests of elongated cells surrounded by fibrous stroma.

well-formed capsule (Figure 3.2). The cells lining the follicles are low cuboidal to flattened and are aligned as a single layer. A variety of architectural arrangements and different cell types can be seen including large and small follicles, hypercellular foci, papillary infoldings, and metaplastic elements, such as Hürthle cells and adipose tissue. There can be considerable fibrosis with foci of dystrophic calcifications and some nodules may appear to be encapsulated and thus appear like a follicular adenoma. It should be recognized that differentiated cancers, both follicular or papillary can arise in adenomatous hyperplasia but are uncommon.

Follicular Adenoma

Follicular adenoma is defined as a solitary, encapsulated benign neoplasm of follicular cell origin that displays distinct differences in cellularity and composition from the adjacent normal thyroid parenchyma. The majority of these exist as painless masses in middle-aged, euthyroid women and are sporadic, although an association with Cowden syndrome has been reported. There are a number of important issues related to the role of FNA in follicular neoplasms. The distinction of cellular benign thyroid nodules such as nodular hyperplasia and follicular neoplasms can be problematic. It must be emphasized that the separation of follicular adenoma from follicular carcinoma cannot reliably be made by FNA and the term "follicular neoplasm" is used. The key cytological findings in FNA samples are cellular smears with numerous equal-sized cell clusters composed of crowded overlapping follicular cell nuclei arranged in microfollicles, rosette patterns, and scant colloid in the background (Figure 3.1). It is necessary to proceed to a surgical excision to establish the correct histological diagnosis. One recent study compared the final histopathology and FNA in fifty-eight patients that showed a microfollicular pattern on FNA (34). After thyroidectomy, 62% had a diagnosis of adenomatous nodules, and 12% had follicular adenoma, but 15% of nodules were a follicular variant of papillary cancer, 9% were papillary cancer, and 2% were Hürthle cell cancer.

Other considerations in the differential diagnosis of follicular lesions include follicular variant of papillary carcinoma, parathyroid adenoma or hyperplasia, and atypical adenoma with bizarre cells. In most instances these distinctions require surgical excision for confirmation.

On gross appearance follicular adenomas are solitary, round to oval, encapsulated and smaller (1 cm to 3 cm in diameter) than nodular hyperplastic lesions. The cut surface displays a tan-white homogeneous appearance (Figure 3.2). Secondary changes such as hemorrhage, cystic degeneration, necrosis, and calcification are less common than in nodular hyperplasia and can be the consequence of prior FNA. The histological patterns have been subdivided into macrofollicular, microfollicular, trabecular or solid, and normofollicular types, but these are of no clinical significance. The lining cells are uniform and closely resemble those of normal follicles. There are at most very few mitotic figures, and the uninterrupted fibrous capsule is distinctive but can vary in thickness. The adjacent thyroid parenchyma often appears compressed. By definition capsular and vascular intrusion are absent.

A number of variants have been reported and are classified on the basis of their distinctive appearance or pattern. Hürthle cell adenomas are defined as benign tumors composed exclusively or predominantly (>75%) of oncocytic cells (35). In FNA samples they are arranged as single cells or clusters with sharply outlined cell borders, abundant basophilic cytoplasm with magenta or violet granules, and show more variation in nuclear size than follicle cells (so-called anisocytosis) (Figure 3.1). Grossly, the cut surface is tan brown. These large oxyphilic cells have a characteristic abundant red granular cytoplasm with round vesicular nuclei showing conspicuous central nucleoli in tissue sections (Figure 3.2). The abundance of mitochondria gives the cytoplasm its appearance. Following FNA sampling, they have the capacity to undergo complete hemorrhagic infarction. Assessing for capsular and vascular invasion is also used to discriminate between benign and malignant lesions. The cells react with Tg, but the staining pattern is less intense and diffuse than in follicular neoplasms; TTF-1 staining is usually negative.

Hyalinizing trabecular or paraganglioma-like adenoma is an uncommon neoplasm that shares the macroscopic features of follicular adenomas but has a distinctive microscopic appearance. As

noted previously, it shares some molecular similarities with papillary carcinoma and there is an overlap of histopathological findings as well. Generally the cells are elongated, oval, and are arranged in small packets separated by fine collagenous matrix and delicate vascular stroma (Figure 3.2). Intranuclear pseudoinclusions, nuclear grooves, and perinuclear vacuoles and occasional psammoma bodies can be found. This overlap of cytological and molecular findings has raised the possibility that it represents a variant of papillary carcinoma, but to date the behavior has been benign and the lesion is retained within the follicular adenoma category.

The term "atypical follicular adenoma" is reserved for encapsulated neoplasms that according to the World Health Organization (WHO) Committee display marked cellularity and unusual architectural and cytological patterns, such as necrosis or increased mitotic activity (36). By definition, there should not be evidence of capsular or vascular invasion, but the lesion has a worrisome appearance. In general these have behaved in a benign fashion. They must be distinguished from the recently coined term "follicular tumor of uncertain malignant potential," which is defined as a follicular neoplasm that shows incomplete or questionable penetration of the capsule (37). It is thought that in some cases there is entrapment of tumor cells within the fibrous capsule or an irregular capsule.

There are other uncommon variants of follicular adenomas. Adenolipoma or adenochondroma has a metaplastic mesenchymal component of adipose tissue or cartilage, respectively. The cells in signet ring cell follicular adenoma have large cytoplasmic clear vacuoles that appear to displace the nuclei towards the cell membranes (38). Adenomas with bizarre nuclei are defined as having clusters of cells with enlarged, hyperchromatic, and irregular nuclei measuring more than 10 times the size of adjacent cells. They are more commonly seen in follicular adenomas than carcinomas and represent an extreme form of "endocrine anaplasia" (33).

There can be a role for a nuclear scintiscan to determine in the case of the indeterminate nodule, which determines whether the nodule is functioning and thus likely to be benign. In the case where scintigraphy is obtained, first there is debate about the value of FNA in a functioning nodule defined as one that shows increased uptake of ^{123}I and suppression of surrounding tissue on scintigraphy (39). Thyroid stimulating hormone is low. Some, including the author, would obtain a scan first in this clinical situation, since the FNA can be indeterminate or even suspicious for cancer. One report of seventeen patients showed papillary lesions in five of them, four of these turned out to be hyperplastic papillary nodules that did not contain nuclear features of papillary cancer. However, the FNA result showing papillary structures would be an indication for thyroidectomy, yet the a priori incidence of cancer in a functioning nodule is less than 1% (40, 41). There are rare reports of functioning nodules being cancers (42). In contrast Liel et al. found that FNA showed benign pathology in twenty-one of twenty-four patients with a functioning nodule, and they felt FNA as the first test was appropriate (43). This produces a somewhat circular argument, but our preference in patients with biochemical hyperthyroidism and a nodule is to obtain the scan first and only proceed to FNA when the nodule has reduced function compared to the normal gland. Advances in molecular biology might provide a means for differentiating benign from cancerous follicular nodules. Cerutti et al. studied genes using polymerase chain reaction (44). Using four genes (DDIT3, ARG2, ITM1, and C1orf24), they had 83% accuracy. This is insufficient to make a decision to operate or not. Additional investigations might increase the accuracy to the point that a decision could be reached to which indeterminate nodules should be referred for surgery and which could be followed clinically (45).

Acute Thyroiditis or Thyroid Abscess

Acute thyroiditis is now an uncommon clinical occurrence and is usually infectious in origin (46). This has been attributed, in part, to the high iodine content in the thyroid that acts as an antiseptic. An abscess is more likely in an immunocompromised patient (47). Most of the early reports were due to pyogenic bacterial organisms such as *Staphylococcus sp.*, *Pneumococcus sp.*, and *Streptococcus sp.* (48). Viral inclusions, such as cytomegalovirus (CMV), display distinctive nuclear inclusions that aid in the

classification of the virus. Fungal organisms such as Cryptococcus, Aspergillus and *Pneumocystis carinii* are now identified in patients with AIDS or in transplant recipients with disseminated infections, as shown in Figure 3.3 (49). Fine needle aspiration produces pus and microscopically there are polymorphonuclear leukocytes and necrotic debris. In tissue sections the thyroid contains one or more abscesses and histologically there are classic features of acute

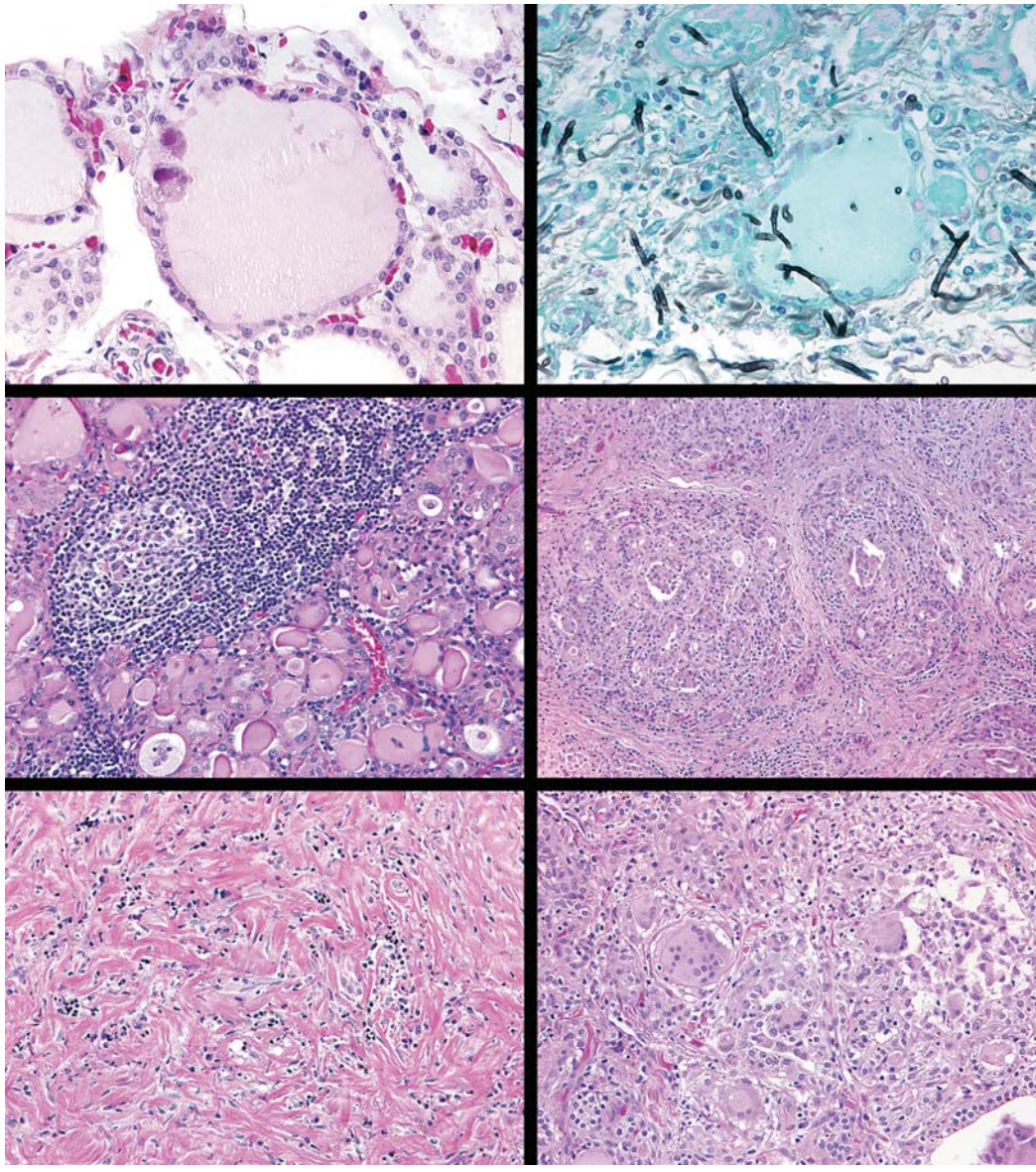

Figure 3.3. Different Types of Thyroiditis. Top Left: CMV Thyroiditis with characteristic eosinophilic nuclear inclusion with follicle cells. Top Right: Aspergillus Thyroiditis with thin, delicate septate hyphae branching at acute angles (GMS stain). Middle Left: Chronic Lymphocytic Thyroiditis showing reactive germinal centers and Hürthle cell change in follicles. Middle Right: Radiation Thyroiditis with preservation of lobular architecture of gland and variable inflammation and fibrosis. Bottom Left: Reidel's Thyroiditis composed of dense keloid-like fibrosis and chronic inflammation. Bottom Right: Subacute Thyroiditis characterized by disrupted follicles containing multinucleated giant cells and histiocytes.

inflammatory exudates with abundant polymorphonuclear cells, necrosis, hemorrhage, and disruption of follicles. In immunocompromised patients stains such as Gomori's-methenamine-silver (GMS) are helpful in identifying fungal organisms, as there is often a minimal host inflammatory response. An abscess in the soft tissues of the neck is more common and can be differentiated from a thyroid abscess by ultrasound or scintiscan. Treatment can require drainage by needle or surgery and antibiotics that are appropriate for the specific organism. Recurrent abscess should be an indication to search for a portal of entry, such as a fistula, from the pyriform sinus or thyroglossal duct cyst (50).

Chronic Lymphocytic Thyroiditis

Chronic lymphocytic thyroiditis or Hashimoto's thyroiditis is an organ specific autoimmune disorder characterized by the presence of circulating antibodies against thyroid peroxidase, TSH receptor, thyroid microsomal antigen, or Tg (51). It is about ten times more common in women, particularly in the thirty-year-old to sixty-year-old age range, and an association with HLA-DR5 has been reported. Nodules are frequent in Hashimoto's thyroiditis and are a common indication for FNA. As there is an association of thyroid cancer and Hashimoto's thyroiditis, an FNA is advised to evaluate a discrete nodule or a hypoechoic region on ultrasound (52). Fine needle aspiration shows benign follicular cells and Hürthle cells admixed with inflammatory cells, including small round lymphocytes, immunoblasts, tingible body macrophages, plasma cells, and occasionally multinucleated giant cells (Figure 3.1). Colloid is scanty or often absent. In the classic type of Hashimoto's thyroiditis the thyroid gland is diffusely enlarged either symmetrically or asymmetrically, if there are nodular lesions. The cut surface ranges from smooth and uniformly lobulated to fibrotic and atrophic. Microscopic sections reveal abundant lymphocytes and plasma cells, reactive germinal centers, and Hürthle cell metaplasia of follicles (Figure 3.3). Occasionally the dense lymphoid component can be difficult to differentiate from a low-grade lymphoplasmacytoid lymphoma but immunostaining demonstrates an admixture of polyclonal B cells and CD4+ T cells. Stromal fibrosis and squamous metaplasia of the follicular elements can be conspicuous in some cases. In some elderly patients dense fibrous replacement of the thyroid occurs and renders the gland woody and firm in texture. This fibrous variant causes marked enlargement of the gland and primary hypothyroidism. The fibrous atrophic variant or "idiopathic myxedema" produces a small shrunken gland that is completely replaced by fibrous scar tissue.

The association of papillary cancer and Hashimoto's thyroiditis is well recognized and some authorities recommend careful search for any evidence of papillary cancer when the cytology is chronic lymphocytic thyroiditis (53). Follicular variant of papillary cancer combined with Hashimoto's thyroiditis is a major diagnostic challenge.

Radiation Thyroiditis

Radiation exposure to the thyroid occurs in a number of settings, including nuclear accidents like the Chernobyl reactor incident, after radioiodine therapy for benign or malignant thyroid disorders, or as part of radiation treatment to a variety of head and neck cancers. The overall effect depends on dosage and length of exposure but most thyroid glands removed surgically or examined at autopsy will demonstrate some changes of radiation thyroiditis. The gland ranges from small and fibrotic to enlarged with features of nodular hyperplasia. The nodules are often hypercellular and the follicular cells display nuclear pleomorphism and hyperchromasia. Variable amounts of chronic inflammation, squamous metaplasia of follicles and stromal fibrosis are present. An important morphologic clue to the benign nature of the process is the preservation of the lobular arrangement of the distorted follicles (Figure 3.3). When radiation thyroiditis occurs after treatment with ^{131}I, there are symptoms of pain and swelling similar to those of subacute thyroiditis. Permanent hypothyroidism is the inevitable outcome. In contrast radiation thyroiditis due to external radiation is painless and there can be transient thyrotoxicosis from release of thyroid hormones, uptake of a tracer

of radioiodine is low (54). This is similar to the syndrome of painless silent thyroiditis.

Subacute Thyroiditis

Subacute thyroiditis or De Quervain's thyroiditis is painful and associated with systemic symptoms like a viral illness plus thyrotoxicosis (55–57). Subacute thyroiditis is a rare cause of fever of unknown origin (58, 59). Mild cases can have less neck pain and there is a spectrum from a syndrome like silent thyroiditis to classic subacute thyroiditis (60). It can be preceded by an upper respiratory viral infection or a viral prodrome. It is self-limiting. Women in the forty-year to sixty-year age range are most often affected, and there is a relation to tissue type HLA-B35. There are familial cases including five members of one family (3 women and 2 men) who were HLA-B35 positive had developed subacute thyroiditis (61). Subacute thyroiditis is very rare in children (62, 63). The thyroid gland is asymmetrically enlarged, and the cut surface displays nodularity. Numerous multinucleated giant cells, inflammatory cells, and cellular debris admixed with degenerating follicular cells and epithelioid histiocytes are seen on FNA (64). In histopathological sections, there is a mixed inflammatory infiltrate of lymphocytes, polymorphonuclear leukocytes, plasma cells, and giant multinucleated cells. The term "granulomatous thyroiditis" is derived from the collection of histiocytes and multinucleated giant cells surrounding aggregates of colloid (Figure 3.3). Currently, it is unusual for the thyroid to be removed surgically, as the process resolves over weeks or months (65). Seventeen patients with subacute thyroiditis were operated on at the Mayo Clinic over a period of thirty-five years, with nearly half of them before 1980 (66). The investigators state that surgery is not the usual method of therapy but is indicated when the clinical features are atypical or FNA shows cells that are suspicious for cancer. Interestingly, this inflammatory process can arise in one region and migrate to other regions of the thyroid, the so-called "march" thyroiditis (67).

Microscopically, the normal architecture is disrupted to a degree that would suggest resolution must be impossible although it is the expected end result. The follicles are disrupted and there is an inflammatory exudate. Early in the disease there are more polymorphonuclear leukocytes, while in later stages, lymphocytes, plasma cells, and giant cells. Li Volsi has listed the thyroidal conditions in which granulomas are found (68). In addition to subacute thyroiditis, they include "palpation thyroiditis," tuberculous or fungal thyroiditis, sarcoidosis, foreign body reaction, and vasculitides (68–70). There are rare reports of plasma cell granuloma that contain sheets of benign plasma cells and have no features of plasmacytoma (71). Immunohistological investigations have been described but are not necessary in the classic case (72). Rarely invasive cancers including anaplastic cancer, lymphoma, or a metastasis can produce a clinical picture like subacute thyroiditis with a painful thyroid mass and clinical and biochemical thyrotoxicosis (73). This is called carcinomatous pseudothyroiditis. Therefore when there is a prior history of cancer that has a propensity to spread to the thyroid, or sudden growth of a nodule in Hashimoto's thyroiditis FNA is recommended.

Painful conditions in the neck are more likely to be due to non-thyroidal conditions such as laryngitis, pharyngitis, esophagitis, and so forth (74). Painful thyroid disorders include subacute thyroiditis, acute thyroiditis, rarely Hashimoto's thyroiditis, and rapidly growing cancers causing pseudothyroiditis (75).

Cysts of the Thyroid

A cystic thyroid nodule is diagnosed by ultrasound, by FNA when the aspirate is fluid or on pathological examination of the thyroid. Cystic lesions of the thyroid gland can be caused by a variety of processes with infectious, inflammatory, degenerative, and neoplastic etiologies. Nodular hyperplasia with cystic degeneration is the most common cause and can be suggested by ultrasound or by FNA when fluid is aspirated. The sensitivity and specificity for determining that a thyroid nodule is a cyst by clinical examination is low. The fluid from a thyroid cyst can have a range of colors from straw colored, through bloody, and to dark brown. The darker fluids usually contain hemosiderin-laden macrophages. These cysts have usually occurred from cystic degeneration with bleeding into a

benign nodule. One of the problems the pathologist encounters is that the cystic lesion contains very few follicular cells, and there are insufficient cells to determine whether the nodule is benign. Occasionally the nuclei of the histiocytes can have characteristics of those in papillary cancer (76). We recommend repeat aspiration, under ultrasound guidance, to ensure sampling of any solid components to further reduce the possibility of a false negative FNA. Immunostaining with CD68 has been found to differentiate the histiocytes, which stain positively from thyroid cells that do not stain.

Other causes of cystic lesions include midline thyroglossal duct cysts, laterally displaced branchial cleft, pharyngeal cysts, lymphoceles, and hematomas. Infective cysts such as echinococcal (echinococcus granulosa) lesions have been described in the thyroid in endemic regions but are very rare (77). Fine needle aspiration sampling is permitted if strict precautions are followed. The dogma is that echinococcal cysts should not be punctured, for fear of releasing antigen and causing anaphylaxis. Rauhofer et al. reviewed the literature and many of the reported cases had an FNA without complication (77).

Midline cysts above the thyroid are thyroglossal duct cysts and they usually are lined with squamous epithelium and contain few follicular cells. The fluid contains a few inflammatory cells, histiocytes, and debris. There are rare reports of thyroid cancer arising from thyroid cells within thyroglossal cysts (78, 79). Some authorities recommend FNA of thyroglossal cysts to ensure cancer is not missed and this is discussed in more detail in Chapters 6 and 7 dealing with differentiated cancer in adults and children.

Reidel's Thyroiditis

Reidel's thyroiditis is rare but produces a rock hard irregular gland that can mimic an anaplastic cancer or lymphoma clinically. The cause is unknown, but it appears to be an inflammatory and sclerosing lesion and can be associated with similar conditions, such as retroperitoneal fibrosis, sclerosing cholangitis, mediastinal fibrosis, and orbital pseudotumor (80). Occasionally the patient can have concurrent conditions. An autoimmune component has been suggested by the presence of antithyroid antibodies. Patients can present with compressive symptoms on account of fibrous infiltration of adjacent structures such as the esophagus or trachea. FNA usually yields scant fibrous material. In surgical resection specimens, the gland is enlarged, stony in consistency, and adherent to adjacent soft tissues. The gland is very hard and woody in consistency. Although there is invasion of surrounding tissues by fibrous material, this is not a cancer. Fine needle aspiration might only produce fibrous material. Because of the hard clinically suspicious gland, this might be interpreted as a desmoplastic reaction to a thyroid cancer. Histologically, the hallmark is dense sclerotic fibrous tissue with few follicular cells or colloid. The vessels show intimal proliferation, phlebitis, and intraluminal thrombi (81). This benign process can be distinguished from the paucicellular variant of anaplastic carcinoma by the absence of cellular pleomorphism and mitotic activity. In some cases the process is self-limiting, while in others surgical excision is required to relieve pressure symptoms.

Miscellaneous Lesions

Other causes of nodular masses in the thyroid that can mimic malignant neoplasms are dyshormonogenetic goiter, malakoplakia, amyloid goiter, plasma cell granuloma or inflammatory myofibroblastic tumor, sinus histiocytosis with massive lymphadenopathy, and solid fibrous tumor. Solid fibrous tumor is a very rare lesion. The reports are in patients of an average age of fifty years, and there is abundant fibrous tissue. These are usually benign. The differential diagnosis is Riedel's thyroiditis, cancer with a desmoplastic reaction, and paucicellular anaplastic cancer (82).

A number of drugs such as amiodarone, lithium, and minocycline can cause thyroid dysfunction or alteration of appearance of the epithelial cells lining the follicles. In particular, minocycline and other tetracycline derivatives cause accumulations of fine black pigment within the cytoplasm of the cells that creates the "black thyroid" (83). Intracytoplasmic accumu-

lations of iron pigment can be found in macrophages in hemosiderosis and in epithelial cells in hemochromatosis.

Well-Differentiated Thyroid Carcinomas

The current classification of malignant epithelial tumors derived from follicular cells is based on the degree of differentiation of the constituent cells and architectural arrangements of the tumor cells. The three groups are well-differentiated tumors (papillary and follicular), poorly differentiated carcinoma including insular type and anaplastic carcinoma and are shown in Table 3.1. In most cases the accurate designation of these neoplasms into one of these categories is made without difficulty. Because prognosis and possible therapeutic interventions depend on these categories it is important that the final pathology report include information that will allow the clinician to determine the most accurate staging of the patient using the Tumor, Node, Metastasis (TNM) classification shown in Table 3.5. The Association of Directors of Anatomic and Surgical Pathology encourages pathologists to use a standardized approach to the macroscopic and microscopic reporting of thyroid carcinoma. This includes the type of specimen, tumor size, location and type, the presence or absence of encapsulation, capsular or vascular intrusion, extrathyroid extension, status of surgical resection margins, presence of tumor multicentricity, histopathological appearance of uninvolved thyroid parenchyma, number and location of parathyroid glands, and status of lymph nodes – including number of nodes involved by tumor, largest dimension of involved node, and presence of extranodal tumor extension (2). In addition to narrative descriptions and summaries some centers use checklists at the end of the surgical pathology report to enumerate the important diagnostic information.

Papillary Cancer

Papillary cancer accounts for about 80% of thyroid cancers in regions where there is adequate dietary iodine. Women are three times

Table 3.5. Tumor, node, metastasis staging of differentiated thyroid cancer.

A. Thyroid Cancer pTNM staging		
Primary Tumor	T0	No evidence of primary cancer
	T1	Recently changed to <2 cm
	T2	Tumor >2–4 cm
	T3	Tumor >4 cm
	T4	Tumor of any size extending beyond the thyroid capsule
Regional Nodes	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
		N1a Ipsilateral cervical nodes
		N1b Bilateral midline or contralateral cervical or mediastinal nodal metastasis
Distant Metastasis	M0	No distant metastasis
	M1	Distant metastasis
B. TNM staging for differentiated thyroid cancer		
Less than 45 years		
• Stage I		Any T, any N, M0
• Stage II		Any T, any N, M1
• Stage III		Not applicable
• Stage IV		Not applicable
45 years or older		
• Stage I		T1, N0, M0
• Stage II		T2, N0, M0
• Stage III		T3, N0, M0 or any T, N1, M0
• Stage IV		Any T, any N, M1

more likely to develop this cancer and the age range of twenty-five years to forty-five years is most often affected. The patient presents with a painless nodule that is sampled by FNA. The cytology specimen is usually very cellular and there can be frond-like papillary structures sometimes with central vessels (Figure 3.1). The sheets of cells show crowding. The nuclei might show grooves and pale inclusions (pseudo-inclusions that are invaginations of cytoplasm). The colloid often has a "bubble gum" appearance and psammoma bodies and multinucleated giant cells are found in some cases. Both psammoma bodies and giant cells are occasionally present in a benign nodule therefore other cytological criteria should be present to make the diagnosis of cancer (84, 85). Nuclear molding, grooves, sharply delineated nuclear membranes, intranuclear cytoplasmic protrusions, and nuclear overlapping have been listed as key findings (46). The positive predictive value of FNA for papillary cancer is high and in some series is 100% (86). When the aspirate is paucicellular but there are a few cells showing features of papillary cancer that diagnosis is likely to be confirmed histologically (87). Renshaw reviewed cases with twenty or less abnormal cells and 54% were confirmed to be malignant. Using computer-assisted image processing there is the ability to diagnose benign lesions such as hyperplastic nodules and adenoma and differentiate from carcinoma (88).

Grossly the appearances depend in part on the size of the cancer. Papillary cancers are often bilateral and multifocal. The lesions are firm to hard and can have foci of calcification, as seen in Figure 3.4. The borders of the cancers are often irregular or poorly differentiated. There is some debate whether multifocality is due to intrathyroidal spread of cancer (monoclonal) along lymphatic channels or a common genetic factor leading to synchronous primaries or to a common insult such as radiation that puts all cells at risk (field defect). It is likely that all three mechanisms are involved. Cystic degeneration can occur but this is more common in metastases in regional lymph nodes (43). Histologically, the cells are arranged in papillary fronds with a fibrovascular core (Figure 3.4). The nuclei appear optically clear and have lateral displacement of the nucleoli near the nuclear membrane (so-called "Orphan Annie" nuclei after the comic strip character). Many of the same features that are seen in cytological preparations are also found in surgical specimens including grooves and pseudo-inclusions. Psammoma bodies are seen in about 50% and derive from individual necrotic tumor cells that undergo calcification in lamellate layers (Figure 3.4). A host lymphocytic response to the cancer cells is common especially at the leading edge of the lesion. In some cases, there are sufficient cells to look like chronic lymphocytic thyroiditis. In fact about one-third of patients with papillary cancer have circulating antibodies to Tg. In early reports from the Mayo Clinic, the coexistence of "Hashimoto's" conferred a better prognosis. It has been hypothesized that an autoimmune reaction had been mounted against the cancer. Papillary cancer associated with chronic lymphocytic thyroiditis can have a desmoplastic reaction, but the degree of fibrosis within the lesion is not related to that in the thyroiditic gland (89). One investigation used multiple criteria in an effort to differentiate cystic papillary cancers from cystic non-cancerous lesions (90). They found the presence of "tridimensional fragments, anisonucleosis, nuclear bars, pseudoinclusions, powdery chromatin, cytoplasmic vacuoles, and metaplastic cytoplasm" were statistically relevant.

A minority of papillary cancers contains solid or trabecular components but the cells have ultrastructural details similar to classic papillary cancer and different from poorly differentiated or insular variants (91). Pure cysts are unlikely to be cancerous but papillary cancers can contain areas of cystic degeneration and there are case reports of cystic components in medullary cancer (92).

Papillary cancer spreads by lymphatics and involvement of regional nodes is common. In some cases FNA sampling of an enlarged cervical node is the mode of presentation. The finding of adenocarcinoma in that site should prompt careful examination of the thyroid to find the primary, which is usually on the ipsilateral side. The nodes can undergo cystic degeneration and necrosis. In one study cystic cervical nodes seen on ultrasound were likely to represent papillary cancer followed by squamous cell head and neck cancer (93). A review of 1,102 aspirates of lymph nodes demonstrated that 28 (5.2%) were cystic metastases (94). Papillary cancer accounted for 43% and squamous cell carcinoma, followed by primary skin cancer

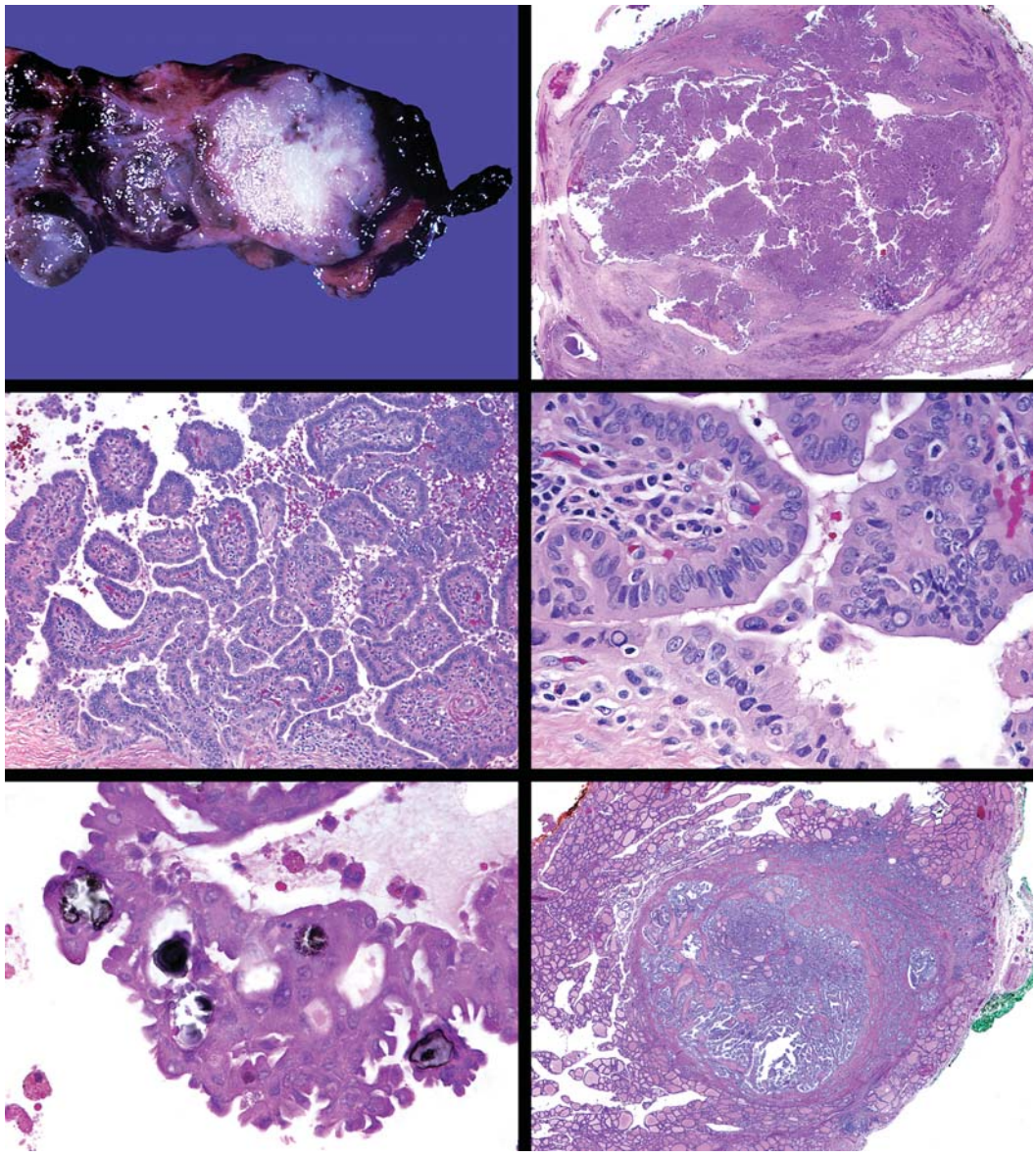

Figure 3.4. Conventional Papillary Carcinoma. Top Left: Gross appearance of papillary carcinoma exhibiting chalky white firm mass with irregular borders. Top Right: Low power magnification showing infiltrative edges and papillary configurations. Middle Left: Scanning magnification of complex branching papillae with central fibrovascular cores. Middle Right: Papillary frond lined by cells showing nuclear overlapping and "squaring off." The cells display vesicular nuclei with optical clearing, nuclear grooves and intranuclear pseudoinclusions. Bottom Left: Psammoma bodies composed of a central degenerated tumor cell surrounded by concentric layers of calcified material. Bottom Right: Papillary microcarcinoma as defined by a mass measuring less than 1 cm.

(31%) and cancers of unknown origin. Fine needle aspiration of cystic lymph nodes has a relatively high false negative rate, so the knowledge that malignancy is probable should prompt a repeat FNA, and this could be obtained under ultrasound guidance and a solid component could be sampled (94). Measurement of thyroglobulin in cyst fluid from a lymph node

Table 3.6. Variants of differentiated thyroid cancer.

Thyroid cancer	Variant	Comment
Papillary	Follicular	The overall appearance looks like follicular cancer but the nuclei are typical of papillary cancer. The prognosis is similar to papillary.
	Tall cell	Cells are twice as tall as wide. Generally accepted to have a worse prognosis
	Columnar	Cells are columnar and show nuclear stratification
	Solid	Solid islands of cells with reduced colloid. This has been found in children in particular after radiation exposure at Chernobyl. Association with RET/PTC3 mutations
	Diffuse sclerosing	Dense fibrous stroma
	Oncocytic	Looks like Hürthle cell lesion but nuclei have typical appearance of papillary cancer
	Cribriform	
	Insular	Some classify this type as poorly differentiated. There are islands of round atypical cells.
Follicular	Hürthle cell	The cells are larger and have an eosinophilic cytoplasm. Hürthle cell carcinoma can only be diagnosed when there is capsular or vascular invasion

Modified from Chan JKC Thyroid and Parathyroid. In Weidner N, Cote RJ, Suster S and Weiss LM. Modern Surgical Pathology. Philadelphia. Saunders Inc. pp 1681–1682, 2003.

confirms the presence of thyroid metastases (95). There has been interest in sentinel node imaging, in the hope that a cancer free sentinel node would predict no metastases in other lymph beds. Unfortunately, skip lesions have been reported (96).

In some patients, the cancer is identified only during histological examination of a thyroid that was removed for some other reason such as Graves' disease or a benign nodule and the cancer is in a different site. In this situation when the lesion is less than 1 cm this is called an occult papillary cancer or microcarcinoma and generally does not merit additional treatment. Small papillary cancers can be identified from 6% up to 36% of glands at autopsy, and they have caused neither symptoms nor signs and have been innocuous (97, 98). With increasing use of imaging tests, small papillary cancers are being diagnosed and this raises the question: Whether a known cancer of 8 mm that results in the patient being referred for operation is actually occult (defined as hidden or concealed)? Reports of local or distant metastasis resulting from occult cancer can be found in the literature, but in general, these are so rare that the conservative approach to management of the micro-cancer found serendipitously is appropriate (99–101). Follow-up of 149 patients identified a recurrence in three (2%) (102). The small cancer and its papillary histology are the reason for the excellent outcome. The ten-year survival of 203 patients was 100% (103). Hay et al. followed 535 patients for a median of 16 years and 2 died (104).

The main histologic variants of papillary cancer are shown in Table 3.6 (105). The follicular variant is the most common and often the most challenging both in cytological preparations and surgical specimens. Different investigators have noted the overlap of features with follicular adenoma and well differentiated follicular carcinoma. The difficulty of diagnosing the follicular variant of papillary cancer by cytology has been discussed (106, 107). Additional support for this comes from a comparison of cytology and histopathology of seventy-two proven papillary cancers compared to twenty-two follicular variant lesions (108). Cytology correctly classified sixty-five of seventy-two classic papillary cancer (90%), but only seven of twenty-two follicular variant cancers (31%). It is true that cytology is often in the indeterminate category, which would prompt an operation, as was the case in forty-five of fifty-six cases (86%) reviewed by Logani et al. (109).

A recent study of interobserver variation reported an overall concordance rate of less than 40% (110). Attention to the nuclear details

in FNA samples provides the cytopathologist with important clues to the correct diagnosis (Figure 3.1). In surgical specimens a variety of patterns have been noted (111, 112) By definition, these tumors are composed predominantly or exclusively of neoplastic cells with papillary carcinoma features that are arranged in follicles, as shown in Figure 3.5. Microfollicular, normofollicular, and macrofollicular patterns can be found. Thick darkly eosinophilic colloid is often present. The diffuse type usually completely replaces the lobe or gland and is

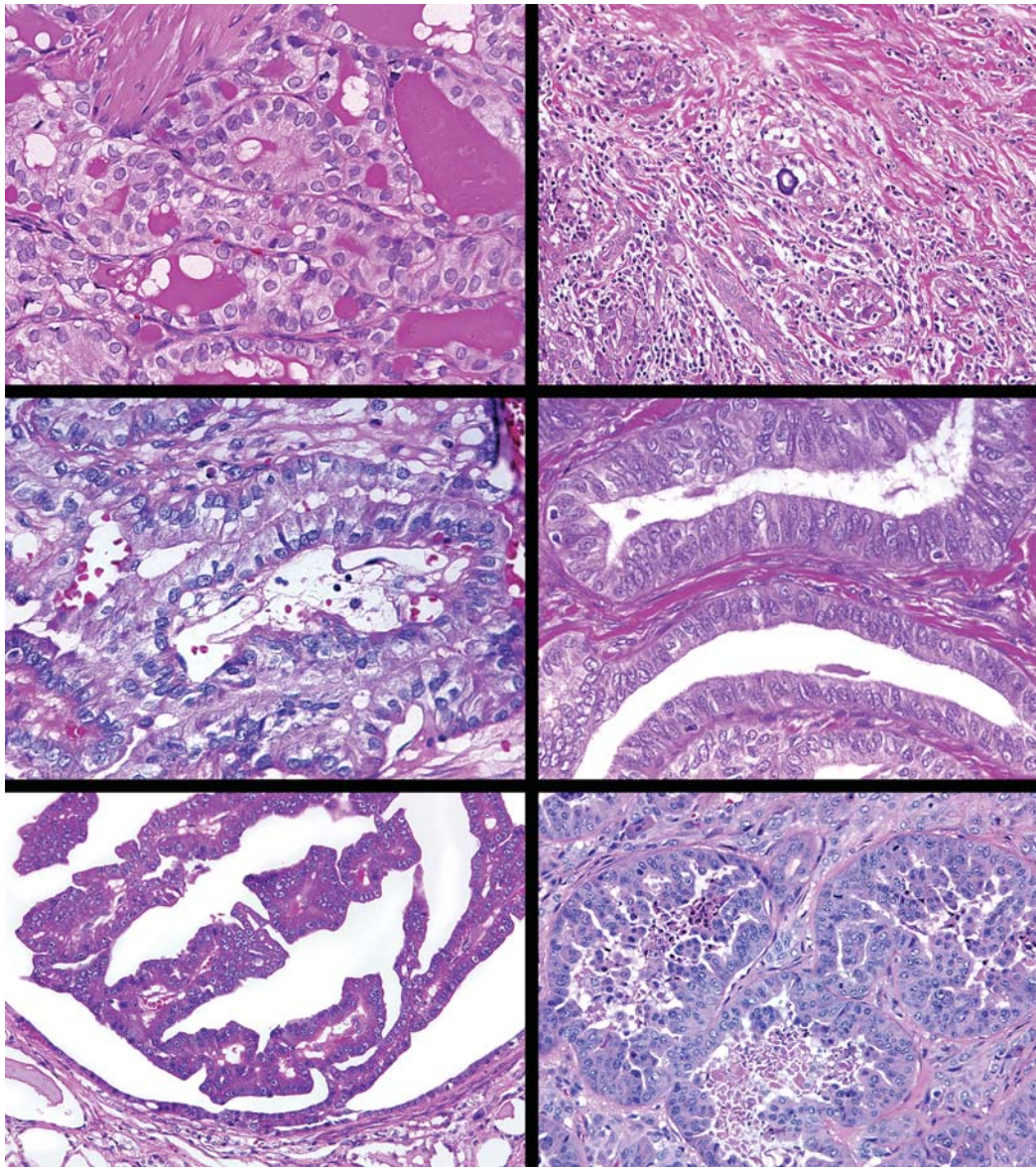

Figure 3.5. Selected Variants of Papillary Carcinoma. Top Left: Follicular variant. Top Right: Diffuse sclerosing variant. Middle Left: Tall cell variant. Middle Right: Columnar cell variant. Bottom Left: Oncocytic or Hürthle cell variant. Bottom Right: Dedifferentiated or insular variant.

associated with a higher rate of lymph node and distant metastases. The encapsulated variant has a well-defined capsule and is associated with an excellent prognosis (113, 114).

The diffuse sclerosing variant is more common in children and adolescents and is characterized by extensive replacement of one or both lobes by hyalinizing fibrous tissue and lymphoid cells (Figure 3.5). This has been described in 60% to 70% of children with papillary cancer that developed after exposure to radiation in the Chernobyl reactor accident (115–117). The neoplastic cells are arranged as small islands and are associated with numerous psammoma bodies and clusters of squamous metaplasia. The behavior of this variant is unclear. Most studies show a more aggressive course, while others suggest a better prognosis (118, 119).

There are variants of papillary cancer that have a worse prognosis. These include tall cell and columnar cell types (Figure 3.5). Both tumors are typically large at presentation (>5 cm). In the tall cell variant the height of the neoplastic cells is twice the width in the majority of the tumor (120, 121). The nuclear features are typical of papillary carcinoma, and the cytoplasm is abundant and eosinophilic. In the columnar cell variant, the nuclei are hyperchromatic and finely dispersed, rather than optically clear. Nuclear stratification and apical papillae are key hallmarks of this pattern (80). The nuclei are oval and lack nuclear grooves and intranuclear inclusions. The cells can be arranged around a fibrovascular core (122). Their appearance has been likened to secretory endometrium with subnuclear vacuoles (123). A very small minority of papillary cancers contains both tall cell and columnar elements (124). These variants can sometimes be suspected on FNA cytology and total thyroidectomy planned. The clinical differences are discussed in Chapter 6.

The Hürthle cell variant of papillary carcinoma must be distinguished from the more common variant of follicular carcinoma. By definition, more than 50% of the cells contain oxyphilic cytoplasm in association with papillary architecture and nuclear features of classic papillary carcinoma (125).

Foci of poorly differentiated carcinoma can be found in cases of conventional papillary carcinoma. These display increased nuclear polymorphism, mitotic activity, and solid or cribriform areas (Figure 3.5). These cases likely represent dedifferentiation with transformation to a more aggressive neoplasm.

Other variants are rare and include cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, and tumor with nodular fasciitis-like stroma. The pathologic hallmarks of some of these variants are shown in Table 3.4 (126–128).

Follicular Cancer

Follicular cancer accounts for 5–10% of thyroid malignancies in the USA. The proportion increases in regions of iodine deficiency (129). The mean age is about a decade older than in papillary cancer and there is a 3:1 ratio of women to men. The usual presentation is a thyroid nodule, but in iodine deficient countries this can be part of a multinodular goiter. These cancers are usually solitary. The morphologic spectrum of follicular adenoma to follicular cancer has been described above. FNA of follicular cancer shows a repetitive microfollicular pattern that is indistinguishable from follicular adenoma. Even with the advances in molecular biology there is no perfect method of making this distinction and surgical excision is necessary to establish the diagnosis. The pathological hallmarks for cancer are capsular invasion and vascular invasion (130). Two types are described, minimally invasive and widely invasive carcinoma. These have important prognostic and therapeutic implications. Grossly, minimally invasive tumors resemble follicular adenomas, as shown in Figure 3.6. In general, they are discovered in lobectomy specimens performed for clinically benign lesions. By definition capsular invasion requires complete penetration of the fibrous band, usually with a ballooning or mushrooming of the neoplastic cell group into the surrounding parenchyma (Figure 3.6) (130). The liberal use of leveled sections is often necessary to confirm this feature. In patients who have undergone a prior FNA, capsular invasion must be distinguished from iatrogenic capsular interruption by the needle tract. In this setting granulation tissue and hemosiderin-laden macrophages are helpful clues. Rosai and colleagues have enumerated the criteria for vascular intrusion in detail (33). The small or medium sized blood vessel is located

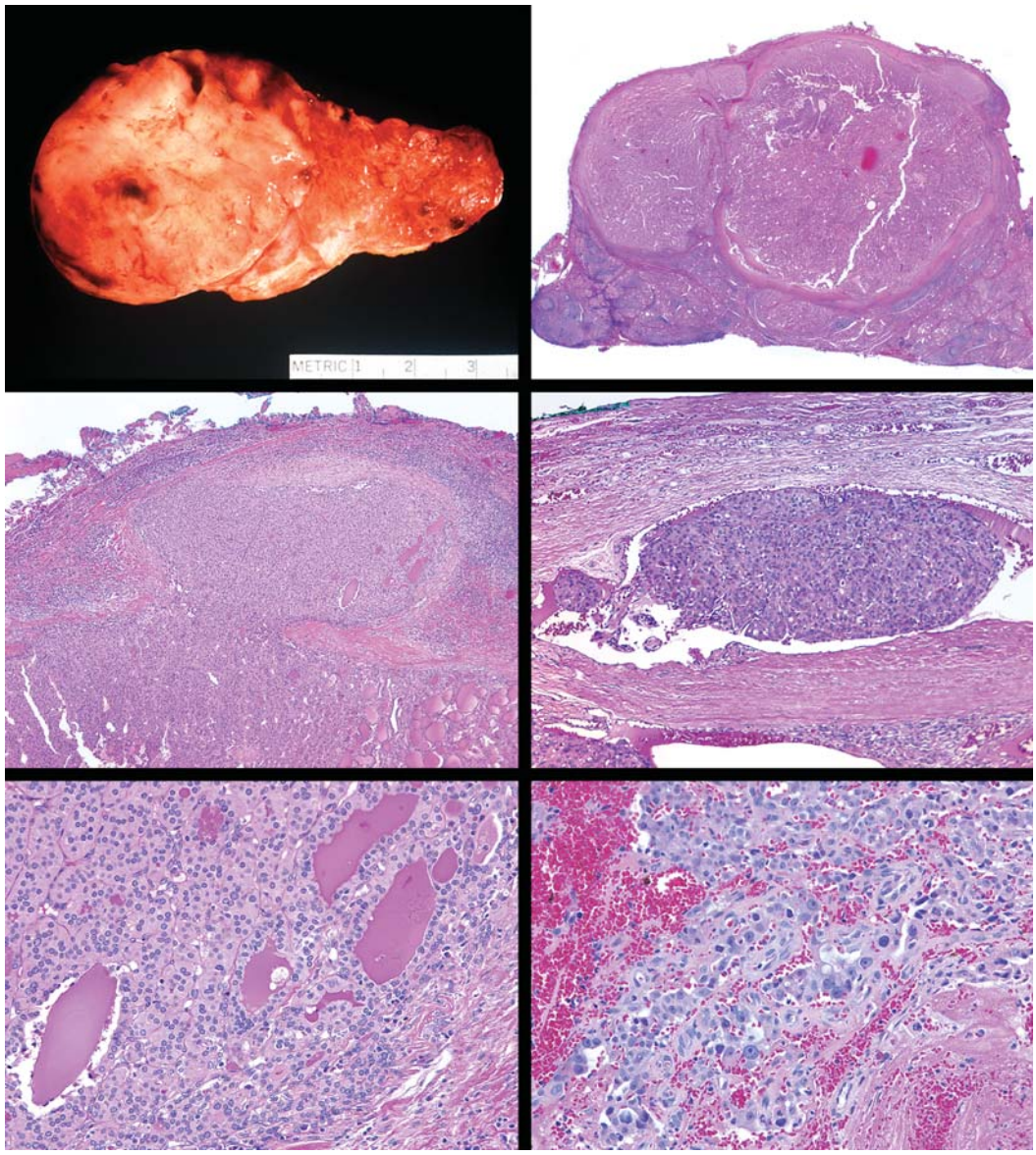

Figure 3.6. Follicular Carcinoma. Top Left: Gross image of sharply delineated type. Top Right: Low power magnification showing well defined capsule surrounding a microfollicular proliferation. Middle Left: Capsular invasion characterized by complete capsular penetration and mushroom expansion of the lesion beyond the capsule. Middle Right: Vascular invasion showing luminal plug of tumor cells within a vein. Bottom Left: High power magnification showing mixture of microfollicular and normofollicular structures. Bottom Right: Hürthle cell variant of follicular carcinoma showing necrosis and increased cytologic pleomorphism.

within the capsule or in the adjacent parenchyma and not within the tumor nodule. The plug of tumor cells is covered by endothelial cells, adherent to the luminal surface or admixed with thrombus (Figure 3.6). Widely invasive carcinomas demonstrate irregular borders grossly and reflect the infiltrative nature of the tumor. Lymphatic invasion and metastasis to regional lymph nodes is uncommon and usually represents the follicular variant of pap-

illary cancer. In countries where nodular goiters are common follicular cancers can go undetected and the first evidence of disease is in a metastasis such as a pathologic fracture. Sometimes the true nature of a follicular lesion is only established when there is a recurrence or with the presentation of a metastasis years after the thyroid was removed (131). We have seen a patient in consultation that had a "benign" nodular goiter removed and presented years later with a mass in her jaw that turned out to be a lytic metastasis of follicular cancer. Minimally invasive carcinoma is treated conservatively with subtotal thyroidectomy and close follow-up, and the outcome is excellent. In particular, tumors with only capsular invasion have a very low risk of recurrence or metastasis, while those with angioinvasive lesions have up to a 50% chance of recurrence or metastasis. Widely invasive carcinomas are treated aggressively with total thyroidectomy and radiolabeled iodine.

Hürthle cells are found in nodular hyperplasia, benign or malignant tumors, and also in inflammatory lesions, such as Hashimoto's thyroiditis and Graves' disease. Hürthle cell neoplasms can be adenomas or carcinomas and the pathologic differentiation can only be made by histopathological examination (132–134). The latter is classified as a variant of follicular cancer by convention, but there are rare examples of oncocytic papillary and medullary carcinomas (134, 135). Recently, an evaluation of mutations of the RET/PTC oncogene has allowed them to be subclassified as Hürthle cell follicular cancer (RET/PTC negative) or Hürthle cell papillary carcinoma. This accounts, in part, for the cases of some Hürthle cell cancers metastasizing to regional nodes (papillary carcinomas), whereas the classic case spreads to the lungs, skeleton, and liver (follicular carcinomas) (136). The patient is older and of female gender (3 or 4:1 predominance). Fine needle aspiration shows a preponderance of Hürthle cells with little colloid. Attempts to improve the cytological diagnosis have not been reproducible or completely successful (137). This is problematic since early diagnosis and treatment by total thyroidectomy is the optimal approach (138, 139). The cancer and its metastases almost never concentrate radioiodine. Infarction of a nodule after FNA is more common with Hürthle cell neoplasms (140).

Hürthle cell carcinoma is usually single, and there can be central necrosis. Invasion into surrounding tissues can occur and is associated with a poorer outcome (141). Histologically, the cells are large polygonal with a granular eosinophilic cytoplasm and prominent nucleoli (Figure 3.6) (142). Nuclear pleomorphism and mitotic activity including atypical forms can be present (143). Both minimally invasive and widely invasive patterns are reported. There has to be either vascular or capsular invasion for a diagnosis of cancer to be established, although some authorities use the third criteria of size of the mass (144, 145). This is based on recurrence or metastases developing in patients with large apparently benign tumors and probably represents minimally invasive tumors where the infiltrative focus was not sampled at the time of original diagnosis.

Poorly Differentiated Carcinoma: Insular Carcinoma

Carangiu and colleagues described insular carcinoma in 1984 (146). It remains unresolved as to whether it represents a distinct neoplastic category or an aggressive variant of follicular cell carcinomas. Since it is associated with an aggressive clinical course, poor prognosis, and has distinctive histopathological features, we think that warrants separate consideration. This tumor is uncommon in the United States. The patients are older and women are affected twice as often as men. The lesions are large (>5 cm) and display invasive margins grossly. In FNA preparations, the smears are cellular with single cells and small syncytial groups of hyperchromatic cells. The histopathological features include well-delineated nests or islands (insulae) surrounded by delicate fibrovascular strands, as shown in Figure 3.7. At high power magnification the neoplastic cells display small round nuclei, minimal pale cytoplasm and are arranged in small clusters. There are numerous division figures, tumor cell necrosis, and vascular invasion. The neoplastic cells show immunoreactivity for Tg, TTF-1, and cytokeratin but not calcitonin. Metastasis to regional nodes and distant sites such as bone and lung occurs and overall survival is around 40% at five years (146).

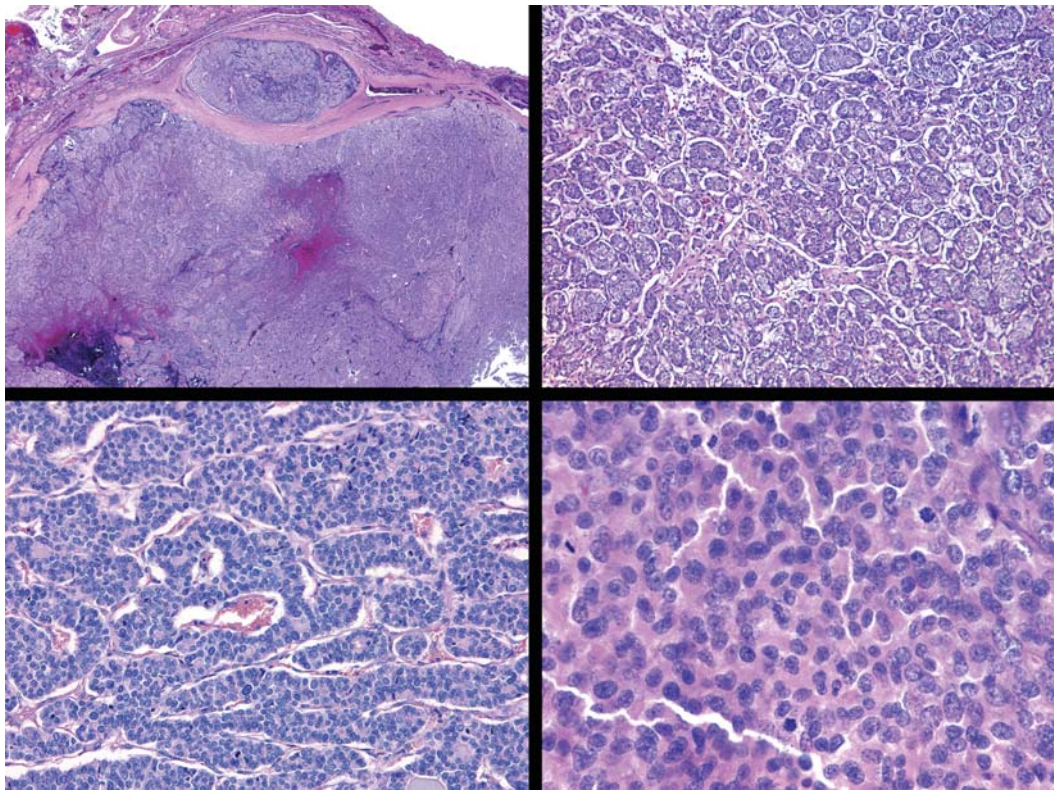

Figure 3.7. Poorly Differentiated Follicular Carcinoma. Top Left. Low power magnification showing invasive nature of this solid appearing neoplasm. Top Right. Scanning magnification showing insular arrangement of tumor cells into small nests and rounded clusters. Bottom Left. Insular carcinoma arranged in trabeculae and ribbons that are surrounded by delicate vascular elements. Bottom Right. The tumor cells display indistinct cell boundaries, eosinophilic cytoplasm and small round nuclei with nucleoli and numerous mitotic figures.

Anaplastic Thyroid Cancer

Anaplastic carcinoma is defined as a very aggressive neoplasm that demonstrates limited epithelial differentiation. Morphologic, immunohistochemical, or ultrastructural analysis confirms the epithelial nature of the tumor (147). They occur in older patients, but we have seen cases in patients younger than fifty-five years of age. They present with rapidly enlarging neck masses often with compressive symptoms such as dyspnea, dysphagia, and hoarseness caused by invasion of local structures. Fine needle aspiration of anaplastic cancer shows a very cellular pattern with necrosis, and the cells are usually pleomorphic and variable in size shape and appearance. There can be also osteoclastic giant cells and multinucleated cells. Mitoses are common.

Grossly, these malignancies are usually very large with infiltration of surrounding tissues, including muscles and trachea. There are abundant regions of necrosis and hemorrhage. It should be recognized that most of these cancers are unresectable. A variety of histologic patterns can be observed often with variation within the tumor itself. In some cases a spindled or nonkeratinizing epidermoid pattern is present, as shown in Figure 3.8. Other patterns include lymphoepithelioma-like carcinomas, pleomorphic cells admixed with multinucleated giant cells, and carcinomas containing heterologous mesenchymal elements, such as cartilage or bone (so-called carcinosarcoma). The neoplastic cells stain for keratin markers in around 50%

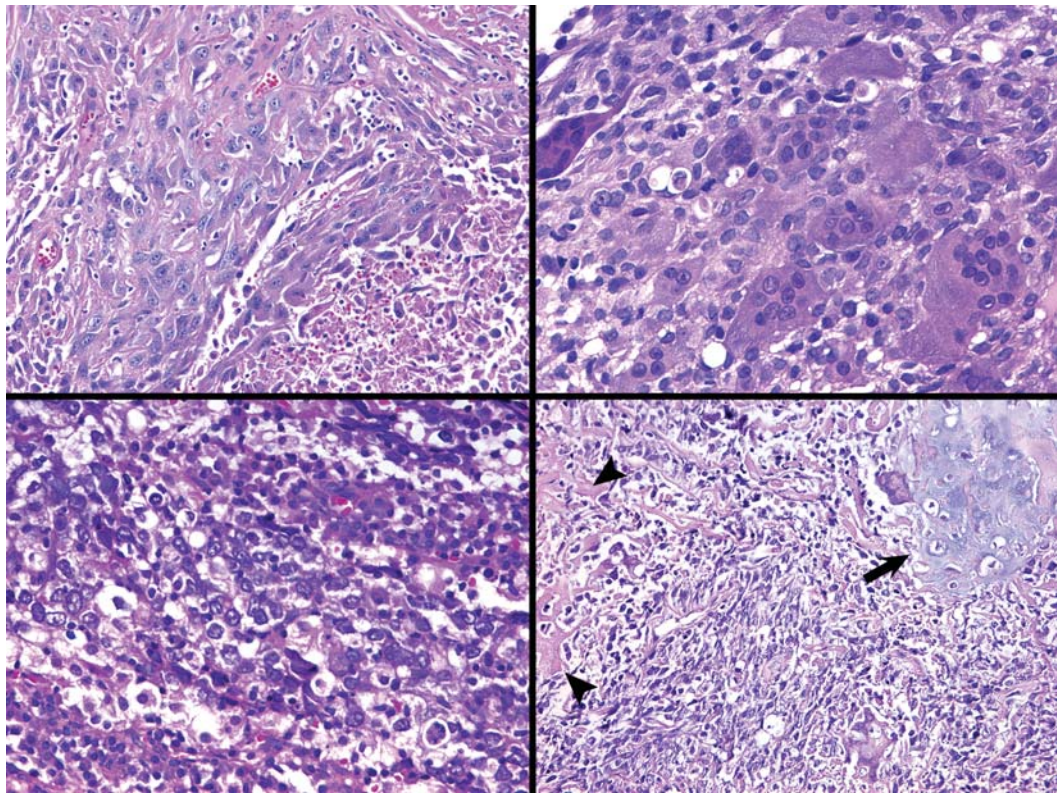

Figure 3.8. Anaplastic Carcinoma. Top Left: Squamoid or spindled pattern. Top Right: Anaplastic carcinoma with numerous osteoclast-like giant cells. Bottom Left: Lymphoepithelioma-like anaplastic carcinoma composed of malignant epithelial cells and a brisk host inflammatory response. Bottom Right: Carcinosarcoma pattern with malignant epithelial cells admixed with neoplastic cartilage (arrow) and osteoid (arrowheads).

of cases, but the staining distribution is patchy. There is no immunoreactivity for Tg or TTF-1. A combination of surgical intervention with adjuvant radiation therapy and chemotherapy are used, but most patients die within weeks to months of diagnosis.

The term "small cell anaplastic cancer" is now recognized as a misnomer and should not used. Using current immunohistochemical techniques these are classified as medullary cancer, malignant lymphomas, or occasionally as metastasis to the thyroid.

Carcinoma of C-Cell Origin: Medullary Thyroid Cancer

Medullary carcinoma is a rare form of thyroid gland malignancy accounting for less than 10% of malignancies. About 25% to 30% of patients with medullary cancer belong to families with familial medullary cancer or Multiple Endocrine Neoplasia type 2 syndromes (MEN 2A and 2B), and patients at risk for medullary carcinoma are screened for germ-line mutation of RET gene on circulating white blood cells. The genetic markers are discussed in Chapter 5 on etiology and Chapter 10 on medullary cancer. Over time mutations in the RET proto-oncogene cause malignant transformation of the cells (148, 149). Normal cells that contain the mutation develop C cell hyperplasia and then micro-cancers and finally clinically apparent disease (150–152). The larger percentage of patients have sporadic disease and diagnosed by cytological or histologic studies of a thyroid mass. Some investigators recommend measurement of calcitonin in all patients with a thyroid nodule to identify patients most at risk for this cancer (153, 154). Fine needle aspiration can suggest the diagnosis in many cases. The speci-

men is very cellular and cells are plasmacytoid, elongated, or spindle shaped. The cells do not form follicles but are arranged in clusters or syncytial clumps. The nuclei are variable in size, hyperchromatic with a stippled appearance. Some cells are binucleated or multinucleated and can be eccentrically displaced in the cells. Red granules within the cytoplasm and nuclear inclusions occur occasionally. Clumps of acellular finely fibrillar amyloid deposits are found in about 50% of the FNA specimens and demonstrate apple-green birefringence under polarized light in Congo red slides. The differential diagnosis includes Hürthle cell cancer, metastasis, and follicular variant of papillary cancer (155). Immunostaining for calcitonin, calcitonin gene related peptide, and carcinoembryonic antigen (CEA) are diagnostic (156).

The macroscopic appearance depends on whether it is familial or sporadic, as familial tumors can be bilateral or multifocal. The most common site is the lateral aspect at the junction of the upper 1/3 and lower 2/3 of the lobes. Sporadic cancers are usually solitary and can have a central fibrous scar and sharply circumscribed or infiltrative borders, as shown in Figure 3.9. The cells are arranged in lobules, trabeculae, nests, or sheets and are separated by amyloid deposits in about 80% of cases. The neoplastic cells have a number of different appearances such as uniform round, oval, and elongated or spindled nuclei. The chromatin is typically hyperchromatic with a "salt and pepper" pattern. Mitotic figures and cellular pleomorphism are infrequent. Immunoreactivity with neuroendocrine markers such as CD57, chromogranin, and synaptophysin, as well as calcitonin, TTF-1 and CEA are used to confirm the diagnosis. In sporadic cases when the cancers are large there is local invasion and infiltration of lymphatics. By this time, there are often clinically apparent metastases to regional lymph nodes or distant spread to the liver, lungs, and skeleton.

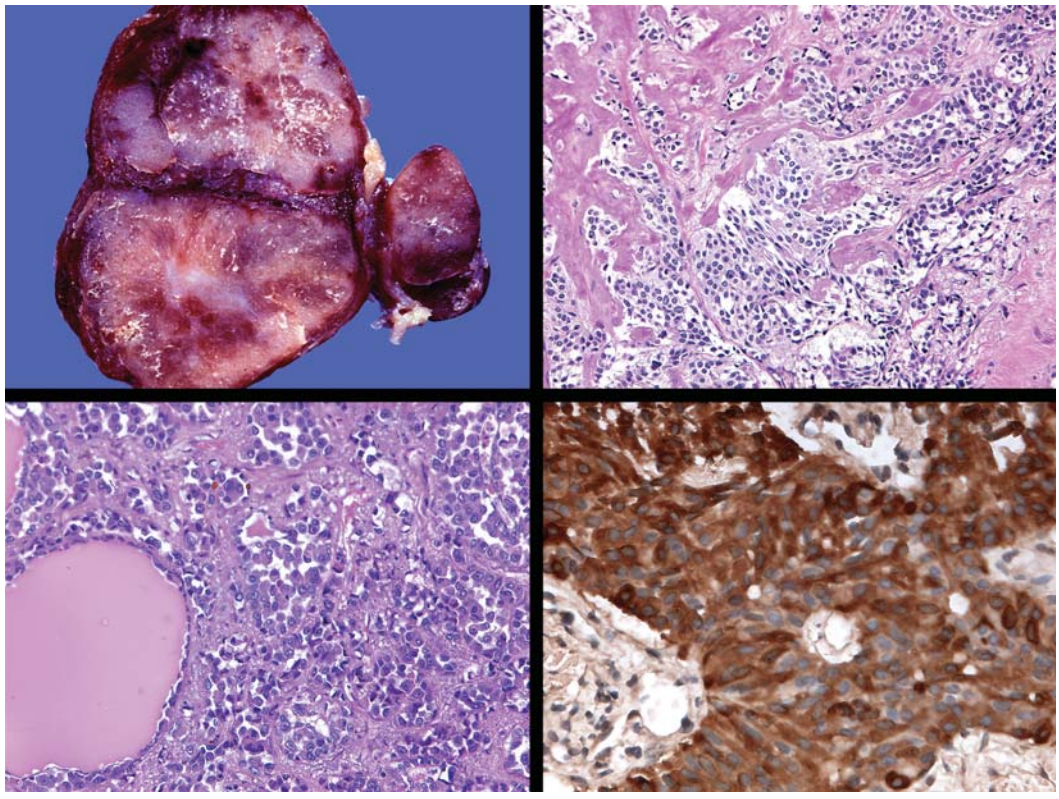

Figure 3.9. Medullary Carcinoma. Top Left: Gross appearance showing complete replacement of the thyroid lobe. Top Right: Classic appearance with nests and sheets of tumor cells embedded in amyloid stroma. Bottom Left: High power magnification showing epithelioid cells with abundant cytoplasm and eccentric nuclei. Bottom Right: Strong immunoreactivity for calcitonin.

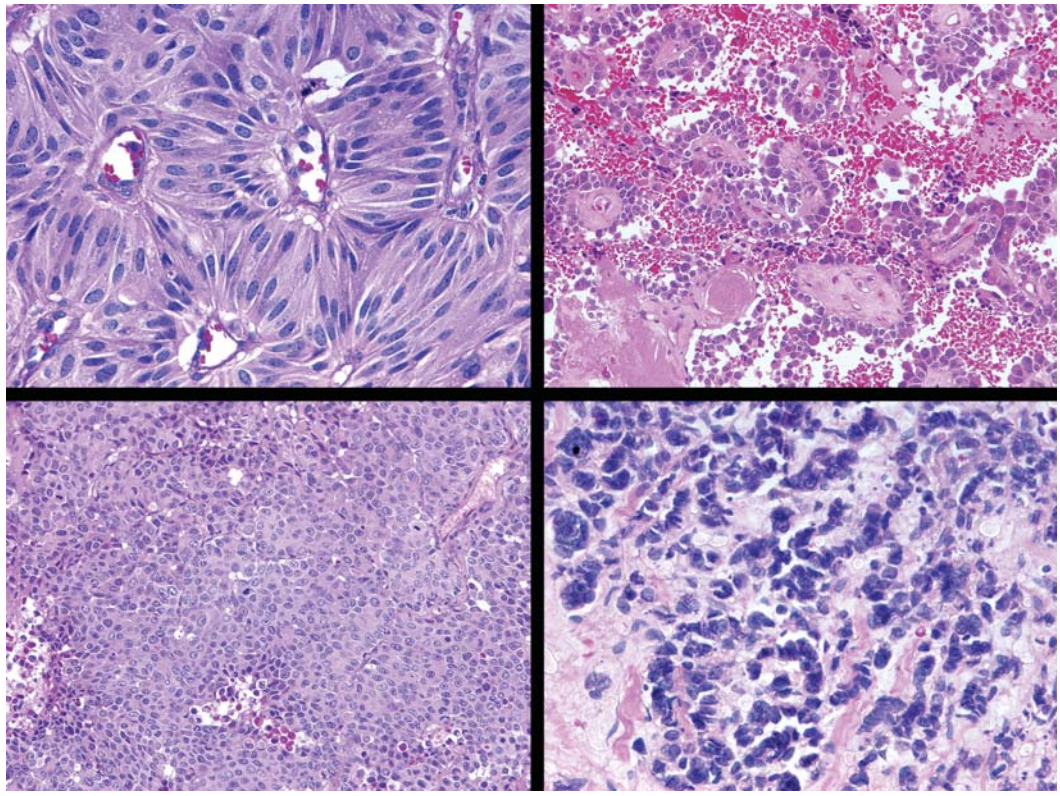

Figure 3.10. Selected Variants of Medullary Carcinoma. Top Left: Spindle cells arranged in carcinoid-like pattern. Top Right: Pseudopapillary pattern. Bottom Left: Solid pattern. Bottom Right: Small cell pattern.

The diagnosis of medullary carcinoma is often missed, in part because of the myriad of histologic patterns that it can display. These are demonstrated in Figure 3.10. These include carcinoid-like, pseudopapillary, solid, small cell, follicular, oncocytic, clear cell, pigmented or melanotic, squamous, giant cell, neuroblastoma-like, paraganglioma-like, and hyalinizing trabecular adenoma-like patterns (147). These variants do not portend prognostic implications. Our practice is to perform immunohistochemical staining using a panel of markers that include Tg and calcitonin for neoplasms having unusual appearances. A broad differential diagnosis is required because of these numerous patterns, including tumors of follicle cell origin, hematolymphoid tumors, and metastases.

Mixed medullary carcinoma and neoplasms derived from follicular cells can be present together (157, 158). These mixed follicular-parafollicular or differentiated carcinomas of intermediate type are rare. The histopathology reflects this admixture of cells types with solid areas intermixed with follicles. Both Tg and calcitonin immunoreactivity is present. They are usually aggressive tumors and can metastasize along lymphatic and hematogenous routes. Survival is variable (159, 160).

Miscellaneous Tumors of Divergent Origin

A number of unusual benign and malignant tumors can arise within the thyroid gland and display histologic features related to other cell types or structures. These include tumors of thymic differentiation, salivary gland-like tumors, paragangliomas, and teratomas.

There are several documented reports of intrathyroidal thymoma including one from our institution. This can be explained by the incomplete migration of the thymus during embryo-

genesis (161, 162). Spindle epithelial tumor with thymus-like element (SETTLE) occurs in children and young adults and presents as a painless mass (163–166). The main histopathologic features are the presence of nodular aggregates separated by dense fibrous bands. The nodules are composed of an admixture of spindled cells intimately admixed with epithelial structures, as shown in Figure 3.11. Both components are immunoreactive for cytokeratin but not CD5. These are thought to arise from intrathyroidal nests of thymic cells and their behavior is unpredictable. The term carcinoma showing thymus-like element (CASTLE) describes a low grade malignancy of adults that is composed of lobules of epithelial cells showing indistinct cell borders, vesicular chromatin and prominent nucleoli and surrounded by dense lymphoid infiltrates (Figure 3.11) (163, 167–169). The epithelial component is positive for cytokeratin and CD5 and the lymphoid cells are host T cells. Cases of malignant intrathyroidal thymoma are documented (170).

As previously described both hyalinizing trabecular adenomas and medullary carcinomas can resemble paragangliomas (Figure 3.11). Therefore the diagnosis remains an exclusionary one. Immunohistochemical stains are required to exclude medullary carcinoma (e.g., negative calcitonin and CEA since both tumors will show immunoreactivity with neuroendocrine markers). Thyroid transcription factor one and Tg immunostaining are observed in hyalinizing trabecular adenoma but not in paraganglioma. These are benign tumors and resection is curative (171).

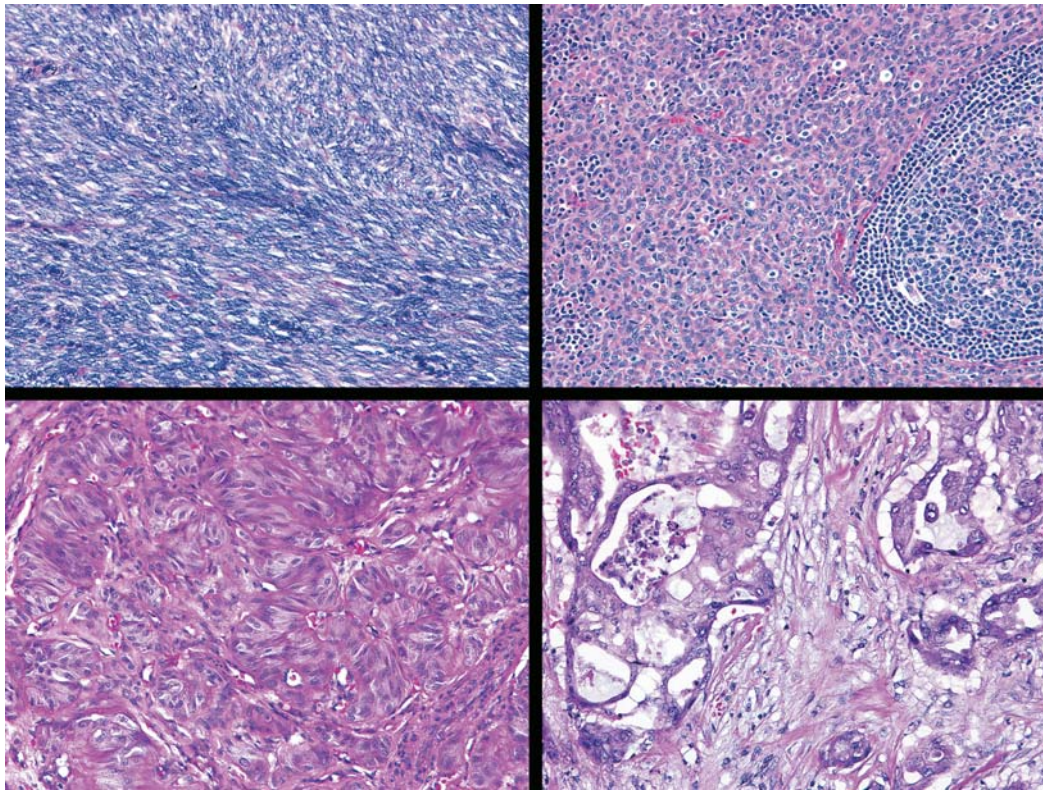

Figure 3.11. Tumors of Divergent Origin and Differentiation. Top Left: Spindle epithelial tumor with thymus-like differentiation (SETTLE) showing cellular spindled cells arranged in compact bundles (epithelial component not shown). Top Right: Carcinoma showing thymus-like differentiation (CASTLE) characterized by aggregates of epithelial cells admixed with reactive germinal centers. Bottom Left: Paraganglioma composed of uniform cells arranged in distinct nests and separated by fibrovascular septa. Bottom Right: Mucoepidermoid Carcinoma showing cribriform arrangement of glandular and epidermoid cells.

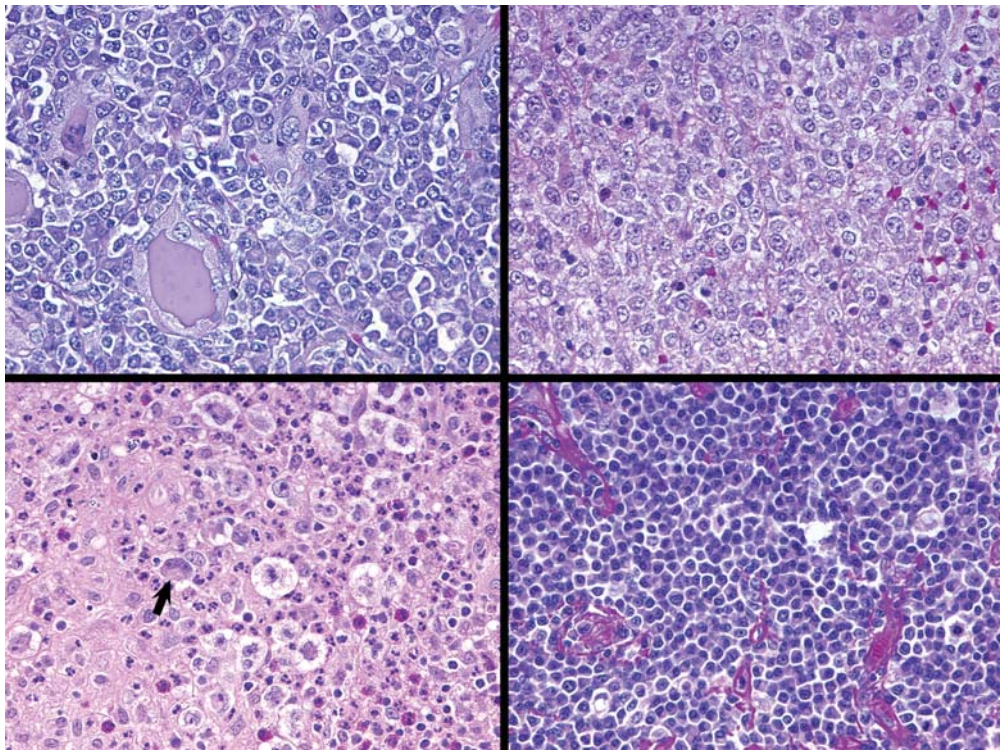

Figure 3.12. Hematolymphoid Neoplasms. Top Left: MALToma. Atypical small to medium lymphocytes with plasmacytoid differentiation infiltrating between follicles. Top Right: Diffuse large B cell lymphoma, showing complete replacement of thyroid by atypical large lymphocytes. Bottom Left: Hodgkin's Lymphoma with diagnostic Reed-Sternberg cell (arrow) admixed with eosinophils, plasma cells, and other inflammatory cells. Bottom Right: Plasmacytoma composed of mature plasma cells that demonstrated light chain restriction (not shown).

Mucoepidermoid carcinoma of the thyroid gland is a controversial entity, as some believe that these are variants of papillary carcinoma. These low-grade malignant tumors are present in middle-aged women, and while regional lymph node metastasis is common, distant spread is rare. They are composed of squamoid cells and mucin-containing glandular cells often arranged in a cribriform pattern (Figure 3.11). The surrounding stroma is richly desmoplastic and psammoma bodies can be present. The cells fail to stain for thyroglobulin (172). Sclerosing mucoepidermoid carcinoma with sclerosis is another uncommon variety.

Hematolymphoid Neoplasms

Malignant lymphoma arising in the thyroid accounts for about 5% of thyroid cancers and about 2.5% of lymphomas (173). The patient is usually a woman aged sixty or more years. There is a close association with pre-existing Hashimoto's thyroiditis for an estimated eighty-fold increased risk of lymphoma (174). The mass in the thyroid grows rapidly, often causing local pressure effects on the trachea and esophagus. Because diagnosis can be made by FNA with flow cytometry confirmation and treated with radiotherapy and chemotherapy there is less need for surgery today (175–177). The cell of origin is the B lymphocyte, and 10% to 30% of the cancers are classified as Mucosa-Associated Lymphoid Tissue (MALTomas) or extranodal marginal zone B-cell lymphoma of MALT, as shown in Figure 3.12 (178). The cells are similar to MALTomas arising in other organs with sheets of small to medium sized cells with irregular nuclear, dispersed chromatin, and pale eosinophilic to clear cytoplasm. Plasmacytoid differentiation is common (Figure 3.12). In some cases the distinction of MALToma and florid lymphocytic thyroiditis can be difficult. In a review of 119 cases FNA established the diagnosis in 90% of cases (179). When an FNA is sought,

material should be prepared for flow cytometry studies. Diffuse large B cell lymphoma is the most common type of primary thyroid lymphoma and accounts for 60% of cases. The atypical lymphocytes are medium to large and display vesicular chromatin and small nucleoli (Figure 3.12). When the lesion is confined to the thyroid it is stage IE extranodal disease). Large rapidly growing lymphomas can cause systemic symptoms of weight loss and fever. Immunohistochemical studies using monoclonal antibodies such as CD3, CD5, CD10, CD19, CD20, CD23, CD30, CD43, CD45, CD79a, and kappa and lambda light chain can define of the clonality of the cells. On gross examination the lesions are large 5 cm to 10 cm and the cut surface has been described like "fish flesh" (180). Histologically, the atypical lymphoid cells efface the thyroid and as the lesion increases in size there can be areas of necrosis and extension into surrounding soft tissue and muscle (180).

Hodgkin's lymphoma involving the thyroid is uncommon (Figure 3.12). Diagnostic Reed-Sternberg cells and immunohistochemical support should be sought to establish the diagnosis.

Plasmacytoma is a neoplasm of mature plasma cell differentiation and is rare in the thyroid gland. It is composed of mature and immature plasma cells (Figure 3.12) and must be distinguished from MALToma and inflammatory myofibroblastic tumor by immunohistochemical staining. It is associated with a favorable prognosis.

Mesenchymal Tumors of the Thyroid

Benign and malignant tumors of pure mesenchymal origin are uncommon in the thyroid gland. Follicular adenomas and anaplastic carcinomas can have metaplastic or heterologous components such as adipose tissue, cartilage, bone, and muscle but in these lesions the underlying process is an epithelial neoplasm (181, 182). Small series and case reports of benign tumors of pure mesenchymal origin include cavernous hemangioma, granular cell tumor,

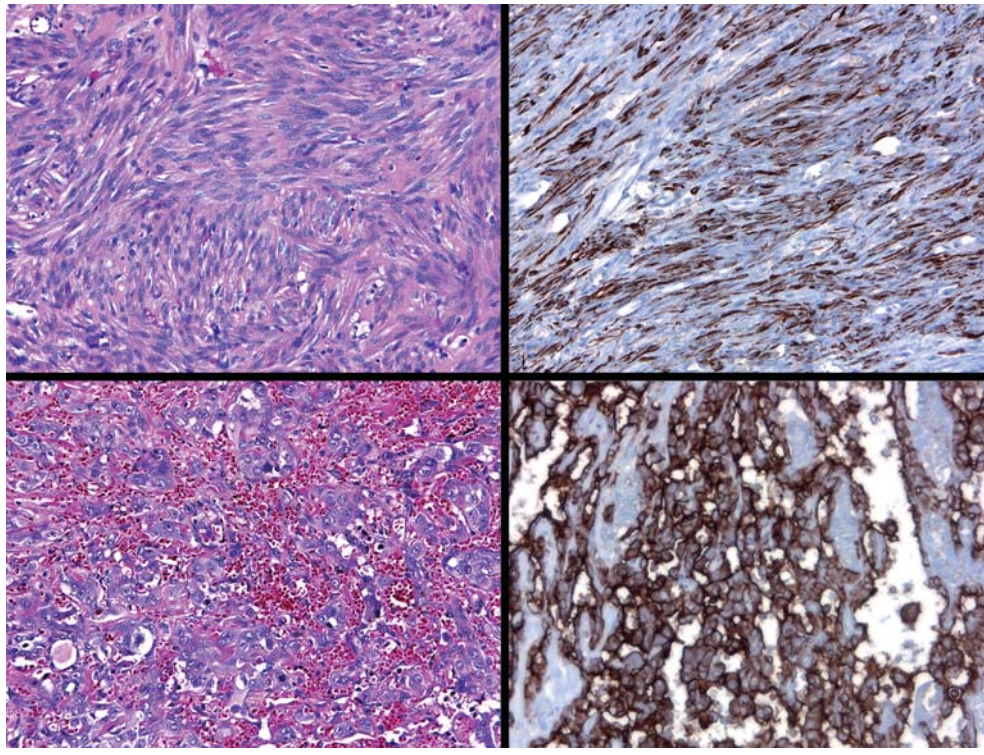

Figure 3.13. Mesenchymal Neoplasms of the Thyroid Gland. Top Left: Leiomyoma occurring in a two-year old child composed of bland smooth muscle cells. Top Right: Strong smooth muscle actin staining in leiomyoma. Bottom Left: Angiosarcoma showing malignant endothelial cells lining blood filled spaces. Bottom Right: Strong immunoreactivity for CD31 in angiosarcoma.

solitary fibrous tumor, and leiomyoma, as shown in Figure 3.13 (183–185). Angiosarcoma is the most important and common of the malignant tumors. A geographic predilection for the Alpine regions of Europe was reported (186). In a recent report of six patients from the Slovak Republic the tumors stained positively for vimentin and CD31 and were negative for thyroglobulin and calcitonin (187). Most patients are elderly and present with rapid enlargement of a preexisting thyroid mass. One patient with angiosarcoma and multinodular goiter was thyrotoxic possibly due to the increased vascularity or to release of hormone from destruction of thyroid by the sarcoma.

Grossly the tumors are large with abundant hemorrhage and necrosis. Even when they appear circumscribed, there is microscopic invasion of thyroid tissue. Microscopically, the characteristic feature is the anastomosing channels filled with blood and lined by enlarged, hyperchromatic nuclei. Mitotic figures are readily found. In some cases the neoplastic cells display abundant eosinophilic or amphophilic cytoplasm and large round vesicular nuclei and prominent nucleoli (Figure 3.13). The epithelioid appearance of angiosarcoma is a well-recognized pattern in its soft tissue counterpart. Immunohistochemical staining with endothelial markers such as CD31, CD34, and Factor VIII-related antigen is helpful. The epithelioid pattern can be immunoreactive for keratin markers and for this reason a panel approach to immunohistochemistry is always recommended.

Malignant teratoma is an extremely rare intrathyroidal cancer (188).

Metastases to the Thyroid

Metastases to the thyroid are not common in clinical practice (189). There is a separate chapter (12) concerning management. When a patient with a prior cancer develops a new nodule in the thyroid the possibility of metastases should be considered. Unless there is evidence of widespread metastases, it is likely that a fine needle aspiration would be obtained for a tissue diagnosis. The prior history should be made available to the cytopathologist. The findings might be characteristic of the previous cancer. In some cases, special stains might be necessary to prove that the nodule does not contain thyroid cells (Tg) and the cell of origin is non-thyroidal (glycogen, melanin, etc). Hematogenous spread to the thyroid is reported in a number of cancers including melanoma; carcinoma of the lung, breast, gastro-intestinal tract; and renal cell carcinoma, as shown in Figure 3.14 (190–196). Most of the patients are euthyroid but rapid destruction of the thyroid can result in release of excess thyroid hormone and the syndrome of carcinomatous pseudothyroiditis (197).

Special Issues of Thyroid Malignancies

Two important issues related to thyroid gland should be mentioned. Firstly, primary squamous cell carcinoma of the thyroid gland is rare. When a patient has a known cancer in a region close to or adjacent to the thyroid a new mass in the thyroid can be the result of direct extension. Seventeen cases were collected at the Mayo clinic and sixteen were squamous cell cancers of the larynx or esophagus (198). The combination of FNA sampling and knowledge of the prior history should establish the correct diagnosis.

A more challenging and controversial problem is the significance of thyroid epithelial elements within subcapsular sinuses of cervical lymph nodes (i.e., benign glandular inclusions or metastatic deposits). Heterotopic thyroid tissue can be found in lingual, tracheal, laryngeal, esophageal, pericardial, mediastinal, and cervical soft tissue locations and are not at issue in this discussion. Likewise parasitic nodules and displacement of thyroid tissue by instrumentation are usually resolved without difficulty. Rosai and colleagues enumerate guidelines and criteria that can help the pathologist in the classification of nodal inclusions (199). Firstly if there is involvement of more than a third of the node by epithelium or multiple nodes contain inclusions the changes are designated as metastases. Likewise, if the cytological features are those of papillary carcinoma or if psammoma bodies are present then metastasis is strongly favored. The diagnosis of benign inclusions is suggested if the clusters

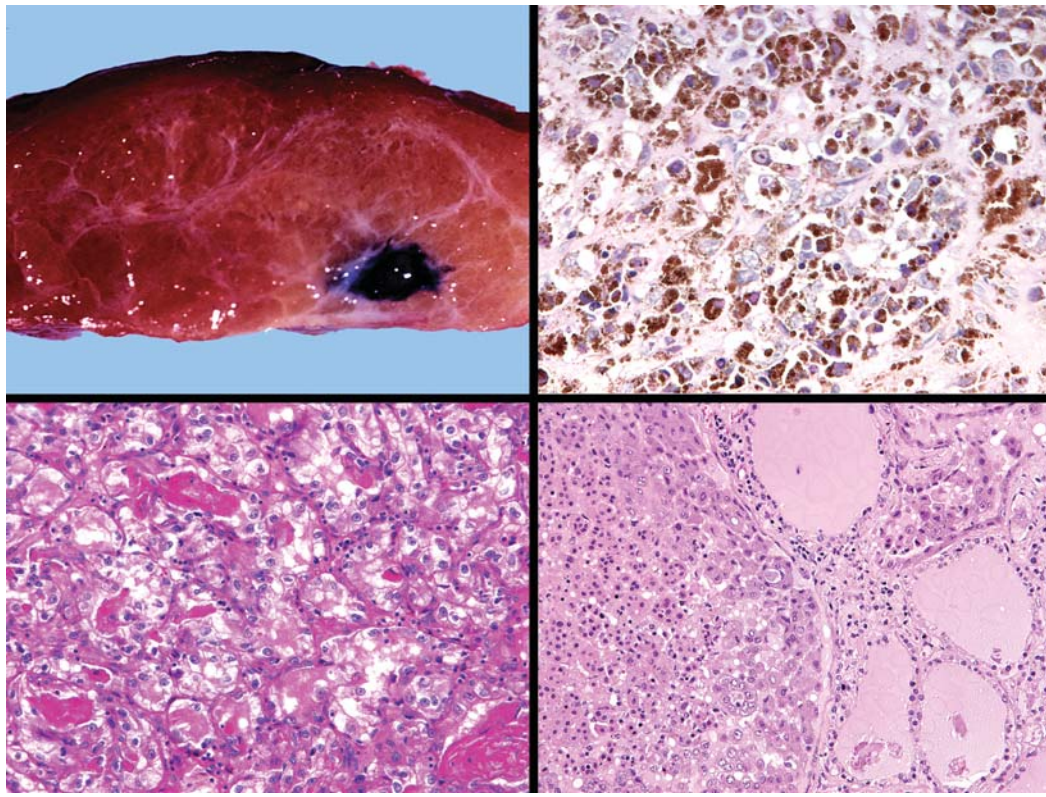

Figure 3.14. Metastatic Tumors Involving the Thyroid. Top Left: Gross picture of metastatic malignant melanoma, showing black circumscribed nodule. Top Right: Microscopic sections, showing abundant intracytoplasmic melanin in tumor cells of malignant melanoma. Bottom Left: Metastatic renal cell carcinoma with abundant clear cytoplasm. Bottom Right: Metastatic malignant mesothelioma within lymphatic spaces in the thyroid.

consist of a few bland follicular elements located in the subcapsular sinus. Multiple leveled sections should be carefully examined before a final diagnosis is rendered.

Summary and Key Points

There are approximately 23,000 new cases of thyroid cancer annually in the United States. More than 90% arise from follicular cells. The remainder develops from C cells (medullary cancer), lymphocytes (lymphoma), blood vessels (hemangiosarcoma) or metastasizes to the thyroid. The natural history of cancers of follicular cell origin cover the spectrum from essentially benign micropapillary cancers to aggressive anaplastic cancer. Using techniques of immunohistochemistry and molecular biology the specific nature of the cancer is defined and its behavior predicted. The accurate classification of thyroid neoplasms is essential for prognosis and management and the pathologist plays a central role in the management of these patients.

- Thyroid nodules are common, and about one in twenty adults has a clinically palpable lesion.
- Thyroid nodules are found in about one-third of people when they have an ultrasound or when their thyroid is examined at autopsy.
- Fine needle aspiration (FNA) and cytological examination usually determines when a nodule is benign or malignant and allows classification of the cancer.

- A microfollicular lesion on cytology is a cancer in 10% to 20% of cases.
- Nuclear features are important in the interpretation of FNA.
- There are 23,000 new cases of thyroid cancer annually in the United States and this number has tripled in thirty-five years.
- The follicular cell is the source of 90% of thyroid cancers and these are classified as papillary, follicular, and anaplastic.
- Papillary cancers are slow growing they are multifocal and spread via lymphatics to regional lymph nodes.
- The histology of classic papillary cancer is characteristic with fronds of follicular cells and nuclear features, such as Orphan Annie nuclei, pseudoinclusions and grooves.
- There are variants of papillary cancer including tall cell, columnar, and insular that are more rapid in growth and spread.
- Follicular cancer is usually single and they invade vessels and metastasize to distant sites, such as the skeleton and lungs.
- The presence of invasion of the capsule or vessels is necessary to diagnose follicular cancer.
- There are variants of follicular cancer including Hürthle cell cancer that have a worse outcome.
- Anaplastic cancer is very rapid in growth, and most patients do not survive six months.
- The cells in anaplastic cancer are bizarre giant and spindle shaped with much mitosis.
- Medullary cancers arise from C cells and they stain positively with antibodies against calcitonin.
- About 25% to 30% of medullary cancers are in families with MEN 2A or 2B or familial medullary cancer.
- Histologically the cells contain neurosecretory granules and there is amyloid in more than 80%.
- Lymphoma of the thyroid consists of a monoclonal aggregation of malignant lymphocytes and can usually be diagnosed by FNA and immunophenotyping and flow cytometry.
- Metastasis to the thyroid occur from primary cancers of the thyroid, lung, breast, melanoma, and gastrointestinal tract and are diagnosed by FNA with knowledge of the underlying disease.
- Rare cancers and sarcomas are identified and classified by their microscopic appearance and immunophenotyping.
- A close working relationship of clinician and pathologist is strongly recommended and personal review of slides can be of great clinical value.

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Chapter 4

Thyroid Nodule

Physicians managing patients with thyroid cancer almost certainly also manage patients with thyroid nodules. In contrast, many physicians caring for a patient with a thyroid nodule are not actively involved in the treatment of thyroid cancer. This chapter is designed for both groups of doctors. Most patients with a proven diagnosis of thyroid cancer originally present the doctor with a thyroid nodule. Thyroid nodules are very common, whereas thyroid cancer is not one of the most common cancers. It is important for the physician to differentiate the thyroid nodule that is cancerous from the large numbers that are not. Nodules found to be cancerous should be treated by surgery, whereas most patients with a proven benign nodule can usually be followed clinically. For these reasons it is necessary to discuss thyroid nodules in detail as a prelude to the management of thyroid cancer. There are many reviews addressing the topic of treating a patient with a thyroid nodule (1–18). Several professional societies have also published guidelines to aid clinicians manage the patient with a thyroid nodule (19–21).

It has been estimated that between 4% and 7% of adults in the United States have a palpable thyroid nodule (12, 22). Thyroid nodules are more common in women, and their prevalence increases with age (23). Unsuspected thyroid nodules are identified at autopsy in about 50% of patients (24). When normal people, or patients, with non-thyroidal conditions have imaging examinations of the cervical area, including the thyroid, nodules are noted in approximately 30% to 50% of exams. Increasingly this is a management problem, because many people have carotid ultrasounds, computed tomography (CT), or magnetic resonance imaging (MRI) for legitimate medical reasons, and unexpectedly, a thyroid nodule is identified. Hardly a week goes by that I am not contacted by my colleagues in radiation oncology. In the course of setting up radiation treatment for a woman with breast cancer, a thyroid mass is identified on CT that is being used for calculating radiation dosimetry and planning for treatment of the breast lesion. Similarly, I am referred many patients from cardiovascular physicians who identify a thyroid nodule while examining the carotid arteries by ultrasound. Also it is becoming more common to consult on healthy (wealthy) people who have treated themselves to a whole-body screening CT and are found to have a thyroid nodule (25–27). Probably the preceding statement applies exclusively to the United States. I presume the incidence of whole body CT screening of normal people would be inversely proportional to gross national product. Many of these nodules picked up by an imaging procedure cannot be felt, even when their presence and position are known. These are called incidentalomas. A recent editorial is entitled "thyroid incidentaloma, the ignorant in pursuit of the impalpable" (28). This is discussed further below.

In one study thirty-six out of 101 normal middle aged women (35.6%) were found to have abnormal glands by ultrasound examination

(29). Of these 47.2% had a single nodule and 38.9% multiple nodules. In a separate report, a nodule was detected in 44% of women and 42% of people of both genders who were older than 50 years, in a study involving 1,000 people (30). When a second ultrasound is obtained after some years, additional normal people who did not have a thyroid nodule will have developed one (31). The incidence of "incidentaloma" in 1475 Korean citizens was lower at 13.4%. (32) The lower percentage might be explained by higher dietary iodine. The likelihood that a nodule is benign is large (90–95%), but once it is recognized by palpation, or a screening test, the patient and physician usually want that confirmed. Nodular thyroids are more common in iodine deficient countries, and the percentages cited above are not representative for these regions.

There are many pathological causes that result in a benign nodule, these include: colloid nodule, adenoma, adenomatous goiter, cysts, cystic degeneration of pre-existing nodule, auto-immune thyroid disease such as Hashimoto's, subacute thyroiditis, and cancer. Cancers include papillary, anaplastic, medullary, lymphoma and metastases that can be diagnosed by fine-needle aspiration (FNA) and follicular cancer, which usually needs histological evaluation to make the correct diagnosis.

The approach to management involves attention to clinical features, biochemical tests, and additional investigations. These are reviewed in this sequence.

Clinical Features

Most thyroid nodules, whether benign or malignant, are asymptomatic and the nodule is usually palpated by a physician before it produces local effects. Occasionally the patient is the first to identify the lesion. The nodule is felt when washing, applying make-up, shaving, and so forth. Rarely a friend, more often one in the medical profession, notes the nodule or neck asymmetry in the patient at a social function. Most frequently, the nodule is diagnosed during a physical examination. A large number of referrals are from obstetricians and gynecologists who find the nodule when patients have routine gynecologic examinations or show up for their first antenatal check-up and the examination includes palpation of the thyroid. This is partly because women are more likely to have a thyroid nodule, and these are common in the twenty-to-sixty age group. A recent survey of obstetricians showed that 80% routinely screened pregnant women for thyroid disease, and 96% recognized the importance of ruling out cancer in a thyroid nodule (33). Mazzaferri makes the point that a man with a thyroid nodule is virtually never referred by a urologist (34).

A large nodule that has gone undiagnosed eventually causes symptoms such as pressure, difficulty swallowing or breathing, and a change in voice. In general, when there are such symptoms the likelihood of cancer increases. Pain in a thyroid nodule is uncommon. One cause is bleeding into a nodule, and I have encountered this in several patients, and many of the painful incidents have occurred when the patients are flying at a high altitude. This raises the question of reduced atmospheric pressure as the cause, but might just reflect the proportion of time we spend in the sky. These painful nodules due to bleeding all turned out to be benign. The differential diagnosis of a painful nodular thyroid lesion includes subacute thyroiditis, thyroid abscess (acute thyroiditis), and rapidly growing cancers such as lymphoma and anaplastic cancer. However, pain as a symptom of thyroid cancer is very uncommon. Painful neck conditions that can be confused with these thyroid disorders are pharyngitis, laryngitis, lymphadenitis, cellulitis, and phlebitis. These can coexist with a nodular thyroid. The finding of an asymptomatic nodule by imaging for other medical purposes has been addressed above.

Once a nodule is found the patient wants to know if it could be a cancer and what needs to be done? The primary physician asks the same questions. The key in most cases is to obtain a tissue sample by fine-needle aspiration (FNA). However, there are important clinical features that increase or decrease the risk of a nodule being malignant, as shown in Table 4.1. The age of the patient is important. A thyroid nodule in a child must be viewed at more risk than in an adult. In older patients, who are found to have a newly diagnosed thyroid nodule, there is a slight increased risk of cancer. When thyroid cancer occurs in an older patients the prognosis is less satisfactory, and it is in this age that rapidly growing and lethal cancers are found (35). Early

Table 4.1. Clinical features of that increase the possibility of a malignant versus a benign thyroid nodule.

Malignant	Benign	Evidence and discussion
Patient age less than 20 years Patient age more than 60 years	Age between 20 and 60 years	Cancer is most common in 30–50 age but there is an even higher incidence of benign nodules
Man	Woman	This seems paradoxical since thyroid cancer is commoner in women (2–3/1) but benign nodules are not so common in men
Nodule single	Multiple nodules	Note thyroid cancer can occur in multinodular goiter
Nodule hard Nodule fixed Nodule irregular	Nodule soft Nodule mobile Nodule smooth	
Nodule painless	Nodule painful	Painful lesions are rare, include thyroiditis and bleeding into nodule
Rapid growth of nodule Invasive Recurrent laryngeal nerve Esophagus Trachea Soft tissues	Slow growth No invasion	However, most thyroid cancers are slow growing
Lymph node metastases	No lymph node metastases	This confirms malignancy
Distant metastases Lung Bone Brain Soft tissues	No distant metastases	This confirms malignancy
Familial thyroid cancer Medullary including MEN syndromes Non medullary familial thyroid cancer	No familial thyroid cancer	Familial differentiated thyroid cancer is being recognized more often

diagnosis and expeditious treatment is required when the nodule in an old patient is cancerous. I would place the age range of concern at less than twenty years and greater than sixty years, but some authorities would use an upper age of fifty years.

A family history of thyroid cancer is important. Medullary cancer has been recognized as familial and this includes multiple endocrine neoplasia 2A and 2B (MEN 2A and 2B). (36, 37) Now it is increasingly recognized that familial non-medullary cancer, usually papillary cancer, is a real entity. (38) There are many reports of families with two or more members with papillary thyroid cancer. (39–42) Some of these families are remarkable in the number of members involved, making chance association numerically impossible. Some of the familial cancers are associated with familial polyposis, Gardner's syndrome, and Cowden's syndrome. This is discussed in detail in the Chapters 5 (Etiology) and 6 (Differentiated Thyroid Cancer).

A history of radiation over the thyroid is also important in increasing the probability of cancer. Most of the literature, up to the last fifteen years incriminated external radiation (43–46). Since the Chernobyl accident in 1986, there has been a rise in the number of thyroid cancers in patients who were children at the time of exposure. This increase has been blamed on internal radiation from radionuclides of iodine (47–49). This is presented briefly here and the topic is discussed fully in Chapter 5. About fifty years ago an association of thyroid cancer in children and young adults who had received external radiation for enlarged thymus "status thymomicus," acne, ringworm, scrofula, and so forth was recognized. A number of publications demonstrated that this was not a rare association. (50–55). The radiation dose was from as low as 10 rad (10 cGy) in the case of the dose to the thyroid from scalp radiation for ringworm. When the thyroid was in the radiation field in patients receiving thymic or skin

radiation the gland received several hundred rad (56–58). There was also an increased risk (18–20 times normal) of thyroid cancer after high dose therapeutic radiation to treat Hodgkin's disease (44, 59). We have recently described the association in patients with treated osteogenic sarcoma whose treatment did not include radiation over the thyroid (60).

Factors on examination that help determine the risks of a nodule being malignant are listed in Table 4.1. A single nodule is more likely to be malignant but there is increasing evidence that the incidence of cancer in a dominant nodule in multinodular goiter is not much less. In one surgical series, 8% of multinodular goiters and 15.2% of single nodules showed evidence of cancer (61). These differences just failed to be statistically significant. Therefore, a dominant, or a growing nodule in a multinodular gland should be investigated in the same way as a single nodule (62). Tollin et al. found fifteen of ninety-three patients with multinodular goiter had suspicious cytologic findings (63). These patients were referred for operation and five had cancer (5.2% of the total group or 33% of those with suspicious FNA). It is stressed that because of various selection biases the cancer incidence is usually higher in publications where operation is the end point.

Cancerous nodules are more likely to be hard, irregular, and fixed to adjacent structures. Nevertheless, 50% of hard nodules in the study of Hamming et al. were benign (64). Even when these clinical features are present the nodule can be histologically benign. Therefore most thyroid cancers cannot be differentiated from benign nodules by history and clinical examination. Invasion of the recurrent laryngeal nerve causes hoarseness and a change in the timber of the voice that is noted by the patient and by friends and family. Very few non-cancerous nodular thyroid conditions cause a change in voice. The presence of vocal cord paralysis was not due to cancer in 17% of cases, when the nodules were subjected to FNA (64). Hoarseness has been described as a complication of subacute thyroiditis and has occasionally been permanent (65, 66). The pain and systemic symptoms of subacute thyroiditis usually establish that diagnosis. It is also rare for benign thyroid nodules to be associated with clinically abnormal cervical lymph nodes, although that has been described in Hashimoto's thyroiditis. The diagnosis of thyroid cancer, usually papillary cancer, can be made by FNA of an abnormal lymph node. Very rarely the diagnosis is first found on biopsy of a distant site, such as the lung or bone. That establishes the diagnosis of malignancy with no equivocation.

Diagnostic Testing

This section deals with diagnostic tests to differentiate cancer from benign thyroid nodule. It also discusses follow-up of patients who have been proven to have a benign thyroid nodule. There is data supporting referral to a thyroid, or endocrine specialist, because that usually streamlines the work-up and the correct diagnosis is reached more expeditiously and with less expense (67). The thyroid status of the patient should be determined first because the approach in hyperthyroid and hypothyroid patients can vary from that in euthyroid patients. However, the great majority of patients with a thyroid nodule are euthyroid, and their management is numerically more compelling. The optimal test in euthyroid patients is FNA of the nodule with cytopathological interpretation of the aspirated cells. Many physicians refer patients for nuclear scintigraphy and ultrasound. As a means of emphasizing that these tests are not as cost effective as the primary diagnostic approach, they are discussed first, but the reader will constantly be reminded that FNA is the best and most cost-effective approach (68, 69). Historically many physicians have prescribed thyroid hormone to lower or even suppress thyroid stimulating hormone (TSH) with the intention or hope of causing the nodule to shrink. Apart from its use in a patient who is hypothyroid, the administration of thyroid hormone as a diagnostic test is not recommended. The role of thyroid hormone in the management of proven benign thyroid nodule is discussed at the end of the chapter. For diagnostic purposes, thyroid function tests, nuclear scintigraphy, ultrasound, and FNA are discussed in that order.

Thyroid Function Tests

Most patients with a malignant thyroid nodule are clinically and biochemically euthyroid. This

is confirmed by normal levels of TSH and free thyroid hormone thyroxine (FT_4). Some authorities recommend measurements of TSH alone, but the paired tests allow the integrity of the pituitary thyroid axis to be evaluated. When a patient with a thyroid nodule has thyroid dysfunction the likelihood of cancer is reduced and the diagnostic approach changes (Figure 4.1). First, let us deal with the less common hyperthyroid patient with a thyroid nodule. There are four probable causes. First, the nodule is an autonomous nodule producing an excess of thyroid hormones, secondly, the patient has Graves' disease and a non-functioning nodule, and thirdly, there is a rapidly growing cancer that damages follicles and releases thyroid hormones, and finally, the patient has Graves' disease with functioning nodules (Marine-Lenhart syndrome) (70–72). All are rare in particular the third and fourth possibilities.

An autonomous nodule is synonymous with "hot" nodule (because of its appearance on scintiscan), functioning nodule, or functioning adenoma. Scintigraphy is described in more detail in the next section, but the topic is introduced here to give continuity of management. There is evidence that a proportion of functioning nodules are caused by an amino acid substitution in the TSH receptor or the G protein messenger associated with the TSH receptor (73). The substitution results in the cell responding as if there was a constant TSH stimulus even when TSH values are low or suppressed. The importance of autonomous nodules in adults is that they are almost always benign. A scintiscan demonstrates whether the nodule is functioning and suppressing the remainder of the gland. If so FNA is not necessary (Figure 4.2A). In fact FNA in this situation is more likely to produce a microfollicular pattern, raising a 10% to 20% chance of follicular carcinoma. A priori, that is very unlikely and most series would place that risk of cancer in a functioning nodule at about 0.5% or less. Although the argument is being developed that FNA is the best first test in patients with a thyroid nodule that is not always the case in an adult with a suppressed TSH. However, some patients with autonomous nodules are euthyroid. In this small number of patients FNA would be the first test. One report of seven such patients showed no false negative results, but of course, these lesions are most likely benign (74). In contrast to the dogma that functioning adenomas are benign in adults, this is not so in children. A hyperthyroid child with a functioning

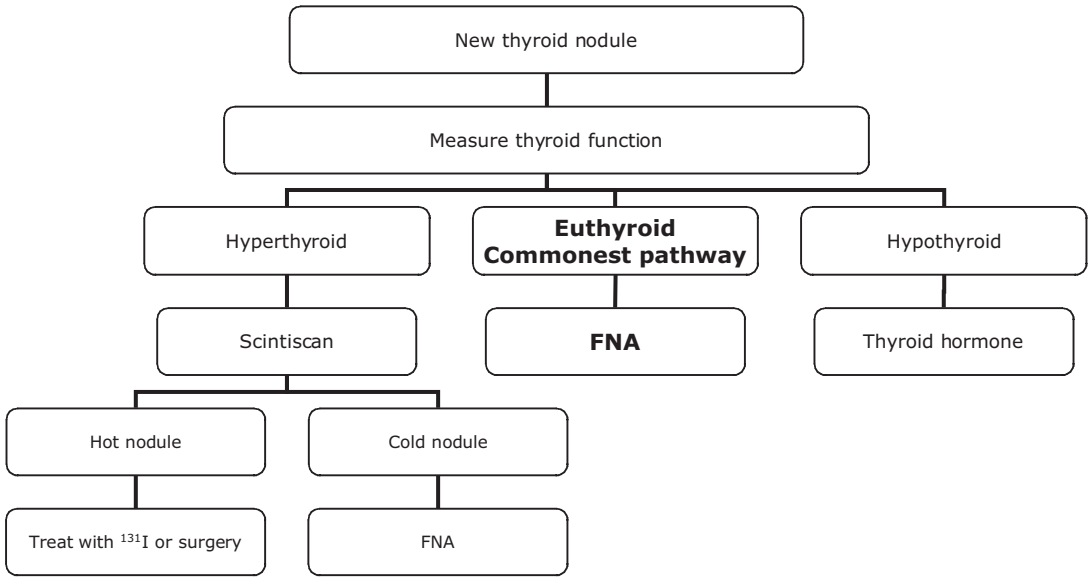

Figure 4.1. A simple algorithm for the management of a new thyroid nodule. Continuation of the algorithm is found in Figures 4.3 and 4.9.

nodule will be seen very infrequently in practice, but the potential for cancer in this setting is high (75). A functioning nodule in an irradiated neck should also be considered with a higher level of concern.

An alternative diagnosis is Graves' disease with a non-functioning nodule (Figure 4.2B). Reports indicating that 20% to 35% of patients with Graves' disease have thyroid nodules are greater than my experience (76). Nevertheless, in one publication, a nodule greater than 5 mm was identified by ultrasound in eighty-six of 245 patients (35%) with Graves' disease (77). Non-functioning nodules in Graves' disease can be benign, or malignant and an FNA of the lesion is important. There has been some debate whether cytological changes from Graves' disease can be difficult to separate from papillary cancer. This is even more questionable when the patient has received therapy with ^{131}I, since the radiation causes an increase in atypical cellular findings. A recent study of fourteen cold nodules in Graves' disease identified three that were suspicious for papillary cancer (78). They were all true positives. When a thyroid nodule is palpated in a patient with Graves' disease prior to treatment of the hyperthyroidism, I advise thyroidectomy rather than ^{131}I treatment. Therefore, one could question why is the FNA necessary? When the FNA suggests the non-functioning nodule is cancer the patient and their primary physicians are in no doubt that surgery is the correct approach. In addition, the surgeon recognizes that total thyroidectomy is the correct procedure. When the FNA is benign, total thyroidectomy is not necessary, but the surgeon should not leave a large volume of thyroid that could cause recurrence of hyperthyroidism. The association of thyroid cancer and Graves' disease is well documented (79, 80). Some authorities describe a higher incidence of cancer in non-functioning nodules in Graves' disease than is the case in euthyroid patients. A recent report described twenty papillary cancers and one follicular cancer in 139 nodules in 557 consecutive patients with Graves' disease

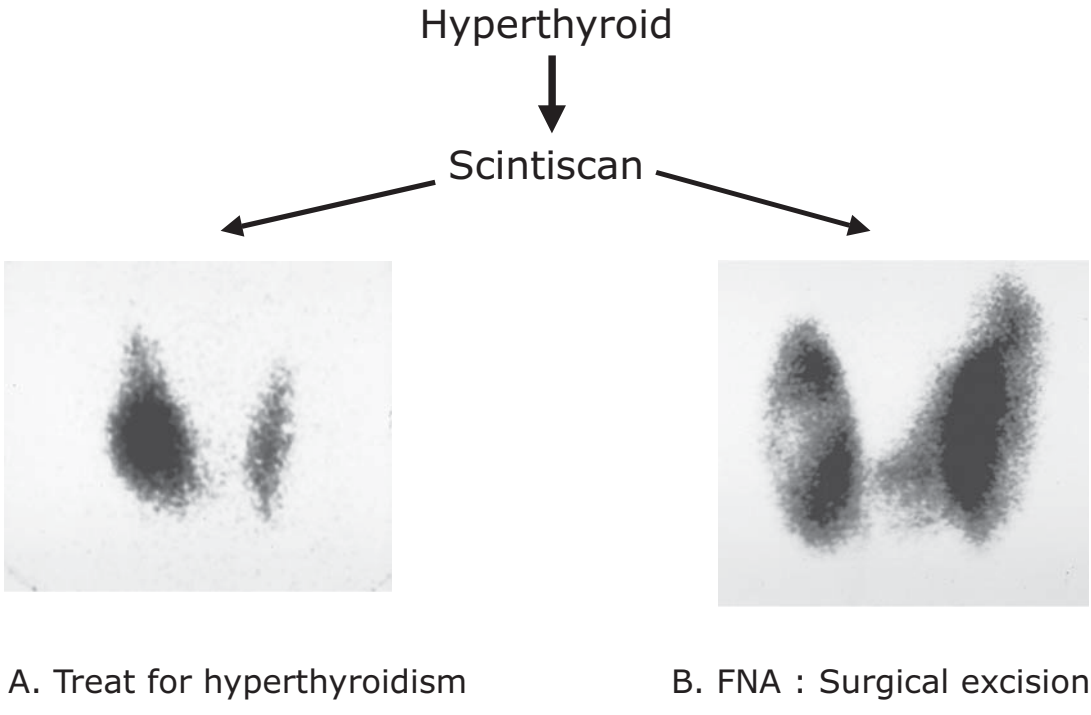

Figure 4.2. Thyroid scintiscans obtained 24 hours 200 μCi (7.4 MBq) ^{123}I in two patients who were mildly hyperthyroid, and each had a right-sided nodule. (A) shows a functioning nodule on the right with some suppression of normal thyroid. (B) shows a cold nodule in the right lobe of a patient with Graves' disease. The cold nodule was a papillary cancer.

(81). There is some evidence that thyroid cancer in patients with Graves' disease is more aggressive, due to the constant stimulus of thyroid stimulating antibodies (82) My experience with these patients is that the management and prognosis is no different from that in euthyroid patients.

Thyrotoxicosis due to release of thyroid hormone has been described in patients with rapidly growing anaplastic cancers, lymphoma, or a metastasis to the thyroid (72). This is called thyrotoxic pseudothyroiditis. Subacute thyroiditis (De Quervain's thyroiditis) is a more common cause of pain in the thyroid associated with thyrotoxicosis and the diagnosis is usually clinically obvious, and an urgent FNA is not necessary. However, when there are any unusual features an FNA is advised. These would include thyrotoxicosis and a sudden enlargement of a mass in a patient with Hashimoto's thyroiditis that could be a lymphoma. A new mass in a patient with a known non-thyroidal cancer could be a metastasis. Treatment of anaplastic cancer, lymphoma, and metastasis are quite different and are discussed in Chapters 10, 11 and 12 respectively.

Marine-Lenhart syndrome is the combination of Graves' disease and functioning nodules. The syndrome was first described by Charkes (83). The diagnosis is reached in a patient with Graves' hyperthyroidism who has an enlarged thyroid and nodules that are functioning autonomously on scintiscan obtained preferably with ^{123}I. There should also be evidence of thyroid auto-immunity. Two recent reports of Marine-Lenhart disease have been questioned as to whether the diagnosis was legitimate (84–86). The criticisms were that one patient did not have an ultrasound to prove that a nodule was actually present and the second patient had no evidence of a nodule on ultrasound. The diagnosis should include definitive proof of Graves' disease, a nodule or nodules, plus evidence that the nodules are functioning. When these criteria are satisfied there is no need for FNA, since the nodules have a very high probability of being benign.

In contrast when the patient is hypothyroid and has a nodule, one likely diagnosis is Hashimoto's thyroiditis. When thyroid hormone is prescribed to lower, or suppress TSH, the entire gland and the nodule can shrink. If this can be confirmed unequivocally by clinical examination and ultrasound, the patient should be followed by annual clinical examination and measurement of TSH. When the nodule does not diminish is size in response to a TSH that has been in the low normal range for three to six months, it should be biopsied (Figure 4.3).

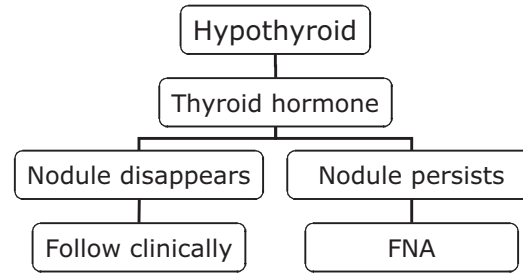

Figure 4.3. Continuation of the algorithm of the management of a single thyroid nodule from Figure 4.1.

Thyroid Scintigraphy

Thyroid scintigraphy is frequently ordered by primary care physicians who believe that the test can help differentiate a benign from a malignant thyroid nodule. This is not true, except in the case of functioning nodules causing hyperthyroidism. The reason for the misconception is as follows: Almost all cancers function less than normal thyroid. Thus, a scintiscan with a radioactive tracer to determine the functional ability of the nodule demonstrates that the cancerous nodule is non-functioning or "cold." Therefore, it could be concluded that scintigraphically "cold" thyroid nodules are malignant. The misconception is also due to the belief that most benign thyroid nodules are functioning or "hot." In fact, almost all benign thyroid nodules are non-functioning or cold on the scan. Let us assume the following hypothetical but fairly accurate possibilities: 5% of thyroid nodules are functioning by scintiscan and 5% of all nodules are malignant. The malignant nodules are for this example defined as non-functioning. We are now faced with 100 patients with a thyroid nodule, and the goal is to separate the 5 patients with cancer from the 95 with benign nodules. The second goal is to be as cost effective as possible. All patients could be referred for thyroidectomy without any preoperative tests, resulting in a definitive diagno-

sis for all. This would be neither cost effective nor risk effective.

In the 100 patients the a priori risk of cancer is 1:20. When we start with scintiscan, five patients are identified with a functioning nodule and can be excluded from further testing for cancer, since that is very rare in that situation. There now remain five cancers in ninety-five patients: That is a ratio of 1:19. If the scan costs $500, a total of $50,000 has been spent, and the five cancers have still not been identified. It is true that 5 patients have been diagnosed with functioning nodules and determined not to have cancer.

In a meta-analysis, Ashcraft and Van Herle found the specificity of scintigraphy to be 15% (11). This statistic is not persuasive for the role of radionuclide scanning. It is surprising that a survey published in 2000 showed 23% of North American thyroidologists and more than 60% of European specialists continue to order a scintiscan as part of the management of a 3 cm nodule in a forty-two year old woman (87).

When scintiscan is ordered there are several important technical factors. There are two commonly used thyroidal imaging agents that can have disparate results in the same patient. The radiopharmaceuticals are ^{123}I and Technetium pertechnetate ($^{99m}TcO_4$). The normal thyroid traps iodine by the sodium-iodide symporter (NIS), a topic discussed fully in Chapters 2 and 6 (88–91). Sodium-iodide symporter is designed to trap non-radioactive iodine (^{127}I). The trapped iodine is subsequently incorporated into thyroid hormones. Sodium-iodide symporter traps all nuclides of iodine; therefore, radioiodines are also concentrated and organified. Cancers express less NIS accounting for their cold appearance on scintiscan (92). The most appropriate radionuclide is ^{123}I, first because it is an isotope of iodine and second it delivers low radiation to the patient due to its relatively short half-life of 13 hours and emission gamma photons with an energy of 159 keV that is suited for high resolution images. Historically, ^{131}I was used but it delivers an unacceptably high radiation dose. Scans and uptake measurements can be made within hours up to one day after its oral administration. For patient convenience, I prefer a twenty-four-hour uptake and scan after 200 µCi to 300 µCi (7.4–11.1 MBq). When the patient is taking thyroid hormone (usually levo-thyroxine) that should be discontinued for a month before imaging. The antithyroid medication methimazole is stopped for five days and propylthiouracil for three days. No radiographic contrast should have been injected in the previous six to eight weeks. The thyroid trapping mechanism also concentrates the anions $^{99m}TcO_4$, ClO_4, and SCN (93). A radiopharmaceutical with a 6-hour half-life $^{99m}TcO_4$ is trapped but not organified. This radioactive tracer is concentrated in the thyroid but then it leaks out of the gland. Scans and quantitative measurements of $^{99m}TcO_4$ are made ten to twenty minutes after the intravenous injection of that radiopharmaceutical. In contrast, ^{123}I is trapped but is retained within the gland. If the scan is to be used diagnostically, a "hot" nodule is regarded as benign. A proportion of nodules are "hot" on $^{99m}TcO_4$ scan but "cold" when scanned with ^{123}I. This pattern actually increases the probability of cancer. The recommendation is to obtain an ^{123}I scan when $^{99m}TcO_4$ shows the nodule to be functioning. Because cold nodules on $^{99m}TcO_4$ scan can be functioning on ^{123}I, some authorities advise ordering an ^{123}I scan if a cold nodule is identified on $^{99m}TO_4$ scan. The circular reasoning is obvious. Although disparate images are not common there must always be concern whether the $^{99m}TO_4$ scan is providing the "correct" result or not. A typical "hot" and "cold' nodule on ^{123}I scans are shown in Figure 4.4 A and C. It has been emphasized that autonomous functioning nodules in adults are usually benign. Not all "hot" nodules are homogeneously hot. Some undergo cystic degeneration and there is a cold area within the hot nodule (Figure 4.4 B). This has been likened to a "fish-eye" or an "owl-eye" and is also usually benign (94–96). It is important that the physician responsible for interpreting the scan palpates the patient's neck and correlates the clinical and scintigraphic findings. Small radioactive markers placed at the edge of the nodule become superimposed on the scan, confirming that what is felt is what is imaged (Figure 4.4 B). The importance of scintigraphy in a hyperthyroid patients with a nodular goiter and of the physician correlating clinical and scintigraphic information is shown in Figure 4.5 A, B and C. The patient, a sixty-eight year old with T_3 toxicosis, had two palpable nodules but on scan the findings were of a multinodular goiter with two cold nodules in the left lobe. A marker placed over a nodule in

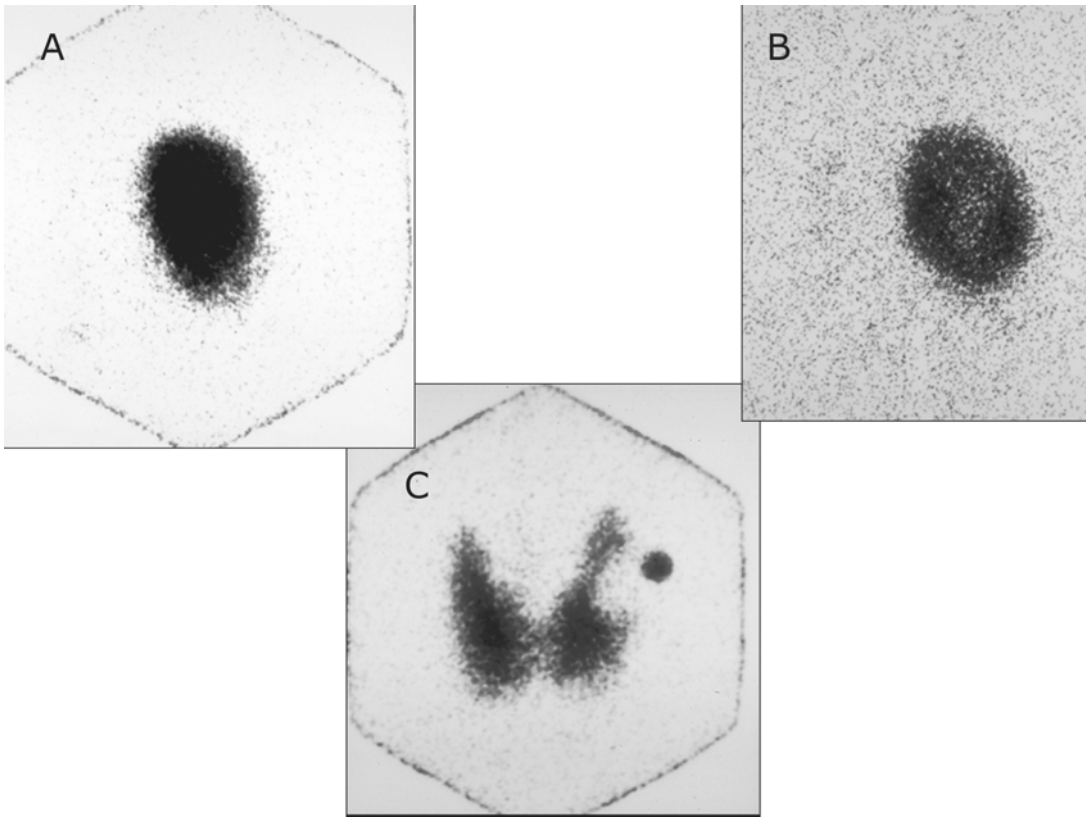

Figure 4.4. Three scintiscans of solitary thyroid nodules all made 24 hours after 200 μCi (7.4 MBq) ^{123}I. (A) is a functioning nodule causing complete suppression of the remainder of the thyroid. (B) is a functioning nodule with central degeneration (owl's eye or fish eye sign). (C) is a cold nodule with a marker placed by the physician on the palpable nodule to prove that the clinical lesion and scintigraphic findings correlate.

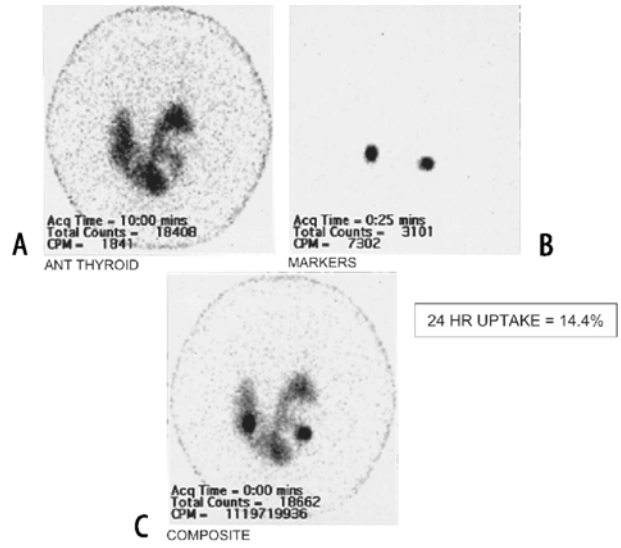

Figure 4.5. A multinodular goiter in a mildly thyrotoxic 68-year-old woman: (A) was obtained 24 hours after 200 μCi (7.4 MBq) ^{123}I. (B) shows markers placed on palpable nodules, and (C) is a composite image. There are two cold nodules in the left lobe that turned out to be cancer.

the left lobe indicates the lesion is non-functioning. At surgery she had a papillary cancer (follicular variant) and Hürthle cell cancer in the left lobe and multiple benign nodules throughout the remainder of the thyroid. The need to place markers on the gland is confirmed by the case of a woman who was found to be thyrotoxic. Her endocrinologist thought she had a goiter. After she became hypothyroid due to antithyroid medication, she was given levo-thyroxine for years. When I saw her she was still thyrotoxic and stopped the levo-thyroxine and her free hormones remained high and TSH suppressed. There was a large nodule palpable in the right lobe and a smaller one on the left. ^{123}I scintiscan showed the large nodule to be nonfunctioning and the left one to be functional, as shown in Figure 4.6 A, B and C. At operation (total thyroidectomy) she had a follicular variant of papillary cancer in the right lobe. She also was treated with ^{131}I and now has no evidence of cancer. In contrast, Figure 4.7 is a scintiscan of a toxic multinodular goiter.

Many non-nuclear medicine physicians who are used to ultrasound, CT, and MRI assume that scintigraphy provides similar resolution. This is not the case. Images produced with a gamma camera are superior to those made with a rectilinear scanner (97). The resolution is about

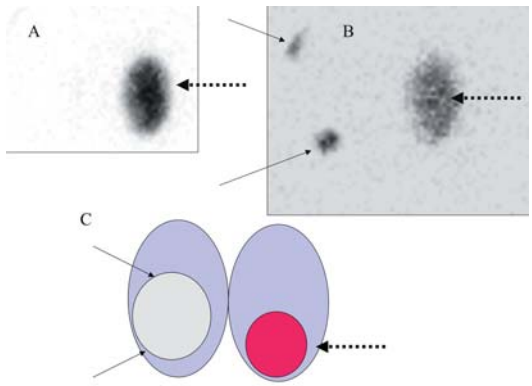

Figure 4.6. Demonstrating a functioning nodule in the left lobe, Figure 4.6A is a scintiscan obtained 24 hours after 200 µCi (7.4 MBq) ^{123}I. Figure 4.6B is the same image with markers at the upper and lower edges of a larger palpable nodule in the left lobe. This nodule is non-functioning and was cancer by FNA and surgical pathology. Figure 4.6C shows the finding schematically with the cold nodule as a white sphere and the hot nodule as a red sphere.

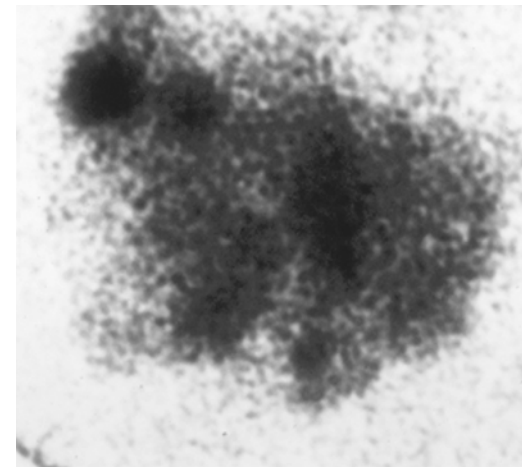

Figure 4.7. Scan obtained 24 hours after 200 µCi (7.4 MBq) ^{123}I showing a "toxic" multinodular goiter.

10 mm to 15 mm when a gamma camera fitted with a pinhole collimator is used. In addition, about 50% of the emitted photons are attenuated by 5 cm of tissue. This is called the half-value thickness. That means that 50% of the photons pass through a 5 cm nodule on the anterior aspect of the thyroid and 50% are lost by interaction with the tissues. Therefore, on scintiscan that nodule would appear to have reduced uptake, but it would not be devoid of activity. Most nodules are considerably smaller than 5 cm and either cannot be identified by scintiscan or cannot be neatly defined as functioning or non-functioning. Sometimes it is possible, by obtaining oblique and lateral views, to image the nodule at an angle that allows its identification and function to be defined (98, 99). Some investigators have introduced tomographic imaging (Single Photon Emission Computed Tomography, SPECT. Note in Europe this is called SPET.), and others have evaluated positron emission tomography (PET) to improve resolution. Using SPECT with a pinhole collimator, Krausz et al. identified twenty-one additional nodules in thirteen patients with multinodular goiter compared with planar images (100). Wanet et al. found the resolution improved to 6 mm to 7 mm with 3 mm and 4 mm pinhole tomography compared to 15 mm for planar imaging (101). Most nuclear medicine facilities have SPECT cameras, but few have the availability of SPECT with a pinhole collimator. Chen et al. also showed

improved resolution in nodules and multinodular goiter with SPECT (102). Single photon emission computed tomography adds considerably to cost, and its added value is questionable. Positron emission tomography is even more expensive and its justification in evaluation of thyroid nodule is hard to support as discussed below.

Cancer-Seeking Radiopharmaceuticals

Radiopharmaceuticals that are trapped by cancers including Thallium (^{201}Tl), ^{99m}Tc-Sestamibi (sometimes represented as MIBI) and ^{99m}Tc-Tetrafosmin have been evaluated to determine whether malignant nodules can be identified by high uptake (103–108). These agents have been reported to have value in differentiating benign from malignant nodules when the FNA is nondiagnostic and when cytopathology demonstrates a microfollicular or Hürthle cell lesion (109). Although in several reports the authors are enthusiastic the number of patients in each studied is usually small (20–40 patients) and frequently there is a selection bias. When 70% to 80% of cancers and 20% to 40% of benign lesions are positive with one of these agents how does this help when, a priori, more than 90% of nodules are benign? The added expense and low specificity do not support their use. Several examples make this clear. In one of the larger studies, Koizumi et al. employed early and late imaging using ^{201}Tl (110). There were 101 cancers and 145 benign lesions. Forty-two percent of the benign lesions would have been interpreted as cancers. The protocol employed 37 MBg to 74 MBq (1–2 mCi) ^{201}Tl injected intravenously and imaging was started after ten minutes and repeated at two to three hours. In an attempt to differentiate malignant from benign Hürthle cell lesions Boi et al. employed early and late ^{99m}Tc-Sestamibi scintigraphy in twenty-four patients; fourteen turned out to have cancer (111). The investigators conclude "MIBI scintiscan has no value in differentiating malignant from benign Hürthle cell thyroid neoplasms." This contrasts with the conclusion of Sharma et al. who employed thirty and 120 minute sestamibi images and state the technique in combination with FNA is helpful (112). However thirty-three of their seventy-seven patients (43%) had cancer, which is considerably higher than usual, and they do not report on the FNA results. FNA alone would be more cost effective. The same authors had previously reported superior results with $^{99c}TcO_4$ flow images in determining whether a nodule is cancerous (113). In a different investigation ^{99m}Tc-Tetrafosmin scintiscans were obtained at five, thirty, sixty, 120, and 180 minutes after injection of the radiopharmaceutical (104). Seventy-nine patients were imaged and sixty had thyroid surgery with nineteen patients having cancer. The authors were unable to differentiate those patients from the forty-one with benign thyroid masses. Should a clinician wish to use one of these ^{99m}Tc labeled radiopharmaceuticals, the dose of both MIBI and Tetrofosmin is 370 MBq to 740 MBq (10–20 mCi) of ^{99m}Tc administered by intravenous injection and imaging conducted within thirty minutes and after a delay of two to three hours.

Gallium-67 (^{67}Ga) has been used for imaging cancer including lymphoma and is discussed again in Chapter 11 on primary lymphoma of the thyroid. The first studies using ^{67}Ga for thyroid nodules are from three decades ago (114). In one experiment the ratio of uptake of ^{67}Ga to blood was higher in cancer than benign nodules; however, the highest ratio was in Hashimoto's thyroiditis (115). ^{67}Ga has shown increased uptake in benign thyroid conditions including adenomatous goiter in addition to Hashimoto's. (116). Therefore there is no role for ^{67}Ga in this setting.

The somatostatin analogue octreotide (^{111}In-pentreotide) is taken up by benign as well as malignant thyroid conditions (117).

Overall tumor-seeking radiopharmaceuticals do not help determine whether a thyroid nodule is benign or malignant. The agents and the tests are expensive and when two or more sets of images are required at early and delayed times this blocks the use of a gamma camera for an unacceptable time. Their use is not encouraged.

There are also a few reports of PET differentiating benign from malignant thyroid nodules, but the numbers of patients studied are small, and the incomplete separation of cancerous nodules from benign are not encouraging. For example, Adler et al. found two of three thyroid cancers were PET positive, but four of six benign lesions were also PET positive (118). Uematsu et al. studied eleven patients and four

with cancer showed high uptake on PET scan, but one benign lesion did as well (119). There might be a small role for PET in helping to differentiate benign from malignant when the FNA shows a microfollicular pattern (17). Positron emission tomography is usually positive in cancer. A simplistic cost benefit analysis would depend on the cost of PET versus surgery. In our institute PET (PET/CT) is billed at $5,000. If we assume 20% of microfollicular lesions are malignant $25,000 would be billed to find one cancer. This is approximately the charge of surgery. The established use of PET in selected patients with proven thyroid cancer is discussed in detail in subsequent chapters (6, 10, 11, and 12).

In summary, standard thyroid scintigraphy has been used for decades in the management of patients with thyroid nodules. Most patients with thyroid nodules are euthyroid and most thyroid nodules are non-functioning on scintiscan. Most thyroid nodules are benign, therefore scintigraphy is not recommended, since it has very low specificity and is not cost effective. Scintigraphy does have a role when the patient is hyperthyroid. Tumor seeking agents do not help.

Thyroid Ultrasound

Many investigators, including my colleagues and myself, are engaged in determining whether ultrasound can differentiate benign from malignant thyroid nodules (120). Ultrasound has superb resolution, it needs no patient preparation, it is relatively inexpensive, it does not take long to complete, it delivers no ionizing radiation, and it causes no risk. These make it acceptable to most patients. However, does ultrasound help establish a tissue diagnosis? Ultrasound is very valuable as an aid to FNA, and this will be expanded in the next section. Our group has also used ultrasound intra-operatively to identify small abnormal nodes (121). I find it valuable to follow the dimensions and characteristics of thyroid nodules. Ultrasound provides objective criteria whether the nodule is enlarging or not. Quadbeck et al. used ultrasound annually to evaluate 109 patients with nodular thyroid disease (122). They determined that half of the nodules increased in volume by more than 30% in three years. The slow rate of growth indicates that studies on the growth of thyroid nodules should not be limited to six or twelve months. Readers are also reminded that volume of a sphere is related to the cube of the radii: $4/3 \cdot \pi \cdot r^1 \cdot r^2 \cdot r^3$ (or $\pi/6 \cdot d^1 \cdot d^2 \cdot d^3$). However, the question under review is, does ultrasound establish the pathologic nature of the nodule? Ultrasound can determine whether the nodule is a pure cyst. That is very unlikely to be cancer, but it is very rare. Nodules surrounded by a "halo," as shown in Figure 4.8 are also more likely to be benign but this appearance does not exclude cancer (123, 124). Interpreting the information in the opposite direction indicates that an absence of a halo increases the risk of a nodule being malignant (125). A "comet tail" appearance is a reliable indicator of abundant colloid and when there is a homogeneous appearance with several comet tails this is a benign colloid nodule (126). In a study of fifty-one nodules proven subsequently by histological to be cancer, malignancies were more likely to be solid and hypoechoic, as shown in Table 4.2 (120). The presence of microcalcifications plus an absence of a "halo," although not present in all cancers, raise suspicion of malignancy, as shown in Figure 4.9. The

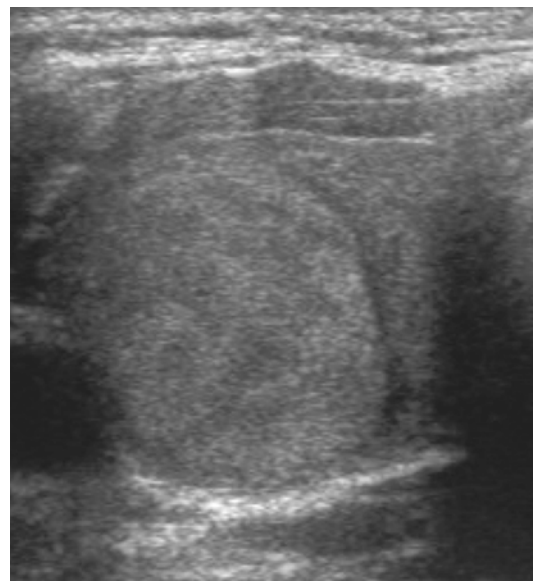

Figure 4.8. Ultrasound of a proven benign thyroid nodule: There is a halo and no microcalcifications. The image was provided by Dr Larry Chow, Radiology Stanford University School of Medicine.

Table 4.2. Sonographic features of papillary thyroid carcinoma.

Sonographic	Findings (n = 51)*	No. of Cases	%
Echotexture	Hypoechoic	43	84.3
	Mixed hypoisoechoic	3	5.9
	Isoechoic	3	5.9
	Hyperechoic	1	2.0
Internal Architecture	Solid	43	84.3
	Solid with cystic elements	4	7.8
	Predominantly cystic	3	5.9
Margin	Well-defined	25	49.0
	Ill-defined	25	49.0
Contour	Smooth and round	46	90.2
	Irregular with sharp angulations	4	7.8
Halo	Absence	46	90.2
	Presence	4	7.8
Vascularity	Intrinsic	33	64.7
	Perinodular	12	23.5
	Hypovascular	5	9.8
Calcifications	None	25	49.0
	Microcalcifications	20	39.2
	Coarse calcifications	4	7.8
	Peripheral calcifications	1	2.0

* One case presented as isolated lymphadenopathy and thus demonstrated none of the above findings.

association of enlarged cervical lymph nodes with a transverse diameter greater than 1 cm on the same side as the thyroid nodule increases the probability of cancer, as shown in Figure 4.10. In another investigation, Frates et al. graded vascularity of nodules from 0 to 4 (127). They found 42% of the 32 cancers were solid and had 4 plus vascularity, but 14% of solid hypo-vascular nodules were malignant. Ultrasound is very helpful in the management of patients with thyroid nodules but it does not establish whether a nodule is a cancer, or not.

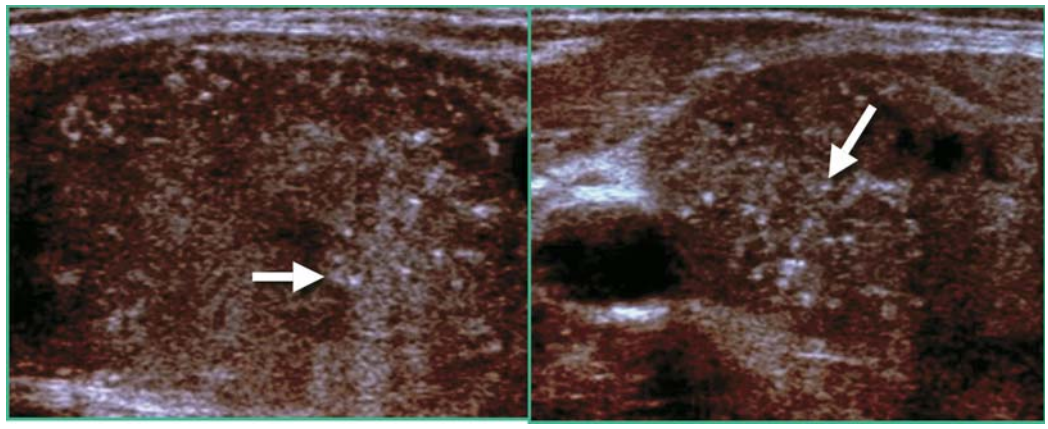

Figure 4.9. Figure shows an ultrasound of a thyroid nodule showing microcalcifications (arrow) that increase the risk of the lesion being papillary cancer. The image was provided by Dr Larry Chow, Radiology Stanford University School of Medicine.

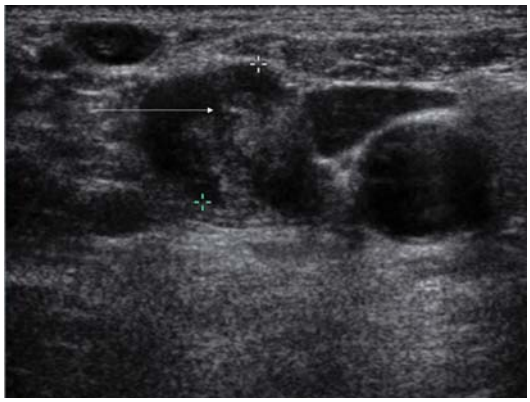

Figure 4.10. Demonstrates enlarged suspicious cervical lymph nodes in a patient with a nodule that was malignant. The image was provided by Dr Larry Chow, Radiology Stanford University School of Medicine.

Ultrasound is valuable in multinodular goiter by demonstrating a nodule that is dominant, or one with suspicious characteristics. Ultrasound defines the optimal site for FNA. There are reports of the use of ultrasonic contrast agents to aid in diagnosing the pathology of thyroid nodules. Doppler vascular pattern before and the time activity curve after an intravenous injection of 2.5 g of Levovist was analyzed (128). Although the authors report a higher diagnostic sensitivity in practice, this is seldom used.

Fine Needle Aspiration

The best and most cost effective test to determine whether a nodule is cancerous is fine needle aspiration (68, 129). I will review both the results of several large series and also how to interpret the results and to manage the patients based on the results. Prior to those topics there is a brief discussion on techniques, however, I stress that although I conducted large numbers of FNAs in the past, I now rely heavily on my colleagues from pathology and radiology. It is important that there is a dedicated core of physicians conducting and interpreting the FNA, including a thyroid specialist, a cytopathologist skilled and interested in interpretation of thyroid aspirates and a radiologist for ultrasound assisted FNA of difficult to feel lesions, or multinodular glands. Over time the members of the group learn from their colleagues, and the sum is greater than the parts. A minimum number of one to five procedures monthly have been recommended for the operators to maintain skills (130). There are several excellent reviews on FNA (131–138). Guidelines have also been published (139).

Techniques

It is important to explain the procedure to the patient. An appropriate consent form should be signed by the patient and witnessed. Most authorities have the patient lie supine with the neck extended, and a pillow under the neck is helpful in making the gland more prominent. It is necessary to identify the nodule and to feel comfortable that its edges can be felt and immobilized. There is debate whether local anesthetic is of value, but if more than two passes are planned then I recommend infiltration with 0.5 ml to 1 ml lidocaine. Some physicians, usually pathologists state that the infiltrate makes the nodule more difficult to palpate and hypothesize that it might have an adverse effect on the cytopathological interpretation. There is little to support either of these concerns. It is helpful if the patients hold their breath while specimens are obtained. Most clinicians use a small bore needle, such as 22 gauge to 27 gauge, and a 10 ml syringe. There are several commercial syringe holders that allow suction to be applied with one hand, while the nodule is stabilized by the other hand. After the needle is inserted in the nodule, suction is applied to the syringe to about mid-way. Two or three passes are made within the nodule. The goal is to have some tissue appear in the hub of the needle. The syringe is removed from the needle and then reattached, and the needle extracted from the nodule using the syringe. When the needle is not detached and the syringe and the combined apparatus is removed while negative pressure is continuously applied, the specimen can be sucked into the barrel of the syringe, and it becomes difficult to expel the cells onto the glass slide. With the sample in the needle rather than inside the barrel of the syringe it is simpler to express a drop onto a glass slide and carefully spread it in the manner of a blood smear preparation. Often several slides can be made with one aspiration. In the case of vascular lesions, the specimen might be bloody, which makes interpretation difficult. In this case, a 25-gauge

to 27-gauge needle can be used without a syringe and the specimen is obtained by capillary pressure.

Alternatively the patient can be seated and the aspiration conducted as described above. Because many thyroidologists prefer to palpate the thyroid by standing behind the patient, some also prefer to place the needle in the nodule – positioned as if to palpate the gland. A scalp vein set can be used, and an assistant in front of the patient can apply negative pressure with the syringe to obtain the sample. Yet another variation has been described where the thyroid physician places the needle in the appropriate site and the pathologist obtains the sample. This might raise concern about who is reimbursed, or do both physicians bill for services? My other concern about this approach is the logistic of having both present in the same place at the same time; however, these authors report on 37,895 patients so that problem must be minor (140). I also worry that one physician might stick the second physician with a needle. As an aside, one fellow in training at Stanford did stick herself at the end of the procedure. This was not reported by the fellow for 24 hours and was not noticed by the attending physician. When the information was transmitted, the patient had to be recalled and tested for blood borne infectious disease that could have been dangerous to the fellow. The patient happened to be a Scot who had recently immigrated to California, and as I anticipated, all her serum tests were negative. Great care must be taken to avoid needle sticks.

Most physicians prefer to employ a small-bore needle and 23-gauge to 25-gauge needles are used most frequently. One report indicated better samples were obtained with a 21-gauge needle (141). The physician conducting the procedure should become comfortable with one size (e.g. 23), but be willing to use another as dictated clinically and discussed below. The procedure is relatively non-invasive when a skinny needle is employed. Complications of FNA using 21-gauge to 25-gauge needles are uncommon but include bleeding, bruising, pain, and infection. There are rare reports of the trachea being transgressed. There are also rare reports of hematoma formation. In the event of bleeding or swelling, pressure over the site for several minutes should suffice. We usually have the patient remain in the department for several minutes to ensure the situation is stable. We have reported a patient who had growth of cancer along the needle track from an FNA conducted elsewhere. The lesion presented as a small warty skin lesion that surprisingly was papillary cancer (142). Several decades ago, when FNA was being introduced and was not yet standard practice in the United States, the potential for tracking cancers was frequently cited by surgeons as a reason against FNA. This is very rare and we could find less than ten reported cases. However, since starting this chapter several weeks ago and revising the text, I have encountered two patients each with a small subcutaneous lesion on the side of their original cancers. To the fingers, these were a few millimeters in diameter, firm and mobile, and felt like undissolved sutures. They were excised by minor surgery and both contained cancer similar to the original pathology. The lesions were not in lymph nodes. The most likely explanation was deposition of a few cancer cells in subcutaneous tissue during the FNA.

Core biopsy was popular for some time; however, it is more invasive and the results are not better than FNA. There is a higher possibility of complication such as bleeding. One report suggests that combined FNA and core biopsy are complementary (143). Another publication indicates that large bore sampling has a role in microfollicular lesions (144). From eighty-two that were suspicious by FNA, twenty-one were inadequate using a large bore needle, thirty were microfollicular, and half had atypia. Therefore the procedure did not help in fifty-one of eighty-two instances (62%). Of the remainder, twenty-one were judged to be benign and ten cancer. At operation, there were three cancers (14%) in the "benign" group" and eight cancers (80%) in the malignant group. Overall it is hard to see how this is an improvement. The results of FNA are usually sufficient.

Thyroid nodules in children are more likely to be malignant. However, the majority are benign. FNA has a role in children. The youngest patient I have conducted an FNA on was a three year old who turned out to have medullary cancer. Young children can be restrained; older children can be treated as adults. The age group four to ten is the most difficult. In one report, FNA was conducted in forty-one children, and two cancers were identified (145). There was no false negative result. There are several references

of the value of FNA in children with thyroid nodules and this is reviewed in depth in Chapter 7 on pediatric thyroid cancer (146).

Interpretation

Results of FNA are usually reported as benign, cancer, suspicious for cancer, indeterminate and nondiagnostic, or inadequate. Only one example is shown comparing the cytology and histology of a case of papillary cancer, which is Figure 4.11. Pathological findings are discussed and illustrated in detail in Chapter 3. An inadequate interpretation usually means there are insufficient cells for a confidant report to be reached. When the nodule is solid, this terminology is correct. However, when the nodule is predominantly cystic, the nodule is drained and becomes impalpable, and, in the cytopathologist reports, there are a few bland follicular cells and macrophages containing hemosiderin; is this inadequate? Some authorities accept that is a benign cystic nodule. This difference in interpretation is one cause for different statistics reported in the literature concerning the value of FNA. Although the incidence of cancer is low in thyroid cysts, when the lesion grows back after aspiration and when there are atypical cells consideration for lobectomy is correct. One series found that 12% were cystic papillary cancers (147). Although an inadequate or nondiagnostic aspirate should be repeated, the incidence of cancer is low. In one series, less than 2% (148). A reason for this is that cancers contain cells that are less tightly bound together and therefore an inadequate FNA is unlikely.

A benign FNA should contain several groups of follicular cells, there is usually abundant colloid and the follicular cells are bland. The specific appearances in benign and malignant thyroid nodules with illustrations are presented in detail in Chapter 3. Normal cells should have no nuclear atypia. The cells should have normal size and there should be no variability in size. Since most thyroid cancers are papillary, features such as papillary structures, Orphan Annie nuclei, nuclear inclusions, reduced colloid, and psammoma bodies establish this diagnosis (149). Fine needle aspiration can make diagnosis of medullary cancer and

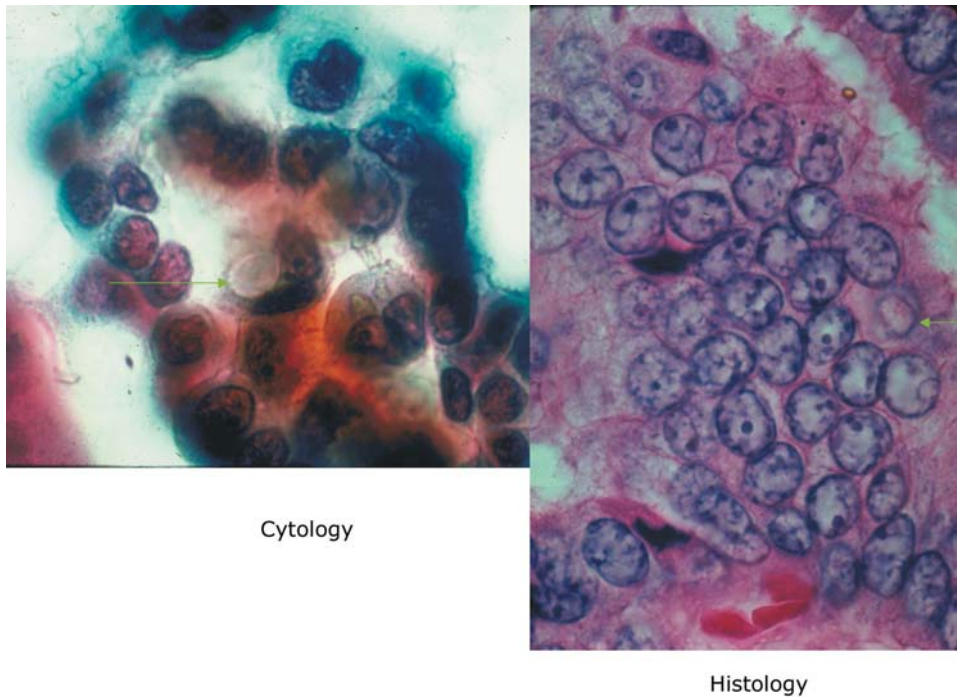

Figure 4.11. Figure shows cytology and histology of a typical papillary cancer.

Table 4.3. Results of several series of fine needle aspiration with more than 300 patients.

Reference	Number of FNA	Sensitivity %	Specificity %	Unsatisfactory %
Altivilla et al. [275]	2,433	71	100	16
Amrikachi et al. [133]	6,226	93	96	29
Baloch et al. [276]	662	92	84	11
Burch et al. [277]	504	80	73	31
Caraway et al. [278]	394	93	91	9
Danesse et al. [279]	4,986	92	69	14
Gardiner et al. [280]	1,456	65	91	15
Gharib and Goellner [131]	10,971	98	99	21
Lopez et al. [281]	872	90	99.8	–
Ravetto et al. [140]	37,895	92	76	1.6
Vojvodich et al. [282]	317	83	88	–

lymphoma but special immunoperoxidase stains are required (see Chapters 3, 10 and 11). Anaplastic cancer can also be diagnosed by FNA.

The main problem with FNA is the inability to differentiate a benign follicular adenoma from low-grade follicular carcinoma or follicular variant of papillary cancer. The pathological requirements for diagnosing follicular cancer are vascular, or, capsular invasion, or both. Invasion can only be determined by histology, not by cytology.

Let us take the same hypothetical group of 100 patients, five of whom have cancer. If FNA was a perfect test, 95 patients should have a benign report and 5 would be diagnosed with cancer. Most series report that from 10% to 20% (because 100 patients are considered percentages and patients are the same) of FNAs are unsatisfactory and have to be repeated. If we accept that the repeat FNAs are adequate, there will be approximately 80% to 85% benign reports. The false negative rate is about 1% to 2%. Therefore, a benign FNA is a reliable indicator of benignity. Approximately four pathology reports will indicate the nodule is cancerous or highly suspicious of cancer. The false positive rate is also about 1%, in my experience, less than that. It should be apparent there are about ten to fifteen patients who are unaccounted for. There is also one cancer missing. This is the indeterminate group. The FNA appearance is a microfollicular pattern with little colloid. This could represent a follicular adenoma, a low-grade follicular cancer, or a follicular variant of papillary cancer. The same is true for Hürthle cell lesions on cytology. The final diagnosis histologically could be Hürthle cell adenoma or Hürthle cell carcinoma, and the differentiation is based on evidence of invasion that can only be made by histologic examination.

Table 4.3 shows FNA results of several series. Most authors demonstrate a high sensitivity and specificity when FNA is compared to histology (150, 151). The reader is reminded that the incidence of cancer in different countries varies. In addition the frequency and type of benign nodules also varies depending on the intake of iodine. Liei et al. address the accuracy of FNA on long-term follow-up (152). They found five cancers in 578 patients (0.87%) whose original FNAs were benign. The average length of follow-up was 4.8 years. The cancers were on the same side as the original FNA: however, the authors could not be certain the lesions were concordant. None of the cancers had metastasized. Similarly, Grant et al. found three cancers (0.7%) over an average follow-up of 6 years in 439 patients (153). If it is accepted that these are false negatives the value <1% is reassuring. The role of "routine" repeat FNA is discussed below. There is evidence that the accuracy of FNA is lower in patients with familial differentiated thyroid cancer (154). This is related to the multifocality of the disease and the coexistence of benign and malignant thyroid nodules.

Methods to Improve Diagnostic Accuracy

The two main problems related to FNA are the 10% to 20% of inadequate specimens and the 10% to 20% of indeterminate results of follicular neoplasms. It has been demonstrated that ultrasound guided FNA reduces the proportion

Table 4.4. Results of ultrasound guided fine needle aspiration.

Report [Reference]	Number of FNA %	Sensitivity %	Specificity %	Inadequate %
Al-Shaikh et al. [145]	41	95	100	7
Danese et al. [279]	4,697	97	71	8.5
Karstrup et al. [283]	77	83	77	3
Khurana et al. [284]	119			3
Ogawa et al. [157]	1,012	84	99	18
Rausch et al. [156]	316	100	92	3

of inadequate results. The technique is operator dependant, but with experience the time required for completion of ultrasound guided FNA is not dissimilar from ultrasound alone (155). Results from several publications are shown in Table 4.4, and these agree with the experience in our institution reported by Carmeci et al. and Rausch et al. (156). With the exception of the results of Ogawa et al., the papers cited in the table all have inadequate rates of less than 10% (157). Using ultrasound, it is possible to ensure the needle tip is in the best situation for obtaining the specimen. In complex mixed solid and cystic lesions, the fluid can be removed and then the remaining solid component sampled. In spite of the use of ultrasound, Alexander et al. only obtained a diagnostic result in 63% of FNAs that were repeated, because the original had been non-diagnostic (158). The chance of a second inadequate biopsy was statistically related to the size of the cystic component. In spite of the relatively low rate of diagnostic studies, they recommend a second ultrasound-guided procedure since 5% showed papillary cancer. All authorities agree that a repeat FNA is necessary when the original FNA is inadequate, and when the nodule is small the repeat could be conducted with ultrasound guidance. When there are two inadequate hand and eye coordinated FNAs, I certainly recommend ultrasound guidance for the third procedure.

Ultrasound also allows small, difficult to feel, and even impalpable nodules to be sampled. Many of these are identified on imaging tests that include the thyroid and as stated above the thyroid lesions have been called incidentalomas. There has been debate about what size should determine whether to biopsy or not. Many authorities use 1 cm as the cut-off. The reasoning is that smaller nodules are increasingly difficult to sample. In addition the prognosis in thyroid cancer is dominated by the size of the primary cancer and almost no patients have their life shortened by 1 cm cancers. When a decision is made to defer FNA, it is important that the patient has a follow-up ultrasound, and when the nodule increases in size, it should be sampled. There are reports of cancers being diagnosed in smaller nodules and my colleague Dr Brooke Jeffrey has established the diagnosis in 5 mm to 6 mm lesions. There are reports confirming successful sampling of this size of lesion (159–161). It is possible that the proportion of very low number of inadequate results from Dr Jeffrey and colleagues is explained by ensuring there is sufficient tissue before terminating the procedure. This requires that a cytopathology technologist be present to screen the material. There is also debate about the value of obtaining a tissue diagnosis in a small impalpable nodule (162). The argument against FNA relates to the lack of knowledge of the natural history of small impalpable cancers. Silver and Parangi pose the following questions: (1) Does the incidentally detected thyroid nodule put the patient at risk for an adverse outcome? (2) Can those individuals with malignant thyroid nodules be identified? (3) Is the treatment of thyroid malignancy more effective in presymptomatic patients? And, (4) do the beneficial effects of presymptomatic detection and treatment in these patients justify the costs incurred (163)? Data in favor of obtaining a tissue diagnosis comes from several publications. Ultrasound guided FNA was conducted in impalpable nodules in 267 patients, the mean nodule size was 9 mm with a range of 0.3 cm to 1.5 cm (164). Thirty-six were cancer (13%), and there was extrathyroidal invasion in 44% of these, lymph node metastases in 50%, and multifocal disease in 39%. Kang et al. obtained ultrasound guided FNAs in 198 of 1475 patients (13.4%) with impalpable lesions of less than

1.5 cm who had ultrasound to identify the small nodules. Of these small nodules, 28.8% were malignant. These results show that malignant nodules can be identified and the presymptomatic diagnosis identifies patients with clinically significant disease.

Routine Repeat for Benign Nodules

Should repeat FNA be a routine test for follow-up? I do not do so routinely, but if the nodule grows, or when either the patient or the physician has concern, a second FNA is appropriate. Aguilar et al. found routine repeat biopsy was not very helpful since the second study also showed features of a benign thyroid (165). Some reports indicate that re-biopsy does occasionally result in a change in report from benign to malignant or benign to indeterminate. Chehade et al. found two cancers in 235 repeat biopsies (166). Erdogan et al. obtained 457 FNAs on 216 patients. Three patients (1.4%) had a change from benign to papillary cancer (167). Even in these publications 98% of the patients had the same result. In contrast, in two reports, with a total of 587 patients, there were no cancers on repeat FNA (168, 169). Therefore when there is a technically good FNA that is unequivocally benign and the nodule remains stable, there is no need to rebiopsy.

One disturbing report that is difficult to reconcile with the data reviewed above studied 678 patients who had FNA of nodules that were all interpreted to be benign. (170). The patients then had ultrasound guided FNA, and 107 of the reports were suspicious for cancer of which 99 had histologically proven cancer. Likely explanations for this unusually high false negative rate for FNA were that 55 of the cancers were impalpable and in a different site from the original FNA, and 44 had inadequate biopsies.

Fine needle aspiration conducted by hand and eye coordination is an excellent test for palpable thyroid nodules. Ultrasound guided FNA is useful for lesions that are difficult to feel or are detected only by imaging. Ultrasound guided FNA is useful for repeat biopsy when the first one did not provide sufficient material for interpretation. The technique allows small contralateral lesions to be identified as well as solid components of cystic lesions. The method is primarily conducted by radiologists with an interest in ultrasound, but there is an increasing trend among endocrinologists to learn and employ this approach. The two techniques, FNA and ultrasound, are increasingly accepted as complementary (63, 171, 172).

Management of Thyroid Nodule

Figure 4.12 is an algorithm for the management of a thyroid nodule. When it is acknowledged that a thyroid nodule is malignant, the clinical

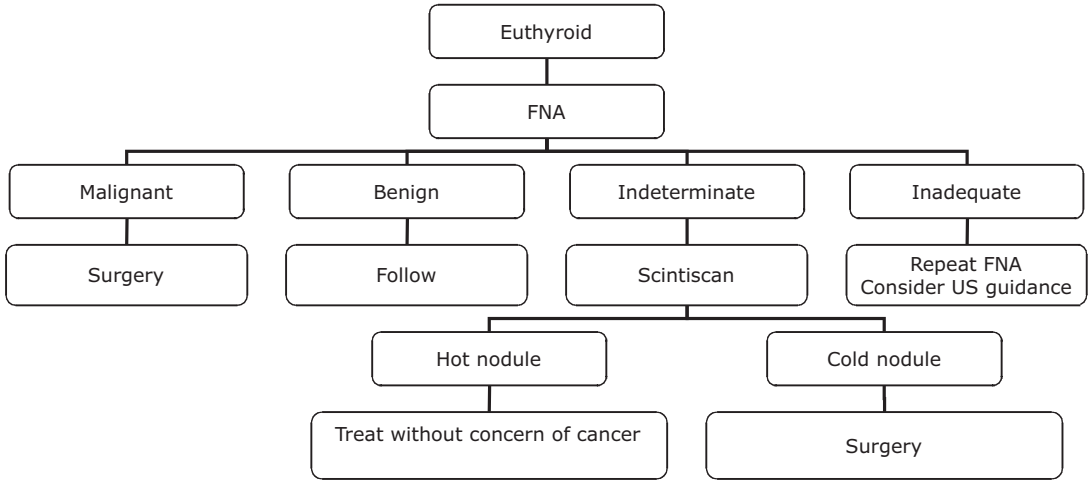

Figure 4.12. This figure completes the algorithm for management of a thyroid nodule, started in Figures 4.1 and 4.3.

decision is straightforward; the patient should be referred for thyroidectomy. This is discussed in detail in Chapter 6. There is no advantage of intra-operative frozen section (10). When the nodule is unequivocally benign the patient can be reassured, but there must be continuity of care. This is because benign nodules can increase in size (173). Alexander et al. found that 89% of nodules increased in size by 15% or more over five years. This would be an indication to repeat the FNA. Although as discussed above, the prevalence of thyroid cancer is low in this population. Seventy-four nodules were reaspirated; these had shown an average increase in volume of 69%. Only one was cancer. An enlarging nodule that causes pressure effects should be treated by operation.

What is the correct operation when the patient with a benign nodule is referred for surgery? Most surgeons recommend a lobectomy or lobectomy and isthmusectomy. There is a probability of new nodules growing in the residual lobe. A recent report from Rome demonstrated that 22% developed a new nodule and an additional 36% a "parenchymal irregularity" in the remaining tissue. Before operation, I routinely recommend an ultrasound examination of the thyroid and when there is a nodule in the contralateral lobe recommend a more complete thyroidectomy. When a lobectomy is conducted in this situation a decision will need to be made at some time concerning FNA of the contralateral nodule and the need for a second operation.

When the FNA is indeterminate there is a 10% to 20% chance of cancer. The cytopathology demonstrates a microfollicular pattern with small amounts of colloid. It is not possible to exclude follicular cancer or a follicular variant of papillary cancer without histology (174). Most thyroid physicians would refer the patient for operation, but the extent of the procedure is debated hotly. When a lobectomy is undertaken and the lesion is diagnosed on fixed pathological sections as cancer, there is usually the recommendation to complete the thyroidectomy. This is based on several factors. One, papillary cancer is often multifocal. Two, treatment with ^{131}I is easier when there is a small volume of residual thyroid. As stated above, nodules can develop in the residual lobe raising the need for completion of the thyroidectomy later. Therefore, some surgeons rely of an intra-operative frozen section histological diagnosis to direct the decision to complete the procedure during the first surgery. This technique is not perfect and one study demonstrated the sensitivity was 51% (175). A separate investigation concluded that frozen section was useless in differentiating benign from malignant follicular neoplasms (176). Udelsman et al. in a randomized study found frozen section was unnecessary in 96% of patients and when used added more than $12,000 for information that would alter management. (177). The clinician has to use judgement in trying to determine a priori those patients who are likely to have cancer and should have total thyroidectomy as the primary procedure. Male gender, a solitary nodule, and a nodule greater than 4 cm would be reasons for that approach (178).

Treatment with Thyroid Hormone

The role of thyroid hormone in treating a patient with a benign thyroid nodule is controversial (179, 180). Historically thyroid hormone was prescribed routinely and stated to be effective in about one-third of patients. However, the measurement of the response to treatment was not objective. When a medicine is prescribed both physician and patient have a vested interest in believing the drug is working. That wish can lower objectivity. Some of the reported beneficial effects of thyroid hormone on reduction of nodule size are not based on measurement but on clinical judgment. Nevertheless, there are some reports based on objective information and the differences of the response of thyroid nodules to thyroid hormone between these publications are disparate, but they are real. Thyroid nodules in iodine replete countries are less likely to respond to thyroid hormone, therefore reports from the United States cannot be directly compared to reports from countries that are iodine deficient, such as Italy. Even within the one region there can be thyroid nodules with different pathologies (181). Cystic nodules are less likely to shrink than solid nodules. In a scientific study to determine efficacy, the treatment and control group should be similar. The nodule should be benign by FNA. The patient and physician should both be blinded to treatment or placebo. Measurement of the nodule should be objective and made by

a person who also does not know to which group the patient belongs. There should be a decision a priori as to the change in volume that would be considered significant. The study should be sufficiently long enough that meaningful changes have time to occur. This should meet the approval of evidence-based authorities.

In a carefully controlled study at the Mayo clinic, patients with benign colloid nodules were treated with thyroid hormone or placebo for 6 months (182). The medications were switched at that time and continued for another 6 months. Ultrasound measurements of the nodules were obtained at the start of the study at the midpoint and the end. Neither the patients, nor the physicians, knew whether the patient was ingesting medication or placebo. Readers will almost certainly have predicted there was no statistical difference in outcome between the treated and non-treated groups, and almost all nodules remained unchanged in size. One criticism is the relatively short study length. In contrast, a report from Italy demonstrated benefit from thyroid hormone and from iodine (183). An additional double blind study organized by the French Thyroid Research Group found that thyroid hormone was statistically effective (184). This paper is informative, since the reader would conclude that thyroid hormone should be prescribed for patients with a thyroid nodule. The goal had been to enroll 300 patients, but only 135 gave consent and 123 could be evaluated. Using serial ultrasound measurements the study reported a statistically significant change in nodule volume of −0.36 ml in the treated group and an increase of +0.62 ml in the placebo group. There was no crossover of therapy and placebo. The investigators also determined by palpation the treated nodules decreased on average by 3.5 mm compared with average growth of 0.5 mm in the placebo group. Are these changes clinically relevant?

One study does report on changes in thyroid nodule volume, which are compelling (185). Four groups of patients were studied. Two started with thyroxine treatment and two with placebo. After one year the treatments and placebos were switched. One treatment group had TSH values of $\leqslant$0.01 mIU/l, the other treatment group had TSH values of 0.4 mIU/l to 0.6 mIU/l. The average thyroid nodule volume decreased from 4.99 ml to 3.2 ml and 3.72 ml to 2.05 ml in the high dose treatment arms, thyroxine first and thyroxine after placebo respectively. Likewise the nodule volume decreased from 4.43 ml to 3.04 ml and 3.59 ml to 2.22 ml in the low dose thyroid arms administered first and then after placebo. The authors conclude that thyroid hormone is effective and the reduction in TSH does not need to be severe. Lima et al. found an intermediate value of thyroid hormone in fifty-four patients with a solid benign nodule and forty-seven with multinodular goiter (186). One out of five with a solid nodule had a reduction of between 20% and 49%. The volume of nodular goiters regressed in one-third of patients. This report is from Brazil, which would be considered an iodine deficient region.

Castro et al. made a detailed review of published reports (187). They conducted a meta-analysis using the results of randomized clinical trials that met stringent criteria. They conclude there is no statistical benefit, but there is a "trend towards a reduction" in nodule size. In a similar meta-analysis, Csako et al. found a reduction in nodule size of $\geqslant$50% in a subset of patients (188). These authors also point out that the volume of peri-nodular thyroid tissue is reduced and this can help cosmesis and pressure symptoms. However, the reduction in normal thyroid volume can result in the nodule appearing to enlarge because it becomes easier to palpate.

The rationale for thyroid hormone is to lower TSH, the physiological stimulus to thyroid cell growth. Therefore, the TSH should be low, but what is an acceptable value? Most reports use values of <0.3 mIU/ml. What is the evidence that nodules are due to TSH stimulation? Also what are the disadvantages or complications of long-term supra-physiological values of thyroid hormones and low TSH? These include potential loss of bone mass, increase in cardiac arrhythmias and behavioral irregularities. It is acknowledged that substantially elevated thyroid hormone values for a long time can cause osteoporosis. The effect is greater in post-menopausal women. It is less clear whether minimally elevated results are detrimental. There is also data indicating a statistically significant risk of atrial fibrillation when the TSH is below 0.03 mIU/l. These are discussed again under management of differentiated thyroid cancer where additional references are cited. The cost/benefit ratio of

these problems is easier to justify in patients with proven cancer who need thyroid hormone than benign thyroid disease where most patients have normal function.

Treatment of Autonomous Thyroid Nodule Causing Thyrotoxicosis

Autonomous, hot nodule, or toxic nodular goiter with multiple functioning nodules is also given the eponym of Plummer's disease. This condition is identified by a low or suppressed TSH and a scintiscan showing increased uptake in the nodule compared with surrounding normal thyroid (Figures 4.2 and 4.4). There is a spectrum of function from normal to biochemically hyperthyroid to frankly thyrotoxic. Functioning nodules secrete a relatively greater quantity of T_3 than T_4 (T_3 toxicosis). This can result in a low TSH being associated with a normal FT_4 and that is an indication to measure FT_3. When FNA is the first and only test the diagnosis of autonomous nodule can be overlooked. When TSH level is the test that starts the work-up of a patient with a nodule and scintiscan is obtained before FNA when the TSH is low, patients with this condition should be diagnosed. There are several investigations demonstrating that patients with functioning nodules who are euthyroid remain so for many years (189, 190). In a longitudinal study from Denmark, an average 4.1% of patients developed hyperthyroidism annually. The conversion rate was 3% over the first seven years, and then this increased to 10% (191). The three factors that are associated with development of overactivity of the nodule are increasing size of the lesion, advancing age of the patient, and exposure to iodine (192). It is uncommon for thyrotoxicosis to occur when the diameter of the lesion is less than 3 cm. It is logical that an increase in size of the nodule is more likely to occur over time, so larger functioning nodules are more common in older patients. Increased intake of iodine can be iatrogenic from medications such as amiodarone or radiologic contrast agents that contain substantial amounts of iodine but even small quantities of iodine can produce an increase in thyroid hormone values (193). This is termed Jod Basedow disease (iodine induced hyperthyroidism, jod is German for iodine, and Basedow was the German physician who described what is known in the English literature as Graves' disease).

Functioning nodules are usually adenomas. It has already been stated that cancer is rare in an autonomous nodule in an adult provided ^{123}I is used for imaging (75, 194–199). Some authorities report no examples (200). A hot nodule on $^{99M}TcO_4$ scintiscan, although still likely to be benign, has a greater chance of being cancerous (201). It is important when reading the literature related to cancer in functioning nodules to decide whether the functioning nodule is the cancer or whether the malignancy is in another part of the gland, in which case it should not be considered as a functioning cancer. The low probability of a functioning nodule being cancer does not apply to children in whom functioning nodules are rare but can be cancer (202–205). One of the patients we reported with cancer in a functioning nodule was nine years old and I have since encountered two other children with functioning cancers (75). In a compilation of case reports, Croom et al. found that 11.3% of functioning nodules in children are cancerous (206). They recommend surgery.

Although the nodule can undergo hemorrhagic necrosis and the function return to normal this is very uncommon and treatment will be advised for most patients (207). There are four options for treatment. First is observation and this is only appropriate when the TSH is normal or minimally reduced. The other treatments are surgical removal of the lobe containing the hyperactive nodule, treatment with ^{131}I, or by injection of ethanol. Antithyroid medications can be administered with the goal of controlling thyrotoxicosis, before preceding with definitive therapy or in a very old patient whose life expectancy is short. This therapy is not advised in younger healthy patients; since, it will be required for life because spontaneous remission is very rare. The situation is different from hyperthyroidism of Graves' disease where 20% to 50% of patients remit after 18 months to 24 months. It should be stressed that thyroid hormones should not be prescribed to suppress an autonomous hyperfunctioning nodule for two reasons. This does not work, the TSH is already suppressed and the nodule functions excessively independent of that. Secondly, the exogenous thyroid hormone adds more fuel to the fire and can make asymptomatic patients symptomatic and those with symptoms worse.

How do the patient and physician decide which therapy is best? In the United States very few specialists have experience with injection of nodules with ethanol and the choice is surgery versus ^{131}I. Each has benefits and drawbacks. Surgery removes the functioning nodule and the condition is resolved in one to two hours (208, 209). The complications of surgery have to be considered but are less than for total thyroidectomy. The patient will have a scar. Not all solitary functioning nodules are solitary, and a scintiscan is recommended prior to lobectomy. When there are functioning nodules in other parts of the gland, including the contra-lateral lobe, the patient has a toxic multinodular thyroid and a subtotal thyroidectomy is a more appropriate operation. In single autonomous nodules, the recurrence of hyperthyroidism after surgery is low. Ferrari et al. in a meta-analysis of nine publications calculated it to be 0.3% (210). Most of the articles included in the analysis were old, and it is unlikely that sensitive TSH measurements were available, so there might have been a higher incidence of subclinical hyperthyroidism. Since the suppressed lobe is usually normal, the expectation is that it will resume normal function, and the patient would become euthyroid without exogenous levothyroxine. This is not always the case and thyroid function should be tested four to six weeks after surgery and again at six to twelve months. When patients are hyperthyroid prior to surgery they should be treated with antithyroid medication for several weeks to produce normal function. Methimazole 20 mg daily or propylthiouracil 100 mg three times a day would be appropriate, and if the tests are still above normal at four to six weeks the doses could be increased. Inorganic iodine is inadvisable for the treatment of an autonomous hyperfunctioning nodule because it can aggravate the hyperthyroidism. The patient should be advised about side effects of the medications including skin rashes and agranulocytosis and counselled to report any abnormal symptoms, or signs.

Iodine-131 Treatment of Functioning Nodule

Iodine-131 (^{131}I) avoids the operation but exposes the patient to radiation and it takes weeks to months to control the overactivity. The nodule usually does not disappear completely. Older literature stated that patients would be euthyroid after either of these procedures since the normal lobe would resume functioning when the source of excess hormone was removed or ablated. Hegedus et al. treated twenty-seven patients with ^{131}I, two required retreatment and none became hypothyroid (211). The volume of the nodule decreased from an average of 41 ml to 23 ml. In a contrasting report, eight of twenty-three patients (35%) became hypothyroid after ^{131}I and 52% of the nodules remained palpable (212). This was probably the first article to draw attention to post treatment hypothyroidism.

There are several methods of determining the dose of ^{131}I to be prescribed. The simplest is to administer a standard dose to every patient. The range of administered doses is considerable. Some physicians employ doses less than 370 MBq (10 mCi), but this usually is insufficient and has to be repeated (213). Clerc et al. support the use of this dose in patients who are young or have mild symptoms, and they found that 75% were euthyroid by 6 months (214). Sharma et al. also recommend this dose for patients with mild disease and nodules smaller than 3 cm (215). Larger nodules did not respond but were cured by a second equivalent dose of ^{131}I. Several investigators have administered 555 MBq (15 mCi) with success (216). Using the higher dose, 48 patients were treated with 555 MBq (15 mCi), and forty-one became euthyroid and none hypothyroid (217). A second report using the same administered dose rendered 73% euthyroid after one year (218). In a similar study of fifty-two patients, the administered dose was 740 MBq (20 mCi), and one patient needed to be retreated, and three (6%) became hypothyroid (219). Secondly, the dose can be calculated from the size of the nodule and its uptake of a tracer of radioiodine. Estour et al. used the area of the lesions πr^2 and administered 37 MBq (1 mCi) per cm^2. Because nine of forty patients remained hyperthyroid, they now recommend between 37 MBq/cm^2 and 55 MBq/cm^2 (1–1.5 mCi) (220). Most who employ this approach would use the volume of the nodule rather than its area, and that can be calculated as discussed above, and it can also be obtained directly by ultrasound or even PET scanning using ^{124}I. A specific dose is adminis-

Table 4.5. Calculation of dose of ^{131}I to be administered to treat autonomously functioning hyperthyroid nodule.

Diameter of nodule (cm)	Volume of nodule (ml^3)	Estour et al. [220] Area of nodule used	Ross et al. [221] 5.9 MBq/g 160 µCi/g	Weiner et al. [222] 7.4 MBq/g 200 µ/g	Gorman and Robertson [223] 300 Gy (30,000 rad)	McDougall 7.4 MBq/g 200 µCi/g
2	4.2	3.15	*2.2*	*2.5*	*5.6*	*2.5*
3	14.2	7.2	*7.6*	*8.5*	*18.3*	*8.5*
4	33.5	10.8	*17.9*	*20.0*	***42.0***	*20.0*
5	65.0	20	***34.7***	***40.0***	***80.0***	***40.0***
6	113.1	29	***60.3***	***67.8***	***139.0***	***67.8***

Numbers in italics assume a 24-hour uptake of 30%.
Numbers in bold text would require hospitalization of patient in many countries.

tered per ml (cc or g since most thyroid tissue is water) and corrected for the twenty-four-hour uptake. Ross et al. recommend 5.9 MBq (160 µCi) per g (221). Wiener et al. employs 7.4 MBq (200 µCi) per g, and that is the quantity I use (222). The uptake in hot nodules is usually close to the upper limit of normal that is 25% to 40%. Assuming a value of 30%, the dose administered for glands of varying sizes is shown in Table 4.5. The larger the nodule, the larger the treatment but the greater the uptake, the smaller the calculated dose. When the nodule has a diameter of 4 cm or more the administered dose is usually greater than 1.1 GBq (30 mCi). This contrasts with the fixed dose regimes.

Finally, the amount of absorbed radiation to be delivered is defined. Gorman and Robertson determined that 300 Gy (30,000 rad) were necessary for successful treatment of a functioning nodule (223). This absorbed dose was also recommended by Heinze et al. (224). Knowledge of the size of the nodule, the uptake and the $T_{1/2E}$ of radioiodine within the nodule are required. The last measurement takes several days but an empiric value, such as 100 hours, can be substituted. The result is an even larger administered dose, as shown in Table 4.5. After administration of this absorbed dose the nodule shrinks by about 40% to 45% (225). In some countries this approach is required by statute. Investigators have calculated the absorbed radiation to thyroid tissue outside of the functioning nodule (226). In a study where the goal was to deliver 300 Gy (30,000 rad) to the nodule, the absorbed radiation to the suppressed tissue in the ipsilateral lobe was 34 Gy (3,400 rad) and 32 Gy (3,200 rad) to the opposite lobe. This could account for post treatment hypothyroidism. These results do not differ substantially from those calculated by Gorman and Robertson in 1978 (223).

There is no consensus that one method choosing the dose of ^{131}I to be administered is superior, but the physician should try to administer a dose that will result in control of hyperthyroidism, without too long a delay or the need to retreat. There is an inverse relation between the percentage of patients who remain hyperthyroid and those developing hypothyroidism. In three publications, where no patient remained hyperthyroid, the incidences of hypothyroidism were 24%, 41%, and 58% (212, 227). When less than 10% become hypothyroid, the recurrence rate can be as high as 73% (228). What is clear is that there is need for follow-up to ensure the patient has normal thyroid function. Hypothyroidism occurs in a proportion and needs to be treated with supplemental levothyroxine. The dose is less than the anticipated full replacement dose, because the nodule can retain some non-suppressible function. A reasonable starting dose would be 50 µg to 75 µg daily with repeat tests after six to eight weeks and titration of the levo-thyroxine as required.

Physicians responsible for treatment with radionuclides, including ^{131}I, must meet with the patient to describe the protocol in depth. A review of laboratory tests and scintiscan would ensure that additional tests could be requested, for example an FNA for a dominant non-functioning nodule. Radiation safety requirements for the country or state would be explained and the patient also given a list of instructions in writing. These are expanded in Chapter 6. A negative pregnancy test should be documented in all women of childbearing age. Informed consent should be obtained in writing and witnessed. Arrangements for follow-up and testing should be made. Complications are uncommon, but elderly patients who might be at risk from worsening of thyrotoxicosis should

be pretreated with antithyroid medication, as discussed above in preparation for surgery.

Intranodular Injection of Ethanol

In Europe, in particular Italy, there is an increasing body of evidence and support for treatment of nodules by injection of ethanol. This has been employed for functional nodules, cystic nodules, and benign non-functioning nodules. The information presented below is not based on personal experience. The method involves instillation of 95% ethanol into the nodule using ultrasound guidance in a volume of approximately 1 ml per 1 ml nodular tissue. The injection is repeated weekly or twice weekly, and thyroid function and the size of the nodule are monitored. Patients who are thyrotoxic are pretreated with antithyroid medication and or beta-blocker, and these have no adverse effect on the outcome. Therapy is stopped when the TSH normalizes. One of the first reports involved fifteen patients who were given a total of seventy-nine treatments (an average of 5.26 per patient) (229). Thyroid function tests improved and suppressed tissue on scintiscan normalized totally or partially on follow-up scan. In a similar review of fifteen patients who received one to two treatments per week to a total of four to seven injections, there was a reduction in nodule size and improvement in thyroid function tests (230). The volume of ethanol was 0.5 ml to 1.0 ml per ml of nodule. A number of publications confirm the findings as shown in Table 4.6. Side effects include local pain, pyrexia, dysphonia, and transient worsening of thyrotoxicosis. Graves' disease has occurred after treatment of autonomous nodule by ethanol injection (231). The authors demonstrated a change from negative thyroid stimulating antibodies before the therapy to positive after. They hypothesize that a release of thyroid antigens at the time of ethanol injection caused the autoimmune response. There is some concern that fibrosis and scarring might make it more difficult to operate on the thyroid should that be necessary. Why has this not been accepted in the United States and United Kingdom? Patients have to attend clinics for therapy once or twice weekly and on average five to seven sessions are required. The time and cost of five to seven ultrasounds and interventions with the need for more frequent tests and scintiscans make this less cost effective.

Which Treatment for the Specific Patient?

Messina et al. summarize the position well by concluding there "does not exist a single therapy to treat the Plummer's disease." In the United States the option is surgery versus ^{131}I. The larger the nodule and the greater the dose of radiation that would be required for treatment moves the decision towards surgery. ^{131}I would be preferred for older patients. Unfortunately larger nodules are present more often in older patients. The decision then incorporates the

Table 4.6. Results of percutaneous injection of ethanol into autonomous nodules.

Author and reference	Number treated	Number improved	%
Martino et al. (285)	37	33	89
Monzani et al. (286)	56	18/22 thyrotoxic	82
Monzani et al. (287)*	117	100	85
Monzani et al.(288) +	132	107	81
Paracchi et al. (289)	28	28	100
Argalia et al. (290)	10	6	60
Livrachi et al. (291)	65	51	78
Lupoli et al. (292)	36	36	100
Papini et al. (293)	20	17	85
Lippi et al. (294) #	429	316	74
Cerbone et al. (295)	22	20	91
Spiezia et al. (296)	47	45	96

* Five year follow-up.
\+ Eight year follow-up.
\# Multicenter study.

input from the patient such as opposition to radioiodine because of fear of radiation and the presence of other factors that would be against operation such as heart or lung disease. Intranodular injection of ethanol is not used in the USA but an Italian study comparing twenty-one patients treated with ^{131}I and twenty-two by ethanol injections found similar outcomes with equivalent reduction in nodule size and normalization of thyroid function (232). Iodine-131 caused hypothyroidism in one patient, and ethanol injections left two patients hyperthyroid. The same investigators have shown that treatment of nodules with ethanol injection followed by ^{131}I reduced the dose of radioiodine and caused a greater reduction in nodule size than ^{131}I alone (233). As I reviewed the results of ethanol injection there is consistency that about 80% to 90% of patients are treated successfully; therefore, I question why there would be need for combined therapies. When there is no good thyroid surgeon or access to nuclear medicine therapy, intranodular injection of ethanol is an alternative.

Treatment of Non-Toxic Nodule with Iodine-131 or Ethanol Injection

Reports indicate that there is some reduction in the size of a non-toxic nodular goiter after treatment with ^{131}I. This treatment might have value in a patient who is elderly or a poor operative risk. The goiter does not disappear and it takes months for a reduction in size. There is no role of ^{131}I for a single non-functioning nodule. The radioiodine is taken up by normal tissue and the nodule receives very little radiation. A few physicians have treated non-functioning nodules by injections of ethanol using the same approach as described above (234). When this is undertaken it is important to have a prior FNA demonstrating benign cytopathology.

Cystic Thyroid Nodule

As discussed above pure cysts are unlikely to be cancer. Most lesions described as cysts are mixed solid cystic lesions and the solid component should be managed as a solid nodule. Ultrasound guided FNA has merit of draining the cystic component of the lesion and then obtaining a tissue diagnosis from the solid part. Five hundred seventy-five cystic nodules were approached this way and 119 referred for surgery (235). Only 9.2% of FNA were non-diagnostic and sixteen cases were judged to be cancer, forty-two were interpreted as benign, and the remaining were follicular lesions. The final diagnosis of was cancer in twenty-one nodules (17.6%) and the remaining 82.4% were benign. When a cystic nodule recurs it can be observed, drained again, injected with sclerosant, or removed. Very few studies on percutaneous ethanol injection are from the United States (236).

In an analysis of the literature intracystic ethanol is effective. A study comparing aspiration, versus aspiration plus ethanol injection into cystic nodules, demonstrated a clinically and statistically superior outcome in those treated with ethanol injection (237). Another study conducted in Rome compared repeated drainage, injection of hydrochloric acid, or injection of ethanol (238). There was no difference in success, defined as a cyst <0.5 ml after five or less interventions, between aspiration and injection of acid (37.5% versus 44%). Both of these were inferior to instillation of ethanol, which had a 90% success. Both types of instillation caused pain in some patients and this was not found in those treated by aspiration alone. Another Italian series dealt with large cystic lesions of average volume 35 ml (239). The outcome was favorable with only six of ninety-two (6.5%) recurring after nine years. The results are confirmed by other investigators. (240, 241). Tetracycline was used in the past but preparations of this antibiotic for injection are no longer produced since there is no role microbiologically for systemic tetracycline (242). It is not clear why the technique of ethanol injection is not used in the United States. Probably the fact that several instillations are required is a factor. When the lesion is persistent and symptomatic surgery by lobectomy cures the problem; there is no chance of recurrence, and the nodule also can be examined histologically.

Management of Multinodular Goiter

The first step is to determine if the patient is hyperthyroid, euthyroid, or hypothyroid. In hyperthyroid patients a scintiscan demonstrates

whether there are multiple functioning nodules or nodules superimposed on Graves' disease (Marine Lenhart syndrome). Toxic multinodular goiter can be treated by surgery, or ^{131}I, and the specific choice is based on age of the patient, size of the goiter, personal preference of the patient, and availability of trained specialists. Nygaard et al. on review of their results using ^{131}I in 130 patients with toxic nodular goiter conclude, "Ninety-two percent of patients with multinodular toxic goiter were cured with one or two treatments. The thyroid volume was reduced by 43%, with few side effects. Iodine-131 should be the choice of treatment in patients with multinodular toxic goiter." A hypothetical reason for not treating with radioiodine is swelling of the goiter and worsening of pressure effects after ^{131}I. This has been shown to be a myth by ultrasound measurements of thyroid volume, 2, 7, 14, 21, 28 and 35 days after therapy in 30 patients, some with toxic nodular goiter and some with non-toxic nodular goiter (243).

In a euthyroid patient living in a region of iodine deficiency, supplemental iodine can have an effect in reducing goiter size. Monitoring of the thyroid size and function is important and some patients can develop Jod Basedow syndrome. A nodular goiter with normal thyroid function in a person who has lived in an iodine replete country will not benefit from iodine. The options are to watch, to operate or to treat with ^{131}I. An investigation in Australia presented a hypothetical patient to endocrine surgeons and endocrinologists. The patient was a 42-year-old woman with a 50–80 g multinodular goiter and the physicians were invited to respond with their management (244). A majority of both the endocrinologists and surgeons advised no treatment (65% and 67% respectively). The remainder of the endocrinologists recommended levo-thyroxine (22%), surgery (10%), or ^{131}I (3%). For the surgeons 31% recommended surgery and 2% levo-thyroxine. The investigators provide eleven variations on the index patient and an after analysis of responses concludes "there are clinically significant differences between endocrine surgeons and endocrinologists in the management of multinodular goiter." When experts give different opinions there is probably no one correct answer. An asymptomatic goiter can be left untreated but a nodular goiter that is causing pressure symptoms should be treated and in the United States the common approach is by operation. This immediately corrects the symptoms and the patient takes replacement levo-thyroxine for life. The complications of thyroidectomy including hematoma, damage to the recurrent, and external laryngeal nerves, and parathyroids are not common when a well-trained experienced surgeon conducts the operation but they need to be addressed with the patient pre-operatively. Treatment with radioiodine is less attractive since the uptake by the goiter is usually low and this coupled with the size of the gland mean that a very large dose of ^{131}I has to be administered. In addition, the reduction in size is not great, and it takes several months to achieve that. Nygaard et al. treated sixty-nine patients with 3.7 MBq/g (100 μCi/g) corrected for uptake. Fifty-six patients received one treatment, one patient had four therapies, and the remainder had two. Comparison of thyroid volume in thirty-nine patients before and twenty-four months after therapy showed a reduction from 73 ml to 29 ml. Eleven percent became hypothyroid. The results are impressive, but it is hard to understand how small administered doses can have this effect. Figure 4.13 shows a scintiscan in a woman with a huge goiter (500 g at surgery), who was referred for ^{131}I treatment. The uptake was 11%. Using the formula of Nygaard et al. the patient would have been treated with:

$$\frac{3.7 \times 500 \times 100}{10} = 18{,}500\,\text{MBq or } 18.5\,\text{GBq or } 500\,\text{mCi}$$

I advise 7.4 MBq/g (200 μCi/g), resulting in a single administered dose of 37 GBq (1,000 mCi) for this patient! Very few would support that. Therefore this treatment might have a role for smaller goiter, but recall two-thirds of the endocrine surgeons and physicians in Australia would wait and watch. Graves' disease has developed in a few patients after radioiodine treatment of both toxic and non-toxic nodular goiter (245, 246). This is probably due to formation of thyroid stimulating antibodies in response to the release of thyroid antigens. Several authorities recommend ^{131}I as the treatment of choice in the elderly (247–249). Nevertheless, the goiter size and low uptake make the treatment ineffective and inappropriate for some patients. I have

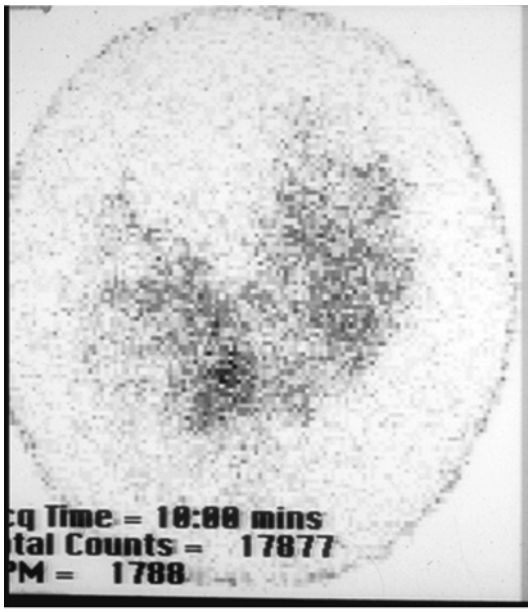

Figure 4.13. Scintiscan produced 24 hours after 200 μCi 7.4 (7.4 MBq) ^{123}I: The patient had a huge goiter and the uptake was 11% at 24 hours. Dosimetry calculations demonstrated that it was impracticable to treat this with ^{131}I.

not been impressed with the results in patients I have treated but the selection of patients could be a factor (250).

Recombinant human thyrotropin (rhTSH) is approved for increasing the uptake in thyroid cancer. This is discussed in detail in Chapter 6. There are several reports of rhTSH to increase the uptake in nodular goiter as a preliminary to ^{131}I treatment. Twenty-two patients were treated with radioiodine after 0.01 mg to 0.03 mg rhTSH (251). The uptake doubled therefore the therapy dose was reduced by a factor of two. There was a reduction in goiter size of about 40%. Duick and Baskin treated sixteen patients with 1.1 GBq (30 mCi), after 0.9 mg rhTSH was administered to ten patients and 0.3 mg rhTSH to six patients (252). The uptakes increased by a factor of four. Some were biochemically hyperthyroid before treatment with ^{131}I, and in all cases TSH became normal or rose above normal after ^{131}I. The authors estimate a 30% to 40% reduction in goiter size over three to seven months and there was symptomatic improvement.

Levo-thyroxine should be prescribed for patients with goiter who are biochemically hypothyroid. This treatment is ineffective for euthyroid nodular goiter (253). It can be dangerous for patients with toxic nodular goiter. Once the patient has been euthyroid for months and the goiter has failed to shrink it is advisable to refer for surgery.

A problem is the recurrence of non-toxic nodular goiter after surgery. This generally is the result of the surgeon leaving too much tissue or conducting a lobectomy. When the recurrent goiter is symptomatic the therapies are surgery or ^{131}I. Repeat thyroid operations are associated with a higher incidence of complications and should be undertaken by an experienced operator who has conducted "redo" procedures. An alternative that has been employed in Europe is injection of the nodules with ethanol as described above (254).

Substernal or Retrosternal Nodular Goiter

Substernal extension of a goiter is more frequent with increasing age and many of the goiters are multinodular. Newman and Shaha report that the first description of retrosternal goiter was in 1749 (255). There are several reviews on this topic (255–257). It is generally accepted that substernal goiter is more common in goitrous regions. In most patients the thyroid starts in the normal position but sags like many parts of the body do with age. Gravity from upright posture causes the goiter to move inferiorly and when the lower edge of the gland enters the superior mediastinum, the reduction on pressure with inspiration causes a vicious cycle and the gland moves more caudal. Fifty percent or more of the goiter should be intrathoracic to qualify as a substernal goiter. This is hard to judge since the relation of the gland to the thoracic inlet can vary substantially depending on whether the patient is sitting, or lying and whether the head and neck are extended or flexed. Almost all substernal goiters are located in the anterior mediastinum but there are rare cases of posterior mediastinal goiter lying inferior to the trachea and even the esophagus (258). Many cases are identified by an X-ray or CT scan obtained for a non-thyroidal

reason but when the diagnosis is established and patients questioned directly the majority have noted a change in breathing. The goiter can cause compression on adjacent structures and can be the cause of tracheal compression, superior vena cava syndrome, recurrent laryngeal nerve paralysis, difficulty in swallowing, and even chylothorax (259–263). There are rare reports of the mass causing pulmonary hypertension and cardiac failure (264).

The diagnosis can usually be made by CT scan, as shown in Figure 4.14. When there is doubt a scintiscan with ^{123}I confirms that there is thyroid present. This is one situation where $^{99m}TcO_4$ is not advised. The usual explanation for this advice is that the photons have too low an energy to penetrate the septum. This is patently incorrect since the same radionuclide is used for Sestamibi and Tetrofosmin cardiac imaging. The reasons are that the uptake of $^{99m}TcO_4$ is so low plus the radioactivity in surrounding great vessels so high that the goiter cannot be imaged. Several authorities recommend ^{131}I with its high-energy gamma photon. but ^{123}I gives excel-

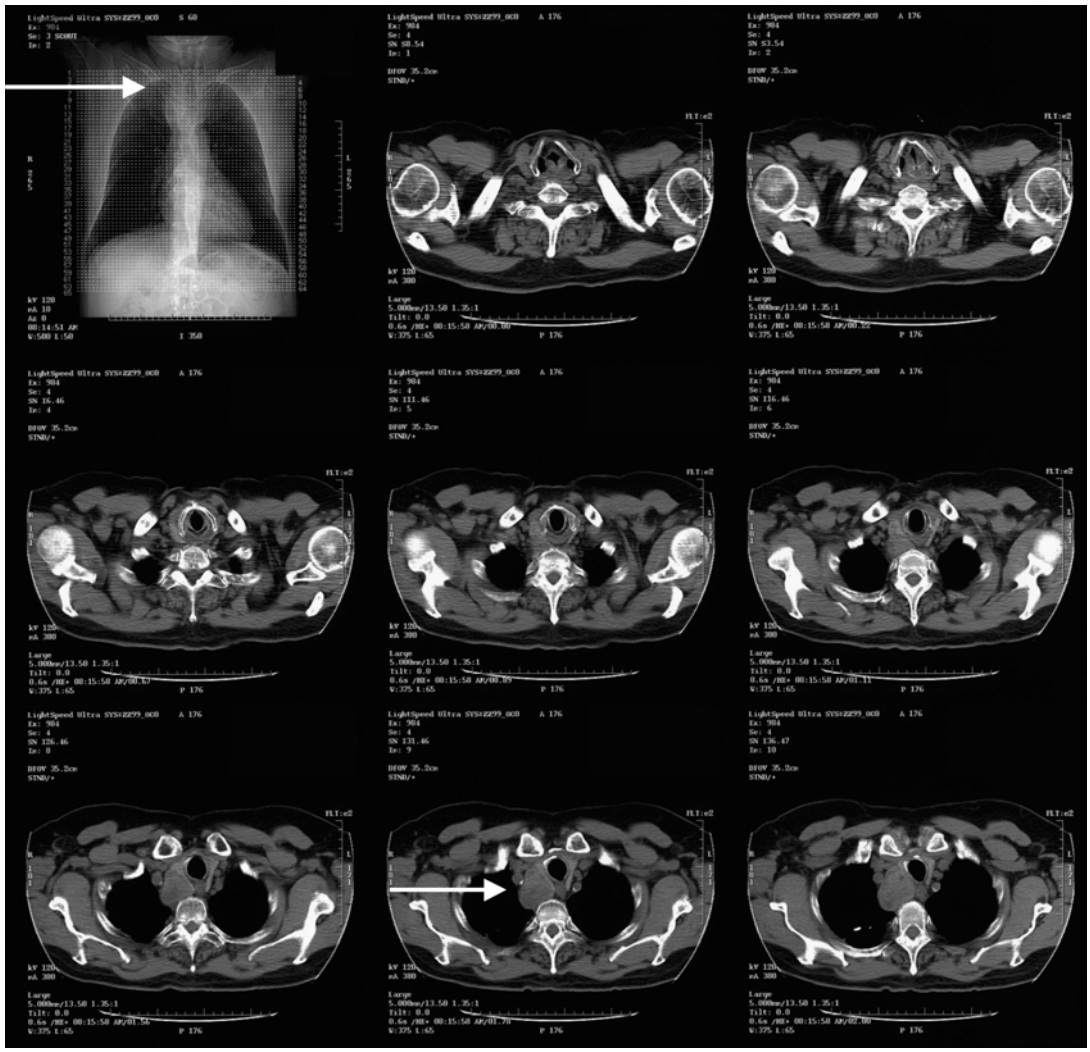

Figure 4.14. CT scans in a patient with a substernal goiter: The image in the top left is a scout film showing the superior mediastinal mass. The remaining images are transaxial slices. The substernal extension is shown by the arrow and the trachea is deviated to the left.

lent information. The uptake of radioiodine is frequently patchy except in the rare case of thyrotoxicosis in the substernal goiter (265). Although interventional radiologists can insert a biopsy needle into almost any site in the body using CT or, in some special circumstances, MRI guidance, most authorities do not recommend FNA of retrosternal goiters. One reason is the proximity of the great vessels and a second reason is that the goiters are large and the cytopathology might not be representative.

The presence of a substernal goiter is usually an indication for surgical treatment (266–269). The size of the goiter and whether it is compressing structures should be evaluated and this information is best obtained from a clinical examination and CT scan. The age and general health of the patient are important. A small substernal goiter in an elderly patient with cardiac failure is best left untreated. When there is high uptake of a tracer of radioiodine ^{131}I can be considered, but the size of the goiter and the twenty-four-hour uptake can be used to determine whether that approach would be appropriate (270). Since most patients have a large volume of tissue and relatively low uptake radioiodine treatment is usually reserved for patients who are poor operative risks. The average reduction in intrathoracic volume of the goiter in fourteen patients treated with ^{131}I was 29.2% (271).

The patient should be evaluated by the anesthesiologist prior to operation and fiberbronchoscopic evaluation made in any patient with tracheal compression to plan the intubation. Most nodular substernal goiters can be removed using a standard collar incision. This was the case in 158 of 170 reported by Erbil et al. (268). A lower percentage (1–2%) have been reported in other series of eighty or more patients (269, 272). All twenty-three patients operated on by Netterville et al. had only a cervical incision (273). The remainder required sternotomy for adequate access. There is a theoretical risk of tracheomalacia from the constant pressure of the goiter but in practice this is uncommon. The proportion of patients who had permanent damage to the parathyroids and recurrent laryngeal nerves was small in all of these reports. One group did report life threatening intraoperative complications during the removal of a giant intrathoracic goiter due to sudden changes in the mediastinal structures when the mass was extracted (274). The size of the nodular goiter placed this patient in a small minority. Therefore in most patients with average sized substernal goiter thyroidectomy is safe and effective. The incidence of cancer in surgically removed glands ranges from 2.5% to 13% and thus mirrors the range for nodular glands in the cervical position (268, 269).

Summary and Key Facts

Solitary thyroid nodules and nodular goiter are common. Most patients are euthyroid and the best investigation is FNA of the nodule or dominant nodule. A scintiscan is a valuable first investigation in thyrotoxic patients since an autonomous "hot" nodule in an adult has minimal risk of being a cancer and can be treated by lobectomy or ^{131}I (or injection with ethanol). The algorithms for work up are shown in Figures 4.1, 4.3 and 4.12.

- Thyroid nodules are common and are clinically detectable in 4% to 5% of adults.
- Thyroid nodules are more common in women.
- Thyroid nodules are identified in 30–50% of normal people on ultrasound.
- Approximately 5% to 6% of clinically obvious thyroid nodules are cancers.
- The risk of a nodule being cancer is greater in a child.
- A history of radiation in particular external radiation over the gland increases the probability of cancer and 7% to 9% of those irradiated develop thyroid cancer.
- A hard solitary nodule is more likely to be cancer, and when there are abnormal feeling cervical nodes the risk is greater.
- The best test to differentiate cancer from a benign nodule is FNA provided the patient is euthyroid.
- An adequate FNA detects most cancers and has a low false negative and false positive rate.
- An inadequate FNA should be repeated.
- A microfollicular pattern on cytological examination has a 10% to 20% chance of being a cancer.

- When the patient is biochemically hyperthyroid a scintiscan can determine when there is a functioning nodule that is almost always benign in an adult.
- Scintiscan can show when there is a non-functioning nodule in Graves' disease.
- Ultrasound can occasionally diagnose that a nodule is cancerous.
- The main roles of ultrasound are to measure size of a nodule, to identify a dominant nodule in multinodular goiter, as an aid to FNA, and for following patients.
- Benign nodules can be kept under observation.
- In iodine replete countries there is little benefit from levo-thyroxine to suppress TSH.
- Cystic nodules benign on FNA can be reaspirated if they recur or they can be injected with ethanol under ultrasound guidance.
- When FNA shows evidence of cancer the patient should be referred for thyroidectomy.
- Hyperfunctioning nodules can be treated by lobectomy or ^{131}I
- The risk of cancer in multinodular goiter is less than in a non-functioning solitary nodule but greater than most textbooks suggest.
- A dominant non-functioning nodule should be investigated by FNA.
- Toxic multinodular goiter is treated by operation or ^{131}I.
- Non-toxic goiter causing symptoms is treated by operation and in selected cases using ^{131}I.
- Reports indicate a value of rhTSH to increase the uptake of radioiodine in euthyroid patients.

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Chapter 5

Etiology of Thyroid Cancer

All cancers are ultimately due to an abnormality in genes. There might be loss of a tumor suppressor gene, activation of an oncogene, damage to repair mechanisms of DNA, or combinations of these. Therefore cancer of the thyroid is due to a factor or factors that cause defects in genes that control cell growth, division, and the ability to invade. Radiation is one of the most important agents that produce alterations to genes. There are also familial thyroid cancers that are associated with genetic abnormalities. The best recognized and understood are the familial medullary cancers, but there is increasing evidence of familial non-medullary cancer (i.e. familial differentiated thyroid cancer). Specific genetic mutations have been identified in the familial medullary cancer syndromes. These are predictable and allow for the diagnosis to be made in those with the mutation before there is clinical evidence of disease. There is also increased knowledge and understanding of mutations in sporadic differentiated and anaplastic thyroid cancer. This chapter focuses first on radiation as a cause of thyroid cancer. The terminology and units of measurement of the *Système International* (SI) and standard units of radiation are defined, and radiation physics is presented briefly. Then the genetic defects in familial cancers are described. The relation of radiation and mutations are discussed. Other less important causes of thyroid cancer are discussed at the end of the chapter.

Radiation as a Cause of Thyroid Cancer

There is abundant information indicating that radiation can cause not only thyroid cancer but cancer of other organs such as the breast, bone marrow, bone, and lung. This chapter focusses on thyroid cancer. Young age and female gender of the person exposed are important. Varying doses of radiation to the thyroid have different effects, with intermediate doses to tissues being carcinogenic and high delivered doses causing death of cells and hypothyroidism. For many years the majority of data supported that external radiation (X-rays), rather than internal radiation from radionuclides of iodine was a more important causal factor for development of cancer of the thyroid. However, the increased incidence of thyroid cancer in children who were exposed to internal radiation at the time of the Chernobyl incident has altered this concept. This has been validated by reports from Ukraine, Belarus, and Russia. Table 5.1 is an empirical but manageable way of reviewing of situations that can result in radiation exposure to humans. These have been classified under four main headings, medical, occupational, atomic bomb, and accidental. In many of the categories it is easy to determine whether the radiation is external, such as treatment of Hodgkin's disease by radiation therapy, or internal, such as treatment of Graves' disease with ^{131}I. Some-

Table 5.1. Potential situations that could result in exposure of humans to radiation and cause radiation to the thyroid.

Major	
Medical	Diagnostic
	Diagnostic X-rays
	CT scan
	Nuclear medicine, thyroid scan
	Therapeutic : external
	Treatment of tinea capitis
	Treatment of acne
	Treatment of hemangioma
	Treatment of Hodgkin's disease
	Treatment of head and neck cancer
	Total body radiation
	Therapeutic : internal
	Treatment with ^{131}I
	Graves' disease
	Toxic nodular goiter
	Thyroid cancer
Occupational	Medical
	Radiology
	Radiation oncology
	Nuclear medicine
	Nuclear power plant
	Other
Atomic bomb	War
	Hiroshima and Nagasaki
	Testing
	Marshall Islands
	Nevada
Accidental	Three Mile Island
	"Hanford"
	Chernobyl

times the distinction is less apparent, for example, in the case of radiation from an atomic bomb, the type and quantity of radiation is related to the proximity to the explosion. Persons close to an atomic explosion are more likely to be irradiated externally, those further away are more likely to inhale or ingest the radioactivity. When there are radionuclides of iodine and they are inhaled or swallowed, a proportion will be trapped by the thyroid and dependent on the dose of radiation delivered, a range of thyroid disorders can evolve. In an individual, the proportion of radioiodine trapped is directly related to the function of the thyroid and to the dietary iodine. A person with an overactive thyroid, such as Graves' disease, will have a high thyroid uptake, as would a person living in an iodine deficient region. In population studies, the average thyroid uptake is more dependent on dietary iodine, since thyroid dysfunction affects only a small proportion of the community. The Chernobyl nuclear accident occurred in an iodine deficient region; therefore, a higher percentage of radioactive iodine was trapped than would be the case in the United States.

An accurate calculation of the dose of radiation delivered to the thyroid can be very difficult. In retrospect, how can the dose delivered to the thyroids of children living hundreds of miles from a nuclear accident, such as Chernobyl, be measured? Most often the estimates are made weeks or months after exposure. In contrast, in some situations it is very straightforward to determine the radiation delivered to the thyroid, for example in patients who have received specific doses for therapeutic purposes, such as treatment of Hodgkin's disease.

In this Chapter, I shall approach the topic by looking at the people who are exposed and then determine whether the radiation is internal, or external, or a combination of these. I shall attempt to provide as specific as possible the doses of radiation delivered to the thyroid and also the specific incidences of thyroid cancer. In interpreting the data it is important to recognize that some reports indicate an increase in the incidence of thyroid cancer, whereas others discuss an increase in mortality from thyroid cancer. Most patients with thyroid cancer do not die from thyroid cancer. However, having thyroid cancer results in thyroidectomy, sometimes treatment with ^{131}I, the need to take thyroid hormone for life, an increased need for biochemical and imaging tests, and visits to physicians, plus many other concerns and fears. Neither the diagnosis of thyroid cancer nor the mortality are good things. We want to eliminate factors responsible for both. First, there are brief sections on terminology, radiation physics, and radiobiology.

Terms and Definitions Related to Radiation, Radiation Doses, and Exposure

At the start, it should be helpful to define the units used to describe radiation exposure and dosimetry. It is also useful at this point to

discuss the types of radiation with an emphasis on radionuclides of iodine and to give details of the radiation delivered internally to the thyroid. This topic is expanded in the discussion of radioiodine therapy in the Chapter 6 on differentiated thyroid cancer.

Two systems of nomenclature are in common usage. This is confusing for patients and also for physicians. The international system (Systeme International d'unites, SI units) is used exclusively in Europe and the non-SI system, or standard system, is used predominantly in the United States. There is an increased effort to use SI units universally and in scientific reports. In spite of that some journals and textbooks use only standard units and others both. Throughout the text I present the units from both systems and hopefully readers will become comfortable making the conversions.

Radiation is energy. The energy of radiation results in ionization of atoms and that causes damage to cellular materials such as DNA and cell membranes. In everyday non-radiological usage, energy is usually measured in Joules (after James Prescott Joule an English scientist 1818–1889). One Joule is the energy required to lift 1 kg to a height of 10 cm. In SI units when 1 Joule of energy is delivered to one Kg it is defined as 1 gray (1 Gy, in recognition of the radiobiologist L.H. Gray). One Gy is equal to 100 rad (radiation absorbed dose) in the non-SI system. These are quantities of radiation absorbed by tissue. All types of radiation do not cause the same amount of damage to tissues. Photons, including x-rays, gamma rays, and Beta particles (electrons, β) are equivalent. Neutrons and alpha (α) particles are considerably more damaging (1). This is because they have substantial mass. An alpha particle is a helium nucleus that has mass (2 protons and 2 neutrons) and also electric charge. Alpha particles released inside the body travel very short distances. Because of their mass and charge they are very destructive to biological molecules in their path. An alpha particle emitted adjacent to a chromosome causes many breaks in DNA. The breaks are in close proximity and are unlikely to be reparable (2). In contrast a photon traversing DNA might cause a single break that would be amenable to the one of the many repair mechanisms for DNA. Therefore, there are simple mathematical conversions that allow the damaging ability of the radiation to be considered. These are derived by multiplying the absorbed dose by a quality factor that depends on the type of radiation. The quality, or weighting factor, for most radiological and nuclear medicine sources of radiation is 1 (i.e., the quality factor is 1 for x-rays, gamma rays, and electrons). The quality factor for neutrons is 10 (range 5–20) and for alpha particles it is 20. The term "linear energy transfer" (LET) describes the delivery of energy in keV/μm (kilo electron volts per millionth of a meter). Particles of mass and electric charge have a high LET, whereas, photons have low LET. The range of LET values is considerable. Photons have LET rates of 0.2 keV/μm to 2 keV/μm. Neutrons have LET rates of 40 keV/μm to 80 keV/μm and alpha particles values as high as 200 keV/μm. The quality factor is a method of correcting for differences in LET.

To describe radiation in man, in the SI nomenclature the Sievert (Sv) is the basic unit and in the non-SI system it is the rem (Roentgen equivalent man). For photons and electrons the Sv and Gy are equivalent and they are equal to 100 rem and 100 rad respectively indicating that rem and rad are also equivalent. In the case of particles with mass such as alpha particles, 1 Gy is equivalent to 20 Sv, and for neutrons, 1 Gy is equal to 10 Sv. The dose equivalent expressed in Sv or rem is a more accurate index of the biological effect of radiation. Table 5.2 lists these terms and the results of conversion from one system to the other.

Next the units of radioactivity are described. In the SI system, the basic unit is the Becquerel (Bq, named after Henri Becquerel). It is equal to a source of radioactivity that decays by one disintegration per second. This is a very low amount and in clinical practice Mega Becquerel (MBq, 10^6 Bq) or even Giga Becquerel (GBq, 10^9 Bq) are employed. In the non-SI system the basic quantity of radioactivity is the Curie (Ci, named after Madame Marie Curie). One Curie is a source of radioactivity that decays at a rate of 3.7×10^{10} disintegrations per second. This is a very large quantity of radioactivity and clinically quantities such as microcurie (μCi, one millionth of a Curie) and millicurie (mCi, one thousandth of a Curie) are used. One mCi is equal to 37 MBq and 1 MBq is equivalent to 27 μCi. The conversion of these units is also presented in Table 5.2.

Table 5.2. Definitions of terms used to describe radiation.

Unit	Definition	Equivalent	Comment
Gray (Gy) SI unit	Unit of absorbed dose of radiation equal to one Joule per Kg	100 rad	
cGy SI unit	1/100 Gy	1 rad	
mGy SI unit	1/1000 Gy	0.1 rad	
Sievert (Sv) SI unit	Dose equivalent from radiation	100 rem	Gy and Sv are the same for photons and electrons
mSv SI unit	1/1000 of a Sv	0.1 rem	
Rad Non SI unit	Unit of absorbed dose of radiation equal to 100 erg/g	cGy, or 10 mGy	Rad and rem are the same for photons and electrons
Rem	Dose equivalent from radiation	10 mSv	
Curie (Ci)	Quantity of radioactivity that decays at a rate of 3.7×10^{10} disintegrations per second (DPS)	3.7×10^{10} Becquerel (Bq)	Usual clinical quantities are mCi, or μCi
Becquerel (Bq)	Quantity of radioactivity that decays at a rate of 1 disintegrations per second (DPS)		Usual clinical quantities are MBq, or GBq

Radionuclides of Iodine

There are twenty-five radioactive nuclides of iodine. The best known medically are ^{131}I used to treat thyroid cancer and hyperthyroidism and for diagnostic whole-body scintigraphy in patients who have thyroid cancer and have undergone thyroidectomy. Iodine-123 is a diagnostic agent used for imaging and ^{125}I is widely used in biological laboratories for radioimmunoassays and for labeling proteins in vitro. Iodine-125 was also used to treat hyperthyroidism in the hope that the low energy Auger electrons (to be described below) would not cause irreparable damage to nuclear DNA and patients would not become hypothyroid (3) Iodine-124 is a positron emitter that has value in imaging called positron emission tomography (PET scanning). Some radionuclides such as ^{132}I and ^{134}I have very short half-lives. They could be important in causing radiation damage to the thyroids of survivors of Nuclear Power plant accidents (4). Iodine-129 has a half-life of more than 15×10^6 years. Table 5.3 lists the radionuclides, their common usages, their half-lives and radiation delivered to the thyroid. Iodine- 131 emits both γ photons and β particles. When ^{131}I is employed for whole-body scanning in patients with thyroid cancer the quantity administered is 37 MBq to 370 MBq (1–10 mCi) and for therapy 1.0 GBq to 7.4 GBq (30 to 200 mCi). The dose of ^{123}I varies considerably from 7.4 MBq (200 μCi) for a routine thyroid

Table 5.3. Important nuclides of iodine.

Radionuclide	Half-life (hours)	Comment
I-127	Non radioactive	Dietary iodine, necessary for formation of thyroid hormones
I-131	193	Used for treatment of hyperthyroidism, thyroid cancer and other diseases when attached to antibodies or ligands Used for whole-body scanning
I-123	13	Used for routine thyroid scintigraphy and for whole-body scanning
I-125	2,880	Used in vitro for radio-immunoassays, protein labeling, autoradiography Was used for therapy
I-124	96	Positron emitter for whole-body scan and dosimetry
I-132	2.3	Was used for early uptake measurements and scans
I-133	20.8	Was used for therapy
I-134	0.8	
I-129	15.7×10^7 years	
Te-132m	29	Decays to I-123

Table 5.4. Radiation levels associated with common events.

Activity	Radiation SI units	Radiation Standard Non SI units
Living one year in the US	0.003 Sv (3 mSv)	300 mrem
Flight from San Francisco to London	0.0001 Sv (0.1 mSv)	10 mrem
Chest x-ray	0.0001 Sv (0.1 mSv)	10 mrem
Computed Tomography (CT) of chest	0.01–0.05 Sv (10–50 mSv)	1,000–5,000 mrem 1–5 rem
To be at 1 meter for 1 hour beside a patient who has just received 3.7 GBq (100 mCi) ^{131}I for treatment of thyroid cancer	0.0002 Sv (0.2 mSv)	20 mrem
Barium enema	0.003–0.008 Sv (3–8 mSv)	300–800 mrem
Occupational (NRCP report 116 1993)		
Annual	50 mSv	5,000 mrem
Cumulative	10 mSv × age in years	1,000 mrem × age
Lens of eye	150 mSv	15,000 mrem
Skin of hands	500 mSv	50,000 mrem
Public (NRCP report 116, 1993) Annual	1 mSv continuous 5 mSv infrequent	100 mrem 500 mrem
Diagnostic nuclear medicine scintiscans eg bone scan	1–2 mSv	100–200 mrem

scan to 37 MBq to 185 MBq (1–5 mCi) for whole-body scan. Because of the two systems of nomenclature, there are two columns related to the absorbed radiation dose one in rem/mCi the other in Sv/MBq.

The radiation associated with common every day events including living is presented in Table 5.4. In the United States the average total radiation is approximately 3.6 mSv/yr (360 mrem/yr). This is made up by cosmic radiation, radiation from radon, internal radiation from natural radionuclides mostly ^{40}K, and medical sources, including x-rays, CT scanning, and nuclear medicine procedures. In the USA it has been estimated that on average we receive on average 0.4 mSv/yr (40 mrem/yr) from diagnostic radiological sources and 0.015 mSv/yr (15 mSv/yr) from nuclear medicine tests. Obviously some people have no such exposure and others, including patients discussed in this book receive higher exposures.

Radiation Exposure

Medical, Diagnostic Procedures: External Radiation

Most people are exposed to medical radiation at some point in their lives. Most commonly this is x-ray (Roentgenogram) for evaluation of dental problems, pulmonary diseases, fractures, and so forth. A regular x-ray gives 0.05 mSv to 0.1 mSv (5–10 mrem) radiation. It is increasingly common for patients to have Computed Tomographic (CT, or CAT) scans. The radiation associated with a CT scan is considerably greater. There are estimates that children can receive 0.05 Sv (5 rem) from a CT scan. The dose to the thyroid in adults undergoing a helical CT of the cervical spine has been determined using phantoms to be 0.026 Sv (2.6 rem) (5). There can be differences in the radiation delivered by CT scanners from different companies and between instruments that appear similar. Even in areas that usually do not raise questions about radiation exposure, such as dentistry, there is increasing use of dental CT to produce 3 dimensional images (6). The thyroid can receive 0.004 Sv (0.4 mrem) (6). Patients being treated for non-thyroidal cancers commonly have a CT scan every several months to judge the response of the cancer to therapy.

Many patients with congenital and acquired heart diseases are subjected to angiographic procedures. The radiation depends on the length of time required for imaging, but it is not uncommon for the dose to the skin to be in excess of 1 Sv (100 rem). Radiation burns of the skin have been described as a result of diagnostic imaging. Since it has been demonstrated that 0.06–0.1 Sv (6–10 rem) from external radiation can cause an increase in thyroid cancer, physicians should be concerned when diagnostic

radiologic procedures or repeated diagnostic procedures reach this dose (7, 8). There is a report of brothers developing thyroid cancer after radiation exposure after cardiac catheterizations (9). There is an increase in non-thyroidal cancers, including lymphoma and melanoma in children who have had cardiac arteriograms (10).

One authority has questioned whether the risks of diagnostic imaging are greater than the benefits (11, 12). Hopefully the answer is no but the question should remind us always to have a good reason for ordering a radiological investigation and to be able to defend the cost to benefit ratio. The cost includes economic, plus potential somatic mutations that could cause cancer plus genetic mutations that could affect subsequent generations who gain no benefit from the test. Diagnostic radiological procedures should be ordered only when there is a benefit to the person exposed to the X-rays and when the result changes the management (13). This is most important in pediatric patients.

Medical, Diagnostic Procedures: Internal Radiation

The thyroid receives radiation from diagnostic procedures using radionuclides of iodine and from ^{99m}Tc (pertechnetate). Iodine-123 is a pure photon emitter with a half-life of 13 hours and it delivers a fraction of the radiation compared to ^{131}I, which has a half-life of 8 days and γ and β emissions. Therefore for routine diagnostic thyroid scintigraphy, ^{123}I is preferred; 200 μCi ^{123}I (7.4 MBq) delivers 2 cGy (2 rad) to a normal sized thyroid when given by mouth to an adult whose thyroid traps 20% of the dose. In contrast, 100 μCi ^{131}I (3.7 MBq) delivers approximately 1 Gy (100 rad). These administered doses are representative of those used in practice but clearly ^{123}I is superior. There is a report of a patient presenting with metastatic papillary thyroid cancer at age 20. She had diagnostic scans with ^{131}I at age four and twelve years. Retrospective calculations determined that her thyroid received 2.4 Gy (240 rad) (14). A multicenter trial in the US evaluated thyroid nodules and cancers arising in children who had prior diagnostic procedure with ^{131}I. These patients were compared to age matched controls with thyroid disease who did not have diagnostic scans. There were five cancers in the 3,503 study patients and one cancer in 2,594 control patients. Although the difference was not statistically significant, there does appear to be a trend (15). A study of 34,104 patients who had ^{131}I scans in Sweden showed 67 thyroid cancers when 49.7 were predicted (16). The thyroids received an average of 1.1 Gy (110 rad). The population included adults and children, and when patients less than 20 years were analyzed, there were 3 cancers versus 1.8 expected. The entire population has been re-evaluated and again the conclusion stands that there was no increase in thyroid cancer in adults who had thyroid scans with ^{131}I that delivered on average 0.94 Gy (94 rad) (17). The authors make several points. When the scan was obtained in the work-up of a thyroid tumor there was an increase in subsequent thyroid cancers. This is likely due to the fact that the cancer was already present. They identified 1,767 of the group who had received external radiation before the thyroid scans and that cadre had 9.8 times the number of cancers expected (95% CI 6.3–14.6). Finally there were insufficient children to make definitive statements about the thyroid cancer risk in that age group.

These studies show a slight increase in thyroid cancer after diagnostic doses of ^{131}I, but the differences are not statistically significant. However in view of the high dose of radiation to the thyroid and increasing evidence that internal radiation can be carcinogenic (see below), it is disappointing that some physicians still use ^{131}I for routine diagnostic scintiscans in all age groups, when ^{123}I has been available for more than 25 years (18).

Medical, Therapeutic Procedures: External Radiation

The doses of external radiation used to treat patients with cancer is usually in the range 40 Gy to 60 Gy (4,000–6000 rad). The effect of this is described below. In the past physicians prescribed lower doses of radiation to treat non-malignant conditions. It is the result of the low dose external radiation treatments that the increases incidence of thyroid cancer was recognized and then quantified. One of the benign conditions treated by external radiation was "status thymomicus" in young children. That

was the presumed association of an enlarged thymus with recurrent upper respiratory infections, or failure to thrive in childhood. It is now recognized as a non-disease. The thymus is larger in all children and is not the cause of medical problems. The unwell child had a chest x-ray that demonstrated an "enlarged" thymus, which was interpreted to be the cause of the symptoms, and then it was subjected to external radiation. The thymus was normal, but the thyroid was an innocent bystander that, in current jargon, became collateral damage. Acne vulgaris in teenagers was also treated by external radiation as was tinea capitis, enlarged tonsils and adenoids, scrofula, and pertussis. The doses employed were usually in the 1 Gy to 10 Gy (100–1,000 rad) range. Early reports of an increase in thyroid cancer in these children treated for these disorders by external radiation is attributed to Duffy and Fitzgerald, (19), Clarke (20), and Hempelman et al. (21). Because this type of therapy was administered to many children in the 1930s to 1950s, five to twenty years later an increasing numbers of patients were found with thyroid cancer of those who had been subjected to these treatments. Several investigators conducted clinical and scintigraphic evaluation of patients who had received external radiation and found that 5% to 10% developed thyroid cancer. Favus et al. examined 1,056 patients (22). They identified 287 patients with abnormal thyroids, either by finding a nodule clinically or an abnormality on scan. One hundred eighty-two had a thyroidectomy and 60 cancers were found. Put simply almost 6% of the study group had cancer of the thyroid and one third of those referred for thyroidectomy had cancer. Maxon et al. not only evaluated irradiated patients but a matched control group who had not been irradiated. Sixteen cancers and fifteen benign nodules were identified from 1,266 study patients in contrast to one cancer and two benign nodules from the 958 controls (23).

Several studies confirm the natural history of radiation related thyroid cancer is the same as in spontaneously occurring cancer (24–26). In all of the reports the latent period between the external radiation treatment and identification of the cancer usually fell within five to twenty years. It was most unusual to find the cancer in follow-up of less than five years. In one review this was the case in only two of 700 patients (7). In addition, in all reports young age was important and the risk decreased in patients 20 years of age or older at the time of exposure to external radiation. Some even subdivide the young into those five years or less who are at the highest risk when compared with those six to nineteen years old. Women are about twice as likely to develop a radiation related thyroid cancer, and because they have a three-fold increase without radiation the risk of external radiation in a young woman are multiplied six fold.

When higher doses of external radiation are administered to treat cancer and the thyroid is in the radiated field the most common disorder is hypothyroidism (27–29). This is the result of radiation damage to the cells that either kills them or leaves them incapable of division. In some patients, several weeks to months after high dose external therapeutic radiation there is a syndrome that is similar to silent thyroiditis. The patient has no neck pain and becomes clinically and biochemically thyrotoxic and after several weeks the thyroid function returns to normal and subsequently the patient becomes hypothyroid (30, 31). In this syndrome the uptake of a tracer of radioiodine is low during the thyrotoxic phase, hence the similarity to silent thyroiditis. The external radiation probably damages the follicles and thyroid hormones leak into the circulation causing the thyrotoxic phase (32). The hypothyroidism is attributable to lethal radiation damage to the follicular cells and when it occurs is usually permanent. Although hypothyroidism is numerically the most important thyroid disorder, after high dose external radiation, paradoxically, there is an increase in Graves' hyperthyroidism and Graves' orbitopathy (33). One hypothesis is that the radiation alters thyroid antigens and the immune system produces antibodies, some of which are against the receptor for thyroid stimulating hormone and act as thyroid stimulating antibodies. Although identifying and treating thyroid dysfunction requires appropriate follow-up and testing, the treatment is usually straightforward. The main clinical concern after neck irradiation is the development of thyroid nodules and thyroid cancer. It used to be thought that high dose radiation was not followed by thyroid cancer because the follicular cells were sterilized and unable to divide. Single case reports and small series demon-

strated this dogma was wrong (34–36). Although numerically the probability of a patient developing thyroid cancer after therapeutic external radiation is small, in our experience at Stanford, there is approximately a twenty-fold increase ten to twenty years after the exposure (33). Similar findings have been reported in a multi-center follow-up study (37). In this investigation the standardized increased ratio for thyroid cancer was thirty-six times. In an additional follow-up study from the Sloan-Kettering Cancer Center thirty-three patients were found to have a thyroid neoplasm after external radiation therapy in childhood (38). Thirteen of the lesions were cancer (11 papillary, 2 follicular), and the average time between treatment of the primary cancer and identification of thyroid cancer was 6.5 years. Those who developed thyroid cancer received a dose of 20 Gy (2,000 rad). In a recent report from Poland four of 849 patients who were treated for Hodgkin's disease developed thyroid cancer (39). The total number and the percentage of patients developing thyroid cancer after external radiation are small, but because thyroid cancer is not common, the relative risk is definitely increased about twenty fold.

Several studies indicate that thyroid cancer can occur after substantially lower therapeutic doses of external radiation than discussed above. In these reports the radiation was delivered to a region unrelated to the thyroid but scattered radiation of relatively small amounts was causal. One large study relates to treatment of tinea capitis (ring-worm) of the scalp (40). These children were treated by scalp irradiation for ringworm where the goal was to deliver a total of 3.75 Gy (375 rad) to the scalp over 5 days, a dose known to cause epilation. Retrospectively it was possible using phantoms to calculate that the thyroid received approximately 6–10 cGy (6–10 rad or 0.06–0.1 Gy) (40). Ten thousand, eight hundred thirty-four exposed children were compared to 10,834 matched non-irradiated children and to 5,392 siblings who were also not irradiated (7, 41). There were 44 cancers in the treated group versus an expected 10.7. The control group had 16 thyroid cancers. The data has been reanalyzed using techniques to control for variables such as movement of the child during radiation and their age at the time of repeat treatments etc. The final data were unchanged and there was an excess relative risk for thyroid cancer of 0.351 cases per cGY (rad) or 35.1 per Gy (100 rad) (42). As an historical footnote, radiation therapy for ringworm of the scalp was introduced in 1909 (43)! Similar increases have been described in children under the age of one year who were treated for hemangioma by radiation. Seventeen cancers were identified in 14,351 patients when 2.26 cancers were predicted. The radiation dose was 28 cGy on average (28 rad). Since the radiation from several CT scans is not dissimilar from these therapeutic doses, there should be some caution to ordering these procedures by rote in children (44). The average time between irradiation and diagnosis of cancer was thirty to forty years.

Total body radiation is used in patients with cancer who are to receive marrow transplantation. In an analysis of 478 patients who received 12 Gy to 13.5 Gy (1,200–1,350 rad), 10% became hypothyroid but there were no thyroid cancers (45). I have encountered a patient who received low dose total radiation for immunologic suppression who developed metastatic papillary cancer.

Almost all cancers associated with external radiation are papillary. Taking all the information related to external radiation it has been calculated that there is an excess relative risk of 7.7 per Gy (100 rad). The absolute risk is four or five cancers per 10,000 (10^4) per year per Gy. From the data available there is a linear effect from low doses, 0.06 Gy (6 rad), to 5 Gy to 10 Gy (500–1,000 rad) as described below. This relationship holds true until the administered dose reaches 5 Gy or higher (500 rad). At about this dose the risk levels off but does not reach zero and has been estimated to be 0.4 cancers 10^4 per Gy per year (46). In addition to the radiation dose, the age of the patient at time of radiation is important. Most cancers arise after a latent period of five years, and the incidence falls but does not disappear after twenty years. Women are at greater risk. It is possible that the type of first cancer can alter the risk of developing the thyroid lesion. One study showed a greater risk in patients with neuroblastoma compared to Hodgkin's disease, non-Hodgkin's lymphoma and Wilm's disease. Patients who have been treated for cancer tend for the rest of their lives to have more extensive contact with physicians and continued medical surveillance. The question arises could the increase in thyroid cancers be due to increased screening and testing? The

actual increases in numbers with thyroid cancer argue that this is not an artifact of surveillance.

For the induction of many cancers there is not a single cause, and this is likely to be true for radiation and thyroid cancer. There is a definite risk, but if radiation was the cause, why do all exposed patients not get thyroid cancer? Thyrotropin (TSH) is an important factor for growth and division of follicular cells. In animals radiation plus a raised TSH is much more carcinogenic than radiation alone (47). Conversely suppression of TSH soon after the radiation produces a reduction in risk in experimental animals. The human model is not so clear but the implication is that patients who have had neck irradiation should have periodic checks of thyroid function as well as palpation of the neck. When TSH rises above 4 mIU/l (some might use 3 mIU/l) thyroid hormone should be prescribed with the aim of lowering TSH to 0.5–1.0 mIU/l.

Medical, Therapeutic Procedures: Internal Radiation

Iodine-131 has been used for treatment of hyperthyroidism for sixty years. Most of the patients had Graves' disease but patients with single and multiple autonomous nodules have also been treated. One of the concerns about treating benign conditions with radiation is that there would be an increase in cancers in the organ being irradiated. I have seen three patients who developed thyroid cancers after ^{131}I treatment for Graves' disease, one patient was treated elsewhere and one treated in each of the two institutes where I have worked (48–50). Therefore the denominator of treated patients is not well defined. Ron et al. conducted a large follow-up study of 23,020 patients treated with ^{131}I, 9,028 received only radioiodine treatment, the remaining patients were also treated with anti-thyroid medications (10,439), anti-thyroid medications and surgery (2,661) or surgery (892) (51). The investigators found 29 patients died from thyroid cancer when 10.47 deaths would have been expected (Standardized Mortality Ratio 2.77: CI 1.85–3.98). The cancers were more likely to be found in patients with nodular glands and within four years of ^{131}I treatment. The conclusions were (1) there was a small increase in thyroid cancer after ^{131}I treatment of thyrotoxicosis (2) because of the short latency period and increased number in patients with nodular glands the cancers could have been present at the time of ^{131}I treatment, (3) dominant nodules especially non-functioning nodules should be sampled by fine needle aspiration. Almost all of the cancers that have arisen after ^{131}I treatment are papillary but there are a few reports of anaplastic cancer (52).

The commonest thyroid disorder after treatment with ^{131}I for thyrotoxicosis is hypothyroidism. In some long-term follow-up this can affect 100% of patients. This probably accounts for the low incidence of thyroid cancer, since the follicular cells receive a large dose of absorbed radiation that either kills them or leaves them incapable of division and hence incapable of producing a cancer. When the internal radiation to the thyroid is very high there can be a transient painful radiation induced thyroiditis (53, 54). The gland is swollen and tender. This is very different from the silent radiation thyroiditis from external radiation. Painful thyroiditis occurs rarely after treatment of Graves' disease or ablation of residual thyroid tissue in patients with thyroid cancer (54). It has been stated that painful radiation induced thyroiditis does not occur unless the tissues absorb several tens of thousand rads. Complete ablation of all cells is the usual outcome.

Iodine-131 treatment of thyroid cancer is designed to ablate all functioning thyroid cells both malignant and benign. When a thyroid cancer of the same type occurs after this therapy it is accepted that the patient has a recurrence of cancer. However when a cancer with a higher grade of disease occurs there is concern that the ^{131}I altered the genes resulting in dedifferentiation of the original cancer (55, 56). Since this can occur in patients whose original cancers were treated by surgery alone, there continues to be debate about the role of ^{131}I causing anaplastic cancer, and this topic is expanded in Chapter 9 (57).

Occupational Exposure: Medical

I am aware of colleagues in Nuclear Medicine and radiological specialties who have had thyroid cancer but the denominator is unknown. The cancer mortality in British radiologists working between 1897 and 1997

showed no increase in those who were registered after 1954 (58). There was an increase in earlier years but radiation safety precautions were less rigorous at that time. The report makes no mention of thyroid cancer. In a different study cancer mortality was quantitated in 146,000 radiologic technologists (59). There were seven deaths from thyroid cancer, six in women. The SMR was less than one. In summary the published data shows no increase in thyroid cancer deaths in medical personnel who work with radiation.

Occupational Exposure: Nuclear Power Plants

Omar et al. reviewed the mortality and cancer deaths of 14,319 people who had worked at Sellafield Nuclear Power plant (previously called Strangeways). The cancer mortality was 3% less than for the region and 5% less than in England and Wales. However, there was an almost threefold increase in thyroid cancer deaths (6 identified versus 2.2 expected) (60). Four of the patients who died of thyroid cancer were radiation workers and two were not. There was also an increase in deaths from mesothelioma that could be attributed to plutonium (60, 61). There is no good explanation for the increase in thyroid cancer deaths, the numbers are small and could be due to chance. There has been no increase in thyroid cancer deaths reported from other analyses of nuclear power plant workers (62).

Occupational Exposure: Miscellaneous

In the United States the average radiation exposure to each member of the population is 300 mrem to 360 mrem (3–3.6 mSv). The radiation increases at higher altitude. Airline pilots and cabin crew receive an additional 500 mrem to 1,000 mrem (95–10 mSv) annually. Therefore a twenty-year career could result in 20 rem (0.2 Sv). The radiation is greater on transcontinental flights over the North Pole. A study of almost 28,000 male cockpit crew, over 550,000 person-years, evaluated cancer mortality (63). There were five thyroid cancer deaths, which was more than 3.6 expected giving a SMR of 1.48, but the 95% CI ranged from 0.47 to 3.48. Overall cockpit crew had a significantly lower than expected risk of dying from cancer, probably explained by healthy life style and rigorous annual physical examinations.

A retrospective study from Canada tried to determine whether there was an occupational risk, including exposure to radiation as a cause of thyroid cancer. One thousand, two hundred seventy-two patients with proven thyroid cancer were compared to 2,666 controls (64). There was a 2.54 times increase in thyroid cancer in wood processors (95% confidence 1.11–5.83) and, in contrast, a 0.81 times risk in clerical workers (95% CI 0.67–0.97). Exposure to radiation did not increase the risk. These differences are hard to explain.

Atomic Bomb: War

There are two populations, both Japanese, who have been studied. They were citizens of Hiroshima and Nagasaki in whom there was an increase in thyroid cancer (65–67). In 1982, 112 thyroid cancers (62 from Hiroshima) were identified from 98,610 exposed residents (68). Increased numbers of breast, colon, lung, stomach, esophagus, urinary tract cancers, multiple myeloma, and leukemia were also identified (69, 70). For thyroid cancer Prentice et al. conclude, "A clear, predominantly linear, increase in thyroid cancer incidence corresponds to increasing levels of gamma radiation to the thyroid gland" (68). The excess relative risk has been calculated to be 1.15 for 1 Sv (71). People less than thirty years of age were at higher risk for radiation associated thyroid cancer. Using various mathematical models the proportion of thyroid cancers attributable to the bomb was between 18.7% and 22.0% (72). One surprising fact, at least unknown to me, is the fact that almost 50% of the radiation exposure the atomic bomb survivors have received is the result of investigations to study the ill effects of the initial radiation (73, 74).

Atomic Bomb: Testing

Testing of atomic bombs in the United States was conducted in Nevada. It has been estimated that the US population received 0.5 mGy (0.5 rad) external radiation from fallout (75). Since radionuclides of iodine were released the

thyroid was a key organ, and it has also been estimated that the thyroid of a child born in 1951 received 30 mGy (3 rad). This resulted in a report from the National Cancer Institute suggesting that this could result in 75,000 additional thyroid cancers (76). This is one explanation for the increasing incidence of thyroid cancer in the United States.

Atomic Bomb: Accidental

The United States tested an atomic device in the region of the Bikini islands near ground level. Two hundred and thirty five occupants of the Marshall Islands were exposed to direct radiation (external) and internal radiation to the thyroid plus exposure to ^{137}Cs, ^{90}Sr, ^{210}Po and ^{239,240}Pu. These non-iodine radionuclides could cause both external and internal radiation. Ten thyroid cancers were identified as well as fifty-three thyroid nodules (77). Six of the ten cancers occurred in people who were 18 years of age or less at the time of exposure. There were thirty-nine islanders in this age category therefore 15.4% developed thyroid cancer. In contrast less than 2% of older people were identified with thyroid cancer. There was a Japanese fishing boat, "The Lucky Dragon" in the region but there is no data on the outcome of the fishermen.

Accidental Release of Radioactivity From Power Plants

In the United States, the nuclear accident that is remembered is Three Mile Island that occurred on May 28, 1979. In fact, the maximum radiation exposure to people in the surrounding region was only 0.1 rem (1 mSv) and the average dose was 1 mrem (1 μSv). From 1954 to 1957 there were releases of substantial quantities of ^{131}I from Hanford in South Central Washington State into the Snake River, which is a tributary of the Columbia River (78). Hanford was a production site for manufacturing atomic weapons. It was not a "power" plant and the releases were not truly accidental. The general conclusion was that no increased incidence of thyroid cancer could be identified, however the methods used to reach this conclusion have been criticized (79). By contrast the accident at Chernobyl on April 26, 1986, released substantial amounts of radioactivity into the atmosphere and resulted in an increase in thyroid cancer in children. It has been estimated that 1.8×10^{18} Bq of ^{131}I were released plus short-lived radionuclides of iodine. Chernobyl caused a change in the understanding of radiation induced thyroid cancer (80). First that internal radiation could be causal. Second, although most of the patients who developed thyroid cancer were young when exposed, older persons could also be at risk. Third, the latent period between exposure and cancer could be less than five years (81). Ron et al. in a study analyzing the effect of external radiation as a cause of thyroid cancer found only two out of 700 cancers occurred less than five years after exposure (7). The incidence of pediatric thyroid cancer in Belarus, an adjacent territory, increased from two per year in 1986 to six cases in 1989 to 114 cases in 1992 (82, 83). Similarly the incidence in Ukraine increased from three in 1986 to 1988 to 324 between the years 1990 and 1998 (84). Previously there was skepticism that internal radiation to the thyroid would produce an increase in cancer. The increase in the number of cases described above argues that there is indeed a relationship. In addition when the incidence in the Gomel region was related to the birth-dates of the children, the following relationship was found (85). There were thirty-one childhood thyroid cancers from 9,720 children born in the three years before the incident. Twenty-four of the thirty-one patients were girls. In contrast there was one cancer out of 2,409 children born in the eight months after the incident. These children were in utero at the time of the incident. There were no cancers out of 9,472 born nine months, or more, after the incident.

The quantities of ^{131}I, ^{133}I, ^{132}Te, and ^{137}Cs released are shown in Table 5.5 (4). ^{132}Te was inhaled and deposited in the lungs, decays to ^{132}I. In retrospect the short-lived radionuclides of iodine have been calculated to contribute

Table 5.5. Quantities of radionuclides released from Chernobyl.

Radionuclide	Quantity
^{131}I	1.8×10^{18} Bq
^{133}I	2.5×10^{18} Bq
^{132}Te	1.1×10^{18} Bq
^{137}Cs	1.2×10^{17} Bq

one-third radiation to those who did not take prophylactic inorganic iodine (4). They accounted for half of the thyroid dose in those who took inorganic iodine. The higher percentage is due to the reduced absorbed radiation from ^{131}I (half life 8 days), which was trapped in smaller quantities because of prophylactic inorganic iodine.

Data related to thyroid cancer occurring in adults is obtained from the incidence in people sent to the area to clean up. These individuals were given the title of liquidators (86). A total of 99,024 liquidators were at risk. 21,392 were deployed between the end of April through July 1986. Twenty-one cancers were identified giving a SIR of 9.16. A similar number were at risk from August through December and 12 cancers developed producing an SIR of 5.14. There was still an increased incidence for those employed in 1987 and 1988–90. The SIR for these periods was 3.78 and 4.08 respectively. The external radiation for the cadre in 1986 was on average 16.8 cGy (16.8 rad). The exposure for 1987 was judged to be 9.3 cGy (9.3 rad) and after 1988 3.3 cGy (3.3 rad). There is little information about the internal radiation to the thyroid of these workers. Two hundred and eight who received higher doses of radiation were studied in detail. One hundred and seventy three had a thyroid dose of 0 Gy to 1.2 Gy (0–120 rad), 18 had doses between 1.2 Gy and 3.7 Gy (120–370 rad), and 17 had doses greater than 3.7 Gy (370 rad). An analysis of people aged fifteen to sixty-five years showed an increase in histologically proven cancer in the years 1991–1998 demonstrated an excess relative risk per Gy was of 0.7 in men and 0.9 in women (87).

Almost all of the cancers were papillary. There is an increased incidence of solid trabecular papillary cancer. Genetic analysis has demonstrated a consistent pattern of mutation. Rearrangements of the RET has been identified in 60–90% of papillary cancers in children exposed to fallout from Chernobyl (88–90). This is a considerable increase over the findings in sporadic papillary cancer. The genetics are described later in the chapter.

Prophylaxis for Radioactive Fallout

When it is known that radionuclides of iodine have been released from a nuclear power plant, or bomb, the thyroid can be protected by ingesting an excess of non-radioactive iodine ^{127}I (91–93). Medical, pediatric and nursing groups have presented position papers on this topic (94, 95). Medical newsletters and editorials have emphasized the role of non-radioactive iodine (96, 97). A large quantity of iodine dilutes the radioactive iodine and a smaller proportion of the radioactive nuclide is trapped by the gland. The thyroid also has internal homeostatic controls to accommodate sudden increases and decreases in available iodine. When there is an increase in plasma inorganic iodine, the trapping of iodine, its organification and coupling are reduced and release of hormone into the circulation is inhibited. In the situation of potential exposure to large amounts of radioactive iodine, the prime requirement is to ingest the ^{127}I before exposure to the radionuclides of iodine. In the case of Chernobyl that was not possible for those in the immediate vicinity because no announcement was made. When there is time to take non-radioactive iodine the questions are how much, what preparation and for how long? A potassium iodide (KI) pill is the most suitable preparation. There are liquid preparations including Lugol's iodine (1 ml, 30 drops, contains 130 mg iodine) and saturated solution of potassium iodide, which are effective. However, the liquid is not so easy to store, it loses potency with time and is more difficult to dispense. Several studies have addressed the dose that reduces uptake of radioiodine by 95% or more. This dose is between 100 and 200 mg (98, 99). There is considerable experience from Poland where a rapid national program to administer iodine to children was implemented when the news about Chernobyl was broadcast. They recommended 15 mg for newborns, 50 mg for children up to 5 years, and 70 mg for older children (100). Because the risk of cancer is predominantly a factor of young age, adults are less likely to get thyroid cancer and therefore get less protective benefit. In the situation where the ingested dose of ^{131}I would be large, inorganic iodine could also prevent the development of hypothyroidism. Because of recent concern about terrorists and atomic, or dirty bombs there has been a run on the sale of KI pills and it is probable that adults would be among the first to take them. Experts caution KI will not be useful for protection against dirty bombs and this is true except in the situation where a large amount of radioactive iodine was attached

to the explosive device. While preparing this segment of the chapter I made a computer search for "potassium iodide" using Google. There were more than 90,000 sites, some were Governmental providing information and advice, others commercial sources selling KI (101). KI pills of 130 mg strength contain 100 mg of iodine and one pill daily is advised while the risk is present. (One web site, selected at random, sells 14 pills for $6, $4.69 to members! No prescription is required.) I was surprised to find advice on how to make saturated solution of potassium iodide in several related web sites.

Whenever a medication is prescribed to large numbers of the population and only a small percentage will benefit, it is important to balance cost effectiveness. At the time of ingestion of the medication, the people are normal; they are not patients because they have no illness. The likelihood of developing thyroid cancer is real but not overwhelming. The fear of illness is also real and can be overwhelming (102). The cost to benefit ratio must include potential problems due to the potassium iodide. Excess of iodine can cause thyrotoxicosis and hypothyroidism. Thyrotoxicosis (Jod Basedow) is more likely to occur in regions of iodine deficiency. Hypothyroidism is more likely to occur in patients with underlying autoimmune thyroiditis (Hashimoto's thyroiditis). In the Polish experience no permanent dysfunction was identified in 12,641 children and adolescents less than 16 years of age. Pregnant women are a special case, since two people, mother and fetus, are being treated. There are prior reports of babies being born with large goiters. Their mothers were taking iodine throughout the pregnancy. In some cases the goiter was large enough to obstruct delivery. The Polish experience demonstrated transient hypothyroidism in twelve of 3,214 (0.37%) babies whose mothers were treated with KI. The expected incidence of neonatal hypothyroidism is about 1 in 4000. Therefore, pregnant women are advised to take half of a 130 mg KI pill. The US recommendations for twelve to eighteen year old adolescents is half a pill (65 mg), but I take issue with that since most of these individuals are adult size and they are at more risk because of their youth, and I would recommend the full dose.

One computer-modeled study evaluated the benefit of KI related to the time of its ingestion relative to inhalation or ingestion of radionuclides of iodine. The investigators determined that there was almost complete blockage of uptake of radioiodine provided the KI was ingested 48 hours or less before the radioactive material (103). Taking the KI 96 hours before had no protective effect. Similarly, taking the KI 16 hours or more after the radioactive iodine had no beneficial effect. In regions of adequate dietary iodine, KI taken 2 hours after ingestion of radioiodine reduced the thyroid exposure by 80%, taken at 8 hours the reduction in radiation was 40%. In iodine deficient regions the protective effect of KI at 2 hours and 8 hours was reduced to 65% and 15% respectively. These data stress the importance or rapid reporting on any incident where radionuclides of iodine are released and the immediate availability and ingestion of KI. Clearly the optimal time to take the KI is before the exposure but this will never be the case. Table 5.6 provides the recommended doses based on age and exposure. Knowledge of the exposure is also problematic because that cannot be determined until some time later when measurements can be made.

Iodine is also used prophylactically for patients who are given radiopharmaceuticals labeled with radioactive iodine. These could

Table 5.6. Recommendations on the dose of inorganic iodine to be given to various "patient" groups exposed to radioactive iodines.

Patient group	Exposure Gy (rad)	Dose of KI (mg)
>40 years	>5 (500)	130
18–40 years	≥0.1 (10)	130
12–17 years	≥0.05 (5)	65
4–11 years	≥0.05 (5)	65
1 month–3 years	≥0.05 (5)	32
Birth–1 month	≥0.05 (5)	16
Pregnant or lactating	≥0.05 (5)	130 some recommend 65 in pregnancy

include radio-iodinated antibodies for treatment of cancer and radioiodinated meta-iodobenzyl guanidine for management of pheochromocytoma and neuroblastoma. In this situation the timing of injection of the radiopharmaceutical is known and the KI can be prescribed to be ingested a few hours beforehand and continued for a few or several days depending on whether ^{123}I or ^{131}I is the radionuclide.

Potassium perchlorate ($KclO_4$) competes with iodine for the sodium iodide symporter (NIS), and reduces the uptake of iodine. This is not advised for treating large populations because of the small but definite incidence of aplastic anemia.

It is equally important to reduce the potential for exposure to more radioactive iodine. Evacuation from the radioactive site should be as quick as possible. This depends on police, administrators and access to vehicles, open motorways, and so forth. Cessation of ingestion of contaminated foods and drinks should be immediate. Important sources of radioiodine to be avoided are milk and water (104). Bottled drinks and tinned foods are recommended.

The following case reports illustrate some of the problems. A 37-year-old woman was an in-patient in another hospital. A gallium scan (^{67}Ga) was ordered to define the extent of her suspected coccidiomycosis. The nuclear medicine technologist mistakenly drew up 4.46 mCi (165 MBq) ^{131}I, thinking that he had prepared ^{67}Ga. The ^{131}I was injected intravenously. The error was noted quickly and steps were taken to block uptake into the thyroid. Consideration was given to injecting radiographic contrast. That could also be administered intravenously and act immediately and the large quantity of iodine would have been beneficial. However, the treating physicians were concerned that protection of the thyroid is not an approved use of radiographic contrast and if the patient suffered a severe (fatal) reaction to the radiographic contrast they would have added a second iatrogenic problem. The patient was given 500 mg potassium perchlorate about 20 minutes after the misadministration and saturated solution of potassium iodide (SSKI) by mouth after 60 minutes. She was hydrated and given a diuretic and SSKI was continued by mouth. The thyroid uptake of the maladministered ^{131}I was measured at 11.4%. The normal range in California is 10% to 30%. Therefore, in this patient, even expeditious steps to block the thyroid were not very successful. Readers should consider what they would have done differently apart from making sure maladministration did not occur. As stated above it should be recognized that aplastic anemia can occur after potassium perchlorate and the medication is not readily available and is not recommended. Retrospective calculations estimated that the thyroid received about 2,000–rad (20 Gy). Based on laboratory data demonstrating a reduction in thyroid cancer in mice given thyroid hormone immediately after thyroid radiation, the patient was advised to take thyroid hormone for life. She is well twenty-years later with no thyroid nodule or cancer.

A fifty-five-year-old patient from Kiev immigrated to the United States. In 2002, she was found to have a small goiter and on ultrasound the gland was heterogeneous. This caused great concern to her and to her physician. She was advised to have a total thyroidectomy. Is this rational? In 1986 she was thirty-nine years old, and review of data in adults living in Ukraine at the time of Chernobyl, excluding "liquidators", shows no increase in thyroid cancer. She was found to have elevated antithyroid antibodies and a slightly elevated TSH and therefore has chronic lymphocytic thyroiditis. I recommended thyroid hormone. However she had two daughters who were seven and nine years old in April 1986, and I was more concerned about them. Ultrasound of the thyroid was normal.

Response of Tissues to Radiation

It is assumed by many authorities that there is no threshold for the carcinogenic effects of radiation. This means that any quantity of radiation no matter how small has some adverse effect. Others accept there is a threshold below which radiation is not deleterious. There is a third body of evidence that small quantities of radiation can actually be beneficial, this is called radiation hormesis (Figure 5.1). Whatever is the case for low doses, different tissues respond differently to increasing exposure to radiation. The relationship is linear for the induction of cancer in solid organs. In contrast, the relationship for development of leukemia is linear quadratic

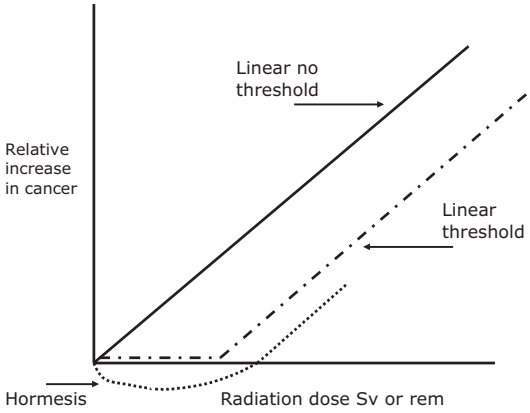

Figure 5.1. A graph of radiation effect on tissues demonstrates linear effect with and without a threshold. It also demonstrates hormesis where low doses of radiation are believed in some situations to be beneficial, in other words reduce the risk of carcinogenesis.

(Figure 5.2). At higher doses there is a levelling off of the carcinogenic effects due to death of cells. Radiation can have stochastic or non-stochastic effects. Fortunately these terms have been changed to more everyday usage. Stochastic is now called probabilistic. This means that not all people, or tissues, exposed to the same amount of radiation experience the same deleterious effects. The term non-stochastic is now replaced by the word deterministic. This relates to effects that are proportional to the absorbed dose of radiation, for example, reduction in sperm count, drop in circulating lymphocytes, or induction of cataract.

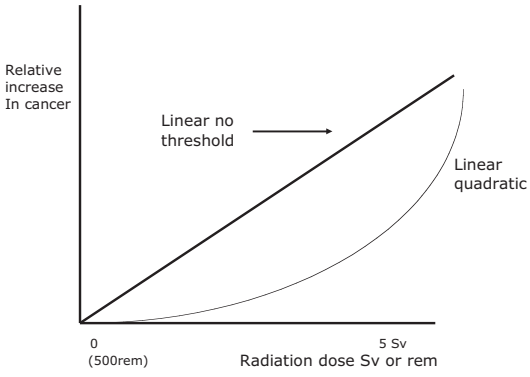

Figure 5.2. Graph shows the difference between linear versus linear quadratic effects of radiation on tissues.

Tissues respond differently to the same dose of radiation when it is administered as a single bolus or, in small (fractionated) doses. Radiological procedures fall into the former category and radiation from ^{131}I into the latter. Radiation delivered over time has less adverse effect, since the damage to DNA has time to repair.

Photons (x-rays or γ rays) can interact with atoms in five ways, three of which are predominant in tissues of the body. These are called the photoelectric effect, Compton scatter, and pair production. In the case of the photoelectric effect the incoming photon loses all of its energy in ejecting an orbital electron from an atom. The photon no longer exists and the electron has kinetic energy equal to the energy of the photon, minus the binding energy of the electron in its orbital shell (Figure 5.3). Provided the energy of the photon is greater than that of an inner shell (K shell) electron, it is much more likely the K shell electron is dislodged rather than electrons from the outer shells. The distance a photoelectron travels is dependant on its energy. For example a photoelectron with 40 keV energy travels 0.034 mm in water and a 400 keV photoelectron traverses 1.24 mm. These photoelectrons are destructive over that path. In addition the atom now has a vacancy in the K shell, which is filled by an electron from an outer shell. The binding energy for outer shell electrons is greater, so there is residual energy that is equal to the binding energy of outer ring elec-

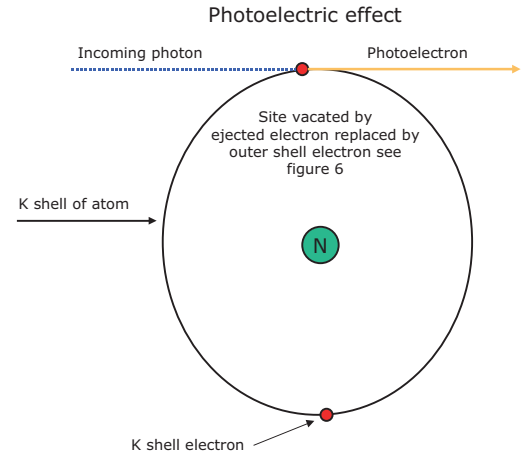

Figure 5.3. Diagram demonstrates the photoelectric effect, when a photon ejects an electron from its orbital shell (usually the inner K shell).

tron minus the binding energy of an electron in the inner ring. This energy is lost either as an x-ray or a low energy electron called an Auger electron. The x-ray is called a characteristic x-ray since its energy is specific for each element. In nuclear medicine imaging scintiscans are produced from photons that are emitted from the patient. In almost all cases these photons are γ rays but the photon that is used for imaging thallium-201 (^{201}Tl) a topic discussed in Chapter 6 is actually a characteristic x-ray of the decay product that is mercury (Hg).

The second type of interaction of photons with atoms is Compton scatter (Figure 5.4). In this situation the incoming photon strikes and ejects an electron, but the photon does not lose all of its energy, and it is deflected to a different trajectory with reduced energy. The electron that is ejected is usually from an outer ring and its energy is equivalent to the energy lost by the photon, minus the binding energy of the electron. This is called a recoil electron. The maximum energy is imparted to the recoil electron when the photon is back scattered at 180° and the minimum energy when the photon grazes the electron with almost 0° deflection. The photon with lowered energy can interact with other atoms by any of the three reactions.

In the third situation, a photon of high energy creates an electron pair consisting of a negative and positive electron (e– and e+) (Figure 5.5). The mass of an electron is equivalent to an

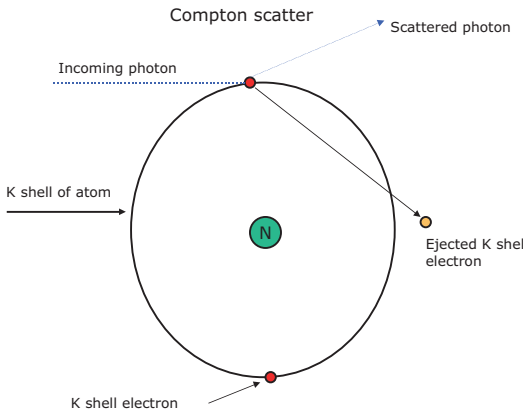

Figure 5.4. Picture illustrates Compton scatter, where the incoming photon ejects an electron but has sufficient residual energy to continue at a deflected angle, and it is capable of additional interactions.

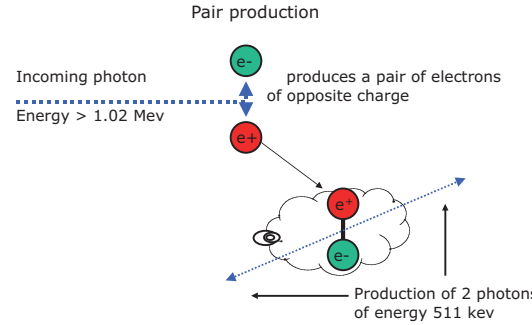

Figure 5.5. Diagram demonstrates diagrammatically pair production that can only occur when the photon has energy greater than 1.22 MeV.

energy of 0.511 MeV or 511 keV (derived from the equation $e = mc^2$) therefore to result in pair production, the photon must have an energy greater than $2 \times 0.511 = 1.022$ MeV. The newly formed electrons have between them kinetic energy equal to the energy of incoming photon minus 1.022 MeV. The e+ travels a short distance then undergoes annihilation on encountering an e– and two photons with energy of 511 keV are emitted (e+ are positrons and this is the basis for positron emission tomography, PET scanning). The emitted photons can also interact with tissues by any of the three methods described.

The electrons that are emitted whether photoelectrons, Compton electrons, pair production electrons or Auger electrons can produce many hundreds of ionizations of surrounding atoms.

The 2 remaining interactions of photons with atoms are coherent scatter and photodisintegration (Figure 5.6). In the former the trajectory of a photon is altered but there is no loss of energy and no damage results. In photodisintegration a very high-energy photon usually >15 MeV is absorbed by a nucleus which then disintegrates. These are of little importance in radiation exposure to people.

Radiation can have a direct, or an indirect effect, on molecules such as DNA. Direct effects are where the radioactive emission has a head on collision with the molecule. This is more likely to occur with large charged particles such as alpha particles or neutrons, in other words those that have a high LET. Electrons can also produce direct effects. Indirect effects are when

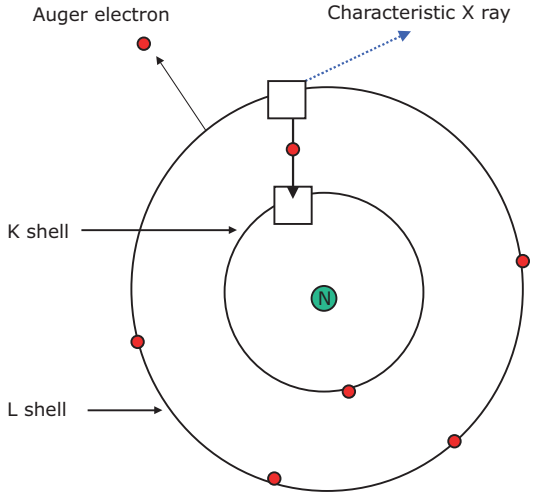

Figure 5.6. Diagram shows how the ejected electron is "replaced" by an outer orbiting electron. The difference in energy for example binding energy of L orbit minus binding energy of K orbit results in either a characteristic X ray or a low energy Auger electron being emitted.

the electron resulting from photoelectric effect, Compton scatter, or pair production, interacts with water (H_2O) to form the free radical HO. This can diffuse into chromosomes and damage DNA by breaking bonds. Approximately two-thirds of the DNA damage by x-rays is due to free radicals.

Radiation damage to cells therefore depends on the type of radiation, the quantity of radiation and the rate at which it is delivered. It depends on the sensitivity of the cells being irradiated. Cells that divide rapidly are more sensitive to radiation. The degree of oxygenation is important; hypoxia confers resistance to radiation. The loss of tumor suppressor genes or the presence of oncogenes can make the radiation more damaging.

Genetic Mutations as a Cause of Thyroid Cancer

Medullary cancer of the thyroid, which is discussed in detail in Chapter 10, was shown to be familial by Williams and his collaborators (105, 106). The cancer arises from parafollicular cells that produce and secrete calcitonin (107, 108). About one third of medullary cancers are familial and phenotypically they fit into three categories. In one category affected family members have medullary cancer and no associated conditions. The other two phenotypes are Multiple Endocrine Neoplasia 2A and 2B (MEN 2A and MEN 2B). In MEN 2A almost all who are genetically at risk have medullary cancer and about 50% develop pheochromocytoma and 20% to 30% hyperparathyroidism. Medullary cancer also occurs in almost all those at risk for MEN 2B, pheochromocytoma arises in about 50% and ganglioneuromas of the lips, tongue intestines, abnormal nerves in the eyeball plus a Marphanoid appearance complete the syndrome. These disorders were differentiated from the syndrome of neoplasms of the pituitary, parathyroid, pancreas and adrenal cortex by Williams and this syndrome is designated MEN 1. A genetic cause for MEN 2 syndromes was identified in 1987 (109). Mutations in the RET protooncogene as a likely cause of medullary cancer were reported in 1993 (110). The RET protooncogene is a transmembrane protein that is encoded by chromosome 10. RET is an abbreviation for rearranged during transfection. RET protein is found on neuroendocrine cells including C cells of the thyroid, cells of the adrenal medulla and parathyroid, and peripheral nerves. The molecule is a single transmembrane protein that has a receptor on the extracellular end of the molecule and protein kinase function at the intracellular end. The extracellular segment adjacent to the cell membrane is rich in cysteine molecules. The presence of a ligand results in fusion of two RET receptor molecules and when a dimer is formed the enzyme tyrosine kinase is activated. Four ligands have been identified, glial-cell-line-derived neurotrophic factor (GDNF), neurturin, artemin and persephin. These are neurotrophic peptides, belonging to the GDNF family. They are important for survival, growth and recovery of nerves. For example artemin is a survival factor for sensory and sympathetic neurons in culture. Artemin is a disulfide-linked homodimer formed by two identical 113 amino acid subunits. GDNF is being used in trials for treatment of Parkinson's disease. These ligands fit into a pocket in the extracellular component of RET protein and for activation there also needs to be accessory peptides. This results in the dimer and activation of tyrosine kinase.

The genetic information for coding the RET protooncogene is determined by a 500 kb length of DNA consisting of 21 exons close to the centromere within chromosome 10 (10q11.2). Point mutations in the gene are associated with the syndromes of familial medullary cancer as shown in Figure 5.7 and Table 5.7. The majority of mutations are on exons 10 (codons 609, 611, 618 and 620) and 11 (codon 630 and 634). The codon 634 mutation is present in the majority of MEN 2A and familial medullary cancer patients. The mutations are in the region of the chromosome that codes for the cysteine rich segment of RET (111). A base alteration in one of these codons results in a cysteine molecule being replaced by an alternative amino acid. The cysteine molecules within a strand of RET form intramolecular disulfide bonds and the absence of one of the pair allows disulfide bonding between RET molecules thus producing dimers. In this formation the protein kinase enzyme is activated without the presence of ligand. This is called constitutive activation. The functions of the enzyme with regard to cellular actions are therefore always turned on (112). In MEN 2B, the point mutation is usually in exon 16, codon 918, which results in methionine being replaced by threonine. This mutation is in the tyrosine kinase segment and induces phosphorylation of alternative substrates.

The parafollicular cells with RET proto-oncogene mutations first develop C cell hyper-

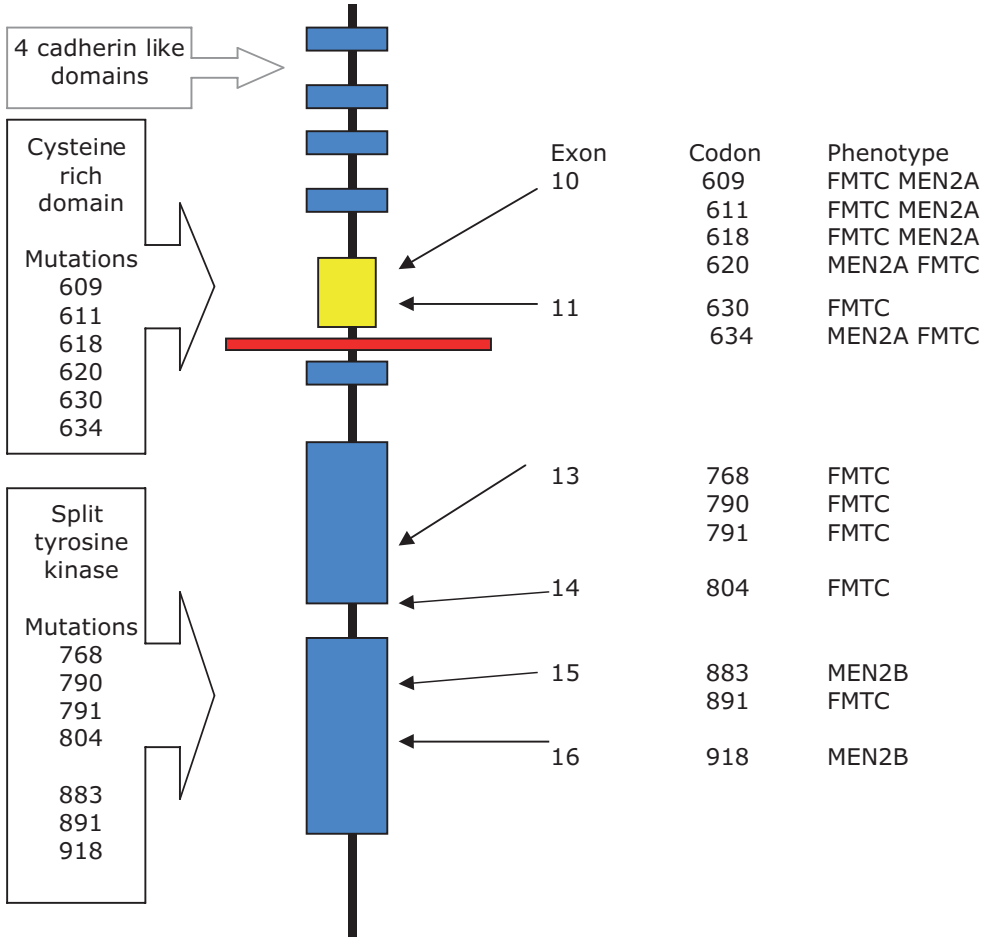

Figure 5.7. This is a schematic of the RET proto-oncogene showing the sites where point mutations occur and the phenotype associated with these lesions.

Table 5.7. Exon and codon involved in MEN syndromes.

Exon	Codon MEN 2A	Codon Familial medullary cancer	MEN 2B
10	609	609	
	611	611	
	618	618	
	620	620	
11	630	630	
	634	634	
Transmembrane			
13	768	768	
		790	
		791	
14		804	
15		891	883
16			918,922

plasia and then become frankly cancerous. In the MEN 2 syndromes the mutation is found in all cells and is therefore a germ-line defect. Cancers if they are given time to form are multifocal. Knowledge of the genetic defects allows preclinical diagnosis of the potential for disease from a peripheral blood sample. There is growth of information of the mutated codons and the phenotypic importance of each mutation so that a genotype/phenotype map is being developed (113, 114). Curative treatment of patients with one of these mutations requires total thyroidectomy before there is clinically significant cancer (115, 116). It is of interest that many of the sporadic (non familial) medullary cancers have similar mutations, but they are restricted to the thyroid cancer cells and are not transmissible.

In contrast, the genetic changes in RET protooncogene in papillary cancer are different. The active enzyme protein tyrosine kinase is intact but the extracellular component that binds ligands such as GDNF is lost. That segment is replaced by a fusion gene. This occurs by interchromosomal translocation or intrachromosomal inversion. The first report was in 1986 and described fusion of protein tyrosine kinase with the gene for tropomyosin. The functions of the fused genes are diverse and include transcription activator of nuclear receptor, transcription activator of androgen receptor to genes with unknown roles. These result in oncogenes called RET-PTC-1, RET-PTC-2, RET-PTC-3 etc and details are provided in Table 5.8. The fusion genes contain segments with three-dimensional configurations that produce dimers and when these are formed the tyrosine kinase is activated without the presence of ligand. These mutations are only found in the thyroid and have been identified in cancerous and benign nodules. These are therefore not hereditary. The relationship between the genetic association and radiation is that 60% to 90% of the papillary thyroid cancers in children who

Table 5.8. RET/PTC oncogenes.

RET rearrangement	Fused gene	Function	Chromosome location
PTC 1	H4	Unknown	10q21
PTC 2	Riα	cAMP dependent protein kinase A	17q23
PTC 3	ELE 1	Transcription activator of androgen receptor	10q11.2
PTC 4	ARA 79		
PTC 5	RF5	Golgi integral membrane protein	14q
	Golga 5		
PTC 6	HTIF 1	Transcription coactivator of nuclear receptors	
PTC 7	RFG 7		
PTC 8	RFG 8	Unknown	18q21-22

were exposed to radiation from Chernobyl have RET-PTC oncogenes. The common ones are RET-PTC 1 and RET-PTC 3. Each of these confers a different phenotype. RET-PTC 1 is commonly associated with "regular" papillary cancer. RET-PTC 3 is strongly associated with solid trabecular papillary cancer.

P53 is an important tumor suppressor gene. Mutations and deletions of this gene have been found in differentiated and anaplastic thyroid cancer. There is increasing evidence that this mutation in addition to other initiators could be the genetic defect that alters the phenotypes of thyroid cancers from slow growing differentiated cancer to the rapidly aggressive and invasive behavior of anaplastic cancer. A recent report identified point mutations in the BRAF gene in 38% of papillary cancers and 83% of anaplastic lesions (117). This also codes a kinase enzyme. A point mutation identified at nucleotide 1,796 results in a substitution of alanine for tyrosine. Another oncogene from rearranged chromosomes is called PAX8-PPARγ. It has been found almost exclusively in follicular cancers (118).

Because TSH is the normal stimulator of thyroid cell growth and division it was logical to determine if there were defects in the TSH receptor that produced constitutive activation. This has been found in some benign autonomous functioning nodules (119). It is thought that a somatic mutation in one cell results in a clone of hyperfunctioning cells that divide more rapidly than normal producing the hyperfunctioning nodule. A germline mutation causes neonatal hyperthyroidism that has to be differentiated from neonatal Graves' disease. Although there is one report of a mutation in the TSH receptor of a Hürthle cell cancer this is not a general cause of thyroid cancer (120, 121).

Familial Non-Medullary Thyroid Cancer

There is increasing evidence that there are familial clusters of differentiated thyroid cancer (122, 123). This was first reported in 1951 and a few case reports were published over the next four decades (124–127). These are called familial non-medullary thyroid cancer, but I think the terms familial papillary or familial follicular cancer are more appropriate. To satisfy that there is a genetic cause it is important to exclude radiation or other carcinogens as an etiologic factor. However, it is possible that a genetic defect might make family members more susceptible to radiation. In one of the families, I have described two brothers with papillary cancer had received neck irradiation in childhood (128). Other reports of the association of family members with thyroid cancer having prior radiation have been published (9, 129). Since most differentiated cancers appear to be sporadic, it is important when a familial relationship is entertained that the probabilities are not explained by chance and that a common gene or genes can be incriminated. The former is easier to prove than the latter. One investigation compared the probability of a second member of a family having thyroid cancer with the risk in families with no evidence of an index case (130). Three hundred thirty-nine families with an index patient were compared to 319 matched control families. There was a 10.6 fold increased risk of a second person having thyroid cancer in the former population. A somewhat similar study in Norway evaluated 5,457 first-degree relatives of 1,025 patients with proven "non-medullary" thyroid cancer (131). There was a five fold increased likelihood of cancer (men: 5.2, women: 4.9) compared to expected, based on national statistics for thyroid cancer. Almost identical increased risks were calculated by Ron et al. (5.2) and Stoffer et al. (4.71) (132, 133). The population of Iceland is about 250,000 people. Seven hundred and twelve thyroid cancers were registered in the period January 1, 1955, to December 31, 1997. Researchers reviewed first, second and third degree relatives for thyroid cancer (134). For male patients, a male relative had a 6.52 fold relative risk and a female relative a 2.55 fold risk increase of thyroid cancer. When the index patient was a woman, a male relative had a 2.92 fold increased risk and a female relative a 2.02 fold increased risk. All are statically significant.

Several authorities interested in familial papillary cancer have calculated the probabilities of having three or more first degree relatives with papillary cancer. One puts the likelihood of a chance finding every 100 years. The chance of five family members with papillary cancer has been estimated at one in 2 billion (135). There are reports of several families with 3 or more first degree relatives with papillary cancer. Lote

et al. present two families with seven and four cancers. (136). Three pedigrees with four, four, and three patients have been described by Stoffer et al. (133). Two kindreds with seven and four patients have also been reported as well as single pedigrees (135, 137–139). These clusters would therefore be extremely unlikely to be due to chance.

There is a definite coexistence of differentiated thyroid cancer with syndromes that are recognized to be hereditary. These include familial adenomatous polyposis and the associated Gardner's syndrome where, in addition to familial adenomatous polyposis, there are soft tissue tumors and osteomas (140–145). Gardner's syndrome is due to the adenomatous polyposis coli (APC) gene. The majority of mutations have been identified in the 5' half of the gene. Papillary cancer has been found in several patients with Cowden's syndrome that is known to be familial (146, 147). Cowden's syndrome includes multinodular goiter, 50% risk of breast cancer, large skull size, multiple hamartomas, and skeletal abnormalities. Thyroid cancer can occur within the nodular goiter (148). A number of germline mutations have been identified in a gene on chromosome 10q23.3 known as PTEN/MMAC1/TEP1 (149). PTEN is a tumor suppressor gene and inactivating mutations have been identified in some sporadic follicular cancers. Thyroid cancer has been reported in other hereditary disorders including Peutz-Jeghers syndrome and ataxia-telangiectasia (150). None of the mutated genes that cause the syndromes mentioned above are associated significantly with thyroid cancer.

RET-PTC 1 and RET-PTC 3 are found in about 20% of sporadic papillary cancer but there does not appear to be an increased risk of familial cancers. There is an association of papillary cancer and multinodular goiter. A gene responsible for familial multinodular goiter called MNG 1 that is localized on chromosome 14q32 has been found only in a minority of familial papillary cancers (151). Other investigators could not even confirm this (152, 153). Familial Hürthle cell cancers are very rare and one report indicates that a gene on chromosome 19q13.2 is a predisposing factor. A multinational multi-author report identified a locus on 2q21 (154). Table 5.9 lists several genes that have been identified in specific familial cancers, but there is not a common thread. Point mutations as seen in familial medullary cancer have not been described. It is likely that multiple genes of low penetrance together play a role. As one group of investigators who have conducted extensive research in the field state "familial non-medullary thyroid cancer is an emerging clinical phenotype that is genetically heterogeneous, and none of the currently identified genes accounts for the majority of families" (155).

In the opinion of some authorities the phenotype of familial papillary cancer is more aggressive than sporadic cancer (156–158). Multifocal lesions are more common. The recurrence rate is higher in one large analysis occurred in 16.3% versus 9.6% for sporadic

Table 5.9. Genes reported to be associated with familial non-medullary thyroid cancer.

Entity	Gene	Chromosome
Non-Medullary Cancer, Familial	MNG1, TCO, RET, TRK, MET, TSHR, APC, PTEN have been excluded	?
Papillary Cancer, Sporadic	RET/PTC1, RET/PTC2, RET/PTC3	10q
Papillary Cancer, Chernobyl	RET/PTC1 (common)	10q
	NTRK1 rearrangement (rare)	1q22
Follicular Cancer, Sporadic		
Familial Multinodular Goiter	MNG1	14q32
Non-Medullary Thyroid Cancer associated with Multinodular Goiter	TCO	19p13.2
Familial Adenomatous Polyposis & Gardner's Syndrome	APC	5q21
Cowden's Syndrome	PTEN	10q23
Thyrotropin Receptor	TSHR	
Familial Medullary Thyroid Cancer (MEN2)	RET	10q11.2

cases (p = 0.0005) (157). Current data suggests that about 5% of papillary cancers are familial. This is somewhat higher than my experience with twenty-one families out of more than 800 patients (approximately 2.5%).

There is some evidence that the prevalence of thyroid cancer is less in association with some medical conditions, and Down's syndrome has been cited as an example (159).

In summary many investigators have conducted detailed analysis of genes in patients with sporadic thyroid cancer, in families with differentiated cancer, and families with papillary cancer and other genetic disorders. There has to date been no common denominator.

Chemicals as a Cause of Thyroid Cancer

In humans there is little evidence that chemicals can cause cancer of the thyroid. Goitrogens in doses sufficient to raise TSH can augment the carcinogenic effects of radiation. There are reports of chemicals causing cancer in laboratory animals. Dioxins cause thyroid cancer in rats and mice but this is only one of the many cancers that occur (160). The flame retardant, 2,2-bis(bromomethyl)-1,3-propanediol also causes thyroid and other cancers in rats. McConnel has reviewed more than 300 experiments to test carcinogenic effects of chemicals on the thyroid (161). A report that smoking and alcohol reduce the risk of thyroid cancer appears flawed (162). The definition of a smoker was one who has smoked more than 100 cigarettes and a drinker as one who takes twelve or more alcoholic drinks in a year. I know a few people where these numbers are close to their daily consumption. A recent report from Serbia compared the smoking habits of 204 women with proven thyroid cancer to gender and age matched controls (163). They show no increase in thyroid cancer in smokers. Mack et al. conducted a meta-analysis and concluded there was a reduced risk of thyroid cancer in people who smoked and was most apparent in those currently smoking (164). The large number of adverse and serious problems caused by cigarette smoking clearly outweigh the benefit of a minor reduction in the number of thyroid cancers.

The Role of Iodine in the Etiology of Thyroid Cancer

The beneficial effect of inorganic iodine in the management of people exposed to release of radionuclides of iodine into the atmosphere has been discussed. Here the role of dietary iodine in the pathogenesis of thyroid cancer is reviewed. It has been known that follicular cancer is more common in regions deficient in iodine and papillary cancer is also less common. Laboratory animals fed a chronically iodine deficient diet develop benign follicular tumors and with time follicular cancers (165). Animals treated with a known carcinogen nitromethylurea and fed a low iodine diet developed significantly more follicular cancers than those given the carcinogen or diet separately (166). The low iodine diet appears to be a promoter of the carcinogen, and an elevated TSH is the likely cause. A study was undertaken to compare the incidence and types of thyroid cancer in Iceland, a country with high dietary iodine, and the North East of Scotland, where the intake is normal (167). Papillary cancer was five times more common in Iceland. Although there were few follicular cancers, this tumor was relatively less frequent in Iceland. The authors suggest, "that the incidence of papillary carcinoma and follicular carcinoma are separately influenced by dietary iodide, papillary carcinoma being high in areas of high iodide intake and low in areas with low dietary iodide." A study from Nigeria a country with low intake of iodine showed a ratio of follicular to papillary cancer of 6.2:1 (168). An epidemiological study in Hawaiian women showed that high dietary iodine judged by intake of seafood and shellfish, a fermented fish sauce, and dietary iodine were associated with an increased risk of papillary cancer (169). Somewhat counter intuitively, high intake of goitrogenic vegetables was associated with a decreased risk.

The histological types of thyroid cancers occurring in a region were studied before and after iodine supplementation (170). The ratio of papillary cancer increased from 1.7:1 to 3.1:1. In addition the incidence of chronic lymphocytic thyroiditis and thyroiditis associated with papillary cancer increased. There were three lymphomas, a cancer known to be associated with chronic lymphocytic thyroiditis, in the

second period (see Chapter 11). A large investigation in the San Francisco Bay area in Northern California tried to determine whether environmental factors such as dietary iodine played a role in development of papillary thyroid cancer (171). Women with proven thyroid cancer were contacted and interviewed, and, when necessary, interpreters were employed. That geographic region is ethnically very multicultural. Against expectations, increased dietary iodine was associated with a lowered risk of papillary cancer. The expected relationships with prior radiation, nodular goiter, and family history of thyroid cancer were confirmed.

In summary, most studies show that follicular cancer is more common in areas of chronic low iodine intake. In the majority of reports, the ratio of papillary cancers increases in parallel with increasing dietary iodine. Lymphocytic thyroiditis also is more common in iodine replete regions. Low iodine potentiates the effect of known thyroid carcinogens.

Estrogen and Thyroid Cancer

All reports of differentiated thyroid cancer with meaningful numbers of patients indicate that women are about three times more likely to be affected. In spite of this remarkable difference, there is not a large volume of data on female sex hormones as a cause of thyroid cancer. In one study there was a statistically significant increase in estrogen receptors in papillary cancer (172).

Summary and Key Facts

Most thyroid cancers are sporadic and there is no one cause to be identified. A proportion of thyroid cancers are associated with radiation, as an etiological factor, and a proportion have a genetic link. The radiation is usually external, and there is a linear relationship from about 0.05 Gy to 0.1 Gy (50–100 mGy or 5–10 rad) to 5 Gy to 10 Gy (500–1,000 rad). There is an excess risk factor of 7.7 per Gy. Children exposed to internal radiation resulting from the accident at Chernobyl have a definite increase in the incidence of thyroid cancer. Genetic defects in the RET proto-oncogene are the cause of 25% to 30% of medullary cancers and 100% of the MEN 2A and 2B syndromes.

- Thyroid cancer occurs more frequently in people who have radiation to that gland.
- Young age and female gender increase the risk of radiation induced thyroid cancer.
- The increased risk starts at low doses to the thyroid such as 6 rad to 10 rad (6–10 cGy).
- This low dose is not too different from the dose delivered by spiral CT imaging.
- Historic data pointed to external radiation being significantly more carcinogenic than internal radiation from ^{131}I.
- Epidemiological evidence from the increased number of thyroid cancers in children exposed to radioactive iodines in the fallout from Chernobyl indicate a risk from internal radiation.
- Thyroid trapping of radioiodine can be reduced by intake of non-radioactive ^{127}I.
- The non-radioactive iodine needs to be taken close to the time of ingestion or inhalation of radioiodines.
- The adult dose is 130 mg KI daily.
- A point mutation in the RET protooncogene is the cause of familial medullary cancer syndromes.
- The specific point mutation can predict the phenotype (i.e., the time of onset of cancer, its aggressiveness, and associated conditions).
- There is no one genetic lesion that explains the occurrence of sporadic or differentiated thyroid cancers.
- Chemicals appear to have very little role in causing thyroid cancer.
- Further studies on the role of estrogen appear warranted in view of the 3 : 1 ratio of women to men with thyroid cancer.

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Chapter 6

Differentiated Thyroid Cancer

The proportion of patients with thyroid cancer that fall into the classification of differentiated thyroid cancer varies from country to country but is always in the majority and in the range of 70% to 90% [1]. Differentiated thyroid cancer includes papillary and follicular cancers and their variants. Papillary cancers are more common and in countries where the intake of dietary iodine is high they constitute 70% to 90%. In countries where there is a low intake of iodine the proportion of follicular cancers increases. The term differentiated relates to the fact that the cells and their structural arrangement look very much like normal thyroid. This applies in particular to well differentiated follicular cancers where occasionally it can be difficult to designate that the lesion is a cancer and only long term follow up with recurrent or metastatic disease confirms that it was malignant. Differentiated cancer cells also retain the ability to function like thyroid in that they trap iodine and produce thyroglobulin (Tg). However, thyroid cancers do not usually function to the level of normal cells. This results in cancers trapping less iodine and appearing as non-functioning or cold lesions on scintiscan when compared to normal surrounding cells.

Papillary cancers are more likely to be multi-focal and they commonly metastasize to regional cervical lymph nodes. Usually follicular cancers are single, and they are more likely to metastasize to distant sites such as the lungs and skeleton. Their pathologies have been described in Chapter 3 and are only repeated briefly in the sections dealing with pathological variants of the classical differentiated cancers. Both papillary and follicular cancers are more common in women with a ratio of approximately three women to each man. In large series patients with papillary cancers have an average age in the thirties and follicular cancers about ten years older. The principles of treatment are similar therefore the management sections of this chapter are common to both papillary and follicular cancers. The differences related to etiology that has been covered in Chapter 5. There are several excellent reviews on differentiated thyroid cancer [1–6].

Presentation

Thyroid cancer usually presents as a new thyroid nodule or growth of an existing nodule. The topic has been addressed fully in Chapter 4. Occasionally the presence of a metastasis in a regional node draws attention to the disease. Even less commonly distant metastasis are recognized, for example miliary lesions in a chest roentgenogram in a child, or a pathologic fracture in an older patient. Very rarely the metastasis can be in an unusual site such as the mandible, orbit, skin, or even the choroid in the eyeball, as shown in Figure 6.1 [7–9]. There should not be a delay in obtaining a fine needle aspiration (FNA) of a newly diagnosed thyroid nodule or newly enlarged cervical node or a swelling outside of the lymphatic system.

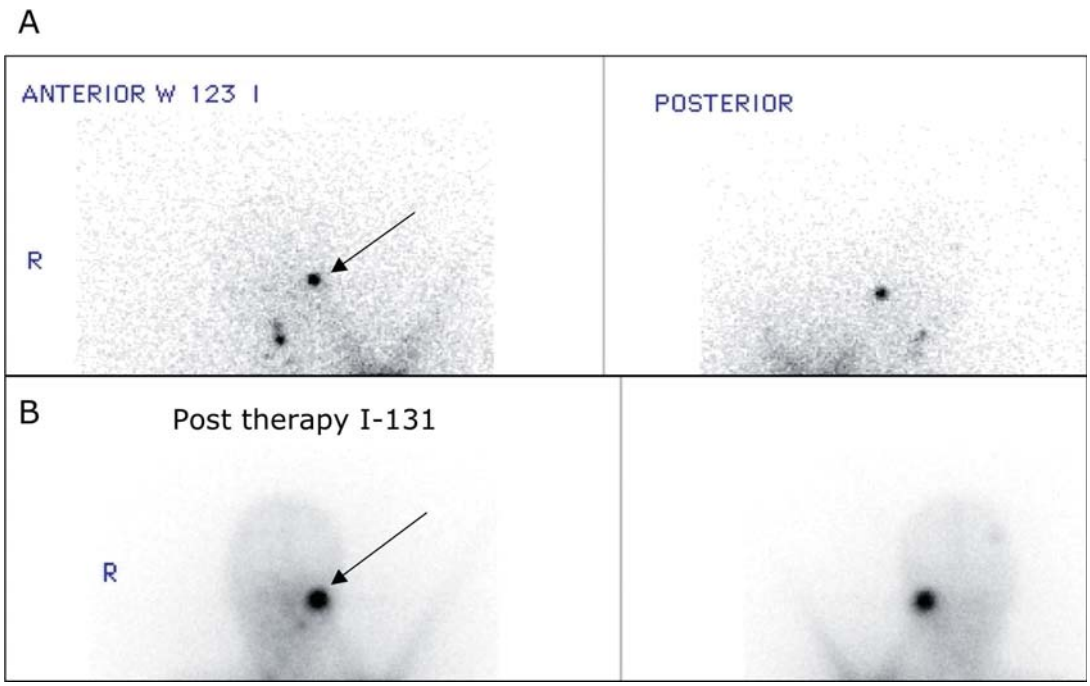

Figure 6.1. Spot views of the head (A) diagnostic scan after 74 MBq (2 mCi) ^{123}I and (B) post-treatment scan after 7.4 GBq (200 mCi) ^{131}I. Both show uptake in the mandible that was the presenting site of metastatic follicular cancer.

Virtually all patients with differentiated thyroid cancer have normal thyroid function but when there is a very large volume of cancer it can produce sufficient hormone to cause thyrotoxicosis. This can be the result of a very large primary cancer or widespread functioning metastases [10, 11]. The metastases can be pulmonary, skeletal or hepatic [12, 13]. A cancer causing thyrotoxicosis is more likely to be follicular than papillary. In some of the historic reports on the use of ^{131}I therapy, the proportion of thyrotoxic patients was greater than the current experience [14, 15]. The thyrotoxicosis is almost always due to the large mass of cancer but there is a report where stimulation of cancer cells by thyroid stimulating immunoglobulin was causal [16].

As the cancer grows it can cause a feeling of pressure in the neck especially when the patient lies supine. Further enlargement can result in breathlessness and difficulty swallowing. A change in voice or hoarseness is a sign that the cancer has pressed on, or invaded into a recurrent laryngeal nerve. One young patient I consulted on for invasive differentiated thyroid cancer first developed hoarseness that was not investigated and then was diagnosed with asthma. The original symptom was the result of the cancer invading the recurrent laryngeal nerve and the second due to invasion through his trachea causing stridor. After some months the correct diagnosis was made when a CT of the chest for the work-up of the asthma showed the thyroid mass. He is well and free of disease after total thyroidectomy, resection of tracheal cartilage and ^{131}I treatment.

A family history of differentiated thyroid cancer should be asked about, since there is increasing evidence of familial clusters of differentiated thyroid cancer. Management of this is discussed at the end of the chapter.

The natural history, prognosis and staging are discussed next since they have a major impact on rational therapy.

Natural History of Differentiated Thyroid Cancer

The natural history of differentiated thyroid cancer indicates that in most cases it is slow growing. There are no reports of patients with

Table 6.1. Thyroid Cancer pTNM staging.

Primary Tumor	T0	No evidence of primary cancer
	T1	Tumor <2 cm (recently changed from <1 cm)
	T2	Tumor 2–4 cm
	T3	Tumor >4 cm
	T4	Tumor of any size extending beyond the thyroid capsule
Regional Nodes	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
	N1a	Ipsilateral cervical nodes
	N1b	Bilateral midline or contralateral cervical or mediastinal nodal metastasis
Distant Metastasis	M0	No distant metastasis
	M1	Distant metastasis

proven thyroid cancer who have been deliberately left untreated to determine the outcome. What is recognized is the long-term outcome is excellent in patients who have been treated by surgery and thyroid hormone or surgery, radioactive iodine (^{131}I), and thyroid hormone. Patients who are young at the time of diagnosis and treatment have the best prognosis. In different publications the cut-off age at which the outcome is less favorable can be 40 years, 45 years, or 50 years. Age is a factor in many of the prognostic staging systems to be discussed below. Women have a slightly better prognosis than men and the older age (50 years) is often applied to women and the younger age (40–45 years) to men. Patients with small cancers have a better prognosis than those with large lesions. Cancers that are intra-thyroidal are associated with a better prognosis than those that have extended outside the capsule. When the cancer has metastasized to a distant site there is an increased mortality. There is mixed information on the significance of lymph node metastases at the time of presentation but most are agreed that mortality is not increased however the risk of loco-regional recurrence is. The age, gender and size of the cancer can be determined before any treatment and all of these factors can be defined immediately after surgery. They can be used for Staging or to formulate a Prognostic Index. This allows an accurate prognosis to be predicted for a specific patient. It also allows patients with similar extent of disease and similar expected outcome to be compared when different therapeutic approaches are delivered. The information before surgery can be used to stratify patients into low or high-risk groups and treatment tailored for the risk of the cancer as a cause of death.

The prognostic variables above are anatomic and pathologic. The nature of treatment has also been shown to be important in some of the Prognostic Indices. However because there are no large controlled trials of treatment options, most of the prognostic indices do not include this.

Staging and Prognostic Indices

The universally accepted staging system is the postoperative tumor, node, metastasis or pTNM. This evaluates the size of the primary cancer, the presence or absence of lymph node metastases and the presence or absence of distant metastases. The characteristics for these are shown in Table 6.1. Recently the size of the primary cancer designated T1 has been increased from 1 cm to 2 cm. The age of the patient then plays a critical role as is shown in Table 6.2. As can be seen from the Table 6.2, a patient less than 45 years is Stage I unless she/he has distant metastases. When a distant metastasis is present

Table 6.2. TNM staging for differentiated thyroid cancer.

Less than 45 years	
○ Stage I	Any T, any N, M0
○ Stage II	Any T, any N, M1
○ Stage III	Not applicable
○ Stage IV	Not applicable
45 years or older	
■ Stage I	T1, N0, M0
■ Stage II	T2, N0, M0
■ Stage III	T3, N0, M0 or any T, N1, M0
■ Stage IV	Any T, any N, M1

the patient is only Stage II. In contrast a patient over the age of 45 who has nodal metastases is Stage III as is a patient with a cancer greater than 4 cm. When that patient has a distant metastasis the Stage automatically is IV.

Several groups of investigators have conducted elegant statistical analysis using univariate and multivariate statistics to determine what factors are important in predicting a good or bad prognosis. They have then developed simple formulae that use criteria such as age, size of the primary cancer, presence of distant metastases etc to provide a score that defines outcome. The first scoring system was introduced by Hay et al. and uses the mnemonic AGES that stands for *A*ge of the patient, pathological *G*rade of the cancer, *E*xtra-thyroidal or distant spread, and *S*ize of the primary lesion [17]. The score is calculated by multiplying the Age in years by 0.05 adding 1 point for a Grade 2 cancer and 2 points for a Grade 3 or 4 cancer. One point is added for extra-thyroidal spread and 3 points for a distant lesion. The cancer size in centimeters is multiplied by 0.2. How the numeric information is used for a specific patient is described below. Because most authorities do not use pathological grading of papillary cancer these investigators developed a second scoring system that does not include that. This is called MACIS, abbreviated for *M*etastasis, *A*ge, *C*ompleteness of resection, *I*nvasion, and *S*ize [18]. The formula is 0.08 multiplied by age in years (or 3.1 if age <40 years), plus 0.3 multiplied by size of cancer in centimeters, plus 1 for incomplete excision, plus 1 for local invasion and 3 points are added for a distant metastasis. AGES and MACIS apply to papillary cancer. A third system AMES stands for *A*ge, distant *M*etastasis, *E*xtent, and *S*ize of primary cancers. [19] The patients are divided into low and high-risk groups. This scoring system applies to both papillary and follicular cancers. The low risk group includes men ⩽40 years and women ⩽50 years with no metastases or older patients who have intra-thyroidal papillary cancer or a follicular cancer with minimal capsular invasion, a primary cancer of less than 5 cm and there are no distant metastases. Conversely the high-risk group includes all patients with distant metastases, extra-thyroidal papillary cancer or follicular cancer with major capsular invasion and older patients with a cancer ⩾5 cm. The Memorial Sloan-Kettering Cancer Center Classification (MSKCC) is similar but defines three groups [20]. Group 1 low risk, includes patients with low grade cancer who are less than 45 years of age. Group 3 high risk, are over 45 years and have high risk cancer. Group 2 intermediate risk, include young patients with high risk cancers and old patient with low risk cancers. The 20-year survivals are 99%, 87% and 57% for low, intermediate and high risk groups.

Let us take 2 hypothetical patients. Patient 1 is a 35-year-old woman with a 2.1 cm papillary cancer that was intra-thyroidal and fully excised. There was no evidence of regional or distant metastases.

$$\text{TNM} = \text{T2 N0 M0} = \text{Stage 1}$$

$$\text{AGES} = 1.75(35 \times 0.05) + 0 + 0 + 0.42(2.1 \times 0.2) = 2.17$$

$$\text{AMES} = \text{Low risk}$$

$$\text{MACIS} = 0 + 3.1 + 0 + 0 + 0.63(2.1 \times 0.3) = 3.73$$

By consulting Table 6.3 it can be seen that by AGES she has a 99% chance of surviving 20 years and similar outcome based on AMES and MACIS sores.

Patient 2 is an 80-year-old man with a 5 cm papillary cancer that was fully excised and showed capsular invasion on pathologic examination. Whole-body scan identified a metastasis in the low thoracic spine.

$$\text{TNM} = \text{T4N0M1} = \text{Stage 4}$$

$$\text{AGES} = 4.0(80 \times 0.05) + 0 + 1 + 3 + 1(5 \times 0.2) = 9$$

Table 6.3. Twenty-year survival based on AGES, AMES, and MACIS prognostic scores

Scoring system	Numeric score	20-year survival
AGES	⩽3.99	99%
	4.0–4.99	80%
	5.0–5.99	67%
	⩾6.0	13%
AMES	Low risk	99%
	High risk	61%
MACIS	⩽6.0	99%
	6.0–6.99	89%
	7.0–7.99	56%
	⩾8.0	24%
MSKCC	Low risk	99%
	Intermediate risk	87%
	High risk	57%

Table 6.4. Comparison of variables in seven scoring systems for papillary and differentiated thyroid cancer.

Variable	AGES	AMES	MACIS	EORTC	OSU	MSKCC	NTCTCS
Patient							
Age	+	+	+	+	−	+	+
Gender	−	+	−	+	−	−	−
Cancer							
Size	+	+	+	−	+	+	+
Multifocal	−	−	−	−	+	+	+
Histol grade	+	−	−	−	−	−	−
Extrathyroidal	+	+	+	+	+	+	+
Nodal metastases	−	−	−	−	+	+	+
Distant metastases	+	+	+	+	+	+	+
Treatment							
Complete resection	−	−	+	−	−	−	−

$$\text{AMES} = \text{High risk}$$

$$\text{MACIS} = 3 + 6.4(80 \times 0.08) + 0 + 1 + 1.5(5 \times 0.3) = 11.9$$

By consulting Table 6.3, he has only a 13% probability of surviving 20 years using AGES score and 24% chance based on MACIS data but 61% probability using AMES. The age is a critical factor and being 80 years of age automatically took the patient out of the best survival groups in AGES and MACIS and by definition did so in the AMES. There are other systems for determining prognosis including the European Organization for Research on Treatment of Cancer (EORTC) [21], Ohio State University (OSU) [22], Memorial Sloan-Kettering Cancer Center (MSKCC) [23], and National Thyroid Cancer Treatment Cooperative Study (NTCTCS) [24]. These are outlined in Table 6.4.

Which method is superior? In one study comparing TNM, AGES, and EORTC, AGES was superior in separating those in the poor prognostic group of whom 57% died [25]. Kerr et al. found the EORTC to be superior to TNM but their paper antedated the publication of AGES, AMES or MACIS [26]. In contrast TNM was reported to be superior to AMES and MACIS in 495 patients treated for papillary cancer between 1967 and 1994 at the Helsinki University Central Hospital [27]. The authors believe the inclusion of nodal status explains the difference since positive nodes in patients 45 years of age or older increased their TNM stage. However when their data is reviewed the conclusions are somewhat different. They summed MACIS patients with prognostic scores of <6, 6 to 6.9, 7 to 7.9, and ⩾8. When the MACIS prognostic score is used as a continuum it is the most predictive. In another investigation the long-term outcome in 406 patients was analyzed using AMES, MACIS, EORTC, NTCTCSR and TNM [28]. The author found that all systems except AMES predicted the cancer specific mortality. The three best were TNM, EORTC and NTCTCSR.

In summary it is important to "stage" patients. This allows prognostication and allows treatments to be compared among similar patients. Tumor, Node, Metastasis is used internationally and is recommended but it is not based on analysis of patients from one center. Metastasis, Age, Completeness of resection, Invasion, and Size (MACIS) provides an excellent alternative and is derived from a statistical analysis of long-term followup of a large number of patients from one medical center.

Fundamentals of Treatment

The principle of treatment is to remove all cancerous cells. This requires thyroidectomy. Some surgeons recommend a total thyroidectomy other a lesser procedure. The reasons for this disparity in opinion are discussed along with the pros and cons of the operations. Small cancers are often confined to the thyroid and therefore all cancer is removed by thyroidectomy. In some patients there are metastases to regional lymph nodes and the approaches to

deal with this by operation and radioiodine ^{131}I are presented. In more advanced cancers there can be metastases to distant sites usually lung and or bone, less commonly brain, soft tissues and liver. The management of these is also presented. Because the thyroid is removed usually in total, the patient will require thyroid hormone for life. Differentiated thyroid cancers are stimulated to grow and function by thyrotropin (TSH) and it is possible to reduce their growth and their production of Tg by prescribing a dose of levo-thyroxine that reduces or even suppresses TSH. How much levo-thyroxine should be prescribed and what preparation should be used and risks and benefits are described. Thyroid cells trap iodine. This can be used to our advantage by prescribing radioactive iodine for diagnostic scans to determine how much tissue has been left post-operatively or whether there are functioning metastases or to define the efficacy of radioiodine treatments after surgery. The testing can be conducted with ^{123}I or ^{131}I that have physical half-lives of 13 hours and 8 days respectively. The treatment is usually with radioactive iodine ^{131}I which suitable physical and effective half lives and emits β particles and γ photons. These radionuclides are discussed further in the appropriate paragraphs. There is a discussion of the preparation of patients for testing and treatment with radioiodine. The complications are addressed since these can be of considerable importance in young patients.

Extent of the Operation

Good surgical treatment is the key to management of differentiated thyroid cancer. There is general but not unanimous consensus that a total thyroidectomy is the operation of choice. There are several factors that cause some surgeons to argue for a lesser procedure. The first is the stage of disease. It has been emphasized that patients who are Stage 1 or who have a MACIS score of <6 are very unlikely to die from thyroid cancer. These patients are usually young, they may wish to have a family, and they are active in work and play. A complication of the operation such as permanent hypoparathyroidism with hypocalcemia can be very annoying and can make completing a pregnancy difficult for a young woman. A permanent paralysis of the recurrent laryngeal nerve can interfere with jobs that require projection of the voice such as lecturing or speaking in public. Therefore some authorities recommend lobectomy [20, 23].

There are fewer recurrences in patients who have had a more complete thyroidectomy [22]. Papillary cancer is often multifocal and Mazzaferri has tabulated from seven articles that 54% of patients (295 of 545) undergoing completion of thyroidectomy had cancer in the contralateral lobe [29]. This has to balanced against the considerably lower percentage of patients who have a clinical recurrence in the residual lobe. In one series this was only 4% [30]. Treatment with ^{131}I is easier when there is less residual thyroid and the complication of radiation thyroiditis is unlikely to occur when there is only a small remnant of residual thyroid. In addition the diagnostic whole-body scan and post treatment scan are more likely to show functioning metastases on the first postoperative evaluation when the thyroidectomy has been complete. Measurement of Tg for followup of patients is more reliable when most of the thyroid has been removed. Total (or near total) thyroidectomy is the preferred procedure but has to be balanced against the risks of the operation. When a lesser operation is undertaken and the primary cancer is <1.5 cm and fully excised the patient should have an excellent prognosis. When the cancer is larger, locally invasive, or there are nodal metastases, completion of thyroidectomy or ^{131}I ablation is advised, as shown in Figure 6.2.

Procedure

I shall not describe the technical aspects of the procedure, since I am not a surgeon but will outline important aspects for the patient and for the clinicians responsible for long-term followup. There are excellent articles addressing the operation [31, 32]. The procedure should be learned in formal residency training program in surgery. A surgeon who has been trained in the procedure and who has had experience with many thyroidectomies should conduct the operation. There is concern that residents are entering practice with less opportunity to be involved with sufficient thyroidectomies [33]. It has been demonstrated that residents can perform thyroidectomy safely provided they are closely supervised by an experienced mentor [34].

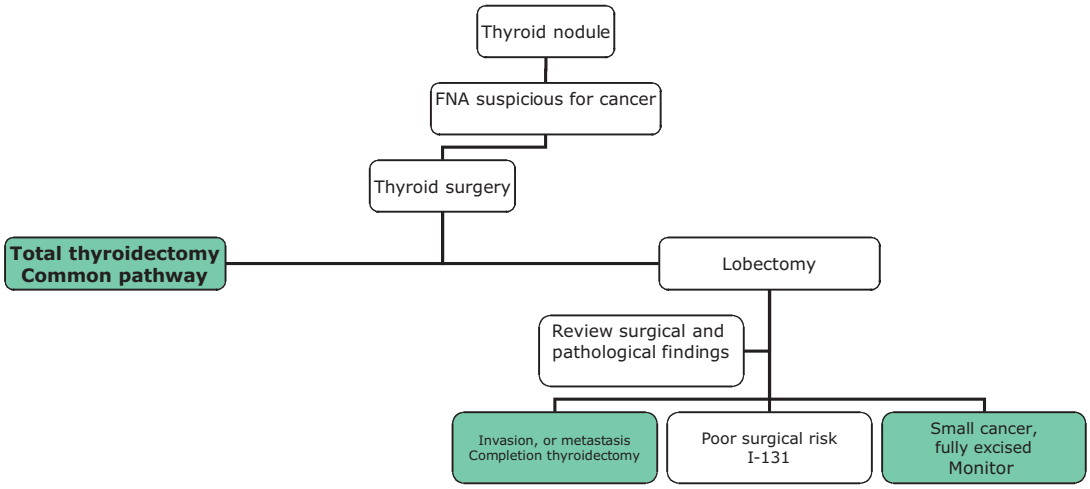

Figure 6.2. Algorithm for surgical treatment of differentiated thyroid cancer.

A 2-year fellowship in endocrine and thyroid surgery has been proposed by leaders in the field and has merit [35]. An analysis of who is and who should be conducting the procedure has been conducted. In the UK, 83% of thyroidectomies are performed by general surgeons and the remainder by head and neck surgeons [36]. Very often the patients have little choice in the selection of the surgeon, their insurance scheme, Health Maintenance Organization, or primary care physician dictates the decision and referral. Nevertheless, when the patients have concerns they should voice them and, if necessary, put the concern in writing. This can help patients accept the decision. The patient should meet with the surgeon and take a written list of questions concerning the procedure, the risks, the recovery time in hospital, time for recuperation, whether the surgeon identifies the recurrent and superior laryngeal nerves or uses nerve monitoring and the involvement by trainees, and so forth. It can be helpful for the patient to be accompanied by a relative or close friend. Often the surgeon will provide the answers spontaneously. In complicated operations such a "redo" procedure, when the first operation did not remove sufficient gland, the surgeon should be one who has experience in this situation, where the complication rate is recognized to be higher [37, 38]. Returning to the question, who should conduct the operation? A surgeon with a record of successfully removing all or most of the thyroid is of prime importance. The surgeon should also have a very low complication rate. The turf war between various types of surgeons should not be a factor. The incision is usually about 1 to 1.5 fingerbreadths (2–3 cm) above the sternal notch. The incision is still called a Kocher incision after Theodor Emil Kocher who reduced the operative mortality from 14% in 1884 to 0.18% in 1898 [39, 40]. More than 7,000 thyroidectomies were performed at his clinic and in 1909 he received the Nobel Prize in physiology and medicine. A minority of surgeons place the incision below the sternal notch for cosmetic reasons, since it is concealed by the majority of out-door clothes. There does not seem to be any reduction in the ability to mobilize the gland with the lower approach. The use of mini-incisions and video-assisted thyroidectomy has been conducted with no increase in complications [41, 42]. Whether this is appropriate for management of patients with thyroid cancer where total thyroidectomy and selective lymph node dissection is required remains to be proven [43–47].

Complications of Surgery

The complications include death, hemorrhage, hypoparathyroidism, recurrent and superior laryngeal nerve paralysis, difficulty swallowing, and displeasure with the scar. The relationships of the recurrent and superior laryngeal nerves

and parathyroids to the thyroid are described in Chapter 2. Complications are generally accepted to be more frequent after total thyroidectomy and most frequent after total thyroidectomy and neck dissection of lymph nodes [48]. They are also more common during reoperation and in the hands of surgeons conducting small numbers of thyroidectomies [37]. Sosa et al. evaluated the outcome of patients depending on whether surgeons conducted one to nine, ten to twenty-nine, thirty to 100, or more than 100 thyroidectomies over a 6 year period [49]. The shortest hospital stays and lowest complication rates were related to the experience of the surgeons. This finding was not confirmed by Bergamaschi et al. [38]. They categorized the surgeons as having experience with less than fifty operations, fifty to 100 operations, or more than 100 procedures. They found no difference in complications, but the less experienced surgeons were assisted by more experienced operators, so their conclusion is not valid.

A recent multi-center trial from Italy analyzed the complication rate in 14,934 patients [50]. The results have been extracted for Table 6.5. Remarkably and thankfully in such a large group of patients no one died. 7.1% had one permanent complication of which 1.3% were recurrent laryngeal nerve injuries and 3.3% hypocalcemia in patients who had total thyroidectomy. The outcome after thyroidectomy in a second large review of 1,163 patients is similar, although one patient died [38]. The complication rates in 5,583 patients treated in the U.S. provides information of complications overall and also separately provides the problems in patients with low risk cancers (T1N0M0) [51]. This is important because these patients have an excellent prognosis, and they are usually young and will have to live with the complication for a considerable number of years. 9.8% of the low risk patients had a complication and 79% of these were hypocalcemic.

The dogma is that there should be less than 1% risk of damage to the parathyroids and the recurrent laryngeal nerves as a result of thyroidectomy [52]. The data from Table 6.5 show higher numbers. It is accepted that any surgeon no matter how experienced and skilled will cause a complication during their working life. How can these be reduced [53]? There has been controversy whether the recurrent nerve should be identified or not. Now the consensus is that it should and that this reduces the risk of

Table 6.5. Percentages of complications after thyroidectomy.

	Rosato et al. [50] 14,934 patients	Bergamaschi et al. [38] 1,163 patients	Hundahl et al. [51] 5,583 patients	Hundahl et al. [51] 1,079 patients T1N0M0
Total	17.4			
Transient	10.3			
Permanent	7.1			
Hypocalcemia (total)	10.0		10	7.7
Transient	8.3	19.9		
Permanent	1.7	3.8		
Permanent after TT for cancer	3.3			
Recurrent laryngeal nerve (total)	3.4	2.9	1.3	0.4
Permanent after total thyroidectomy	1.3	0.5		
Bilateral after total thyroidectomy	0.6			
Superior laryngeal nerve	3.7 ?			
Hemorrhage	1.2 of these 15% intraoperative 85% postoperative	1.59	0.7	1.0
Infection	0.3	0.5	0.2	0.2
Airway problem	NA	NA	0.8	0.5
Miscellaneous Thoracic duct transection Horner's syndrome Ulnar nerve paralysis	Rare	0.25		
Deaths	0	0.08	0.3	0

damage [39]. In a study using multivariate analysis this technique reduced the complication by a factor of 1.6 [54]. However, the operations in these patients were for benign thyroid disorders. There is an increasing interest in intraoperative neuromonitoring to ensure the nerve is both identified and preserved [55, 56].

Injury to the superior laryngeal nerve that supplies the cricothyroid muscle has a more subtle effect on the speaking voice but can impact on singing high notes in particular. The lesion is often referred to as damage to the nerve of Amelita Galli-Curchi who was an operatic coloratura soprano singer. She underwent a thyroidectomy for a goiter and her career was reputed to have been ended by this nerve injury. A review of the facts and comparisons with the careers of coloratura operatic singers suggests that her age was the reason for ending her professional career rather than the operation. The role of untreated hypothyroidism in her case cannot be answered. The anatomy of the nerve was described in Chapter 2 and there is also consensus that this nerve should be identified at the upper pole of the thyroid and left intact.

Permanent hypoparathyroidism leading to permanent hypocalcemia can be treated but requires additional medications including large doses of calcium (2–3 gm daily) plus 0.25–0.5 microgram 1:25 dihydroxycholecalciferol. The problem is particularly difficult to manage in a young woman who wants to become or is pregnant. To prevent hypoparathyroidism, surgical authorities recommend identifying two parathyroids [57]. Knowledge of the embryology, anatomy, and blood supply of the glands and an experienced surgeon are important. Although normal calcium can be maintained by one normal parathyroid, Pattou et al. found there was an increased risk of permanent hypocalcemia when less than three glands were left in situ [58]. When it appears that the blood supply to the parathyroid(s) has been compromised, the gland can be autotransplanted into a pocket in the sternocleidomastoid or the forearm [32]. Expertise in auto-transplantation of the parathyroid is an important skill [59]. The function of the transplanted parathyroid has a high probability of being intact and some recommend this as a routine during total thyroidectomy [60, 61]. It would be preferable to preserve all four parathyroids intact and functioning. Pattou et al. have shown that an early parathormone value less than 12 pg/ml, a serum calcium less than or equal to 8 mg/dl or a phosphorus greater than or equal to 4 mg/dl with the patient taking calcium are predictive of permanent hypocalcemia [58]. In the case of hypoparathyroidism there is a requirement for long-term followup with biochemical monitoring to ensure the serum calcium value is physiological. My preference is to measure ionized calcium rather than total calcium.

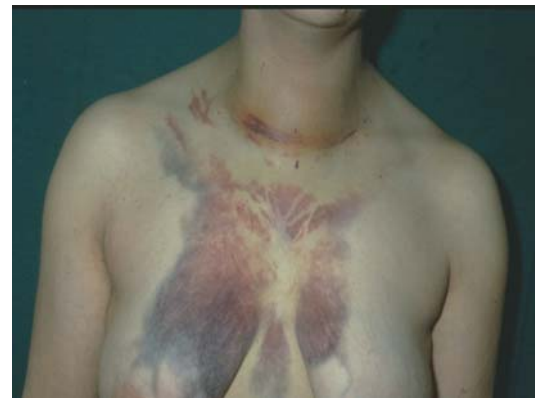

Figure 6.3. Extensive bruising that resulted from tracking of blood from a postoperative hematoma. The patient had an emergent bedside procedure to reopen the wound during the first post-operative night.

The main immediate risks of thyroidectomy are the life threatening ones. Post-operative bleeding and hematoma formation are of great concern because unless treated expeditiously can cause closure of the trachea and death. Postoperative bleeding occurred in 0.7–1.59% of the 21,680 patients from Table 6.5. When the patient is having breathing difficulties postoperatively the wound should be opened urgently even in the ward. Time is of the essence. Figure 6.3 shows a patient whose life was saved in the middle of the first postoperative night by the fast action of a resident. This complication is also a factor in my belief that same day thyroidectomy is less advisable than an overnight stay for continued medical observation. Death after thyroidectomy is rare and is more common in the elderly and those with preexisting medical conditions [62, 63]. In an old report the mortality in patients over 70 years was 0.66% compared to 0.02% for those less than 50 years. However when thyroidectomy is necessary in an older patient it can be completed

successfully as one report in 12 patients older than 80 years confirms [64].

Most operations are performed with the patient under general anesthetic, which has inherent risks. There is a role for local anesthesia in older patients, those with cardiovascular disease and pregnant women. Several years ago colleagues of mine compared twenty-one patients whose operations were performed using local anesthesia with twenty-two who had general anesthesia. The results were excellent and patient satisfaction high [65]. Hisham and Aina found no significant postoperative complications in 65 patients but 58 only underwent a lobectomy [66]. 34% were discharged within 6 hours. Surgeons at the Columbia College of Physicians and Surgeons in New York use local anesthesia as their standard and have experience with more than 600 patients [67]. Local anesthesia has been combined with video-assisted minimally invasive thyroidectomy. [68] Patients were discharged after an average of 26 hours. Apart from the benefit of avoiding general anesthesia the patients are awake and able to speak to the surgical team. As is often the case with a "new" discovery or technique it is often not new. This has been exemplified in George Bernard Shaw's play "The Doctor's Dilemma" [69]. Vellar has given credit for conducting thyroidectomy under local anesthesia to Thomas Peel Dunhill who graduated in medicine in Melbourne in 1903 and removed a lobe of thyroid under local anesthesia in 1907 [70]. He subsequently conducted many thyroid operations using local anesthesia. Details of his life culminating in receiving a Knighthood in 1933 are presented in the same reference.

Keloid scars are very unsightly and they are difficult to correct. A keloid in the neck is unattractive and seems to act like a magnet for the attention of almost all people. Articles on the topic advise against elective surgery in patients at risk such as African Americans or those with heavily pigmented skin [71]. Thyroidectomy for thyroid cancer does not fall into the category of an elective procedure. I have consulted on a patient who developed a massive keloid on the trunk after a surgical procedure. That patient has a nodular goiter that is benign on FNA and both the patient and I are in agreement that thyroidectomy should be avoided. Mustoe et al. state that only silicone gel sheeting and intralesional corticosteroids have proven value in reducing keloids as judged by evidence-based medicine [72]. External radiation has been used but raises concern of long term complications such as malignant transformation [73]. One patient I have followed for years had neck irradiation for an unsightly scar at another medical center. It could be argued that her thyroid had been removed and was not a risk from external radiation but there are other structures such as the larynx and trachea that could be so.

Summary of Thyroidectomy

The quality of thyroidectomy is central to the outcome of patients with differentiated thyroid cancer. Total or near total thyroidectomy is the operation of choice. There are more complications with a more extensive operation therefore a near total thyroidectomy is appropriate for low risk patients. The published incidences of permanent hypothyroidism and recurrent laryngeal nerve paralysis are higher than 1% for each (the generally quoted acceptable percentage). An experienced surgeon capable of removing the thyroid with a low complication rate is a huge advantage.

Radioactive Iodine

Radioactive iodine has an important role in the management of patients with thyroid cancer. The treatment is usually preceded by a diagnostic whole-body scan using a radionuclide of iodine. For decades the radionuclide for diagnostic whole-body scans has been ^{131}I, but this is being replaced by ^{123}I. For therapy, ^{131}I is used almost exclusively and has been for 60 years [14]. This section describes the methods for diagnostic scanning, how to interpret the scintiscans and how to recognize false positive findings. Because the trapping of iodine is by the sodium iodide symporter a brief review of that is introduced. The preparation of the patient including elevating TSH and maintaining a low iodine diet are discussed.

Sodium Iodide Symporter

The ability of thyroid cells and differentiated thyroid cancer cells to trap iodine are the basis of diagnostic scanning and treatment of resid-

ual thyroid and functioning metastases with radionuclides of iodine. There has been interest in this mechanism for several decades [74]. It was known that follicular cells could transport iodine against an electro-chemical gradient from serum to cell. The field has expanded greatly with the cloning of the gene and knowledge of the molecular structure of the trapping mechanism and the factors that regulate it. The iodine trap transports one atom of iodide and two atoms of sodium and hence is known as the sodium iodide symporter (NIS). The cloning was achieved by two groups [75, 76]. The NIS gene is on chromosome 19 (19p12–13.2), and it consists of 15 exons and 14 introns. The mRNA that it encodes is 3.9 kilobase (kb) and the NIS protein contains 643 amino acids. It is located in the laterobasal segment of the follicular cells that abut on the capillaries. The protein has 13 intra-membrane segments and the amino terminus is extracellular and the carboxyl terminus is intracellular. The gene that encodes the NIS protein is controlled by TSH. There are several excellent reviews concerning NIS and the molecular details are presented in Chapter 2 [77–83]. Sodium iodide symporter is expressed in other tissues including salivary gland, breast, stomach, thymus, kidney, and choroid plexus [84–86]. As a result these organs can be seen on whole-body scans using radionuclides of iodine. There is evidence that NIS in thyroid cancer cells is present in reduced amounts or it is not targeted to the correct site [87]. Efforts to normalize both of these are under study. One such approach is the use of retinoic acid that is discussed below [88]. The importance of NIS cannot be stressed enough. It could potentially provide treatment for solid cancers using ^{131}I similar to thyroid cancer therapy. This could apply to cancers that express the molecule such as breast cancer. There are also reports of transfer of the NIS gene into cancer cells in vitro and in animal models.

Diagnostic Scanning

There are five purposes for conducting a diagnostic scan. (1) to determine how much residual thyroid has been left after thyroidectomy; (2) to define the presence of functioning metastases, (3) to determine whether treatment with ^{131}I is appropriate, (4) to determine whether treatment with ^{131}I has been successful or not, and (5) to ensure the proposed high dose of therapeutic ^{131}I does not irradiate a physiological site such as the breasts.

Preparation

The preparation of the patient for scanning and treatment with radioactive iodine requires that the treating physician meets with the patient and it is preferable when the patient's spouse, parent, or significant other is present as well. There needs to be enough time to outline the protocol and for the patient to understand this is a protracted procedure. The patient has to understand the need for TSH to be elevated and to achieve this usually requires that she or he will become hypothyroid with unpleasant symptoms and signs. The requirement for a low iodine diet for 2 weeks must be explained and advice given about what foods that can be taken as well as a list of those that should be avoided. Eating in restaurants should be avoided during this time. The patient needs to be informed about possible side effects of radioactive iodine. Parents of children with thyroid cancer are particularly interested about long-term complications as are young patients who wish to start a family. A discussion of radiation safety issues and precautions is included. I believe it is beneficial to use paper and pen and draw a "road map" in a step-by-step manner. The final document is not identical for each patient because there may be additional aspects to be covered for one patient but in general it looks like Figure 6.4. It could be argued that the patient could be presented with a printed protocol and a list of instructions, but I prefer the former since many patients understand the spoken plus written word better than the written alone. In addition the patient is under considerable stress and reading the information can result in both reduced understanding as well as reading too much between the lines. The step-by-step personal approach allows the patient time to ask questions at a point where she/he is unsure or wants more details.

Hypothyroidism

It is generally accepted that thyroid cells trap more iodine when stimulated by TSH. The need for an elevated TSH was identified early in the

Surgery for thyroid cancer	Day 1
Withdraw thyroid hormone 4 weeks	Expect tiredness,weight gain depression, costipation etc
Low iodine diet for 2 weeks	Day 15
Blood test Measure TSH Measure Tg Pregnancy test	Day 26-27 > 50 mIU/l Baseline Negative
Test dose of ^{131}I (74 MBq) Whole-body scan and spots and uptake	Day 28 Day 30 or 31
Select dose for treatment and administer (decision about inpatient or outpatient)	Day 30 or 31
Or	
Test dose of ^{123}I (74 MBq) Whole-body scan and spots and uptake	Day 28 Day 29
Select dose for treatment and administer (decision about inpatient or outpatient)	Day 29
Post therapy scan	Day 34-37 review with physician
Follow-up	6-8 weeks

Figure 6.4. "Road map" for patient and family for testing and treatment with ^{131}I.

use of ^{131}I therapy. Thyrotropin values are elevated in primary hypothyroidism and after thyroidectomy patients who are not given thyroid hormone become hypothyroid. The easiest way for the physician to render a patient hypothyroid is to undertake a total or near total thyroidectomy and wait about 4 weeks without prescribing thyroid hormone. By that time TSH is usually significantly elevated. There is no consensus about how high TSH should be but most authorities recommend values above 30 mIU/l. I hope to have the value greater than 50 mIU/l. The level of the first TSH measurement is largely dependent on the completeness of the thyroidectomy and when the surgeon has left a small remnant the TSH can be expected to be greater than 50 mIU/l. When the patient has been started on thyroid hormone postoperatively and a decision is made to withdraw thyroid hormone, there are two approaches. One is to withdraw levo-thyroxine and after 4 weeks; the TSH is almost always greater than 100 mIU/l in the case of total thyroidectomy [89]. Alternatively, levo-thyroxine is stopped and replaced by triiodothyronine for 4 weeks. This allows time for the levo-thyroxine to be metabolized. Then the triiodothyronine is stopped for 12 days to 14 days and equivalent TSH values are found [90]. The benefit of using triiodothyronine is that the patient is hypothyroid for a shorter period of time. However the onset of hypothyroidism is more abrupt when triiodothyronine is stopped and patients often prefer the slower onset of hypothyroidism induced by stopping levo-thyroxine. Individual physicians feel strongly that one way is superior to the other but it would be unethical to conduct a study to determine which is better. The patient

would be made hypothyroid by stopping either levo-thyroxine or triiodothyronine and determining the rise in TSH and how badly the patient felt. Then the opposite thyroid hormone would be prescribed to restore normality only to stop that medication and render hypothyroidism for a second time and measure the rise in TSH and compare their symptoms with the first study. What is agreed is that all patients dislike the symptoms and signs of hypothyroidism [91]. Brans et al. studied depression and anxiety in forty-eight patients, ten of whom were admitted for treatment of thyroid cancer with ^{131}I [92]. They confirm that the diagnosis of cancer, the worry about treatment with internal radiation, and the need for isolation all lead to depression and anxiety. Added to these factors are the symptoms and signs of hypothyroidism that can cause or worsen depression. The investigators felt there were preexisting traits that could predict which patient would develop the symptoms. Important issues for the treating physician are to take sufficient time to explain the procedures in detail, to try and determine a priori which patients are at most risk and to have additional consultations if necessary and to emphasize that the patient is being treated as a person and will not be left in isolation without medical attention. Patients receive information and misinformation from many sources, and a patient (not one on mine) faxed me a document containing statements such as "Iodine-131 is so dangerous it is dispensed by a doctor shielded in lead from head to toe." This epitomizes the need for time for discussion of the treatment and any questions and fears the patient expresses.

In an effort to avoid hypothyroid symptoms one group of investigators advised patients to take half of their usual dose of levo-thyroxine [93]. The patients preferred this to stopping thyroid hormone completely and they had a mean TSH of 63.2 mIU/l although three of the fifteen patients studied had values less than 20 mIU/l. The authors point out that, when the TSH is slow to rise, the patient can remain on this protocol until the desired level is reached. One problem is that the patient needs to keep coming to the laboratory for TSH measurements until the appropriate value is achieved. This makes it impossible to plan the dates for diagnostic testing and treatment and starting the low iodine diet.

For followup whole-body scans the patient can be made hypothyroid by withdrawing thyroid hormone, or the study can be completed using recombinant human thyrotropin (rhTSH) as discussed below.

Historically physicians used to achieve an elevated TSH by prescribing antithyroid medications. [94] This is not recommended. There are potential side effects from the medications but more importantly the radioiodine is not retained by the thyroid cells. Patients were also given injections of bovine TSH [95, 96]. Repeated exposure to bovine TSH caused allergic reaction in 43% of forty-two patients in one retrospective review [97]. Some of these reactions were severe. Other investigators found that the antibodies against bovine TSH could neutralize the actions of both the bovine and endogenous TSH and make radioiodine testing and treatment impossible [98, 99]. Nowadays there would be concern about prion-induced diseases and other infectious disorders that could be transmitted by injection of animal pituitary tissue. A recent review discusses this topic and provides additional references [100]. The use of bovine TSH stopped more than two decades ago and has been replaced by recombinant human thyrotropin.

Recombinant Human Thyrotropin

The biochemical synthesis and production of recombinant human thyrotropin (rhTSH) was a triumph in molecular medicine. For those interested in the details of its synthesis see references [101, 102]. The structure of TSH and the understanding that it is constituted from 2 peptides was recognized for decades. The α chain is common to TSH, follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (HCG). The β chain provides functional and immunologic specificity. The β subunit gene was cloned in 1988 by 2 groups of investigators [103–105]. The α and β genes of TSH were inserted in Chinese hamster cells that produced in vitro human TSH (rhTSH). There were some differences between this TSH and native TSH that were reduced by desialylation. [106]. Experiments in monkeys showed the clearance of rhTSH was slower than native TSH [106, 107]. Purified rhTSH was injected into volunteers and shown to cause a rapid rise in measurable serum TSH [108].

Studies were then conducted on patients with surgically treated thyroid cancer. Ladenson et al. reported on a Phase III trial in 127 patients [109]. The patients had a whole-body diagnostic scan after 2 intramuscular injections of 0.9 mg on consecutive days. On the following day they received 2 mCi to 4 mCi (74–148 MBq) ^{131}I. A scan was obtained 48 hours later. The patients then had a diagnostic scan after withdrawal of whatever thyroid preparation they were taking. 97 of the patients were being treated with levo-thyroxine. They were scanned 48 hours after a second dose of 2 mCi to 4 mCi (74–148 MBq) ^{131}I and the scans were compared. 106 of the 127 pairs of scans were concordant (83%), with 41 pairs being positive and 65 pairs negative. There were 21 discordant pairs, 18 of these were positive on the withdrawal scan but negative after injection of rhTSH. This was disappointing but there were some criticisms of the study. One objection was that the first scan was always conducted after injection of rhTSH. This is understandable because it would not be ethical to withdraw thyroid hormone find a significant lesion, then replace thyroid hormone for weeks and then repeat the scan with rhTSH and finally withdraw thyroid hormone again to induce hypothyroidism for a second time and proceed with treatment. The second objection was that Tg was measured in only thirty-six of the 127 patients, but at the time of the investigation, it was recognized to be a standard requirement for evaluation of these patients. Also the diagnostic dose of ^{131}I and the quality of scans were variable. Finally the accepted TSH was >25 mIU/l, which is lower than many clinicians recommend. An accompanying editorial ended "the old way still seems better" [110].

A second Phase III trial was conducted using 4 mCi (148 MBq) ^{131}I for the diagnostic scan and stimulated Tg was obtained and the data were compared in euthyroid patients first and then after withdrawal of thyroid hormone [111]. Two hundred twenty-nine patients were studied. There was concordance in 195 of 220 (89%) pairs of scans that could be evaluated. In this study, like the previous one, when the discordant scans were analyzed, there were more judged to be superior after withdrawal of hormone. In this case, seventeen scans were interpreted to show more in hypothyroid patients versus eight, which were obtained after injection of rhTSH. The difference was not statically different. The addition of Tg increased the sensitivity of the procedure. Using a Tg of 2 ng/ml as the cut-off, stimulated Tg values above this identified metastatic disease in 100% whether the patients had been given rhTSH or were hypothyroid. Therefore, 100% with metastatic disease were identified by rhTSH scan and Tg. In 93% of the patients with thyroid tissue or disease in the thyroid bed the combination of rhTSH scan and stimulated Tg established the diagnosis. There is some circular reasoning since it is not clear what the gold standard is. Is it the diagnostic scan or the Tg or both or some other factor and how do we know that the classification of the patients with and without metastases is correct? These studies were funded and designed by Genzyme Corporation, who produce and market rhTSH under the trade name Thyrogen. In both of the phase III trials, patients were studied at several medical centers in the U.S. and Europe. Within the second Phase III study, some patients received three injections of rhTSH and the protocol extended over two weeks. There was no benefit and the additional time and prolongation of low iodine diet to be discussed suggest this should not be pursued. In the Phase III investigations, approximately 10% of the patients reported a headache and a similar proportion were nauseous after the injection of rhTSH. The FDA approved the use of rhTSH in December 1998.

I have conducted more than 200 diagnostic scans after rhTSH stimulation. Preliminary results have been published [112, 113]. The patients' characteristics were typical for differentiated thyroid cancer. 69% were women and the average age (±SD) was 44.7 ± 13 years. The incidence of side effects was higher than reported in the Phase III trials. 13% had a transient headache and 21% had mild nausea or queasiness of the stomach. A few patients reported that they felt tired. With the exception of one patient who vomited, the symptoms were both mild and transient and needed no specific treatment. Almost all of the patients had undergone scanning previously when they were hypothyroid. With one exception all patients preferred the study conducted with rhTSH compared to when they were hypothyroid. The study was generally conducted for followup of patients who had been operated on and had received ^{131}I treatment and a negative study was

anticipated in most cases. The mean TSH was 133 mIU/l, 24 hours after the second injection. I obtain a TSH to prove that a negative scan and low stimulated Tg are true negatives and there is no technical defect that could result in a false negative. The package insert recommends injection in the buttock, but these high TSH values were achieved after intra-deltoid injection. Two patients with the lowest TSH values lived some distance from Stanford. Before the procedure I educated them on how to reconstitute the rhTSH and administer it. They had a nursing colleague follow my instructions and inject the rhTSH. Both had values between 25 mIU/l to 30 mIU/l. It is possible that the assistant diluted the rhTSH with too much sterile water. All other measurements were 50 mIU/l or greater. There was an inverse relationship to patient weight. This is intuitive since the same amount of rhTSH is injected irrespective of patient mass. The serum TSH value drops rapidly after injection of rhTSH and in a small number of patients who had TSH measured at the time of the Tg measurement 72 hours after the second injection, the TSH values had fallen to about 20 mIU/l. One patient studied elsewhere had a negative scan and undetectable Tg but her TSH was 8 mIU/l. Her endocrinologist who was conducting an rhTSH test for the first time informed the patient that the study was of no value and there must have been something wrong with the rhTSH. A second endocrinologist confirmed that opinion. On review of her test results the TSH measurement was made 72 hours after the second injection and I believed the test was in fact valid. Nothing I could do would change the fear of the patient that there was a problem. The study was repeated after withdrawal of thyroid hormone with the same good results. The TSH should be measured within 24 hours of the second injection of rhTSH.

90% of the diagnostic whole-body studies were negative and Tg values $\leqslant$5 ng/ml which I accept as not meriting additional tests or treatment. When the stimulated value was $\geqslant$10 ng/ml and the scan was negative additional testing was undertaken to try and identify the site of Tg production a topic discussed below. Several patients who were Tg positive and scan negative after withdrawal of thyroid hormone were studied using rhTSH and they were still scan negative and Tg positive. Therefore rhTSH is not the answer to the management of this situation, which is discussed in detail under controversies. There has been a small amount of data indicating that Tg values are higher after withdrawal of thyroid hormone. This has been attributed to the prolonged TSH stimulus in hypothyroid patients contrasted with the short rapid rise and fall of injected rhTSH. It has also to be attributed to slower metabolism of Tg in hypothyroid patients. In my experience no patient with an elevated Tg when hypothyroid had a normal Tg after rhTSH stimulation.

The clearance of iodine was determined to be slower in hypothyroid patients due to reduced renal function in the hypothyroid condition. In a small series the uptake over the thyroid bed was 0.1% in patients given rhTSH but 0.24% in the same patients when they were hypothyroid [114]. The whole-body retentions were 5.5% and 14.3% respectively. This gave a ratio of increased retention in hypothyroid patients of 2.4 and 2.58 for the thyroid bed and whole-body respectively. I studied twenty patients who had negative scans by both techniques. In each case the withdrawal scan had been obtained before the rhTSH one. The only source of excretion in these patients was the kidneys and because there was no thyroidal uptake, and 100% of the iodine would be excreted by that route. Therefore it would be predicted the rate of clearance should be considerably prolonged in the studies conducted in hypothyroid patients. Images were obtained 48 hours after administration of the tracer in the case of rhTSH and at 72 hours in hypothyroid patients since most physicians conduct ^{131}I whole-body scanning after that delay in hypothyroid patients. The uptake measurements over the thyroid bed, the actual counts of that site using a probe and the counts over the thigh that were used for correction of background activity were compared. The 48-hour measurements of uptake after rhTSH were 0.051 $\pm$ 0.03% compared to 0.045 $\pm$ 0.04% when the patients were hypothyroid. The average neck counts 3,892 versus 2,616 per minute were higher after rhTSH as were the counts over the thigh 2,207 versus 1,130 per minute. Therefore the marked difference in clearance reported by Park et al. could not be confirmed. The data from Park et al. has been taken from an abstract, I am not aware of a full publication. It is possible that some of the difference could be explained by radioactivity in the intestines.

This tends to be higher in hypothyroid patients and would be included in whole-body counts. That gut activity would have no influence on neck and thigh measurements of radioactivity. Reliable knowledge of clearance and residency time is important when it comes to treating patients with ^{131}I. Is it different when they are euthyroid and the cells are stimulated with rhTSH? Should the patients be treated with a higher therapeutic dose? This is still the cause of disparate information that is discussed under treatment. It also questions why the scans after 2 mCi (74 MBq) ^{131}I should be technically inferior using rhTSH. I find this dose acceptable and other authorities including a co-author of the Park et al. abstract have continued to employ 2 mCi (74 MBq) [115].

One other technical issue that has not been resolved is whether the iodine released from levo-thyroxine is sufficient to lower the uptake values. It raises the question whether patients should be advised to take triiodothyronine for 4 weeks prior to testing with rhTSH. Triiodothyronine is more potent, the dose is smaller and it contains less iodine (3/4 per molecule) and overall there would be approximately 1/5 of the iodine. This is a study worth pursuing.

There is no evidence that patients develop antibodies after repeated injections of rhTSH [116]. Therefore when rhTSH is clinically indicated it is legitimate and safe to obtain followup studies using repeated administrations of rhTSH. When this is used in patients with bone and brain metastases the TSH stimulus can cause growth of lesions resulting in pain, respiratory problems and central nervous system complications such as hemiparesis [117–119]. It had been hoped that the short sharp TSH stimulus might avoid such complications and that these complications would be more common in hypothyroid state with a prolonged elevation of TSH. Therefore, when a patient has a lesion within a fixed space such as the skull or spinal cord it is prudent to have a neurosurgical consultation to determine whether treatment by excision, cyber knife radiation or external radiation should precede any TSH stimulus. The use of corticosteroids prior to injection of rhTSH has been reported to prevent “subacute” complications [120].

There are now many reports on the use of rhTSH for diagnostic purposes. When scan and Tg values are used the test is equal to withdrawal of thyroid hormone [121–123]. Since stimulated Tg has a very high sensitivity some authorities have advocated that measurement alone and no diagnostic scan is sufficient [124]. One review makes the point that approach is acceptable after a negative followup scan and Tg have been achieved [120]. My preference is to obtain at least one followup scan and stimulated Tg since there are reports of undetectable Tg in patients with known residual cancer [125]. When both are negative stimulated Tg values could be used after that.

There have been no published reports of the consistency of repeated studies with rhTSH. I have compared results in 12 patients who had repeat followup studies usually 1 year and 5 years after the original treatment by operation and ^{131}I. There was an average of 38 months between the 2 studies. The TSH values (mean ± SD) of the first and second procedures were 149 ± 47 mIU/l and 147 ± 56 mIU/l which are not statistically different and the correlation coefficient was 0.63. The mean neck uptakes at 48 hours were 0.043% and 0.05% respectively which are also not statistically different and the correlation coefficient was 0.797. In patients with no residual disease repeated tests are therefore both reliable and consistent.

A recent report in 4 patient demonstrated the rhTSH can be administered subcutaneously and result in a satisfactory rise in serum TSH [126]. The reason for subcutaneous injection was that the patients were anticoagulated and there was concern about intramuscular hematoma formation. Other investigators have used a single injection of rhTSH to stimulate uptake in multinodular goiter [127]. In most patients with thyroid cancer the 2 dose intramuscular protocol would be advised.

Low Iodine Diet

The goal of diagnostic imaging and therapy is to have thyroid cells trap as much radioiodine as possible. When there is a high plasma inorganic iodide (or high urinary iodide as a surrogate measurement of dietary iodine) the tracers of radioiodine are diluted and the uptake is reduced. This has been demonstrated in the United States in normal people undergoing 24-hour uptake measurements where the reference ranges fell as the dietary iodine increased. [128] The average intake of daily iodine in the United

States is about 500 µg. This high intake of iodine is important in patients with thyroid cancer where there can be small remnants of cancer that have reduced ability to trap compared to normal cells. The tracer of radioactive iodine is diluted by the non-radioactive ^{127}I. Most authorities recommend a low iodine diet for 2 weeks before testing and treatment. Several simplified diets have been published [129]. However these diets are not that simple for the patients. There should be no intake of seafood, iodized salt, dairy products, eggs, tinned, or cured meats, flour containing iodates, soy products and restaurant meals. Pills with red dye should be avoided as well as vitamin and minerals that usually contain 150 µg iodine per pill. The diet requires planning and is boring and not pleasant for a patient who is hypothyroid, low in spirits and forced to watch family members eat with abandon. I find discussion of the diet early in the planning of scanning and therapy is helpful. Figure 6.5 is a patient on day thirteen of the diet. There is an excellent recipe book available on line from the web site www.thyca.org. There are diets for patients who are tube fed and a low iodine liquid tinned supplement is available [130].

Morris et al. do not agree about the importance of the low iodine diet [131]. Their study has several flaws. Patients who were not given advice about the low iodine diet were assumed to be on a regular diet. Nowadays most patients are very educated about their disease and have already researched treatment options and methods. A significant proportion of patients already have the low iodine recipe book before I meet with them! The investigators also did not express urinary iodine as a ratio to urinary creatinine. A recent study by Park and Hennessey has shown that the two-week diet is important [132]. Previously they had used one week of low iodine for patients undergoing testing with rhTSH. They compared urinary iodine expressed as µg iodine/g creatinine and found that only 41% of patients had values less than 100 µg/g compared to 71% on 2 weeks of low iodine. As stated earlier there has been concern that the levo-thyroxine could contribute about 50 µg iodine from deiodination [112]. Park and Hennessey found the diet to be more important than the levo-thyroxine. There is a place for an investigation substituting triiodothyronine for thyroxine and measuring plasma or urinary iodine.

Figure 6.5. Patient on day thirteen of low iodine diet around festive season, published with her permission.

One of the worst sources of very large doses of iodine is radiographic contrast. It is not unusual when a patient is diagnosed with thyroid cancer that a CT scan with contrast is ordered by a general physician to define the regional anatomy and extent of disease. How long should clinicians wait before nuclear imaging? We conducted a study by measuring iodine in nail clippings in patients who had received intravenous contrast [133]. The iodine remained in those tissues for months. I recommend waiting eight weeks after a patient has received intravenous contrast and then measuring plasma inorganic iodine or urinary iodine.

These tests are usually not available in all clinical laboratories but are at through the Mayo Clinic. An excellent resource for all aspects of the practice of thyroid function testing is the Laboratory Medicine Practice Guidelines [134]. This includes 495 references and urinary iodine measurement can be found on pages 75–79. I prefer plasma inorganic iodine to urinary iodide, and when that value is within normal range, the patient has excreted the contrast and can proceed with the protocol for testing and treatment. In patients taking levo-thyroxine that is stopped and after two weeks the low iodine diet is started and continued for two weeks. Therefore the patient does not take levothyroxine for 4 weeks. When the patient is taking triiodothyronine the low iodine diet is started at the same time the medication is withdrawn and testing can proceed in 12 days to 14 days. The patient continues on the diet until the diagnostic scan is completed and shown to be negative or until one day after treatment with ^{131}I. Therefore patients who are treated with ^{131}I are on the diet for two weeks plus two or three days. In the case of rhTSH the low iodine diet is prescribed for two weeks and continued during the administration of rhTSH and imaging on the third week [113]. These patients are on the diet for nearly three weeks. Almost without exception at the end of the testing patients express with glee that they are going straight to a restaurant for a pepperoni pizza, or double cheese burger and fries with extra salt preceded by a shrimp salad. One added benefit of the diet is that hypothyroid patients do not gain weight and those being tested when euthyroid lose weight. Family members who support the patient by adhering to the same diet also lose weight. Fruit, vegetables and white meats are healthy.

A rare but difficult situation is the patient with thyroid cancer who needs amiodarone for treatment of cardiac failure [135]. The dose of amiodarone is usually 200–400 mg daily and this contains 75–150 mg iodine of which about 10% (7.5–10 mg) is free iodine. Amiodarone has a very long half-life due to its solubility in fat. If the medication cannot be stopped, it is unlikely that testing or treatment with radioiodine will be of value. In an occasional patient the medication can be replaced by an alternative but because of the long half-life it is necessary to wait many months before testing and treatment with radioiodine. Periodic measurement of plasma or urinary iodine can help with the appropriate timing of nuclear medicine testing and treatment.

Which Radioactive Tracer?

Iodine-131 was used for diagnostic whole-body imaging for decades. But there were concerns that the diagnostic scan on occasion did not provide as detailed an analysis as the post therapy scan. Several authorities did not find a significant difference [136, 137]. There was added concern that diagnostic doses of ^{131}I could damage the trapping ability of thyroid cells so that therapeutic ^{131}I would be concentrated in lower amounts and not be so effective in killing the cancer cells. This is called "stunning" and is covered in detail in that section on controversies. Because of these factors several investigators evaluated ^{123}I. ^{123}I is a pure gamma (γ) emitter and with a half-life of 13 hours. Therefore in comparison with ^{131}I which has an 8 day half-life and beta (β) plus γ emissions ^{123}I should not cause stunning. The 159 keV energy of the γ of ^{123}I compared to the 365 keV γ of ^{131}I is much better suited to high resolution imaging with a gamma camera. This has led some to state it is the ideal radionuclide in this situation [138]. Historically there was an abstract that was presented at the Annual Meeting of the Society of Nuclear Medicine that indicated ^{123}I was not as sensitive as desired. Subsequently Park et al. showed that ^{123}I did not cause stunning and produced high quality images [139]. Then Mandel et al. reported that ^{123}I was superior to ^{131}I for imaging thyroid remnants [140]. Several other groups of investigators showed the value and high sensitivity of ^{123}I for whole-body scanning [141–143]. The dose administered varies from less than 37 MBq (<1.0 mCi) to 155 MBq (5.0 mCi). In contrast Sarkar et al. found more lesions in four of twelve patients on the post treatment ^{131}I scan compared to the ^{123}I diagnostic scan [144]. Our group also found that to be the case in seven of thirty (23%) pairs of scans [145]. Cohen et al. also found what could be judged to be stunning on post treatment scans in four patients who had diagnostic scans with ^{123}I [145]. A similar finding is noted in one patient in another publication [146].

Because of concern about stunning it is reasonable to restrict the dose of ^{131}I to 1 mCi to 3 mCi (37–111 MBq) ^{131}I. This is administered orally as a capsule or liquid and whole-body scan conducted after 48 hours to 72 hours. There is some evidence that the sensitivity of the scan is greatest at 72 hours after administration of ^{131}I [147, 148]. Iodine-123 is administered orally and scintiscanning conducted at 24 hours. The usual dose is 2 mCi (74 MBq). Some investigators have been able to produce images as late as 48 hours after 3 mCi to 5 mCi (111–155 MBq) ^{123}I. The optimal dose has not been defined.

Interpretation of the Whole-Body Scan

I prefer to obtain anterior and posterior whole-body scans and anterior and posterior spots of the neck and chest with the patient lying supine. Over the past 10 years the instrument has been a Siemens Body Scanner with a half-inch crystal and the images shown in the text were obtained using that. High-energy parallel hole collimators are used when the radionuclide is ^{131}I and a low energy collimator for ^{123}I. A 15% window centered around the 364 keV photopeak of ^{131}I, or the 159 keV photopeak of ^{123}I is employed. When ^{131}I is imaged with a medium or low energy collimator there is considerable scatter and counts are picked up outside the body and the images are difficult to interpret. A transmission scan is helpful. This produces an outline of the anatomy so that regions of uptake can been correlated with exact position in the patient, as shown in Figure 6.6. External markers containing a small tracer of radioactivity, such as ^{99m}Tc-pertechnetate, can be placed at anatomic sites such as the thyroid cartilage and sternum to help determine the site of uptake of radionuclide. A quantitative measurement of the percentage uptake is both important and useful. It is important in determining whether the surgeon has removed most of the thyroid. When calculations for determining the dose of therapeutic ^{131}I are made the measurement of uptake is essential. For unknown reasons few nuclear medicine physicians make this measurement. The measurement can be made using a probe to obtain counts over the region of the thyroid

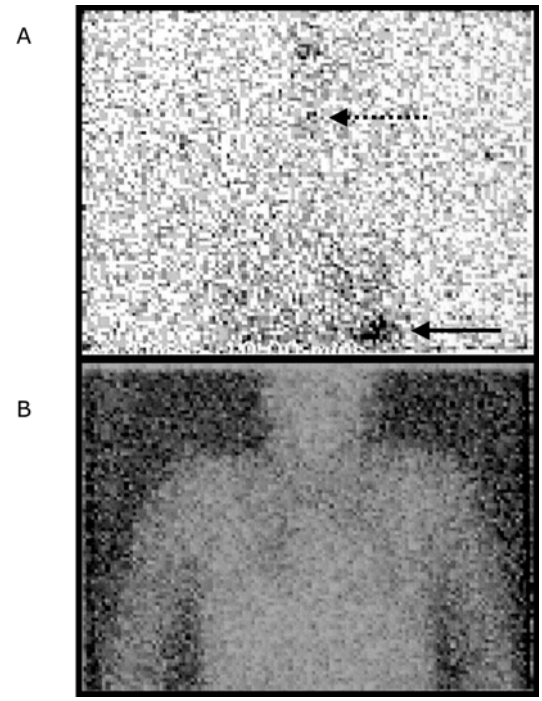

Figure 6.6. (A) Spot view of the neck and chest 72 hours after 74 MBq (2 mCi) ^{131}I. Broken arrow shows salivary activity and solid arrow the stomach. The relation of these can only be recognized by (B) the transmission scan using a flood source of Cobalt positioned behind the patient. The scan is negative and Tg was undetectable.

and then the thigh as an index of patient background. The formula is:

$$\frac{(\text{thyroid counts} - \text{thigh counts}) \times 100}{(\text{sample counts} - \text{room background}) \times \text{decay factor}}$$

The decay factors for ^{131}I at 48 hours are 0.842 and 0.772 at 72 hours, as shown in Table 6.6. For ^{123}I the decay factor at 6 hours is 0.73 and at 24 hours it is 0.284. Alternatively a small source of a known quantity of ^{131}I is positioned beside the patient and included in the whole-body scan. The counts in the sample are obtained using an area of interest from a digitized image and are compared to counts from the region of the lesion. Background counts from an equivalent area over the thigh are subtracted from lesion counts.

Some clinicians obtain multiple spot views in place of a whole-body scan. This is acceptable

Table 6.6. List of false positive findings on whole-body scan based on previous tabulations by the author [150, 151].

Site	Disorder	Reference
Head	Meningioma	[624]
	Wig	[625]
	Hair	Current chapter
	Scalp artificial eye	[304]
	Dacryocystitis	[304]
	Cranial clips	[626]
	Subdural hematoma	[627]
Nose	Sinusitis	[304]
	nasal secretions	[628, 629]
	"hot nose"	[629]
	frontal sinus	[630]
	Mucocele	[630-632]
Salivary glands	Physiologic	[150, 151]
	Sialoadenitis	[301]
	Warthin's tumor	[633]
Mouth	Saliva	[634, 635]
	peridental disease	[636]
	oral disease	[636]
	chewing tobacco	[637]
	lingual thyroid	[638]
Neck outside thyroid bed	Tracheostomy	[639]
	Thyroglossal duct	[640]
	Carotid ectasia	[641]
Thorax and lungs	Undifferentiated bronchogenic cancer	[642]
	Adenocarcinoma	[643]
	Squamous cell cancer	[644]
	Inflammatory lung disease	[645, 646]
	Bronchiectasis	[646]
	Pleural effusion	[647]
	Bronchogenic cyst	[648]
	Pectus excavatum	[649]
Cardiac	Pericardial effusion	[647]
	Struma cordis	[650]
	Pleuropericardial cyst	[651]
Thymus	Physiologic	[152, 652–654]
Breast	lactating, or recent pregnancy	[304, 320, 647]
	breast cyst	[655]
Esophagus	Esophagus	[647]
	Barrett's esophagus	[656]
	esophageal stricture	[657]
	Zenker's diverticulum	[658]
	esophageal scarring	[659]
	hiatal hernia	[660–662]

Table 6.6. *Continued*

Site	Disorder	Reference
Liver	*diffuse uptake*: physiologic uptake on late "post treatment" scans	[150, 151, 663]
	focal uptake: probable functioning metastases	[664]
Biliary tract	Gallbladder	[665]
	dilated intrahepatic duct	[666]
Stomach	Physiologic	[151]
	gastric carcinoma	[667]
Colon	Physiologic	[668]
	Meckel's diverticulum	[669]
	colonic graft	[670]
Urinary tract	physiologic on early scans	[634]
	renal cyst	[671]
	polycystic kidneys	[672]
	ectopic kidney	[304, 673]
Reproductive system	Ovary	[674]
	ovarian cystadenoma	[675]
	struma ovarii	[664]
	Endometriosis	[676]
Contamination	contaminated handkerchief	[150, 677, 678]
	skin contamination: head	[151]
	skin contamination: leg	[151]
	hair contamination	Current chapter
Perspiration	perspiration in axillae	[679]
	perspiration under a watch	[151]
Reviews	multiple sites	[150, 151, 304, 628, 647, 680, 681]

but is more difficult to read since there are overlapping images and usually the entire body is not included.

Iodine is absorbed rapidly from the upper intestine as shown by an early ^{123}I scintiscan shown in Figure 6.7. Any nuclide of iodine including radioiodine is trapped wherever there is NIS. It is also excreted through the kidneys into the urine. Some iodine passes through the intestines, but most radioactivity seen is in the bowel is iodine that has been incorporated into thyroid hormone and metabolized in the liver by conjugation. The conjugated radioiodinated hormones then enter the biliary system and pass into the gut. Normal thyroid traps more efficiently than malignant thyroid. It is usual to identify functioning thyroid tissue in the thyroid bed even after total thyroidectomy. When the thyroid has been removed and there are metastases in lymph nodes or distant sites these lesions are often imaged on the first diagnostic scan after total thyroidectomy. However when there is a large residuum of thyroid that can result in metastases going undetected. Figures 6.8 through 6.13 show the appearances of a negative scan, residual thyroid, functioning lymph node metastases, metastases to the lungs and the skeleton. There are other organs that normally trap iodine, and they are seen on the scan. They include the salivary glands and stomach. Low lying submandibular glands can be confused for metastases to cervical lymph nodes. The bladder is usually seen on scans made over the first two or three days. Scans

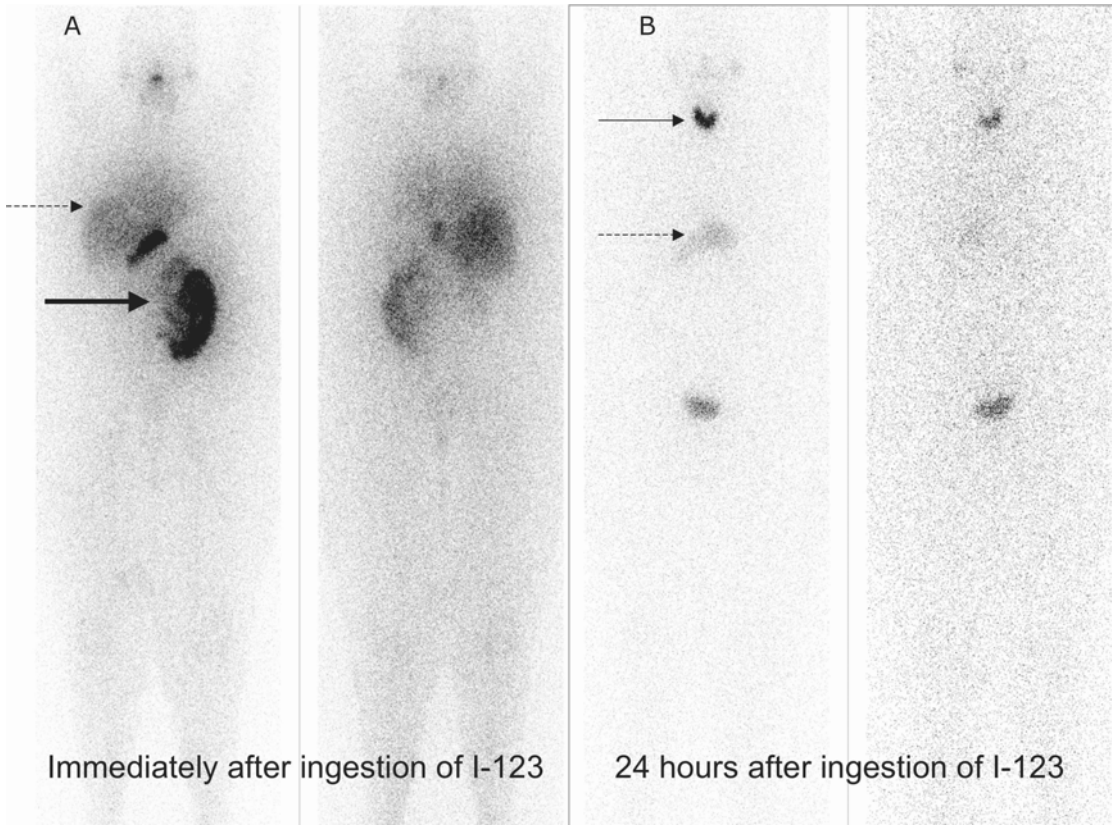

Figure 6.7. (A) Anterior and posterior whole body scans made 20 minutes after oral intake of 37 MBq ^{123}I, and (B) images made 24 hours later. The early images show intense uptake in the upper intestines (solid arrow) but even at this time there is considerable amount of ^{123}I in the blood pool as shown by soft tissues and liver (broken arrow). By twenty-four hours the thyroid (solid arrow) and stomach (broken arrow) are seen. This patient was taking triiodothyronine and had a low TSH, the study was part of a research protocol trying to identify breast cancer metastases.

made later often show uptake in the colon and rectum. I have encountered two patients who were worked up extensively by other physicians because there was uptake in the rectal area on post treatment scans made about one week after therapy. The activity was interpreted as metastasis to the pelvis. The finding is physiological but the patients had barium enemas, CT and MRI scans to try and identify a metastasis at that site. Although no abnormality was identified the uncertainty caused considerable anxiety that was finally relieved by an explanation of the excretory routes for iodine and a negative followup scan and undetectable Tg. In the next section, false positive scan findings are discussed and the following advice will be repeated. When interpreting the scan it is important to recognize normal patterns. It is also important to know where thyroid cancer spreads. It does not metastasize to the rectum; therefore, uptake there is most likely physiological and least likely to be distant spread of cancer. Breast tissue that is lactating or has recently been active traps and secretes iodine and can be imaged [149]. Although the choroid plexus traps iodine, it is extremely uncommon for sufficient uptake to be recognized on scintiscan. The liver can be imaged on delayed diagnostic scans with ^{131}I and scans made several days after treatment (Figures 6.11 and 6.14). The appearances of ^{131}I and ^{123}I scans are similar with regard to distribution but the resolution of the latter is superior (Figure 6.15).

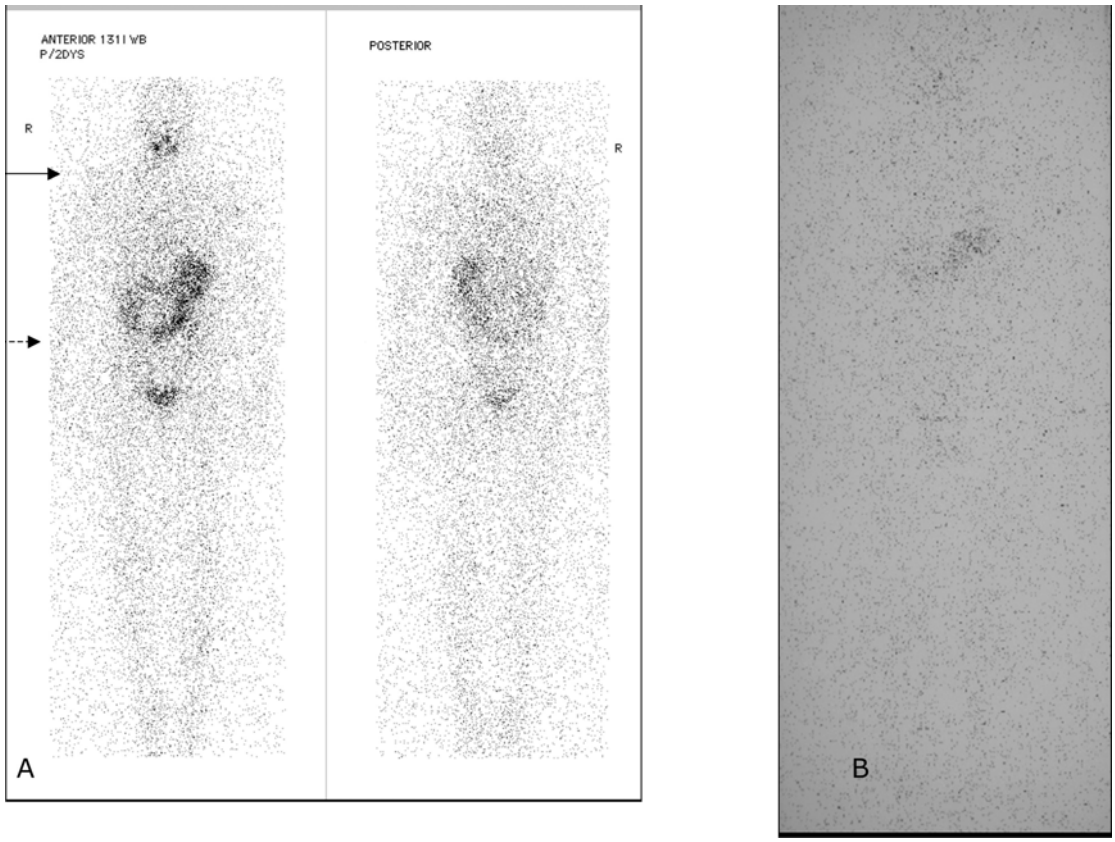

Figure 6.8. Negative whole body scans. (A) Anterior and posterior whole body scans made 72 hours after 74 MBq ^{131}I. There is no uptake in the thyroid or cervical nodes. The salivary glands are noted (solid arrow) as is the intestine (broken arrow). (B) Anterior scan also 72 hours after 74 MBq ^{131}I shows almost no activity in any site. These are typical negative scans.

False Positive Findings

Uptake of radioiodine in non-thyroidal organs or tissues that is or could be interpreted as thyroid cancer is considered a false positive. This can occur in either the diagnostic or post treatment scan or both. There are several comprehensive reviews of reports of benign or non-thyroid cancer disorders that have caused difficulty on interpretation [150, 151]. Table 6.7 provides an extensive tabulation of reported false positive findings. To avoid making an error in interpretation knowledge of the distribution of iodine and spread of thyroid cancer are very important. When a lesion on scintiscan does not make sense a review of the literature to determine whether there is a report of a similar finding might establish the reason for accumulation of radioiodine. The patient should be examined with an emphasis on the region showing abnormal uptake. Compare the scan with Tg result. It is not very common to have widespread metastases and a low Tg value. Common causes of false positive interpretation relate to excretion of iodine in saliva,

Table 6.7. Decay of Iodine-131 and fraction remaining with time.

Day	Fraction remaining
0	1.000
1	0.917
2	0.842
3	0.772
4	0.708
5	0.650
6	0.596
7	0.547
8	0.500
10	0.422
15	0.274
20	0.178
80	Considered 0

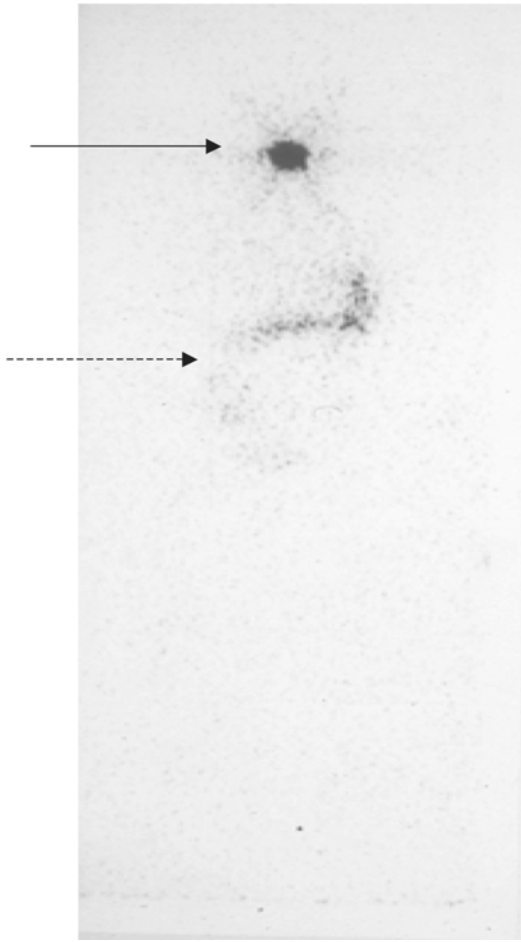

Figure 6.9. Whole body scan showing remnant in thyroid bed after surgery. Anterior whole body scan made 72 hours after 74 MBq ^{131}I. There is uptake in the thyroid bed (solid arrow) and in the intestine (broken arrow).

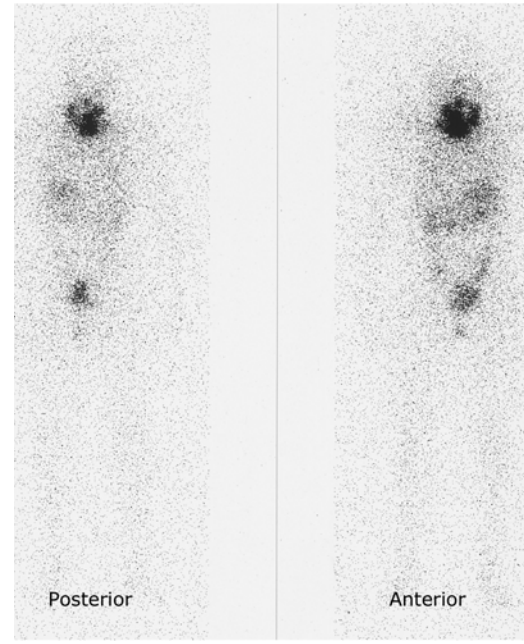

Figure 6.10. Positive whole-body scan. Anterior and posterior whole body scans made 72 hours after 74 MBq ^{131}I. There is intense uptake in the thyroid and cervical nodes. There is excretion through the intestines.

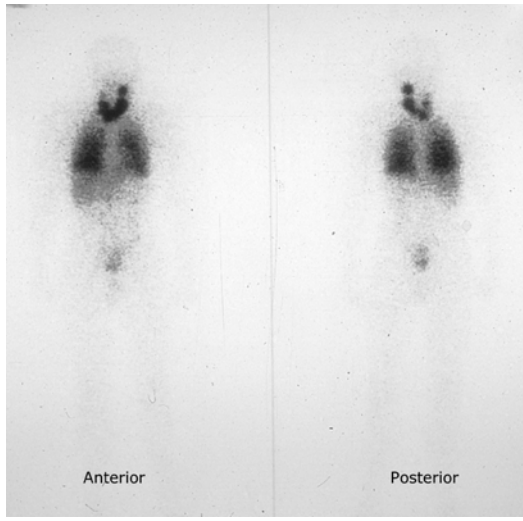

Figure 6.11. Anterior and posterior whole body scintiscans in a patient with widespread pulmonary and cervical nodal metastases. Patient was scanned 72 hours after 74 MBq ^{131}I.

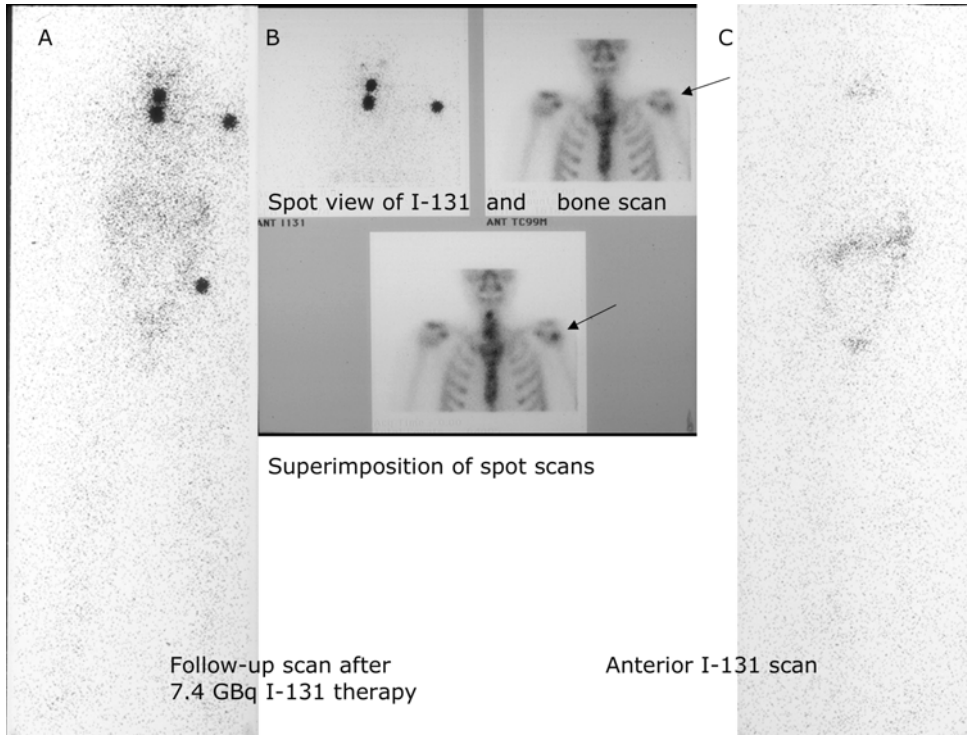

Figure 6.12. (A) In whole-body scan 72 hours after 74 MBq MBq I-131, there is uptake in the thyroid bed and two bone lesions one in the left shoulder and one in the left ilium. (B) Spot views of the ^{131}I scan and a bone scan over the same are and these two scans superimposed to show the site of the shoulder lesion is the humerus. (C) Followup scan 12 months after 7.4 GBq ^{131}I demonstrates resolution of the thyroid, humeral, and ischial lesions.

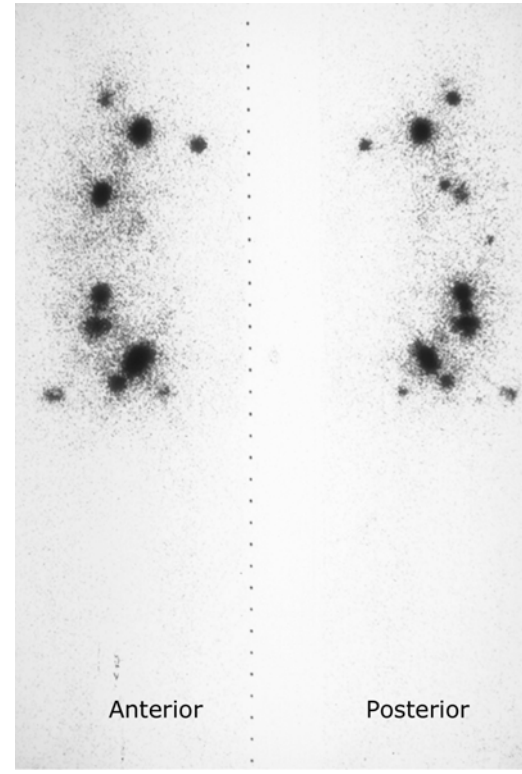

Figure 6.13. Shows anterior and posterior scans in a patient with widespread functioning metastases in the skeleton.

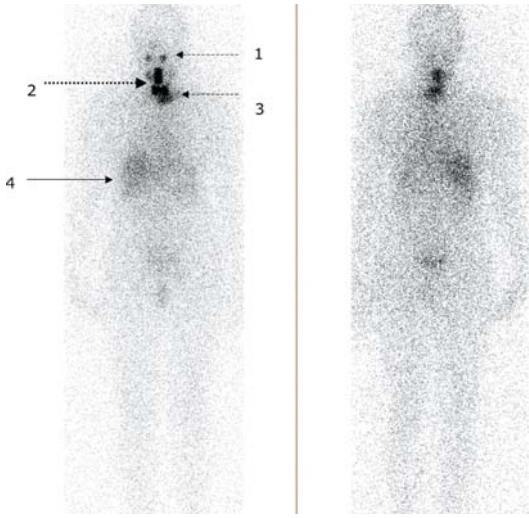

Figure 6.14. Anterior and posterior post therapy scans obtained one week after treatment shows (1) salivary activity, (2) residual thyroid, (3) functioning metastases in lymph nodes, and (4) hepatic uptake.

urine and occasionally feces causing contamination (Figures 6.16 through 6.18). Non-thyroidal cancers can occasionally trap iodine. Because iodine is taken up by parietal cells and secreted into gastric fluid, acid reflux or hiatal hernia can produce uptake in the chest that can be misinterpreted as mediastinal or lung metastases (Figure 6.19). There are several reports of uptake in the thymus. We found this to be rare but it is a real finding more often in young patients on the post-therapy scan (Figure 6.20) [152]. The high energy of the photons of ^{131}I can produce a "star" artifact (Figure 6.21). This is more common when there is high uptake in a lesion, and it is due to the high-energy 364 keV photon penetrating the thinner sides of the hexagonal "bee-hive" shaped septae of the collimator. Hence, the six points to the star. Collimators constructed with square apertures produce a star with four points.

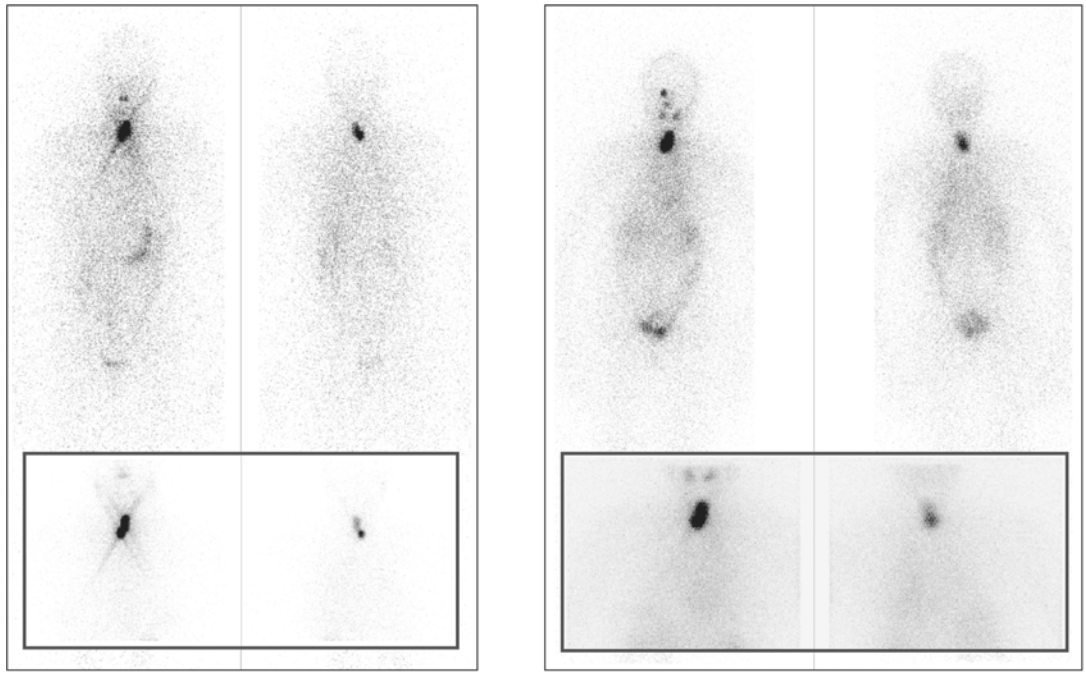

Figure 6.15. (A) Anterior and posterior scintiscan obtained 24 hours after 74 MBq I-123. There is uptake in the thyroid bed that appears as 3 confluent ares best seen in the spot view in the inset at the bottom of the panel. (B) Posttherapy scan obtained one week after 3.7 MBq ^{131}I shows similar distribution but the resolution is inferior.

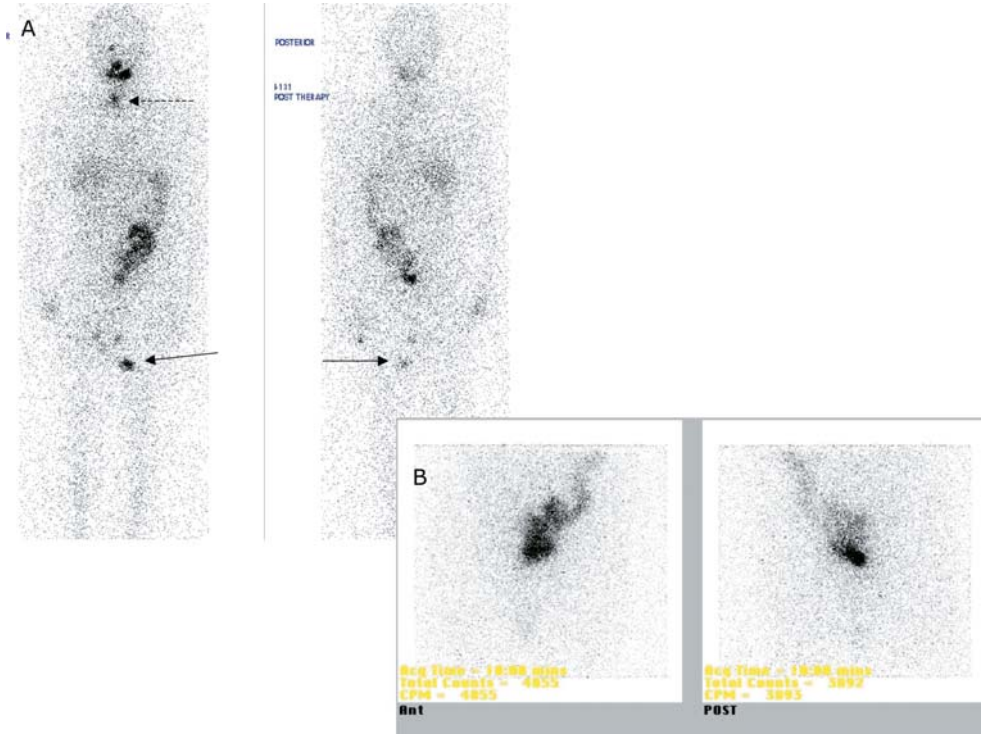

Figure 6.16. (A) Anterior and posterior whole body scans obtained one week after treatment with 3.7 MBq ^{131}I shows uptake in a small remnant in the thyroid bed (broken arrow). There is considerable radioiodine in the intestines and a small focus in the left groin consistent with a metastasis in the femur (solid arrow). (B) The patient removed his trousers and undergarments and was re-imaged and the spot disappeared.

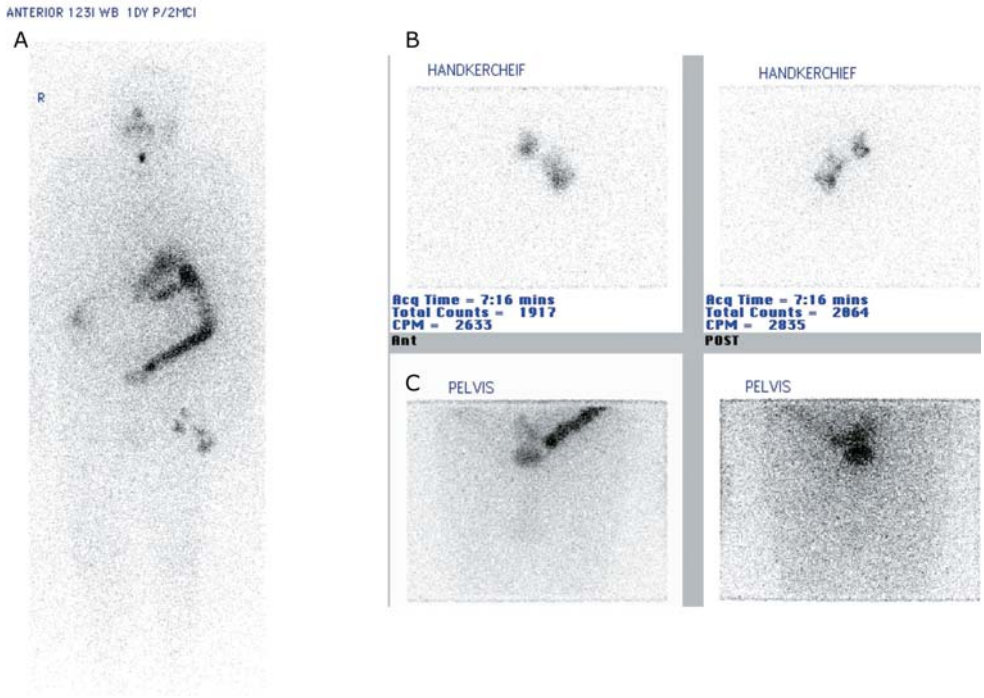

Figure 6.17. (A) Anterior whole-body image was made 72 hours after a diagnostic dose of 74 MBq ^{131}I. There is a small focus in the thyroid bed. There is irregular uptake in the left hip region. The patient had trouble post-operatively with coughing and he had a handkerchief in his left hip pocket. A scan of the handkerchief is shown in (B) is a spot view of the hip without the handkerchief in (C) shows no lesion.

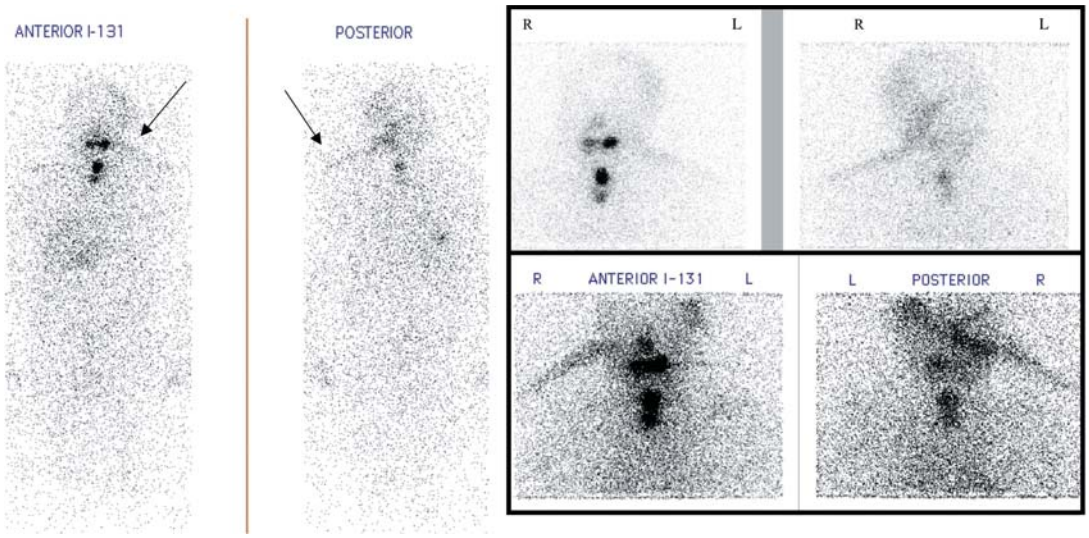

Figure 6.18. (A) Whole-body scans obtained several days after therapy. There are two regions of uptake in the thyroid bed but a strange linear strip of activity along the left shoulder that is hard to explain anatomically. The patient had a braided pigtail and when this was moved from the left side to the right and the patient re-imaged the activity was now on the right as shown in (B). He licked his fingers to aid with the braiding.

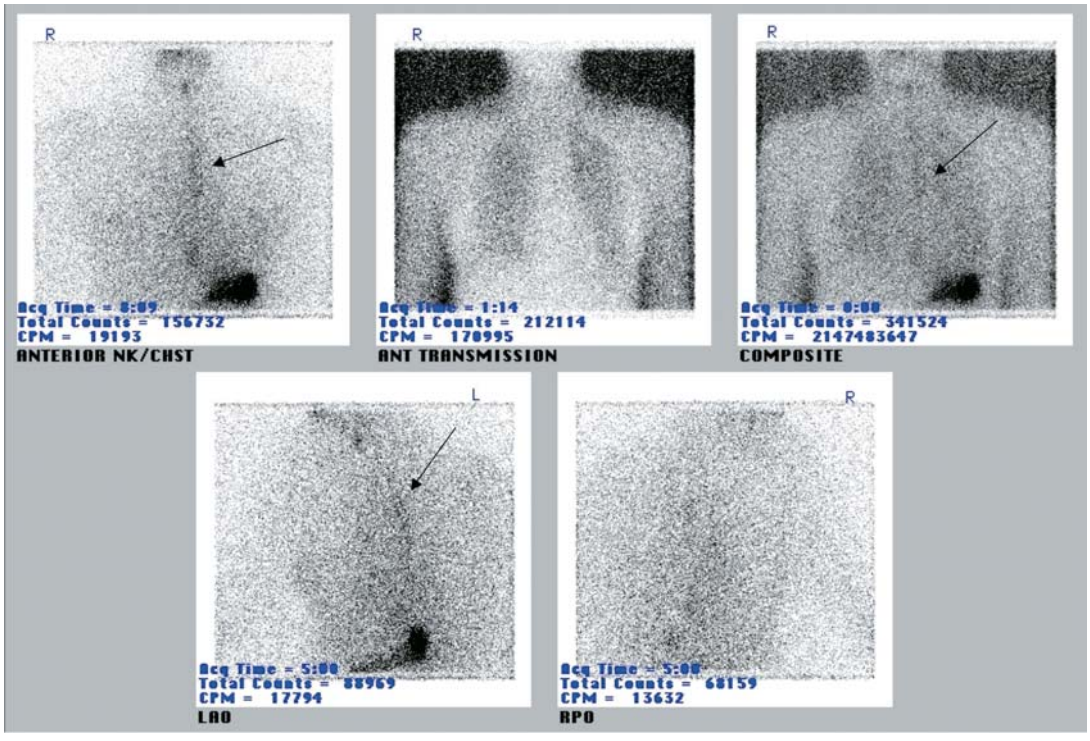

Figure 6.19. A series of spot views including a transmission scan and a composite of anterior neck and chest and transmission scan are shown. The patient was imaged 24 hours after 74 MBq ^{131}I. There is a vertical line of activity that runs towards the fundus of the stomach. This is due to ^{131}I in the esophagus and can be due to activity moving inferiorly from radioactive saliva or superiorly from reflux of radioactive gastric juice.

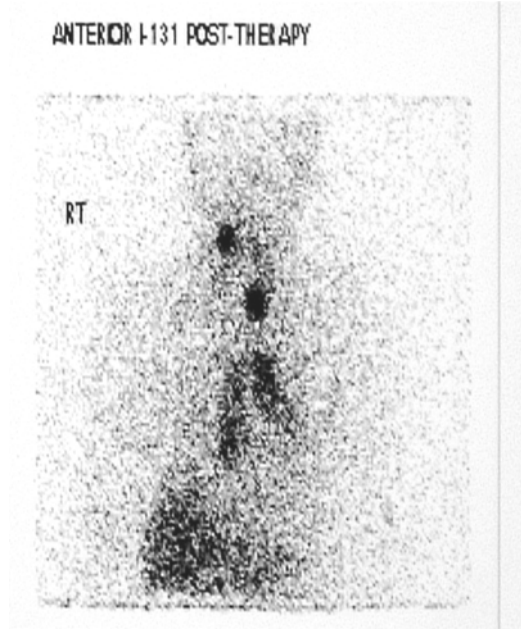

Figure 6.20. Anterior spot view of the chest of a young boy made one week after therapy with ^{131}I. There is a trace of uptake in the thyroid bed and in a low left cervical lymph node. The uptake in the thorax has the typical shape and appearance of the thymus in a youngster. The liver is also identified.

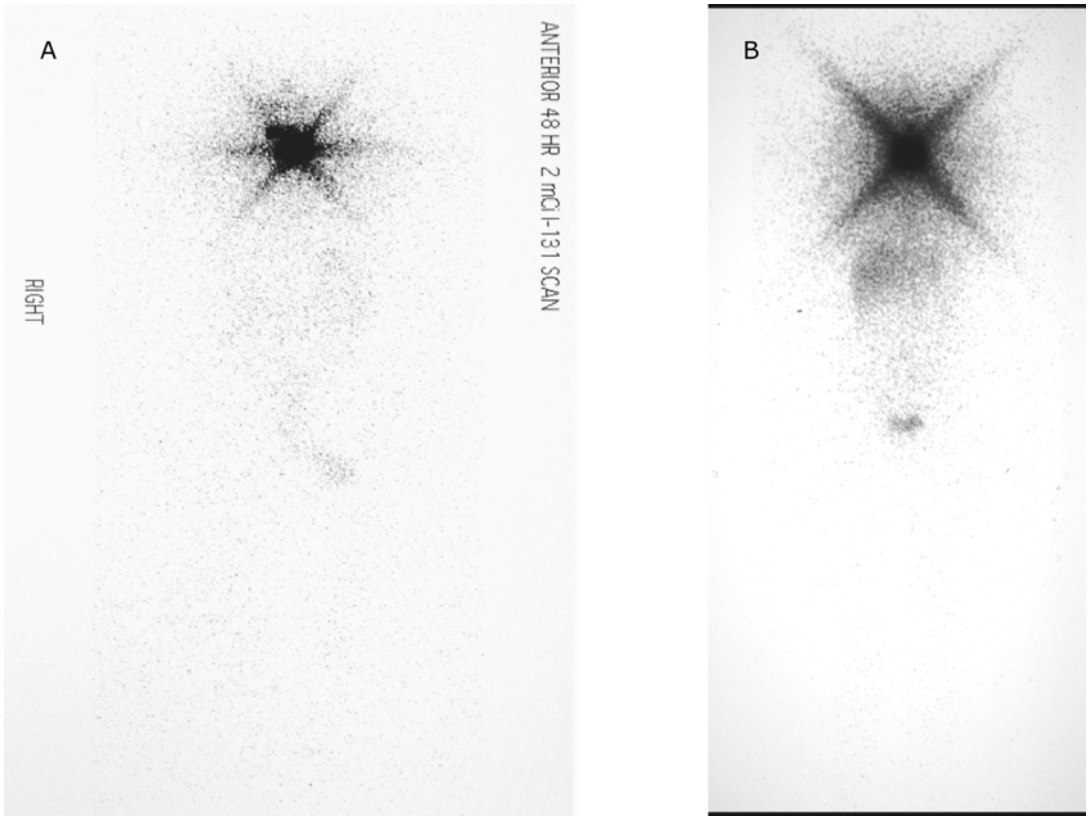

Figure 6.21. Star effect from two patients. (A) Star when the collimator consists of hexagonal channels. (B) was obtained with an older collimator made up of four sided channels. The high-energy photons "break through" the thinner walls but not the thicker angles of the collimator.

Thyroglobulin

The main role for thyroglobulin (Tg) measurement is in patients who have had surgical and ^{131}I treatment. The topic is introduced here since it can have a role at the time of the first diagnostic scan and indeed some authorities even recommend a measurement when the thyroid cancer is diagnosed. This is to ensure the cancer secretes Tg.

Thyroglobulin is a glycoprotein produced by follicular cell; it has a molecular weight of 660,000 daltons and is composed of 2 large peptides. For years it was believed that Tg did not leave the normal thyroid and that autoimmune thyroid disorders where antibodies are formed to Tg were the result of leakage of Tg into the circulation, where it would encounter the immune system that had not been exposed previously to this antigen. This dogma was shown to be incorrect when Tg was identified by radioimmunoassay in the sera of normal people [153]. Measurement of Tg for followup of patients with thyroid cancer was introduced by several groups of investigators and the Tg result compared to whole-body radioiodine scans [89, 154–158]. Thyroglobulin measurement has been one of the most important developments in the management of patients with thyroid cancer. It is generally accepted that Tg is of most value in patients who have had thyroidectomy and ablation of residual thyroid with ^{131}I. There are several important considerations. Thyroglobulin is produced by normal thyroid cells, by benign thyroid conditions, and by differentiated thyroid cancers. Therefore measurable Tg, even an elevated Tg, does not diagnose thyroid cancer. Tg levels are high in patients with benign thyroid nodules and with Graves' disease. The level of Tg is dependent on the level of TSH. This has been recognized for more than two decades [159]. Patients who have had a thyroidectomy for thyroid cancer and have undetectable Tg, while they take levo-thyroxine can have measurable values when thyroid hormone is withdrawn or the patient is given injections of rhTSH [160]. When there is substantial residual thyroid left post operatively it should be anticipated that Tg would be present in proportion to the mass of thyroid [161]. This is discussed in more depth in the controversy do all patients need ^{131}I treatment? Since the measurement of Tg uses antibodies against Tg, the serum of patients containing endogenous antithyroglobulin antibodies presents a dilemma as to the diagnostic value of the Tg measurement. This is a hotly debated topic. My colleagues developed an two step immunoradiometric assay (IRMA) that could measure Tg quantitatively in the presence of anti-Tg [162]. Not all authorities accept that this goal is achievable [163, 164]. Autoimmune thyroid disorders are common in particular in women therefore antithyroglobulin antibodies are found in up to 10% of women and 3% of men. The prevalence of anti-Tg in patients with papillary cancer is substantially higher and has been reported in 25–30% of patients [165]. When the pathology is reviewed it is common to see lymphocytic infiltration of the papillary cancer and this can be so intense that it gives the appearance of coexisting papillary cancer and Hashimoto's thyroiditis. There is some evidence that patients with papillary cancer and anti-Tg antibodies or Hashimoto's have a better prognosis. There is also some data indicating that those with persistently measurable anti-Tg have persistent thyroid tissue. The implication being that there is still residual thyroid cancer, which acts as an antigen to maintain the antibody production. I argue against that principle in general. I have not been immunized against many infectious diseases since childhood but I am still immune to those disorders. Nevertheless there has to be caution in the interpretation of Tg values in the 30% who are anti-Tg positive. One method of increasing the relevance of the measurement is to add known amounts of Tg and determine what percentage is assayed; this is called the recovery test [166, 167]. One hundred percent recovery would imply the assay is capable of measuring Tg even when antibodies are present. Since antibodies can differ in quantity and their tenacity of binding Tg, recovery measurements need to be conducted on all antibody positive sera. It should be apparent that every assay for Tg should be accompanied by an assay for anti-Tg to alert the physicians of their presence.

Different Tg assays can give different results in the same sample. Radioimmunoassays are one-step procedures; immuno-radiometric assays and chemo-luminescent assays are two-step assays. One study compared three assays (2 IRMA and 1 RIA) in fifty patients, Ten of whom

had metastases [168]. Also known amounts of Tg were assayed. Two assays identified all ten patients with metastases the third assay identified eight. In those without disease, one assay reported undetectable values in 30% the other two assays in 75% and 85% of patients. Recently a similar comparison of RIA and IRMA showed significant differences [169]. Sera from eighty-three patients were compared and there was a disparity in seventeen (20%). Eleven patients who had measurable Tg by IRMA assay that was undetectable by RIA developed metastases over the next three years. In contrast 2 patients with negative Tg by IRMA and measurable by RIA also developed metastases. In an additional experiment sera from fifty patients were assayed using seven different IRMAs [170]. Values less than 1 ng/ml were reported in 14% to 22% of patients depending on the assay. Values of 1 ng to 10 ng were found in 18% to 42% and values greater than 10 ng/ml in 34% to 62%. The difference between the values of 10 ng/ml or 11 ng/ml might not be clinically important, but an undetectable versus a detectable value is relevant.

In an effort to increase the reproducibility of Tg measurements the Community Bureau of Reference of the Commission of the European Communities have accepted a standard reference Tg, CRM-457.

Although in most series there is a close relationship between the measurement of Tg and whole-body scan findings, in other words both are positive or both are negative there can be disparities [89, 109, 111]. The more common one is a measurable (elevated) Tg with a negative scan. This is both a vexing and controversial problem and is discussed separately in the section on controversies. In addition as the sensitivity of the assays increases and the lower limit that is detectable decreases what Tg level will determine whether the patient has an abnormal value or not? Many accept less than 1.0 ng/ml as undetectable. For several years I have used a cut-off of less than 0.5 ng/ml. More recently supersensitive measurements can detect 0.03 ng/ml [171]. The concern about such low values is whether a reading of 0.04 ng/ml is clinically relevant?

Provided the same assay is used and the TSH remains constant an increase in Tg usually represents an increase in the mass of thyroid cancer.

A further technical problem that can produce a relatively low value of Tg in a patient with extensive disease is explained by the "hook" effect. Very large quantities of Tg swamp the capacity of the anti-Tg antibody that captures Tg in the first step of IRMA. This is most common in patients with very high Tg values. This potential false negative result can be identified when diluted samples of serum give a higher Tg value that the natural specimen [134].

In summary, Tg is a very valuable measurement in followup of patients with differentiated thyroid cancer. Thyroglobulin measurements are most sensitive when TSH is high. Not all methods for assaying Tg give the same result with the same specimen. The presence of anti-Tg antibodies makes interpretation of the value less reliable. Thyroglobulin should be measured routinely when whole-body scan is conducted either after withdrawal of thyroid hormone or with rhTSH stimulation. It should be a routine measurement when patients are seen for followup while taking thyroid hormone. The optimal condition is when the Tg is undetectable both when the patient is taking thyroid hormone and when the TSH is high. I accept a stimulated Tg of 5.0 ng/ml and others use values of 2.0 ng/ml to 10 ng/ml. Some authorities use an empiric Tg value such as 10 ng/ml as an indication to administer ^{131}I. This is discussed further when the management of Tg positive/^{131}I negative patients is presented.

Thyroglobulin Messenger Ribonucleic Acid

It was my belief that normal cells from solid organs would not be found in the circulation. It was also my belief that thyroid cells would not be found in the circulation of patients who had small intrathyroidal carcinomas. Both of these beliefs are wrong. As a result it has been possible to identify mRNA for thyroglobulin using the technique of polymerase chain reaction. This discovery opened up the possibility that measurement of thyroglobulin messenger ribonucleic acid (Tg mRNA) would provide a sensitive test for persistence of thyroid cells, and the measurement would not be influenced by the presence of anti-Tg antibodies. Early reports were encouraging. Two recent reports, however, show the test has very poor specificity. Span

et al. measured Tg mRNA in fifty-eight patients with treated thyroid cancer [172]. They compared the results with clinical information, whole-body scan findings and Tg values. Some of the patients had elevated TSH levels. They found Tg mRNA in all samples. The test did not differentiate Tg positive from Tg negative patients or scan positive from scan negative patients. The sensitivity of the test was good but the specificity zero. Similar results were presented by Elisei et al. [173]. They compared Tg mRNA in 80 patients to clinical information including followup, scan findings, and Tg measurements. Tg mRNA levels in twenty controls were compared to the patient values. These investigators also could measure Tg mRNA in all patients. They comment that the lower level of cut-off separating negative from positive results is arbitrary but using the conventional lower limit they defined a sensitivity of 82.3% and a specificity of 24.2%. Because this is a complex, time consuming and expensive test they do not recommend its use and recommend reliance on Tg measurement.

Circulating Radiolabeled Thyroxine

When there is residual thyroid left after thyroidectomy and or ^{131}I treatment that tissue theoretically can produce trace amounts of thyroid hormone. After the patient is given a diagnostic or therapeutic dose of ^{131}I the thyroid will secrete ^{131}I labeled thyroid hormones, predominantly radiolabeled thyroxine. Older readers will remember the protein bound iodine-131 test (PB ^{131}I) that was used as a diagnostic test for hyperthyroidism and thyroid cancer. We conducted a study using a sensitive high-pressure liquid chromatographic technique that separated free ^{131}I from hormone bound radioiodine, ^{131}I-thyroxine [174]. Nineteen patients were studied either after 74 MBq (2 mCi) ^{131}I for diagnostic scanning or 7 days after treatment with large doses of ^{131}I. Serum ^{131}I-thyroxine correlated well with whether the scan was positive or negative. However, the results did not match with Tg. Thyroglobulin was undetectable in three patients with uptake on scan and measurable ^{131}I-thyroxine. In two patients the functioning tissue was in the thyroid bed and in one patient in regional nodal metastases. In contrast two patients had positive Tg but negative scans and unmeasurable ^{131}I-thyroxine levels. Unfortunately this does not resolve the problem of the patient who is Tg positive but radioiodine negative. This test is also time consuming and expensive and not commonly available. It is not recommended.

Treatment with Thyroid Hormone

All patients who have had surgical treatment for thyroid cancer will be given thyroid hormone postoperatively. Thyroid cancer that is well differentiated responds to an increase in TSH by growing. Experimental models of thyroid cancer in animals also respond to the level of TSH and lowering the TSH can reduce the growth. Therefore, it would appear important to ensure the TSH level is low by prescribing sufficient thyroid hormone. However there are no well-controlled prospective studies showing a benefit of a low TSH; although, retrospective studies show a worse prognosis in patients who did not receive any thyroid hormone [48]. There is some question whether patients with low risk cancers need to have a prolonged suppression of TSH. There is also concern that high doses of thyroid hormone can have adverse effects particularly on the cardiovascular system, the skeleton and on the brain. Therefore the main issues relate to how much thyroid hormone should be prescribed for an individual patient? There is also debate about what preparation should be used?

Let us consider the side effects and theoretical side effects of supra-physiological doses of thyroid hormone. Knowledge of their importance can allow a rational approach to their prescription in patients with low versus high-risk thyroid cancer. There are many articles and reviews about thyroid hormone and the skeleton [175–178]. In thyrotoxicosis, there is increased bone resorption and bone biopsy demonstrates reduced trabecular bone, and osteoid surface and an increase in the resorptive surface. Urinary hydroxyproline levels are increased and in severe cases the serum and urinary calcium levels are increased. Alkaline phosphatase levels are increased and remain so for months after thyroid function has been normalized. Bone density measurements of the

spine hip and radius are reduced. Older studies using x-rays of the skeleton showed a 14% reduction [179]. Measurement of bone density by dual photon absorptiometry and dual energy x-ray (DEXA) show a 10–20% reduction and that a proportion of this can be gained back when the patient's hyperthyroidism is treated [175]. Ross et al. demonstrated that subclinical thyrotoxicosis from excess thyroid hormone reduced the radial bone density by 5% [180]. He has summarized the literature up to 1994, showing that several investigators confirmed the reduction of bone density in the radius, hip, spine, or calcaneus [175]. Some of the patients were premenopausal and some had incomplete suppression of TSH. In contrast Franklyn et al. found no difference in DEXA measurements in forty-nine patients with treated thyroid cancer who had higher T_4 and lower TSH levels compared to bone densities in normal age matched controls [181]. Greenspan and Greenspan conducted a meta-analysis of papers listed in MEDLINE from 1966 to June 1997 [182]. These authors conclude that suppression of TSH can reduce bone density in pre and postmenopausal women although not all the studies they reference support this conclusion. They also did not find evidence that physiological doses of thyroid hormones had a negative impact on the skeleton. A reduction in bone density is predictive of an increased risk of spontaneous stress fracture. A long-term followup of 9,704 women of whom 686 were over 65 years demonstrated that a TSH $\leqslant$0.1 mIU/l in the older women was associated with a 3.6 times increase in hip fracture and a 4.5 times increase in vertebral fracture [183]. There was no increase in fractures in patients taking thyroid hormone who had normal thyroid function. In contrast Mikosch et al. conclude from their investigations "A well-adjusted suppressive levo-thyroxine therapy of less than 2.6 microg/kg and normal estrogen levels do not seem to increase bone metabolism in estrogen-sufficient patients with differentiated thyroid cancer" [184]. The length of time the TSH is suppressed could be a factor and one study in fifty women given doses of levothyroxine to suppress TSH for one year showed no difference in bone density measured by DEXA [185]. In summary, older women with prolonged suppression of TSH are at risk of developing reduced bone density and an increase in hip and vertebral fracture.

Cardiac manifestations of thyrotoxicosis include tachycardia, palpitations, ectopic beats, atrial fibrillation, increased pulse pressure, left ventricular hypertrophy, and high output cardiac failure. There is a moderate body of data that demonstrates that these features are found in patients with subclinical hyperthyroidism with TSH values <0.1 mIU/l. These are referenced in comprehensive reviews [186–189]. One of the major concerns is the increase in atrial fibrillation. Sawin et al. found a three-fold increase in patients older than 60 years [190]. In turn this can lead to embolic complications and the need for anticoagulants and their potential risks.

The neurological and psychological effects of excess thyroid hormone include anxiety, nervousness, difficulty sleeping, irritability, and anger. These are not helpful symptoms in a patient with a recent diagnosis of thyroid cancer who is apprehensive about long-term problems and the need for followup.

Patients with mild thyrotoxicosis have more difficulty conceiving and there are risks to the fetus including miscarriage, early fusion of cranial sutures, and small birth size. Since patients with thyroid cancer are often young women the goal of having a baby can be inhibited.

Supra-physiological doses of thyroid hormones are associated with side effects and complications. However, supra-physiological doses of thyroid hormones appear to be beneficial in some patients with thyroid cancer. A reasonable approach would be in patients with newly diagnosed and treated low risk cancer to have the TSH in the range close to the lower end of normal, for example 0.1 mIU/l to 0.6 mIU/l. After a period of followup showing a negative scan and low values of Tg the TSH could be titrated to the range of 0.3 mIU/l to 1.0 mIU/l. There is no evidence that range of TSH would be associated with increased risks from the medication or the disease. In contrast in patients with high-risk cancer, or in patients where there is persistent disease in spite of appropriate treatments, there is a role for prescribing more thyroid hormone to keep the TSH lower. Unfortunately these patients are usually older and are more likely to be intolerant of the side effects and more likely to get complications such as bone loss and atrial fibrillation. Therefore it can be necessary to compromise and

accept the lowest TSH the patient can tolerate. It is important to have bone density measurements at intervals of 18 months to 24 months in postmenopausal women.

The logistics of treatment require attention to the dose of thyroid hormone and the timing of ingestion. The dose is usually close to 1 µg per pound body weight. Levo-thyroxine is the preferred medication and it is supplied in 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 µg tablets (100 µg = 0.1 mg). There are six FDA approved preparations and they are not interchangeable. There has been considerable pressure from insurance companies and HMOs to prescribe generic rather than brand medications. In California pharmacists can autonomously substitute the prescription from one brand to a cheaper one or to a generic unless the physician specifies this should not be done. Klein and Danzi have reviewed the therapeutic efficacy of levo-thyroxine preparations and make the point that when a substitution is made there is considerable risk that the TSH level can change and can put the patient at risk for sub-clinical thyroid dysfunction [191]. Hays has conducted several studies concerning the absorption of thyroid hormones [192–194]. She has demonstrated how much and where the hormone is absorbed. Pharmacists advise patients to take the medication on an empty stomach one hour before eating. This is not easy for those who take their medication in the morning and have to leave early for work or school. I am less concerned about adhering to the delay of an hour but recommend the patient adhere to the same schedule. In other words take the levo-thyroxine at the same time under the same conditions. If there needs to be a minor adjustment in dose that can be identified by serum measurement and corrected by a change in strength of the pill. That is easier than an adjustment in life style. There are several foodstuffs and medications discussed below that have a significant effect on the absorption of thyroid hormone and these should be ingested at a different time.

I start thyroid hormone 24 hours after treatment with ^{131}I and bring the patient back for testing after 6 weeks to 8 weeks. It takes this time for equilibration of FT_4 and TSH. It is acceptable to start the full replacement dose since patients have been hypothyroid for only one or two weeks. Some recommend prescribing tri-iodothyronine with the aim of shutting down TSH quickly. The theory behind this is that TSH not only increases trapping of iodine but it facilitates its release of ^{131}I as formed hormone. Therefore by quickly suppressing TSH the radioiodine will have longer biological and effective half-lives within the thyroid. The theory is probably correct but there is no objective proof of this. When the patient returns for followup after 6 weeks to 8 weeks thyroid function and Tg can be measured. When the TSH remains elevated in spite of the fact that an appropriate dose of levo-thyroxine has been prescribed based on the size of the patient there are several things to consider. First check the pills to make sure they correspond to the strength that was prescribed. In the US the strength is imprinted on the pill and the pills are color coded. I am aware of two patients who received 0.025 mg (25 µg) when the prescribed dose was 0.25 mg (250 µg). Both patients were symptomatic for months and were unhappy when the situation was identified. This should not happen since there is no 0.25 mg strength of levo-thyroxine. The next step is to ensure the patient is taking the medication and this can be done by sensitive questioning and, if necessary, by counting pills. When this is excluded it is important to make sure the patient is not ingesting something that would interfere significantly with the absorption of levo-thyroxine. These include iron, calcium, soya, cholestyramine, and sucralfate [195–197]. There are a few reports of malabsorption of thyroid hormone resulting from intestinal bypass and loss of absorptive surface [198]. Intestinal infections have also been reported to cause malabsorption of levo-thyroxine [199]. In some cases the cause of malabsorption cannot be determined [200]. In exceptional cases it is necessary to deliver the levo-thyroxine parenterally. In one teenager, where I was certain that non-compliance was the cause of persistently elevated TSH, three intramuscular injections of levo-thyroxine normalized the TSH, and it remained normal for months with oral medication. Instead of non-compliance some physicians have used the term pseudo-malabsorption and suggested a similarity to factitious thyrotoxicosis [201–203]. Finally some patients need more than the average dose. Once the correct dose is established thyroid function tests and Tg can be measured at intervals of 6 months for a few years and then annu-

ally. It is remarkable how constant the results remain in the majority of patients. The patient should be advised that any change in weight or the diagnosis of pregnancy should be a signal to recheck the values. There is evidence that all pregnant women who have no thyroid reserve need to increase their intake of levo-thyroxine during pregnancy [204, 205]. They should also take supplementary iron and vitamins at a different time. This is emphasized in Chapter 8 dealing with thyroid cancer and pregnancy.

In recent years there have been a few reports that patients feel better when they combine levo-thyroxine with triiodothyronine. Normally the thyroid secretes 10% to 20% of the total triiodothyronine, the remainder resulting from deiodination of T_4. This is used as an argument for combined therapy, although the vast majority of patients with no endogenous source of thyroid have normal FT_4 and FT_3 values. In other words the serum levo-thyroxine is converted as needed to T_3 as required. Nevertheless some patients swear that combined treatment or Armour (desiccated) thyroid that contains triiodothyronine and levo-thyroxine and other iodinated compounds makes them feel better. Part of this perceived benefit could be related to the use of triiodothyronine in depressed patients usually in addition to standard antidepressive medications. In addition some physicians prescribe Cytomel even when thyroid tests are normal but the patient has symptoms such as depression or constipation that are found in hypothyroidism. This is called "sub-laboratory hypothyroidism" [206]. One physician has published a book entitled "Wilson's syndrome" in which the thesis is to diagnose lack of thyroid function by a "subnormal" temperature and administer triiodothyronine in progressively increasing dose until the temperature is judged to be normal. This form of testing and therapy is not recommended. Objective data to prove that combined levo-thyroxine plus triiodothyronine or triiodothyronine alone is superior to levo-thyroxine are very limited. In one study of 46 patients, one half received combined therapy and 50 µg levo-thyroxine was replaced by 2 doses of 7.5 µg triiodothyronine [207]. There was no difference in symptoms, TSH values, weight or serum lipids, mood or thought processes in patients receiving combined treatment. Sawka et al. evaluated forty patients taking levo-thyroxine who had depressive symptoms [208]. Twenty were allocated to receive combined levo-thyroxine and triiodothyronine in a double-blinded randomized trial. There was no difference in outcome between the treatment groups. This was the conclusion in a similar study [209].

In summary thyroid hormone is necessary for life after thyroidectomy. The dose and the desired level of TSH depend on the risk factors of the thyroid cancer. Physiological levels of TSH are not associated with an increase in osteoporosis or cardiac arrhythmias. In high-risk patients, where the goal is to have a low TSH, there is an increase in bone loss in postmenopausal women and a theoretical risk of arrhythmias. In the occasional patient who feels levo-thyroxine is not achieving the expected degree of well being, a sensitive discussion of the data and enquiry into concern about the cancer etc are very reasonable but do not always achieve satisfaction. It might be necessary to substitute a small dose of triiodothyronine in a ratio of 1 : 4 for levo-thyroxine, that is 12.5 µg to 15 µg for 50 µg levo-thyroxine. This is preferable to prescription Armour thyroid since with the combined treatment the exact doses are known and can be titrated individually by measurement of FT_4, FT_3, and TSH [210]. Forty to fifty percent of the thyromimetic action of preparations of desiccated thyroid hormone is due to triiodothyronine [211].

Treatment with Radioiodine

Thyroid cells trap and retain iodine and therefore also trap and retain radionuclides of iodine. Several of the radionuclides have physical characteristics of half-life and emissions that would deliver sufficient radiation to kill the cells that trap the iodine or are in close proximity to the trapped radioiodine. In practice only ^{131}I is used therapeutically but ^{125}I has been used historically, and it has properties that could be beneficial for small miliary lesions in the lungs. Most of the discussion relates to ^{131}I. The goal of all therapies is to deliver enough damage to the diseased cells to kill them at the same time delivering as little toxic effects to normal tissues so that complications would be absent or mild. Several examples unrelated to radioiodine therapy make the point. Chemotherapy for cancer is designed to kill cells that divide rapidly. Sometimes the cancer cells divide less

often than normal cells, such as those in the bone marrow or lining of the intestine. Therefore side effects to marrow and intestine are to be accepted when chemotherapy is administered to kill cancers. When external radiation is delivered to kill cancer cells, all tissues within the radiation field are exposed to the same radiation dose. Irradiation of normal tissues that are radiosensitive can cause side effects. For example when external radiation is used to treat aggressive, invasive thyroid cancer early and late complications in the esophagus, salivary glands and soft tissues can be expected. In contrast ^{131}I treatment can deliver remarkably high doses of radiation to the desired sites at little expense to the rest of the body.

History of Iodine-131 Treatment

The early history of studies and then treatment with radioiodine came soon after the production of artificial radionuclides [212, 213]. In 1936 investigators at the Massachusetts Institute of Technology (MIT) produced ^{128}I with a $T_{1/2P}$ of 25 minutes [214]. This radionuclide emits β particles and γ rays. With the development of the cyclotron the MIT group produced ^{130}I which has a $T_{1/2P}$ of 12.6 hours and also emits β particles and γ rays. ^{131}I was produced using the cyclotron at the University of California Berkeley in 1938 [215]. With the availability of these radionuclides studies on the physiology of thyroid function started [216, 217]. This led to testing of pathophysiological conditions and the first treatment of hyperthyroidism by Hertz and Roberts(Boston) in March 1941 using ^{130}I that had a contaminant of ^{131}I [218]. In 1942 the Boston and Berkeley (Hamilton) investigators reported their experience with treatment of 10 and 3 hyperthyroid patients respectively [218, 219]. The patients in California were treated with ^{131}I. Hamilton and colleagues investigated the uptake of ^{131}I in normal and cancerous thyroid. They concluded "The failure of cancerous thyroid tissue to acquire appreciable quantities of radioiodine – suggests the impracticality of therapeutic application of this radio element in malignancies of the thyroid" [220]. They were the first to recognize that normal thyroid functions better than cancerous thyroid. In 1942, Keston et al. demonstrated uptake of a tracer of radioiodine in bone metastases but their patient had a thyroidectomy 35 years earlier [221]. The patient was treated with 10 mCi (370 MBq) "mainly of the 12.6 hour" $T_{1/2P}$ radionuclide (mostly ^{130}I). This information led Seidlin to treat a patient who also had a prior thyroidectomy and presented after 19 years with thyrotoxicosis due to functional metastases [222]. He conducted diagnostic tests to prove there was concentration of the radioiodine (a mixture of ^{130}I and ^{131}I) in the metastases. The patient was treated with several doses of radioiodine, and the thyrotoxicosis was replaced by hypothyroidism. The patient improved considerably and functioned well for several years but died nine years later, and at autopsy, there was widespread anaplastic thyroid cancer. It is remarkable that these investigators using crude techniques, including a hand-held Geiger counter, to identify functioning sites, autoradiography of biopsies, surgically excised lesions, and measurement of urinary radioactivity developed an approach for management of thyroid cancer that is not too different from that in current use. They recognized the importance of removing normal thyroid by operation or preliminary radioiodine. The role of stimulation by thyrotropin was identified and in early cases was obtained by prescribing antithyroid drugs [223].

At the time of these early investigations the radioactive iodine was expensive and because the majority was excreted, steps were made to collect the urine, extract the radioiodine and reuse it. The person in Seidlen's group assigned this task was Roslyn Yalow, who won the Nobel Prize for a different reason, the discovery and development of radioimmunoassay [214].

Principles of Treatment

There are several clinical situations where radioiodine (^{131}I) treatment is administered (Figure 6.22). First is treatment with a dose of ^{131}I that is sufficient to remove residual thyroid left after near total or subtotal thyroidectomy. This is called remnant ablation. I am not so rigid to always label the first treatment remnant ablation for the following reasons. When the surgeon has removed the primary cancer and all or nearly all normal thyroid, the first treatment can be designed to deal with regional or distant metastases. These would have been documented

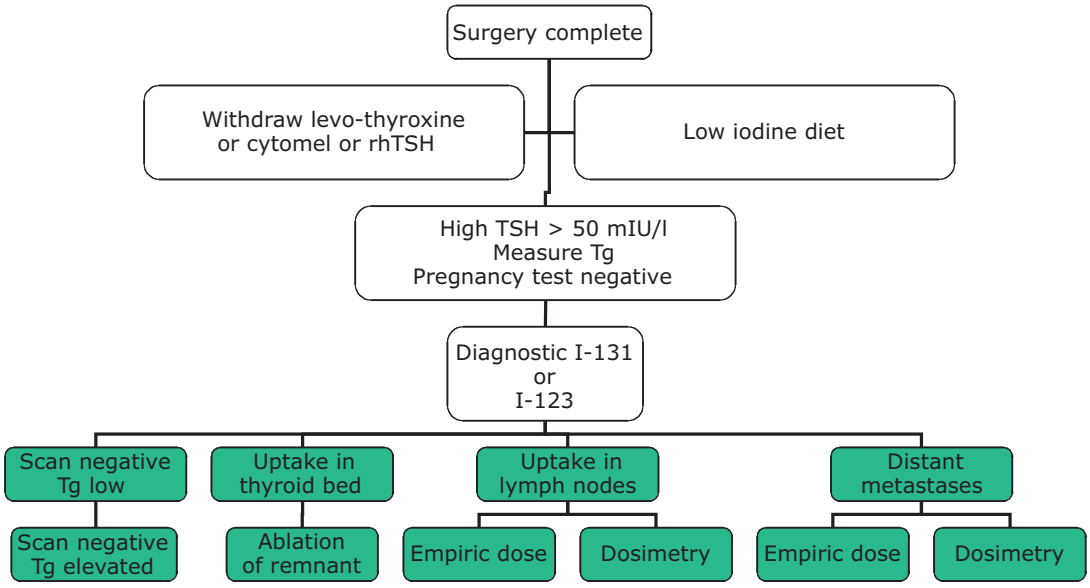

Figure 6.22. Algorithm for treatment with ^{131}I.

by prior diagnostic whole-body scan. Normal thyroid functions more efficiently that cancerous thyroid but when there is only a small remnant coupled with a high TSH and low plasma inorganic iodine level, metastases can be identified and treated.

Secondly, when the cancer is multifocal, the remnant could well contain additional foci of thyroid cancer that are killed by β emissions from ^{131}I concentrated in normal cells surrounding the lesion. I believe "remnant ablation" should be dependent on knowledge of what is being treated, hence the need for a pre-treatment scan. There is increasing policy to treat without this information. The therapy is given postoperatively as a "fixed" routine dose. Empiric therapy ignores all the variables to be discussed and is dependent on prescribing a specific quantity of radiation that could be insufficient for some patients or inappropriately large for others. One hundred (100) mCi (3.7 GBq) ^{131}I administered to treat 2 gm of thyroid with an uptake of 5% has the same effect as 50 mCi (1.85 MBq) to treat 2 gm with 10% uptake provided the half-life is the same. In addition, there is now the concept of treating an elevated Tg with ^{131}I, without a diagnostic scan to find where the Tg is coming from. Discussion of this is deferred to the section on controversies.

Next, I shall discuss treatment of thyroid metastases. Most authorities advocate empiric doses to treat specific degrees of metastases, but this implies the extent of disease is known from a diagnostic scan. There are other authorities who recommend dosimetric calculations. There are two different reasons for conducting dosimetry. One is the use of dosimetry to deliver specific absorbed doses to residual thyroid or metastases, and this is the third topic. Historically it became apparent that high doses of radiation from ^{131}I to the marrow or lungs could be dangerous. Therefore another reason for dosimetry is to ensure the quantity of radiation administered will not cause such complications. Radiation dosimetry to avoid excess radiation to non-thyroidal tissues is the fourth and last topic.

Introduction to Radiation Physics

Before presenting these four therapeutic situations it is necessary to discuss several general issues related to treatment with unsealed radiation. The absorbed radiation to thyroid tissue is dependent on the volume of thyroid, the quantity of ^{131}I administered, the percentage uptake of the administered dose in the thyroid tissues and its effective half-life at that site. The most

common approach to calculate the absorbed radiation is called the MIRD method (Medical Internal Radiation Dose committee of the Society of Nuclear Medicine). This involves some mathematics and the formulae are developed gradually over the next several pages starting with basics and completed after the discussion of empiric treatments. A brief review of terms and units is provided, and this complements the discussion in Chapter 5 on radiation as a cause of thyroid cancer. The word dose has two meanings. First, "dose" applies to the quantity of radiation administered and for this usage throughout the text I employ the term "administered dose." This is in units of Becquerel (Bq), usually MBq or GBq, in the SI system or Curies (Ci), usually mCi, in the standard system. The administered dose of radioactivity emits radiation and 1 Bq produces one emission per second and 1 mCi gives off 3.7×10^7 emissions per second. One hundred (100) mCi is equivalent to 3.7 GBq and 1 GBq is equivalent to 27 mCi. The second use of dose refers to the quantity of radiation deposited (D) in or absorbed by tissues and this is referred to the absorbed dose throughout. The SI unit for absorbed dose is the Gray (Gy) and that is equal to 1 joule of energy deposited in 1 Kg of tissue. The standard unit is the rad (radiation absorbed dose) which is equal to 100 ergs deposited in 100 g. 1 joule is equal to 10^7 ergs therefore 1Gy equals 100 rad, alternatively 1 rad is equal to 1 cGy or 10 mGy. Not all radioactive emissions are equal and it is necessary to account for that using a weighting factor designated Q to calculate the equivalent absorbed dose (H). The formula is $H = D \times Q$; the equivalent dose is equal to the absorbed dose multiplied by the weighting factor. The SI unit for equivalent dose is the Sievert (Sv) and in the standard system the rem (roentgen-equivalent-man). One Sv is equal to 100 rem and 1 rem is the same as 10 mSv. For diagnostic procedures in radiology and nuclear medicine and for most nuclear medicine treatments the weighting factor is 1. Therefore in most situations Gy and Sv are equivalent as are rad and rem. This is the case for γ rays and x-rays, electrons and positrons. Sv = Gy × Q or rem = rad × Q. The weighting factor is five to twenty for neutrons depending on their energy, five for protons and twenty for alpha particles.

Thus throughout the text administered dose is differentiated from absorbed dose and I have provided both sets of units, SI and standard. The derivation of the formulae for calculation of absorbed radiation is presented in detail below and the result is given first to set the scene. In short, 1 μCi (37 Bq) ^{131}I delivers 0.433 rad (0.433 cGy) to 1 gm of tissue in 1 hour. This number can be employed to calculate how much radiation is delivered when the administered dose, the size of the lesion, the percentage uptake and half-life of the radioiodine are known.

Let us now discuss half-life. There are four relevant half-lives. First the physical half-life $T_{1/2P}$ of the radionuclide, which in the case of ^{131}I is 8 days (actually 8.04 days or 193 hours), one half of the activity disappears in 8 days. Table 6.7 shows the fraction of radiation remaining over 1 through 80 days. Secondly, there is the biological half-life $T_{1/2B}$. This is the turn over of the substance, in this case iodine, by the body. There can be several biological half lives for iodine. For example the $T_{1/2B}$ in the blood is approximately 12 hours, but in the thyroid, it is significantly longer. In a normal thyroid where the iodine is trapped, organified and stored the $T_{1/2B}$ can be several weeks and in thyroid cancer where there is trapping but less retention the $T_{1/2B}$ can be 4 days to 8 days. These two half-lives are combined to calculate the effective half-life $T_{1/2E}$. The formulae are:

$$\frac{1}{T_{1/2E}} = \frac{1}{T_{1/2P}} + \frac{1}{T_{1/2B}}$$

or

$$T_{1/2E} = \frac{T_{1/2P} \times T_{1/2B}}{T_{1/2P} + T_{1/2B}}$$

Assuming the $T_{1/2B}$ is 7 days, the effective half-life is:

$$T_{1/2E} = \frac{8 \times 7}{8 + 7} = 3.7 \text{ days}$$

The $T_{1/2E}$ is the half time the material is in tissues having taken into consideration both the physical properties of the radionuclide and its biological turnover. $T_{1/2E}$ has to be shorter than the smaller of the values, whether that is $T_{1/2B}$ or $T_{1/2P}$. There is a final half life called the average half life designated T, that is the $T_{1/2E}$ multiplied

by 1.44. The derivation of this is $T = T_{1/2E}$/natural logarithm of 2 which is 0.693 and 1/0.693 = 1.44. This allows all of emissions from the decaying radioactivity to be incorporated into the calculation of absorbed dose. Many therapists obtain an uptake measurement but few determine the $T_{1/2E}$. This would require several measurements of radioactivity in the patients over 4 days to 7 days. This is an introduction that is expanded below.

Empiric Therapy for "Ablation of Remnants"

This usually implies ablation of residual normal thyroid. The point was raised earlier that when the surgeon has achieved a complete thyroidectomy and the patient has metastases that the first treatment with ^{131}I can eradicate residual thyroid and metastases provided the dose is sufficient. The remnant can contain microscopic foci of cancer. However, if the goal is to ablate a normal remnant which patients should be treated, what dose of ^{131}I should be used and why? There is little advantage of treating a 35-year-old woman with a solitary cancer less than 1.5 cm that has been completely excised. Her stage is T1N0M0 and her prognosis is so good that no one could provide evidence that ^{131}I would improve it. The reader can return to AMES, AGES, MACIS, and so forth to calculate her risk of dying from the cancer is 1% after 20 years. The reasons that are promoted for treatment are that a negative followup scan is very appealing, and undetectable Tg values are more likely when all thyroid cells have been removed. There is no evidence that either of these improve the prognosis for the patient described above. In a patient with a larger primary cancer or of older age when a decision is made that treatment would be beneficial how is the administered dose determined? The goal should be to administer the lowest dose that will eradicate 100% of cells in 100% of patients. From the preceding discussion on radiation physics it is clear that one dose does not fit all. When a large remnant has been left, or when the uptake is low, or the effective half-life in the tissues short, the administered dose would need to be increased. However, most therapists prescribe a fixed dose of ^{131}I. A popular dose was 29.9 mCi (1.1 GBq), because in many countries and in the United States, until recently, that was the maximum administered dose that was allowed for outpatient therapy (NRCP Report No 37). The results are somewhat conflicting. McCowen et al. treated 36 patients with less than 30 mCi (1.1 GBq) and 28 with doses of 80 mCi to 100 mCi (2.96–3.7 GBq) ^{131}I. They used negative followup scan and low levels of Protein Bound ^{131}I (PB^{131}I < 0.005%) and whole-body retention of less than 3.0% at 7 days to determine success of ablation. 56% of the low dose group and 67% of the high dose group were successfully treated by one dose. The authors concluded there was no difference. In contrast in another publication only one of thirteen patients was successfully ablated [224]. The determination of success was based on whole-body scan after 5 mCi (185 MBq) ^{131}I. Only eight patients had scans before ^{131}I treatment, and there were no measurements of uptake. These authors recommend larger administered doses. Twenty patients were treated with 30 mCi (1.1 GBq) at the National Institute of Health (NIH) [225]. The investigators employed followup scan and whole-body retention to define success. Although only eight (40%) had a negative scan on the first followup analysis, nine of fifteen became negative without further treatment. The investigators prescribed a second dose of 30 mCi (1.1 GBq) when the repeat followup scan was positive. They concluded that the outcome was similar to their success in six of nine (66.6%) patients treated with 75 mCi (2.8 GBq). They stress the benefit of the reduced total body and gonadal radiation from the lower administered dose and suggest that two such therapeutic doses are reasonable. In a similar study sixty-nine patients were treated by Snyder et al. [226]. Prior to therapy the range of uptake was 1% to 23%. Eighty-one percent (81%) were successfully ablated as judged by uptake less than 1.0% on followup scans using 1 mCi (37 MBq) ^{131}I. However, six patients developed a recurrence two to five years later. It is important to recognize that thirty-one patients had lymph node metastases and in some cases biopsy of the enlarged nodes led to the diagnosis of thyroid cancer. Usually these patients would be treated with a larger administered dose. One factor that increased the non-success was a large thyroid remnant. The authors state, "treatment doses of 30 mCi (1.1 GBq) ^{131}I are convenient and safe and

because they do not require hospitalization, they are economical." They also suggest that two treatments with 30 mCi (1.1 GBq) are reasonable.

A retrospective study of eighteen patients treated with 30 mCi (1.1 GBq), twenty-one treated with 50 mCi (1.85 GBq), and six treated with 60 mCi (2.2 GBq) showed that the two higher doses had 100% success [227]. Uptake of less than 0.2% was used as a negative, that is, a successful result. Five of the eighteen patients treated with the lowest dose had positive nodes and five also had extra-thyroidal invasion or fixation of nodes. Three of the eighteen patients (17%) needed retreatment.

A 95% ablation rate was reported by Leung et al. [228]. This was achieved in 60 patients who had undergone subtotal or total thyroidectomy. They used an uptake of less than 1.0% as an indicator of successful ablation. The pretreatment uptakes ranged from 1% to 49%. Patients whose remnants had high uptakes were less likely to have a successful ablation with one dose. They also treated nine patients who had a residual lobe and five (56%) had a negative followup. The median uptake in this group was 37%, with a high of 57%. The high uptake values after total thyroidectomy suggest that there was considerable residual thyroid. The values are also difficult to understand if the patients originally had normal thyroid function. Our group used an uptake of less than 0.3% over the thyroid bed at 72 hours as a negative value [229]. The most important factor determining success was the pretreatment uptake. When that was less than 10% the success rate was 92%, while patients with values above this had only a 56% chance of ablation with one dose. Bal et al. conducted a randomized study of eight different administered doses ranging from 15 mCi (555 MBq) to 50 mCi (2.2 GBq) [230]. There was a statistically significant benefit from doses of 25 mCi (925 MBq) or greater.

Maxon et al. have published several important articles dealing with dosimetry for treatment of thyroid cancer. This is expanded in the subsequent section. He determined that 30,000 rad (300 Gy) was required for ablation of residual thyroid [231]. This achieved approximately 80% one dose efficacy. When the appropriate measurements were made and low dose treatment was predetermined to be likely successful, there was no difference compared to those who needed higher doses by dosimetric calculations (79% versus 84% success).

Let us take two examples. Patient 1 has an uptake of 2% and a $T_{1/2EFF}$ of 100 hours. The surgeon estimates that 1 g of tissue remains after near total thyroidectomy. The patient is treated with 30 mCi (1.1 GBq). The absorbed dose to the thyroid is derived from the formula:

$$30{,}000\,(\text{dose administered in }\mu\text{Ci}) \times 2/100\,(\text{uptake}) \times 100(T_{1/2EFF}) \times 1.44 \times 0.433(\text{radiation delivered to 1 gm in 1 hour by 1}\mu\text{Ci } ^{131}\text{I}).$$

This delivers 37,411 rad (374 Gy). Therefore the treatment has a greater than 80% chance of success.

Patient 2 has an uptake of 2% but the surgeon left 5 gm tissue and the $T_{1/2EFF}$ is 72 hours. The absorbed dose to the thyroid is:

$$(30{,}000 \times 2/100 \times 72 \times 1.44 \times 0.433)/5\,(\text{mass of thyroid})$$

This delivers 5387 rad (54 Gy) and has almost no chance of success.

Where does all this data lead? First, there is evidence that low dose outpatient therapy works in some patients. Second, it is very difficult to compare patients or articles since the mass of thyroid, the $T_{1/2EFF}$ and in many cases the uptake are not known. Third, the studies reviewed above use different criteria for judging success. Some use uptake values of less than 0.2% and some as high as 1%. Some use a totally negative followup scan and some allow faint uptake. None of the early studies include Tg measurements. In 1983 Sisson wrote in an editorial "to ablate or not ablate is a question that will haunt us for some time to come" [232]. He was correct but how do we resolve this? I suggest that low dose treatment should be used in patients who have a small remnant with a 48 hour to 72 hour uptake of less than or equal to 5%. This would exclude most patients who have a lobe left after surgery. The patient should not have a locally invasive cancer or metastases to lymph nodes. There should be no evidence of distant metastases. Significant multifocal disease would weigh against this approach. The stimulated Tg should not be significantly elevated, and I would empirically place a cutoff of 50 µg/l (50 ng/ml). I would consider the treatment successful when the followup uptake at 72

hours is less than or equal to 0.2% and stimulated Tg less than or equal to 5 ng/ml.

In other situations higher administered doses are recommended but they are not always successful. Beierwaltes et al. reported an 87% success rate in 233 patients with thyroid tissue confined to the thyroid bed using a dose of 100 mCi (37 GBq) [233]. These investigators also found that the success rate was lower in patients with high uptake values. In a separate study high "fixed" doses were administered to 242 patients [234]. In a sense the dose was not fixed since 50 mCi (1.85 GBq) was prescribed when the residual thyroid volume was 3 cm^3 or less and 100 mCi (3.7 GBq) for larger remnants, 150 mCi (5.55 GBq) when there were known cervical node metastases and 200 mCi (7.4 GBq) when there were distant metastases. Although the title of the paper is "post-surgical ablation of thyroid remants" patients with more extensive disease were also being treated. Two hundred eighteen of 241 (90%) had no visible thyroid on followup scan after a single treatment. It is probable that the metastases would have been identified by a diagnostic whole body scan using ^{131}I or ^{123}I and the doses, which would have been in a similar range, could have been selected for the individual patient.

When a lobe has been left there are 3 outcomes, (1) when the cancer is small and excised to prescribe levo-thyroxine, (2) to complete the thyroidectomy, and (3) to treat with ^{131}I [37, 235]. With regards to the third option, the question is whether it is reasonable to try and ablate a lobe using ^{131}I? The large mass of tissue reduces the absorbed dose, but the increased uptake offsets that. Ninety-three patients with mean uptake of 17% were treated by Bal et al. using low doses ranging from 15–60 mCi (555–2200 MBq) [236]. Fifty-three of ninety-three cases (56%) were successfully ablated. A further 36% had a successful outcome after a second therapy. Because of the variability in administered doses and mass and uptakes, the calculated absorbed radiation was wide ranging from 120 Gy to 790 Gy (12,000–79,000 rad). In contrast to Maxon et al., who calculated that greater than 300 Gy (30,000 rad) was necessary, these investigators determined that 30% of those treated successfully with one administration received an absorbed dose of less than 200 Gy (20,000 rad). In a different investigation 40/50 (80%) had uptake of less than 1.0% after treatment with 29.9 mCi (1.07 GBq) and were judged to have been treated successfully [237]. There are no details of the uptake before treatment. Hoyes et al. conducted a retrospective analysis of 60 patients treated with 95 mCi (3.5 GBq) ^{131}I [238]. The average uptake was 18.4% and they successfully ablated 54/60 (90%) defined as less than 1.0% on followup scan after a delay of 3 months. Because of the high-administered dose and percentage uptake, the retained radiation is high for several days and this necessitates prolonged hospitalization when regulations require a burden of less than 30 mCi (1.1 GBq) for release. There is also an increased incidence of radiation thyroiditis and radiation induced thyrotoxicosis after large administered doses to ablate a residual lobe [239, 240].

Some investigators have taken a different approach. They argue that when a large therapy dose is to be administered that several small doses at weekly intervals could achieve this as outpatient treatment with less expense. Arad et al. compared the results in twelve patients treated with two or three fractionated doses administered weekly and reported 75% success [241]. This compared with 80% success in twenty patients who received a single large therapy and were admitted to hospital for radiation safety precautions. However, these authors have also demonstrated that fractionated therapy should not be used to ablate a residual lobe [242]. A report from Taiwan also covers the use of fractionated treatment [243]. In that country, hospitalization is required when patients receive 50 mCi (1.85 GBq) ^{131}I or more. The investigators administered three doses at intervals of a week. They used whole-body scan to define success, which they achieved in seventy-one of ninety-nine patients (72%). They found that fifty-four of these patients had Tg values below 10 µg/l (10 ng/ml). Of interest, fifteen of the patients with a positive followup scan had undetectable Tg.

The problems with fractionated therapy include whether there is a need for second and third administrations, since the first fraction might be all that is required. Secondly, there must be concern that the first treatment could cause "stunning" so that subsequent doses would not be trapped (see controversies later in this chapter). Thirdly, there would be the need for radiation safety requirements for

outpatients for several weeks rather than days. Finally the patient would be hypothyroid considerably longer.

Many countries have regulations relating to the release of patients who have been treated with ^{131}I, and this requires that the patient be kept in hospital until the radiation burden falls to a specific levels such as less than 20 mCi or 30 mCi (0.74 or 1.1 GBq) or the emitted radiation at a distance such as 1 meter is less than 5 mrem/hour. The regulations in the US have changed and these are discussed under radiation safety below. It is important to address expenses, the fears, and anxiety of hospitalization, however the efficacy of treatment is more important. When it appears that the patient would be successfully ablated by one small dose based on a low uptake and little residual thyroid proceed that way. In other situations prescribe a dose that will have a high likelihood of working (e.g., 100–150 mCi [3.5 5.5 GBq]). Then deal with the logistics as dictated by country or state. Figure 6.23 shows a diagnostic scan, a post-therapy scan, and followup scan in a patient successfully treated with 30 mCi (1.1 GB) ^{131}I.

Treatment of Metastases: Empiric Therapy

There is fairly consistent advice on the treatment of metastases. Most would treat functioning lymph node metastases using 100 mCi to 175 mCi (3.7–6.5 MBq) with a median of 150 mCi (5.5 GBq). Pulmonary metastases are usually treated with 150 mCi to 200 mCi (5.5–7.4 GBq) and skeletal lesions with 200 mCi (7.4 MBq). These empiric doses do not take into consideration the mass of cancer, the percentage uptake or the $T_{1/2EFF}$. The outcome in patients with nodal and pulmonary metastases is good when patients are treated this way.

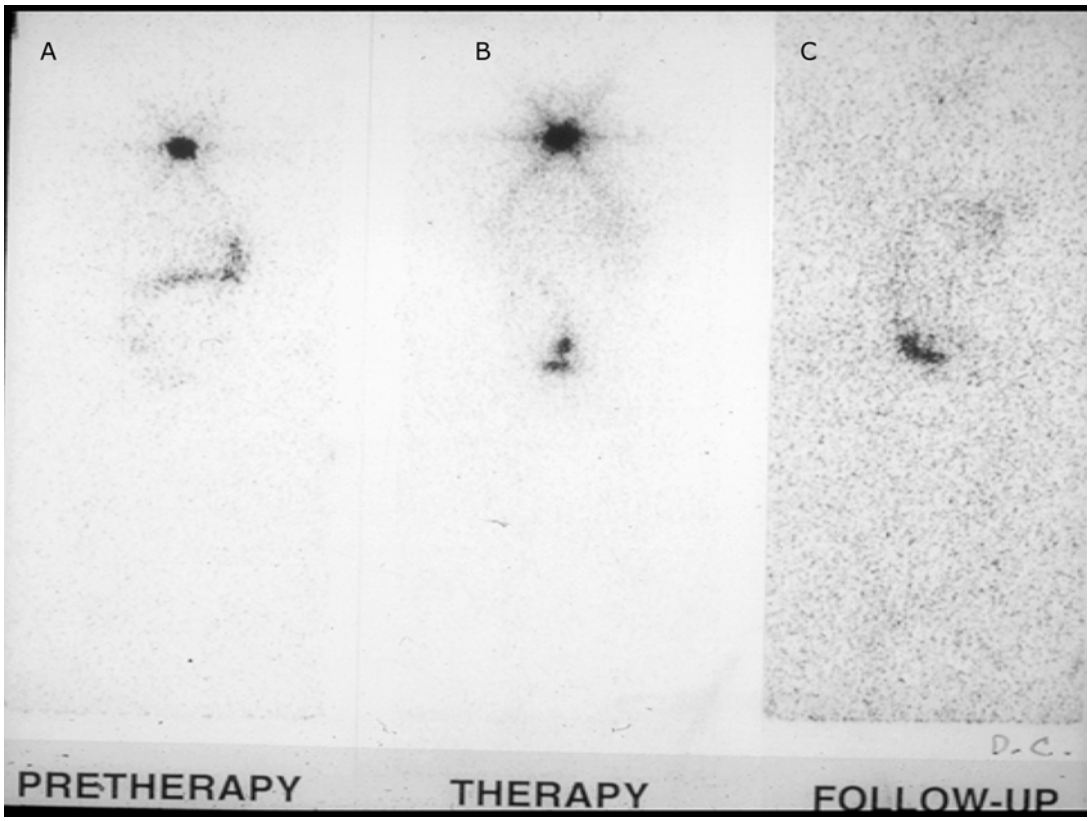

Figure 6.23. (A) Anterior whole body scan obtained three days after 74 MBq ^{131}I showing uptake in the thyroid bed. (B) Anterior projection one week after 1.1 GBq ^{131}I showing uptake in the same region and no evidence of stunning or additional lesions. (C) Followup scan after one year demonstrating that remnant had been ablated by an "outpatient" dose of radioiodine.

Samaan et al. treated 101 patients with pulmonary metastases who were a subset of a total population of 1127 patients (9%) [244]. Sixty-seven of the 101 patients (66%) died of their cancer, but twenty-four also had bone metastases. The authors included eleven patients with Hürthle cell cancer that seldom traps iodine, and this biased the results in a negative fashion. The prognosis was better in those who were less than 40 years of age. Treatment with ^{131}I prolonged survival ($p < 0.002$). The administered dose was 150 mCi to 200 mCi (5.5–7.4 MBq). The best outcome was in patients who had a negative chest x-ray but had uptake of ^{131}I in the lungs. Scan positive, chest x-ray negative pulmonary (micronodular) metastases have been recognized for decades [245–247]. Thin section CT has a higher sensitivity [248]. Massin et al. treated fifty-eight patients with pulmonary metastases that constituted 7% of their total group [249]. They administered 100–200 mCi (3.7–7.4 GBq) for lung lesions. The overall eight-year survival was 28% but for those with micronodular disease it was 77%.

In contrast Schlumberger et al. treat with fixed doses of 100 mCi (3.7 GBq) and repeat the treatment after 6 months [250]. His large series of 394 patients combine those with pulmonary or skeletal metastases and it is not possible to look at the outcome of each independently. Nevertheless, the same beneficial prognostic factors were young age, the ability of the cancer to trap ^{131}I, and small volume of cancer. When cancer could be ablated using ^{131}I, 89% survived for fifteen years. Hindie et al. studied the outcome in twenty patients with lung metastases out of their 509 with differentiated thyroid cancer [251]. They asked several questions. Does ^{131}I ablation offer early diagnosis of functioning metastases? The answer was yes since this is how 55% of their patients with pulmonary metastases were diagnosed. Can ^{131}I ablation prevent late onset of functioning metastases? They believe the low rate of pulmonary metastases and late distant metastasis of one in 509 supports that claim. Does early discovery of functioning metastases improve the prognosis? Again the answer was positive since eight of eleven patients with lung lesions and a normal chest x-ray have lasting remissions. What are the benefits and risks of continuing ^{131}I treatment beyond a cumulative activity of 500 mCi (18.5 GBq)? The authors believe that therapy should be continued when the chest x-ray is abnormal and the lesions trap iodine. Clinical researchers at the University of Michigan caution that ^{131}I might not be the ideal radionuclide for treatment of microscopic foci of cancer since the β particles travel 2 mm to 2.2 mm and might deposit their energy outside of a small lesion [252]. They reviewed the course of twelve patients with micronodular disease and were only able to prove cure in two. Nevertheless the long-term outcome in these patients treated with ^{131}I in several series discussed above is excellent. There are concerns that ^{131}I radiation absorbed in the lungs would cause radiation fibrosis and that large cumulative doses would increase the risk of other cancers and these are discussed below under complications of radioiodine treatment.

Unfortunately, some patients are found to have significant (macronodular) pulmonary metastases at the time of diagnosis, and the outcome in these patients is guarded.

Skeletal metastases are most commonly associated with Hürthle cancer, then follicular, and least likely in papillary cancer [253]. Bone metastases from thyroid cancer are usually lytic and when the lesion is in a weight bearing bone there is a risk of a pathological fracture. The treating physician should include a consultation with a radiation oncologist and orthopedist to determine the role for external radiation therapy and or surgical stabilization of the cancer. The first evidence that the patient has thyroid cancer can be pain in the skeletal lesion, and this was the case in twenty-nine of thirty-nine (74.4%) patients in a report from China [254]. In the series of Schlumberger et al., 115 patients received external radiation plus ^{131}I and 22 external radiation alone [250]. Seventy-one were also treated surgically. Occasionally the lesion can be fully excised [255, 256]. Because the lesions are slow growing and lytic the presence and extent of disease can be underestimated by standard skeletal scintigraphy (Figure 6.24) [257]. A report form Italy also included all 214 patients with distant metastases including lung and bone, confirmed that the prognosis was worse in older patients, in those with follicular cancer and lesions that did not trap iodine [258]. One-hundred forty-eight patients with bone metastases were treated at the Memorial Sloan Kettering Cancer Center. [259] More than 50% had multiple metastases. The sites of

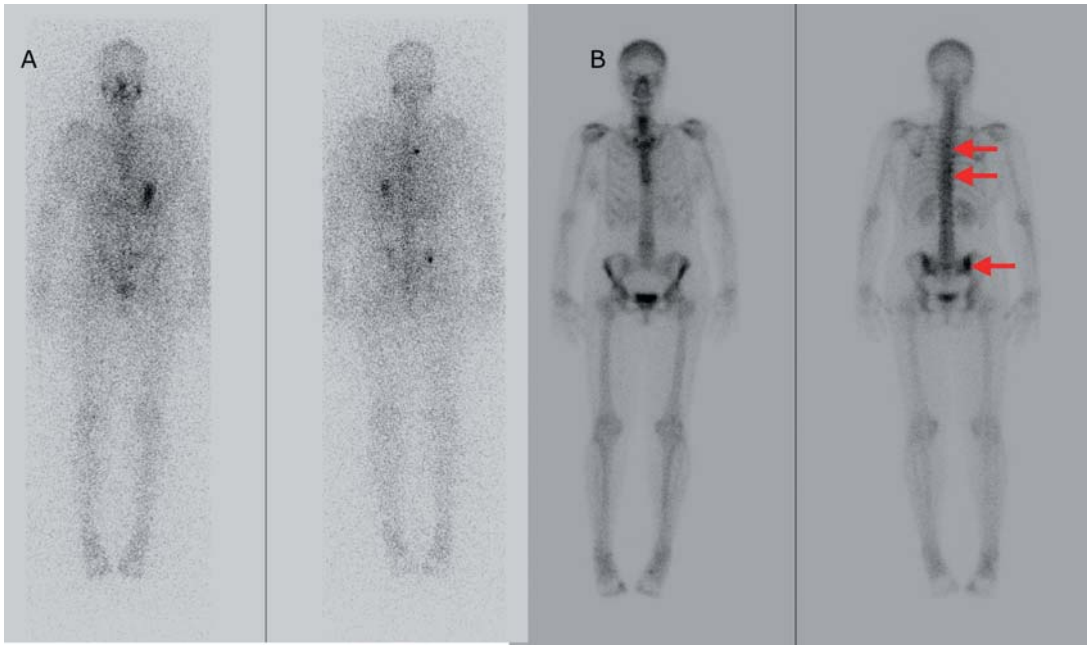

Figure 6.24. (A) Anterior and posterior whole body scans obtained twenty-four hours after 74 MBq ^{123}I. (B) Anterior and posterior images of a bone scan obtained three hours after intravenous injection of 740 MBq ^{99m}Tc-methylene diphosphonate (MDP). This scan shows three lesions in the skeleton (red arrows) that are very hard to distinguish on the bone scan demonstrating the poor sensitivity of bone scan for thyroid metastases.

cancer were vertebrae (29%), pelvis (22%), ribs (17%), and femur (11%). Unusual sites of metastasis include the orbit and mandible [260]. The 10 year survival from the time of metastases was 13%. Trapping of ^{131}I was a statistically significant good prognostic factor. Figure 6.12 shows successful ablation of bone metastases with ^{131}I. The role of embolization of skeletal metastases is discussed below.

Historically, forty or fifty years ago, therapies were repeated after one month then the time between therapies was increased to three months. Now, most authorities wait 6 months to 12 months before retesting and if necessary retreating. In patients who are well clinically and have undetectable Tg while taking levo-thyroxine the 12-month delay is appropriate. This delay is particularly important when large dose of ^{131}I are administered and when the marrow receives significant radiation from functioning skeletal metastases and from circulating radiolabeled thyroid hormones. A differential blood count 4 weeks to 6 weeks after treatment is advised.

Dosimetry

Let us return to the calculation of internal dosimetry. Specific cancer dosimetry, that is the calculation of the absorbed radiation, requires information of the administered dose, the fractional uptake in the lesion (measured), its effective half-life (measured) plus the size of the lesion. The dose to be administered is the unknown. The size of the lesion to be treated is problematic especially when there are several metastases. The uptake and retention can differ between sites of cancer leading to further difficulty and inaccuracies. There are two established approaches to dosimetry the MIRD and International Commission on Radiological Protection (ICRP) methods. The methods give similar results but the MIRD calculation is deemed to be more accurate.

The principles of MIRD calculations are first to measure the activity and retention time of the ^{131}I in the source and target organs. Thyroid tissue is both the source organ and also the target organ. Radiation to the thyroid from

other sources such as the stomach and bladder are small and can be omitted from calculations. Secondly the total amount of radiation emitted from the source is based on knowledge of the types of emissions, their frequencies and their energies. $^{131}_{53}$ I has a complex decay scheme to $^{131}_{54}$Xe emitting 6 different β particles and 12 γ photons. In addition there are five internal conversion electrons and two characteristic x-rays. In practical terms there are three important β emissions and one with an average energy of 192 keV and maximum energy of 0.606 MeV accounts for 89% of the electrons. γ photons of 364 keV energy make up 81.2% of the photons. Finally the fraction of the energy absorbed by the target is calculated and this also depends on the same factors of types of radiation and their energies. For example, an energetic photon will be emitted without delivering absorbed radiation whereas an electron deposits most of its energy close to its site of emission. When the source and target are of the same organ its size is important. Because if it is very small, even electrons do not deliver their radiation energy within the lesion.

The first step in the MIRD method is to determine the quantity of radiation in the thyroid (the fractional uptake of the administered dose D) and its occupancy time. These are determined using a diagnostic tracer of ^{131}I. These are multiplied and the result is called the cumulative activity, designated Ã. This incorporates the quantity of radiation defined in Bq or Ci and time. The units in the SI system are Bq.sec and in the standard system μCi.hr. Using the conversion of 1 μCi equalling 3.7×10^4 Bq and 1 hour equal to 3600 seconds, 1 μCi.hr is equal to 1.332×10^8 Bq.sec ($1.332 - 10^2$ MBq.sec). When the radioactivity remains in the thyroid the formula is:

$$\tilde{A} = \frac{\text{Activity at time } 0 \times T_{1/2P}}{0.693}$$

or

$$\text{Activity at time } 0 \times T_{1/2P} \times 1.44$$

Assume a patient is treated with 100 mCi (3.7 GBq) ^{131}I, and the uptake is 1%, and instantaneous and the radioiodine does not leave the thyroid (that is the $T_{1/2E}$ is equal to $T_{1/2P}$). There would be:

$$(37{,}000{,}000\,\text{Bq} \times 8 \times 24 \times 60 \times 60 \times 1.44) = 3.7 \times 10^{13}\,\text{Bq.sec or } 276{,}480\,\mu\text{Ci.hr}$$

When the radioiodine is turned over by the thyroid the formula is now:

$$\tilde{A} = \frac{\text{Activity at time } 0 \times T_{1/2E}}{0.693}$$

or

$$\text{Activity at time } 0 \times T_{1/2E} \times 1.44$$

$(37{,}000{,}000 \times 5\ [T_{1/2E}] \times 24 \times 60 \times 60 \times 1.44) = 2.3 \times 10^{13}$ Bq.sec or 172,800 μCi.hr

The 2 equations above are for a radionuclide that is trapped instantaneously which is not the case with radioiodine. However, the delay in uptake is small compared with the effective $T_{1/2E}$ of 4 days to 5 days. To make a correction for the delay in trapping the formula incorporates the effective uptake half-life designated $T_{1/2UE}$. This is obtained using the same formula for calculating $T_{1/2E}$:

$$\frac{T_{1/2P} \times T_{1/2B}}{T_{1/2P} + T_{1/2B}} \text{ substituting the half uptake time for } T_{1/2B} = \frac{T_{1/2P} \times T_{1/2U}}{T_{1/2P} \times T_{1/2U}}$$

Assuming $T_{1/2u}$ is 10 hours the $T_{1/2UE}$ is $(193 \times 10)/(193 + 10) = 9.5$ hours. The formula for Ã is $1.44 \times$ Activity at time $0 \times T_{1/2E} \times (T_{1/2UE}/T_{1/2U})$. Returning to the patient the cumulative activity corrected for the delay for uptake is $1.44 \times 37{,}000{,}000 \times 5 \times 24 \times 60 \times 60 \times (9.5/10)$. That is a reduction of 5% as a result of the delay in time for trapping. The next step is to calculate the energy from the radioactive decay of the cumulated activity Ã. This is called the equilibrium-absorbed dose constant and is designated Δ. The formulae for SI and standard systems are:

$$\Delta = \frac{1.6 \times 10^{-13} \times \text{N(frequency of emission)} \times \text{E(energy in MeV)} \times \text{Gy.Kg}}{\text{Bq.sec}}$$

or

$$\Delta = \frac{2.13 \times \text{N} \times \text{E} \times \text{rad.g}}{\mu\text{Ci.hr}}$$

The equilibrium absorbed dose constant has to be calculated for every emission and for ^{131}I this is laborious but fortunately there are tables providing this information. Δ for ^{131}I is

1.2131 g.rad/μCi.hr but the contribution of non-penetrating radiations is 0.409 g.rad/μCi.hr. The conversion from SI to standard units is:

$$\frac{1\,\text{rad.g}}{\mu\text{Ci.hour}} = 7.51\times10^{-8}\,\frac{\text{Gy.kg}}{\text{MB.sec}}$$

and from standard to SI units

$$\frac{1\,\text{Gy.kg}}{\text{B.sec}} = 1.332\times10^{13}\,\frac{\text{rad.g}}{\mu\text{Ci.hour}}$$

Having arrived at this result the next step is to calculate the absorbed fraction designated ϕ. The absorbed fraction is the amount of energy absorbed in an organ compared to that emitted. For non-penetrating radiation that is one. In other words all of the energy is deposited in the source organ. In the case of photons the ϕ depends on the energy of the individual photon but in round numbers is 0.03 (Table 6.8). Δ of the photons of ^{131}I equals 0.8041 (1.1231 − 0.409) and this multiplied by 0.03 = 0.0241 and when that is added to 0.409 it gives the result 0.433. This is the derivation that 1 μCi in 1 g for 1 hour deposits 0.433 rad a statement that was made boldly without explanation before. In SI units this equals 3.252×10^{-14} Gy.Kg/Bq.s, or 3.252×10^{-8} Gy.Kg/MBq.s.

A patient is referred for therapy and you want to deliver more than 30,000 rad (300 Gy) to ensure ablation let us say you select 40,000 rad (400 Gy). There is 2 g of tissue and the uptake is 1%. Measurements using a tracer of ^{131}I define the $T_{1/2E}$ is 120 hours. What dose of ^{131}I should be administered?

$$X = \frac{40{,}000\times100\times2}{0.433\times120\times1.44\times1} = 106{,}919\,\mu\text{Ci or } 107\,\text{mCi } (3.96\,\text{GBq})$$

Until recently there was a software program MIRDOSE3 but this was withdrawn in 2000 because the Food and Drug Administration (FDA) classified this as a treatment-planning device that require cleared premarket notification [261]. During a third editing of this section the news broke that the program has been re-released (12/1/2004).

The International Commission on Radiation Protection and Measurements (ICRP) developed a method for calculating absorbed radiation. The method incorporates several facts that are not true for clinical practice. It is assumed that uptake in an organ is instantaneous and homogeneous. The system uses a standard man with spherical organs of specific mass such as a liver of 1800 g and 28,000 g of muscle. Keeping these inaccuracies in mind, the radiations delivered by electron and photons are considered separately. The Beta dose (D_β) equals 73.8 × C (concentration in μCi/g) × $\overline{E}_\beta$ (average energy of β particles in MEV) × $T_{E1/2}$ (effective half life in days). As an example a patient is treated with 100 mCi (3.7 GBq) ^{131}I. The uptake is 1% (1 mCi or 1000 μCi), the mass of thyroid is 1 g and the $T_{E1/2}$ is 5 days. $D_B = 73.8 \times 1000/1 \times 0.192 \times 5 =$ 70,848 rad. The gamma dose equals 0.0346 × C (concentration in μCi/g) × Γ (gamma constant

Table 6.8. Physical characteristics of Iodine-131 for important β, γ, conversion electrons, and x-rays (β and γ in bold italics are key emissions).

Radioactive emission *I*	Mean energy MeV *Ei*	Mean number of disintegrations *Ni*	$\Delta i\ 2.13 \times E \times n$	Φ
β 4	***0.192***	***0.904***	***0.370***	***1***
β 3	0.096	0.690	0.014	1
β 1	0.070	0.016	0.002	1
B 6	0.286	0.006	0.004	1
β 6	0.143	0.005	0.001	1
γ 19	0.723	0.016	0.025	0.03
γ 17	0.637	0.069	0.093	0.03
γ14	***0.365***	***0.833***	***0.646***	***0.03***
γ 7	0.284	0.048	0.029	0.03
γ 1	0.080	0.017	0.003	0.035
K α1 X ray	0.030	0.038	0.002	0.15
ce-K1, γ1	0.046	0.029	0.003	0.03
ce-L1, γ14	0.330	0.017	0.012	1

in R/mCi-hour at 1 cm) ×g (geometric factor 3 Πr) × $T_{E1/2}$. This contributes 0.0346 × 1000/1 × 2.27 × 3 × 22/7 × 0.5 × 5 = 1851 rads. The sum of the γ and β radiations produces 72,700 rad (727 Gy). When the value 0.433 rad per g per μCi.hour (the sum of all β and γ emissions) is employed this results in 87,292 rad for the patient under discussion. Thus the MIRD and ICRP give close but different results.

Dosimetry Using Diagnostic Iodine-124

Dosimetry discussed above uses diagnostic ^{131}I measurements from anterior and posterior planar images to determine uptake in lesions and retention. The shorter half-life of ^{123}I of 13 hours allows measurements over 24 hours or up to 48 hours when large doses are administered [262]. Several groups have recommended ^{124}I which is a positron emitter with a 4 day half life [263, 264]. The physics of positron images is discussed later in the chapter in relation to imaging thyroid cancer with deoxyglucose labeled with ^{18}F (^{18}FDG). The benefit is that high-resolution three-dimensional images can be generated and in the case of ^{124}I the tracer is a positron emitting radionuclide of iodine. Investigators at Sloan-Kettering Cancer Center have developed three-dimensional software for internal dosimetry [265]. They administered 2 mCi to 4 mCi (74–148 MBq) and imaged at 4, 20, 44 hours and after 4 days to 6 days. The results in 15 patients demonstrate the method is feasible. The added value is an accurate measurement of the predicted absorbed dose not only for the lesions but for different regions within the cancer. The variability of absorbed dose is considerable and knowledge that regions of cancer are not going to receive an adequate dose would be reason to consider additional treatment such as external radiation.

Dosimetry to Ensure Marrow and Lung and Total Body Radiation are not Excessive

The absorbed radiation to the patient as a whole from ^{131}I is the sum of the radiation from (1) ^{131}I after it is ingested and is present in the circulation over the time it is absorbed up to its trapping by the thyroid or excretion by the kidney, (2) the radiation emitted from ^{131}I trapped by thyroid tissue and other organs, (3) radiation from radio-iodinated thyroid hormones produced and secreted by thyroid cells. In a patient with a large volume of functioning cancer, the highest total body radiation results from the circulating radiolabeled hormones. ^{131}I-thyroxine has a $T_{1/2B}$ of about 8 days or longer in hypothyroid patients. This contrasts with the $T_{1/2B}$ of about 12 hours for inorganic iodine. Early investigators found that hematologic complications were significant when the blood received 200 rad or more (2 Gy) [266]. It was determined that retention of 120 mCi (4.4 GBq) at 48 hours would deliver a cumulative dose of 200 rad (2 Gy) to the blood. It was also recognized the severe pulmonary complications occurred when the lungs retained 80 mCi or more (⩾ 2.96 GBq) at 48 hours after treatment. Physicians at the Sloan Kettering Cancer Institute who identified these limits have been responsible for detailed dosimetry and these have been adopted by others [266]. Originally these calculations required serial blood samples, whole-body scans, and urine collections. Most have replaced the urinary measurements of excreted radioactivity by whole-body retention. Urinary tests are fraught with inaccuracies due to incomplete collection, spillage, inaccurate pipetting etc. The chance of a spill of radioactive urine is of concern. Sisson has simplified the dosimetry [267]. The method is to measure whole-body retention of a diagnostic dose of ^{131}I at 2 hours and use this as the 100% baseline. A repeat measurement is made after 48 hours and the retention used to ensure the administered dose could not result in retention of 120 mCi (4.4 GBq). He has data demonstrating that the retentions of the therapy and diagnostic doses are similar. The whole body retention uses a probe at a distance of 2.5 m from the seated patient and the geometric mean of the anterior and posterior counts are calculated. The geometric mean equals the square root of the product of the anterior and posterior counts. The majority of retention measurements were between 10% and 25% but there was a wide range from less than 5% to 50%. Using this approach the administered dose can be scaled up when the retention is low and vice versa. The information should be coupled with a diagnostic scan to demonstrate where the activity is located. Retention of 10% due mostly to a large remnant would not be treated with the same administered dose as the same retention by

skeletal metastases. When the retention is unexpectedly high due to functioning tissue Sisson recommends measuring FT_4 based on the principle that the higher that value the more likely there will be high levels of radioiodinated thyroid hormones and excessive blood, marrow, and whole-body irradiation [268]. He advised reducing the administered dose empirically by 10% to 20% when the FT_4 is between 0.25 and 1 ng/dl, by 20–40% for a FT_4 between 1.0 and 1.8 ng/dl, and by 40–60% for a value greater than 1.8 ng/ml.

Prevention of the retention of 80 mCi (2.94 MBq) in the lungs is achieved by calculating the percentage of whole-body radioactivity from a diagnostic dose that is retained in a region of interest over the thorax. Using a whole-body scan at 48 hours to 72 hours after 1 mCi to 3 mCi (37–111 MBq) counts from a region of interest over the anterior and posterior thorax are divided by counts from the anterior and posterior whole-body. For example when the geometric mean of counts from the chest show that 30% is retained at 48 hours, 60mCi (2.2GBq) would be retained from an administered dose of 200 mCi (7.4 GBq). Therefore that quantity could be prescribed.

Who Needs dosimetry?

This heading can be interpreted in two ways. First which patients need dosimetry and second the disparaging response of some physicians suggesting that no one needs it. Dosimetry is not required in most patients, but when there is a desire to deliver a specific absorbed dose to a lesion it is obviously necessary. When there are widespread functioning metastases including multiple pulmonary lesions it is important to determine that the marrow and lungs are not exposed to an excess absorbed dose. A minority of physicians administers megadoses (400–600 mCi, 14.8–22.2 GBq) of ^{131}I as a routine and in this situation measurements to ensure the radiation deposited in the blood and lung is safe would be prudent.

Treatment after Stimulation with Recombinant Human Thyrotropin

Recombinant human thyrotropin was approved by the FDA in the United States for diagnostic use in 1999. At the time of editing (12/1/2004) rhTSH has not been approved for treatment by the FDA. Recombinant human thyrotropin is now widely available throughout the world. Its use for treatment is exciting but there are still some facts that need to be resolved. In the section in diagnosis there was some evidence presented that the clearance of iodine was faster in euthyroid with elevated TSH values compared to hypothyroid patients [108, 114]. My data presented above suggested the difference was less. Authorities who have treated patients with ^{131}I after rhTSH stimulation originally advocated a higher administered dose [117, 269]. In a retrospective analysis of the efficacy of rhTSH stimulation versus hypothyroidism in the ablation of thyroid remnants investigators found no difference [270]. These clinicians treated 42 hypothyroid and 45 euthyroid patients and achieved 81% and 84% success respectively. Perros successfully treated twelve patients [271]. Lippi et al. treated twelve patients and noted good uptake on post treatment scans and subsequently a fall in Tg [117]. In another report of treatment of eleven patients rhTSH was used for ablation of remnants in three [272]. I have used this for ablation of remnants in seven patients. Six had negative followup scans, the seventh patient has resisted the followup scan. The use of rhTSH therapeutically was originally for compassionate need. This included patients with pituitary problems who could not secrete endogenous TSH and patients in whom it would have been dangerous to have them hypothyroid for weeks. Its use now is considered an "off-label" use. It have also been promoted that therapeutic rhTSH is actually still diagnostic, because the post therapy scan is considered to be a very sensitive diagnostic test of the extent of disease.

To determine the biokinetics of ^{131}I, Luster et al. conducted detailed studies in 9 patients with Stage I or II disease [115]. Each patient was studied first when euthyroid after two doses (4 patients) or three doses (5 patients) of rhTSH. They were then studied when they were hypothyroid and again after treatment. The effective half-life for clearance of radioactivity from the blood was 9.7 hours in euthyroid versus 11.7 hours in hypothyroid condition giving a ratio of 0.75. Therefore there was a slight difference but not as great as suggested by the data of Park et al. discussed previously under the section on diagnosis [114]. What was very surprising was that the percentage uptake

in lesions was greater as was the residence time in euthyroid patients tested after injection of rhTSH. When the results of residency of ^{131}I was expressed as a ratio, rhTSH had a 5.7 times advantage over the hypothyroid condition. Therapy with ^{131}I would produce a higher radiation to the lesion but the blood and whole-body radiation would be less. These data indicate there would be significant value to treatment using rhTSH. The shortcomings of the study are the small number of patients since four received two injections of rhTSH and five received three injections and the studies were always in the sequence with rhTSH first. In contrast measurements made after therapy in 64 patients treated with ^{131}I after injections of rhTSH and in 163 hypothyroid patients showed more rapid clearance in the former [273]. The average times were 10.3 versus 12.9 hours. The difference is explainable. These results are whole-body measurements. Both studies show that blood or whole-body counts fall somewhat quicker in euthyroid patients. However the lesion retains radioiodine longer in euthyroid patients. This is probably explained by the more rapid fall in TSH after exogenous injection compared with hypothyroid patients who are treated with levo-thyroxine starting 1 day or 2 days after ^{131}I treatment. This point was made earlier about the timing of replacing thyroid hormone treatment after administration of ^{131}I and could be a reason for prescribing triiodothyronine for several days to produce a more rapid fall in TSH. I am not aware of any study that addresses this issue.

In four other publications six patients, seventy patients, sixteen patients, and fifty-four patients respectively have been treated with ^{131}I after rhTSH at various centers with successful outcome [274–277]. In contrast a patient was treated first with 100 mCi (3.7 GBq) ^{131}I after injection of rhTSH and 9 months later treated with the same dose when hypothyroid [278]. The post treatment scan in the latter protocol demonstrated diffuse pulmonary metastases that were not identified on the former images. It is worth noting the patient was known to have pulmonary metastases and had already received 1528 mCi (56.5 GBq) ^{131}I. Therefore a negative study using rhTSH in a euthyroid patient in whom there is a high suspicion of disease would be an indication for a repeat test after withdrawal of thyroid hormone.

In summary rhTSH is very useful for preparing patients for diagnostic scanning. At present its use for therapy is being expanded and it is valuable both for remnant ablation and treatment of functioning metastases. More data will be needed to define its exact role versus withdrawal of thyroid hormone including what administered dose of ^{131}I is optimal.

Technical Notes

It is important to confirm that the dose of radioiodine that the patient receives is the same as that prescribed by the treating physician. This applies whether the dose is an empiric or calculated one. In the United States the actual therapy dose has to be measured to confirm it is within ±10% the prescribed dose. Administration of the wrong quantity or to the wrong patient is a misadministration and must be reported to the patient, the patient's physician, and to appropriate regulatory bodies. The NRC report of April 16, 1999 describes illustrative cases [279]. In one situation two patients with the same name resulted in the wrong one being treated. It is important that two methods are used to verify the correct patient receives the therapy; the name alone is insufficient. It is optimal when the treating physician has met the patient to discuss treatment and to review scintiscan and laboratory findings and therefore recognizes and knows the patient when treatment is administered. A second patient received a therapy dose for hyperthyroidism rather than a diagnostic tracer. The point here is there should be a written and signed directive by the licensed treating physician. In a third situation two patients were to receive ^{131}I therapy, one for hyperthyroidism and the other to ablate a thyroid remnant (8 mCi [296 MBq] versus 29.9 mCi [1.1 GBq]). The technologist prepared both dose at the same time and switched the caps of the containers and the doses were given to the wrong patients. It is preferable for one treatment to be prepared, measured, and administered at a time (hurry slowly). A recent similar report involved a patient scheduled to receive 200 μCi (7.4 MBq) ^{123}I, being given 2 mCi (74 MBq) ^{131}I. Again attention to details and adherence to protocol are critical. The dose should be measured, checked and signed off as correct. Two methods should be used to identify the patient, for

example name and date of birth (social security number), or knowledge of patient and verification of name.

The therapy can be a capsule or liquid. Some of the iodine can seep through the capsule and volatilize and is inhaled by those present at the time of treatment. For this reason it is wise to vent the capsule in a hood. We have conducted thyroid counts of technologists and physicians and found no uptake of radioiodine. Liquid ^{131}I should be in a vial with a tight non-removable lid containing a rubber center through which a needle attached to a straw can be inserted. It is necessary to insert a second needle to allow air to enter the vial so the patient does not have to suck up the treatment against negative pressure. The vial should be refilled with water with extreme caution and that fluid ingested by the patient to ensure the complete dose is ingested. The empty vial should be counted in a well counter to verify that is the case. The radiation emitted from the patient is measured at 1 meter and documented.

Disposal of radioactive excreta varies from country to country. In the United States this is discharged into regular sewers. Approximately 50% of the therapy is excreted in the urine in 24 hours and 85% in 4 days to 5 days [280]. When this is diluted by all the discharge from a large hospital the impact on the environment and of workers in sewage plants is minimal. In some European countries where water discharge is reused after multiple filtrations the urine is collected in lead holding vats and allowed to decay. In Canada the situation is midway between these and the use of a holding tank has been described [281]. Since the half-life of ^{131}I is 8 days, the material is "free" of radioactivity after 80 days (10 half lives).

Regulations for Release of Radioactive Patients

Patients treated with radioactive iodine are a source of radiation and there has to be careful planning to prevent family members and the public from being exposed to excess radiation. The as low as reasonably acceptable (ALARA) principle has to be the rule. The regulations for release of patients who have been treated with ^{131}I differ from country to country and practitioners must know and adhere to those rules that apply. The U.S. regulations are discussed here. The regulations changed in 1997 and many physicians and patients are still reacting to earlier ones. The prior regulations stated that a patient treated with less than 30 mCi (1.1 GBq) could be released from hospital. That is a patient given less than 30 mCi (1.1 GBq) could be treated as an outpatient, or a patient treated with a larger dose could be released from hospital when the retained radioactivity fell below 30 mCi (1.1 GBq). The units, mCi, are presented first because this is U.S. regulation. Alternatively if the emitted radiation was less than 5 mrem/hr at 1 meter the patient could be released. These two indications for outpatient treatment or release from hospital do not match. The less than 5 mrem/hr at 1 meter is somewhat lower than is measured in practice when the patient retains 30 mCi (1.1 GBq). The regulations appear to have been accepted very arbitrarily [282]. Who developed these numbers and how were they translated into regulation are not clear from the historic records. In addition they make no allowance for personal situations. For example, does it make sense to hospitalize a patient who lives alone in a home on an acre lot at a distance of a few miles from the hospital? Conversely, does it make sense to send someone home after therapy with 29.9 mCi (<1.1 GBq) to a single room, one bathroom house where there are three children under five years of age? These regulations were the genesis of administering a fixed dose of 29.9 mCi for ablating remnants that was discussed earlier.

The current regulations U.S. Nuclear Regulatory Commission (USNCR) revised Title 10 of the code of Federal Regulations (10 CFR 35.75) now allows release of patients with higher retained doses of ^{131}I [283]. The regulations allow release under the following circumstances. The retained dose is less than or equal to 33 mCi ($\leqslant$1.22 GBq). The emitted radiation is less than or equal to 7 mrem/hr at 1 meter. Alternatively when it can be documented that no adult person could be exposed to 500 mrem (5 mSv) the patient can be released. There has to a method of documenting that one of these is in place. Provided a quantity of radiation less than 33 mCi is administered or if the emitted radiation is less than 7 mrem/hr at 1 meter after treatment even with a larger dose the patient can be released. When a larger dose is to be prescribed and the measured emitted radiation greater

than 7 mrem at 1 meter over an hour and the patient is to be sent home; it is necessary to ensure that no adult could receive 500 mrem from the radioactive patient. Before treating and release the patient (and family) should be interviewed to evaluate the home situation. Does the patient have a separate bedroom? Can a separate bathroom be designated for the sole use of the patient? Who is in the home and how many hours are family members at home? How many meters are the family members from the patient? It is then possible to develop a formula using the distance in meters and the inverse square rule, the occupancy time, the actual emitted radiation at 1 meter at the time of discharge to determine whether outpatient treatment is appropriate. For example a patient treated with 100 mCi ^{131}I emits 20 mrem/hr at 1 meter. She lives at home with her husband and two children ages 14 years and 12 years. She can have a separate bedroom and bathroom. The husband is home 12 hours and the children 16 hours. The husband will be no closer than 3 meters and the children 5 meters.

With regard to her husband using the formula and recognizing that release of the patient whose emitted radiation is 7 mrem/hr at 1 meter would not expose any one to 500 mrem we obtain:

$$\frac{7\ \text{mrem/hr/meter} \times \text{distance from patient in centimeters}^2 \times \text{occupancy}}{100\ \text{centimeters}_2}$$

$$\frac{7 \times 300^2 \times 0.5}{100^2} = 126$$

Therefore the patient could be released emitting 126 mrem/hr at 1 meter and she would not expose her husband to 500 mrem over the decay of the ^{131}I. It is preferable that children be exposed to the least radiation possible. The 5 meter distance would reduce the radiation by $1/5^2$, therefore the children would receive less than 1 mrem/hr. A third factor that reduces radiation is shielding. Brick and concrete walls reduce the exposure to family members, but in California the thin plasterboard structures provide no such benefit.

The patient excretes significant amounts of radioactivity in the urine in 24 hours to 48 hours and the emitted radiation falls proportionately. The diagnostic whole-body scan obtained before treatment allows calculation of the percentage excreted using a whole-body scanner or the probe method developed by Sisson and described earlier [267]. Another publications relating to this is referenced [284]. Grigsby et al. measured the exposure of 65 family members and seventeen pets of thirty patients who were treated as outpatients [285]. The results were reassuring. The mean dose to relatives was 0.24 mSv (24 mrem with a range of 10–109 mrem). The mean dose to pets was 0.37 mSv (37 mrem). The authors conclude, "^{131}I doses to household members of patients receiving outpatient ^{131}I therapy were well below the limit (5.0 mSv) mandated by current NRC regulations." There is also concern that members of the family might inhale ^{131}I. One study from Germany of family members showed very low uptake with a mean of 0.2 mSv (20 mrem) [286].

A printed document of recommendations that the patient should follow at home is shown in Figure 6.25. This should be signed by the patient and physician and it should have phone numbers that the patient can use to contact the physician if there are questions or problems. A checklist to ensure all steps are systematically followed is of value (Figure 6.26).

The European regulations are described briefly. The International Committee on Radiological Protection (ICRP) recommends that the annual dose to a member of the public be 1 mSv or less [287]. The European Commission allows a person to receive more than 1 mSv (100 mrem) in one year but the dose over five years should not be greater than 5 mSv (500 mrem). There have been proposed dose constraints. Children including unborn children of family and close friends can receive up to 1 mSv (100 mrem), adults up to 60 years 3 mSv (300 mrem), patients older than 60 years 15 mSv (1.5 rem) and members of the public 0.3 mSv (30 mrem) [288]. Measurement of radiation to relatives of patients treated with 370 MBq (10 mci) ^{131}I using thermoluminescent dosimeters demonstrated that 97% of carers and 87% of children received less than the "constrained' doses. However, these patients were not treated for cancer.

Most patients with thyroid cancer are fairly well and do not need a lot of nursing. When the patient is frail and helpless it is important to work closely with nurses and family explaining the quantities of emitted radiation that will

Write patient's name and ID number here.

Stanford Hospital & Clinics

SAFETY MEASURES FOR OUT-PATIENTS
WHO RECEIVED IODINE-131
FOR THERAPY

Identification (check 2): Name DOB SSN ID band by friend photo ID known
Confirmation (all three): Radiopharmaceutical Dosage (mCi +/-10%) Route
Dosage measured in-house: _____millicuries at ___:___am pm by _____

Administered by: Date: Time:

Exposure rate at 1 meter		date	time	mR/hr @ 1m
initials				
When released				

Discuss arrangements for travel from Stanford.

First eight hours: Some radioiodine is still circulating in your body.
- Drink at least one glass of fluid each hour.
- Urinate at least every two hours.

First two days: You are excreting the circulating radioiodine.
- Most of the radioiodine is excreted in your urine. If it is spilled or splashed on the toilet seat, wash and rinse the area with disposable towels.
- Some of the radioiodine is in your saliva and sweat. To minimize radioiodine contamination in your home:
  - Use disposable cups, plates, and utensils
  - Do not share washcloths, towels, bathroom cup, or toothbrush
  - Sleep in a separate bed
  - Wash your clothing, underwear, pajamas, towels, and bed linen separately from your family laundry
  - Avoid all contact with infants, children, and pregnant women

Next five days: The residual radioiodine in your thyroid can expose people near you.
- Do not sit within one foot of others for extended periods, such as at a movie theater. Short periods near others do not cause them measurable exposure.
- Avoid close contact with infants, children, and pregnant women.

Additional guidance: The Society of Nuclear Medicine pamphlet *Guidelines for Patients Receiving Radioiodine Treatment* provides additional information. By day ___ after the radioiodine dosage, your thyroid will have less than 2 millicuries of radioiodine and there will be no need for further safety measures.
It is your responsibility to inform the physician / staff providing care for you, should you need emergency medical care, a surgical procedure, or be hospitalized in the next week, that you have received a therapeutic administration of Iodine-131.
In the event of difficulty, if you have questions, or if you come back to the hospital in the next week, call:

Physician Day Night Pager

Patient Date Physician Date

Figure 6.25. Instructions for patients receiving outpatient treatment with ^{131}I.

be present and what they mean in day-to-day terms. There needs to be explanation of the relationship of radiation dose to time (direct relationship) and distance ($1/d^2$). The input of radiation safety officers and radiation physicists is very important. For hospitalized patients the nurses should wear dosimetry badges and that can be arranged for family members as well. The readings are obtained retrospectively but are generally low and reassuring. I have treated a paraplegic patient and one on dialysis and patients who were tube fed and the dosimetry measurements of nurses and family were satisfactory. The radiation instructions for inpatients should be reviewed with nurses and ward personnel. Periodic inservice tutorials for medical personnel are beneficial. Printed instructions as shown in Figure 6.27 should be in the chart or electronic record for review at any time. Figure 6.28 is a diagram that can be posted on the door of the patient's room to advise nurses how long they can be at the bedside, at 1 meter or at the doorway. This is developed by making measurements at

those sites after the patient has been treated. Publications for more details include [289, 290].

An unexpected radiation emission problem has arisen in the United States. Because of concern about terrorists who might set off a dirty bomb or release radioactivity, airports now have radiation detectors. Some patients have been arrested and their only crime was to be treated with ^{131}I. Therefore before treatment with ^{131}I patients should be questioned about travel plans. In general, they should not be in close contact with people for several days after treatment. I have treated patients, who because of an emergency had unexpectedly to fly a few days after ^{131}I treatment for cancer. I

WRITE PATIENT'S NAME AND ID NUMBER

PHYSICIAN'S CHECKLIST
I-131 AS SODIUM IODIDE FOR
(IN-PATIENT) THYROID THERAPY

Write patient's name and ID number on Form 15-21-11

Review SNM ***Guidelines*** and Stanford ***Safety Measures*** Form 15-410

Mark ***Identification*** using two methods:

- Name: the patient stated first and last name and they matched the patient record
- DOB: the patient stated date of birth and it matched the patient record
- SSN: the patient stated social security number and it matched the patient record
- ID band: the name on the identification band matched the patient record
- known: the physician knows the patient from previous interviews
- by friend: a friend or family member stated the patient's name and it matched the patient record
- photo ID: the name and photo matched the patient record

Compare dosage requested, dosage measured, and pharmacy dosage label. Record dosage administered on form 15-21-11.

Administer dosage

Measure and record dose rate at 1 meter

Line out any ***In-patient Standard Instructions*** that do not apply

Complete ***Special orders***

Check ***Maximum Daily Exposure Times***

Sign ***Physician's Orders. . .***

Apply wrist band, label chart, post room

Place original **PHYSICIANS ORDERS** in chart, return remainder to Nuclear Medicine

Comments:

Signature: Date:

Figure 6.26. Checklist for physicians administering treatment with ^{131}I.

Stanford Hospital & Clinics

Write patient's name and ID number here

PHYSICIAN'S ORDERS
IODINE-131 AS SODIUM IODIDE
FOR IN-PATIENT THYROID THERAPY

Identification (check 2): Name DOB SSN ID band by friend photo ID known
Confirmation (all three): Radiopharmaceutical Dosage (mCi +/-10%) Route
Dosage measured in-house: _____millicuries at ___:___am pm by _____

Administered by: Date: Time:

Exposure rate at 1 meter	**date**	**time**	**mR/hr @ 1m**	**initials**
When administered				
When released				

In-patient Standard Instructions:

1. Patient must remain in private room.
2. For first eight hours, have patient drink one glass of water every hour, and urinate frequently. Provide guidance on urine contamination. Flush toilet twice after each use.
3. Patient may have bath or shower.
4. Each individual providing patient care should use a separate film badges. Do not share.
5. No staff or visitors who are pregnant or under age 18. Staff and visitors observe "Maximum Daily Exposure Times"; see table below.
6. Order disposable dishes and utensils. Discard all waste in special containers provided.
7. Wear gloves when changing linens, wash hands with gloves on, then discard gloves. Save linens in special containers provided.
8. If patient vomits or is incontinent, or urine is spilled, contain the spill, avoid spreading contamination, put on gloves, then proceed to remove contaminated clothing; wash contaminated skin, retain all contaminated items for survey by Health Physics. Summon Nuclear Medicine physician and call Health Physics at 723-3201.
9. After discharge, do not admit housekeeping until room is surveyed. Page Health Physics at 723-7422 for room survey.

Special orders: In the event of difficulty or if you have questions, call:
Dr._____ Day:_____ Night:_____ Pager:_____
If physician cannot be reached promptly, consult "Telephone Call List for Radiation Emergencies" at Nursing Station. Notify Health Physics at 723-3201 if the problem involves radiation.
Surgery: If within 2 days of therapy, call the Nuclear Medicine physician and Health Physics, before surgery. If surgery involves thyroid tissue, extend notification period to 45 days.
Death: Notify Nuclear Medicine- and Pathology-Residents-On-Call, and Health Physics.

MAXIMUM DAILY EXPOSURE TIMES

	mCi administered	**Nurses (hours)**	**Visitors (hours)**
q	**0 - 30**	**4**	**unlimited**
q	**30 - 100**	**1**	**4**
q	**100 - 200**	**1/2**	**3**

COMMENTS

_____
_____
_____

Figure 6.27. Instructions for nurses caring for radioactive patients.

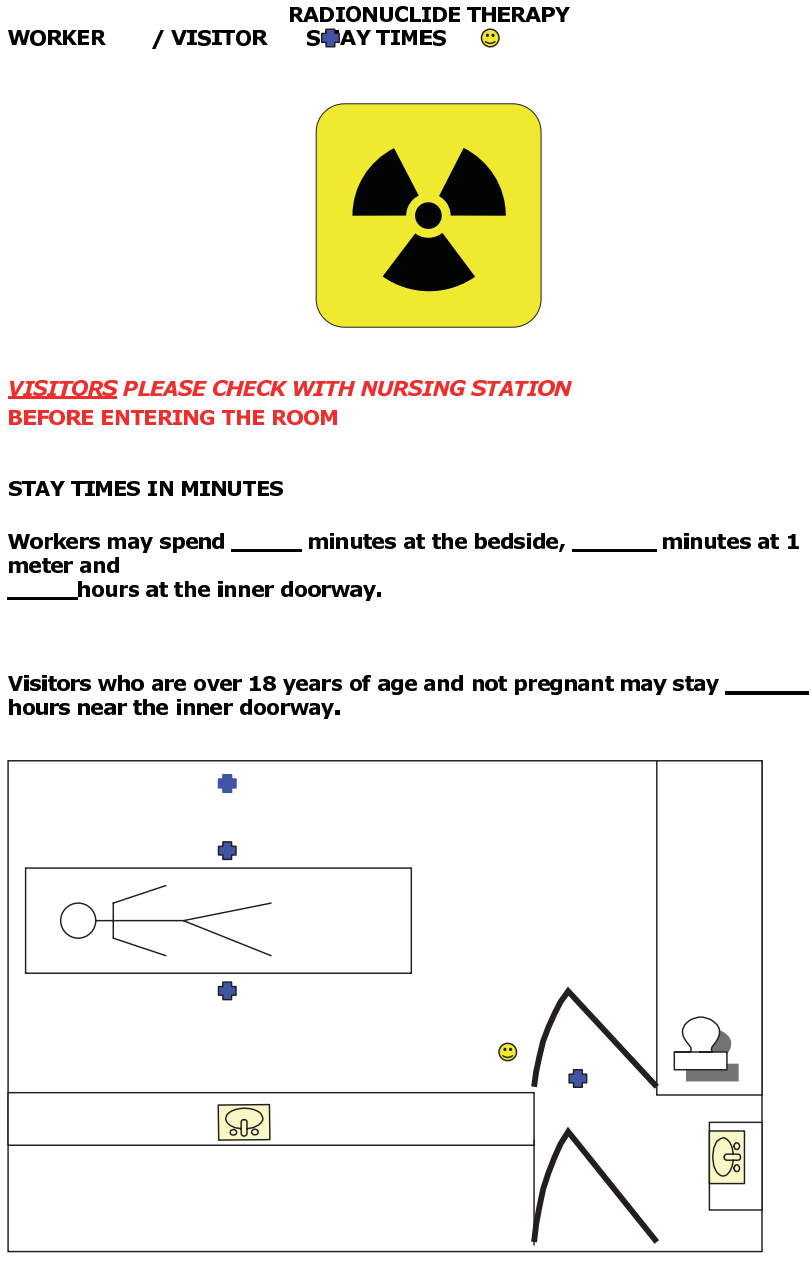

Figure 6.28. Notice posted outside the radioactive patient's door for time allowed to be spent in the room at specific distances from the patient.

recommend they come quickly to the department so that the emitted radiation can be measured and documented. I provide a document that they have been treated with details of dose and date. So far the alarms were not activated or the patients detained.

Side Effects and Complications

There is a paradox that some physicians state that ^{131}I therapy is simple and safe, yet the patient is ingesting a significant dose of radiation and the patient's family is given extensive

information to avoid close contact with their loved one. Usually these physicians simply refer the patient for the treatment and are not involved with the administration of the ^{131}I. It is true that ingesting the treatment is simple but the preparation and radiation precautions and long-term followup are weighty and time consuming. In addition the treatment can cause side effects and in one report these occurred in 77% of patients [291].

The side effects of ^{131}I are most conveniently divided into those that occur early after treatment and those that occur late (Table 6.9). The early complications are related to the effects of radiation as well as those from an elevated TSH. The radiation effects are both to the whole-body and in particular to organs that concentrate or are in prolonged contact with ^{131}I. Permanent hypothyroidism is to be expected and is not considered a complication or side effect of therapy.

Problems related to the elevated TSH are growth of cancer in an enclosed space. There are reports of sudden worsening of patients with brain or spinal cord metastases. It was hoped that the short rise in TSH using rhTSH would reduce or prevent such problems but several have been reported. One patient developed a stroke [118]. A second almost died from respiratory complications of cancer growth in the lungs [292]. When there is a mass lesion within a fixed space there is a need to consider other therapeutic steps such as surgery, external radiation or cyber knife before proceeding with ^{131}I. With regard to side effects of the radioiodine, nausea is common when doses greater than 100 mCi (3.7 GBq) are administered. Standard medications such as prochlorperazine (Compazine) can be prescribed. Vomiting is rare and when this occurs early it creates a problem of radiation contamination should the vomitus be on bedclothes, floor, and so forth. In addition the patient might not receive the intended dose of ^{131}I. Therefore, when a large dose is to be administered it is prudent to pretreat the patient and to have standing order for additional anti-emetic as required. Several other medications are of value. These include meclozine, metoclopramide (Reglan), aprepitant (Emend), granisetron (Kytril), ondansetron (Zofran), and dolasetron (Anzemet). Experience with one such as aprepitant (Emend), which has proven value in patients treated by chemotherapy is advised.

When there is a large remnant of residual thyroid the early radiation from ^{131}I can cause radiation thyroiditis. Symptomatically this is similar to subacute thyroiditis with pain over the thyroid that radiates to the jaw and ear. The symptom can start as early as one day after treatment but is commonest between 2 days to 5 days. Swallowing and talking worsen the pain. The skin over the thyroid is red and the area is extremely sensitive to touch. This complication is rare after total thyroidectomy and when the uptake of a tracer of radioiodine on diagnostic scan is less than 2% is unlikely to occur. Therefore the better the surgeon and the more complete the operation the less this will occur. In one study eight of sixty-three patients (12.7%) treated with an average of 3.7 MBq (101 mCi) developed this complication, but the incidence was related to unilateral thyroidectomy [293]. When ^{131}I treatment of a residual lobe is under-

Table 6.9. Side effects and complications of Iodine-131 treatment.

Early side effects	Late side effects
Growth of cancer by TSH stimulation	Permanent hypothyroidism
Thyroiditis	Xerostomia
Transient thyrotoxicosis	Low sperm counts
Sialadenitis	Reduced fertility
Loss or change of taste	Increased risk of congenital abnormalities
Stomach pain	Increased incidence of cancer (leukemia, breast and bladder)
Nausea	Early menopause
Vomiting	Radiation pneumonitis and fibrosis
Neck edema	Reduced parathyroid function
Recurrent laryngeal nerve paralysis	Anaplastic transformation of cancer
Dry eyes	

Some are hypothetical and are discussed in detail in the text.

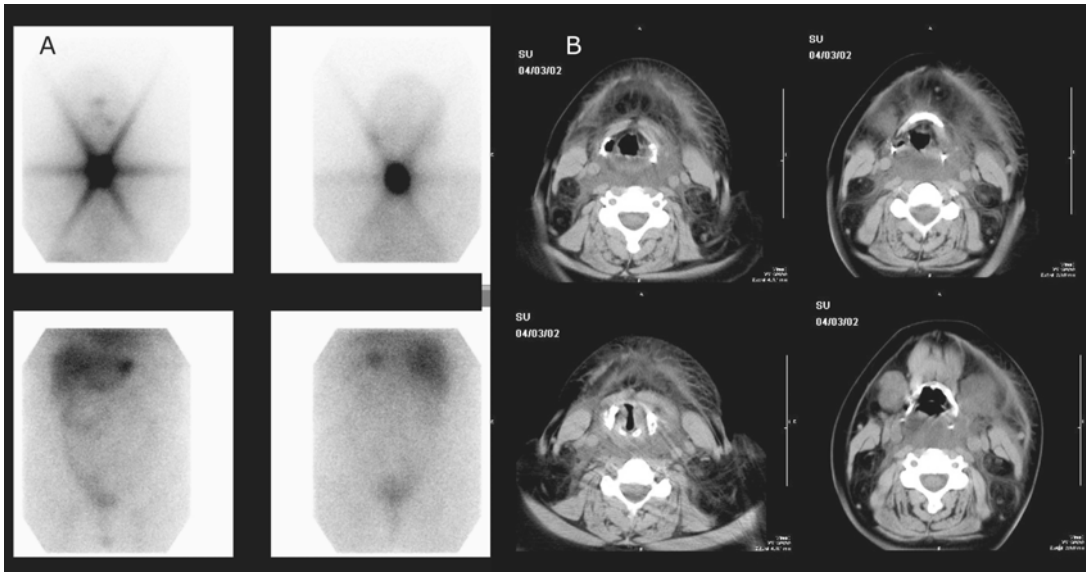

Figure 6.29. Patient with aggressive locally invasive cancer was treated with 7.4 GBq ^{131}I. After two days she developed pain, redness, and swelling in the neck. The four panels (A) show intense uptake in the thyroid bed with the star effect and hepatic activity. The four panels (B) show CT appearances of swelling and edema of tissues adjacent to the thyroid. This is severe acute radiation thyroiditis. (Provided and approved by Dr Fred Mishkin)

taken the likelihood of thyroiditis increases and there is a possibility of thyrotoxicosis caused by release of thyroid hormone from the damaged follicles [240]. A report from more than 40 years ago described thyroiditis in 100% of eleven patients who had ablation of the residual lobe with 1.28 GBq to 3.7 GBq (40–100 mCi) [294]. A later report from the same physicians described neck edema in six patients; three of them developed thyrotoxicosis. Figure 6.29 shows a CT in a patient who developed radiation thyroiditis demonstrating edema as well as the scintiscan with the "star" effect due to the high uptake of therapeutic ^{131}I [295]. Burmeister et al. described thyroiditis in six to ten patients (60%) who had ^{131}I ablation of a lobe [296]. One developed transient thyrotoxicosis. Treatment of thyroiditis involves predicting that it is likely from knowledge of the surgical report of residual thyroid and the diagnostic scan indicating a large residuum of tissue. It is probably better to complete the thyroidectomy but when the recurrent laryngeal nerve has been damaged during lobectomy there might be reluctance for the second surgery. The patient should be alerted of the possibility and advised to report any symptoms as soon as they occur. Antiinflammatory medications given in adequate doses are often all that is required. If the symptoms persist after 24 hours a short course of prednisone such as 60 mg for 2 days to 3 days, 40 mg for 2 days to 3 days, 20 mg for 2 days to 3 days, and 10 mg for 2 days to 3 days has a dramatic effect. When the steroid is stopped, there is usually no flare up. This is different from subacute thyroiditis where prednisone appears to prolong the course of the disease. The ^{131}I destroys all the cells and the pain should not persist. These symptoms almost always predict successful ablation. When radiation thyroiditis occurs it has been estimated that the thyroid has received 100,000 rad (1000 Gy). The thyrotoxic symptoms are treated with beta-blockers such as propranolol 20 mg to 40 mg three times a day, or atenolol 50 mg once or twice daily.

Sialadenitis was found in 33% of patients (67/203) interviewed by Alexander et al. [297]. This has been reported in variable percentages from less than 2% up to 60% [293, 298]. Methods to reduce sialadenitis include sucking lemon candy and lemon drops to encourage salivary flow and to ensure the patient is well hydrated. The use of amifostine appears to have helped reduce the incidence and severity of

sialadenitis [299]. In one study, seventeen patients were treated with 6 GBq ^{131}I, eight were pretreated with 500mg/m^2 amifostine [300]. The patients and controls had scintigraphy of the salivary glands with ^{99m}Tc-pertechnetate before and after treatment. There was a 35% reduction over the parotids and 32% reduction in ^{99m}Tc uptake over the submandibular glands in controls and no reduction in the treated patients. Three of nine controls and no treated patient developed xerostomia. The parotids are involved more often than the submandibular glands. This has been attributed to the higher proportion of serous cells in the parotids compared to the submandibular glands [297]. The glands become swollen and tender and the onset can be within 24 hours of treatment. The complication can be predicted in some patients by the degree of salivary uptake on the diagnostic scan. Dramatic uptake has been described [301]. On rare occasions the glands become symptomatic weeks or months after ^{131}I therapy. A proportion of patients end up with a dry mouth. Some patients develop a dry mouth many months after therapy, but they had no acute symptoms of sialadenitis. The salivary symptoms are dose related and are not common in patients receiving less than 3.7 GBq (100 mCi). A transient change or loss of taste occurs days to weeks after ^{131}I treatment. In a review of fifty-six patients who received 1.48 MBq (40 mCi) ^{131}I, pain in the thyroid bed, pain over the parotid, submandibular gland, change in taste and vomiting were each found in 1 patient (1.7%) [302]. Nausea and dry mouth occurred in three patients (5.35%) and stomach pain in two (3.6%). An increase in salivary gland tumors (and melanoma) has been identified in one report [303].

Based on reports of radioiodine accumulation on a glass eye and contact lens, Zettinig and colleagues conducted a prospective study of lacrimal function in patients treated with ^{131}I [304–306]. They used three tests of lacrimal function and found one abnormality in eighty-one of eighty-eight patients (92%). I have not been aware of clinical problems but one group using questionnaires identified chronic conjunctivitis in 27% of treated patients [291]. There are reports of blockage of the nasolacrimal duct after ^{131}I [307]. The effects of ^{131}I on the lacrimal apparatus merits further studies.

The parathyroid glands receive radiation from the γ photons and from electrons emitted from thyroid cells adjacent to the posterior capsule. The function almost always remains intact. Hypoparathyroidism is usually related to surgery rather than ^{131}I. After treatment of hyperthyroidism with ^{131}I there are reports of changes in parathormone (PTH) levels, but these are influenced by the metabolic bone disease caused by the very high values of thyroid hormone producing "hungry bones."

There is concern that ^{131}I could cause neoplastic transformation of marrow cells and cells of organs where it is concentrated or excreted including the stomach, colon, kidney, and urinary tract, breast and salivary glands.

In people exposed to radiation from atomic bombs, there is evidence of an increased risk of leukemia. There was also an increase in patients who received spinal radiation for ankylosing spondylitis. Therefore there would be concern that circulating radiation from radioiodine and raidoiodinated thyroid hormones could cause leukemia. Leukemia was described early after the introduction of ^{131}I therapy for thyroid cancer [308, 309]. A case report in 1963 identified nine additional patients [310]. The index patient received 805 mCi (29.7 GBq) over four years. Pochen found three patients with leukemia among those he had treated in the 1950s era. This number was statistically greater than 0.25 cases expected based on the size of the treated population. These three patients had all received more than 1050 mCi (38.9 GBq) [311]. The patients were treated with substantial doses at shorter intervals than is current practice. However, there are reports of this occurring after smaller doses. One patient developed acute myeloid leukemia after 300 mCi (11 MBq) [312]. Two patients out of 194 developed acute myelogenous leukemia when 0.097 cases were expected [313]. The case of acute myeloid leukemia reported by Laurenti et al. is confounded by the fact that the patient was treated with ^{131}I and ^{131}I-Metaiodobenzylguanidine (MIBG) because he had medullary cancer [314].

Chronic myeloid leukemia has been identified in several patients. Two such cases occurred 4 and 10 years after 56 mCi (2.1 GBq) and 130 mCi (4.8 GBq) respectively [315]. Edmonds and Smith had no patients with this disease [316]. Similarly followup of 1497 patients who had received an average of 195 mCi

(7.2 GBq) found no case of leukemia [317]. In summary, when ^{131}I is administered there is a theoretical risk of leukemia. This increase is real when large doses are prescribed at short intervals. The risk is higher when the marrow receives a high dose of radiation. When standard doses are used at intervals of more than 6 months the risk is low.

The incidence of breast cancer is known to be increased after exposure to external radiation [318]. There is increasing concern about a relationship of breast cancer occurring after treatment of thyroid cancer. The implication is that ^{131}I causes the breast cancer since iodine can be concentrated by NIS in breast cells. There are several reports of breast uptake on whole-body scans using radioiodine and although this is usually explained by recent lactation the finding can be asymmetric and occur in non-lactating breasts [149, 319, 320]. Alternative explanations for an increase in breast cancer include the fact that thyroid cancer is a disease of young women and breast cancer a disease of older women. Therefore, it would not be unexpected for one cancer to follow the other. Alternatively it could be possible that the women with both conditions have a genetic predisposition for cancer in general. One report showed a 1.5 relative risk for breast cancer after a diagnosis of thyroid cancer and also a relative risk of 1.5 for thyroid cancer after a diagnosis of breast cancer [321]. In addition a patient under medical attention for cancer is more likely to be followed carefully and thus identified to have a second problem. Edmonds and Smith identified six of their patients with breast cancer after ^{131}I therapy, and this was more than double the expected number of 2.53 ($p < 0.044$) [316]. In a different study an increased risk of breast cancer was identified in 252 women after they had thyroid cancer [322]. The relative risk was 1.18 ($p < 0.007$). However when women were premenopausal at the time of diagnosis and treatment of thyroid cancer the relative risk was 1.49 ($p < 0.001$). These investigators did not find an increased risk of thyroid cancer in patients who already had breast cancer. An analysis of 2365 women treated for thyroid cancer in three French Cancer Centers identified forty-eight women with breast cancer [323]. There was a significant excess of these cancers in women younger than 59 years. Some of the patients received external treatments, as well as ^{131}I treatments. In a retrospective analysis it was calculated that the breasts received 0.7 Gy (70 rad), and the investigators concluded there was no relation to the radiation treatment. The dosimetry was based on ICRP tables and the dose administered and 24-hour uptake. However there was no discussion on whether there was breast uptake on diagnostic or post therapy scans and the investigators' calculations might be an underestimation. This is a topic that merits further research. It also indicates that there should be a degree of caution when treating young women with thyroid cancer. The treating physician should always question what is the benefit versus risk in treating a patient who will have an excellent outcome without that treatment. When a diagnostic whole-body scan shows focal uptake in the breast the same question should be asked a second time. What is the benefit of ^{131}I treatment? This is an excellent role for ^{123}I whole-body diagnostic scans in a young post partum woman when there could be a possibility of breast uptake of radioiodine. When that scan shows no breast localization it would be appropriate to administer ^{131}I therapy [324]. When there is breast uptake the therapy would be deferred and the low radiation from ^{123}I would not pose a risk.

The majority of ^{131}I is excreted through the kidneys, and they and the bladder can receive a substantial radiation dose. In one study there was a statistically significant increase in bladder cancer [325]. The patients who developed this cancer received a large cumulative dose of ^{131}I, and bladder cancer was not diagnosed in any patient who received less than 37 GBq (1000 mCi). The bladder doses were calculated between 22.5 and 103.5 Gy (2250–10,350 rad). In a second study three bladder cancers were diagnosed versus an expected incidence of 0.46 ($p < 0.012$) [316]. Every effort should be made to keep the patient well hydrated and to empty the bladder frequently. Treatment early in the day is optimal so that the bladder is not exposed to high-prolonged radiation at night.

The effect on gonads and fertility of patients of both gender and the outcome in their offspring is very important. One of the first studies evaluating offspring found no difference in children born to 33 patients who had received an average of 196 mCi (7.25 GBq) when they were 14.6 years of age on average. The patients were followed for 18.7 years. In a combined French and Italian investigation information was

obtained on the outcome of 2113 pregnancies in women treated for thyroid cancer [326]. There was a slight increase in miscarriage after surgery and after surgery and radioiodine therapy compared with before any intervention. This was highest in the year after treatment and four of ten women miscarried (40%). This was attributed to be more likely related to hypothyroidism, or thyroid dysfunction than the radioiodine. There was no difference in the "incidences of stillbirth, preterm birth, low birth weight, congenital malformation, and death during the first year of life before or after ^{131}I therapy." Of the 1398 women treated at the Royal Marsden Hospital there were 496 who were 40 years or younger [327]. Three hundred twenty-two of the younger patients were treated with a single dose of 80 mCi (3 GBq) ^{131}I to ablate residual thyroid. One hundred seventy-four patients received between 230 mCi and 1500 mCi (8.5–59 GBq). There were transient problems with menses in 17% but no permanent effect on the ovaries. Two hundred seventy-six of the women bore 427 children, only one woman who wished to get pregnant failed to conceive. Surprisingly there were no congenital abnormalities, since about 2% of normal women have children with a significant congenital problem. Dottorini and colleagues compared the fertility and offspring of 627 women who were treated with ^{131}I to 187 untreated matched controls [303]. There was no difference in fertility. There were also no differences in the risk of prematurity or the birth weight of the babies. Therefore there appears to be no obvious reduction in fertility in women treated with ^{131}I. The importance of obtaining a pregnancy test before therapy is stressed and the topic is discussed in depth in chapter 8 on thyroid cancer and pregnancy.

The data in men is slightly different. There are a few documented cases of reduced testicular function [328–330]. Pacini and colleagues studied 103 men who had been treated on average 15 months before [331]. They demonstrated a higher Follicle Stimulating Hormone (FSH) than in controls. Patients who were treated annually had a stable elevated FSH, reduced sperm count but the sperm were normally motile and testosterone levels were normal. Physicians at the Royal Marsden Hospital also evaluated men who were 40 years of age or younger when treated with ^{131}I [332]. There were 59 men who wished for children and they fathered 106 babies 3.5 years to 18 years after treatment. The investigators measured testicular radiation using thermoluminescent dosimeters and followed serial FSH levels in fourteen patients. The dose to the gonads was 6.4 cGy (6.4 rad) after 3 GBq (80 mCi), 14.1 cGy (14.1 rad) from 5.5 MBq (150 mCi), and 21.2 cGy (21.2 rad) from a cumulative dose of 9.2 GBq (250 mCi). These investigators also identified a rise in FSH that returned to normal in all fourteen patients by one year. Measurements of radiation to the testes were obtained over two weeks in three men who received 1.256 GBq (34 mCi). The absorbed doses were 30, 33, and 43 microGy/MBq or approximately 3 cGy to 5 cGy (3–5 rad). These absorbed doses of radiation are less than would be required to interfere with spermatogenesis. Other researchers confirmed the rise in FSH, but it normalized after 18 months [333]. Therefore, provided patients are treated with conventional doses of ^{131}I and wait 12 months to 18 months the fertility should be normal. When there is widespread disease and it might be necessary to prescribe repeated large therapeutic doses, sperm could be banked. One publication suggests this when the cumulative dose would be 14 GBq (380 mCi) [332]. Both genders should be encouraged to drink copiously and to empty their bladders frequently to reduce radiation to the gonads as well as the urinary tract.

Women who received ^{131}I for treatment of thyroid cancer and were then treated with levothyroxine had an earlier menopause than women given suppressive doses of levo-thyroxine to treat goiter [334].

Transformation of a differentiated to an anaplastic cancer has been described and is also addressed in Chapter 9. When the mass of differentiated thyroid cancer is substantial it is unlikely that it would be eradicated by ^{131}I. In this situation the viable cancer has been exposed to radiation that could cause dedifferentiation. This was described early in the history of ^{131}I therapy [222]. There are well-documented reports of transformation [335]. However in a review of the literature Kapp et al. could not find a cause and effect relationship [336]. The accuracy of this conclusion was already challenged.

In patients with miliary metastases to the lungs there has to be consideration that ^{131}I

might cause damage to normal surrounding lung resulting in radiation pneumonitis and or fibrosis. It is known that external radiation can produce both and radiation oncologists are very careful in the design of radiation ports and determining the dosimetry when administering external radiation to the lungs [337]. Unfortunately children are more likely to have pulmonary metastases as discussed in Chapter 7 and their lungs might be more sensitive to radiation. The first report of this complication after ^{131}I makes uncomfortable reading [15]. Fifteen patients with pulmonary metastases were treated and two died. At autopsy although there was residual cancer, the major findings were those of radiation pneumonitis and fibrosis. The patients were 27 years and 32 years of age when first treated. Four other patients had radiological evidence of fibrosis. The methods of calculating the dose to the chest were crude and the results questionable. They depended on the percentage of radioactivity in the urine, which was subtracted from the administered dose and the remainder was judged to have been retained in the patient. Uptake measurements were made over the neck with a hand held Geiger counter. One patient received an administered dose of 300 mCi (11 GBq) and was thought to have retained 193 mCi (7.1 GBq) in the chest. The second patient was judged to have retained 162 mCi of the 212 mCi administered (6 MBq of 7.8 MBq). The authors conclude that the retained dose in the chest should be less than 125 mCi (4.6 GBq) and that therapies should not be repeated sooner than 6 months. Most authorities now recommend that no more than 80 mCi (2.96 GBq) be retained in the thorax. There is an abundance of reports of radiation pneumonitis related to external radiation but all attempts of computer searches related to ^{131}I come up with only one additional reference [338]. These investigators used ^{99m}Tc-Pentetate (DTPA) pulmonary clearance as an index of pulmonary stability. The material is inhaled and its rate of clearance from the lungs over time is measured using a gamma camera. It is a sensitive test. They compared results in thirty-five patients with pulmonary metastases, thirty-two with no lung metastases, and fifty-two controls. The thyroid cancer patients had received between 158 mCi and 1194 mCi (5.9–44.2 GBq) ^{131}I. There were no differences in clearances with the exception of one patient whose results were consistent with radiation pneumonitis. In practice the complication appears rare but the absence of data and the adverse outcomes in the report by Rall et al. are difficult to explain. It has been stated that absence of data does not necessarily mean absence of effect. The consensus is that a retained dose of 80 mCi or more ($\geqslant$2.96 GBq) ^{131}I in the lungs should be avoided. This is possible by determining the lung uptake on the diagnostic scans and administering an appropriate therapeutic dose. Repeat treatment should be deferred for 6 months to 12 months.

In summary, ^{131}I is remarkably well tolerated when compared to systemic chemotherapy and external radiation therapy. Nevertheless, there are early and late complications some of which are troublesome such as permanent dry mouth and some clinically serious such as second cancers. The expected benefits of treatment have to be weighed against the risks for the individual patient. In the case of a small cancer ($\leqslant$2 cm) that has been fully excised in a young patient it is hard to decide that the balance favors therapy.

Treatment of Rare Clinical Situations: End Stage Renal Disease

A patient on dialysis can develop thyroid cancer. Treatment with ^{131}I is problematic since the majority of the radioiodine is normally excreted through the kidneys. Most patients on machine dialysis are dialyzed three times a week; therefore, the occupancy time of ^{131}I in the circulation is prolonged, whereas with normal where there is continuous clearance of radioiodine through the kidneys. There are a few publications addressing this topic [339–341]. In a patient treated at Stanford we conducted whole-body scanning with measurement of whole-body counts before and after 2 sets of dialysis. Each dialysis resulted in a reduction of about 60% of the radioactivity and dosimetry was conducted to ensure the marrow did not receive excess absorbed radiation. The patient was treated on two separate occasions with 100 mCi (3.7 GBq) without problems. She died several years later due to complications of her systemic lupus and renal failure. Other clinicians also recommend dosimetry [342]. Once the testing demonstrates feasibility the therapy can be administered one day prior to dialysis for example on a Tuesday

followed by dialysis on Wednesday and Friday. There was concern that the dialysis machine including filters and tubing might be contaminated, but we found no evidence of that. The nurse conducting the dialysis was educated on radiation safety and remained behind a thick lead shield throughout the procedure and her radiation-monitoring badge did not register above background. There are reports of patients on peritoneal dialysis being treated [342, 343]. Preliminary diagnostic testing should be conducted and dosimetry for safety undertaken [344]. In the case described by Jimenez et al. less than 10% of the radioiodine was excreted daily and the safe administered dose was only 22 mCi (814 MBq) [342]. These investigators and Kaptein et al. demonstrated a prolonged retention of ^{131}I [343]. The latter group calculated a very similar safe dose of 26.6 mCi (980 GBq). The added issues are containment and disposal of the radioactive dialysate.

Therefore the situation differs whether the patient is on mechanical or peritoneal dialysis but whatever the case dosimetry to ensure the blood and marrow are not exposed to an excessive absorbed dose is strongly advised.

Followup after Treatment of Cancer

After treatment by surgery and ^{131}I it is important for the patient to be followed long-term. Recurrences can occur and although most do so in the first 5 years, a minority can occur over decades. There is no consensus about a single test, or group of tests, agreed on by all authorities, but all are of the opinion that followup for a longtime is required. There is an article entitled "consensus report" that was a consensus of the authors and not all of them are in agreement of all the recommendations [345]. The TSH would be adjusted depending on the severity of the cancer. In most patients the goal would be a value between 0.1 mIU/ml to 0.5 mIU/ml. My approach is to check thyroid function and Tg 8 weeks after therapy. The Tg would be compared to the pretreatment value and used for comparison with subsequent measurements. An undetectable value is very reassuring. Six months after therapy a followup visit would include physical examination of the neck, measurement of thyroid function and Tg. After 1 year, a whole-body scan with measurement of a stimulated Tg is obtained along with physical examination. An ultrasound of the neck can be included at this time and some authorities might include that at the six-month visit. There are differences of opinion about the value of the diagnostic scan at this time. In the low risk patient some omit the scan and measure a stimulated Tg. I prefer both. It is helpful and reassuring for the patient to see the before treatment and followup scans. In those with high-risk cancer, all would accept that scan, and Tg should be measured. The lack of consensus here is whether the patient should be hypothyroid or euthyroid and given injections of rhTSH. The decision is best based on whether it is likely the patient would need a second treatment with ^{131}I. Therefore, when the Tg remains elevated and residual tissue is present thyroid hormone would be withdrawn. When Tg values are low or undetectable the scan could be conducted using rhTSH. There had been a policy to repeat scans annually for 5 years but that approach has gradually been altered in favor of less imaging. Some physicians plan for two scans. When the first followup scan is negative and Tg less than 2ng/ml, I arrange visits at six-month intervals for physical examination, thyroid function, Tg measurement, and ultrasound. At five-years a second followup scan is obtained using rhTSH stimulation and Tg is measured at that time. After that, annual visits are arranged until the ten-year anniversary, and then depending on patient attitude, the visits are organized at two-year intervals.

When the patients needs a second treatment with ^{131}I or has a late recurrence the type of testing and frequency of clinic visits increases until a stable situation is reached.

In the patient who is treated by operation and no ^{131}I (see below) visits are arranged at intervals of 6 months to palpate the neck and measure TSH and Tg. Periodic ultrasounds are obtained usually annually for two to three years and then biannually.

External Radiation as an Alternative to Iodine-131

Although there is a role for external radiation in a patient with anaplastic cancer, skeletal metastases of differentiated thyroid cancer that do not

trap ^{131}I, and invasive medullary cancer, it has no role in the management of patients with stage I and II or low MACIS or AGES scores. External radiation damages the cells without killing all of them. The cancer then fails to trap ^{131}I, but can also become more aggressive in behavior. Carr et al. in 1958 called this a "common error in the treatment of carcinoma of the thyroid." [346]. Several years ago I consulted on a young man who had already undergone a lobectomy and external radiation for differentiated thyroid cancer. He developed distant metastases. When studied with a tracer of ^{131}I, the residual lobe had normal uptake on whole-body scan and, therefore, had not been ablated by external radiation. The metastases did not trap iodine at that time or after the lobe was ablated. He developed brain metastases in his mid-30s and died shortly thereafter. This course is virtually unheard of in a patient of this age after conventional therapy. External radiation is damaging to normal tissues and when the neck is palpated it has the texture of a wooden board. It is impossible to distinguish normal landmarks. The long-term effects include induction of cancer in the irradiated tissues. Figure 6.30 is a spot view of a bone scan of the neck and chest in a woman who in the distant past also had a lobectomy and external radiation for differentiated thyroid cancer. She developed an osteogenic sarcoma in the manubrium that was almost certainly the result of the external radiation.

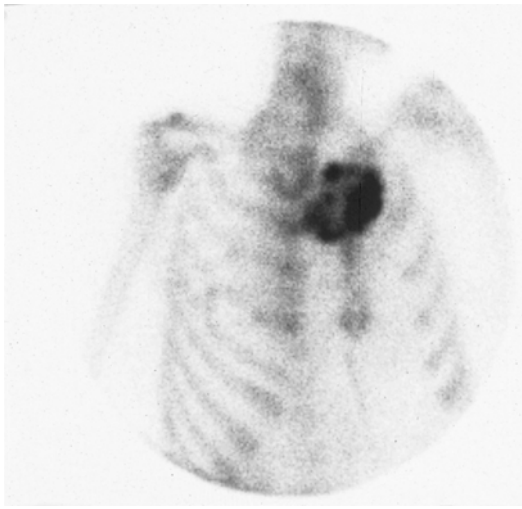

Figure 6.30. Figure shows a spot view of the neck and chest of a bone scan made 3 hours after intravenous injection of 20 mCi (740 MBq) ^{99c}Tc-methylene diphosphonate. There is intense uptake of radiopharmaceutical in the manubrium in an osteogenic sarcoma.

Controversies

There are many controversial aspects on the management of differentiated thyroid cancer. This is difficult to understand because the prognosis is excellent, and most patients survive a normal lifespan and live normal productive lives. It is true that some patients have a relapse but these can usually be treated successfully. Why is there so much controversy? One reason is that there are no controlled trials. A second reason is related to the excellent prognosis that results in physicians believing that they alone are responsible for that outcome and therefore all patients must be treated using their formula for success. The controversy about how much thyroid should be removed by operation has been covered and is not repeated. Controversy about the dose or preparation of thyroid hormone has also been covered. Here the topics are related to radioactive iodine therapy. The first two topics, "is ^{131}I beneficial?" and "do all patients need ^{131}I?" are clearly related.

Is Iodine-131 Beneficial?

Earlier in the chapter, the review of the results of several investigators appeared to demonstrate improved outcome in patients treated with ^{131}I. Those with metastases whose cancers trapped iodine and were treated lived longer. The therapy can be shown to work by removing functioning tissue and scintiscans after therapy demonstrate that thyroid cells in the thyroid bed or in sites of metastases can no longer be imaged and have been successfully ablated. Serum Tg values fall after treatment and in many patients become undetectable. It is comforting even exciting for patient and physician to see the improved results on scan and serum tests. However, does the treatment reduce the rate of recurrence or improve survival? Death from thyroid cancer is a very clear endpoint. However, what is meant by recurrence? Do all physicians follow patients in the same manner? Is the clinical examination always the same and are followup scintiscans and measurement of Tg in different facilities equal? Is a late rise in Tg a

recurrence when no site of disease can be identified? Finding cancer in the thyroid bed a few months after partial thyroidectomy is likely to be cancer that was present at the time of operation but was not removed. This is residual cancer not a recurrence. Where is the objective data from a controlled trial in matched patients randomly selected for ^{131}I therapy or placebo who are managed by a defined protocol? A search of "Pub MED" for evidence that ^{131}I is beneficial produced no reference. A more focussed search identified six articles, including one written by me, in which I did not address this topic. Therefore reliance has to be placed on decision models, meta-analysis or retrospective evaluations. In one computer model of a patient with localized cancer there was an improvement in life expectancy of four to eight months and the reduction in recurrence was deemed to out way the risk of leukemia [347]. This benefit seems small, but in opinion of the researchers, it is similar to the benefit of annual mammograms for 10 years or using medications to lower cholesterol below 200 mg/dl. It is important to recognize that the models cannot and do not take all factors into consideration. In the study under discussion leukemia was the only complication of ^{131}I treatment that was considered. These investigators also determined that it would be necessary to enroll 4000 patients and follow them for 25 years to demonstrate a 10% improvement in mortality, and it should be recalled the mortality for thyroid cancer is low. Sawka et al. presented a meta-analysis of whether remnant ablation is effective [348]. They confirm that they did not identify one randomized controlled study. They identified 267 "unique full-text papers" and, using a panel consisting of an endocrinologist, nuclear medicine physician, radiation oncologist, epidemiologist, and methodist, selected 23 articles that met stringent inclusion criteria. Although the data from different reports were inconsistent, when the data were pooled, there was a reduction in recurrence (relative risk 0.31) and a slight reduction in distant metastases. The authors point out that distant metastases are rare and in their analysis occurred in 4% of those who did not receive ^{131}I. The article concludes, "in the meantime, the decision for RAI (radioactive iodine) ablation must be individualized based on the risk profile of the patient, as well as the patient and physician preference, while balancing the risks and benefits." The investigators did not address complications from the treatment. A permanently dry mouth is very unpleasant and can lead to dental caries and although not life threatening cannot be condoned in patients who would not benefit from ^{131}I. The same applies to a small increase in cancer or infertility. Editorials accompanying the original article come down on the side of favoring the radioiodine treatment. Mazzaferri argues that ablation allows accurate measurement of a stimulated Tg and a negative post therapy ^{131}I scan [349]. The destruction of microscopic foci of cancer has theoretical and probably real value. He identifies the reduction in mortality from thyroid cancer in women over recent years; however, this is in part due to earlier diagnosis. I shall return to his important personal contributions in the discussion of retrospective outcomes. Haugen entitles his contribution "patients with differentiated thyroid carcinoma benefit from radioiodine remnant ablation" and concludes that older patients and those with large cancers and lymph node metastases have a better outcome when treated with ^{131}I. He also confirms prior analysis that "the benefit of radioiodine in younger patients with smaller tumors is less clear, and the potential risks of therapy need to be thoroughly considered" [350].

Several retrospective analyses show an advantage from ^{131}I [351]. Mazzaferri and Jhiang conducted a very detailed retrospective analysis of 1322 patients with differentiated thyroid cancer who at onset did not have distant metastases [22]. The patients were from two sources, the hospitals of the US Airforce and Ohio State University. Twenty-three percent received treatment with radioiodine. The investigators found as has been reported by others that older age, cancer size and local invasion increased the risk of recurrence significantly. The relative risk of recurrence was 0.4 (95% confidence intervals 0.2–0.9, $p < 0.05$) in those treated with ^{131}I. This confirms an earlier report in 576 patients with papillary cancer [352]. In the latter investigation the cancer specific mortality was 8% after 30 years. In these and all other reports concerning ^{131}I it is difficult to know what were the clinical features or personal biases that led to treatment of some patients but not others. There is the possibility that patients who received ^{131}I had more advanced disease and therefore the reduction in recurrences could be an underestimate

of benefit. In several separate studies there was a statistically significant decrease is recurrences in patients treated with ^{131}I [353]. The outcome in 303 patients treated in fourteen U.S. and Canadian centers was improved in those treated with ^{131}I [354]. Eighty-five percent of those with papillary cancer received this and there was a reduction in cancer specific mortality and progression of disease. That benefit was not statistically significant when patients with tall cell variant (to be discussed below) were excluded. The authors conclude "this study supports improvement in overall and cancer-specific mortality among patients with papillary and follicular thyroid cancer after postoperative iodine-131 therapy." Two thousand, two hundred eighty-two patients entered into a cancer registry from seventy-six hospitals in Illinois confirm an improvement in survival after ^{131}I treatment [355].

Do All Patients Need Iodine-131?

Almost all endocrinologists recommend that all patients with differentiated thyroid cancer receive treatment with ^{131}I after surgery [22, 351, 356]. The term "recommend" does not do justice to the pressure that is put on patients. However, as stated above, no controlled study has been conducted to confirm that ^{131}I is beneficial. The retrospective studies showing there are fewer recurrences in patients who received ^{131}I have been presented with their limitations. A followup scan showing no uptake is reassuring that there are no residual cells and by inference no cancer. Thyroglobulin measurement is more reliable when all thyroid has been ablated. Neither of these statements is totally correct.

Hay et al. have reported on the outcome in 2444 patients with papillary cancer treated at the Mayo clinic [357]. They discuss their experience of more than 43,000 patient years of followup. The patients were not entered into a controlled experiment to prospectively compare the benefit of various treatment options such as lobectomy versus total thyroidectomy, or ^{131}I versus no ^{131}I. However, over the years, there were changes in therapeutic philosophies so that retrospectively it is possible to judge the effect of treatments. The Mayo physicians have developed the scoring system MACIS that was discussed earlier in the chapter. Patients with MACIS score less than 6.0 have an excellent prognosis. In most series these patients make up the majority with papillary cancer. When the data of the last fifty years were analyzed by decade between 82% and 86% of the patients had low MACIS scores. There was no difference in cancer related mortality or recurrence of cancer in 1917 patients with MACIS less than 6.0 whether or not they received ^{131}I. The patients were evaluated over each decade and the recurrence rate after ten years ranged from 7.1% to 8.8% from 1950 to 1990. There was zero ten-year cancer related mortality in the low risk patients. Therefore these authorities do not recommend ^{131}I in low risk patients. The authors do recommend ^{131}I for high-risk patients with MACIS scores greater than or equal to 6.0 who are at greater risk of recurrence or death. The shortcomings of the report are that there was no controlled decision to treat or not and the means of determining recurrence is not defined. The authors do not discuss in detail the methods for followup. Nevertheless the large numbers and careful statistical analysis should make endocrinologists step back and reflect on benefits versus risks of ^{131}I in the patient with low risk differentiated thyroid cancer.

I have followed a number of patients treated by operation and thyroid hormones. These patients did not receive ^{131}I as part of their initial therapy. The patients have been divided into two groups the first who had more complete thyroidectomy the second who had lobectomy with or without isthmusthectomy. In the first group, 125 patients had more complete surgery, which could have been total thyroidectomy or near total thyroidectomy. There were ninety-seven women (78%) and 28 men (22%). The mean age was 37.8 years with a standard deviation of 11.6 years. There were several reasons for not treating with ^{131}I. Some patients were opposed to the treatment; some desired an early pregnancy and some had T1 and T2 disease and no evidence of metastases. When the decision had been made to withhold ^{131}I treatment the patients did not have diagnostic whole-body scans. They were followed by clinical examination, measurement of Tg and in some cases ultrasound of the neck. No patient died from thyroid cancer. Six patients (4.8%) had a clinical recurrence and were treated by a second surgery. Three (2.4%) patients then received ^{131}I treatment. Preliminary results in a

smaller group of patients have been published [161]. These patients constitute a much smaller number of patients compared to the Mayo Clinic experience and the followup is shorter but the low recurrence rate is similar. In contrast in the second group eight of twenty-four patients (33%) who had lobectomy had second surgical procedures. There were seventeen women (71%) and seven men (29%), and the average age was 37.8 years with a standard deviation of 17.1 years. The two groups were similar except for the type of original surgery. The reason for completion of thyroidectomy was a rise in Tg or the appearance of nodules in the residual lobe that were detected by ultrasound. Only two of these patients were found to have cancer, so the actual recurrence rate was low at 8.3%. Because they had known cancer and new thyroid nodules developed in the contra-lateral lobe, it was difficult to avoid the second procedure. This study also argues against the dogma that all thyroid has to be ablated for accurate interpretation of Tg measurements. Seventy percent of the patients who had more complete thyroid surgery had persistently undetectable values while they took levo-thyroxine. A further 23% had values less than 5 ng/ml. Therefore, 93% had persistently low results. Of the remaining 7%, their values were stable and showed no evidence of increasing. It would appear that Tg is helpful when there is very little residual thyroid. In contrast only 21% of patients in Group 2 had undetectable Tg values and a further 16% had values less than 5 ng/ml. Thirty-seven percent had low values compared to 93% in Group 1.

The following case report illustrates the indolent nature of the disease in young women. This patient came to see me 30 years after her original surgery for papillary cancer. In 1970, when she was 19 years old, she had a hemithyroidectomy. The pathology showed locally invasive cancer and the recurrent laryngeal nerve on that side was removed because it was invaded with cancer. The patient did not have completion of thyroidectomy, and she was not treated with ^{131}I. She took levo-thyroxine, she married and had a family and has continued to be fit and healthy and work full time. There is no doubt that were she to present with this history today, all physicians with an interest in treating thyroid cancer would have recommend removal of the opposite lobe and most likely administration of ^{131}I postoperatively. When I met her in 2000 and reviewed the surgical and pathology records, I was surprised and concerned. Although there was no clinical evidence of disease, there was a small atrophied lobe seen on ultrasound. Over four years since then the Tg values remain in the range of 10 ng/ml to 20 ng/ml that would be reasonable for a normal person with one lobe. We have had extensive and repetitive discussions about what should have been done and what might be done now. It is hard to recommend an aggressive approach when the patient continues to be well 34 years after the original diagnosis.

In summary, not all patients with differentiated thyroid cancer need treatment with ^{131}I. Patients with T1 and T2 disease and no metastases have such a good prognosis that it would not be possible to demonstrate a benefit. Evidence shows no reduction in recurrence or mortality in patients with MACIS scores less than 6.0 who are treated with ^{131}I. Older patients, those with locally invasive disease, regional and or distant metastases have less recurrences and mortality when treated. Each patient must be judged individually and the benefits and risks defined and a rational decision reached. In his Presidential Address to the American Association of Endocrine Surgeons, Cady states, "Our current attempt to achieve perfection in outcome in the very few by over treatment of the majority of patients with differentiated thyroid cancer will be viewed with bemused regret."

Stunning?

When a well-tried protocol that has been successful for decades is suddenly found wanting, it causes a mixture of emotions in practitioners who have used that protocol with apparent success. This is the case with "stunning." Stunning is the term given when a diagnostic dose of radioiodine (^{131}I) causes enough radiation to thyroid cells that the therapeutic dose of ^{131}I is not able to be concentrated by those cells. Stunning results in a post treatment scan showing no uptake in a region where there was uptake on the preceding diagnostic scan. The term has been broadened in two ways. The diagnostic scan shows more uptake than the post treatment one, but there is not an absence of uptake on the post treatment scan. Secondly, the result of treatment with ^{131}I is less successful because the

diagnostic dose did not allow sufficient uptake of therapeutic ^{131}I and a followup scan 6 months to 12 months later shows residual functioning thyroid that might not have been present if the therapeutic ^{131}I had been trapped more efficiently. There are reviews and editorials on this topic [358–361].

The first body of data that is opposed to the importance of stunning is the excellent outcome after treatment by operation and ^{131}I. If stunning interfered with therapy the good outcome would not be expected. The second body of information is that for decades physicians have obtained post treatment scans and have demonstrated that these show more, not less lesions than the diagnostic scan, as shown in Figure 6.31. Figures 6.23 and 6.32 show diagnostic and post treatment scans where there is no evidence of stunning. In one study of 206 patients diagnostic scans using 0.5 mCi (18.5 MBq) ^{131}I demonstrated 25% less lesions than post therapy scans after 100 mCi (3.7 GBq). [362] In a comparison of 10 mCi (370 MBq), ^{131}I, and 30 mCi (1.1 GBq) in nine patients, there were more lesions in five post therapy scans [363]. The same investigators demonstrated more

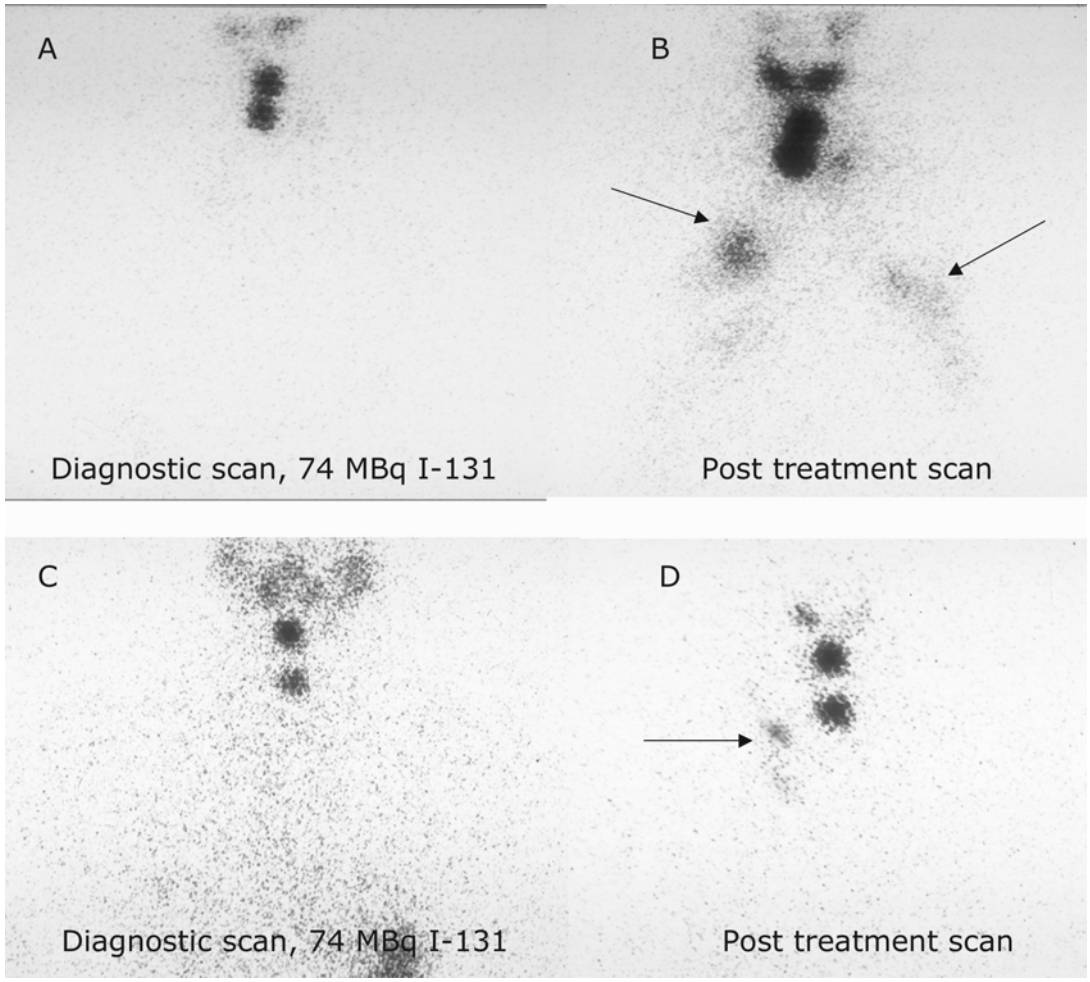

Figure 6.31. (A) Anterior and posterior spot views of the neck and chest made 72 hours after 74 MBq of ^{131}I. (B) Spot views of the same region made 1 week after treatment with ^{131}I demonstrating areas that show more uptake on the post treatment scan. (C) Anterior and posterior spot views of the neck and chest made 72 hours after 74 MBq of ^{131}I. (D) Spot views of the same region made 1 week after treatment with ^{131}I demonstrating areas that show more uptake on the post treatment scan.

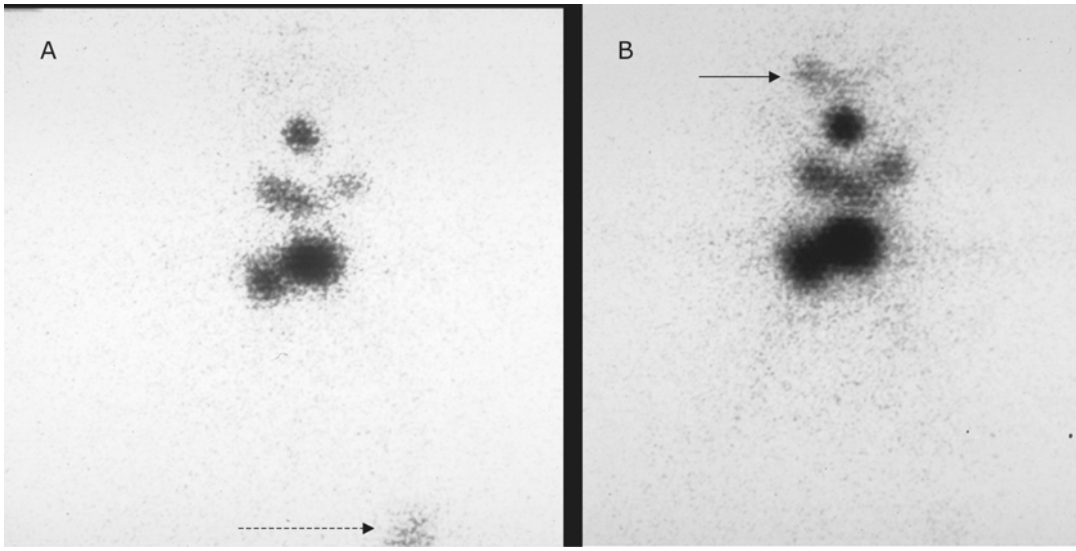

Figure 6.32. (A) Figure demonstrates a spot view of the neck 72 hours after 74 MBq ^{131}I. There are several focal areas of uptake. (B) Shows the post therapy scan one week after treatment with ^{131}I demonstrating an identical pattern in the region of the thyroid. There are 2 differences the stomach is seen on the early scan shown by the broken arrow, and salivary glands are seen on the post treatment scan solid arrow. There is no stunning.

lesions in 50% of post therapy scans in a comparison of 10 mCi (370 MBq) and 100 mCi (3.7 GBq). Spies found 40% more lesions on the post treatment scan [364]. To take this point to the extreme, investigators have shown uptake on post treatment scans in patients who had negative diagnostic scans but positive Tg values [365–367]. Although not designed to answer the question "Does stunning occur?," these studies provide proof that it does not.

Studies specifically asking the question of stunning include one in 122 patients who received diagnostic doses of 185 MBq (5 mCi) ^{131}I and were scanned after 72 hours. They were treated on the same day as the diagnostic scan with a range of doses from 30 mCi to 200 mCi (1.1–7.4 GBq) ^{131}I (104 of 122 patients received 150 mCi or 5.5 GBq) [368]. The investigators found no stunning and on followup 84% of patients who had a near total thyroidectomy were treated successfully by a single dose of ^{131}I. In a study from the Mayo Clinic, 117 patients had diagnostic scans 48 hours after an average dose of 2.6 mCi (96 MBq) ^{131}I and post treatment scans after 3 days to 5 days [137]. There was less uptake on only 4% of the post therapy scans but the authors conclude that there were alternative explanations in these patients and they state that stunning is unlikely. The Sloan Kettering Group is well recognized for their excellent dosimetric studies. They conducted dosimetry with scans made 1 day, 2 days, and 4 days after diagnostic doses of 1 mCi to 5 mCi (37–185 MBq) ^{131}I [369]. They did not find a relationship between the administered diagnostic dose and stunning.

Morris et al. addressed the problem by comparing the outcome in patients treated with ^{131}I who did not have a diagnostic scan to patients who had diagnostic doses of 3 mCi to 5 mCi (111–185 MBq) ^{131}I. Treatment was administered 2 days to 5 days after the diagnostic scan. There was no difference in the success of ^{131}I treatment in the two groups, which argues against stunning [370]. An additional study evaluating outcome as a determinant of stunning did not show that higher diagnostic doses had a detrimental influence [371].

One study that has been used to support the concept of stunning, in fact, promotes the opposite [372]. Three hundred seventy-three patients had diagnostic scans with 185 MBq ^{131}I. There was a mean delay of 7.2 weeks between the diagnostic scan and treatment. Then the patients had post treatment scans and after a delay of several months they underwent followup scans

and measurement of Tg. Seventy-eight (21%) patients had what appeared to be stunning on the post treatment scan. Seventy-six of the seventy-eight completed the followup study and sixty-eight scans were negative, and an additional seven had less uptake and low values of Tg. Therefore, even when stunning was identified it had little effect on the outcome.

I have compared diagnostic scan made 72 hours after 2 mCi (74 MBq) ^{131}I with post treatment scans obtained on average 8 days after therapy. An effort was made to treat as soon as the diagnostic scan demonstrated that was indicated, and 76% were treated within 1 day of the diagnostic scan. There were 305 patients who were consecutively scanned using ^{131}I. The patients were all hypothyroid and all were ingesting a low iodine diet for 2 weeks. In the last three years ^{123}I was used in preference, but when that radionuclide was unavailable, ^{131}I was administered. There were 230 women (75%) and seventy-five men (25%) and the average age of the group was 40.6 years. Stunning was demonstrated in ten comparisons (3.5%), and an example is shown in Figure 6.33. Followup studies including scan and measurement of Tg were negative in eight of these ten patients. Earlier results from this study have been published [136].

A criticism that has been leveled at all of these reports is that they lack quantitative measurements. In defense of this is the fact that the scans are conducted at different times in relation to administration of ^{131}I. Is it correct to compare uptakes at 48 hours to 72 hours after a diagnostic dose with those at 150 hours to 200 hours after treatment? If both measurements are made at 48 hours there are technical issues related to

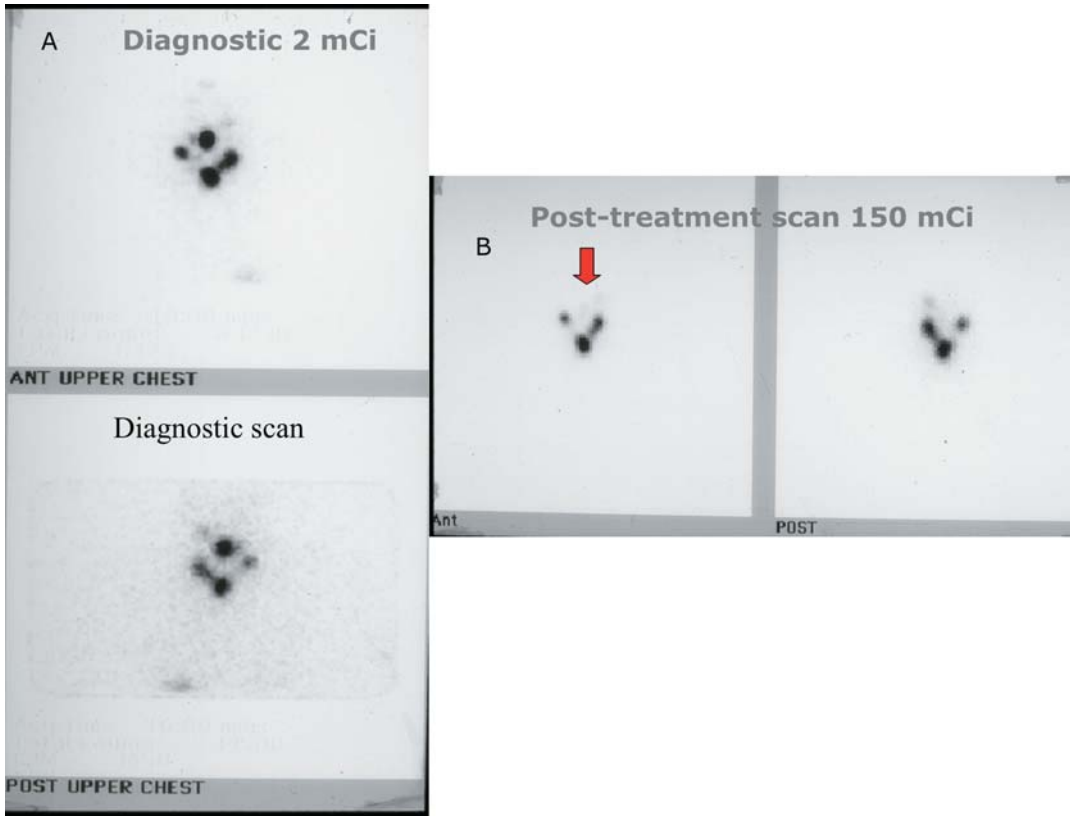

Figure 6.33. (A) Figure demonstrates a spot view of the neck 72 hours after 74 MBq ^{131}I. There are 4 focal areas of uptake. (B) Shows the post therapy scan one week after treatment with ^{131}I demonstrating 3 areas of uptake and one is absent shown by arrow. This is consistent with stunning.

measurement of such high count rates in the post therapy patients.

There are several publications that support stunning. One that is frequently quoted by proponents of stunning was published in 1951 [94]! This is worthy of scrutiny. The patient was treated with a "thyroidectomizing" dose of 25 mCi (925 MBq) ^{131}I. There was no imaging and the outcome was determined by collecting urine and measuring the percentage of ^{131}I excreted. If there was no residual thyroid all of the ^{131}I should be found in the urine. The plan had been to deliver several equivalent doses of ^{131}I. However, the urinary measurements led the investigators to conclude that the first dose interfered with the cancer's ability to trap iodine. This patient was also pretreated with antithyroid medication. The fundamentals of treatment cannot be compared with those in current use and the dose of ^{131}I was therapeutic not diagnostic. This cannot be used as an argument that diagnostic doses of ^{131}I cause stunning.

In 1988 Jeevanram et al. compared the uptake in fifty-two patients after treatment with ^{131}I and compared that to the earlier uptake of a diagnostic dose. There were five different diagnostic doses administered, but 36% of the patients received between 3 mCi and 4 mCi (111–148 MBq) ^{131}I and 40% between 4 mCi and 5 mCi (148–185 MBq) ^{131}I. All patients had uptake values of more than 5%; therefore, there was significant residual thyroid tissue. The investigators attempted to calculate the radiation delivered to the residual thyroid. This required an estimation of the volume of residual thyroid and then they used the concept that 1μCi ^{131}I would deliver 1.2 rad to a 20 gram thyroid with a 24-hour uptake of 30% (using the number 0.433 rad to 1 g in 1 hour from 1 μCi and a $T_{1/2E}$ of 125 hours this concept is accurate). The uptake was measured using a beta-gamma exposure meter positioned over the thyroid. Recognizing that there are possibly significant errors in the estimations because of inaccurate results for the mass of residual tissue, they found that a radiation dose of 17.5 Gy (1,750 rad) reduced the uptake of the therapy by 25%. When the diagnostic dose delivered 35 Gy (3,500 rad) the uptake of therapeutic ^{131}I was reduced 75%.

The term "stunning" is attributed to Park. His group demonstrated that there were an increasing percentage of patients whose post therapy scans showed less uptake as the diagnostic dose increased [373]. The number of patients was small but two of five (40%) who received 3 mCi (111 MBq), two of three (67%) who received 5 mCi (185 MBq), and sixteen of eighteen (89%) who received 10 mCi (370 MBq) had stunning on the post treatment scan. These post treatment scans were obtained the day after therapy, but the investigators did not provide information on the percentage uptake or the delay between testing and treatment. In a subsequent publication, comparing the outcome of treatment in forty-seven patients who had diagnostic scans with ^{123}I to twenty-five who received ^{131}I for the diagnostic scan, there was no statistical difference. The authors also comment, "Since we have reduced the scanning dose to 2 mCi to 3 mCi ^{131}I (74–111 MBq) we have not observed a scintigraphic stunning effect" [139].

Muratet et al. compared the outcome after ^{131}I treatment in two groups of patients [374]. One group had a diagnostic scan using 1 mCi (37 MBq) and the other 3 mCi (111 MBq) ^{131}I. A total of 229 patients were studied. The outcome was statistically better in those who received the smaller diagnostic dose (76% success vs 50% $p < 0.01$). The patients were not randomized and there was no discussion of the use of a low iodine diet and there was no control of the delay between testing and treatment.

In a different study the outcome after ^{131}I treatment was compared in patients who had diagnostic scans with ^{123}I to those whose scans were obtained using ^{131}I [375]. The success rate was 93% and 29% respectively. These data indicate that ^{131}I does cause stunning and ^{123}I rarely does. The authors do not describe the scintigraphic features of stunning. It is unlikely that 100% success will be achieved in treating a sizeable number of patients with ^{131}I irrespective of which radionuclide is chosen for the diagnostic scan or whether a scan is obtained or not. Lees et al. also compared the outcome of ^{131}I treatment in two groups of thirty-six patients [376]. The first group had diagnostic scans after 5 mCi (185 MBq) ^{131}I the second group received 10 mCi (370 MBq) ^{123}I. The success rates based on negative followup scans were 47% and 86% respectively. This points to a stunning effect of 5 mCi ^{131}I(185 MBq).

An in vitro experiment was designed to test whether diagnostic doses of ^{131}I could produce

enough damage to the thyroid cell membrane that trapping of iodine was subsequently inhibited [377]. The investigators demonstrated that as the absorbed dose of radiation increased from 1 to 30 Gy (100–3,000 rad) the transport of iodine from the basal membrane to the apex decreased. Addition of the equivalent quantity of non-radioactive iodine as a control had no inhibitory effect. How much radiation would the thyroid receive from diagnostic doses of ^{131}I? This would depend on the quantity of ^{131}I administered, the percentage uptake in thyroid tissue, the mass of tissue trapping the ^{131}I and its occupancy time. It is apparent that two variables that can be controlled are the dose of ^{131}I and the time between the administration of the diagnostic dose and the therapeutic dose. Let us take two examples.

(A) 74 MBq (2 mCi) ^{131}I are given to a patient who has 1 gram of thyroid that traps 1% at 72 hours. Treatment is administered 80 hours after the diagnostic dose. *One μCi ^{131}I delivers 0.433 rad to 1 gm over 1 hour. Therefore the thyroid tissue would receive:*

$$\frac{2000 \times 1 \times 0.433 \times 80}{100} = 693\,\text{rad}\,(6.93\,\text{Gy})$$

(B) 740 MBq (10 mCi) ^{131}I are given to a patient with 1 gram of thyroid that traps 4% at 72 hours. Treatment is prescribed 3 weeks later. We shall assume that the effective half-life is 6 days. *Therefore the thyroid tissue would receive:*

$$\frac{10000 \times 4 \times 0.433 \times 6 \times 24 \times 1.44}{100} = 35{,}915\,\text{rad}\,(359\,\text{Gy})$$

The dramatic increase in example B is due to the larger administered dose, the higher percentage trapped, and the longer residency 168 hours for the effective half-life, multiplied by 1.44 for the average half-life. There is no question that this dose would cause enough damage to inhibit trapping of therapeutic ^{131}I. It could kill cells and the diagnostic dose could in fact act as a therapeutic administered dose in this example.

These examples illustrate the importance of the prescribed quantity of ^{131}I. It highlights the importance of the percentage uptake and almost no study gives that information. It also demonstrates the importance of the mass of tissue being irradiated and no studies provide this. The length of time that the diagnostic ^{131}I irradiates the cells, that is, the delay between administration of the diagnostic and therapeutic doses, is also important and many reports omit this information.

Could there be an alternative explanation for the reduced uptake on the post treatment scans that have been attributed to stunning? Cohen et al. have demonstrated what appears to be stunning in patients who received 74 MBq ^{123}I for diagnostic scanning [145]. The patients were hypothyroid with a mean TSH greater than 80 mIu/L, they were ingesting a low iodine diet. Eighty-three percent were treated on the same day as the diagnostic scan. The radiation dose over 24 hours from ^{123}I that only emits γ rays cannot possibly cause enough damage to induce stunning. Nevertheless, 23% of the post treatment scans obtained on average after 5.8 days showed stunning. The best explanation is that iodine is taken up and released from different regions of thyroid tissue at different rates. It has been shown that cancerous thyroid traps less and releases quicker. This could be the explanation for some of the findings after diagnostic ^{131}I. An alternative explanation is that the early intense absorbed radiation from therapeutic ^{131}I could produce enough cellular damage that the cell or trapping mechanism is damaged so that no more iodine could be trapped and that already present leaks out of the dead cells. Calculations of the absorbed radiation over the first 24 hours after administration of 100 mCi to 200 mCi (3.7–7.4 GBq) are much higher than from diagnostic doses. Tables 6.10 and 6.11 adapted from Kalinyac and McDougall condense the evidence for and against stunning [360].

In summary there is considerable disagreement about the importance of stunning. How can these opposite positions be reconciled? Reports by reliable investigators show different percentages of post therapy scans showing this effect. Reports by reliable investigators also show differences in the percentage of successful treatments and poorer outcomes are attributed to stunning. Stunning is more likely when large diagnostic doses of 10 mCi (370 MBq) of ^{131}I are administered, but doses of 1 mCi to 3 mCi (37–111 MBq) would appear to be more appropriate. The longer the delay between the diagnostic dose and prescription of therapeutic ^{131}I

Table 6.10. Publications that support stunning.

Publication Year	Number of scan comparisons	Diagnostic Dose MBq	Number (percentage) with stunning	Outcomes	Comments
Rawson et al. 1951	1	925			Patient had a "thyroidectomizing" dose of I-131 then received 925 MBq I-131. This was not a diagnostic dose. Outcome was determined by urinary excretion of I-131. Patient was also treated with thiouracil
Jeevanram et al. 1986	52	<17.5 Gy 17.5–35 Gy >35 Gy	25% reduction 63% reduction 75% reduction	Not discussed	Very variable diagnostic doses used 3.7–185 MBq Major assumptions such as mass of tissue subjected to radiation Different methods for measuring diagnostic and post treatment uptake
Park et al. 1994	5 3 18	111 185 370	2 (40%) 2 (67%) 16 (88%)	Not discussed	TSH usually above 30 Diet not discussed Therapy within hours to days. PTS usually at 24–48 hours
Park et al. 1997	I-131 25 *I-123 40*	111–370 *3.7*		15/25 (60%) had negative followup scan *30/40 (75%) had negative followup scan*	"Since scanning dose reduced to 74–111 MBq we have not observed stunning" No uptake of therapy in 2 patients 2 and 4 weeks after 370 MBq The success rate appears to be better after I-123 but was statistically not different
Muratet et al. 1998	102 127	37 111	Outcome a surrogate for stunning	78/102 (76%) 64/127 (50%)	No details of patient preparation Imaging at 3 days Therapy 6 days after imaging
Bajen et al. 2000	373	185	78 (21%)	295/373 (79%)	7.2 week delay before therapy, outcome good in 75 of 76 who had followup scans
Lees et al. 2002	36	185		19/36 needed retreatment	36 patients after 185 MBq I-131 compared to 36 patients after 740 MBq I-123 19 versus 5 needed retreatment

Table 6.11. Publications that do not support stunning.

Publication	Number of scan comparisons	Diagnostic dose (MBq)	Number (percentage) with stunning	Outcome	Comments
McDougall 1997	299	74	10 (3.5)	8 of 10 who had "stunning" had negative followup scan	74 MBq I-131, treated as soon after diagnostic scan as possible, 76% within 24 hours
Cholewinski et al. 2000	122	185	0	84% ablation with single dose after near total thyroidectomy	Therapy prescribed immediately after diagnostic scan
Fatourechi et al. 2000	117	37–130	5 (4)	No evidence of disease in 3 of 5	Delay between diagnostic scan and therapy not discussed
Bajen et al. 2000	489	185	99 (21)	76 of 99 who have been rescanned had negative followup scan	Long delay between and treatment (7.2 weeks)
Morris et al. 2001	37 with diagnostic scan, 63 with no diagnostic scan	111–185	Outcome used as surrogate for stunning	No difference in patients with diagnostic scan, versus no scan	Post-treatment scans were not compared with diagnostic scan
Karam et al.	214	92.5–185		No difference	"We could not demonstrate a stunning effect of the diagnostic dose"

the greater the risk of stunning. ^{123}I can be used for whole-body scanning and it should not cause stunning but a proportion of post-therapy scans will show less lesions. By planning the timing of scan and coordinating treatment to follow with as little delay as possible appears to be the optimal approach.

Thyroglobulin Positive, Iodine-131 Negative Patients

Thyroglobulin measurement in the management of patients with thyroid cancer provides a serum test that reflects the presence or absence of thyroid cells. The methods for measurement and the factors that dictate the value in an individual patient were discussed earlier in the chapter. They include the mass of functioning thyroid, whether the residual thyroid contains cancer or benign cells, the level of TSH, the method of measurement and the presence of anti-Tg antibodies. There could be other factors as well. In general the Tg values and whole-body scan results are congruous. A patient with extensive metastases has high values of Tg. A patient with a small residuum of tissue in the thyroid bed has low values and a patient with lymph node metastases intermediate results. Unfortunately, not all patients who have negative scans have undetectable Tg values. This disparity in results leads to concern for the patients and their physicians. The implication is that there are cancer cells somewhere and the concern is that these cells are going to cause a problem in the future. Hypothetically these potential problems include a clinical recurrence, spread of cancer to distant sites or reduced lifespan. The Tg value should be compared with preceding ones and if there is a disparity the test should be repeated. False positive results are not common but do occur and errors in reporting have to be considered. The scan data should be reviewed to ensure all technical factors were appropriate, such as was the TSH elevated and low iodine diet adhered to? The images should be looked at personally and the dose of radionuclide and the camera settings confirmed. The patient should be examined for residual tissue in the thyroid bed and

cervical lymph nodes. When all of these fail to provide an answer there are several ways that this has been dealt with in practice. The first is to wait and monitor. The second is to treat with a high dose of ^{131}I, and the third is to use alternative imaging tests to identify where the Tg is coming from. Each of these is discussed in more detail.

Management by Waiting and Monitoring

Sisson and colleagues argue that a non-aggressive approach is warranted in patients with low risk papillary cancer [378]. They reiterate the fact that young patients with differentiated thyroid cancer have an excellent prognosis. The thyroid cancer mortality is less than 1% after twenty years. Low risk patients are very unlikely to have or to develop distant metastases. They point out that none of the staging systems or prognostic classifications uses Tg measurement to stratify patients. They reviewed thirty-five low risk patients treated over a two-year period and found that nine (26%) had persistently measurable Tg. Testing found no evidence of disease and there was no evidence of recurrence after 1 year. They state that these patients are "unlikely to benefit from additional ^{131}I therapy".

Role of High Dose Iodine-131

Treating the Tg positive, scan negative patient with a large administered dose of ^{131}I is based on facts that have already been discussed. There is data from several investigators proving that scans made days after treatments with large doses of ^{131}I show more lesions than prior diagnostic scans [362–364]. This expanded into the concept that post treatment scanning is an integral part of the management of patients treated with ^{131}I. This was extended further to demonstrate that the post treatment scan demonstrates lesions when the prior diagnostic scan is negative [365]. Therefore when a large dose of ^{131}I was administered there can be some uptake of the radioiodine into cancer cells. Next it was logical to treat the Tg positive/scan negative patient with a large dose of ^{131}I and when the post treatment scan showed uptake to declare success. This has almost become a routine, but does it work, does it improve the prognosis, and does it make Tg undetectable?

Pineda et al. treated sixteen patients with large doses of ^{131}I. The patients had already been treated by operation and ^{131}I and had measurable Tg but negative diagnostic ^{131}I scans. The average Tg value was 74 ng/ml and the patients were treated with a mean dose of 169 mCi (6.2 GBq) ^{131}I. Thirteen of the sixteen had a drop in Tg to an average of 62 ng/ml and they then received an additional average administered dose of 217 mCi (8.0 GBq). There was followup in five whose Tg had fallen to 32 ng/ml and they received an additional 208 mCi (7.7 GBq). Although the Tg values fell after the first and second treatments, there was no statistical difference in the starting Tg compared to the last Tg values. I have been criticized by the investigators for quoting the average Tg values and not reporting each patient's individual results, and the authors and I have debated this issue and published for and against arguments [379]. In this investigation no patient achieved an undetectable Tg result. The authors state that post therapy scans showed uptake but there are no images to judge the quantity of uptake.

Schlumberger et al. using doses of 100 mCi (3.7 GBq) found that an average dose of 150 mCi (5.5 GBq) had a significant effect on Tg values [367]. They treated fifteen patients and fourteen achieved a negative post therapy scan and nine had Tg values less than 5 ng/ml when TSH was elevated. They argue that uptake of 0.03% of 3.7 GBq (100 mCi) in 1 gm thyroid would deliver 10 Gy (1,000 rad), assuming an effective half-life of 4 days. They suggest two to four doses could deliver a "curative dose". There is no data to suggest that 40 Gy (4,000 rad) would kill thyroid cancer cells.

In contrast investigators from the Mayo clinic treated twenty-four patients with less satisfactory results [380]. The patients had a diagnostic scan with an average of 3 mCi (111 MBq) ^{131}I. They were treated with a mean dose of 207 mCi (7.7 GBq) and post treatment scans were conducted when the emitted radiation fell below 7 mrem/hr/meter. Six (25%) showed some uptake on the post therapy examination, four in distant sites and two in the thyroid bed. There was no improvement in Tg value, the mean values while patients took thyroid hormone rose from 162 ng/ml to 696 ng/ml. The values off thyroid

hormone rose from 2,721 ng/l to 4,250 ng/l. Thirteen had progression of disease and five died. The authors conclude, "Therefore widespread use of empiric radioactive iodine therapy for such patients who have a large tumor burden should not be encouraged." Another publication found that patients with macrometastases were seldom helped by this therapy [381]. There are several editorials and commentaries for and against this issue [382–389].

My argument against this approach in general is what is being treated [390]? A blood test is being treated, not a patient, and not an anatomic abnormality. Patients do not die from an elevation of Tg. Patients do not die from small foci of cancer in regional lymph nodes. They die from extensive cancer in important locations such as the lungs, spine, brain, and so forth. Large masses of cancer are not difficult to find clinically or by imaging tests. Fortunately, patients with extensive metastases are not common. Secondly, it is important to look at the prognostic information in the patient. When the patient is young, the prognosis is going to be excellent. In contrast the presence of widespread metastases in an old patient predict a bad prognosis. Third, it is important to judge whether the treatment is likely to improve the prognosis. When there is no uptake of 1 mCi to 3 mCi (37–111 MBq) ^{131}I in a technically high quality scan (low iodine diet, high TSH, good camera) what is the likelihood that a therapy dose will deliver sufficient radiation to kill the cells that are producing the Tg? The example of Schlumberger et al. that 20 Gy to 40 Gy (2,000–4,000 rad) could be therapeutic is against most of the evidence, which indicates that considerably larger doses are necessary to kill the cells. Although several studies have demonstrated that post therapy scans show more lesions as was discussed in the section on post treatment scanning I have found this to be less common. In a series of more than 300 pairs of diagnostic and post treatment scans only 3% of the latter showed uptake in a site that would increase the stage of disease and an example is shown in Figure 6.31. This has been published in a smaller series [136]. This was also the conclusion of Fatourechi et al. [137], and argues against a likely therapeutic benefit. The bigger the mass of cancer that does not trap a diagnostic dose of ^{131}I, then the less likely that treatment is to work. One might ask could the small amount of radiation taken up by poorly functioning differentiated cells actually worsen the situation? The patient has cancer and a sublethal absorbed dose might produce dedifferentiation. Fourth, when a blood test is the reason for treatment, the resolution of the blood test is the endpoint, but if the Tg does not become undetectable when do we stop treating with ^{131}I? Some have set an empirical limit, for example 600 mCi (22.2 MBq) [250]. Why pick 600 mCi (22.2 MBq) why should the limit not be 1,000 mCi (37 MBq) or a different number? The authors state that little benefit can be gained by higher doses. It should be apparent that diagnostic ^{131}I scan is not going to be useful for followup; therefore, studies reporting this test is negative are confirming what was already known, that the patient is Tg positive and radioiodine negative. Some argue that a negative post treatment scan could also be an end point. That would mean that patients would receive a large dose of ^{131}I, which by definition would not be therapeutically helpful.

Proponents for ^{131}I treatment state that they find evidence of pulmonary disease on post treatment scan [365–367]. None of these publications cited provides images so the degree of uptake is hard to judge. Additional fuel against this approach is based on dosimetry by Sisson et al., which indicates that the Beta emissions of ^{131}I would deposit their energy outside of micronodular lung metastases [252]. The authors calculate that for a 1 mm lesion (diameter 0.5 mm) ^{131}I delivers less than 40% of its energy within the metastasis [391].

There has to be consideration for the additional down sides of this approach. The patients have to be properly prepared by taking a low iodine diet and having an elevated TSH. For therapy that usually means a period of hypothyroidism. The treatments are likely to be repeated. The side effects have to be considered and repeated large doses of ^{131}I are likely to cause permanent xerostomia and other complications discussed previously in the chapter. That is a large price to pay for a small drop in Tg. More serious long-term problems are not common but it is a fact that repeated large doses of ^{131}I are being prescribed more often in recent years and there has not been adequate long-term followup. When the patient is a young

woman it could mean delaying a wanted pregnancy. The cost of time off work, hospitalization in countries where this is mandated, separation from family all has to be factored into the decision.

In summary the treatment of a Tg positive and scintiscan negative patient with high doses of ^{131}I is problematic. When should this approach be recommended, and when should it be avoided? It should not be advised when there is obvious clinical disease. That should be treated by surgery or external beam therapy depending on its site. This approach might have a role when there is no evidence of bulky disease in a patient who has a clear understanding of the controversy who also recognizes that the Tg value will rarely become undetectable.

Role of Other Imaging Techniques: Positron Emission Tomography

The third approach in the Tg positive radioiodine negative patient is to try and identify the source of Tg production by an alternative imaging test or tests. Radiological procedures such as CT or MRI provide excellent anatomic information but abnormalities in cervical lymph nodes are based on size greater than 1 cm in transverse diameter. Therefore, a node smaller than 1 cm is by definition judged to be normal. Ultrasound is excellent but is also dependent on the size of nodes. However an experienced operator can use criteria such as roundness rather than almond shape, hypoechogenicity, loss of the fatty hilum and increased vascularity to increase the sensitivity of the test. Unfortunately by incorporating these features the specificity of the ultrasound is lessened. Pacini et al. found that ultrasound and FNA of suspicious nodes plus measurement of Tg had the highest sensitivity [160].

This section deals with nuclear medicine tests that demonstrate the cancer using radiopharmaceuticals that are trapped by malignant cells and can be imaged by external detectors. It is generally accepted that these radiopharmaceuticals are of most value when radioiodine scan is negative [392]. Historically the first agent was Thallium (^{201}Tl) [393, 394]. This is an agent used primarily to image myocardial perfusion, but it is trapped by some cancers including thyroid cancer. The energy of its photon emission (x-ray) is lower than ideal for a gamma camera and the images are of moderate resolution. The low energy photon is also attenuated by less tissue, therefore lesions deep in the patient might not be identified. Other myocardial perfusion agents labeled with ^{99m}Tc have also been investigated in patients with thyroid cancer. These include ^{99m}Tc-Sestamibi (MIBI) and ^{99m}Tc-Tetrafosmin [395–399]. The results are satisfactory. Seabold et al. found ^{201}Tl and MIBI to have equivalent sensitivities (54% vs 58%) in detecting sites of cancer [400]. Rubello et al. evaluated MIBI, ultrasound, CT and MRI in 219 patients of whom 122 were Tg positive, iodine negative [401]. They reported a sensitivity of greater than 90% and a specificity of 100%. The positive rate of 68% for residual thyroid, 56% for metastasis in lymph nodes and 46% for pulmonary metastases are closer to the usual results [402]. Data for Tetrofosmin is limited but shows it is equivalent to MIBI [403, 404]. The somatostatin receptor analogue Octreoscan labeled with indium (^{111}In) has also been used [405]. In a study of 15 patients ^{111}In-Octreoscan was positive in 80% who had negative scans with radioiodine. The authors indicate this could open the possibility of treatment with somatostatin receptor analogues labeled with β emitters [406]. Pentavalent ^{99m}Tc dimercaptosuccinic acid (^{99m}Tc-v-DMSA), which is used in Europe for identifying medullary cancer, has a very minor role for differentiated thyroid cancer. There is no patient preparation for these scintiscans and the usual administered doses are 3 mCi to 5 mCi (111–185 MBq) for ^{201}Tl, 20 mCi (740 MBq) for MIBI and Tetrofosmin and images are obtained early after ten to twenty minutes and later at two to three hours. Five (5) mCi to 6 mCi (185–222 MBq) of ^{111}In-Octreoscan is injected 6 hours prior to imaging and delayed scans are obtained after 24 hours to 48 hours.

With the increasing use of Positron Emission Tomography (PET) using fluorodeoxyglucose (^{18}FDG) the other radiopharmaceuticals have been relegated to the second level. Fluorodeoxyglucose PET imaging has become very important in the management of many cancers including lung cancer, melanoma, lymphoma, breast cancer, colorectal cancer, and head and neck cancer (Figure 6.33). The technique is based on the fact that most cancers use more glucose than normal cells. Glucose labeled with the positron emitter ^{18}F as the compound ^{18}FDG.

Fluorodeoxyglucose is trapped like glucose by the GLUT transporters, but it is metabolized slowly. The positron emitter ^{18}F has a half-life of 110 minutes. Positron emitters decay by emitting a positive electron. This travels a short distance in tissues and quickly meets a negative electron that are abundant in biological tissues. The positive and negative electrons annihilate one another and the energy of the lost mass of the two electrons is released as two γ photons of energy 511 keV. These photons travel away from the site of annihilation at an angle of 180 degrees. The patient is placed in a ring of detectors that is designed to identify two "hits" occurring on opposite sides of the ring at precisely the same time. This is called coincidence counting. The image is produced by back projection similar to CT and MRI, although current algorithms are more advanced and accurate. Photons arising in different parts of the body travel different distances to reach a detector, for example an annihilation at the skin results in one photon passing through the entire breadth of the body to reach the detector on the far side, while the second photon does not pass through organs before it reaches the closer detector. This difference in how much matter the photons traverse requires a correction to be made for attenuation of the photons by body tissues. Dedicated PET cameras use an external source of radiation, usually Gadolinium, for attenuation correction, but a major advance in technology has been the combination of PET with CT. The CT provides excellent information for attenuation but also provides anatomic images that can be read side by side with the functional PET scan or the two images can be superimposed. For PET scanning the preparation is simple; the patient should be fasted for six to eight hours, serum glucose should be normal, and an intravenous injection of 555 MBq (15 mCi) ^{18}FDG administered. The patient is kept in a quiet room without speaking, chewing, and so forth for 1 hour then the images are obtained. The PET scan covers a volume of the patient from the base of the brain to the midthigh and takes about 30 minutes to 40 minutes to acquire. Attenuation correction with a standard PET scanner requires a second scan lasting about 20 minutes; however, attenuation correction using CT is completed in about one to two minutes. Although more expensive, PET/CT instruments provide combined anatomy and function, the images are in identical position, so the problems of fusing data from different instruments, with patients in different positions, and made at different times are overcome. The resolution of current PET instruments is about 4 mm to 6 mm so lesions that are significantly smaller than 1 cm can be identified (the volume of a sphere is $4/3 \times 22/7 \times r^3$). The speed of throughput is also improved. In the United States, PET has been approved for the management of a Tg positive, iodine negative patient.

The first publication on PET scan in patients with thyroid cancer was in 1987 [407]. Since then, there have been many reports and experience is developing in its strengths and weaknesses. Normal thyroid takes up very little ^{18}FDG, as shown in Figure 6.34. Similarly very well differentiated thyroid cancer traps less ^{18}FDG than less well differentiated lesions. This is not a major disadvantage because well-differentiated cancers trap ^{131}I and PET scan is not required. Several series with meaningful numbers of patients have been published [408–414]. My experience is with 102 scans in 76 patients most of whom presented with Tg positive, radioiodine negative dilemma examples are shown in Figures 6.35 and 6.36. Sixty-three percent of the scans were positive, which is about the average compared to published data. There are several important issues. Patients with high levels of Tg are more likely to have positive PET scans. Small micro-nodular lung metastases are often too small to be identified. PET positive lesions are more likely to be resistant to ^{131}I treatment [415].

One of the unanswered questions is whether the PET scan should be conducted when TSH is normal or elevated. Most of the studies reported were on patients taking thyroid hormone who had normal or low TSH values. Some reports showed no advantage from a high TSH [416]. This view has been challenged by an investigation where patients were studied with and without injections of rhTSH. The scans after rhTSH showed lesions in nineteen patients compared to nine without an elevated TSH and the number of lesions identified increased from forty-five to eighty-two [417]. A smaller study of 7 patients showed lesions in one patient only on the stimulated scan [418].

There are potential false positives. Uptake of ^{18}FDG in muscles in the neck can sometimes be confused with cervical node metastases as

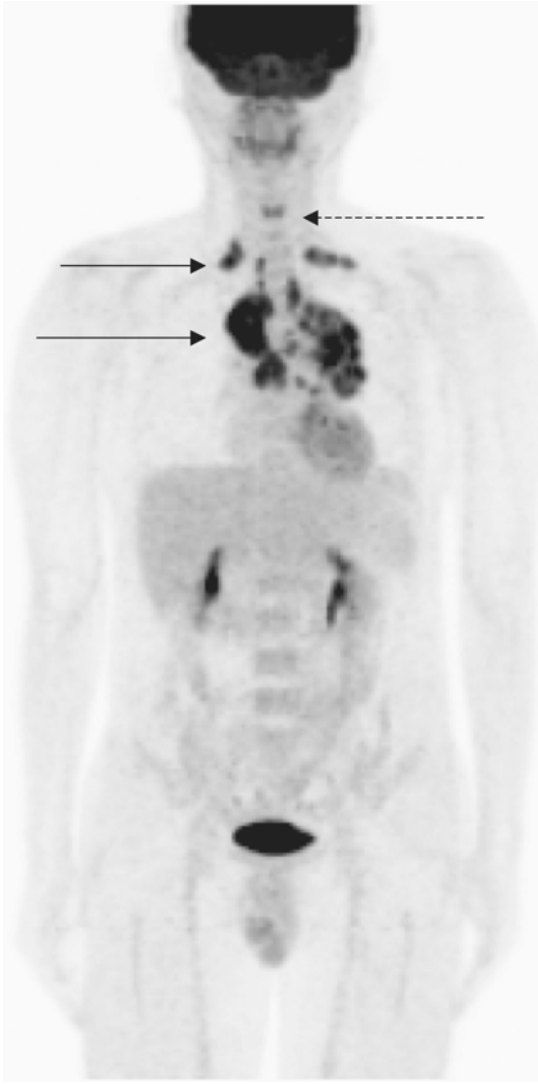

Figure 6.34. PET scan in a patient with Hodgkin's disease. The scan is obtained 60 minutes after injection of 550 MBq ^{18}FDG. There is normal uptake of labeled glucose in the brain and excretion through the kidneys into the bladder. There is normal but fainter uptake in the heart, liver and skeleton. The lymphoma shows intense uptake in the mediastinum, hila and supraclavicular nodes (solid arrows). The muscles of speech are shown by the broken arrow.

shown in Figure 6.37 [419]. In patients who are nervous some authorities suggest pretreatment with muscle relaxants, but this is not universally successful [420]. More recently similar uptake has been attributed to brown fat (Figure 6.38). This has been confirmed by PET/CT where the uptake of ^{18}FDG corresponds with fat on CT. Diffuse uptake in the thyroid is characteristic of autoimmune thyroid disease, in particular Hashimoto's thyroiditis (Figure 6.39) [421]. This should not be a diagnostic problem in a patient who has had a thyroidectomy, but it has caused confusion preoperatively [422]. When there is damage to a recurrent laryngeal nerve during thyroidectomy, this results in an asymmetric uptake of ^{18}FDG in the muscles of articulation on the normal side that can be misinterpreted as residual cancer [423, 424]; PET/CT resolves this (Figure 6.40).

Positron emission tomography has a role in Hürthle cell cancer, medullary cancer, anaplastic cancer, and lymphoma of the thyroid, and these are discussed in the relevant sections.

Treatment of Lesion Identified by Positron Emission Tomography

When a lesion is identified by PET or an alternative method of imaging, how is it treated? The debate above has argued that ^{131}I is unlikely to deliver sufficient radiation to be of clinical value. Therefore, the alternatives are to accept there is a lesion and monitor it, to treat it with external radiation, or to remove it surgically. With regard to the last two, the decision of surgery versus radiation depends on the site, accessibility, and size of the lesion. When the lesions are regional and potentially amenable to operation we have taken the following approach. The site of the lesion is identified by PET, or PET/CT and then ultrasound of that area is obtained and ultrasound guided FNA of the anatomic abnormality conducted. This provides two pieces of information. First, whether the lesion contains thyroid cancer, and secondly, its exact anatomic relations are defined. The patient is taken to the operating room and an intraoperative ultrasound pinpoints the lesion, which is excised, and a followup intraoperative ultrasound, at that time, demonstrates that the lesion is no longer there [425]. The ultrasound probe is protected with a sterile cap and is introduced into the incision. A 9 mHz instrument using a linear array transducer produces real time gray scale and color Doppler images. Other suspicious nodes can be removed at the same time. Thirteen patients had nodes removed using this approach, eleven under general anesthesia and two using local anesthesia. Preoperatively, eleven of thirteen had elevated Tg values

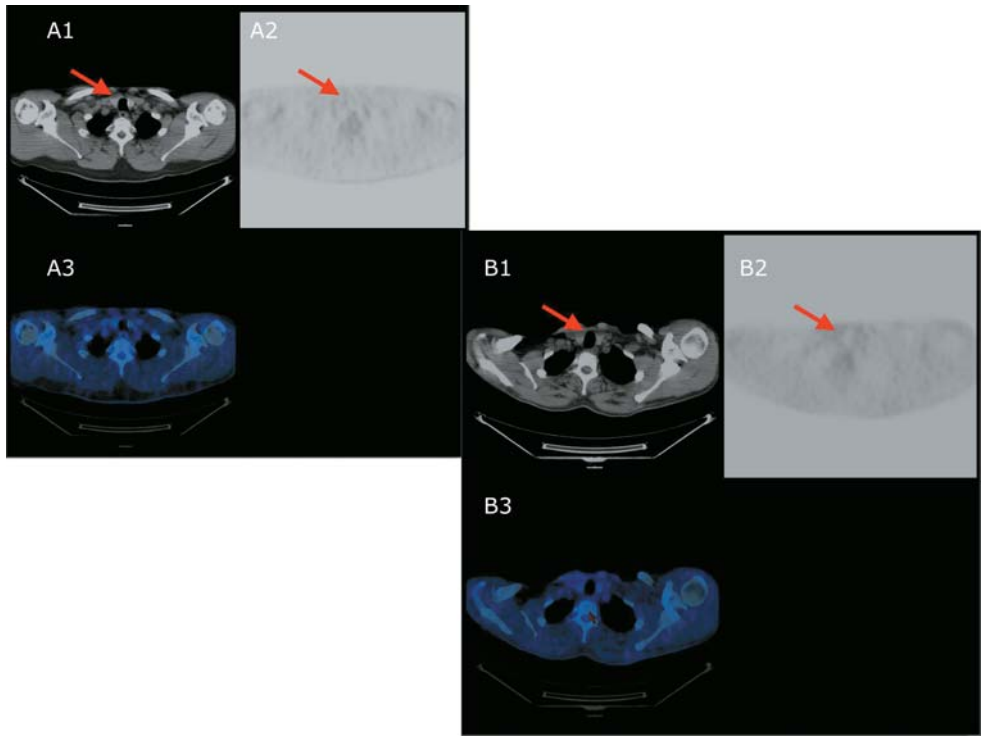

Figure 6.35. Two sets of PET/CT scans in different patients obtained 60 minutes after injection of 550 MBq ^{18}FDG. They are to demonstrate that the normal thyroid traps little ^{18}FDG. A1 and B1 are the CT scans, A2 and B2 are the PET scans and A3 and B3 are composites of images 1 and 2. The thyroid is shown by the arrow and is almost imperceptible on PET.

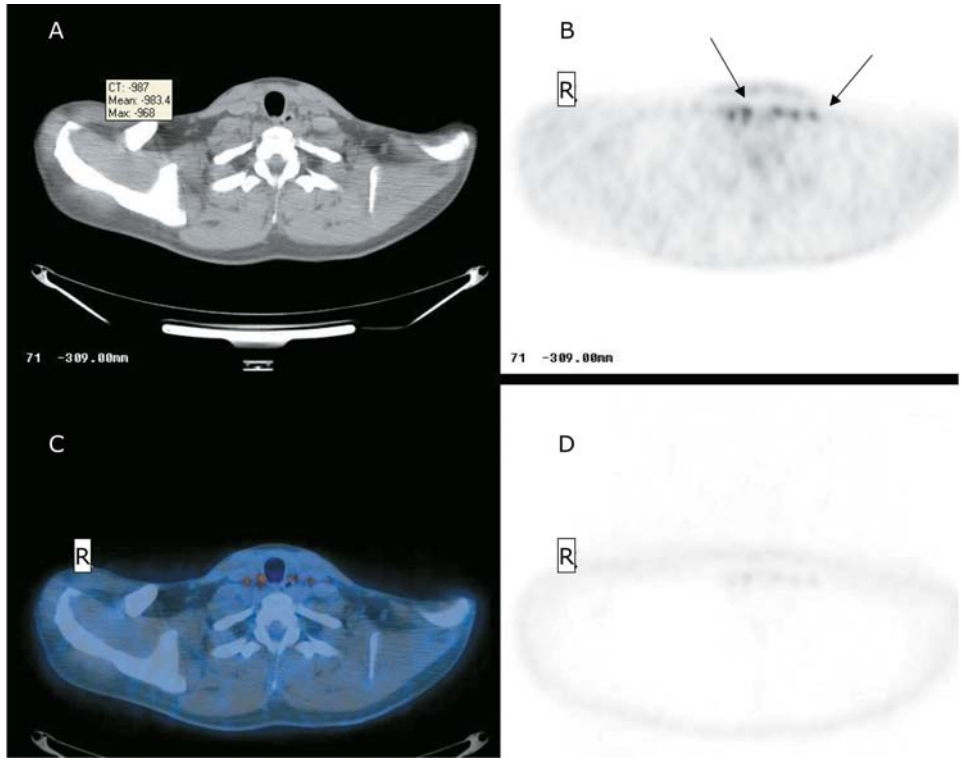

Figure 6.36. Figure shows a PET/CT scans in a patient obtained 60 minutes after injection of 550 MBq ^{18}FDG. (A) is the CT scans, (B) is the PET scan and (C) is the composite of images A and B. (D) is a non attenuated image. The patient was Tg positive iodine negative and the PET scan shows 5 focal areas of uptake due to metastases in lymph nodes.

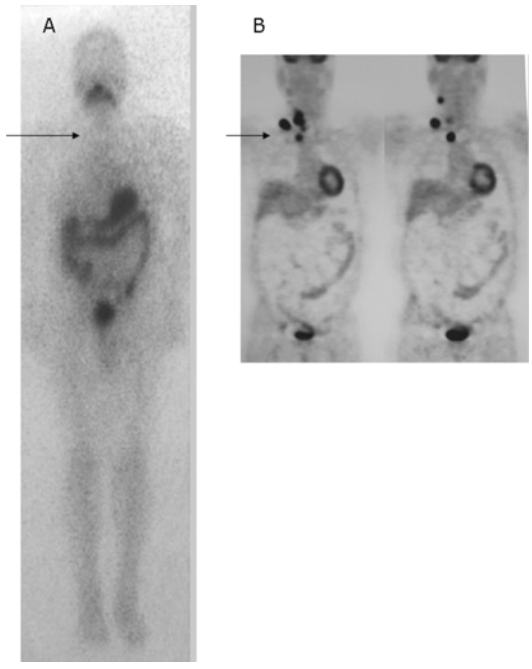

Figure 6.37. (A) Whole-body scan using ^{131}I. (B) PET scan in the same patient obtained 60 minutes after injection of 550 MBq ^{18}FDG. The PET scan shows regions of intense uptake of FDG but the radioiodine scan is negative. (Courtesy of Dr Marie Carlisle)

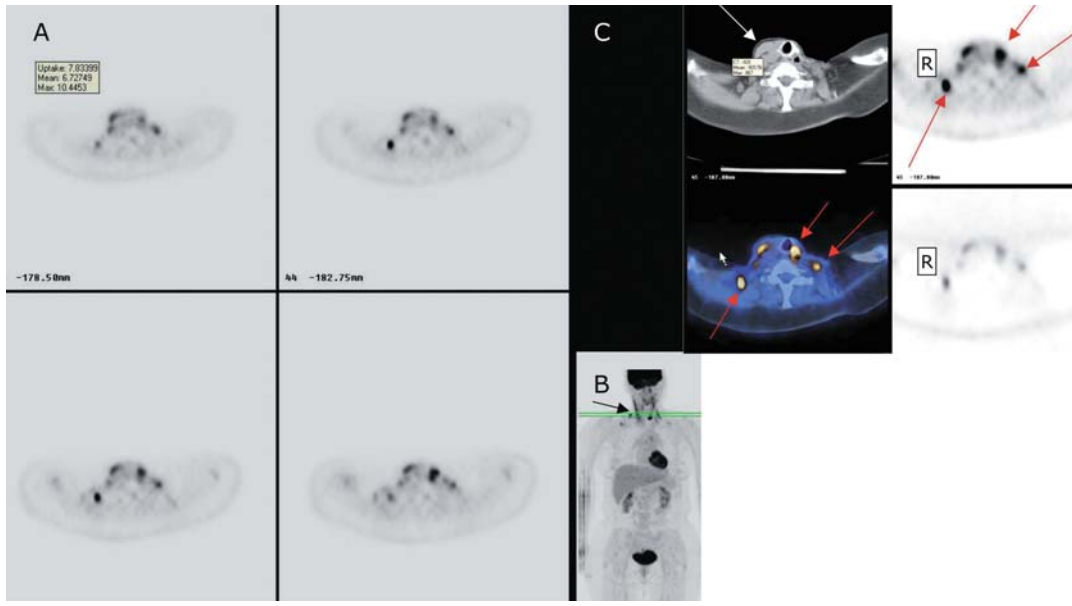

Figure 6.38. (A) Figure shows four panels of transaxial images of a PET scan in a patient suspected of having recurrent thyroid cancer. The slices are at the level shown by green lines on the coronal image (B). The patient has had eleven surgeries including removal of the sternocleidomastoid on the left. The PET scan shows multiple areas of focal uptake strongly indicative of metastatic cancer. (C) PET/CT scan demonstrates CT, PET, and combined PET/CT. The PET/CT shows that most of the focal abnormalities are metastases and the function and anatomy are defined (red arrows). Some are explained by uptake of FDG in the right sternocleidomastoid white arrow. Uptake in muscle can be a cause for a false positive PET scan.

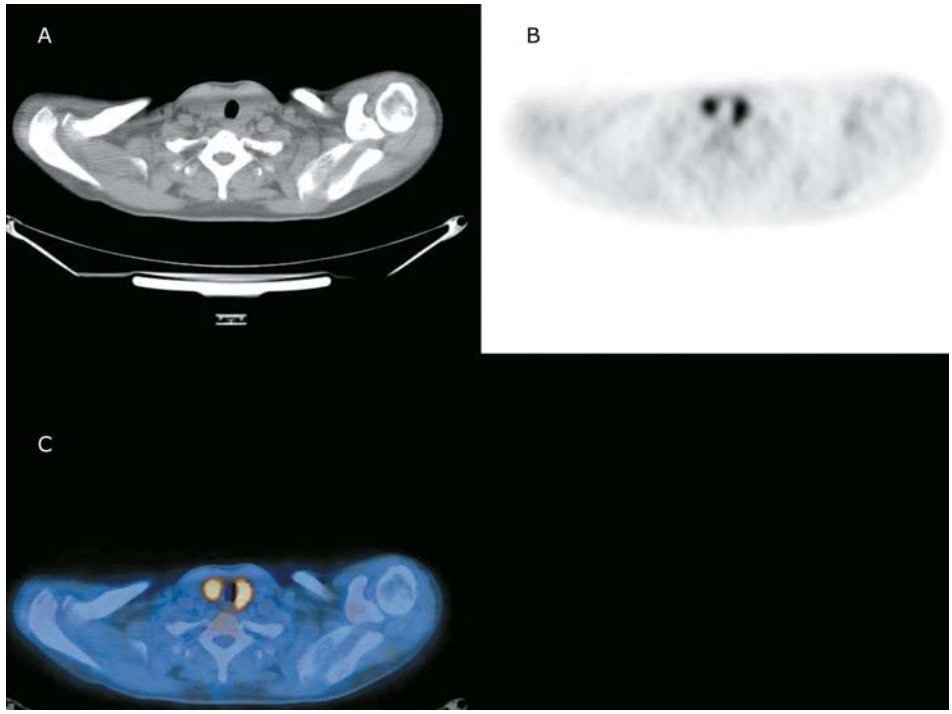

Figure 6.39. Demonstrates transaxial cuts of a PET/CT at the level of the thyroid. (A) is the CT, (B) is the PET and (C) is a composite. There is intense uptake of FDG in the thyroid and this is confirmed anatomically by the CT and composite images. This is characteristic of autoimmune thyroid disease in particular Hashimoto' thyroiditis. This is a potential false positive PET scan.

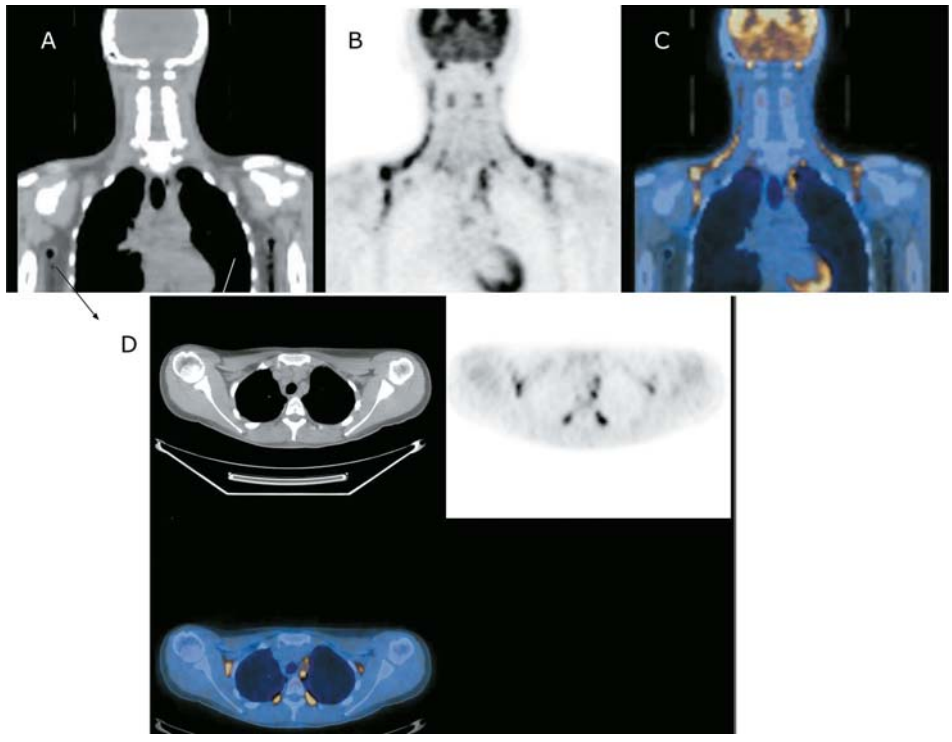

Figure 6.40. Figure demonstrates coronal cuts of a PET/CT of the neck and upper chest. (A) is the CT, (B) is the PET and (C) is a composite. There is intense uptake of FDG in the linear configuration in the lateral neck, which is due to uptake of FDG in fat (brown fat). This is confirmed anatomically by the CT and composite images where fat is dark on CT and running between the muscles and subcutaneous soft tissues. (D) demonstrates the brown fat in the planes of the lower thorax.

with a mean of 10.5 ng/ml, while TSH was low. Thyroglobulin fell in all patients to a mean of 0.84 ng/ml, and in seven it became undetectable. Therefore we would prefer this approach to treating Tg positive, iodine negative patients when the lesions are accessible.

Surgery followed by external radiation is recommended for skeletal lesions that are in weight bearing sites and are at risk of pathological fracture. For example, a femoral lesion could be treated by an intramedullary pin. Consultation with an orthopedic surgeon who specializes in oncology is advised. Lesions in non-weight bearing bones would also be treated by external radiation.

Additional Methods of Treatment

The therapies to be discussed below are employed in a small minority of patients with differentiated thyroid cancer. The majority of patients are treated by thyroidectomy, in selected cases with ^{131}I and with levo-thyroxine.

External Radiation

When sites of thyroid cancer do not trap iodine and are in regions that are not suited to operation, they can be treated by external radiation. Most of these patients would already have received ^{131}I, but when metastases no longer are functional, continue to grow, and are symptomatic external radiation is appropriate. In a report from France, the dose ranged from 30 Gy (3,000 rad) over 15 days to 45 Gy (4,500 rad) over 28 days [250]. Some authorities recommend this prophylactically in patients with pT4 lesions. One study used larger doses 59.4 Gy or 66.6 Gy (5940–6660 rad) to the thyroid bed depending on whether the excision was complete or not [426]. The patients received 50 Gy (5,000 rad) to the cervical, supraclavicular, and mediastinal nodes, when the stage was pT4N0 and the dose was increased to 54 Gy (5,400 rad) in the case of pT4N1. Several articles on this topic are of interest [427]. There is some evidence that the addition of external beam therapy can extend the local relapse free interval in patients with extrathyroidal invasion and small volumes of residual disease [428, 429]. The treatment is associated with side effects to the skin, trachea, and esophagus in the majority of patients [426].

External radiation has an important role in the patient with a brain metastasis. Fortunately this is rare. Most of the publications deal with only six to twelve patients; therefore, no person or center has a huge experience [430–435]. The patients usually have other sites of metastases [434]. The primary cancer can be papillary or follicular and in one report seven of seven were papillary [433]. Neurological symptoms such as persistent headache, altered vision, or a seizure should be taken seriously and be an indication for a thorough clinical examination and MRI of the brain. The symptoms can be atypical because of an unusual site of spread [436]. Sometimes the first evidence of a brain metastasis occurs when a patient is taken off levo-thyroxine for diagnostic tests and treatment with radioiodine and most likely is the result of TSH stimulated growth. The presence of a metastasis can be recognized for the first time a few days after ^{131}I therapy when a neurologic catastrophe occurs dramatically. This is thought to be due to edema or bleeding into the cancer [433, 437]. When a brain metastasis is diagnosed its treatment could be surgical provided the lesion is in a nondominant, less critical region of the brain. In many cases, external radiation or gamma knife radiation is preferred. An urgent consultation with a neurosurgical or neuro–radiation oncology team should be organized. High dose dexamethasone should be prescribed until specific treatment is delivered. Most of the cases do not show good uptake of radioiodine, but in cases where there is, it is reasonable to treat with ^{131}I but only after the lesion has been treated by gamma knife or external radiation. The patient should be taking dexamethasone and the neurosurgeons or radiation oncologists should be aware about the plans and potential for problems described above. The prognosis is not good, and almost all patients will die from their disease, although some live for several years. Currently, I follow one patient who is more than 4.5 years since her first cerebral metastasis was treated.

Embolization of Cancer

Bulky symptomatic lesions, in particular those in the skeleton, can be reduced in size by embolization of their arterial supply using particles such as polyvinyl alcohol, sponges, or microcoils. The technique has been used for about three decades and is not specific for

thyroid metastases, but because they tend to be vascular, the method is suited to them [438–443]. The treatment is palliative not curative [439]. This should be under the care of an interventional radiologist experienced with the technique. In one report, forty-one procedures were conducted in sixteen patients [440]. The outcome was judged to be successful in 59% by a reduction in symptoms and no further growth of the cancer. The therapy need not be used in isolation and can be a means of making a lesion surgically treatable. It reduces the blood loss during surgery [444]. Investigators interested in the procedure have administered therapeutic ^{131}I, and after a short delay shrunk the lesion by arterial embolization [441]. The theory being that the radiation has a smaller volume to treat and should give a higher absorbed dose. In another investigation, two groups of patients were compared. One group received two treatments with ^{131}I, the other had embolization between the two therapies of radioactive iodine [442]. The latter group had a statistically greater drop in Tg. When a patient has a spinal metastasis that is causing pressure effect and the patient is a candidate for ^{131}I, there is concern that growth of the cancer under TSH stimulation could produce a neurologic catastrophe. Pretreatment embolization is an option [445].

There are several important issues. In the case of vertebral lesions it is critical that the arteries supplying the spinal cord are not embolized. This would cause immediate paraplegia. Preliminary angiography to define the exact vasculature is essential. Secondly there is a report of a patient developing a severe respiratory distress syndrome 10 days after embolization of a massive sacral lesion [446]. This coincided with a significant rise in Tg and was attributed to Tg being released in large quantities from irradiated cells and microembolizing the pulmonary circulation. However, in general the procedure is well tolerated and can be repeated.

Methods to Induce Redifferentiation of the Cancer: Retinoic acid

Retinoic acid receptors were discussed in Chapter 2. They play an important role forming heterodimers with thyroid hormone receptors. Retinoic acid receptors (RAR) can accept all retinoids including trans and cis forms. Retinoid X receptors (RXR) only interact with 9-cis-retinoic acid. All vitamin A derivatives are called retinoids. Retinoids in excess have a teratogenic effect on the developing fetus, and in physiological doses they have a very crucial role in growth, development, and maturation of cells. Retinoic acid has a role in the treatment of some cancers. The classic example is promyelocytic leukemia, caused by a translocation, such as 5 : 17, 11 : 17, or 15 : 17, which couples the gene for the alpha retinoic acid receptor to other genes. Treatment with retinoic acid produces a remission in 90% of these patients. The first experimental evidence that retinoic acid has a beneficial effect on thyroid cancer cells in vitro is attributed to van Herle et al. [447]. That group showed a four-fold increase in trapping of radioiodine in cultured cells. More recently retinoic acid has been shown to increase mRNA for NIS by a factor of 2.5 in cultured thyroid cancer cells and to have an effect on the promoter of NIS [448, 449].

Clinical trials in single patients showed effects that were judged to be beneficial. The benefits cited were increased trapping of iodine and a change in Tg. In one patient the Tg rose from about 100 ng/ml to 28,000 ng/ml [450]. Metastases of the cancer, which were not seen on a diagnostic scan, were identified on post treatment images. Other investigators describe a fall in Tg. In a trial of 13-cis-retinoic acid in nineteen patients there was a decrease in Tg in six (32%) and no change in one (5%) [451]. The same investigators have increased their experience and reported on the results in fifty patients [88]. Thyroglobulin values decreased or stabilized in twenty patients (40%). The disparate Tg responses reported to point to a beneficial effect have been explained as follows. A rise in Tg could be due to the cancer redifferentiating and regaining the ability to produce and secrete Tg. A fall in Tg could be attributed to a reduction in cancer cells. Clearly both positions could be correct but the alternative explanations that a rise in Tg is due to cancer growth and a fall is due to dedifferentiation could also be correct. Therefore, Tg cannot be the only marker to judge success of retinoic acid. Increased uptake of radioiodine in lesions is a better indicator but the questions remains does that result in trapping of sufficient ^{131}I to produce a more successful treatment and a better outcome? Simon et al. answer yes, by demonstrating a response in six patients out of thirty-seven that could be

evaluated [88]. Not all responses were attributed to ^{131}I and retinoic acid was thought to have an independent action. In contrast Ain et al. could find no benefit in 12 patients [452]. Gruning and colleagues pretreated 25 patients with isotretinoin [453]. They found the response to be disappointing and conclude "an indiscriminate use of isotretinoin in all patients with otherwise untreatable thyroid cancer cannot be recommended."

Experimental studies confirm there are several forms of retinoic acid receptors, and they can function differently in various cancer lines [454]. There might be altered binding to the retinoic acid receptor elements or dysfunctional receptors. This could explain why some cancers respond and others do not [455].

Retinoic acid is prescribed in a dose of 1.5 mg/Kg daily for at least 5 weeks. The side effects are mainly to the skin, mucosa, and conjunctiva and include dryness of the mouth and eyes. When the patient finds these difficult to tolerate a reduction in dose to 0.75 mg/Kg to 1.0 mg/Kg can be tested. An increase in liver enzymes is an indication to stop this treatment. The treatment is not advised as a long time management strategy [456].

In summary the use of retinoic acid might produce a slight increase in ^{131}I uptake in a small percentage of patients whose cancers have lost their ability to concentrate iodine. There are troublesome side effects and its routine use is probably not advisable.

Increasing Retention of Iodine in Thyroid Tissue: Lithium

It has been recognized for many years that lithium prescribed for the treatment of bipolar disorders could produce alterations in thyroid function. When this was investigated, one of the actions was to inhibit the release of iodine and thyroid hormone from thyroid. This could provide an advantage when treating thyroid cancer, where there is little uptake by increasing the residency or $T_{1/2B}$ of the radioiodine. There are precedents for the use of lithium in the treatment of hyperthyroidism, where alone it has a minor role, but it increases the $T_{1/2B}$ of ^{131}I, and a lesser administered dose results in a higher absorbed dose to the gland [457]. The first patient with thyroid cancer who was pretreated with lithium was reported in 1976 [458]. Preliminary dosimetry studies demonstrated longer retention in the cancer, but when the patient was treated with ^{131}I there was an increase in blood radioactivity that was sufficient to cause depression of the marrow. The authors advised caution. Schraube et al. pretreated eight patients with a goal of a serum lithium level of 0.3 mmol/l to 0.9 mmol/l and six patients with higher doses to achieve serum values greater than 0.9 mmol/l [459]. They report that neither dose altered the uptake or retention of ^{131}I. The investigators concluded that the high TSH was responsible for the faster turnover. Ang et al. could not demonstrate an increase in uptake using lithium [460]. In contrast, two publications report an increase in $T_{1/2B}$ after ingestion of lithium. In the first uptake was measured without and then after lithium, and there was a statistically significant increase in that and in the $T_{1/2B}$ ($p < 0.001$). The authors state that lithium "could be helpful." The second positive report is from the investigators quoted above who advised caution, and they reported on the use of lithium in fifteen patients employed over twenty-three years since the original report [461]. They measured an increase in $T_{1/2E}$ of 50% (recall the relationship of $T_{1/2E}$ to $T_{1/2B}$ and $T_{1/2P}$) and suggest this could be a useful adjunct. I have not studied this in detail, but in the few cases when I have prescribed it, the uptake was still low and there appeared to be little benefit. The NIH researchers prescribed a dose of 600 mg followed by 300 mg three times a day with the aim of having a serum lithium between 0.6 mEq/l to 1.2 mEq/l. When that is achieved the tracer of radioiodine is administered. The patient should already have an elevated TSH and have been on a low iodine diet for two weeks.

In summary lithium has a minor role and may help in Tg positive low iodine uptake patient by prolonging the $T_{1/2B.}$ It is not advised in patients with bulky cancers.

Differentiated Thyroid Cancer Arising in Ectopic Sites

Cancer in Thyroglossal Tract

In early embryologic development the thyroid originates at the base of the tongue and migrates to the cervical position. By the seventh week, it

is in the normal anatomic position and approximately five weeks later it is able to function. The foramen cecum at the junction of the anterior 2/3 and the posterior 1/3 of the midline of tongue marks the site of original development. The route from the foramen cecum to the thyroid is the thyroglossal tract or because it is originally tubular it is also called the thyroglossal duct. The duct usually closes but can persist as a fibrous remnant. In some patients the thyroid fails to migrate inferiorly and remains in an undescended ectopic position. This can result in a lingual thyroid or functioning thyroid at some location between the foramen cecum and the cervical thyroid. The ectopic thyroid tissue produces a midline mass and the patient is frequently hypothyroid. A persistently elevated TSH causes further growth of the ectopic thyroid and further enlargement of the midline mass. In the case of lingual thyroid this leads to dysphagia, dysphonia, and dyspnea. More commonly the thyroid migrates to the correct position but the thyroglossal duct does not close off and cysts can develop at points along the tract which also results in a midline swelling that is situated between the foramen cecum and thyroid bed. About 80% are inferior to the hyoid bone. In order of frequency the common midline swellings in the neck are goiter, thyroglossal cyst, and ectopic thyroid. These midline (or almost midline) structures should not be confused with branchial cleft cysts or cystic hygromas that are lateral [462].

Thyroglossal cysts are lined by stratified squamous epithelium or ciliated pseudostratified epithelium. On occasion they contain microscopic foci of thyroid tissue. The reported frequency of this finding is markedly variable and some report thyroid is present in up to 60% of thyroglossal cysts. The differences most likely depend on how much effort is put into identifying the thyroid cells [463].

The work-up of a midline lesion should include thyroid function tests and an imaging study to determine whether the lesion is solid or functional. Ultrasound is simple and effective in demonstrating solid lesions that are ectopic thyroid or cystic lesions that are thyroglossal duct cysts. The ultrasound can also determine whether the thyroid is in its normal cervical position. Alternatively a thyroid scan using ^{123}I demonstrates function in the ectopic thyroid but not in the cyst because there are too few follicular cells to be imaged. Ultrasound is preferred to scintigraphy. Some authorities recommend FNA of thyroglossal cysts to identify the occasional cancer. However, this is more cost effective in older patients (16 years or older is a reasonable cut off), since cancer is rare in a thyroglossal cyst in a child as discussed below. At the time of editing the manuscript, a case report of thyroglossal duct cancer in a 15 year old with an extensive review of the literature confirm this [464]. The authors identified seventeen patients less than 16 years of age from the world literature, in contrast with the incidence of a thyroglossal remnant in 7% of normals.

The patient with an ectopic thyroid is treated with thyroid hormone to lower TSH and this often causes the thyroid tissue to shrink and it makes the patient euthyroid. Thyroid hormone has no effect on thyroglossal cysts and is unnecessary since these patients are usually euthyroid.

Thyroid cancers can arise in any site where there are thyroid cells. Therefore, they can occur in thyroglossal cysts and in ectopic thyroid. Cancers in thyroglossal cysts are more common, but these are still quite rare, and there are only a few publications with information on more than ten patients. In the mid-1970s there were about seventy case reports [465]. Heshmati et al. in their 1997 report of 12 patients indicated that there were fewer than 200 cases in the literature [466]. The first case they could find was published in 1915. A brief report in 2002 increased the number of cases to 250 [467]. There are many case reports several of which are referenced [468–475], but there are likely to be many unreported patients including five patients I have managed who are discussed below. In contrast there are only about thirty reports of cancer in lingual thyroid, so thyroglossal duct cancer is addressed first. There is a slight increase in the ratio of women but not to the degree of differentiated cancer in the thyroid itself (Table 6.12). The average age of the patients is about forty to forty-five years, and it is unusual to see this cancer in a patient of less than twenty years, although there are isolated case reports [476].

Diagnosis of thyroid cancer in a thyroglossal duct cyst is almost always a surprise. This was true in eleven of twelve patients at the Mayo clinic [466]. The patient has surgery because the

cyst is enlarging and cosmetically unsightly, or it has been infected. Infection can occur because of continuity of mouth flora and the cyst through a patent thyroglossal duct. The patient, surgeon, and pathologist are all startled by the finding of malignant thyroid tissue, usually papillary cancer. Because of this, some physicians recommend FNA of thyroglossal duct cysts, and when papillary cancer is identified the surgical approach is altered [477].

The literature indicates that 80% to 90% of thyroglossal cyst cancers are papillary. There are rare follicular, Hürthle cell, and anaplastic cancers [478]. In addition it is possible for cancer to arise from the squamous cells but a patient with squamous cell cancer would not be referred to an endocrinologist or nuclear medicine physician for management [479]. Reviews indicate that 5% to 7% of cancers in thyroglossal cysts are squamous in origin. There is even a report of a thirty-eight-year-old patient who had both squamous and papillary cancer in the cyst [480]. That patient received external radiation in addition to thyroidectomy and ^{131}I ablation. The authors of that case report reviewed thirteen other case reports concerning the treatment for and outcome of squamous cancer. Most had surgery and six of thirteen had external radiation. The prognosis was quite different from thyroglossal thyroid cancer in that four patients died. As would be understood from the difference in embryological development, there are no reports of medullary cancer in thyroglossal cysts.

In patients with differentiated thyroid cancer in thyroglossal cyst there is seldom a predisposing cause such as neck irradiation [466, 477, 481]. The question then is what should be done after the diagnosis is established pathologically? Because the situation is rare occurring in 1% to 2% of patients being operated on for thyroglossal cysts and accounting for less than 1% of those with thyroid cancers, there is not a large body of data. What is clear is that the correct operation for thyroglossal cyst whether benign or malignant is the "Sistrunk" procedure [482]. This involves removal of the thyroglossal tract from the base of the tongue, a small segment on the hyoid bone, the cyst, and the tract down to the isthmus of the thyroid. There is a very high recurrence when the cyst alone is removed. Some authorities state that the Sistrunk procedure is sufficient therapy for thyroglossal cyst cancer [481]. In contrast others recommend completion of thyroidectomy, yet others argue in favor of ^{131}I treatment after thyroidectomy. Review of Table 6.13 demonstrates that no patient with cancer in a thyroglossal duct cyst died from the disease, and almost none developed distant metastases. One of five patients I have managed a twenty-one-year-old man presented with a huge cancer in the thyroglossal cyst as well as palpable disease in the thyroid and regional nodes. Management of this clearly required surgical removal of the thyroid and regional nodes. Diagnostic whole-body scan with radioiodine demonstrated residual thyroid and local and pulmonary metastases, and he was treated with ^{131}I. In contrast, in a patient with an unexpected cancer in the thyroglossal duct cyst and no apparent residual disease is it necessary to complete thyroidectomy? The authorities at the Mayo Clinic and in Pisa recommend that it is [466, 477]. One reason for this is the theory that the cancer might have arisen in the thyroid and migrated along the thyroglossal duct into the cyst. Pathologically this is not a common finding. A coexisting cancer was found in the excised thyroid in only 25% to 33% of patients. When it is certain that the cancer is in a thyroglossal cyst and it has clear margins and is not a metastasis in a lymph node or a cystic cancer in the isthmus or pyramidal lobe, I question whether it is always necessary to

Table 6.12. Characteristics of patients with thyroglossal duct cyst cancers.

Reference	Number of patients	Women %	Men %	Mean age (range)
Doshi et al. [682]	14	57	43	39 (22–68)
Heshmati et al. [466]	12	50	50	40 (17–60)
Jaques et al. [465]	18	50	50	38 (15–56)
Miccoli et al. [477]	18	78	22	38 (21–67)
Patel et al. [483]	5	60	40	45 (27–63)
Personal	5	80	20	40 (21–55)

Table 6.13. Treatment and outcome of patients after the diagnosis of cancer in thyroglossal duct cyst.

Reference	Thyroid surgery (%)	Cancer in thyroid (%)	^{131}I (%)	Thyroid hormone (%)	Death (%)	Distant metastases (%)
Doshi et al. [682] 14 patients	57	38	71	86	0	7
Heshmati et al. [466] 12 patients	75	25 yes 50 no 25 NA	25%	83	0	0
Jacques et al. [465] 18 patients	22	25	NA	NA	0 1 patient NA 3 died from other causes	0
Miccoli et al. [477] 18 patients	100 1 patient had prior surgery	33	100	100	0	0
Patel et al. [483] 5 patients	80 Lobectomy Isthmusthectomy	0	0		0	0
Personal 5 patients	80	20	20	100	0	20

remove the thyroid in every patient. One of my patients had only the primary lesion removed and has no evidence of recurrence after twenty-five years. This is also the opinion of authorities at the Memorial Sloan Kettering Cancer Center [483]. Careful clinical examination and ultrasound of the thyroid are recommended to ensure there is no mass there and if not followup annually for several years would be reasonable. However, the presence of a palpable mass or a thyroidal lesion seen on ultrasound would bias the decision towards thyroidectomy. In the case of patients whom have clinically apparent metastases, such as the young man described above, thyroidectomy and removal of involved nodes is recommended. Post operatively scanning with radioiodine and treatment of functioning tissue with ^{131}I is advised.

Benign thyroglossal cysts are most likely to be operated on in childhood [484]. Thyroid cancer is most often found in patients sixteen years of age or older [464]. Therefore it is appropriate to obtain an FNA preoperatively in a patient with a thyroglossal cyst who is sixteen years of age or older. In the experience of some specialists this should identify almost all with intracystic cancer [477]. The true positive results are lower in other reports and 60% to 70% is a reasonable average. Then a decision can be made in the majority of patients preoperatively after clinical examination, FNA, and ultrasound of what would be the optimal surgical procedure. Review of the clinical findings the size of the cancer, ultrasound appearance of the thyroid, the age of the patient, and so forth can then allow an informed decision about the Sistrunk procedure or Sistrunk procedure plus thyroidectomy. There are reports of the use of CT and MRI to establish a diagnosis of cancer in a thyroglossal cyst [485]. The images show a small solid region at the site of the cancer, and in one report allowed six cancers to be differentiated from eighteen benign cysts. However, a tissue diagnosis is preferred and CT or MRI could be used in selected complicated patients after FNA diagnosis, when there is a need for preoperative staging. In most patients ultrasound and FNA will suffice.

In summary, cancer in thyroglossal duct cyst is rare. Most of these cancers are not suspected preoperatively. Because the cancers are more likely to be found in sixteen to sixty year old patients, FNA of a thyroglossal cyst is recommended in this age group. Thyroglossal cyst cancer is very rare in pediatric patients, and FNA is less helpful. The correct operation for thyroglossal cyst is the Sistrunk procedure. Distant metastases and death from this cancer are extremely rare. Therefore in patients with cancer that is fully excised and who have a normal thyroid clinically and by ultrasound, the Sistrunk operation is usually adequate. When there is also an abnormality in the thyroid that gland should be removed. In patients with

residual or metastatic disease after Sistrunk and thyroid surgeries testing and treatment with radioiodine should be considered.

Cancer in Lingual Thyroid

Maldescent of the thyroid resulting in lingual thyroid is very uncommon. There are approximately 400 reports. There are likely to be several unreported cases, including one I have discussed in a previous book but have not submitted for publication in a journal [486]. Cancer of this maldescended thyroid is very rare and Massine et al. identified and reviewed twenty-eight cases from the literature [487]. In contrast to cancers found in the thyroid gland and thyroglossal cysts only a minority found in the tongue are papillary cancer. Many of the early reports only describe the lesion as being a cancer or adenocarcinoma and there is no specific pathological description. When reports from 1970 onwards are reviewed the majority is follicular cancer and Masssine et al. could only identify one additional patient with papillary cancer [487, 488]. Since that analysis there are 3 more cases of papillary cancer in lingual thyroid [489–491]. The majority of patients with a lingual thyroid are hypothyroid because ectopic thyroid glands usually do not function like normal thyroid. In 80% or more the lingual thyroid is the only site of thyroid and in the vast majority it is benign. Therefore in most patients with a lingual thyroid, testing of thyroid function and obtaining a diagnostic scan with ^{123}I confirm these facts. Treatment with levo-thyroxine to keep the TSH at 0.2 mIu/L to 0.6 mIu/L should cause shrinkage of the tissue and return of general health to normal. When the lingual mass does not shrink or when it is bleeding or ulcerated, a biopsy should be obtained. The best treatment for cancer in the lingual thyroid is surgery. There is debate about the optimal operative approach. Some recommend an oral incision, others a lateral approach, and thirdly some indicate a transhyoid incision as best. The correct approach depends on the specific skills of the surgeon and the size and stage of the cancer. Because there can be edema in the base of the tongue and upper pharynx postoperatively, it can be necessary to conduct a prophylactic temporary tracheostomy. The goal of surgery is to remove all normal and malignant thyroid cells, but when the cancer is large and invasive the procedure will be damaging to the tongue. Therefore, early diagnosis is preferred. This unfortunately is usually not the case. As an example, the patient with lingual thyroid in our clinic was middle aged and hypothyroid. He had gone through life not recognizing his limitations until the mass caused severe symptoms. He had several fillings in his teeth so a dentist had looked in the mouth, but made no suggestion of referral for further work-up.

After surgical excision there is a role for scanning with radioiodine using the techniques discussed previously [492]. Abnormal uptake can be treated with ^{131}I. The patient presented by Massine et al. refused surgery and was treated with 111 mCi ^{131}I and then 200 mCi (4.1 and 7.4 GBq) ^{131}I. The lesion responded transiently but then grew, and when the patient agreed to have surgery the operative procedure was extensive. Early diagnosis and surgical treatment are stressed. The patient should then be treated for life with an adequate dose of levo-thyroxine and followed as for intrathyroidal cancer by scan and measurement of Tg.

Squamous cell cancer of the tongue is much more frequent and it would be treated by head and neck surgeons in collaboration with radiation oncologists and oncologists. These patients would not be referred to an endocrinologist. To confuse matters there are reports of squamous cancer overlying a benign lingual thyroid [493]. Each condition should be managed by the appropriate specialist.

In summary lingual thyroid is very rare. Benign lingual thyroid usually responds to adequate doses of levo-thyroxine. When there is failure to shrink or ulcerations or bleeding the mass should be biopsied. Thyroid cancer in that site should be treated by surgery the approach being dictated by the training and skill of the surgeon. Residual disease can be identified by scanning with radioiodine and ablated with ^{131}I. Followup scan and measurement of Tg are standard. Treatment with levo-thyroxine is required for life.

Malignant Struma Ovarii

Struma ovarii is an uncommon ovarian neoplasm. It is classified as a teratoma in which the predominant cell components are thyroid. Most authorities require that more than 50% of the

lesion consist of thyroid cells. Approximately 15% to 20% of clinically significant ovarian neoplasms are mature cystic teratomas. Five to 15% of these contain small elements of thyroid but do not meet the definition of struma ovarii [494]. About 2% of teratomas contain sufficient thyroid to be called struma ovarii and about 5% of these are malignant. Benign struma ovarii can be asymptomatic, they can present as an ovarian mass found on routine pelvic examination, they can have sufficient thyroid tissue that they cause thyrotoxicosis and they can cause ascites [495]. Ascites and pleural effusion has been described in patients with struma ovarii and is one of the causes of pseudo-Meig's syndrome (Meigs syndrome is limited to ovarian fibroma) [496]. When they are identified they should be removed surgically. The differentiation of malignant from benign struma ovarii is not straightforward. In teratomas unrelated cell types that could include bone, hair and teeth as well as thyroid intermingle. One of the requirements of a pathological diagnosis of cancer is invasion of one cell type into another. When does intermingling become invasion? In addition many thyroid cancers are low grade and do not show cellular atypia that would point to a diagnosis of malignancy. Some authorities require evidence of capsular or vascular invasion or peritoneal involvement to establish that a struma ovarii is malignant. Devaney et al. reviewed the histology of thirteen malignant versus forty-one benign struma ovarii [497]. They accept cellular features including nuclei with ground glass appearance, nuclear pleomorphism, nuclear grooves, or overlapping nuclei [497]. When there are distant metastases it is important to exclude thyroid cancer in the cervical position as the site of the primary cancer. If this can be confirmed the struma ovarii has to be malignant. To add further difficulty the tumor marker CA-125 has been reported to be significantly elevated in a patient who was found to have a benign struma ovarii [498].

When there is sufficient evidence to establish a pathological diagnosis of malignant thyroid tissue in a surgically removed ovary, the following questions need to be answered. Is the thyroid cancer a primary ovarian lesion, that is, malignant struma ovarii, or is it a metastasis from a thyroid cancer? Secondly, with excision of the ovarian mass has all of the cancer been removed? Thirdly, is there evidence of metastases from the struma ovarii? Thyroid cancer seldom metastasizes to the ovary but there are reports of this [499, 500]. In this situation there is a history of thyroid cancer and usually additional evidence of widespread distant metastases. The patient reported by Young et al. had an invasive follicular cancer twelve years before she developed abdominal swelling [499]. She also had a cerebral metastases. At laparotomy there was a 17 cm cystic ovarian tumor that contained malignant thyroid tissue. The pathologist should examine the ovary to determine if the thyroid cancer contains only thyroid cells or are there other components that would allow a diagnosis of struma ovarii to be made.

The answer to the second question is important for determining the extent of therapy. When the cancer has been completely removed surgically there is no need for additional surgery on the thyroid and there is no need for radical hysterectomy and bilateral oophorectomy in particular in young patients who wish to have children [501]. I have recommended no additional treatment than oophorectomy to 2 women who each had a small papillary cancer in a large volume of benign struma ovarii. Removal of the ovary and Fallopian tube should suffice. Some authorities support a more extensive surgery for patients who are postmenopausal. One of the arguments in favor of this is that in 6–10% of patients the lesions can be bilateral [502]. There are a number of case reports of one or two patients with malignant struma ovarii and in the majority the recommended fundamentals of treatment are as described [498, 501, 503–507]. Even in the case of benign lesions there should be followup because the pathology is not absolute as demonstrated by the case history presented in the next paragraph and an additional patient who developed a recurrence and distant metastases 6 years after removal of a "benign" struma ovarii [508].

When there are distant metastases it is important to undertake a thyroidectomy for two reasons. One to ensure there is no evidence of primary thyroid cancer [509, 510]. Secondly the patient is a candidate for treatment with ^{131}I. That therapy will not be trapped by metastases until the thyroid is removed. Distant metastases from a malignant struma ovarii are rare. None of thirteen patients in one series developed

metastases [497]. In 1983 Pardo-Mindan and Vasquez identified eighteen reports in the world literature [511]. My colleagues and I added another [509]. A forty-two-year-old woman presented with spinal cord compression at the level of T2. She had consulted with chiropractors and physicians about high backache for several years before and had been treated symptomatically. When she was admitted emergently she had a large expansile lytic lesion in and around T2. An urgent neurosurgical procedure was undertaken to support the spine, debulk the lesion, and obtain a pathological diagnosis. Frozen section diagnosis intraoperatively was metastatic follicular thyroid cancer. The surgical approach to stabilize her spine was through an anterior cervical incision and an expert thyroid surgeon was called to examine the gland intraoperatively but he could feel no abnormality. In retrospect, the patient had an ovary removed 14 months before. This had been interpreted to be a benign teratoma. Review of the pathology showed a struma ovarii, but there were not enough abnormal features to make a definitive diagnosis of malignant struma ovarii. In order to facilitate treatment of the spinal metastasis with ^{131}I the thyroid was removed. The operation was technically hazardous because of the high spinal cord symptoms and signs but was concluded successfully. No cancer was identified in the thyroid thus confirming the cancer consisting of thyroid cells had arisen from the ovary. The patient was treated with 200 mCi (7.4 GBq) ^{131}I on two occasions. She is now eighteen years from her original surgery and is neurologically intact and has an undetectable Tg. Coincidentally her daughter presented with papillary thyroid cancer fifteen years after the mother, but the primary lesion was thyroidal, and she is also well after two operations and one treatment with ^{131}I.

There are several other reports of malignant struma ovarii and the majority were papillary or variants of papillary cancer. A recent review of the literature indicated 46% were papillary, 29% follicular, 14% mixed papillary-follicular, and 11% follicular variant of papillary cancer [512]. The ratio of papillary to follicular is less than for cervical thyroid cancers. In general the follicular cancers are more likely to metastasize widely and they have the same predilection for the skeleton and lungs [494, 513]. In their summary of sixteen case reports of patients with distant metastases Tokuda et al. identified seven (44%) with skeletal, four (25%) with pulmonary, and, surprisingly, six (38%) with liver metastases. Some patients had metastases to more than one site [513]. Liver metastasis from cervical thyroid cancer is very rare and the high incidence with malignant struma ovarii is almost certainly explained by the ovary being the site of the primary lesion.

Patients with functioning metastases can be treated by removal of the primary lesion, the thyroid, and bulky metastases followed by ^{131}I using the protocol described previously using diagnostic scan with radio-iodine and measurement of Tg [504–506, 509, 514, 515]. A report by Chan et al. was similar to the personal case described above since the patient presented with a pathologic fracture at T8 [510]. There are reports of the use of rhTSH to stimulate uptake in this setting usually because the tumor mass and function secretes sufficient thyroid hormone that there is a rise in endogenous TSH [494, 516].

In summary, struma ovarii is rare and malignant struma ovarii is exceptionally rare. The pathological diagnosis is not straightforward because tissues in teratoma appear to invade one another. When the primary cancer has been excised totally, salpingo-oophorectomy is curative. When there are metastases it is necessary to remove the thyroid and then treat the metastases with ^{131}I. Followup of patients with metastatic disease includes whole-body scan with radioiodine and measurement of Tg. In patients who have undergone a thyroidectomy levo-thyroxine is necessary for life.

Thyroid in Atypical Positions

In the chapter on anatomy and physiology ectopic thyroid in regions such as the heart and trachea were described. The problem is to ensure such ectopic thyroid is not metastatic cancer, or invasive cancer. The pathologist can help by analyzing the histologic features with an emphasis on nuclear features. Should there be nuclear grooves, or pseudo-inclusions or papillary structures consideration must be given to the diagnosis of thyroid cancer. The thyroid should be examined clinically and by ultrasound and any nodule should be subjected to FNA. When a primary thyroid cancer is

identified thyroidectomy and ^{131}I are recommended. Only after the thyroid is determined to be normal and meticulous histological evaluation of the thyroid tissue shows no feature of cancer should the label of ectopic thyroid be used.

Follicular Variant of Papillary Cancer

The follicular variant of papillary cancer is the commonest histological subtype. It was fully characterized by Chem and Rosai [517]. There is a wide range of what proportion of papillary cancers are called follicular variant but 10% to 15% would be fairly accurate. To the uninitiated the histology looks like follicular cancer but careful evaluation of the nuclei show characteristic features of papillary cancer with nuclear clearing, overlapping nuclei, grooves, small nucleoli and pseudo-inclusions. There is some disagreement about the proportion of cancer that should be follicular in appearance before given this designation. Several accept 80% or more [517, 518]. Other authorities require there to be no non-follicular component [519, 520]. It is generally accepted that there is no prognostic significance of this pathological diagnosis. It behaves like the standard papillary thyroid cancer, and its management is exactly the same.

Tall Cell Variant of Papillary Cancer

Tall cell papillary cancer is a pathological variant that has important clinical implications. Microscopically, the cells are longer than usual and the disease tends to be more aggressive and results in more invasion, nodal metastases, recurrences, and a higher death rate. This variant of papillary cancer was first described in 1976 [521]. The length of the cells should be at least twice their breadth. Some authorities require 30% of the cancer cells to have this feature, others insist on 50% or more being this dimension. When these strict criteria are used and not the presence of a few tall cells, these comprise less than 10% of papillary cancers [522]. The cytoplasm is acidophilic and abundant. No difference in DNA ploidy has been documented. One study demonstrated a significantly higher expression of the proto-oncogene c-met in tall cell variants of papillary cancer compared with papillary cancer or follicular variant of papillary cancer [523]. The levels were highest in cancers with extracapsular spread and invasion of surrounding muscles. This could explain the more aggressive characteristics.

Clinical Features

Patients usually presents with a new thyroid nodule or increase in size of the thyroid. They are usually euthyroid. The mean age of the patients is older than for standard papillary cancer and the size of the cancer is larger. The first investigation in those with a new or enlarging thyroid nodule should be FNA. Establishing the diagnosis at this time is important since it points to a cancer that untreated can be very invasive and cause death. Therapy is designed to remove all cancer. Solomon et al. have addressed this issue [524]. They conducted a semi-quantitative investigation comparing cytologic features of 30 tall cell cancers and 32 papillary cancers. The presence of single cells, elongated cells with nuclear grooves and central nucleoli were statistically more common in the tall cell variant. When the diagnosis is established and testing is undertaken to define the extent of disease there is a high frequency of local invasion and metastases to regional lymph nodes. Several case reports describe the more extensive disease and poor prognosis [525–531]. On occasion the presence of local or a distant metastasis, for example, in the bone, can be the symptom that prompts work-up [532]. There are several reports of metastases to the breast and this is very rare with usual differentiated thyroid cancers [533]. There is even a report of tall cell cancer metastasizing to the pancreas [534].

Treatment

Thyroidectomy should be complete and abnormal lymph nodes removed by modified neck dissection. Residual functioning thyroid should be ablated with ^{131}I. These cells are often lacking NIS and might not trap radioiodine efficiently

and hence there can be residual disease that is not identified on scan. This results in a patient who is scan-negative, Tg positive and raises the therapeutic dilemma presented earlier in the chapter. A fifty-seven-year-old woman was found to have metastatic thyroid cancer in a right-sided neck lymph node. She had a total thyroidectomy and regional nodal dissection. There were two cancers in the thyroid and evidence of extra-capsular invasion. Nineteen of twenty-six lymph nodes contained cancer. The cells had acidophilic cytoplasm and were twice as long as broad and classified as tall cells. The patient had recurrent disease treated by surgery ten months later and there was invasion into muscles of the neck and seven regional nodes were involved with cancer. In spite of these operations, two treatments with ^{131}I, a third surgery, external radiation, and systemic chemotherapy the cancer grew relentlessly in the neck and thoracic inlet, and she developed pulmonary metastases. She died of the cancer five years after presentation. It was doubly unfortunate that during her terminal illness all efforts to have her seventy-plus-year-old sister visit her from Vietnam, including television interviews and letters to the White House fell on deaf ears. This case confirms that tall cell cancer can be a lethal disease.

Prognosis

Because of the aggressive nature of the cancer and its propensity to metastasize this is one variant of papillary cancer from which patients die [535].

In summary tall cell cancer is defined by cells whose length is more than double their width. The cancer is more aggressive than usual papillary cancer. Local invasion, regional and distant metastases are more common. Treatment should be designed to remove all cancer by surgery followed by ^{131}I treatment.

Columnar Cell Variant of Papillary Cancer

This cancer is also associated with a worse prognosis. The classification as columnar depends on histologic criteria described below. It is generally accepted that columnar cancer was originally described by Evans et al. who described two patients with this aggressive variant of papillary cancer [536]. Both patients died within two years of diagnosis and one had nodal metastases the other distant metastases at presentation. Some sources suggest this is more common in men, but I could not confirm this in analyzing the literature. Most publications describe only one or two patients and more are women. The cancerous thyroid cells look like respiratory epithelium. The pathological hallmarks are columnar shape of the follicular cells, nuclear pseudostratification, prominent papillations, cytoplasmic clearing, and subnuclear vacuolization that also looks like secretory endometrium [537]. By contrast tall cell cancers have a more eosinophilic cytoplasm their nuclei, they are more like the usual papillary cancer and there is no pseudostratification of nuclei. The unusual columnar pathology might raise question whether the cancer is a metastasis from adenocarcinoma of the nasopharynx, lung, ovary, or colon. Columnar cell cancer is positive for Tg and TTF-1, the other cancers are not. Occasionally it can be misinterpreted as medullary cancer but immunostaining for Tg, TTF-1 and calcitonin differentiates these [538].

Clinical

The patient is usually elderly and has a new thyroid nodule that is hard and irregular. Thyroid function is normal. The key is to establish a tissue diagnosis before surgery so that total thyroidectomy rather than lobectomy is undertaken. This is a rare variant and there are only a small number of reports of diagnosis by FNA [539–541]. The patients often have metastases at presentation and in that case the prognosis is poor [542]. The site of metastasis can be atypical such as the parotid [538].

Treatment

Early and accurate diagnosis with excision of all cancer by total thyroidectomy and eradication of residual functioning thyroid by ^{131}I is important for better survival.

Prognosis

This cancer has a significantly poorer prognosis than papillary thyroid cancer and many of

the patient reports end with death [536, 542, 543].

In summary columnar cell variant of papillary cancer of the thyroid is very rare. The diagnosis is based on histopathological criteria. The cells are tall and look like respiratory epithelium. The cancer has a propensity to invade and metastasize locally and distantly. The treatment is total thyroidectomy and ^{131}I. The prognosis is poor.

Solid or Trabecular Variant of Papillary Cancer

Histologically as the name indicates, this cancer consists of solid nests of thyroid cells. Most agree that 70% of the cancer should be solid for this designation. The nuclear features are typical of papillary cancer including nuclear clearing, pseudoinclusions, and nuclear grooves. This pathologic appearance has been described in children exposed to radioactive fallout from Chernobyl. Histologically the cancer is made up of nests of solid follicular cells that have nuclei that are typical for papillary cancer. There is usually little or no evidence of necrosis and there are few mitotic figures. Local invasion is common. There is a strong correlation with RET/PTC3 rearrangement in children with radiation-associated cancer [544]. In sporadic cases this is not found and there is a similar percentage of patients with RET/PTC1 rearrangement as in classical papillary cancer.

Clinical

The patient is more likely to be a child or young adult. Ten of twenty patients (50%) in a report from the Mayo Clinic were less than thirty years of age [545]. There is a 3:1 ratio of women to men. The patient presents with a nodule and there might be a history of exposure to radiation. FNA should be conducted and typically it shows features of papillary or follicular variant of papillary cancer [546].

Treatment

The patient should undergo a total thyroidectomy with removal of abnormal nodes. Postoperative treatment with ^{131}I to ablate residual thyroid and metastases is usually recommended.

Prognosis

The outcome is inferior to classical papillary cancer and there is higher probability of distant metastases. The outcome is better than insular cancer. In one report there was 90% survival after an average followup of 18.7 years [545].

In summary solid variant of papillary cancer is not common except in children whose cancers are secondary to radiation exposure. The treatment is the same as for classical papillary cancer including total thyroidectomy, surgical removal of pathologically involved nodes and ^{131}I. The followup involves diagnostic whole-body scan with radio-iodine and measurement of Tg. There is a greater propensity for solid cancer to metastasize to lungs or skeleton and the prognosis is less satisfactory than standard papillary cancer.

Insular Cancer or Poorly Differentiated Cancer

Insular cancer, like Hürthle cell cancer, lies pathologically and clinically between differentiated thyroid cancers and anaplastic cancer. The term, insular is attributed to Carcangiu et al. [547]. This is often called poorly differentiated thyroid cancer. That designation is somewhat nonspecific and I prefer the term insular. The descriptive term "poorly differentiated insular cancer" is used by some pathologists as a single phrase and that also makes the designation more specific. Some authorities state that insular cancers account for 4% to 6% of thyroid cancers, but I think this is an over estimation. In my experience it accounts for less than 1%. The patients are usually forty to sixty years of age, but there are reports of children as young as ten years and adolescents with this diagnosis [548–550]. There is approximately a 2:1 ratio of women to men.

Clinical

The lesion usually presents as a thyroid mass. The lesions are frequently large and cause local pressure and dyspnea and dysphagia. The

patient should be referred for FNA to obtain a tissue diagnosis. The cytological features to make a diagnosis of insular cancer are not straightforward. In part this is due to the rarity of the condition, many pathologists have not encountered this type of cancer. In part it is due to some cancers containing mixed lesions with papillary and insular, follicular and insular, or anaplastic and insular cancers. In part it is due to nonspecific cytopathologic findings. Articles that report on cytopathological features indicate that the specimen is cellular and there is little or no colloid [551]. The cells are small and similar in appearance. The nuclei are round and smooth and nuclear inclusions and grooves are uncommon. The cytology is often reported to be a microfollicular lesion or high-grade microfollicular lesion. Occasionally the cells are sufficiently abnormal to be classified as anaplastic cancer. It has been recommended that when nests of cells 0.2 mm to 0.4 mm in diameter are noted on a cytology specimen that insular cancer is likely [552].

In patients with a thyroid nodule, although FNA is the preferred first test, many physicians continue to order a scintiscan. Insular cancers are usually cold on scan, although there are some exceptions. One report indicated that the nodule was functioning and caused hyperthyroidism. This was due to an activation of the TSH receptor resulting from a mutation in codon 633 [553]. Guanine at position 1896 was replaced by cytosine and CAC instead of GAC substituted aspartic acid for histidine. There was some debate about the classification of this cancer pathologically, but the figures presented in the article are convincing to me as a nonpathologist [554].

Some patients with insular cancer present with distant metastases [555]. These are usually to the lung and or skeleton. A very unusual case of myocardial metastases caused acute demise [556]. In one study designed to determine factors that led to distant metastases from differentiated thyroid cancer, Decaussin et al. found insular histopathology to be important [557]. They reviewed 1,230 patients with differentiated thyroid cancer and determined that 111 had or developed distant lesions. They were able to review the pathology in eighty patients. There were four pure insular cancers (5% [4/80] or (0.3% [4/1230 of total group]). However, an insular component was found in forty-five of the eighty pathological specimens. The odds ratio of distant metastases when there was an insular component was 17 ($p < 0.0001$). The cancers tend to be large and there is a higher incidence of capsular and vascular invasion than with well-differentiated thyroid cancers. Some consider insular cancer to be a variant of follicular cancer. Histologically there is little colloid and the cells form islands (insulae) separated by connective tissue and fibrovascular bundles. In some cases the islands are created by artifactual boundaries. Frequently there are areas of necrosis. The cells are small; there is high mitotic activity. There are usually no nuclear grooves, or nuclear inclusions. Nucleoli are not prominent. The cells stain positively for thyroglobulin and do not stain for calcitonin.

One study in forty-six specimens with insular features demonstrated a mutation in the p53 gene [558]. p53 is a cancer suppressor gene and mutations are found in several human cancers. The investigators found that the mutation rate was 38%. p53 normally has 11 exons and mutations were identified in exons 5, 6, 7 and 8. The mutation was a base substitution that resulted in the exchange of an inappropriate amino acid. A second investigation found a high rate of mutations in the N-Ras gene, usually a substitution of CAA with AAA [559]. These cancers are not anaplastic, however, because its definitive description is fairly recent, retrospective reviews of anaplastic cancers can result in some specimens being reclassified as poorly differentiated insular cancers. This was the case in five of thirty-five cases in one report [560]. Four of the patients were treated with ^{131}I and metastatic lesions in one patient responded.

Management

When the diagnosis is established, the standard therapy is total thyroidectomy, removal of suspicious cervical lymph nodes and postoperative radioiodine ^{131}I. The fundamentals have been described earlier. In practice it is not uncommon for the patient to have a lobectomy because the cytopathology demonstrated a microfollicular lesion and not a definitive cancerous pattern. In this situation, completion of the thyroidectomy is recommended. Total thyroidectomy results in minimal thyroid tissue being left and diagnostic whole-body scanning and

therapy with ^{131}I are facilitated. The patient should have an elevated TSH, be ingesting a low iodine diet and when the patient is a woman of child bearing age, there needs to be proof of a negative pregnancy test. Serum Tg should be measured and that value used as a baseline for comparison with followup studies. There is no consensus that all insular cancers and their metastases trap iodine. However, there are reports of distant metastases, including skeletal metastases demonstrating uptake [561, 562]. When the cancer is locally invasive and it appears from diagnostic and post therapy scintigraphy with radioiodine that the extent of disease imaged is an under-estimation of the disease expected, external radiation should be prescribed.

Followup includes physical examination, measurement of thyroid function, and Tg and repeated whole-body scan. When there is uncertainty about the stage or extent of disease, ^{18}F-FDG PET scan should be considered. The published data, although limited, indicate that PET has a definite role [563]. There are isolated reports of ^{99m}Tc-Tetrafosmin [564], ^{99m}Tc-Sestamibi [565] and ^{99m}Tc-DMSA [566] for imaging insular cancer, but PET is preferred. In reference [564] the Tetrafosmin scan shows more lesions and demonstrates them better than the diagnostic ^{131}I scan. Unfortunately the authors do not show a post treatment scintiscan.

The following case report is illustrative of this disease. A thirty-four-year-old woman noted a subtle increase in dyspnea, which was worse after exercise. She also noted a vague difference when swallowing. At a physical examination a left thyroid nodule was discovered. A fine needle aspiration showed a follicular lesion, and she had a left lobectomy. The mass was $4 \times 4 \times 4$ cm and there was capsular, vascular and lymphatic invasion. At the time she was far removed from academic medical centers, and the slides were reviewed at the Armed Forces Institute of Pathology, and the diagnosis of insular cancer was determined. Her physicians made conference calls and received a consensus of advice to complete the thyroidectomy and to conduct modified bilateral neck dissections. The patient was then referred to Stanford. She had not been taking thyroid hormone and her TSH was greater than 100 mIu/L, the Tg was 23 μg/l. Plasma inorganic iodine was below normal, this was measured because she had received two injections of contrast for CT scans at the time of her workup and surgeries. The pregnancy test was negative. Diagnostic whole-body scans twenty-four hours after 74 MBq ^{123}I demonstrated minimal uptake in the mid-line. Positron emission tomography scan also showed no abnormal uptake in the neck. The patient was treated with 150 mCi (5.5 MBq) ^{131}I, and the posttherapy scan showed similar distribution. The large size of the cancer, the presence of symptoms, capsular and vascular invasion, and locoregional metastases are typical.

Prognosis

Patients with insular cancer of the thyroid have a prognosis that is worse than papillary or follicular cancer, but better than anaplastic cancer. Because there are few large studies and many reports are single case reports it is hard to get a definitive answer. However, because of the aggressive nature of the cancer and its potential for local and distant spread, there is an argument for more complete surgery and larger doses of ^{131}I to try and remove all cancer cells at the time of presentation. A report in a fifty-six-year-old woman with an 8 cm cancer treated by total thyroidectomy, 100 mci (3.7 GBq) ^{131}I and external radiation indicated that she was alive 6 years later [567]. One report in a fourteen-year-old adolescent indicated a good outcome after twenty-four years [568]. In contrast a sixteen-year-old adolescent treated by surgery and several doses of ^{131}I (cumulative 725 mCi [19.6 GBq]) died with brain, spinal cord, mediastinal, and lung metastases after 31 months [569]. Flynn et al. described recurrences and metastases in three of four patients. These three patients died within two years [570].

In summary, insular cancer arises from follicular cells and the pathology shows islands of cells separated by thin fibrovascular fronds. The diagnosis is difficult to make by cytology, but large (>0.2 mm) nests of cells should raise that possibility. Treatment is total thyroidectomy, removal of involved lymph nodes, and ^{131}I treatment. Followup includes radioiodine scan, measurement of Tg. In the long-term the TSH should be as low as can be tolerated by the patient. In selected patients PET scan is valuable to identify lesions not seen on radioiodine scintigraphy. In patients with incompletely

excised or ablated cancer external radiation has a role.

Variants of Follicular Cancer: Hürthle Cell Cancer

Hürthle cells are follicular cells, which are large and have an intense eosinophilic cytoplasm [571]. The cells were first described by Askanazy and sometimes are referred to by his name. Other terms are oncocytic or oxyphil cells. Some early reports on neoplasms of these cells use the terms oxyphil or oncocytic tumor [572]. Hürthle cells also occur in the thyroid in a variety of benign conditions including Hashimoto's thyroiditis, and Graves' disease in addition to neoplasia. There is now no doubt that this is a follicular cell with abundant cytoplasmic mitochondria [573]. The cells appear microscopically to be very active but paradoxically they usually do not trap iodine. Hürthle cell cancers develop from follicular cells and they appear pathologically to have the general structure of follicular cancer and many authorities classify these as variants of follicular cancer [574]. Because their behavior, such as the ability to trap iodine is usually lacking, the age of the patient is older, the behavior of the cancer more aggressive and their management different this cancer merits separate discussion. For these reasons some authorities classify Hürthle cell cancers separately from differentiated thyroid cancer [575]. Hürthle cell cancer is included here by convention. The main controversies are: (A) How to distinguish Hürthle cell carcinoma from Hürthle cell adenoma, both on FNA and on final pathology, and (B) How best to treat and follow patients with proven Hürthle cell cancer. It has been stated that that one of the most controversial subjects in thyroid pathology is the area of Hürthle cell tumors [576]. Pathologists do agree that the majority of follicular cells in the cancer must have oncocytic features and Rosai et al. require more than 75% [577]. In order to establish that the lesion is cancerous, it is necessary for there to be evidence of regional or distant metastases or pathologically for the lesion to have angioinvasion or capsular invasion. The pathologists at the Memorial Sloan Kettering Cancer Center use three categories of malignancy. These categories are widely invasive cancer, minimally invasive cancer, and tumors of unknown malignant behavior [578]. The difference between the first two relates to the degree of vascular and or capsular invasion. Widely invasive cancers have more than one site of capsular and or angioinvasion. The invasion should also be definitive. In their experience 88% had both angioinvasion and capsular invasion. Diagnostically none of these distinctions can be determined on FNA. There has been an effort to identify criteria on FNA that would allow a diagnosis of Hürthle cell cancer and exclude Hürthle cell adenoma or Hürthle cell metaplasias [579]. The FNA characteristics include sparse colloid, preponderance of Hürthle cells, small cell size compared to the size of the nucleus, crowding of nuclei, single cells, nuclei with irregular outlines, and prominent nucleoli. This approach has been criticized because the features that allow 100% of cancers to be identified also are present in 67% of adenomas and 25% of nonneoplastic Hürthle cell accumulations [580]. The definitive diagnosis depends on histopathology. Nevertheless FNA showing a preponderance of Hürthle merits strong consideration for surgical intervention. When there are a few Hürthle cells and abundant lymphocytes Hashimoto's is the most likely diagnosis. Even with excisional biopsy one pathologist's description of capsular invasion might not cross the threshold of the next pathologist and the same applies for angioinvasion. Rosai et al. require complete penetration of the capsule and projection of tumor cells into the vessel lumen to establish these criteria [581]. I have consulted on two patients, one whose original lesion was judged to be a benign Hürthle cell lesion but he died from metastases. On review the thyroid tumor was judged by a second pathologist to demonstrate significant angioinvasion. The second patient underwent lobectomy for a thyroid nodule and then was advised to have completion of thyroidectomy and treatment with large doses of ^{131}I (sufficiently large that she developed bone marrow insufficiency) based on the pathologist's interpretation of capsular invasion. Subsequently two other pathologists could not confirm this finding. Thomson et al. have reported the development of metastases in patients whose original pathologies were reported to be benign [582]. The message is that the differentiation of benign from malignant

Hürthle cell neoplasm is not straightforward and a second opinion is warranted in borderline cases. When there is some uncertainty this should be discussed with the patient and a consensus reached about management. Therefore, the reporting system by investigators at the Sloan Kettering Cancer Center by considering the spectrum from Hürthle cell adenoma, to tumors of unknown malignant behavior, minimally invasive carcinomas, and widely invasive carcinomas has merit [578]. This allows the role of treatments and other prognostic facts to be judged in patients with similar extent of disease.

Tall cell variant of papillary cancer can sometimes be difficult to differentiate from Hürthle cell cancer.

Clinical

The patient usually presents with a thyroid nodule. Although these cancers tend to be larger at time of diagnosis this is not specific. There is usually no way of differentiating this nodule clinically from other thyroid cancers. The average age of the patients is fifty to sixty years and there is a 2:1 ratio of women to men (Table 6.14). These characteristics overlap with conventional differentiated cancer. Uncommonly a metastatic lesion is the feature that brings the patient to medical attention. This was true of 9% of the patients reported by Lopez-Penabad et al. [583]. Thyroid function is usually normal. Between 10% and 20% have a history of neck irradiation.

Diagnosis

The work up includes measurement of FT_4 and TSH and obtaining a FNA. When the report of the FNA report comes back it will generally be worded, Hürthle cell neoplasm, it is not possible to differentiate Hürthle cell adenoma from Hürthle cell carcinoma: recommend surgical excision. Hürthle cells are characteristic of Hashimoto's thyroiditis; therefore, when there are accompanying lymphocytes, measurement of serum thyroid antibodies can be helpful.

Treatment

Once the diagnosis of a Hürthle cell neoplasm has been made, surgery should be conducted. The dilemma is whether to advise a lobectomy versus total thyroidectomy. The authorities from the University of Michigan recommend a simple decision mechanism, when the lesion is greater than 2 cm, they accept it is a cancer and remove the entire thyroid [584]. This is based on finding metastases on followup in three of twenty-six patients whose pathology was judged to be benign but who had large lesions. These patients developed metastases.

Most authorities advise total thyroidectomy for invasive Hürthle cell cancer, but the problem is that the FNA does not diagnose cancer and frozen section evaluation of the lesion is more difficult than examination of slides from the paraffin blocks. In one study of forty-nine patients with proven Hürthle cell cancer and sixty-seven with Hürthle cell adenoma, intraoperative frozen section diagnosis was correct in 19% and indeterminate in 75%. A second differentiated thyroid cancer was identified in 6% [585]. There were no false negative results. Therefore the frozen section can help determine the extent of operation in one-fifth of patients. This can result in only a lobe being removed and the need to complete the thyroidectomy when the final pathology confirms features of cancer. I would not like two thyroid operations, and most of my patients would prefer only one thyroid operation. Therefore, the advice from Michigan has much practical merit. That eliminates the need for completion of thyroidectomy,

Table 6.14. Patient characteristics of Hürthle cell cancers.

Reference	Number	Age mean (range)	% Women	% Men
Lopez-penabad et al. [583]	89	52	67	33
Stojadinovic et al. [592]	56	56 (9–94)	61	39
Thomson et al. [582]	25	50 (26–76)	68	32
Watson et al. [575]	29	55.5 (32–75)	67	33
Tollefsen et al. [683]	35	Largest number between 51–60	57	43
Dahl et al. [585]	49	55	67	33

and the entire gland can be examined pathologically. Hürthle cell cancers can be multifocal and can occur along with papillary cancer. Authorities also recommend that residual tissue be ablated by ^{131}I to remove all possible sources of potential thyroid cancer and to make evaluation of Tg easier [583]. I question this advice for all patients. It is reasonable to prescribe ^{131}I in patients with large cancers, widely invasive cancers, those with high Tg values after surgery, and those with local invasion. Metastases from Hürthle cell cancer seldom trap radioiodine; therefore, this therapy is generally of no benefit when the cancer has spread. A diagnostic scan will determine whether lesions are capable of being identified and treated in patients with high Tg levels. In one report three of thirty-three patients with known bone metastases and two of twenty-seven with pulmonary metastases had uptake of ^{131}I.

What is the best method of finding invasive or metastatic lesions that produce Tg? ^{18}FDG-PET has excellent sensitivity and specificity and is recommended when there is suspicion of metastases. One of the original reports used ^{18}FDG and a gamma camera [586]. A dedicated PET camera or PET/CT is preferred. A sensitivity of 92% specificity of 80% and accuracy of 89% was calculated in an analysis of seventeen patients, most of whom had elevated Tg [587]. A second report indicated that PET identified lesions in seven of fourteen scans that had not been found by any other imaging tests [588]. The uptake of ^{18}FDG is usually intense. When PET is not available ^{99m}Tc-Sestamibi can be useful. The intracellular uptake of ^{99m}Tc-Sestamibi is into mitochondria and Hürthle cells are packed with these. There are several reports of the value of ^{99m}Tc-Sestamibi in identifying and staging Hürthle cell cancer [395, 589, 590]. ^{201}Thallium (^{201}Tl) has also been used but with less success [395]. Hürthle cells express somatostatin receptors and can be imaged with ^{111}In-octreoscan [591]. When there is intense uptake of this radiopharmaceutical it raises the possibility of treatment with analogues of Octreoscan labeled with β emitting radionuclides.

Once the site, or sites of metastatic cancer are identified a decision about surgery versus external radiation can be made based on the location of the lesion. There is evidence that such approaches can extend survival but will not result in cure. In patients with widespread disease chemotherapy using doxorubicin and cis-platinum can be considered but the cancers are not very responsive.

Prognosis

Bad prognostic characteristics are cancers larger than 4 cm, presence of extensive capsular and angioinvasion, lymph node, and distant metastases. When reviewing published series it is important to separate minimally from extensively invasive cancers. Thirty-five percent of the patients studied by Watson et al. died of their cancer and bad prognostic features were lymph node metastases, high-grade histology, and local invasion [575]. None of their patients had distant metastases at presentation, but this has previously been shown to be bad. No patients with lymph node metastases at presentation lived 8 years and 77% who developed distant metastases also died [592]. Some series indicate that older patients have a poorer prognosis.

Summary

Hürthle cell cancers are uncommon and they should be diagnosed when greater than 70% of cells are oncocytic and there is capsular and or angioinvasion. They have a worse prognosis than standard differentiated thyroid cancer. The cells usually do not trap iodine but they do produce Tg. Complete excision usually by total thyroidectomy is the key to a good prognosis. ^{18}FDG is useful to identify metastases that do not trap iodine. Hürthle cell cancer should be classified separately from differentiated thyroid cancers because of differences in pathology, natural history, response to therapies, and prognosis.

Mixed Columnar Cell, Tall Cell, and Hürthle Cell Variants

There are a few reports of thyroid cancers showing histopathologic features of columnar and tall cell variations in different segments of the cancer [593]. There are also reports of mixed tall cell and Hürthle cell variants diagnosed by FNA and histology [594, 595]. Patients with these cancers have a worse prognosis and merit

more aggressive therapy with total thyroidectomy and treatment with ^{131}I.

Familial Differentiated Thyroid Cancer

It has been recognized for several decades that medullary cancer and multiple endocrine neoplasia (MEN 2A and 2B, [or 3]) can be familial and the genetics are well defined [596]. This is discussed in Chapter 5 on etiology of thyroid cancer and Chapter 10 on medullary cancer. Although familial differentiated thyroid cancer was described more than fifty years ago, it is only recently that the significance of non-medullary thyroid cancers demonstrating familial aggregations has been widely recognized [597–604]. The term familial differentiated thyroid cancer would appear better than familial non-medullary cancer but they are interchangeable [605, 606]. In the author's clinic there are twenty known families with two or more first-degree relatives with differentiated thyroid cancer. When two members of a family have the same cancer this could be the result of chance, it could be due to a common etiological factor, or there could be a genetic cause [607–609]. It could also be that a family with a genetic predisposition to thyroid cancer would be more susceptible to an etiological insult such as external radiation. Among the twenty families there is one with two brothers who received head and neck irradiation in childhood. When the number of relatives with thyroid cancer increases, the probability of a genetic factor also increases, and chance becomes less important. Several families reported in the literature stand out [610, 611]. One patient I consulted on had four maternal relatives, two sisters, her mother, and maternal grandmother, as well as a paternal uncle, with thyroid cancer. When there are three members of the family with thyroid cancer chance becomes increasingly unlikely [612, 613]. Several studies demonstrate that when one person has thyroid cancer, that is thought to be sporadic, there is a five to ten times increase in likelihood that a first-degree relative will also have thyroid cancer [614, 615]. This is expanded in Chapter 5 on etiology. Many investigators have searched for the responsible gene but there is no single culprit. A genetic link found in one family is not present in others [616, 617]. One study of eighty families showed that a susceptibility gene localized to chromosome 2q21. A detailed review of all the genes that have been implicated is found in reference [618].

There is some evidence that familial thyroid cancer is more aggressive and has a less good prognosis [599, 619]. Uchino compared the outcome of 258 families with two or more differentiated thyroid cancers with 6200 sporadic cases [600]. The numbers of patients are compelling, and 4% of the series were familial (258/6458). They found a significant increase in multifocal disease, 40.7% vs 29.8%, and recurrence rate. 16.3% vs 9.6%. There was no difference in survival. A second publication also compared familial cases with age and gender matched controls [619]. Patients who had a family history and a distant metastasis and those with several cancers in the family had poor survival. This is not borne out by the followup of my patients. One did die when the cancer dedifferentiated but that patient was one who had received external radiation.

Familial differentiated thyroid cancer can be part of syndromes such as familial adenomatous polyposis, Cowden's disease, Gardner's syndrome and Peutz-Jegher syndrome [613, 620–622]. We have reported on an association with osteogenic sarcoma [623].

Because familial thyroid cancers are more likely to be multifocal and the perception is that they have a less good prognosis there is more strength to the recommendation for total thyroidectomy. When the cancer is large and there is local invasion or nodal or distant metastases ^{131}I ablation is advised. When one family member has proven thyroid cancer and a second member has a thyroid nodule it is important to obtain a tissue sample by FNA. When three or more relatives have proven thyroid cancer there should be a prospective evaluation of the thyroids of close relatives.

Summary and Key Facts

Differentiated thyroid cancers make up the majority of thyroid cancers and in iodine replete regions papillary cancers predominate. The diagnosis is made by FNA of a thyroid nodule. Treatment is total thyroidectomy and in

selected patients ^{131}I. The patient should take levo-thyroxine for life. The prognosis is excellent in most patients and staging systems, such as TNM, and prognostic indices, such as MACIS, AGES or AMES, help predict the outcome with considerable accuracy.

- Cancers of follicular cells are classified as differentiated based on histopathology findings.
- These cancers look similar to and have some functional characteristics of normal thyroid cells.
- The most common differentiated cancer is papillary in type.
- Papillary cancers grow in fronds with vascular bundles and the nuclei have grooves, pseudoinclusions, and "Orphan Annie" appearance.
- Papillary cancers are multifocal and spread to regional lymph nodes.
- Follicular cancers are commoner in regions of iodine deficiency.
- Follicular cancer is diagnosed when there is vascular invasion, capsular invasion, or metastasis.
- Follicular cancer is usually single, and when it metastasizes it does so to the lung and skeleton.
- Treatment is total thyroidectomy, which is followed by fewer recurrences than lobectomy.
- Complications of surgery are hematoma, death, recurrent laryngeal or superior laryngeal nerve paralysis, hypoparathyroidism, and keloid scar.
- Post operatively ^{131}I or ^{123}I can be used for a diagnostic whole-body scan to determine how much residual tissue or functioning metastasis are present.
- Recognition of potential false positive scans is important.
- The patient should have an elevated TSH and low plasma inorganic iodine when diagnostic scan or treatment with ^{131}I is undertaken.
- TSH elevation is achieved by withdrawing levo-thyroxine or injection of rhTSH.
- Low plasma inorganic iodine is achieved by two weeks of low iodine diet.
- Residual thyroid tissues can be ablated with ^{131}I.
- There is no evidence to prove that ^{131}I is beneficial in a patient with a small cancer that has been fully excised.
- Iodine-131 is usually well tolerated but can cause swelling and pain in the salivary glands and a dry mouth.
- Large doses of ^{131}I can cause suppression of the bone marrow and there is some evidence of an increase in breast cancer.
- Followup using whole-body scan and Tg measurement is excellent for defining absence or presence of disease.
- When the radioiodine scan is negative and Tg positive some authorities treat with a large dose of ^{131}I.
- Alternatively the site of cancer can be identified by ^{18}FDG and treated by surgery or external radiation therapy.
- Several variants of differentiated cancer including tall cell, columnar cell, solid trabecular, and insular have a worse prognosis.
- Hürthle cell cancer is considered a variant of follicular cancer but should be a separate category based on features such as its inability to trap iodine.
- Familial differentiated thyroid cancer is recognized but the exact method of transmission is not clear, and no single gene has been incriminated.

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Chapter 7

Differentiated Thyroid Cancer in Children

The news that a child has cancer is devastating to the patient and often more so to his or her parents. Therefore, it is essential that the patient and family be treated with utmost sensitivity. Thyroid cancer in children is rare. As a result most physicians, whether they are pediatricians, surgeons, endocrinologists and nuclear medicine physicians have little experience with its diagnosis and management. The earliest sign of uncertainty and insecurity of the physician is quickly recognized by both the child and parents. When the treating physician has discomfort, the patient should be referred to a center where there is more experience. Although the types of differentiated cancer and the fundamentals of treatment are similar to the adult situation, there are several differences, and this chapter is written so that it can be read without cross-reference to the prior chapter that deals with the adult. This results in some overlap, but I make no apology for that. The causes of childhood cancer are discussed briefly, and those interested in more details and references can find them in Chapter 5. The first major difference is that thyroid cancer in the pediatric patient is usually more advanced. The primary cancer is larger; it is more likely to be multifocal and locally invasive. A much higher proportion of patients have regional metastases to cervical lymph nodes and distant metastases to the lung. In spite of these adverse characteristics, the prognosis is very good. The second difference is there are few surgeons trained in the skills of conducting total thyroidectomy in children. Thus either too much thyroid is left, or the complication rate is too high. The next difference is that the morbidity from complications of surgery, or ^{131}I, in young active patients is going to be problematic for many decades. Finally the recurrence rate is higher than in adults.

Parents are usually very concerned when treatment with ^{131}I is advised and they want to know the long-term ramifications in detail. They will think ahead to what happens when their child leaves home, gets married and wants to start a family. Most articles discuss the good prognosis but recurrences are common. Therefore, it is important for the physician to be responsible for delivering long-term management with sensitivity and equanimity. That physician should be armed with personal experience and information on published reports. The patient and family need to recognize there will be periodic setbacks, some of which will be real and some false alarms. The doctor needs to be constantly there for the patient and family.

I have tried to distill my personal experience and published reports and highlight areas of controversy. There are reviews on thyroid cancer in children that complement this chapter [1–12]. The chapter does not cover medullary cancer. The management is different and it is more appropriate to discuss childhood and adult medullary cancer together in Chapter 10. The genetics of familial multiple endocrine neoplasia (MEN) syndromes are discussed there.

Etiology of Thyroid Cancer in Children

In the United States most thyroid cancers arising from follicular cells in children are sporadic and there is no obvious precipitating factor. However, in some patients radiation is a clear causal agent [13, 14]. Nowadays it is unusual to see a child where external radiation can clearly be incriminated, but historically, the role of external radiation was first recognized as a cause of thyroid cancer by the increased incidence in children who had received radiation treatment for a variety of medical and non-medical conditions [14, 15]. Most of the patients who developed thyroid cancer received several hundred rads (several Gray, [Gy] or Sievert, [Sv]) for conditions such as "status thymomicus", acne, scrofula, conditions that now are not treated by external radiation. Higher doses of external doses that are used to treat cancer and include the thyroid in the irradiated field are more likely to cause hypothyroidism, but there is an increased risk of thyroid cancer in children who receive neck radiation to treat Hodgkin's disease. We have reported a twentyfold increase [16]. This has been confirmed by other investigators [17, 18]. Thyroid cancer has arisen in children treated with radiation for primary brain cancer [19].

In recent years in Belarus, Ukraine and Russia there have been many reports indicating a dramatic rise in thyroid cancers in children who were exposed to radioactive fallout from the Chernobyl nuclear accident [20–29]. Children younger than 2 years, at the time of exposure, were more likely to present with aggressive cancers with local invasion, lymph node, and distant metastases [25]. There is an increase in RET/PTC3 (RET oncogene/papillary thyroid cancer 3) in these children and the cancer is more likely to be of the solid type on histologic examination. Rearrangement of the RET/PTC oncogene is found in 70% of these children compared to 20% of adults [30–33]. In one report, mutations in the p53 gene were identified in four of twenty-two patients who developed thyroid cancer after exposure to neck irradiation [34, 35]. There were no mutations in eighteen age and gender matched controls. The four patients with mutations were male, and all had capsular invasion and metastases to lymph nodes. An increase in the number of children and young adults with thyroid cancer in the North of England has been attributed to fallout from Chernobyl [27, 36]. A recent report from Belgium supports this conclusion [37].

There are rare reports of childhood familial thyroid cancer [38, 39]. These neoplasms could be due to radiation to both siblings, to a genetic factor, to both radiation and a genetic predisposition, or to chance [30].

Incidence

Thyroid cancer in children is not common accounting for approximately 7.5% of childhood cancers, (approximately 1–3 per million children) [40]. Fortunately cancers in general are less common in children. The common cancers are lymphoma (20–25%), sarcoma (17%), leukemia (15%), testis (14%), and brain (10%) and thyroid cancer is ranked eighth in fifteen to nineteen year-old adolescents. In adolescents there is a significant female to male ratio of approximately four to one. As a result thyroid cancer is the second most common cancer in women age 15 to 19 years. In prepubertal children, there is a small excess of males [41]. An important fact to be remembered when reviewing publications on the management of pediatric thyroid cancer is that the upper age limit varies from report to report. Some authorities use 16 years as the dividing line, others use 18 years or 21 years. Patients older than 21 years should not be considered as children or adolescents [42]. I use 21 years, but acknowledge that the implications of treating a 6 year old compared to a 20 year old are substantial. I have experience in the management of sixty children average age 14.5 years, fifty-nine were 20 years or younger at the time of diagnosis. 67% are female. Eleven patients were 10 years or younger, and 64% of those were female; this ratio favoring female gender is different from national statistics. In the United Kingdom only 154 cases of thyroid cancer were reported over 30 years in children under the age of 15 years [43]. Seventy-nine percent were differentiated thyroid cancer. This approximates to 0.5% per million per year.

Presentation, Diagnosis, and Investigations

The patient usually presents with a thyroid nodule. Less commonly abnormal cervical lymph nodes are noted. Thyroid nodules are less common in children than in adults but the risk of the nodule being a cancer is proportionately greater [1, 10, 44]. There is a higher incidence of lymph node metastases in children, therefore, a higher percentage present with enlargement of cervical nodes [45–48]. One of the explanations for the more advanced disease in the pediatric patient is a delay in diagnosis. This is partly explainable by the rarity of thyroid nodules and thyroid cancer, in contrast to the great frequency of enlarged cervical lymph nodes due to inflammatory or infectious causes. Pediatricians and family physicians do not expect to diagnose thyroid cancer in a child. Most pediatricians will not have a patient with thyroid cancer under their care, and most are both surprised and shocked when one of their patients is diagnosed with thyroid cancer. The message is to establish a diagnosis expeditiously in any child with a thyroid nodule, an enlarging thyroid, or enlarged cervical lymph nodes. Although delay in diagnosis is cited as an important factor, it is hard to find data to support this; one report states the average delay was 13 months [49].

In children, the best investigation is fine needle aspiration (FNA) of the thyroid nodule, or lymph node [6]. Fine needle aspiration can usually be conducted on children. Older children and adolescents can be reasoned with and younger ones restrained. The parents should sign an informed consent. Thyroid scintiscan is not advised. It is of even less value in children than in adults. This is remarkable because it is of very limited value in adults! The reason is that functioning nodules in children, although very rare, have a high risk of being malignant [50]. This is also the case in pediatric patients who are hyperthyroid as a result of the functioning nodule. In contrast a functioning nodule in an adult is usually benign. Thus, in a child, it does not matter whether the thyroid nodule is "hot" or "cold" on scan, the risk of cancer is there. Corrias et al. reported on forty-two children with thyroid nodules who had thyroid scan, ultrasound and FNA [51]. The forty-two patients were recruited from nine pediatric endocrinology departments in Italy, which underlines the rarity of thyroid nodules and cancer in children. Twenty were diagnosed with cancer, and twenty-two had benign nodules. The positive predictive value (PPV) of thyroid scintiscan was 12%, and the negative predictive value (NPV) was 68%. In contrast the PPV and NPV for FNA were 67% and 100% respectively. The PPV for ultrasound was also low at 15%. The authors conclude that FNA is safe and accurate. Arda et al. evaluated FNA in 46 children [52]. The PPV and NPV were identical to the previous study at 67% and 100%. The PPV for ultrasound was also 15% and for scan 12%. Table 7.1 lists the results of FNA in thyroid nodules in children. In general, both the sensitivity and specificity are satisfactory with some authors reporting 100%. The results confirm that FNA is accurate and the best single test to differentiate a benign from a malignant thyroid nodule in a pediatric patient. The test requires a clinician skilled in the procedure who also has expertise in handling pediatric patients. It is worth repeating that a thyroid scan is not recommenced. Thyroid ultrasound is not diagnostic but has some merits. It can help direct FNA, ensuring the nodule and not surrounding tissue is biopsied by imaging in real time that the tip of the needle is in the mass. Ultrasound can also be used to determine whether nodules that are benign on FNA are stable, or increasing

Table 7.1. Value of fine needle aspiration (FNA) in thyroid nodules in children.

Author	Number	Sensitivity %	Specificity %
Al-Shaikh et al. [135]	41	87	100
Arda et al. [52]	46	100	95
Corrias et al. [51]	42	100	95
Degnan et al. [136]	18	73	80
Khurana et al. [54]	57	93	81
Lugo-Vincente et al. [137]	24	60	90
Raab et al. [138]	57	80	86

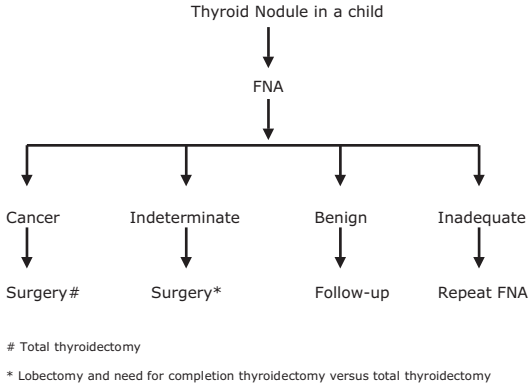

Figure 7.1. Algorithm for work up of a thyroid nodule in a child. The first investigation is FNA and decisions on management are based on the results of that.

on size on followup. The results of FNA are usually presented in four categories, cancer, indeterminate, benign, and inadequate. Surgery is recommended for the first two and the nature of the operation discussed below. When the result is inadequate the FNA should be repeated. There is value of having a cytology technologist present during the FNA to stain the specimen and make a judgement that there are sufficient cells for interpretation, and then, the procedure can be stopped. This does away with the need for a repeat biopsy in most cases. When a second FNA is necessary there is data showing a superior result with the use of ultrasound guidance [53, 54]. When the FNA is adequate, unequivocally benign, and the nodule is not too large or clinically suspicious, it is reasonable to follow the patient. Annual clinic visits should be arranged at which time there should be careful examination to determine the size and consistency of the nodule and whether there is any evidence of fixation. The cervical nodes should be examined. An ultrasound is valuable for an accurate measurement of length, width, and depth of the nodule. Because the incidence of cancer in a thyroid nodule is greater in children the threshold for referral for surgery should be lower. Any increase in size or change in characteristics of the nodule would be an indication for a repeat FNA, and if the result is not benign, the patient is referred to a skilled surgeon.

Unfortunately there is a habit of referring a child with a thyroid nodule for surgery with limited workup. For example in a multicenter study conducted by the Surgical Discipline Committee of the Children's Cancer Group, only 25% of 327 patients with thyroid cancer had a preoperative FNA [55]. The surgeon who proceeds to operate without a tissue diagnosis has to rely on a frozen section intraoperative diagnosis to direct the extent of the operation. The pathology at that time is often reported as indeterminate [56, 57]. This results in a decision to remove the lobe containing the nodule. When the definitive diagnosis of cancer is made several days later, the child and family will often receive conflicting advice. On the one hand there can be advice to complete the surgery and on the other that nothing else is necessary. Other opinions could be that thyroidectomy needs to be completed in order to administer ^{131}I treatment, while others state that radioiodine can be prescribed even in the presence of the residual lobe. The patient and family are in a quandary. I consulted on an 8 year old who had a lobectomy for a 4 cm follicular cancer. The referring physician and I advised completing the surgery. The pathology slides were reviewed at a third center, and the bottom line of that report was that there was no need for a second surgery. The mother clung to that advice and resisted advice from the referring physician and myself for completion of the thyroidectomy. Only time will tell if the pathologist who had not seen the patient was correct, hopefully so. However most children who have had a lobectomy and are then found to have thyroid cancer are operated on for a second time to complete the thyroidectomy. This can be troubling for the patient and parents. The second procedure also increases the complication rate. Total thyroidectomy is preferred because most pediatric thyroid cancers arising from follicular cells are papillary, and there is a high incidence of multifocality and invasion and lymph metastases. Therefore, it is important to obtain a tissue diagnosis preoperatively. Total thyroidectomy is advised when the FNA result is cancer. The problem of the microfollicular lesion, that is, the indeterminate lesion on FNA in a child, is the same as in the adult. About 10% to 20% of cytologically microfollicular lesions are cancer. The final diagnosis can be follicular adenoma, follicular variant of papillary, or papillary cancer. Scintiscan does not help exclude even a small percentage of these from surgery because as stated above cancers in children can be functioning on scan. There has to be a lengthy dis-

cussion about the possibility of a second operation, if cancer is diagnosed histologically, when only a lobe has been removed. The role of intraoperative frozen section in diagnosing cancer and aiding the decision to conduct total thyroidectomy needs to be addressed. The patient and family need to know that test has a sensitivity of about 50%.

A less common presentation is a midline swelling caused by a thyroglossal cyst. Occasionally there can be a cancer, usually papillary in type within the cyst. Because treatment of thyroglossal duct cancer is removal of the thyroglossal tract including the cyst (the Sistrunk procedure) plus thyroidectomy, some authorities recommend FNA of all thyroglossal cysts. Because less than 1% of thyroglossal cysts contain a cancer the cost effectiveness of this is debatable [58]. Peretz et al. reviewed the world literature of cancer in thyroglossal duct cyst and identified seventeen patients under the age of sixteen, including a 15 year old they treated [59]. This contrasts with the fact that thyroglossal cysts are the second commonest cause of a nodule in the neck of children. Cancer in a thyroglossal duct cyst is relatively more common in older patients; therefore, FNA in patients older than 16 years has a higher diagnostic value. When there is no evidence of cancer in the FNA most surgeons agree the Sistrunk procedure alone is the correct procedure [60]. When there is cancer there is some debate whether that alone is sufficient or whether it should be coupled with thyroidectomy. The reasons for thyroidectomy are that there can be cancer in the thyroid in 30% to 40%, when there are nodal metastases they cannot be treated with ^{131}I until the thyroid is removed and thyroglobulin (Tg) cannot be used as a reliable tumor marker. However several reports demonstrate a good outcome in patients who have not had thyroidectomy. When the cancer in the thyroglossal duct is small and fully excised and when there is no palpable mass or abnormality on ultrasound of the thyroid, the Sistrunk operation is sufficient.

Pathology

Papillary cancers account for a large majority of childhood differentiated cancers. Table 7.2 lists the proportions from several international studies. The exact ratio depends on the iodine content of the diet, with a higher ratio of papillary cancer in regions with high dietary iodine and follicular cancers in iodine deficient countries [61]. Fifty-seven of sixty-two (92%) in pediatric patients at Stanford are papillary. The cancers are frequently multifocal. When the size is discussed in a publication, the average is 3 cm to 4 cm [55]. Local invasion is also common. Lymph node metastases are found in more than 50% of patients. Distant metastases are reported in about 20%, most often to the lungs. In my experience, 76% had lymph node metastases and 34% pulmonary involvement. In contrast to adults, papillary thyroid cancer metastasizes to the lungs in children. Table 7.3 gives the percentages with metastases from several publications. Histologically differentiated thyroid cancer, especially papillary cancer frequently shows infiltration with lymphocytes [11, 26, 46, 61–65]. There is some evidence this is an immunologic effort against the cancer, one report indicating a prolonged, disease free survival [66]. The histologic type of cancer in those exposed to nuclear fallout is commonly the solid variant of papillary cancer [67, 68]. This variant is more aggressive, and there are reports of children dying as a result of this [68].

The sodium iodide symporter (NIS) is essential for normal trapping of iodine and the

Table 7.2. Ratio of papillary and follicular cancer in different countries.

Author	Papillary %	Follicular %	Comments
Arici et al. [3]	60	40	Turkey
Bal et al. [61]	85	15	India
Ceccarelli et al. [63]	92	8	Italy
Chen et al. [64]	81	19	Taiwan
Fassina et al. [47]	83	17	Italy
Furmanchuk et al. [26]	96.5	3.5	Belarus
Jarzab et al. [65]	71	29	Poland
Jin et al. [139]	93	7	China
La Quaglia et al. (multi-center) [55]	90	10	USA
McDougall	91	9	California USA

Table 7.3. Characteristics of differentiated thyroid cancer from published reports.

Author	Number of patients	Size of cancer (cm)	Local invasion %	Lymph node involved %	Distant metastases %
Bal et al. [61]	80	NA	NA	66	29
Ceccarelli et al. [63]	49 (1 medullary cancer)	NA	NA	73	23
Chen et al. [64]	37	NA	NA	62	22
Chow et al. [92]	60		23	45	15
Furmanchuk et al. [26]	101	NA	61.5	74	7
Giuffrida [46]	48	NA	52	54	21
Jarzab et al. [65]	109	NA	NA	59	16
Jin et al. [139]	83	NA	NA	69	13
La Quaglia et al. (multi-center) [55]	327	3	48	90	NA
McDougall	58	NA	NA	76	34
McGregor et al. [8]	56	NA	21	55	0
Zimmerman et al. [140]	58	3.1 ± 1.7	24	90	24

formation of thyroid hormones. It has a pivotal role in diagnostic scanning and treatment with radioiodines. Thyroid cancers often have lower concentration of NIS. One study in thirty-two children with differentiated thyroid cancer demonstrated that absence of NIS was associated with distant metastases and recurrences [69]. Patients whose cancers had undetectable NIS required higher doses of ^{131}I.

When a patient has been operated on in a different medical center and is referred for a consultation or for postoperative ^{131}I it is important to request the pathology slides and have them reviewed. This is to confirm the diagnosis and to define the size of the cancer, to look for invasion and to identify any unusual features of the cancer. I encourage the treating physicians to look at the slides with a pathologist.

Very rarely poorly differentiated cancer such as insular cancer or anaplastic cancer occurs in a child [70–73].

Treatment

The fundamentals of treatment are similar to that in adults. The most important therapy is surgery and total, or near total thyroidectomy, with removal of abnormal lymph nodes is critical. In selected patients ^{131}I is prescribed after the operation and thyroid hormone is prescribed for life.

Surgery

It is worth repeating, the most important treatment is thyroidectomy. The most important aspect of the thyroidectomy is to have a skilled surgeon who can remove the thyroid without complications. There is controversy about how complete the thyroidectomy should be, but retrospective studies show a higher recurrence rate after lobectomy [4, 63, 74–76]. Because there are few surgeons trained in the practice of pediatric thyroid surgery, the complication rates are high. The complications of surgery include damage to the recurrent laryngeal nerves, the superior laryngeal nerve, the parathyroids, and in rare situations the spinal accessory nerve or the cervical sympathetic nerve. Hypoparathyroidism is very problematic in a child, and if permanent, is even more problematic in a young woman trying to conceive, and then retain the fetus to term. Table 7.4 lists some of the published figures of the major complications. It is surprising that some authors state the complication rate after total thyroidectomy is low, but quote numbers that I consider substantial. It is unlikely that unpublished data are superior to that available in print.

How should the patient be managed who has only had a hemithyroidectomy? When the cancer is small and fully excised that operation might suffice [77]. However, the data presented above indicates that many cancers are multifocal and many patients have lymph node and pulmonary metastases. Local recurrence is to

be anticipated and treatment of metastases with ^{131}I is difficult when there is a lobe of normal thyroid. One study addressing this systematically reevaluated forty-seven children from Belarus whose parents desired a second opinion at a Western European center (Pisa) [74]. A decision was made to complete the thyroidectomy in nineteen patients who had only undergone a hemithyroidectomy. Of these nineteen, five (26%) already had a vocal cord paralysis and two (10.5%) hypoparathyroidism (the latter is hard to understand after lobectomy). After the second operation, four more (21%) became hypoparathyroid and one (5.2%) had a paralyzed vocal cord. Examination of the excised lymph nodes and ^{131}I scan demonstrated residual or metastatic thyroid cancer in 61% of these patients. This data argues for a more complete primary operation by a skilled and experienced surgeon. Even in excellent hands the complication rate of "redo" thyroidectomy is high.

In the United States, patients with private insurances are frequently held captive by their insurance scheme, resulting in referral to surgeons within that program. When a patient or family requests a referral to a recognized specialist outside the group that is often denied by a non-medical administrator. After an appeal, the medical director, an employee of the company who is trying to keep costs low, denies the request. This can result in operations being done by the "best" surgeon available. To the group administrator, the local surgeon is interchangeable with the recognized national expert. When the patient and family are persistent and insist on being treated by the "outside" authority, the insurance company may deny payment, resulting in the patient's family being responsible for the costs.

Thyroid Hormone

Thyroid hormone will be required for life. It is difficult for a child to be compulsive about taking a pill daily. The need must be reinforced at each clinic visit. In children less than 12 years, it is preferable that a parent accepts the responsibility. Pharmacists advise taking the pill one hour before eating. This is impracticable for a child or adolescent. Any parent who has had the task of getting children to school properly clothed, fed, and on time understands that. Although it is true that iron and calcium interfere with absorption of thyroid hormones, breakfast has a minor effect that can be controlled by testing thyroid function and adjusting the dose of levo-thyroxine as necessary [78–80]. What is the correct dose? Children require a higher dose than adults relative to their weight. When the decision is to have a TSH in the low end of the normal range, the correct dose of levo-thyroxine is the one that achieves that goal (close to 1 µg/lb body weight). Similarly when the goal is to suppress TSH, this has to be determined by biochemical testing.

Radioiodine

Almost all authorities recommend treatment with ^{131}I after surgery [6, 45, 81, 82]. In contrast physicians at the Mayo Clinic do not recommend ^{131}I and rely on surgery and thyroid hormone [83]. They demonstrate an excellent outcome in fifty-eight children of whom only 17% received postoperative ^{131}I. Nevertheless, they did treat twelve of fourteen pediatric patients who had pulmonary metastases with ^{131}I after thyroidectomy. A similar non aggressive management is advised by Sierk et al. [84]. Ten of the patients that I have managed were not

Table 7.4. Complications after thyroid surgery in children.

Reference	Number	Hypoparathyroid	Recurrent laryngeal nerve	Total %
Arici et al. [3]	15	2	1	20
Iurato et al. [141]	33	2	0	6
Hallwirth et al. [142]	18	0	3	16.7
Jarzab et al. [65]	109	6	11	17
Kowalski et al. [143]	38	6	2	21
Miccoli et al. [74]	Surgery in Belarus 19	2	5	36.5
	Reoperation 19	4	1	26

treated with radioiodine, but they had early disease. In contrast, other authorities advise an aggressive approach with surgery and ^{131}I [6]. The difference in opinion is in part due to the paradoxical course of the cancer. Although the disease is often more advanced at the time of diagnosis in comparison to adults, patients do not die from this cancer. The first step is to determine whether ^{131}I is likely to be beneficial. When the cancer is small (<1.5 cm), single, non-invasive, and fully excised by an appropriate operation, no authority has data showing that ^{131}I will reduce the recurrence rate, or improve survival [85, 86].

When a decision is made to consider ^{131}I, the protocol we conduct is to withdraw thyroid hormone (thyroxine) for 4 weeks, or to wait 4 weeks from the time of thyroidectomy. It is extremely valuable when there is an opportunity to meet the patient and family before the surgery and outline the sequence. I find going through step by step and drawing a diagram labeled with dates of testing and treatment helps (Figure 7.2). If a preoperative consultation is not possible, my next preference is to meet the patient and family about a week after surgery. This gives time for the family to plan and have any questions answered. It is unfortunate when the patient is referred for ^{131}I therapy and arrives out of the blue, hypothyroid, unprepared mentally, and not on a low iodine diet. The patient and family have no idea of what to expect. I liken this to me sending a patient directly to surgery without the patient or family meeting the surgeon or having a chance to discuss the procedure, complications, and followup. With the exception of very young children, I believe it is possible to engage the patient as well as the parents with all aspects of this treatment. Honesty and frankness are appreciated by all parties. Most children tolerate hypothyroidism well, but the symptoms they will experience should be discussed. I have been surprised to find TSH values in the 200 mIU/l to 300 mIU/l range in children who are still active at school and in sports. When the diagnosis of thyroid cancer is made, the parents usually want to proceed with surgery and ^{131}I testing and

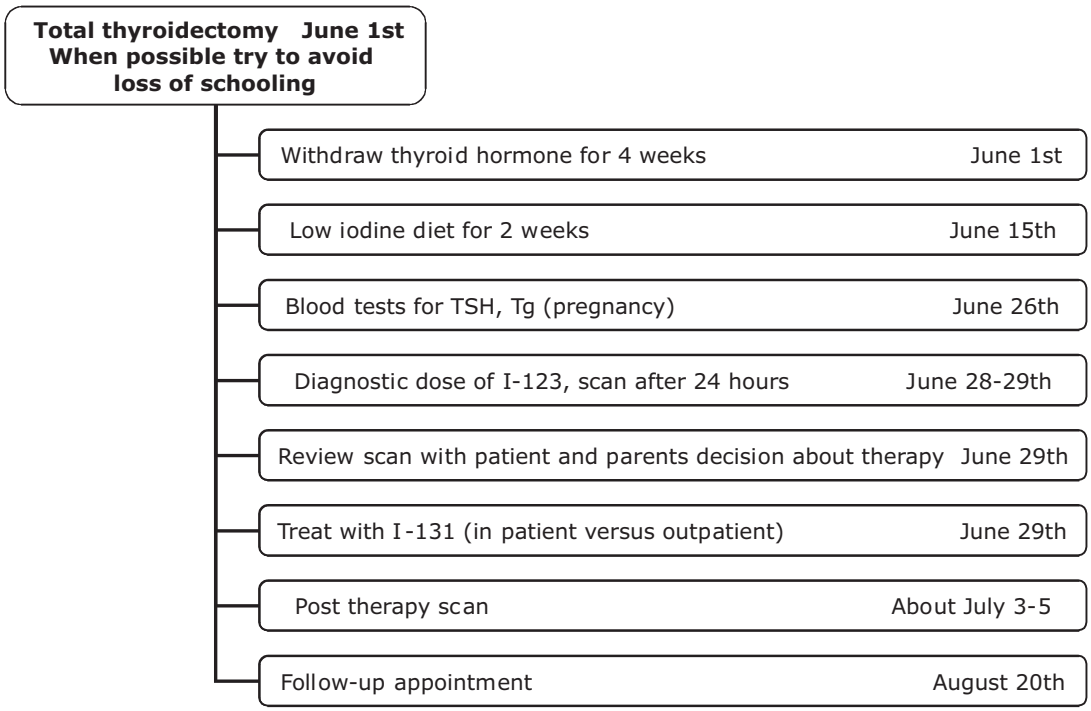

Figure 7.2. Flow chart for discussion of management with patient and parents. This allows dates of testing and treatment to be coordinated and questions to be answered.

treatment expeditiously. This means the patient will lose time from school. Letters indicating the need for medical care, without being explicit, are often required. The teachers can provide homework and reading materials for the patient, so she or he will not be left behind their friends and peers. It is important to ensure that the patient's friends and schoolmates are not exposed to radiation so there will be an enforced time of separation.

With regard to low iodine diet it is helpful to provide a simple list of foods that can be eaten and those that should be avoided for 2 weeks prior to and through testing and treatment. The detailed diet available from www.thyca.org is helpful for some parents. Junk food such as chips, fast foods etc can be problematic but discussion with patient and parents can result in a change in eating habits, at least temporarily. After 4 weeks blood is drawn for measurement of TSH, thyroglobulin (Tg) and in women after menarche a pregnancy test. Some physicians proceed straight to ^{131}I treatment. Most authorities obtain a whole-body scan with a diagnostic dose of radioiodine. Historically ^{131}I was and still is prescribed for the diagnostic scan. The usual dose is 37–155 MBq (1–5 mCi). I have used 37–74 MBq (1–2 mCi) and scanned 48 hours 72 hours later. More recently several groups have recommended ^{123}I for various reasons [87, 88]. ^{123}I only emits photons and subjects the patient and thyroid to less radiation than ^{131}I. ^{131}I has a longer half-life (8 days versus 13 hours for ^{123}I) and emits beta particles (electrons e^-) as well as photons. The images with ^{123}I are superior but when 37–74 MBq (1–2 mCi) is prescribed imaging at times longer than 24 hours is impracticable because the count rate is so low. One down side for ^{123}I is its cost, although the radiopharmaceutical manufacturers are recognizing its more widespread use and hopefully the price will come down. Some experts are concerned that diagnostic ^{131}I might cause "stunning", that is the radiation delivered to the thyroid by the diagnostic dose of ^{131}I could cause sufficient cellular damage that the therapeutic dose of ^{131}I would not be trapped, or have less effect [89]. I do not subscribe to the concept of stunning, provided the dose of ^{131}I is 74 MBq (2 mCi) or less and the treatment is prescribed as soon after diagnostic scanning as possible [90]. The diagnostic scan allows the amount of residual thyroid to be determined and when adequate surgery has been conducted it also allows functioning metastases to be identified. Therefore, the therapeutic dose can be prescribed with knowledge of this information. Those who proceed directly to therapy have to make an empiric judgment about what therapeutic dose to administer. Because I have met with the patient and family ahead of time, the planning includes not only the dates for scanning but also treatment. Treatment is usually planned for the same day as the diagnostic scan. Therefore, if the patient is to be admitted to hospital for radiation safety requirements, the room should be available, the necessary authorizations from the insurance company should be in place, and radiation safety officers informed. Pediatric nurses are not used to caring for radioactive patients and one or two educational meetings prior to administering the ^{131}I are beneficial.

There is little in the literature about specific doses of ^{131}I. In Werner and Ingbar's textbook Mazzaferri presents an excellent, carefully referenced, overview of treatment with radioiodine, but there are nine lines for this in children [91]. He recommends 1.1 GBq (30 mCi) for ablation of thyroid remnants. This is the same dose recommended by Hung and Sarlis [1]. Physicians in Groningen administered doses of 0.925 GBq to 5.5 GBq ^{131}I (25–150 mCi) for ablation. [81] An average first dose of 2.5 ± 0.96 GBq (67.5 ± 26 mCi) was administered by Chow et al. [92] The dose should be related to the size of the patient, their age and the extent of disease. In children of 80 pounds (36 Kg) 1.1 GBq to 2.8 GBq (30–75 mCi) would be reasonable. When there is local invasion or nodal metastases the range of doses would be between 3.7 GBq and 5.5 GBq (100–150 mCi) ^{131}I. In the case of pulmonary metastases depending on size 1.85 GBq to 5.5 GBq (50–150 mCi) and for bone metastases that are uncommon in children 3.7 GBq to 7.4 GBq (100–200 mCi) are advised. For smaller and younger children the administered dose would be reduced. Grigsby et al. prescribed 0.74 GBq to 1.48 GBq (20–40 mCi) in children 6 years of age or less [93]. One patient aged 7 years received 4.4 GBq (120 mCi) and the cumulative doses of ^{131}I in forty-six patients ranged from 1.1 GBq to 30 GBq (31–810 mCi). This was similar to the range of 0.74 GBq to 21.5 GBq (20–580 mCi) in the report of Chow et al. [92] and the maximum cumulative dose of 32.7 GBq (885

mCi) administered by Haveman et al. [81]. A series of patients with pulmonary metastases received cumulative doses of 4.6 GBq to 38.7 GBq (125 mCi to 1.05 Ci) [94]. In each of these reports some patients received four or more treatments. Smaller doses were administered by other investigators 0.37 GBq to 1.85 GBq (10–50 mCi) for ablation and 1.85 GBq to 3.7 GBq (50–100 mCi) to treat local or distant metastases [2]. It could be argued that the lower dose might work. When it does not, a second dose can be prescribed. Most would advise the higher range with the concept of treating effectively on the first occasion. There is no controlled trial to judge the success of treatment. Some authorities place an upper limit of 22.2 MBq (600 mCi) [95]. This is based on two concerns. First, higher doses could increase the risk of complications, such as second cancers or marrow aplasia, and second, when this quantity has not worked, it is unlikely that an additional dose will. Neither of these are absolutes. In patients with extensive metastases, it is reasonable to obtain objective data that the blood would not receive an absorbed dose of 200 rad (2 Gy) or that 80 mCi would be retained in the lungs [96]. This can be obtained by using counts over the lung and whole body at 48 hours after the administration of the diagnostic tracer of ^{131}I and, alternatively, the simple method of Sisson, using a probe at a distance of 2.5 meters and comparing an early whole body count at 1 hour to 2 hours and the 48 hour measurement [97].

Recombinant human thyrotropin (rhTSH) has become a very important tool for conducting whole-body scintigraphy and measuring TSH stimulated Tg [98–100]. In the United States, rhTSH has been approved for use in patients 16 years of age or older. There is almost no data in the literature applicable to children, the youngest patient I have studied is sixteen, and the result confirmed a prior withdrawal scan. Children tolerate hypothyroidism well, and because of that and the small number of pediatric patients with thyroid cancer, it is not likely that much will be written on this topic.

There are important logistical issues. Usually the diagnostic and therapeutic ^{131}I is packaged in capsule form. Some small children have difficulty swallowing capsules. I was surprised by a 5 year old who chewed and then spat out the capsule. Fortunately, it was the diagnostic dose, and, doubly fortunately, it was caught in a cup. This should be assessed ahead of time and when necessary diagnostic and therapeutic doses of radioiodine can be obtained in liquid form.

Radiation Safety

For small doses of diagnostic ^{131}I and for ^{123}I radiation safety, issues are simple, but, for therapeutic doses of ^{131}I, it is usually necessary to admit the patient to hospital. Readers should be cognizant of the regulations that apply in their country or state. In California, a patient can be released home when any one of the following pertains. (1) The patient receives 1.2 GBq (33 mCi) or less. (2) The emitted radiation is 7 mrem/hour/meter or less. (3) No adult member of the public could receive 5 mSv (500 mrem) from the patient. The first two are easy to document. In the case of a patient receiving 3.7 MBq (100 mCi), the emitted radiation is approximately 20 mrem/hour/meter at the time of treatment. If the patient is to be discharged, the treating physician has to document that the home situation would make it impossible for other members of the family to receive 5 mSv (500 mrem). The child would need to be an appropriate age and intellect so that an informed discussion about radiation safety can be conducted. The child should have a separate bedroom and preferably a separate bathroom. The distance from and the time that other members of the house will be exposed the patient (occupancy factor) must be predetermined. Then a simple calculation allows the decision between discharge to home and admittance to the hospital to be made. Grigsby et al. conducted a study to measure radiation to family members, pets, and rooms when radioactive patients were discharged directly to their home [101]. The patients who were adults received treatments of 2.8 GBq to 5.6 GBq ^{131}I (75–150 mCi). The mean dose to sixty-four family members from thirty patients was 0.24 mSv, and the highest exposure was 1.04 mSv. The dose to pets was 0.37 mSv. These data are reassuring for those who discharge patients after treatment with large doses of ^{131}I. Nevertheless, I admit most pediatric patients to hospital. Many have siblings or the mother might be pregnant, therefore separation is prudent. Because of the rarity of pediatric thyroid cancer, nurses in pediatric wards usually have had no

experience with radioactive patients. Therefore, personal discussions with the ward team by the treating physician, and by members of the radiation safety group are advised. It is better to answer questions and spot problems before treating the patient. We have, at our disposal, a room in the children's hospital that is large enough to have a relative (usually the mother) sleep in that room at a distance of about ten feet behind a movable lead shield placed close to the edge of the patient's bed. This is comforting for children 10 years or younger and their parents.

Management After Iodine-131 Treatment

The patient starts thyroid hormone and regular diet 24 hours after ^{131}I treatment. I usually arrange for a post-therapy scan after 5 days to 8 days. That scan can show better uptake in lesions and in rare cases it demonstrates new lesions. There is debate about how often. In my experience, when near total thyroidectomy is achieved, and the patient studied by whole-body scan at the time TSH is greater than 50 mIU/l and on a low iodine diet, the post treatment scan seldom increases the stage of disease. The publications that show a greater sensitivity deal with adult rather than pediatric patients [102–104]. At this appointment the emitted radiation can be measured at a distance of a meter and this allows an informed decision about whether to maintain radiation safety regulations or to permit the child back into the real world.

The patient returns at about eight weeks for examination and for measurement of thyroid function, Tg, and, if applicable, calcium. Plans are made for a followup scan with measurement of stimulated Tg 6 months to 12 months after the original therapy. It is usually more convenient to arrange for this during school vacation, because of the hypothyroidism, low iodine diet, absence from classes, and radioactivity (albeit relatively low dose). When the scan is negative and stimulated Tg low, I arrange followups at 6-month intervals. These visits include careful examination of the neck; measurement of thyroid function and Tg. Ultrasound of the neck can be obtained at intervals of 1 year to 2 years. Should several negative scans be sought? It is reasonable to have another scan 2 years later. I think it is also reasonable, provided the first scan and stimulated Tg are negative and non-stimulated Tg values are consistently undetectable, to wait until 5 years to scan and measure stimulated Tg. There is no trial to support that one approach is superior. The fact that recurrences can occur is the driving force for long-term followup. Pediatricians, by definition, relinquish their patients when they reach adulthood, some sooner, some later. This supports the benefit of followup in a thyroid clinic that can be attended for life. The patient and parents knows the staff and the medical team have access to records, surgical reports, pathology findings, scans and laboratory tests. Followup visits and when necessary ultrasound scans and scintiscans with radioiodine are arranged on the same day to minimize time lost from school. Figure 7.3 provides an algorithm for treatment and follow-up.

When the followup scan and Tg are positive and there is no palpable disease consideration should be given for additional ^{131}I. This is more likely in the case of distant metastases. Pulmonary lesions are usually micronodular in children and they can be inapparent on chest roentgenogram and even CT. They can be identified on diagnostic whole body scan and post treatment scan, the latter having a higher sensitivity. In one series twenty-eight out of 122 patients had pulmonary metastases and these were identified on scans with radioiodine as follows [105]: 54% were identified by the first diagnostic scan, 14% on the scan made after "remnant ablation," 25% after second treatment and 7% after the third treatment. The evidence from Sisson et al. that the majority of the energy of β particles of ^{131}I is deposited outside of millimeter-sized nodules should be remembered [106]. When the roentgenogram is normal and Tg low the benefit of repeated doses of ^{131}I in relation to risk decreases as the cumulative administered dose increases. Schlumberger recommends a limit of 22.2 GBq (600 mCi). Others have placed that at 29.6 GBq (800 mCi). There is no absolute cut-off, but the clinical situation, desires of patient and parents, the age of the patient, the desire to have children, and level of Tg should all be entered into the decision process.

There is no controlled trial to prove or disprove the benefit of ^{131}I in children.

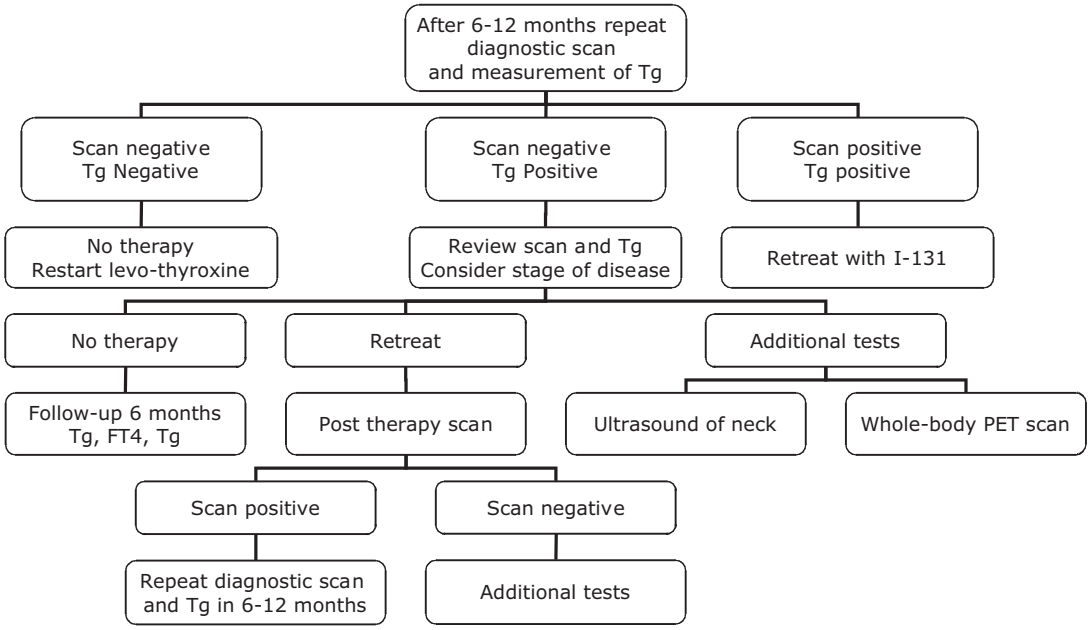

Figure 7.3. Algorithm for long-term management of a child with thyroid cancer.

False Positive Scans

The normal distribution of radioiodine should be to residual thyroid and functioning metastases that are most often in regional cervical nodes and the lungs, salivary glands, stomach, intestines, and urinary tract. Diffuse uptake in the liver is seen on post therapy scans made 4 days to 8 days after treatment [107]. When a diagnostic scan shows accumulation of radioiodine in an unusual site the physician should take time to determine whether this is a true or false positive. The questions should be asked does this make sense and what alternative explanation is there? Several reviews give comprehensive lists of potential causes [108–113]. The scan should be reviewed for technical qualities and compared to serum Tg. When Tg is negative metastases are very uncommon. The appearance on scintiscan might give an immediate answer such as the shape of a thymus in the mediastinum, which is more frequent in younger patients (Figure 7.4) [114, 115]. The most likely cause of a false positive is contaminant with radioactive saliva, mucus, or urine, and sites that are superficial should be washed and the area rescanned.

Complications and Long-Term Problems After Iodine-131

High dose ^{131}I can cause nausea. Depending on the dose of ^{131}I to be administered a decision can be made before treatment whether to prescribe an antiemetic. Swelling of the salivary glands can occur; however, chronic salivary problems and permanent dryness of the mouth are rare in children. Concerns about fertility of the child and the effect of ^{131}I on future offspring are high on the minds of every patient's parents. Vini et al. studied 496 women under the age of 40 at the time of ^{131}I treatment [116]. Two hundred seventy-six women gave birth to 427 children and there were no congenital abnormalities. Only one woman who desired a baby was unable to conceive. In another retrospective review the pregnancies and offspring of 70 women aged 15 years to 36 years who were treated with a mean dose of 4.39 MBq (118 mCi) ^{131}I were evaluated [117]. Seventy-three children were born, three had low birth weight, and one had tetralogy of Fallot. There were two miscarriages. Dottorini et al. compared the fertility and offspring of 627 women who were treated with ^{131}I to 187 patients who did not receive ^{131}I [118]. There was

no statistical difference in fertility, prematurity, or birth weights of the babies. Several other series confirm that it is safe for patients to conceive after an appropriate delay from the ^{131}I treatment (see below). There is no increase in thyroid cancer recurrence during pregnancy, there are no reports of cancer spreading from mother to baby, and the risk of congenital defects appears to similar to the baseline. My advice is that patients do not become pregnant until a followup scan and measurement of Tg demonstrates successful treatment. Then I recommend a wait of several months to ensure the thyroid function tests are "physiological," usually with a TSH in the range of 0.3 mu/l to 1.0 mu/l. This usually means a 12-month to 18-month delay from the time of surgery, but in adolescents that is usually not an issue. Many authorities recommend a delay of one year after ^{131}I [119]. I believe that proof of normal thyroid function prior to conception is equally important and a window of 6 months to 12 months is acceptable. Ayala et al. presented a higher incidence of problems within one year of ^{131}I, suggesting that as an appropriate delay [120]. There are reports of reduced sperm counts after ^{131}I in men, but this is rare. Dottorini et al. described oligospermia in one patient who received 3.33 GBq (90 mCi) [121]. In contrast, Hyer et al. evaluated fertility in 122 men who were less than 40 years old at the time of treatment with ^{131}I [122]. Fifty-nine patients who wanted children fathered 106 offspring; none of the children had a significant malformation. The testicular doses were 6.4 cGy (6.4 rads) after 3 GBq and 14 cGy (14 rads) after 5.5 GBq. Follicle stimulating hormone (FSH) rose transiently but was normal after 9 months.

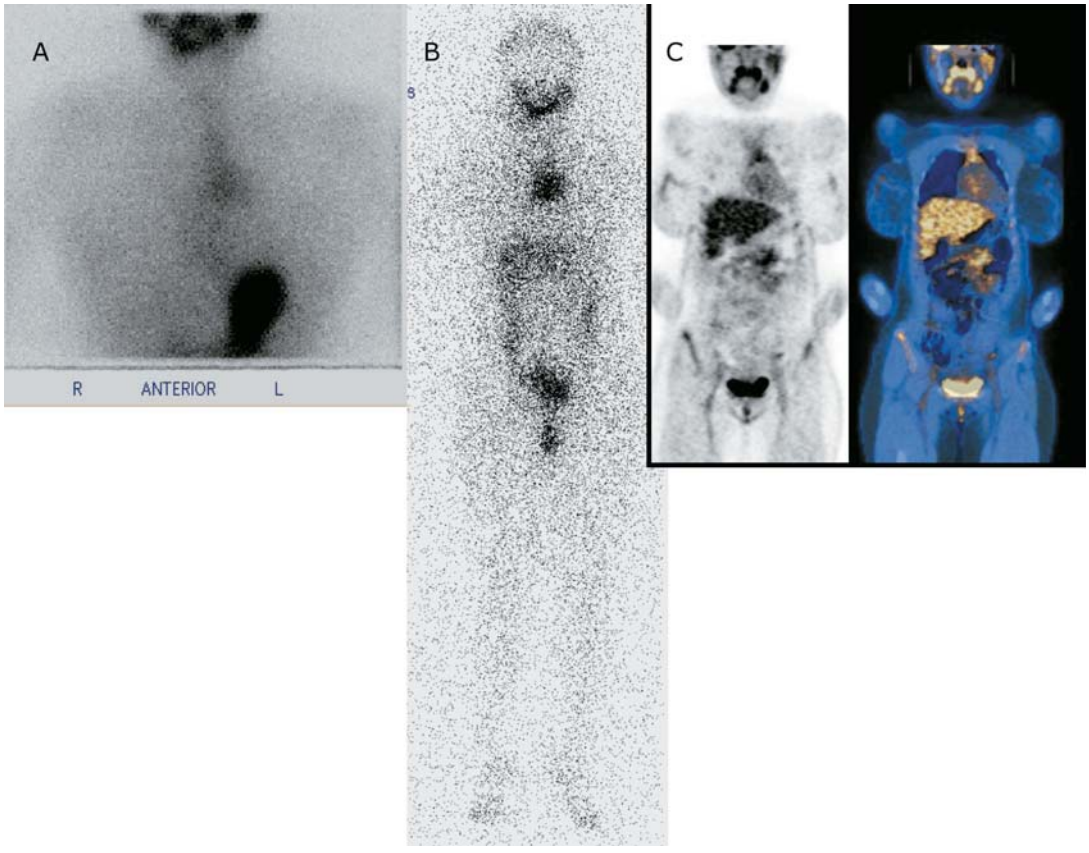

Figure 7.4. (A) is a spot view of the chest of a young woman after 74 MBq ^{123}I. It shows the typical appearance of the thymus. In (B) the thymus is also seen on the post therapy scan. (C) PET/CT scan also shows the thymus.

It is important to ensure that female children are not pregnant when they are treated with ^{131}I [123]. A pregnancy test must be obtained in any female who has reached menarche. I prefer a serum measurement, the result is available within an hour, and it is more sensitive than urinary testing. The parents should understand the need for the test due to both medical and legal purposes, and they would not wish a grandchild to be exposed in utero to radiation. I was referred a teenager who at 14 years of age had been treated with 1.85 MBq (50 mCi) ^{131}I. Unknown to all but herself she was 4 months pregnant and no pregnancy test had been obtained. Her daughter was born athyreotic. The topic is discussed in detail in the adult section and in the next chapter on thyroid cancer and pregnancy, since this is more likely to occur in 20-year-old to 40-year-old patients. Several references are provided for convenience [124–126]. Hypothyroidism of the offspring is to be expected when it is 11 weeks to 12 weeks at the time of exposure. There is a reduction in I.Q. of 30 points per Gy (100 rem) and a 3% risk of cancer per Gy (100 rem). The decision on what to recommend depends on the stage of the pregnancy, the dose of ^{131}I administered, the thyroid uptake in the treated patient, and personal and religious factors. When a large dose has been prescribed and calculations indicate a high-absorbed dose by the fetus there could be an indication for termination. Treatment of a pregnant patient without a pregnancy test is difficult to defend legally [127].

There is also concern that the radioiodine will cause or increase the risk of a second cancer. Most of the data relates to adults and overall the risk appears very small. One situation is of concern to me. When the patient is a post-pubertal woman and there is uptake of the tracer of ^{123}I or ^{131}I in the breasts, I would defer radioiodine therapy. The breast is sensitive to radiation, and there is evidence of an increase in breast cancer that could be attributed to this. When the child belongs to a family with Gardner's syndrome or Cowden's syndrome appropriate screening is necessary for associated precancerous lesions and cancers.

In patients with extensive pulmonary metastases, there is the risk that ^{131}I could damage normal lung surrounding the miliary cancer and cause fibrosis and reduced lung function. Early reports were of concern [128]. More recent evidence suggests the balance of evidence points to unchecked growth of the cancer being more likely to cause difficulty with breathing than the ^{131}I treatment [94].

Controversies

The absence of a controlled study to determine whether ^{131}I improves the prognosis or reduces recurrences is a major limitation. The fact that an abnormality on scan can be shown to disappear on followup scans after radioiodine treatment is taken to mean success. Similarly a reduction in Tg is accepted as evidence that cancer cells have been killed. However the high recurrence rate is substantial (see below). In one study 90% of children younger than 10 years of age at diagnosis had a recurrence [129]. The authors make the point that only 1/3 of the patients were treated with ^{131}I and the numbers are too small to reach conclusions, the relative risk of a recurrence was 2.483 (95% confidence intervals 0.544–11.332) in those treated. In comparison the relative risk after total thyroidectomy was 0.616 and thyroid suppression 0.293. Because of the small number of patients there is little published about "stunning" of thyroid cells by diagnostic doses of ^{131}I in children. Stunning has several meanings primarily that there is no uptake of therapeutic radioiodine as a result of the absorbed radiation from a diagnostic dose [89]. Alternative definitions are reduced uptake of the therapeutic dose and lowered efficacy because insufficient radiation was emitted in the thyroid cancer. The debate for and against is included in chapter 6 with references, which largely deal with adults. I found no evidence of this in 26 children who had comparable diagnostic and post therapy scans. Patients who had to be retreated had extensive metastases. The diagnostic doses were always less than or equal to 74 MBq (2 mCi) and therapy administered as soon as possible after the diagnostic scan, usually on the same day or within 24 hours.

There is no publication dealing specifically with Tg positive scan negative pediatric patients. The problem is the same as in the adult should the patient be monitored without intervention, should a large dose of ^{131}I be administered or should other test such as ^{18}FDG PET scan be conducted? The origin of Tg could be in miliary lesions in the lungs and when they were

identified on prior diagnostic and post-therapy scans it is reasonable to administer one additional therapy dose in the hope that the cells will trap enough ^{131}I to be killed. When a prior post-treatment scan was negative it is hard to argue in favor of another large dose. At the time of writing there are no articles on ^{18}FDG PET in the management of thyroid cancer in children. My experience with PET in children with thyroid cancer is limited to four patients and therefore cannot determine policy. Lesions less than 4 mm to 5 mm are unlikely to be identified. Therefore when a posttreatment scan and PET scan (and ultrasound of the neck) are negative waiting and monitoring is recommended.

Prognosis

Survival of children with differentiated thyroid cancer is excellent. Fortunately it is very rare that a child dies of thyroid cancer [18, 130–132]. Childhood thyroid cancers are seldom undifferentiated [5]. However, occasionally differentiated cancer that has not been excised or ablated transforms to anaplastic cancer and results in death. This occurred in one patient out of thirty-four in a series from Hong Kong, 18 years after the primary treatment [133]. A later report from that center defined a 98.3% 10 year survival [131]. The majority of publications cited in this chapter do not document a single death. Buckwalter et al. believe that one reason for the favorable outcome is that childhood cancers are more sensitive to TSH [130]. However, the recurrence rate is significant and higher in those who present with cervical node metastases and in younger patients. In one report only 10.1% of children who were 10 years of age or younger at the time of diagnosis did not relapse [129]. In contrast, 48.3% of older children were free of disease ($p = 0.022$). Jarzab et al. conducted a multivariate analysis of factors effecting outcome in 109 patients aged 6 years to 17 years. No child died, and the 5-year and 10-year disease free survivals were 80 and 61% [65]. They found that total thyroidectomy was the single most important factor for disease free survival and was statistically significant. ^{131}I improved disease free survival, but that did not reach statistical significance. An analysis of 327 children conducted by the Surgical Discipline Committee of the Children's Cancer Group reported no death at 10 years [55]. The 5-year and 10-year disease free survivals were 76% and 66%. (One somewhat confusing fact is that a second report on the same patients records 2 disease-related deaths [134].) These reports highlight the need for long-term follow-up and the recognition that there can be setbacks, but they should be addressed by diagnostic FNA, surgical excision of palpable cancers and ^{131}I for non-palpable recurrences. It is disappointing to report that an analysis of prognostic factors of 30 children treated at the Royal Marsden Hospital in England found "no therapeutic intervention could be shown statistically to impact on survival" [71].

Even when a very poor outcome might be expected, for example in a child presenting with extensive invasive cancer, cervical and distant metastases the outcome can be favorable after treatment by total thyroidectomy and ^{131}I [71]. One pediatric patient died at Stanford, but not from thyroid cancer. This young boy had Hodgkin's disease that was treated by external radiation and chemotherapy. The thyroid was included in the radiation field. He then developed thyroid cancer that was treated by operation and ^{131}I. He subsequently developed acute myelogenous leukemia. It is possible the second and third cancers were due at least in part to the prior therapies. The complications related to therapies of thyroid cancer have been addressed above.

Summary and Key Points

Thyroid cancer is not common in children, but when a thyroid nodule or enlarged cervical node is recognized, it is important to proceed to FNA for a tissue diagnosis. A skilled thyroid surgeon should conduct a total thyroidectomy. In some cases ^{131}I is advised to ablate residual thyroid and definitely in the case of functioning metastases. The importance of a sensitive easily available physician for long-term followup is stressed.

- Differentiated thyroid cancer is uncommon in children.
- The vast majority of childhood thyroid cancers are papillary.
- The cancers are more likely to be large, multifocal, and locally invasive.

- There is a high incidence of metastases to regional lymph nodes (50–90%) and distant metastases (15–30%).
- In spite of the advanced stage at presentation virtually no child dies from thyroid cancer.
- The relapse rate is significant.
- Patients 10 years of age or less have a higher recurrence rate.
- Those with lymph node metastases also have a higher recurrence rate.
- The majority opinion is that total thyroidectomy and removal of involved nodes is the surgical procedure of choice. Some studies show this improves disease free survival and is of statistical significance.
- Most authorities recommend ^{131}I therapy, but no study demonstrates that this reaches statistical significance for preventing recurrence. It has a role but should not be used in patients with small cancers that are completely excised.
- Patients with pulmonary metastases are usually treated with ^{131}I.
- On occasion more than one dose of ^{131}I is required.

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Chapter 8

Thyroid Cancer and Pregnancy

There are several interrelated topics concerning a pregnant woman and thyroid cancer. First is the impact of pregnancy on thyroid function and thyroid function tests. Second is the management of a patient who is pregnant, usually in early pregnancy, and is then found to have a thyroid nodule. Third is the management when that thyroid nodule is found to be a cancer. Fourth is how to take care of a patient who has been treated for thyroid cancer and wants to become pregnant and her treatment when she is pregnant. Fifth, the impact of pregnancy on the thyroid cancer is discussed along with the effect of thyroid cancer on the pregnancy. The effect of altered thyroid metabolism on the offspring is addressed. The situation when a patient is inadvertently exposed to radioactive iodine at a time she is pregnant and the effect of that on the pregnancy and offspring and the legal implications are presented. Finally, the impact of pregnancy on a radiological or nuclear medicine worker is discussed.

Changes in Thyroid Binding Proteins and Thyroid Function Tests

The increased levels of estrogen in pregnancy cause a rise in thyroid binding proteins, in particular thyroid-binding globulin (TBG) (1). This is due to the combined effects of increased production of TBG by the liver and by reduced peripheral metabolism and therefore longer half-life. By the last trimester there is a two to three fold increase in the concentration of TBG. Transthyretin and albumin levels are similar to nonpregnant values (2). The level of total thyroid hormones (thyroxine [T_4] and triiodothyronine [T_3]) is dependent on the levels of the binding proteins and the function of the thyroid. In contrast the free or unbound hormone levels (FT_4 and FT_3) are primarily dictated by thyroid function and are not strongly influenced by the binding proteins. In pregnancy, because of high levels of TBG, total T_4, and total T_3 values are considerably higher than nonpregnant results, and the numbers can be difficult to interpret (3, 4). Measurement of free hormones is recommended (5). However, because of the rise in thyroid binding proteins, there is a slight fall in free hormone levels, since the free hormone is related to the ratio of total hormone divided by thyroid binding capacity. When it is not possible to have measurements of free hormone it is necessary to combine the measurement of the total hormones with a value for thyroid binding capacity. This can be obtained directly by assay of TBG or indirectly by the T_3 resin uptake, which is often abbreviated to T_3 uptake and should not be confused as a T_3 measurement. An estimate of FT_4, usually called the "free T_4 index," can be calculated using the equation:

$$FT_4I = \frac{T_4 \times T_3 \text{ resin uptake}}{100}$$

Table 8.1. Thyroid tests throughout pregnancy.

Thyroid test	Not pregnant	12 weeks	24 weeks	36 weeks
T4 μg/dl	4.5–12	***6.5–12.5***	***8.6–12.6***	***8.0–14.4***
T4 mmol/l	58–154	***84–160***	***111–161***	***102–184***
T3 ng/dl	80–180	***105–230***	***115–223***	***120–260***
T3 mmol/l	1.2–2.7	***1.58–3.46***	***1.73–3.35***	***1.8–3.96***
FT4 ng/dl	0.7–1.9	***1.15–2.9***	0.72–1.55	1.01–1.7
FT4 pmol/l	9–24	***14.8–27***	9.3–20	13–22
	10.7–18*	***11.1–22.9****	8.1–16.7*	8.5–14.4*
FT3 ng/dl	2.0–4.4	1.7–3.25*	1.6–2.39*	1.37–2.33*
FT3 pmol/l	3.5–7.7	3.0–5.7*	2.8–4.2*	2.4–4.1*
TSH mIU/l	0.4–4.0	***2.35***	***2.71***	***3.5***
TBG mg/l	16–34	***22–39.8***	***35.7–47.5***	***33–62.5***

Combined data from references (2, 4) and * at 11, 23 and 35 weeks (107).
Results higher than normal.
Results lower than normal.

This value has also been designated T_7, from T_4 and T_3, although T_{12} would be mathematically more correct. The normal values of thyroid tests throughout pregnancy are shown in Table 8.1. An analysis of the responses of 441 practicing obstetricians and gynecologists demonstrated that they had training in and knowledge of thyroid function testing in pregnancy (6). Although there is a slight reduction in FT_4 compared with non-pregnant values, the values in a pregnant euthyroid woman do not fall below the lower limit of the expected normal distribution, but the range is tighter.

Chorionic Gonadotropin and Thyrotropin

Thyrotropin (TSH) is usually the single most valuable measurement of thyroid function but there can be also physiological alterations from the normal nonpregnant range. (7) Human chorionic gonadotropin (HCG) has considerable structural homology with TSH, the alpha chains being identical. Human chorionic gonadotropin in high concentrations has some TSH action. This results in a slight rise in free hormones followed by a slight drop in TSH (8, 9). Human chorionic gonadotropin increases the trapping of iodine in thyroid cells in vitro (10). In vitro experiments also demonstrated an increase in mRNA of the sodium iodide symporter (NIS) and an increase in NIS protein. There is an inverse relationship between HCG and TSH levels. Very high values of HCG are found in patients with hyperemesis gravidarum and they have low TSH values and can be misdiagnosed as thyrotoxic (9, 11–15). The high values of HCG have been blamed for causing growth of thyroid nodules and accelerated growth of existing cancer (16–19). This is discussed below and not all authorities accept this is inevitable.

Goiter, Nodules, and Multinodular Goiter in Pregnancy

There is conflicting data on whether goiter is a normal occurrence in pregnancy. In regions of low iodine intake goiter is common. There is a legend that in ancient Egypt a thread tied around the neck of young women was used as a pregnancy test. Breakage of the thread due to enlargement of the thyroid signalled pregnancy. I cannot find published information on the sensitivity or specificity of the test. In contrast in the United States goiter in pregnancy is not normal, and should be judged to be due to some other factor such as autoimmune thyroid disease. The advised daily intake of iodine for a pregnant woman is 200 μg (0.2 mg). Although the amount of iodine in the diet in United States is falling, most adults take more than that. Pre-

natal vitamins also incorporate iodine, usually 150 µg per pill. This is not the case in Europe where some prenatal supplements do not contain iodine. The differences between countries of whether goiter is normal in pregnancy lie in dietary iodine and the level of plasma inorganic iodine (PII) (20). As discussed in Chapter 2, the kidney and thyroid compete for iodine. In pregnancy, there is a considerable rise in the glomerular filtration rate. When the intake is limited and the PII level is low the thyroid might already be maximally stressed to trap sufficient iodine to produce an adequate quantity of thyroid hormones. The increased renal filtration of iodine causes a further drop in PII. The thyroid is now at a disadvantage, and TSH rises to maintain normal free levels of thyroid hormones. The high level of TSH causes the gland to enlarge. In regions of iodine deficiency, there is also an increase in the incidence of multinodular goiter in women who are multiparous. Therefore in iodine deficient countries, goiter can develop in most women during pregnancy, and, in patients who have a goiter before conception, the gland can increase further in size. Very occasionally the increase in goiter size can be dramatic (21). The goiter becomes nodular as the number of pregnancies increase. Clearly women living in iodine deficient regions should receive supplemental iodine when pregnant or nursing (22). Urinary iodine measurements are often used to determine the sufficiency of iodine for an individual or a population. Values can be low in advanced societies. A recent investigation of Turkish women obtained a mean value of 30.2 µg/l compared with an expected result of 150–200 µg/l (23). Twenty-six percent of an Israeli population was moderately iodine deficient (24). This emphasizes the need for knowledge of iodine intake and treatment when it is deficient.

Studies on thyroid nodules in iodine deficient countries show that they can increase in volume during pregnancy. In a study in 221 healthy pregnant women in China, a thyroid nodule was identified by ultrasound in 15.3% in the first trimester (25). Five percent had a palpable nodule. The average dimension of the nodules increased in size through the third trimester, and even in the 3 months postpartum. In addition, 11.3% developed a new nodule as the pregnancy advanced. In iodine replete regions these physical changes are not found.

Thyroid Nodule in Pregnancy

Young women commonly have a nodule or nodules in the thyroid. This occurs in 2% to 5% of normal young women (26). Pregnancy is restricted to women, most of whom are young. Therefore, about 2% to 5% of young pregnant women have a thyroid nodule. Thyroid cancer is also more common in young women. In most series there are three times as many women than men, and the most common age is 30 years to 40 years. In nonpregnant women approximately 5% to 6% of nodules are cancerous (27). Some authorities put the likelihood of cancer in the pregnant woman higher in the range of 39% to 43% (16). This range is higher than other reports and my experience leads to a divergence of opinion on how to proceed as discussed below. Marley et al. compared FNA in fifty-seven patients, forty-four of which were pregnant and thirteen were early postpartum with 5,380 women between the ages of 15 years and 45 years who were not pregnant (28). The incidence of papillary cancer in the former group was 21% and in the latter 3.4%. These investigators did not find evidence to support "hyperplasia of pregnancy" as a pathological entity and recommend using standard criteria for interpretation of malignancy.

The joy of a woman going for her first antenatal visit is dampened when the obstetrician finds a thyroid nodule. When the nodule is diagnosed as cancer, the patient and husband are distraught. Not infrequently this is the first physical examination for the woman for several years; therefore, it is difficult to determine how long the nodule or cancer has been present. On finding a thyroid nodule thyroid function should be tested by measuring FT_4 and TSH. In most cases these are normal, a low TSH could be evidence of thyrotoxicosis but can be found in early pregnancy especially when there is malignant vomiting. When the free hormones are elevated and TSH is low the patient probably has an autonomous nodule alternatively she could have mild Graves' disease with a nonfunctioning nodule. In a nonpregnant patient this would be resolved by scintiscan using ^{123}I, but this test is contraindicated during pregnancy. As discussed in Chapter 4 the optimal procedure is an FNA of the nodule in this case in patients who

are euthyroid or biochemically hyperthyroid (29). There is some debate whether it should be done at this time or whether to wait until after delivery of the baby. The arguments some authorities make for waiting is that the likelihood of cancer is small, probably using the range 5% to 6% for young women, and, even if the lesion is cancer, it has a very high probability of being papillary cancer with slow growth and an excellent prognosis. Therefore, they argue do not worry the mother and let the pregnancy proceed. The opposite point of view is based on the higher likelihood of cancer. Secondly, knowledge of the tissue diagnosis is helpful both for the patient and her doctors. A report indicating the specimen is adequate and benign is obtained in about 70% to 80% and this is a great relief. Then the nodule can be monitored clinically, but no specific treatment is required. When the result is cancer, the usual decision is to refer for surgery. A minority of physicians would still wait until after delivery and these are the same ones who would advise no cytologic testing of the nodule and thus they are consistent. The knowledge of the presence of a slow growing cancer would not force them to operate and jeopardize the pregnancy (30). In a report published more than 30 years ago, three of five babies died as a result of maternal thyroid surgery in the second trimester (31). The mothers all underwent total thyroidectomy with radical neck dissection. This information is used as a reason for deferring workup and surgery. More recent publications indicate that surgery in a pregnant woman is safe for mother and fetus. Nevertheless in most cases the patient and physician want to know the diagnosis and would proceed with FNA and when there is evidence of cancer deal with that surgically.

An inadequate FNA result is an indication to repeat the procedure and in the pregnant woman there is reason to consider having a cytopathology technologist present for the original procedure to ensure there are sufficient cells for a definitive interpretation. An indeterminate FNA diagnosis is a dilemma recognizing that this is reported in 10% to 20% of nodules and 80% to 85% of these turn out to be benign. In this situation, I would, after careful discussion with the patient and often her husband, usually wait until after delivery before referring for surgery Figure 8.1.

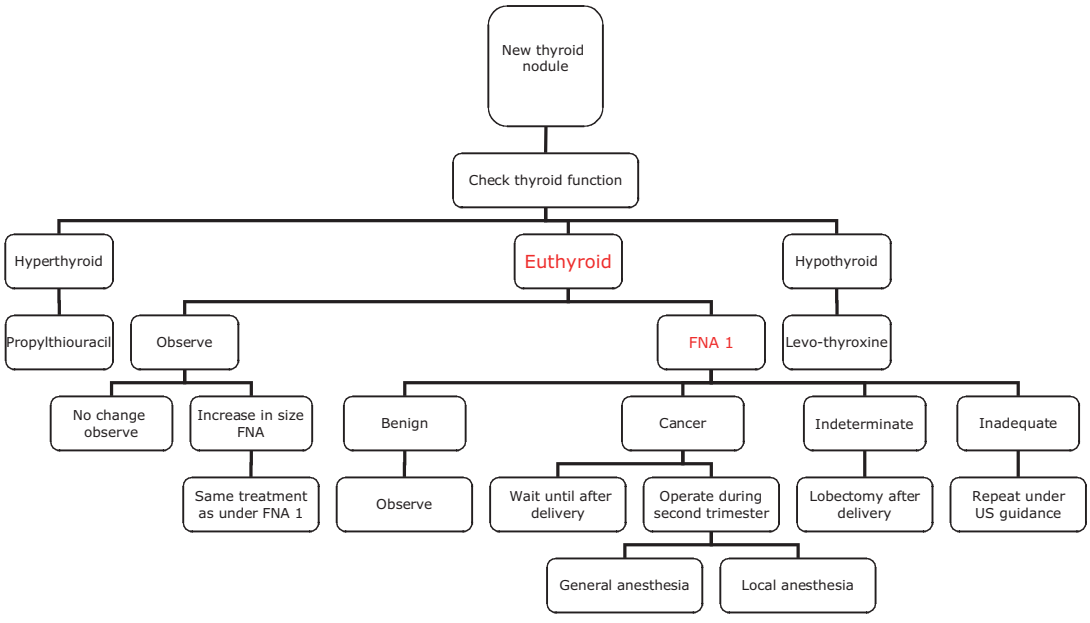

Figure 8.1. Algorithm lays out workup of pregnant patient with a new thyroid nodule. Most patients are euthyroid and there are two philosophies, to either wait and watch or proceed with FNA. Most would recommend the latter and base treatment on the resulting tissue diagnosis.

When the nodule is found in the third trimester, it is reasonable to delay FNA until after delivery.

Treatment of Thyroid Cancer Diagnosed in Pregnancy

The major questions are (32): (1) "Should the therapy of choice be different in the presence of a pregnancy?" (2) "Should the pregnancy be terminated?" (3) "What is the possible effect of therapy or avoidance of therapy on maternal wellbeing?" Thyroid cancer in a nonpregnant patient is usually treated by total thyroidectomy, in selected cases with ^{131}I and doses of levo-thyroxine, to maintain a low or later in follow-up a low normal TSH. Iodine-131 must not be administered to a pregnant or nursing woman and in general it is desirable that a pregnant woman is euthyroid. Therefore, there are differences in management. There is usually no reason to advise an abortion, and the goal is to have a healthy mother and baby. The omission of ^{131}I and a suppressed TSH for several months in a young woman with papillary cancer should not have an adverse effect.

In the case of a proven cancer, my decision to refer for operation is determined by the stage of the pregnancy. In the first and second trimester I would recommend operation. In late pregnancy, I would recommend waiting until about 3 months after delivery. There is obviously no controlled trial. The reason is based on not wanting to leave a known cancer untreated for the remainder of an early pregnancy plus a 3-month period post partum to allow the mother and child to bond. That would mean a delay of about 8 months to 10 months for a cancer diagnosed in the first trimester. The reason for delaying surgery in those diagnosed late in pregnancy is to avoid precipitating early delivery and birth of a premature baby. It has been determined that there is on average a delay of 10 months from discovery of the nodule until the diagnosis of cancer is made (30). This is not statistically different from the delay in non-pregnant women. In an analysis of outcome in sixty-one pregnant patients, Moosa and Mazzaferri found the average delay to operation in patients who waited until after delivery was 16.1 months compared to 1.1 months for those who proceeded to thyroidectomy when pregnant ($p < 0.001$) (30). When the decision is not to operate until after delivery, levo-thyroxine should be prescribed to keep the TSH at the low end of normal in the hope of reducing further growth of the lesion. It is inadvisable to use supraphysiological doses during pregnancy. In this situation the responsible physician should consult with the patient monthly to ensure the cancer is stable. An increase in growth or symptoms makes it necessary to change the conservative approach and to proceed with surgery. Driggers et al. reported on a woman diagnosed early in pregnancy by FNA to have papillary cancer (33). A decision was made to defer surgery until after the delivery. The lesion grew, and, at surgery at 24 weeks, the cancer was found to have invaded the trachea and recurrent laryngeal nerve and metastasized to lymph nodes. The authors argue for surgery during the second trimester and cite several publications where the baby had a normal outcome (34–36). In general surgery during pregnancy is safe for mother and fetus (37). Figure 8.1 shows an algorithm to ensure decisions are made at appropriate times.

After the decision is been made to operate most authorities accept that is safest in the second trimester. The surgery can be conducted under general anesthesia but this is a situation where operating under local anesthetic has a role. The first thyroid operation under local anesthetic is attributed to Dunhill, in Australia, almost a century ago at the time of writing (38). Although this is not the common approach, several surgeons have published their results (39, 40). The procedure is safe, generally well tolerated, and has a high degree of acceptability by patients. Rarely the procedure has to be changed intraoperatively to a general anesthetic. One of the major impediments is the concept since most surgeons receive no training in conducting a thyroidectomy under local anesthesia and this causes uncertainty about the first case especially when there are two patients at risk. The surgeon should have experience in thyroid operative procedures and have a low complication rate. Every effort should be made to preserve the parathyroids since hypoparathyroidism at this point in the pregnancy is very difficult to manage (41–44). When there is concern that the parathyroids have been jeopardized, one should be implanted in the neck or forearm. If hypoparathyroidism does occur the

patient needs to be treated with high doses of calcium and vitamin D. The baby has a large requirement for calcium for development of the skeleton. Two grams (2 g) to 3 g calcium and 0.25 μg to 0.75 μg 1,25 dihydroxy cholecalciferol (calcitriol) can be required and occasionally larger doses are necessary. Serum calcium should be measured at frequent intervals and the dose of calcium and vitamin D adjusted to maintain normality. The patient should be advised to report symptoms such as tingling or cramps. These can occur in normal pregnancy but can also be sign of hypocalcemia. There do not appear to be adverse effects to the fetus from calcitriol (43). The requirement for calcitriol decreases after delivery and during lactation; therefore, serum testing should continue (45).

The patient should be started on levo-thyroxine prior to surgery and the dose titrated to keep the TSH at the low level of normal. The dose of levo-thyroxine is greater in pregnancy and it is reasonable to start with 0.15 mg daily and check levels after 6 weeks and then titrate the dose dependent on TSH. (46–48) This is addressed again in the section on the patient with a history of thyroid cancer who wants to become pregnant. Total thyroid hormone values are usually elevated and more reliance should be given to FT_4 and TSH. Oral iron has a significant effect in reducing the absorption of levo-thyroxine from the gastrointestinal tract therefore prenatal vitamin and mineral preparations should be taken several hours apart from thyroid hormone (49, 50). Both ferrous sulfate and ferrous fumarate interfere with absorption (51). The patient should have measurements of FT_4 and TSH at intervals of 6 weeks to ensure that she is euthyroid. I do not recommend measuring thyroglobulin (Tg) at this time. The pregnant patient has endured a lot, first the finding of a nodule, then the diagnosis of cancer resulting in thyroidectomy. She and the baby are well. There is no benefit from knowing the Tg value, since nothing is going to be done about it until after delivery.

After delivery the requirement for levo-thyroxine decreases. This can be managed either by reducing the dose by 25 microgram when the patient is discharged postpartum and measuring thyroid function after 6 weeks. Alternatively the dose is not reduced until the patient is seen for postpartum followup at 6 weeks and tests are obtained at that time and the dose titrated appropriately (48). Because the patient has a diagnosis of thyroid cancer Tg should be measured now. This will help, along with the pathology results and surgical findings to determine whether there should be testing and treatment with radioiodine to be discussed below.

It is hoped that there is little thyroid tissue left after the operation. In the case where there is a large remnant it can be affected by postpartum thyroiditis in about 10% of normal people (52, 53). This results in release of thyroid hormone causing thyrotoxicosis followed after a few weeks by hypothyroidism. If these fluctuations in thyroid function are grafted on top of the "physiological" changes and alterations in the prescribed dose of levo-thyroxine there can be unexpected changes in thyroid function. The patient, her family and physician have to work closely together over the 2 months to 3 months postpartum to obtain stability of thyroid function.

The next decision relates to testing and treatment with radioiodine. Because the patient is a young woman, she is in the best prognostic group. The pathology and surgical report should be reviewed and her stage or prognostic score determined as discussed in Chapter 6. Most patients will be stage I or have low MACIS, AGES, or AMES scores, thus predicting an excellent outcome. The patient with a small intrathyroidal cancer that has been totally excised would not benefit from ^{131}I. When the Tg is undetectable the patient can be followed by clinical examination, measurement of thyroid function and Tg at intervals of 6 months over several years and then annually. Long-term followup of patients at the Mayo Clinic who had low MACIS scores demonstrated no benefit from ^{131}I. Radioiodine did not affect the recurrence rate and the mortality was so low there could be no benefit shown in that.

In the case of a cancer that is large, invasive, not fully excised or associated with nodal metastases there is a role for ^{131}I. The implications of administering ^{131}I to a woman who has recently delivered a baby are substantial. The patient most likely wants to breast feed her baby, and the active breast avidly traps iodine to supply that essential mineral in the milk. The sodium iodide symporter is active in this setting and NIS mRNA and the NIS protein have been identified in breast tissue (54, 55). As a result the maternal breast and the baby would be exposed

to radiation. No testing or treatment with any radionuclide of iodine should be considered while a patient is breastfeeding. Even after discontinuation of nursing there is milk production for weeks or months and the breast can be identified on whole-body scans (56, 57). Therefore treatment with ^{131}I could expose the breast, which is a radiosensitive organ to a substantial absorbed dose of radiation. There is evidence of an increased incidence of breast cancer in women with a prior diagnosis of thyroid cancer and one of the explanations could be prior treatment with ^{131}I (58). A historic paper calculated that 27% of the iodide was secreted in milk over 48 hours (59). When it is deemed essential to obtain a diagnostic test ^{123}I can be used. Iodine-123 has an effective half life ($T_{1/2E}$) of 5 hours to 8 hours (60). Nursing can be stopped for 48 hours and a sample of milk counted in a well counter. When the radioactivity reaches background, nursing could recommence. Because of the long physical half life ($T_{1/2P}$) of ^{131}I, nursing has to be stopped for more than 50 days, even after tracer doses (61). There are mathematical models to calculate the fall off in radioactivity, but, in practice, if any dose of ^{131}I is administered, nursing should stop (60, 62, 63). The question needs to be asked why expose the breast to radiation? My recommendation is to wait 6 months after the patient stops nursing before proceeding with diagnostic scanning and therapy with ^{131}I. Thus, there can be a delay of 9 months to 12 months in a woman who nurses for 3 months to 6 months. This should not present a problem since the thyroid and cancer have been removed surgically and the patient treated with levo-thyroxine. This is a reason not to proceed directly to therapy with ^{131}I without a diagnostic scan. At a recent scientific meeting during a panel discussion one speaker promoted proceeding directly to therapy. I brought up concern of irradiating normal radiosensitive structures such as the breast. After the conclusion of the session a member of the audience came up to me and confessed that a patient had been treated that week without a diagnostic test, and she was lactating but fortunately not nursing. Whose responsibility is this? The patient is usually asked could you be pregnant (see below) and are you nursing? The answer to both questions would have been no. Further questioning might have resolved the issue of lactation. An ^{123}I scan would demonstrate whether the breast trapped and retained iodine, if so therapy should be deferred.

The next consideration is separating the mother who will be radioactive from her child (64). This is not required when ^{123}I or a low dose of ^{131}I is used for the diagnostic scan. I try and administer the test dose in the morning and keep mother and child apart until evening. After treatment separation is definitely required for a minimum of a week. This is dependent on the dose of ^{131}I administered and the amount of functioning thyroid. Since the baby is young and usually not walking, the separation is easy in theory but in practice can be difficult. When the patient is in the same house as the baby there is a natural tendency to visit the baby. Continuous help over the week is essential. If the baby can be looked after by grandparents, other relatives, or another trusted party in a different home that is ideal in terms of radiation protection. When the testing and treatment are conducted after withdrawal of thyroid hormone, the patient is hypothyroid and the emotional issues related to cancer and treatment with radiation are compounded by the mood changes of hypothyroidism. These all need to be worked out well in advance using sufficient time to cover all questions, concerns, and so forth.

The protocol is the same as presented in Chapter 6. TSH should be elevated and the patient on a low iodine diet for 2 weeks. Serum Tg is measured and a negative pregnancy test needs to be documented. Whole-body scan is obtained 24 hours after 74 MBq (2 mCi) ^{123}I. As soon as possible after the results of the scan are reviewed the patient would receive a therapy dose of ^{131}I based on the scan findings and stage of cancer. Levo-thyroxine is started after 24 hours and the low-iodine diet replaced by regular food at that time. A posttreatment scan after 6 days to 8 days would demonstrate whether there were additional lesions although we find this to be uncommon. A measurement of emitted radiation is obtained at this time to determine whether the baby can be reunited with the mother. A followup visit is arranged for 6 week to 8 weeks to confirm thyroid function is in the appropriate range aiming for a low or low normal TSH. Thyroglobulin would also be measured to compare with the pretreatment value. When the thyroid tests are physiological and the Tg value low the patient is scheduled for a visit in 6 months.

There is debate whether differentiated cancer is more aggressive during pregnancy. We and others did not find that to be the case (65, 66). A study comparing the outcome in sixty-one pregnant women and 528 age-matched controls and concluded the outcome was not statistically different (30). One patient who developed bone metastases deferred therapy for several years, and this should not be used as evidence of a worse prognosis (67).

Management of Patient with Thyroid Cancer Who Wants to Become Pregnant

A young woman with thyroid cancer might desire to have a baby. When the patient has had a thyroidectomy for thyroid cancer and there is judged to be no need for ^{131}I treatment she can try to conceive after 6 weeks to 8 weeks. This is to allow time to recover from the stress of the diagnosis and surgery and to ensure the dose of replacement levo-thyroxine is appropriate and serum calcium is normal. In a patient treated with ^{131}I it is necessary to wait some time before conceiving. Advise about how long to wait varies. Some recommend waiting 4 months. This is to ensure that all radioactivity has disappeared. For practical purposes when 10 half lives have passed there is no radioactivity therefore assuming the $T_{1/2E}$ and $T_{1/2P}$ are the same, 80 days (8×10 or just less than 3 months) would be sufficient. My philosophy is different. When it is judged that there is a need for ^{131}I treatment, it is reasonable to have a followup scan and measurement of a stimulated Tg to ensure the therapy was successful. This would usually be conducted 6 months to 12 months after ^{131}I treatment. I would then recommend waiting 3 months after that. The delay is to ensure all of the tracer has been eliminated and equally important to make sure that thyroid function is in a range that is good both for management of thyroid cancer and for conception. The TSH should be at the low end of the reference range. The patient should be taking prenatal vitamins and minerals at a different time from levo-thyroxine and any adjustment for this interfering with absorption of levo-thyroxine should have been made. Therefore, there would be a delay of at least 9 months but more often 12 months to 18 months between treatment of the cancer and conception. A further reason for this delay is presented below.

Effect of Iodine-131 on Fertility and Offspring

There are many publications attesting to the fact that women can conceive and carry a pregnancy after they have been treated for thyroid cancer (68–70). The ovary is exposed to radiation from circulating ^{131}I, from ^{131}I in the bladder, from the thyroid and other sites of functioning metastases and from ^{131}I labeled thyroid hormones. Most of the measurements and calculations have been conducted in hyperthyroid patients rather than patients with cancer of the thyroid. Robertson and Gorman calculated 0.14 rad/mCi or 14 rad/100 mCi (14 cGy/3.7 GBq) (71). Studies using direct measurements in the uterus produced a similar result of 0.18 rad/mCi (1.8 mGy/37Bq) (72, 73). These doses would not cause ovarian failure and would be associated with a theoretical risk of birth defects that would be low (74). Schlumberger et al. noted an increased incidence of miscarriage in the year after treatment, and this was probably related to abnormal thyroid function rather than gonadal radiation (68). There was no difference in the offspring after radioiodine treatment compared with those born before treatment. Vini et al. found only one woman who wished to become pregnant could not (70). In a different report, six children conceived within a year of maternal ^{131}I were compared to thirty-three pregnancies after a delay of more than a year (75). There were three anomalies in the six, including trisomy 18, aplastic anemia, and congenital hip dysplasia. There were two miscarriages and one case of ureteral stenosis out of the thirty-three later pregnancies. This argues for a delay of twelve months that fits well with my philosophy. The delay also allows a followup scan and measurement of a stimulated Tg.

In patients with recently diagnosed and treated thyroid cancer, it is generally advisable to maintain TSH below normal. This produces biochemical and, sometimes, mild clinical thyrotoxicosis. Clinical thyrotoxicosis causes menstrual abnormalities and the most frequent is

oligomenorrhea (76–78). Fertility is reduced. When a patient with treated thyroid cancer tries to conceive subtle abnormalities in thyroid function can reduce fertility. The dose of levo-thyroxine should be adjusted to maintain TSH at the low end of normal. This also allows some flexibility for the changes in thyroid function that take place after conception.

Management of Patient with Treated Thyroid Cancer Who Is Pregnant

When the patient is pregnant, the central issues are maintenance of the best health possible for mother and child. The patient should be counselled to contact you as soon as pregnancy is suspected or confirmed. Referral to the obstetrician, whom will be responsible for monitoring the pregnancy and the delivery, should be made when that has not already been arranged. There should be communication between physician in charge of the cancer and obstetrician. The patient must be advised to continue taking thyroid hormone, since some patients have heard they should not take any medications during pregnancy. The patient must also be advised that the dose of levo-thyroxine will increase as the pregnancy advances (Figure 8.2) (47, 79). The increased requirement occurs early, thus measurement of FT_4 and TSH should be obtained as soon as the conception is confirmed. A recent report demonstrated a 47% increase in requirement over the first half of pregnancy that levelled off at that time (80). However changes can occur in the last trimester and testing and readjustment are recommended through the entire 9 months. Supplemental iron, vitamins, minerals and folic acid should be taken but iron and calcium can interfere with the absorption of levo-thyroxine (49, 50). Therefore they should be ingested at different times. Sulfacrate and cholestyramine also cause malabsorption but these are not taken commonly during pregnancy (81, 82). I recommend checking thyroid function at intervals of 6 weeks and adjusting the dose of levo-thyroxine when the TSH increases. The goal is to keep the value at the low end of the range. There is data that children who are born to women who are hypothyroid throughout pregnancy can have a reduced I.Q. In addition hypothyroidism can result in maternal hypertension, preeclampsia, and premature delivery (46, 78). Some simply recommend increasing the dose empirically by 50 µg daily. We found the increased requirement of levo-thyroxine was on average about 50 µg/day and approximately 1 µg for every gain of 1 lb (79). However, there was great variability, and a uniform empiric increase in dose would be too much for some and too little for others. I argue against measuring Tg during pregnancy. The test should be low or undetectable before conception. If the value were to change there would be anxiety, but in general nothing different will be done; therefore, do not measure Tg until after delivery. Thyroglobulin values rise in pregnancy, but that is in people who have their thyroids in place. When the gland has been removed the value should be low and stay low, but the risk of a minor change causing concern argues for waiting until after delivery before obtaining the result. There is definitively no place for testing with radionuclides of iodine, and surgery is to be avoided whenever possible.

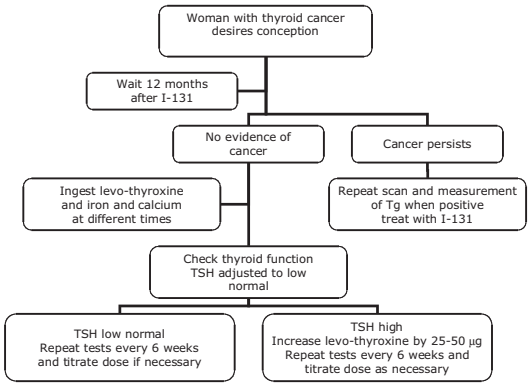

Figure 8.2. Algorithm shows options for managing a patient who has had thyroid cancer and wants to conceive.

Effects of Cancer on the Pregnancy and Pregnancy on the Cancer

The cancer should have no adverse effects on the pregnancy, provided thyroid function is kept physiological. There is no report of cancer

spreading from patient to fetus. There is some evidence to suggest that thyroid cancer is more aggressive during pregnancy due to stimulation by HCG (16, 18). We and others found the natural history to be similar to thyroid cancer in nonpregnant women (65, 67). In most patients, the cancer would have been removed and no growth would be expected.

Inadvertent Exposure of Pregnant Patient to Internal Radiation

It is generally accepted that the fetus should not be exposed to radiation. As a result diagnostic tests or treatments with radioactive materials are not usually justified in pregnancy. An exception would be the diagnosis of a disease that could kill the mother for which there is a therapy, though that would not be justified without a firm diagnosis. An example would be a lung scan in a patient suspected of having a pulmonary embolism. The cost of overlooking that diagnosis could be death of the mother and unborn child. Treatment with anticoagulants is associated with risks to both. The radiation dose to the fetus from the perfusion lung scan would be equivalent to a month of background radiation. In contrast radioiodine for testing or therapy are contraindicated at this time. The fetal thyroid traps iodine at about the tenth or eleventh week, in one report by day 74 (83). It traps more avidly than the adult gland, and it is very small. As a result, a relatively small dose of ^{131}I administered to the mother can ablate the fetal gland and cause permanent hypothyroidism. The radiation delivered to the fetal thyroid is expanded below.

It is remarkable how things change in medicine. On reviewing the literature I was reminded that a nuclear medicine test for placenta previa used albumin labeled with ^{131}I (84, 85). I conducted some of these tests more than 3 decades ago. Fortunately this has been replaced by ultrasound. I was also reminded that there were investigations of thyroid function in pregnant women using radionuclides of iodine (86, 87). This is now recognized to be inappropriate.

Patients most likely to be at risk for exposure are young women with hyperthyroidism, because this condition is more common than thyroid cancer (83, 88–91). Authorities state clearly that the patient should not be pregnant (92–94). The advice of how this is to be practiced is less clear. In the UK guidelines the committee say "no patient in whom there is a chance of being pregnant may receive radioiodine therapy; ***if necessary*** a pregnancy test should be performed" (94) (the bold italics are my editing not how the report appears). Stoffer and Hamburger polled 963 members of the American Thyroid Association and the Endocrine Society asking how many patients they had seen who were inadvertently treated with ^{131}I, did they advise abortion or carriage to term and when the pregnancy continued what problems were identified in the babies? Fifty-four percent responded and the investigators obtained reports of 237 patients who were treated with ^{131}I when pregnant (89). Fifty-five patients were advised to have a therapeutic abortion. One hundred eighty-two were counselled that it would be safe to continue with the pregnancy. Six children became hypothyroid, but four children were 12 weeks or older at the time of exposure. It is recognized neonatal hypothyroidism could occur at this time in pregnancy, since the fetal thyroid is functional. The diagnosis of hypothyroidism was not established until 6 months, 12 months, 18 months, and 48 months after delivery in these four children. There were two miscarriages, two stillbirths, and two congenital anomalies. The conclusions were that younger fetuses were at low risk of hypothyroidism and there was no increase in congenital abnormalities. The authors also conclude that the data does not support abortion for a woman treated in the first trimester. They also make the following statements: "We assumed by this time everyone administering ^{131}I therapy would routinely perform a pregnancy test," and, "It is difficult to justify reliance upon menstrual history." There are additional case reports of hyperthyroid women receiving ^{131}I treatment in the second trimester and delivering hypothyroid children. Fisher et al. presented a hypothyroid child whose mother received 536.5 MBq (14.5 mCi) (95). Based on an estimated age of 3 months, they calculated the fetal thyroid absorbed 250,000 rad (2,500 Gy). A similar hyperthyroid patient decided to have a thyroidectomy, but changed her mind and underwent ^{131}I treatment with a dose of 500 MBq

(13.5 mCi) (83). Ten days later she was recognized to be pregnant and ultrasound measurement estimated the fetus was 22 weeks at the time of treatment. Starting at the time of recognition of the pregnancy, the physicians measured the fetal thyroid uptake and the effective half-life $T_{1/2E}$ of ^{131}I. By extrapolation they estimated that 2% of the dose was trapped resulting in an absorbed dose to the thyroid of 600 Gy (60,000 rad). The trapping of iodine increases exponentially with age of the fetus. Book and Goldman calculated that 1 μCi administered to the mother would deliver up to 6 rad to a 22-week fetal thyroid and 8 rad at the end of pregnancy. Therefore a therapy dose of 10 mCi (370 MBq) would deliver 60,000 rad and 80,000 rad (600 and 800 Gy) at these times respectively (96). Another pregnant woman received repeated small doses of ^{131}I, 111 MBq, 44.4 MBq, 111 MBq, and 185 MBq (3, 1.2, 3, and 5 mCi) over 3 months. Her baby was hypothyroid. In each of these cases there was no pregnancy test. Evans et al. presented three women who were found to be pregnant at the time of ^{131}I treatment. The fetuses were 4-weeks to 6-weeks old, 7-weeks old, and 8-weeks old when exposed to ^{131}I (91). No pregnancy tests were obtained and reliance was placed on the patients' menstrual history. The therapy doses ranged from 370 MBq to 572 MBq (10–15.5 mCi) and none of the babies was hypothyroid. A woman treated early in pregnancy with 740 MBq (20 mCi) delivered a normal baby (97). This illustrates the importance of fetal age and damage to thyroid from ^{131}I.

Many of the older reports relied on tests to diagnose hypothyroidism in the baby such as protein bound ^{127}I that are now obsolete. Although all babies in most developed countries are tested for thyroid function using a blood sample from a heel stick, in this setting, the testing should include TSH and FT_4. Even when the thyroid tests are normal, they should be repeated to ensure the thyroid does not fail at a later date from continued radiation effect on the follicular cells. When the tests are normal at birth there is no data to advise when the followup measurements should be made but 3 months and 12 months seem appropriate. In a child who was exposed by intrauterine age of 10 weeks or more, it would be wise to start levothyroxine immediately after delivery. The hope would be that normal physical and mental development would follow. There is very limited data on the use of intraamniotic treatment. Agrawal et al. report on a fetus treated with intraamniotic triiodothyronine and then levothyroxine for a goiter and hypothyroidism (98). The therapy was successful in reducing the size of the thyroid. They could find only seven other publications. A similar case was treated using fetal TSH to determine the dose (99). Triiodothyroacetic acid (TRIAC) has been employed with success (100). Intraamniotic treatment is not without risk to the fetus and should be under the management of an obstetrician skilled in the procedure. Avoidance of the problem is the goal.

Most attention focuses on the effects of radiation on the thyroid. Other considerations include the increased risk of cancer in the baby and the possible deleterious effect on intelligence. With regard to cancer there is a 3% risk per Gy (100 rad). Stabin et al. have developed a method of calculating the dose to the fetus when a hyperthyroid pregnant woman is treated in error with ^{131}I (101). They based this on the thyroidal uptake in the mother and age of the fetus. The fetal radiation is less when the maternal thyroid traps avidly since a smaller proportion of ^{131}I is excreted in the urine. The highest dose is when the fetus is small, in the first and second months. Table 8.2 is an extract from their paper. There is debate whether there is a threshold for radiation effect on intelligence or whether the reduction in I.Q. is linear without a threshold dose. The estimate is a reduction of 30 points per Gy (100 rad). The brain radiation is the sum of radiation from the mother including from radioactive urine in the bladder, from circulating radioactivity in the fetus, ɤ radiation from ^{131}I concentrated in the fetal thyroid, and the distance between the brain and thyroid. O'Hare et al. have used several models to allow determination of absorbed brain doses (μGy/MBq) as a function of gestational age (102). The same group have developed a phantom for calculating absorbed doses to the fetus from maternal radioiodine (103).

Patients having diagnostic scans for thyroid cancer usually receive a diagnostic dose of ^{131}I (usually 1–10 mCi). It is important to ensure they are not pregnant. Treatment of thyroid cancer with ^{131}I usually involves larger doses from 1.1 GBq to 7.4 GBq (30–200 mCi) and documentation of a negative pregnancy test is even

Table 8.2. Radiation to fetus from mother treated with ^{131}I mGy/MBq.

Fetal age months	20% uptake biological half-time for uptake = 6.1 hours	60% uptake biological half-time for uptake = 6.1 hours
1	0.083	0.072
2	0.055	0.043
3	0.055	0.046
4	0.042	0.035
5	0.032	0.028
6	0.029	0.026
7	0.027	0.024
8	0.026	0.024
9	0.024	0.022

Extracted from Stabin et al. (101).

more important. Apart from the fact that the therapy doses to treat cancer are greater than for hyperthyroidism there are other differences. The proportion of radioiodine that passes through the placenta is usually greater in the patient with cancer because the thyroid uptake is considerably less. In cancer, the 24-hour uptake is usually less than 5%, and in hyperthyroidism it is almost always greater than 30%. In contrast there is more maternal circulating protein bound ^{131}I in hyperthyroidism, since the hyperactive thyroid produces more radioiodinated hormone. The fetal thyroid gets a higher relative radiation in treatment of maternal cancer; the fetal whole-body gets a relatively higher absorbed dose in maternal hyperthyroidism. When the diagnostic scan and therapy are planned with the latter following immediately, one negative pregnancy test before the administration of the diagnostic dose should suffice. In patients who have had a hysterectomy or documented tubal ligation the pregnancy test is not necessary. Table 8.3 lists several examples of hypothyroidism in babies born to mothers who were 12 weeks or more pregnant when treated for thyroid cancer with ^{131}I.

Even the most sensitive pregnancy tests can be negative in the first days of conception. Wilcox et al. studied this systematically using urine pregnancy tests (104). Implantation can occur as early as 6 days after ovulation, but about 10% occur after the expected date of the next menstrual period. Therefore a false negative result is possible. Home kits have a sensitivity for HCG of 25 mIU/ml to 50 mIU/ml. The level at implantation is 0.13 mIU/ml. This is an argument in favor of a serum test. Some patients are offended by the recommendation to be tested for personal, family, ethnic, or religious reasons, but usually this can be resolved by sensitive discussions. This is tricky when the patient is a teenager, but the patient and parents are usually understanding and recognize the importance of the test not only for the patient but more so for an unborn child. The medicolegal reason is also understood.

Although every effort should be made to avoid this problem when it occurs the fetus is likely to be very young, and there should be no concern about hypothyroidism. More significant is the situation when no test is conducted and the patient has a more advanced

Table 8.3. Effect of large doses of Iodine-131 administered in pregnancy on fetal thyroid function.

Reference	Age of mother	Age of fetus	Dose of ^{131}I GBq(mCi)	Outcome
Russell et al. (108)	33	16	7.3 (225)	Hypothyroid
	35	12	2.77 (75)	Hypothyroid
Hamill (109)		12	2.84 (77)	Hypothyroid
Arndt (110)	28	6 and 24	3.7 and 3.7 (100 and 100)	Hypothyroid
Goh et al. (111)	18	6	3.7 (99)	Hypothyroid
Exss et al. (112)	21	12	1.85 (50)	Hypothyroid

pregnancy. How should the mother of an exposed fetus be advised and managed? Again avoidance of the situation is preferable. The effects of radiation on brain development, embryogenesis, and carcinogenesis have to be determined. It is worth repeating that it has been estimated that there is a drop of 3 points in I.Q. for 10 rad (10 cGy). The increased risk of cancer is estimated to be 3% after 100 rad (1 Gy). When the fetus is about 12 weeks, or older, permanent hypothyroidism is anticipated and replacement for life is necessary. Several publications confirm permanent hypothyroidism in this setting. In earlier pregnancy, the data of Stoffer and Hamburger in hyperthyroid women support allowing continuation of the pregnancy (89). When larger doses are administered for cancer the treating physicians and patient need to be in detailed discussion and the advice of a radiation safety expert and genetic counselor is recommended to quantitate dosimetry for the specific case, based on the dose administered, thyroid retention, the stage of pregnancy, the risk to fetus, and so forth. Using the data of Stabin et al. a dose of 7.4 GBq (200 mCi) would deliver 0.6 Gy (60 rad) to a 1-month fetus assuming the maternal uptake was 20% (101). This is calculated to cause a reduction in I.Q. of 18 points. When there is maternal concern and no personal objections, therapeutic abortion should be considered.

Whenever there is inadvertent treatment of a pregnant woman the treating physician needs to discuss the case with care review and contact medical legal defense. This brings up the issue of who is responsible for obtaining the pregnancy test. I believe it is the duty of the physician who administers the ^{131}I. In a recent legal case where I was asked to give an opinion, the patient sued not only that doctor but also the family doctor and the endocrinologist. I felt the family physician had no such responsibility and happily this was judged to be the case. The situation of an endocrinologist who has cared for the patient and refers her to nuclear medicine for the procedure is less well defined, but I still think the responsibility belongs to the treating doctor.

As discussed earlier, patients are advised not to conceive for some time after radioiodine therapy. There is debate about how long but the philosophy of waiting for a few months after the followup scan has merit. A negative scan and low Tg are reassuring that a pregnancy with this information would not be a time for worrying about the cancer. Should the patient be eager to get pregnant earlier at least a 4 month to 6 month delay is advised but the high incidence of abnormalities described by Ayala et al. merits consideration of even a longer time (75, 94). There are cases where the advice is ignored or forgotten or the method of contraception fails. What advice should be given to the patient who becomes pregnant earlier than planned? The dose administered and the delay between therapy and conception should be considered. When this is several months, there should be less need to advise abortion. An additional factor is the degree of maternal hypothyroidism. Hopefully, the patient would have started on levo-thyroxine and be euthyroid or very close to euthyroid.

With increasing use of ^{123}I for whole-body diagnostic scans and the potential for use of the positron emitter ^{124}I and the low energy ^{125}I, Table 8.4 provides a comparison of radiation from these to fetal thyroid with ^{131}I. In the third trimester, 1 MBq ^{131}I would deliver 1.85 Gy (185 rem), and 1 MBq ^{123}I, ^{124}I, and ^{125}I would deliver 10.9 mGy (0.109 rem), 1.02 Gy (102 rem), and 1.52 Gy (152 rem) respectively (105).

In summary, there has to be a policy in place to ensure that a woman receiving radioiodine testing and therapy is not pregnant. I recommend documentation of a negative serum pregnancy test. It is also advisable that there are notices in the department asking any patient who thinks she might be pregnant or is unsure of this to report to the technologist or physician. This applies for all nuclear medicine procedures but for therapy no physician should treat a young woman without documentation of a negative test. A recent court report illustrates that a signature of a technologist who verified the

Table 8.4. Absorbed radiation dose in rem (same as rad) from 37 MBq (1 mCi) of radionuclides of iodine.

Fetal age Days	^{123}I	^{124}I	^{125}I	^{131}I
100	28	1,200	880	2,300
150	34	1,900	1,300	3,200
200	21	1,300	880	2,100
250	13	790	700	1,400

Extracted from Johnson (113).

patient did not think she was pregnant was insufficient evidence (106). The patient had thyroid cancer and received a scanning dose of 2 mCi ^{131}I (throughout the report, written by a lawyer, the units are misstated to be μCi rather than mCi). The patient turned out to be 15 weeks pregnant and the baby was born hypothyroid. The patient denied providing the information to the technologist so this resulted in a "he said, she said" dilemma. The reader can judge whom the jury would side with. A counter signature of the patient confirming she was not pregnant might suffice. It is of interest that there is no explicit recommendation in this legal presentation for an objective report of a pregnancy test. In my opinion that is not only optimal but also essential. The test could be a urine or serum one but the serum test is more sensitive and can be reported in less than an hour. Therefore it can be obtained immediately before treating. Additional reports can be accessed through www.nrc.gov/reading-rm/doc.

Working with Iodine-131 when Pregnant

In the US, a woman in the workplace is not considered to be pregnant until she declares so in writing. The woman and her fetus should not be exposed to 500 mRem (5 Sv) or more during the pregnancy. The worker should wear her radiation monitoring badge and an additional one for the fetus. When the technologist measures a therapy dose of ^{131}I to determine whether it is within the 10% degree of equivalence of the desired dose or vents the container to dissipate volatilized iodine great care is required and these tasks are best undertaken by a nonpregnant colleague. The pregnant technologist should stay as far as reasonable when she is scanning a radioactive patient. If the patient has retained 20 mCi (740 MBq) ^{131}I the emitted radiation at 1 meter would be approximately 4 mrem/hour. Therefore 125 hours of scanning patients with this amount of radiation would be permissible during the course of the pregnancy. By moving to 2 meters, the radiation exposure would be 1 mrem/hour since it is related to 1/distance^2 ($1/2^2$). With appropriate planning the pregnant worker should be exposed to considerably less than 500 mrem.

Summary and Key Facts

Thyroid nodules are identified in 2% to 5% of pregnant women. The incidence of cancer in a nodule is greater in pregnancy. The best test is FNA. When thyroid cancer is diagnosed in early pregnancy it can be removed safely by surgery in the second trimester. Patients who are pregnant or nursing should not receive diagnostic or therapeutic radioiodine. When a woman of childbearing age is treated with ^{131}I it is important to document that there is no possibility of pregnancy.

- Thyroid nodules are found in 2–5% of pregnant women.
- 15% to 30% of the nodules are cancerous.
- Most patients are euthyroid and the best investigation is FNA.
- Thyroid cancer diagnosed early in pregnancy can be treated by surgery during the second trimester.
- Surgery can be delayed until after delivery when the cancer is diagnosed later in pregnancy.
- Young women with differentiated thyroid cancer are in the best prognostic group.
- Most authorities support that the natural history of thyroid cancer in pregnant women is the same as in nonpregnant women.
- Diagnostic or therapeutic ^{131}I should not be administered to patients who are pregnant or nursing.
- A woman who has been treated with ^{131}I can conceive and the offspring are normal but a delay of 12 months is reasonable.
- The requirement for levo-thyroxine increases during pregnancy.
- It is important to ensure the pregnant patient is clinically and biochemically euthyroid and the dose of levo-thyroxine should be determined by measurement of FT_4 and TSH.
- Iron and calcium supplements should be taken at a different time from levo-thyroxine.
- A negative pregnancy test should be documented before administration of ^{131}I.

- Inadvertent treatment of a pregnant woman with ^{131}I has important medico-legal ramifications.
- Administration of ^{131}I to a pregnant woman with a fetus that is 11 weeks to 12 weeks or older results in permanent hypothyroidism in the baby.
- Exposure of the fetus to radiation earlier does not result in hypothyroidism, but there is an added risk of cancer and reduced I.Q.
- A pregnant woman can work in Nuclear Medicine or Radiology departments, but, when the pregnancy is notified in writing, she should not receive an absorbed dose of 5 mSv (500 mrem).

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Chapter 9

Anaplastic Carcinoma of the Thyroid

Anaplastic carcinoma of the thyroid is the most lethal solid cancer in humans. This cancer arises from follicular cells, and its aggressive behavior is a dramatic contrast to the outcome in differentiated cancer. Fortunately anaplastic cancer is not common and accounts for about 2% to 3% of thyroid cancers in the US but the majority of deaths from thyroid cancer. Anaplastic cancer is becoming less prevalent in many countries (1). A recent publication from Japan indicated that 1.6% of thyroid cancers were anaplastic (2). In the report from the National Cancer Data Base there were 893 anaplastic cancers (1.7%) out of a total of 53,856 registered thyroid cancers (3). Although anaplastic cancer is becoming less frequent in modernized countries, in other countries the proportion of anaplastic cancers remains high and in one series reached 16%. These findings are generally from countries where the intake of iodine is low (4). The patient with anaplastic thyroid cancer is more often a woman and usually 60 years or older. The cancer grows explosively and locally invasive disease as well as regional and distant metastases occur. The only hope for cure is early detection and total surgical excision but usually this is not possible and combined radiation and chemotherapy in addition to surgery may reduce the speed of demise. Several reviews are recommended (5–7).

Etiology

Based on serial pathological sections, many cases of anaplastic cancer appear to arise from preexisting differentiated thyroid cancer most frequently papillary cancer. This relationship has been recognized for almost fifty years (8, 9). In a review of the literature, Wiseman et al. found this association in 23% to 90% of anaplastic cancers (10). The transformation from differentiated to anaplastic cancer can be shown histologically and by molecular techniques. (10–20) Some pathologists find the transition from differentiated to anaplastic cancer in all patients and they believe that is due to more complete examination of the entire specimen. (21, 22) The association of differentiated thyroid cancer with anaplastic cancer has in the opinion of some investigators indicated a better prognosis (23). This has been disputed by others (24). The difference almost certainly is dependant on the relative sizes of the differentiated versus anaplastic components. As described below incidental anaplastic cancer within a differentiated cancer has a significantly better outcome. Less commonly there is the association of anaplastic cancer with preexisting follicular cancer, including Hürthle cell cancer (25). In a minority of cases the cancer erupts from a

longstanding apparently benign goiter, although a dormant differentiated cancer usually cannot be excluded (26). That presentation is more likely to be the case in regions of iodine deficiency where multinodular goiter is common, and in these regions the prevalence of anaplastic cancer is higher. There is one report of anaplastic transformation of a follicular cancer in a patient who had a goiter resulting from Pendred's syndrome (15). Aldinger et al. described anaplastic cancer arising from papillary cancer or goiter in forty-nine of eighty-four patients (27).

Anaplastic transformation has been attributed to prior external radiation for lymphoma, or ^{131}I radiation for differentiated cancer. (28–32) In one report a 7-year-old patient received low dose external radiation to treat lymphoma and twenty-five years later developed papillary cancer and one year later was found to have metastatic anaplastic thyroid cancer. However, this transformation can occur without radiation and the association is not absolute. Carcangiu et al. found no patients with anaplastic cancer who had received neck irradiation (33). In contrast Kapp et al. reported two cases, one after external radiation, the other after ^{131}I for treatment of differentiated thyroid cancer and they reviewed the world literature (32, 34, 35). They identified 115 cases of differentiated cancer that progressed to anaplastic cancer, 30% had prior radiation (mostly ^{131}I) and 70% had not. They concluded radiation was not a risk factor, but on reflection the numbers do not support that. It is clear that 30% of the population at large has not received external radiation over the thyroid; therefore, that percentage is disproportionately high in these 115 patients. Nine out of sixty-seven patients treated at the Massachusetts General Hospital had received ^{131}I supporting that as an etiological factor (36). When radioactive iodine is prescribed in the treatment of differentiated thyroid cancer, the goal is to ablate all thyroid tissue, benign or malignant, and when that goal is achieved there should be no normal or differentiated cancer cells to dedifferentiate. When anaplastic cancer arises from differentiated cancer there has generally been residual cancer that could not be ablated, probably as a result of its inability to trap ^{131}I. One could hypothesize that the anaplastic cancer could represent a less well-differentiated clone, which subsequently loses all differentiation. Therefore, the theoretical risk of ^{131}I has to be accepted, and clinicians should attempt to follow ^{131}I treated patients over the long term. Nevertheless the probability of an anaplastic cancer being the result of ^{131}I has been estimated at about 5% to 10%. Anaplastic cancer has also been diagnosed after ^{131}I treatment of thyrotoxicosis. One patient developed cancer 30 weeks after ^{131}I treatment (37). This is probably too short a latent period to ascribe cause and effect.

Molecular genetics indicates there is a "two hit" cause. In poorly differentiated cancers there is a high incidence of mutations in the cancer suppressor p53 gene. Between 50% and 90% of anaplastic cancers have mutations in this gene, compared with 0% to 9% of papillary cancers (38–43). Lam et al. in a metaanalysis found mutations in 52% of 265 anaplastic cancers (44). One cancer has been shown to have N-ras mutation in a region of differentiated cancer of thyroid and to have mutations of both N-ras and p53 in the undifferentiated region (45). A different report on anaplastic cancers occurring after treatment of more differentiated cancers including ^{131}I in some patients brought out a link with radiation treatment and development of mutated p53 and anaplastic cancer (46). A recent analysis of 16 anaplastic cancer showed that 50% had a missense mutation in the BRAF gene with a thymine → adenine missense mutation at nucleotide 1796 (47). An investigation looking at chromosomal abnormalities in anaplastic cancers found them to be more common when these cancers evolved from follicular than papillary cancer (48). Another investigation has tracked chromosomal changes from follicular cancer to poorly differentiated thyroid cancer to anaplastic cancer (49). In the first step, there was an increase in gains at 3q and 20q, and an increase of losses at 7q and Xp. Then in the transformation from poorly differentiated to anaplastic cancer there were statistically less DNA gains at 7p and 12q, and more losses at 7q and 13q. Knowledge of the genes related to these sequences could help define the stepwise genetic changes from normal to well differentiated to poorly differentiated to anaplastic cancer. In contrast Yoshida et al. transferred a normal human chromosome 11 into anaplastic cancer cells growing in vitro (50). The cells lost some of their anaplastic phenotype.

Anaplastic cancers are more frequent in regions of iodine deficiency, which in turn causes endemic goiter and multinodular goiter. The association with preexisting nodular goiter has been confirmed recently (51). In regions where iodine supplementation has been instituted, there has been a statistically significant reduction in the number and proportion of anaplastic cancers (52). There is no direct evidence for a familial etiology of anaplastic cancer. Although a report from the Swedish Cancer Registry appeared to find such a relationship, the authors attribute this to misclassification of medullary cancers as anaplastic (53). A statistically significant relationship to preexisting diabetes has been reported but is difficult to explain (51).

Pathology

The pathology is discussed in Chapter 3. These cancers are usually giant cell, or spindle cell type with each representing about half of the cases. Squamous cell cancers are rare (54). Squamous cell cancers accounted for seventeen of 2,214 (0.7%) thyroid cancers in one series (55). Some authorities indicate squamous cell cancers are best classified with anaplastic cancer based on the similar very poor prognosis (54). They are discussed in this text in Chapter 6 but could have been included here as well. In anaplastic cancer the cells are large, bizarre, and are often multinucleated with hyperchromatic nuclei. There is significant DNA aneuploidy (56). The same investigators found the prognosis was worse for cancers with the greatest aneuploidy. Other authorities agree that aneuploidy is very common but did not appear to influence the outcome (57). Standard histologic staining techniques with monoclonal antibodies against thyroglobulin, calcitonin, cytokeratin, lymphocyte antigens, and immunoperoxidase stains usually make it possible to prove the origin of the cells with considerable accuracy (58–60). Nevertheless, when the cells are extremely dedifferentiated they do not make thyroglobulin. The cancer usually is invasive into adjacent tissues including muscle and trachea. There is also vascular invasion. The doubling time has been estimated at 1 week and I have seen patients in whom sites of disease could be seen to enlarge day by day. A rare form called paucicellular anaplastic cancer has extensive fibrosis and few follicular cells. It is thought to result from infarction of the primary lesion (61). Its prognosis might be slightly less gloomy.

In older reports there were some patients whose carcinomas were classified as small cell anaplastic small cancers. These patients survived longer and in retrospect these cancers were either lymphomas or medullary cancers rather than anaplastic cancer (62).

Clinical Features

Most of the patients are older than 60 years and there is a about a twofold increase in women as shown in Table 9.1. The symptoms include a rapidly enlarging neck mass that occurs in almost 100% of patients (63). Breathlessness, choking, hoarseness, and difficulty swallowing (the three D's, dysphagia, dyspnea and dysphonia) are each found in about 30% to 50% of patients and many patients have more than one of these major symptoms (64). The frequency of symptoms and signs are shown in Table 9.2. The duration of symptoms is usually 2 weeks to 6 weeks. Extremely rapid growth of

Table 9.1. Patient characteristics for anaplastic thyroid cancer in publications with more than 20 patients.

Reference	Number of patients	Average age * median age	Ratio women/men
Pierie et al. (36)	67	73	2/1
Heron et al. (64)	32	64*	1/1
Shvero et al. (60)	26	66	2.7/1
Aldinger et al. (27)	84	64	1.5/1
Carcangui et al. (33)	70	67	3.1/1
Junor et al. (124)	91	70*	2.4/1
McIver et al. (65)	134	67	1.5/1
Besic et al. (120)	79	65	2/1

Table 9.2. Percentage of symptoms and signs in patients with anaplastic thyroid cancer.

Reference	Number	Thyroid mass %	Dyspnea %	Dysphagia %	Dysphonia %	Pain %
Shvero et al. (59)	26	81*	31	15	16	
Lo et al. (63)	28	96	29	46	36	25
Nel et al. (58)	82	87	50	33	43	40
Pierie et al. (36)	67	99	28	33	51	9
Heron et al. (64)	32	72	9	37	13	6
Junor et al. (124)	91	100	36	34	16	
Simpson and Carruthers*	17	35	6		29	24

* Squamous cell cancer.

the primary cancer is the predominant feature, however, lymph node metastases are present in 80% and distant metastases have occurred in about 50% at the time of presentation (65). The local disease invades midline structures. The diagnosis can be made with considerable accuracy from the bedside. The patient has a rock hard fixed thyroid mass that is usually more than 5 cm in diameter. There can be hoarseness and difficulty speaking and breathing. Stridor can be present. This cancer can cause obstruction of the superior vena cava. About 20% to 30% of patients have neck pain. The cancer can metastasize to any organ. The most frequent sites of distant metastases are the lungs and skeleton and less commonly to the brain and meninges (66–69). There are cases of metastases to very unusual sites including the heart, tonsil, and small bowel (70–73). Metastases to the skin have been described (74). These carcinomatous infiltrates cause an "erysipelas" like reaction (75). Very rarely there is an associated neutrophilia or even leukemoid reaction in the blood (76, 77). Granulocyte colony stimulating factor has been produced by cancer cells in two patients with neutrophilia (78). Anaplastic thyroid cancer is a rare cause of pyrexia of unknown origin (PUO, or fever of unknown origin, FUO) (79). An 85-year-old patient with anaplastic cancer had both leukocytosis and low-grade fever (80). Hypercalcemia has been attributed to anaplastic thyroid cancer (81, 82).

When the cancer is explosive in growth the destructive disease can cause release of preformed thyroid hormones resulting in symptoms and signs of thyrotoxicosis (83). This could be misdiagnosed as subacute thyroiditis and when there is doubt a fine needle aspiration (FNA) is recommended. The syndrome has been called carcinomatous pseudothyroiditis. This is discussed further under diagnosis.

Occasionally the cancer is found in a surgically removed nodule when there has been no clinical suspicion of anaplastic cancer. When the lesion is small and completely removed, a very fortunate circumstance, this is the only hope of long-term survival (84).

Diagnosis

Because of the rapid onset of the disease and its terrible prognosis an early tissue diagnosis is important. This is achieved by immediate FNA (80). Scintigraphy, or ultrasound do not help in the diagnosis and can delay urgent care. Chest radiograph with views of the thoracic inlet help define encroachment on the trachea and whether there are pulmonary metastases. Computed tomography (CT) scans of the neck and thorax give information about the relationship of the cancer to the aerodigestive tract and the vascular bundles and should be ordered as an emergency. In this clinical situation, it is legitimate to use iodine contrast, since if the diagnosis is anaplastic cancer there is unlikely to be a role for radioiodine, and if the lesion is not anaplastic there would be a delay of 4 weeks to 6 weeks after surgery for withdrawal of thyroid hormone. This would allow the iodine contrast to be excreted and then testing and treatment with radioiodine could be organized.

The differential diagnosis includes lymphoma of the thyroid, De Quervain's (subacute) thyroiditis, Reidel's thyroiditis, and rapidly growing but differentiated thyroid cancers, including medullary and Hürthle cell cancers. There is a report of Rosai-Dorfman disease, sinus histiocytosis with massive lym-

phadenopathy, in the thyroid that was originally diagnosed as anaplastic cancer (85). The FNA generally establishes the correct diagnosis. Some clinicians recommend an open biopsy but when the therapeutic decision is to proceed with combined chemotherapy and radiation therapy the incision might not heal well and cause a delay in completing these treatments (86).

Most patients have normal thyroid function. As stated above there are reports of patients presenting with thyrotoxicosis (83, 87–90). The invasive cancer causes release of stored hormone in the same fashion as an inflammatory thyroiditis (malignant pseudothyroiditis). There is a role for an ^{123}I uptake and or scan in a thyrotoxic patient with a hard mass in the thyroid to clarify the cause of excess circulating hormones. In this situation there is almost no uptake of the tracer of radioiodine. A patient with pseudothyroiditis will rapidly become hypothyroid and serial thyroid function tests are recommended. Unfortunately, the rapid course of this lethal cancer does not leave sufficient time in most patients for this to occur (87).

Sometimes the extent of disease is not clear and the local features drive the management. It should be recognized that about 50% of patients have distant metastases. I have found ^{18}FDG-PET scan is helpful in selected patients to define the extent of disease (Figures 9.1 and 9.2). The technique is to inject 370–555 MBq ^{18}FDG (10–15 mCi) intravenously with the patient fasted and to make the images after one hour. A full description of PET is provided in Chapter 6.

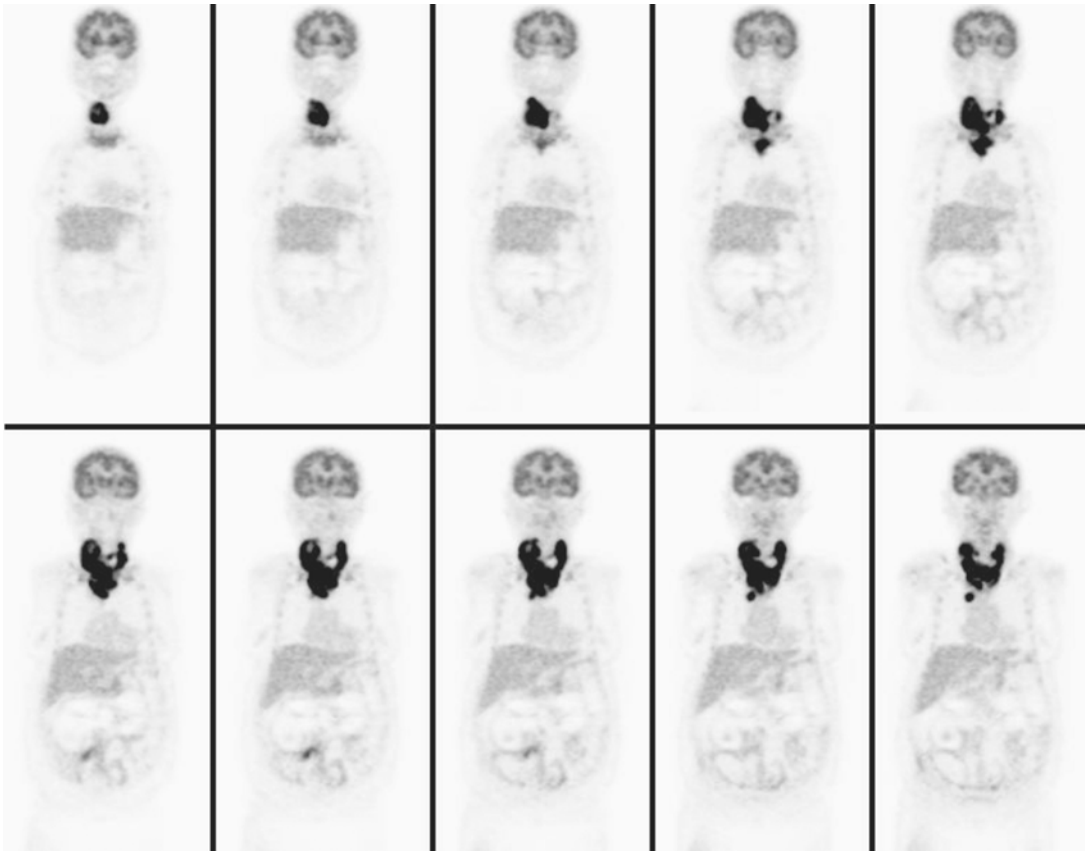

Figure 9.1. ^{18}FDG whole body scan in an eldely woman who presented with a rapidly growing mass in the thyroid. The lesion was hard and fixed on clinical examination. Fine needle aspiration demonstrated anaplatic cancer. The PET scan shows intense uptake in the cancer. There is no evidence of distant metastases.

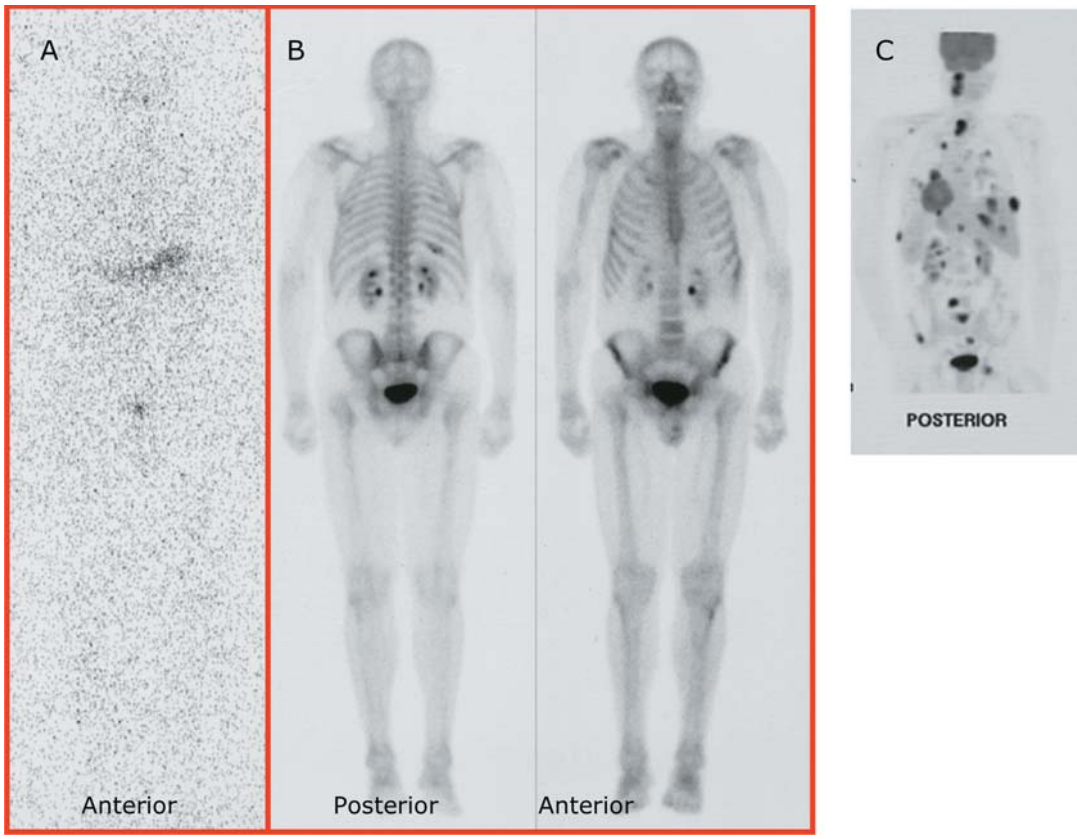

Figure 9.2. (A) is a negative whole-body scan using radio-iodine. (B) shows anterior and posterior whole-body bone scans showing subtle lesions in the ribs. (C) is ^{18}FDG PET scan showing widespread metastases. The patient had anaplastic transformation of papillary cancer that had been treated with surgery and ^{131}I and external radiation.

The uptake of ^{18}FDG is greatest in cancers with the poorest differentiation, therefore it would be expected that anaplastic cancer would be well visualized and that is the case. No large series has been reported, but there are publications of the potential of PET in this setting (91–95). Positron emission tomography allows the local extent of disease to be determined and to stage the extent of spread. Intense uptake of ^{18}FDG implies that the cancer has a poor prognosis and is likely to be resistant to radiation (96, 97). Starting in 1978 there are reports of ^{67}Ga showing uptake in the primary lesion but this is not recommended as a routine investigation unless PET scan is unavailable (98–101). ^{99m}Tc-sestamibi (MIBI) and ^{99m}Tc-tetrafosmin have been used for scintigraphic imaging but are inferior to PET.

Treatment

It is difficult for one center to develop and report on meaningful numbers of patients treated using a controlled protocol because this cancer is not common, the progression of disease is very rapid, and the patients are elderly, usually frail, and unable to tolerate severe therapeutic regimes. Most of the reports about therapy are from regional centers, or multi-institutional trials. The options are surgery, external radiation, and chemotherapy. These are discussed separately but the modern emphasis is on a combined approach whenever the condition of the patient can tolerate that. Many of the published reports include patients who have not all been treated the same way, some have had greater or lesser surgical procedures, some

have had higher doses of radiation, in others hyperfractionation has been delivered, some have received one chemotherapeutic agent, and others have received combinations of chemotherapy. This along with the very poor prognosis makes interpretation of the benefit of specific treatments even more difficult. Irrespective of the treatments prescribed, the outcome is, by all criteria, disappointing. As a result there is no ideal multimodality protocol that is clearly superior and fits all.

General

There has to be cooperation of thyroidologist, pathologist, surgeon, radiation oncologist, and medical oncologist and a rapid referral to an institute that can provide a team approach is recommended (102, 103). Because of the dreadful nature of the disease, the patient must be given adequate relief of suffering with strong analgesia and sedatives as required, and the family should receive every support available. The individual treatments are discussed then integrated management.

Surgery

When needle aspirate of a less sinister clinical lesion shows anaplasia and clinically and radiologically, there is no evidence of invasion complete surgical excision should be advised (36, 84, 104, 105). This is the only hope of long-term survival (1). Aldinger et al. reported a mean survival of 5.4 years in 3 patients in whom the disease was confined to the thyroid and surgically removable, compared to 4.8 months in 81 patients with more advanced disease. The prognosis of these incidental anaplastic cancers should be analyzed separately from anaplastic cancers that present rapidly and invasively. Since most patients die from invasion and obstruction of vital structures in the neck, the treatment should be designed to relieve and prevent these distressing symptoms, as well as to improve survival. In advanced cases, several reports confirm that the prognosis is improved by removal of the thyroid or debulking the cancer (36, 106, 107). Because of the local extent of the cancer, complications from the surgery, including recurrent laryngeal nerve paralysis and hypoparathyroidism, are more common than after operation for other thyroid cancers in adults (36). If the patient is in respiratory distress tracheostomy is necessary but this can be technically difficult because of the extent and site of the malignancy. When the gland is clinically adherent to and invading into surrounding structures there is debate of role for surgery at that juncture. Thyroidectomy may be appropriate after combined chemotherapy and external radiation provided the cancer shrinks. However, some authorities argue in favor of surgery as the first treatment and indicate that approach provides a better outcome. The survival was better in forty-four of sixty-seven (66%) patients who underwent operation and was best in twelve who had complete excision (36). The one-year survival was 92% after complete excision, 35% after debulking, and 4% in those who were not treated by surgery. The facts that some patients were judged to be operative candidates and that some cancers could be removed totally indicate that some patients presented with a lesser degrees of cancer compared to those who were inoperable. In patients with invasive disease, radical surgery does not improve the outcome when compared to a less invasive procedure (108). With regard to the thyroid operation Clark recommends removal of the more normal lobe first to identify anatomic landmarks such as the trachea (109). He emphasizes that, since the surgery is palliative, every effort should be made to avoid complications.

External Radiation

Because of the poor outcome and the view of some clinicians that surgery as the primary treatment is ineffective, many oncologists have recommended external radiation as the primary treatment (110). There is now a consensus that high dose external radiation should be prescribed to all patients should they live long enough. Some recommend this prior to operation and those who operate first support postoperative radiation. There is evidence that hyperfractionation improves the survival. The radiation dose recommended is 40 Gy to 50 Gy (4,000–5,000 rad) and various fractions such as 2 Gy (200 rad) per day, or 1.6 Gy (160 rad) twice daily or 1 Gy (100 rad) four times a day have been prescribed. Many of the series have small numbers of patients and the authors

compare current treatment protocols with historic ones. As an example Heron et al. compared nine patients treated between 1952 and 1980 and twenty-three patients treated between 1981 and 1999. The first group received once a day radiation to a median dose of 40 Gy (4,000 rad), whereas the latter group received 1.6 Gy (160 rad) twice daily to a median dose of 60 Gy (6,000 rad) and this was combined with chemotherapy (64). The two-year survival for the twice-daily regime was 52% but different combinations of therapies including surgery and a variety of chemotherapeutic drugs make it difficult to identify the best regime. Nilsson et al. compared six groups of patients treated from 1971 to 1972, up to 1994 to 1997 (1). The therapeutic regimes changed from once a day radiation at the start, to twice a day, and finally the individual dose was increased to 1.6 Gy (160 rad) twice daily, to a total of 46 Gy (4,600 rad). This was part of a multimodality approach whose results are discussed below. Methods for delivering external radiation are described by Posner et al. (111).

Complications from hyperfractionated radiation are to be expected and include dry mouth, tracheitis and esophagitis. Osteonecrosis of the mandible has occurred (64). Care must be taken to ensure the spinal cord does not receive an excessive dose. In one early report two patients died as a result of spinal cord necrosis (112).

Chemotherapy

Almost all reports about chemotherapy support the use of doxorubicin, which was originally shown to have benefit by Kim and Leeper (113, 114). There is some evidence that combinations of chemotherapeutic drugs have added value. In one trial combination of doxorubicin and cisplatinum resulted in three complete and three partial responses in eighteen patients, contrasted with one partial response to doxorubicin. Another report supported the combination of bleomycin, Adriamycin, and cisplatinum (115). Most protocols use doxorubicin as a radiosensitizer as well as a chemotherapeutic agent. It is given in a dose of 10 mg/m^2/week (some use 20 mg/week). In spite of early shrinkage of the lesion with chemotherapy, when this is used alone the cancer grows back relentlessly and causes death by local invasion. Occasionally, chemotherapy causes sufficient reduction in size of the primary lesion to make it possible to consider surgical excision.

Ain et al. showed anaplastic cultured cells responded to Paclitaxel (116). Based on this information a multicenter trial using a 96 hour infusion of Paclitaxel (140 mg/m^2) every 3 weeks was conducted on nineteen patients (117). One patient had a complete response and seven (47%) had partial responses. The median survival in the responders was 32 weeks compared to 10 weeks in the non-responders. Recently other investigators have shown that low doses of Paclitaxel (Taxol) caused apoptosis of anaplastic cells grown in culture (118). In vitro some newer chemotherapeutic agents such as Gemcitabine have a beneficial effect in doses that could be achieved in patients. These plus novel approaches discussed below might give hope of an improved prognosis.

Multimodality Treatments

Multimodality treatment includes chemotherapy that should include doxorubicin plus simultaneous radiation, for example, 20 mg doxorubicin weekly plus twice daily external radiation of 1.6 Gy to a total of 46–60 Gy (4,600–6,000 rad). This can produce sufficient shrinkage of the cancer to allow thyroid debulking. Kim and Leeper produced complete remission in eight of nine patients treated with adriamycin 10 mg/meter^2 and hyperfractionated radiation 160 cGy twice daily to a total of 57.6 Gy (5,760 rad) (113). In the experience of other therapists the prognosis is terrible even after combined therapies. Aldinger et al. reported success in four of fourteen with combined surgery, radiation, and chemotherapy, in one of sixteen with surgery alone, in one of seven with surgery and radiotherapy, and in zero of seven with surgery and chemotherapy (27). In a separate investigation thirteen patients treated by surgery, external radiation, and chemotherapy had a significantly better outcome than twelve treated without operation or eight who did not receive chemotherapy (119). In this study, twenty-one patients who had local invasion of the cancer were excluded from the analysis and unfortunately many patients present in that way. In a report from the Mayo Clinic, multimodality treatment could not

be demonstrated to improve the outcome (65). These investigators reemphasize the "grim" prognosis and found that external radiation was somewhat beneficial in that the median survival was 5 months rather than 3 months. In contrast investigators in San Francisco found a "reasonable prognosis" in patients treated by operation and then radiation and chemotherapy (107). Results in 79 patients treated in Ljubljana found a better outcome when radiation and chemotherapy were delivered first (neoadjuvant therapy) and then the cancer was removed by operation (120).

Brain metastases might be amenable to surgical excision when they are in a noncritical region of the brain. Otherwise, treatment by external radiation therapy or "gamma knife" should be prescribed.

In summary almost all clinicians who take care of patients with anaplastic cancer of the thyroid advise multimodality therapy. When the cancer appears to be amenable to surgery that could be undertaken first and followed by external radiation and chemotherapy. When the lesion is massively invasive external radiation and chemotherapy can be started and if the cancer shrinks surgery can be planned at that time. Veness et al. sum up the situation "most patients with anaplastic thyroid cancer are incurable; however, a multimodality approach incorporating surgery and radiotherapy and chemotherapy, in selected individuals, might improve local control and extend survival" (121).

Radioiodine

Anaplastic cancers do not express NIS. Therefore in most patients there is no role for ^{131}I. However, when there is dedifferentiation in the center of a differentiated cancer it is advisable to ablate all functioning tissue with ^{131}I as described in Chapter 6. Reports of anaplastic cancers that show uptake of ^{131}I usually are explained by this relationship (122). Retinoic acid has been administered with the intention and hope of increasing ^{131}I uptake by poorly differentiated cancers (123). This is almost never successful for anaplastic cancer. The retinoic acid pretreatment needs several weeks by which time the patient could have died. See Chapter 6 for details in differentiated thyroid cancer.

Summary of Therapy

It appears that no matter how this cancer is treated, the outcome is extremely bad. There is some evidence that by combining surgery, radiation, and chemotherapy the survival is extended. Some favor operation first others recommend the surgery should come after radiation and chemotherapy.

Prognosis

The prognosis for patients with anaplastic cancer of the thyroid is dismal. Since the patient usually has far advanced local disease and regional or distant metastases when first seen, the physician and patient have to accept the disease is incurable. Carcangiu et al. report that 82% of the patients they followed died within 1 year (33). The median survival in another series of 91 patients was 21 weeks (124). Kobayashi et al. prescribed surgery, hyperfractionated radiation therapy, and chemotherapy (104). In spite of the intensive treatment thirty-four of thirty-seven patients died within one year. Casterline et al. felt that survival for longer than 2 years was sufficient to warrant a case report, and they summarized the results of ten publications and showed that the two-year survival in 420 patients was 2.6% (125). I have one patient alive and well 17 years after the original diagnosis. He had a new thyroid mass, hoarseness, a surgeon removed the left lobe, and the lesion was 4 cm × 3.4 cm × 3 cm with some attachment to the trachea. A bone scan and CT of neck chest and abdomen showed no metastases. He had completion of thyroidectomy at Stanford followed by external radiation. The relatively small size of the cancer and his age of 52 were favorable features. We did not publish this report.

When evaluating prognostic factors and the effect of therapies, readers must separate data from patients who have incidental anaplastic cancer from the outcome in patients whose disease is truly anaplastic cancer. In the former situation, the pathologist identifies an undifferentiated component within the excised tissue, but it is confined and treated by operation. In the other situation the disease is rapid in growth, relentlessly invasive and locally and distantly metastatic. Few patients with non-incidental anaplastic thyroid cancer survive 1

year and most are dead in 3 months to 6 months. By staging systems almost all anaplastic cancers are Stage TIV, but they are not all equal. Bad prognostic factors include rapid onset, cancers greater than 7 cm in size, dyspnea, dysphagia, old age, and distant metastases (126, 127). Unfortunately, patients with non-incidental anaplastic cancers have many of these unfavorable prognostic factors. The prognosis is best when the cancer can be totally removed and patients who have their cancer debulked have a better outcome than those who do not. This is also a reflection on the size and extent of disease; smaller cancers are more likely to be operable.

Prophylaxis

It is gratifying that the incidence of anaplastic cancer is declining. Part of the reason appears to be earlier diagnosis and more effective therapy of papillary cancer. It is also apparent that anaplastic cancers that are small and excisable have a better outcome. The correction of iodine deficiency by iodized salt is also a factor. These facts point to the importance of obtaining an early tissue diagnosis of a new thyroid nodule, a dominant nodule in a multinodular goiter and a gland that starts to enlarge. Thyroidectomy would be advised when there was any evidence of malignancy. With increasing knowledge in the molecular events that lead to cancer and to differences in characteristics of histologic varieties of thyroid cancer, it might be possible to identify genetic changes that are indicative of a more aggressive cancer and to treat these lesions early and vigorously.

The Future

There are a number of experimental approaches that could well translate into clinical use and these are presented below. Most of these are related to advances in molecular biology but some to new physical treatments. One patient was treated using percutaneous laser thermal ablation that was directed by ultrasound (128). As discussed above Paclitaxel (Taxol) has been shown to be beneficial in anaplastic cells in vitro. Other investigators have cautioned the interpretation of the results and suggest there might be a narrow therapeutic window (118). A combination of maumycin and paclitaxel was superior to either one alone in cell cultures and in nude with implanted with cancer (109). One study in mice bearing grafted anaplastic cancers has shown benefit of interleukin-12 injections. (129) A different experiment demonstrated that interleukin-12 (Il-12) gene product that was transfected using CMV into anaplastic thyroid cancer cells in culture caused failure of these cells to grow in mice (129). In another experiment an adenovirus was designed to grow in cells containing mutation of p53 (130). The virus designated ONYX-015 kills cells with this mutation. ONYX-015 has also been found to increase the anti-cancer effects doxorubicin and paclitaxel. This virus plus radiation had significant killing effect on anaplastic cells growing in culture. The combination was also successful in arresting growth of grafted cancers in mice (130). An alternative approach of killing cells with mutated p53 is the specific tyrosine kinase inhibitor, STI571 (imatinib mesylate, Gleevec) (131). This inhibited anaplastic cells growing in culture but had no effect on differentiated cells that contained wild p-53. ST1571 also inhibited growth of anaplastic cancers in mice. Other investigators found no beneficial effect of Gleevec on anaplastic cancer cells in vitro (132). There have been concerns that these experiments do not mean that these treatments will necessarily be of clinical value (133, 134).

Because ^{131}I is effective in differentiated thyroid cancer there are efforts to re-educate anaplastic cells to trap and retain ^{131}I. One set of experiments transfecting anaplastic cells with human thyroid peroxidase (hTPO) did not increase trapping of iodine (133). Gene transfer of NIS and hTPO genes could well provide an approach where ^{131}I would be trapped and organified. A novel approach was gene transfer of Thyroid Transcription Factor 1 introduced into cells by an adenovirus vector (135). This increased trapping and retention of radioiodine in vitro.

Transfer of suicide genes by retrovirus caused death of anaplastic cells in vitro (136). Another group of investigators found that NF-kappaB which is a nuclear transcription factor that is expressed after cellular stress, such as radiation caused resistance to radiation. Inhibition of NF-kappaB helped increase the response to radia-

tion in transplanted cells in nude mice (137). Valproic acid has been demonstrated to increase mRNA of NIS in anaplastic cells in culture. It did not result in an increased ability of cultured cells to trap radioiodine (138). In contrast lovastatin, a cholesterol-lowering drug, not only increased apoptosis of anaplastic cells but also caused them to produce Tg indicating a degree of redifferentiation (139). There are many groups of investigators studying the cellular defects in anaplastic cancer and attempting to design means of reversing them. It is hoped that the sum of these efforts will result in a breakthrough in management.

Summary and Key Points

Anaplastic cancer accounts for about 2% of thyroid cancers in iodine replete regions. It is the most aggressive solid cancer and few patients survive 6 months from diagnosis. The patients are elderly and might have a preexisting differentiated cancer or nodular goiter. The cancer grows very rapidly and causes local pressure effects and there are usually nodal metastases and in 50% distant metastases. Combination therapy with external radiation, systemic chemotherapy, and surgery produce a minimally better outcome.

- Anaplastic cancer of the thyroid is a lethal disease.
- It accounts for 1–3% of thyroid cancers.
- The patients are usually 60+ years and there is a 2:1 ratio of women to men.
- A high proportion of anaplastic cancers arises from differentiated thyroid cancer.
- A mutation in p53 gene is found in 80% to 90% of anaplastic cancers.
- Local metastases are present in 80% and distant metastases in about 50% at presentation.
- The average survival is 3 months to 6 months and long-term survivors are distinctly uncommon.
- Death is usually from local invasive effects.
- Treatment should include surgery, hyperfractionated radiation therapy, and chemotherapy. The sequence will vary from center to center.
- Prevention by early detection and treatment of differentiated thyroid cancer is recommended.
- A novel therapeutic approach is eagerly awaited.

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Chapter 10

Medullary Cancer

Medullary cancer arises from parafollicular cells that are also called C cells. Parafollicular cells produce and secrete the hormone calcitonin. This cancer accounts for 2% to 10% of thyroid cancers [1, 2]. The higher proportion is usually reported by physicians who have an interest in the management of familial medullary cancers. These authorities, thus, fall heir to familial clusters of patients. In practice about 2% to 5% of thyroid cancers seen by endocrinologists are medullary type, for example, 2.8% of thyroid cancers in the Surveillance Epidemiology and End Results data base were this type [3]. The proportion of medullary cancers that are familial also varies between reports (11–44%) and approximately 25% to 30% is a reasonable estimate [4–6]. Publications with a higher percentage of familial patients often are biased by kindreds with many patients with these disorders [7]. The familial cancers are transmitted as autosomal dominant and fall into 3 categories. One category consists of kindreds where there is an aggregate of medullary cancer and no associated conditions and is labeled familial medullary cancer [8]. The second category is the association of medullary cancers in families where the index patient or a first degree relative also has pheochromocytoma and or hyperparathyroidism. This is called Multiple Endocrine Neoplasia 2A (MEN 2A). The addition of "A" is to separate this syndrome from MEN 2B, which is described below. The differentiation of families with the MEN 2A from familial medullary cancer is not absolute because a patient with what appears to be isolated familial medullary cancer or one of his relatives might be diagnosed with pheochromocytoma thus changing the label to MEN 2A. The genetic abnormality to be discussed below can be the same in familial medullary cancer and MEN2A. There are additional rare subsets of MEN 2A one is associated with cutaneous lichen amyloidosis [9–11] another with Hirschsprung's disease [12]. Recently lichen amyloidosis has also been found in patients of a kindred with familial medullary cancer [13]. The third type of MEN syndrome, IIB has the major constituents of IIA including medullary cancer and pheochromocytoma [14]. It also includes a characteristic phenotype described as Marfanoid and the patients have neuromas of the lips, tongue and intestine. MEN 2B usually has an earlier age of onset [14, 15]. Ganglioneuromas can occur in other organs including the salivary glands, pancreas, gallbladder, upper respiratory tract, and urinary bladder [16]. The other manifestations of Marfan's syndrome are absent. MEN 2B can also be sporadic.

The largest groups with medullary cancer are those with sporadic cancer, but, again, this classification can be altered by the finding of a germline genetic abnormality and by the later occurrence of a similar cancer in a family member. Data on the percentages of these syndromes from several clinical reports are presented in Table 10.1.

The familial cancers are associated with a mutation in the RET protooncogene. Screening

Table 10.1. Relative percentages of patients with different phenotypes of medullary cancer.

Reference	Number of patients	Sporadic %	Total familial %	Familial medullary cancer	MEN IIa	MEN IIb	No data
Kebebew et al. [7]	104	56	44	22	15	7	–
Esik et al. [180]	91	31	38	11	26	1	32
Gharib et al. [181]	65	89	11	–	–	–	–
Raue et al. [182]	741	75	25	5	17	3	–

of family members for one of the mutations allows the diagnosis and treatment to be instituted before clinical disease occurs. The treatment of genetically identified or clinical disease is total thyroidectomy. In patients with established carcinoma a central lymph node dissection is also required. The lateral cervical nodes should also be removed in patients with large cancers and or significant metastases to the central nodes. After surgery, thyroid hormone is prescribed for life, but the TSH does not need to be suppressed, since C cells are not responsive to that hormone. External radiation of the neck is of benefit when there is residual disease. Chemotherapy is not effective. The prognosis is excellent when patients are treated in the early phase of the disease. The prognosis decreases when the cancer is large when there are nodal metastases and especially when there are distant metastases. Measurement of calcitonin is valuable for monitoring patients after therapy.

Historical Perspective

Medullary cancer is a relatively "new" disease. Before the origin of the cancer was understood it was originally classified as anaplastic cancer. Historically, it was one of the so-called small cell anaplastic cancers that are now known not to be anaplastic cancers. The cell type of the cancer was identified by a series of discoveries. For some years it had been predicted that there would be a hormone to oppose the effects of parathormone (PTH), which causes serum calcium levels to rise and calcium to be released from bone [17]. It was anticipated there would be a second hormone with the function of lowering serum calcium. This hormone was isolated and subsequently shown to be produced in and secreted by parafollicular cells or C cells in the thyroid [17, 18]. In the early days after its discovery, there was debate whether the calcium-lowering hormone was secreted by the parathyroids, the thyroid, or the thymus. When its origin was proven to be thyroidal, it was called thyrocalcitonin, but now it is universally called calcitonin. Calcitonin contains thirty-two amino acids and has a disulfide ring with seven amino acids at the N terminal. Radioimmunoassays for precise measurement of calcitonin were developed [19]. Most measurements are now made by ELISA methods. Readers interested in the detailed structure, genetics, molecular effects and therapeutic uses of calcitonin are referred to Zaidi et al. [20]. Parafollicular cells are sparse and are identified very infrequently on histological examination of normal thyroid glands.

The first pathological description of medullary cancer is attributed to Hazard et al. in 1959 [21]. The fact that the medullary cancer arises from the parafollicular cells is attributed to Williams [22]. Cunliffe et al. and Tashjian and Melvin confirmed this by extracting high concentrations of calcitonin from medullary cancer cells [23, 24]. Then procedures to stimulate the level of calcitonin including the infusion of calcium and pentagastrin or both were validated [25–27]. Since, the cancer cells secrete calcitonin measurement of that hormone became a diagnostic test to determine who had the disease [28]. This measurement was also shown to distinguish those patients who have been successfully treated from those who have residual disease.

The coexistence of thyroid cancer and pheochromocytoma in the same patient was recognized by Sipple [29]. The demonstration that the thyroid cancer was medullary cancer and its association with pheochromocytoma and hyperparathyroidism was described in the mid 1960s [30–33]. Many clinical reports followed [34–37]. Williams recognized and

reported on the association with pheochromocytoma and with cutaneous neuromas (MEN 2B) [14]. He also differentiated the familial syndromes with medullary cancer from the familial syndromes with tumors of the pituitary, pancreas, parathyroid, and adrenal cortex now known as MEN 1. Ganglioneuromas of the intestines were then recognized to be part of the MEN 2B syndrome [15]. The MEN syndromes were known to be familial and the genetic basis of the diseases was discovered when a germline abnormality was identified on chromosome 10 in patients with MEN 2A [38]. This was subsequently shown to be a mutation in the RET protooncogene [39].

Etiology

Familial cases of medullary cancers are associated with a mutation in the RET protooncogene [40, 41]. This topic was presented in Chapter 5 and the basic facts are reviewed here. RET is a 170 kd glycoprotein with an extracellular domain that has a ligand binding site (Figure 10.1). The region close to the cell membrane is

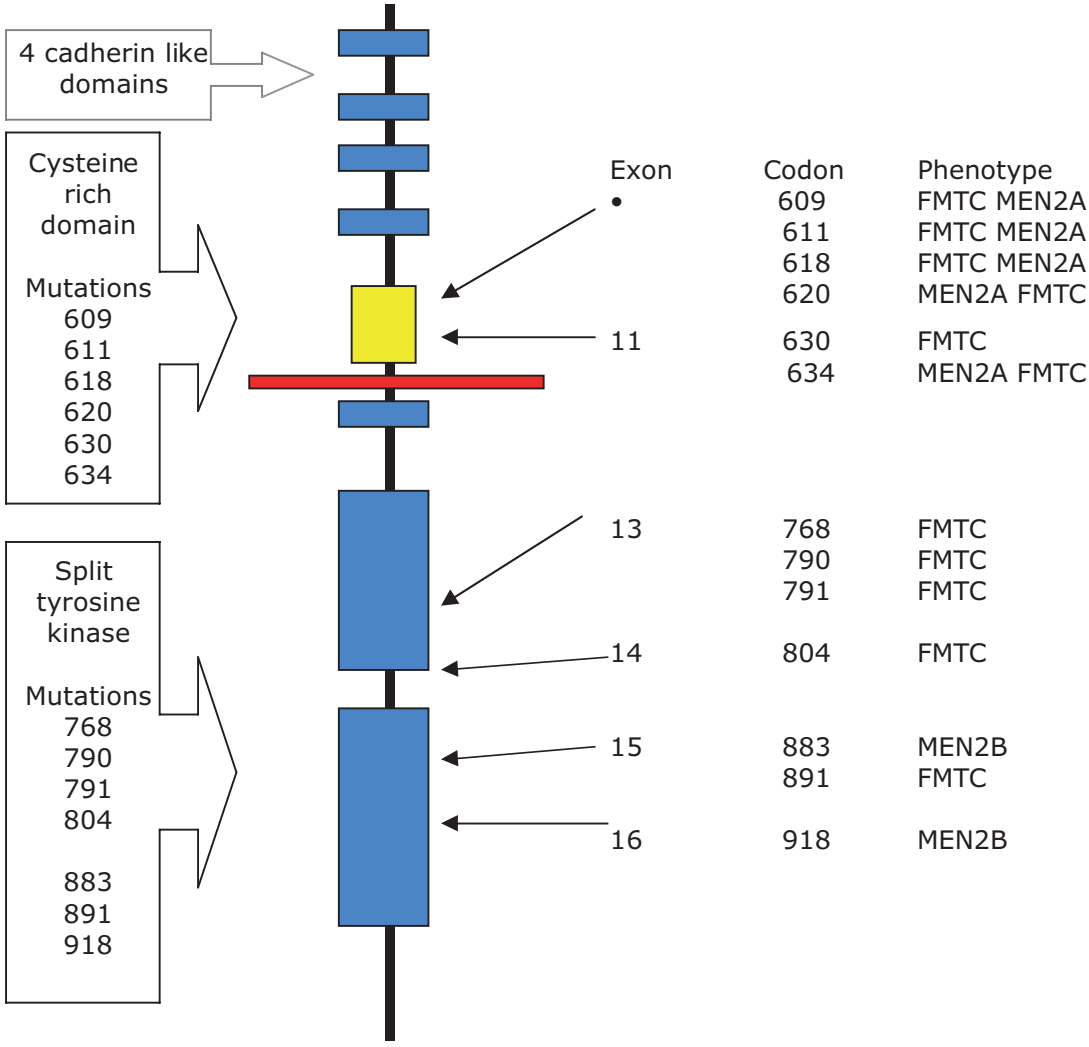

Figure 10.1. Schematic demonstrates the sites of mutations of the RET protein that result in familial medullary cancer syndromes.

rich in cysteine molecules. The intracellular component contains the enzyme tyrosine kinase. The enzyme is activated when two RET molecules form a dimer and this occurs in the presence of the activating ligand (Figure 10.2A). In medullary cancer there is a base exchange in the gene coding for one of the amino acids of the RET protein. This results in substitution of an alternative amino acid. Missense mutations of four codons in exon 10, two in exon 11, three in exon 13 and single defects in exon 14 predispose to MEN 2A (Table 10.2). In MEN 2B there have been two RET mutations identified in codon 16 and one in exon 15. In the case of familial medullary cancer not associated with MEN 2 syndromes several of the same mutations found in MEN 2A have been identified. The goal of genetic studies is not simply to identify individuals at risk for developing the syndromes but to try and predict the phenotypic behavior of the syndrome and the aggressiveness of the cancer. For example will a patient with a specific altered codon develop cancer early or late? Will a patient with MEN 2A due to a specific mutation be more or less likely to develop a pheochromocytoma? A multinational study of 207 young patients who were diagnosed by genetic testing has produced important information [42]. The commonest mutation was in exon 11, codon 634, and this accounted for

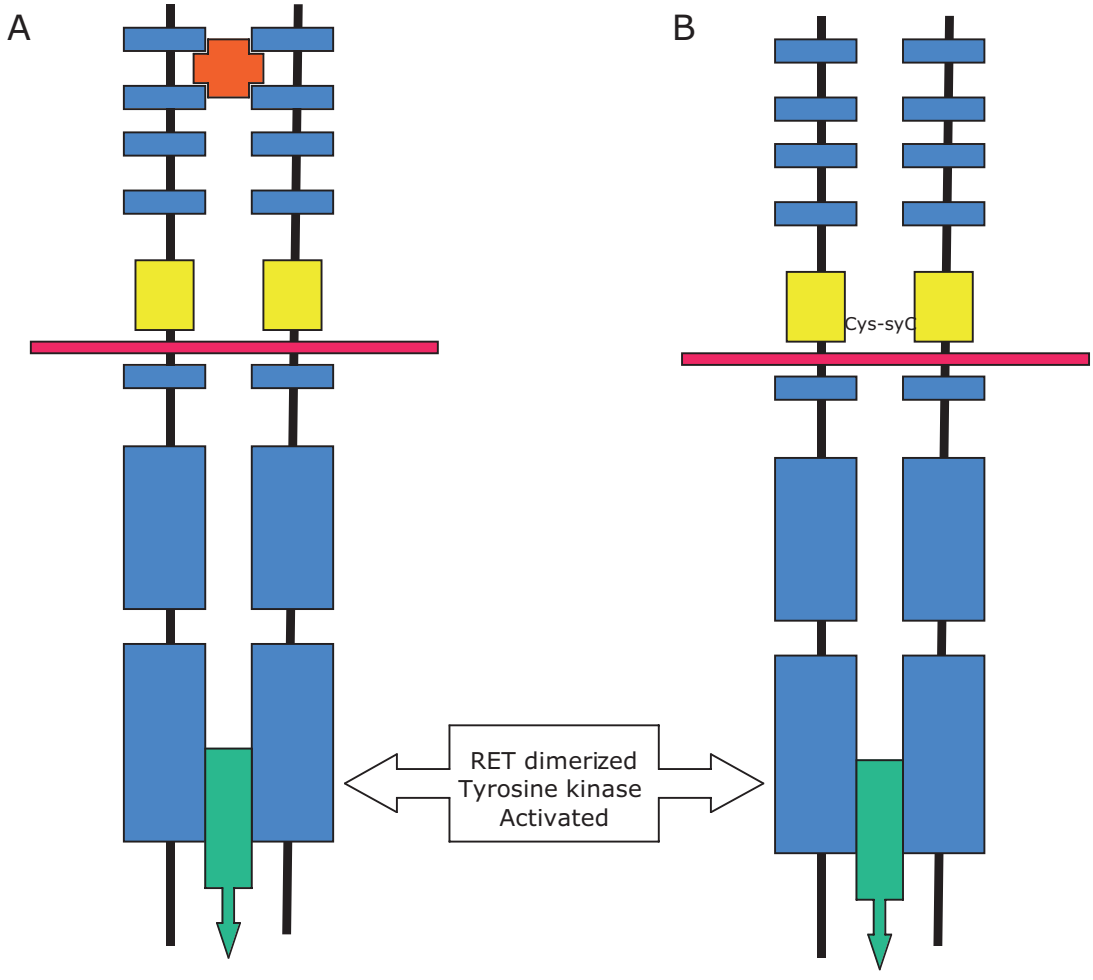

Figure 10.2. (A) shows activation of tyrosine kinase when the ligand results in formation of a dimer. (B) shows the same outcome when a mutation in the cysteine rich segment of RET produces a dimer by cross linkage of cysteines in two monomers.

Table 10.2. Mutations associated with familial medullary cancer syndromes.

Syndrome	Exon	Codon	% with proven RET mutation
Familial medullary cancer	10	609, 611, 618, 620	85
	11	630, 634	
	13	768, 790, 791	
	14	804	
	15	891	
MEN 2A	10	609, 611, 618, 620	97
	11	630, 634	
	13	768	
MEN 2B	15	883	95
	16	918, 922	

Adapted from references [94, 95, 183].

63% of the defects. The nucleotide sequence TGC that encodes the amino acid cysteine was altered in six possible ways. Two examples are that TGC could be mutated to TTC, which encodes for phenylalanine rather than cysteine, or to TGG that encodes for tryptophan. Recently a mutation from a GAG (Glutamine) to a GAC (Asparagine) in exon 13, codon 768 was found in a pedigree with familial thyroid cancer phenotype.

Patients in these kindred also had adrenal medullary hyperplasia, but this was not the case in any patient with this specific mutation [43]. The authors state the findings suggest that codon 768 is an accurate predictor of medullary thyroid cancer phenotype but lowers the likelihood of adrenal medullary hyperplasia. Genetic studies also allow prediction of the potential for cancers to grow and metastasize, and, in the future, might allow more precise timing of surgical procedures. Patients with specific mutations that historically have proven to be associated with slow growing cancer could be treated at an older age and vice versa. Yip et al. were able to stratify patients into three categories of risk [44]. This was based on genetic analysis of seventy-one patients in thirty-nine families. Mutations in codons 609, 768, 790, 791, 804 and 891 predicted a lower risk. The highest risk mutations were in codons 883 and 918. Mutations in codons 611, 618, 620 and 634 were intermediate risk factors. Twenty of twenty-one patients who had pheochromocytoma had mutations in codon 634 or 918. Seven of ten patients with hyperparathyroidism also had a defect in codon 634. Other investigators have described three groups; highest risk mutations at codons 883, 918 and 922 related to MEN 2B, high-risk mutations in 611, 618, 620 and 634 associated with MEN 2A or familial medullary cancer, and intermediate risk 609, 768, 790, 791, 804 and 891 [45]. In essence these are the same.

Mutations that substitute an amino acid for cysteine in the extracellular segment of RET are thought to cause activation as follows. Normally the cysteine molecules form intramolecular disulfide bridges, but loss of a cysteine allows the partner molecule to combine with a free cysteine in a second monomer thus forming the dimer, which activates intracellular tyrosine kinase (Figure 10.2B). Normally this happens when ligand is present but in the mutated state there does not need to be a ligand attached to the RET protein. The enzyme is constitutively active. Mutations in exons 10 and 11 cause this. Mutations in exons 13 through 16 that are intracellular are in the regions encoding the tyrosine kinase and result in activation of the enzyme without the formation of a dimer.

An analysis of risk factors for medullary thyroid cancer demonstrated a higher incidence in patients with a thyroid nodule or hypertension [46]. Cigarette smokers were less likely to develop this cancer.

Pathology

Malignant parafollicular C cells are eosinophilic in appearance and round or polygonal in shape. These cells were given the name parafollicular by Nonidez [47]. LiVolsi prefers the term C cell rather than parafollicular, because the cells lie within the follicular basement membrane [48].

"C" stands for calcitonin producing cell. Embryologically, these cells do not develop with the thyroid from tissue that arises at the base of the tongue; rather, they are neuroendocrine and migrate with the ultimobranchial bodies from the fourth and fifth branchial pouches. Medullary cancers cannot occur in ectopic sites of thyroid that are due to defects in embryologic migration from the region of the foramen cecum. C cells are difficult to identify in normal thyroid using hematoxylin and eosin stains. At a higher magnification, they can be seen to contain neurosecretory granules containing calcitonin. Multiple mitochondria are present in these cells. Approximately 80% of medullary cancers exhibit amyloid, which is best identified by polarized light. It appears yellow-green. The cells stain positively with antibodies against calcitonin [49]. In hereditary syndromes there is a transition to C cell hyperplasia and then to frank malignancy. Because the number of C cells in a normal thyroid is not well known, the definition of C cell hyperplasia is somewhat arbitrary. Machen et al. have used the criteria when more than 50 intrafollicular cells stain for calcitonin in a low power field or more than 6 per thyroid follicle or both [42]. Several authors have taken issue with the term C cell hyperplasia [16, 50]. They interpret the cells to be atypical and precancerous. Nevertheless, the term C cell hyperplasia is in common use.

Because all C cells in genetically predisposed patients are potential sources of cancer, the lesions can be bilateral and multifocal. In contrast sporadic medullary cancer is usually a solitary lesion. Familial cancers are more likely to occur at the junction of the upper 1/3 and lower 2/3 of each lobe since this is the region where there is normally a higher concentration of these cells. Thin sections of the thyroid should be examined to ensure that small cancers are not overlooked in familial cases. Invasion of lymphatics, blood vessels, and surrounding soft tissues is common. Metastases to regional lymph nodes occur early. As the cancer becomes less well differentiated the secretion of calcitonin can decrease and the production of carcinoembryonic antigen (CEA) and other peptides occur [51, 52]. Occasionally the cancer can dedifferentiate and become anaplastic. Patients can even develop Cushing's disease from excess secretion of adrenal corticotrophic hormone (ACTH) [53, 54]. There are rare reports of carcinoid cancers of the ovary that secrete calcitonin, but these will seldom be confused with primary medullary cancer arising from the thyroid [55, 56]. Calcitonin can also be secreted by pancreatic tumors and therefore a significantly elevated calcitonin is usually but not always due to medullary cancer [57]. Other conditions associated with elevated serum calcitonin values are described below.

There appears to be an increased risk of papillary cancer in thyroid glands containing medullary cancer. There are case reports and statements of association in papers discussing medullary cancer [7, 58–64]. Three patients with both papillary and medullary thyroid cancer and twelve patients with medullary cancer and C cell hyperplasia were identified from sixty relatives over four generations in one kindred [65]. There was a mutation in codon 891 in exon 15. The phenotype was familial medullary thyroid cancer. One member had metastatic colon cancer; however, there was no evidence for familial polyposis coli or Gardner's syndrome. There is also a report of lymph node metastases containing both pathological varieties of cancer [66]. Incidental cancer arising from follicular cells would be identified when the gland is examined carefully for the extent of medullary cancer.

For experimental purposes, there are human medullary cancer cell lines that can be propagated in mice [67, 68]. The tumor models can be used to evaluate diagnostic imaging and therapy. They can also be valuable in studying factors that modify penetrance of the cancer [69].

Clinical

There are several discrete clinical presentations. First and most common is the adult patient who has no family history of medullary cancer. Usually this patient is found to have a thyroid nodule. In one report of 104 patients, 74% had a thyroid mass and 15.5% had local symptoms of dysphagia, dyspnea, or dysphonia resulting from the cancer [7]. This group of patients has therefore not been diagnosed early by genetic testing. When the patient presents with a thyroid nodule the optimal test is a fine needle aspiration (FNA). The cytopathology indicates the diagnosis of medullary cancer. Because this is an uncommon cancer, the pathologist might

require an addition FNA specimen to stain for calcitonin and thyroglobulin (Tg) to confirm the diagnosis. Medullary cancer is positive for the former and negative for the latter. In Chapter 4, the debate was presented on whether to measure calcitonin in a patient presenting with a thyroid nodule. This topic is expanded below, but in practice it is more cost effective to proceed directly to FNA.

The clinician should then review the family history and investigate the patient by genetic testing to define whether this is familial and whether it is associated with other endocrinopathies. When a germline mutation is present family members should be investigated for this defect. The importance of genetic screening of relatives of "sporadic" medullary cancer has been shown by several investigators. Ponder et al. identified four families with seven patients by screening thirty-nine families where the index patient was thought to have sporadic medullary thyroid cancer [70]. Previously families were screened by calcitonin testing, in particular using stimulated calcitonin values. Genetic testing is now central for the index patient and for first-degree relatives. Based on the codon involved the index patient should also be tested for pheochromocytoma and hyperparathyroidism.

The second presentation is when there is no FNA or when the FNA is indeterminate and the patient is referred to surgery to treat a thyroid nodule. The diagnosis is established after, rather than before, the operation. The difference is that appropriate investigations, which are important prior to surgery, have not been obtained. The surgical procedure is usually inadequate.

The final and best situation is identification of the patient by genetic screening because a family member has an established diagnosis. This patient has no symptoms or signs and when the thyroid is examined pathologically there is no significant cancer. The goal is to identify the carrier of the gene before there is cancer, specifically clinical cancer that already has a high probability of metastasizing. Therefore the reported age of the patients varies greatly depending on whether they are familial cases identified by genetic screening or patients presenting with a thyroid mass. In the latter situation the average age is 40 years to 50 years. There is a very slight increase in women between 1.1 : 1 and 1.5 : 1.

The patient undergoing surgery without a diagnosis could be a member of a MEN 2A or 2B family and might have a pheochromocytoma or hyperparathyroidism. The pheochromocytoma can cause episodic or persistent hypertension, sudden onset of anxiety, tachycardia, and sweating. It can also cause death during surgery or stressful situations such as pregnancy or delivery. Therefore the goal is to make the diagnosis of pheochromocytoma before undertaking the thyroid surgery, and when it is present, its treatment takes precedence. Some of the families have relatives who had sudden deaths at relatively young age and these might be attributed to hypertensive crisis.

Pheochromocytoma is bilateral in about 90% and is usually adrenal in site and benign. There has to be testing to define whether the patient has this condition and, if so, where the tumors are located. The tests are discussed in the next section. Hyperparathyroidism produces hypercalcemia, which in turn can cause general malaise, tiredness, depression, dehydration, renal stones and constipation. Hyperparathyroidism can be the result of overactivity of one or all glands.

Calcitonin does not exert important physiological changes. Most patients have normal calcium levels, although I did consult on one patient who had hypocalcemia. His calcitonin values were persistently above 50,000 pg/ml. Originally in the 1950s, when he had thyroid surgery, he was diagnosed with anaplastic cancer, but the correct pathological diagnosis was established when medullary cancer was described as a separate entity. In patients with extensive metastatic disease and very high values of calcitonin, there can be troublesome watery diarrhea (this was the main symptom of the patient described above).

Cutaneous lichen amyloidosis is found in patients with MEN 2A. This is characteristically found in the skin of the back between C4 and T5 dermatomes. Severe itch is the first symptom. The combination of the pathological infiltration and persistent scratching results in a papular pigmented rash between the scapulae. Biopsy specimens stain positively for amyloid. Investigators in Milan found that 36% of patients with a mutation in codon 634 developed this skin disorder [71].

The patient with MEN 2B has a typical phenotype with long thin arms, pectus abnormality

of the chest and neuromas of the lips and tongue. There are intestinal neuromas that are not apparent clinically.

Diagnosis and Genetic Testing

The diagnosis of medullary cancer in a patient with a thyroid nodule is best achieved by FNA. Thyroid scintigraphy is not advised. When the nodule is sufficiently large it appears as a cold nodule. However in a study from the Mayo Clinic rectilinear scans showed cold nodules in twenty-four of sixty-eight lobes (35%) [72]. This is not particularly helpful. In familial cancer, which is more often bilateral, the scan shows cold regions in both lobes close to or just above the middle of the lobes. Although this is the classic pattern it can be found in nodular goiter and FNA should be the first investigation. Ultrasound can be helpful as an aid to FNA to ensure the appropriate site is sampled. Thyroid function is almost always normal.

Once the diagnosis has been established or strongly suspected by FNA, it is important to embark on a series of investigations. These are to determine if the disease is familial, to stage the cancer and to determine whether there are associated pathologies. It is logical to start with screening for RET protooncogene mutations. These are located on exons 10,11,13–16 and because they are germ line mutations they can be identified in peripheral white blood cells. When there is a RET mutation, the patient has familial thyroid cancer, and with specific mutations there is a risk of pheochromocytoma or hyperparathyroidism. When there is no mutation, the patient does not have familial variety. However even in those with sporadic medullary cancer, it is often necessary to proceed with wider testing to expedite surgical treatment of the thyroid cancer. There needs to be testing to rule in or out the diagnosis of pheochromocytoma. This is achieved by serum measurements of norepinephrine and epinephrine and 24 hour urine measurements of these plus metanephrines and vanyl mandelic acid. When one of these investigations is abnormal, an anatomic image such as CT or MRI should be obtained to determine the site or sites of the tumor. Treatment of pheochromocytoma takes precedence and should be undertaken by a surgical and anesthetic team experienced with this disorder. There is an increased emphasis on laparoscopic procedure [73]. There are also surgeons who remove the pheochromocytoma and spare adrenal cortical function [74]. There should also be testing for hyperparathyroidism by measurement of serum calcium or ionized calcium, and, when the result is high, a paired calcium and parathormone (PTH) level should be obtained. An elevated calcium and PTH is diagnostic. This would result in a change in the thyroid operation in that the parathyroid glands would be identified during the total thyroidectomy.

For staging of the cancer, it is prudent to have an imaging study of the neck such as ultrasound or CT to define the anatomy of the thyroid and determine whether there is more than one lesion, to examine central and lateral nodes for characteristics of metastatic disease, and to look for parathyroid abnormalities. Because the patient is going to be followed long-term using measurements of calcitonin and CEA, it is important to have baseline measurements that can be used for comparison. When the calcitonin level is very elevated, there is increasing concern of regional and distant metastases. Distant lesions can occur in the liver, skeleton and lungs. Liver metastases can be present early in the course of the disease. Occasionally metastases to rare sites such as the breast and skin occur [75–77]. A positron emission tomography scan is excellent in identifying sizable metastases (>5–6 mm) but is not useful for miliary pulmonary or hepatic lesions. Helical CT of the chest and liver with thin sections after intravenous contrast should be conducted. One group recommends hepatic angiography as a sensitive test for small liver lesions [78]. This could be considered when PET scan and CT are thought not to have identified sites of cancer.

In all familial cancers and in such cancers that can be diagnosed by genetic testing the clinician and medical team have to provide sensitive, knowledgeable information. A team that looks after many patients with these diseases combine skills in all the necessary aspects of counseling, advice for treatment, and followup and information for planning of pregnancy. A physician with no experience in familial cancer who consults on one of these patients is advised to refer the patient to a genetic counselor. There has to be a discussion of the specific defect and what likelihood there is to develop medullary cancer

(approximately 95%) pheochromocytoma (approximately 50% for MEN 2A and 2B) and hyperparathyroidism (approximately 20–30% for MEN 2A). Information about prognosis based on the type of syndrome and extent of disease should be presented. The risk of specific mutations should also be addressed. The probability that children are carriers, the need for screening relatives, and the probability of finding disease should be presented. Negative aspects of genetic testing should also be addressed. Since the implications of having or not having a specific mutation is great, and, because no test is 100% sensitive and specific, some advise a duplicate genetic test to confirm the situation [45]. The investigation is expensive and there may be reluctance for insurance companies to reimburse the second measurement. Arguments put in writing that there can be false negative and false positive results, some resulting from simple problems such as a mislabeled specimen, usually address this. As in all medical interactions there needs to be great efforts to protect privacy. This is not easy since family members have to be included in testing. This can also lead to friction, when some normal people are unwilling to be tested and when they have children who are tested and found to be carriers for the gene. The untested parent must carry the gene. The possibility that the information could be used by insurance companies to deny medical care, based on preexisting illness, cannot be excluded. The emotional stress to carriers in particular children must be considered and followup should be arranged and where necessary referral for psychological and or psychiatric consultation. There are articles addressing the logistics of operating such a clinic [79]. One study has shown that people with mutations to RET protooncogene have a lower quality of life than normal matched controls [80]. The same investigators found that carriers have "a high level of frustration and latent dissatisfaction related either to the management of the genetic information given by the clinicians and its psychosocial consequences or simply to the knowledge of the genetic risk of cancer" [81].

Measurement of calcitonin is accepted as a very valuable test to follow patients after operation. It is important to recognize that the sensitivity of different assays and the normal ranges varies considerably. In the past basal and stimulated calcitonin values have been recommended to identify patients at risk for medullary cancer in kindreds who have one or other familial syndromes [28, 82, 83]. The use of these tests for screening families have been replaced by genetic screening. Measurement of calcitonin does have a role in followup of treated patients. For historical interest the stimulatory tests are discussed. After it was recognized that basal values of calcitonin were not sensitive for diagnosing precancerous lesions (C cell hyperplasia) stimulation tests were introduced. The two methods of provoking the release of calcitonin that were commonly used were calcium infusion and pentagastrin. For any interested in their use the methods are as follows. There are two protocols for calcium stimulation. In the calcium test that is employed more frequently, 15 mg calcium per Kg is infused intravenously over 4 hours and calcitonin assayed at time zero, 3 hours, and 4 hours. Samples of blood for measurement of calcitonin should be collected in tubes containing lithium heparin and the specimen should be frozen immediately. The second method involves intravenous injection of 0.2 ml/kg of 10% calcium gluconate (2 mg/kg) over 1 minute. Blood samples are obtained after 1 minute, 2 minutes, 3 minutes, 5 minutes, and 10 minutes. Some patients are nauseated by infusion of calcium.

Pentagastrin is injected in a dose of 0.5 µg/Kg. Some recommend injecting over 10 seconds, others over 3 minutes. There can be a transient feeling of burning and abdominal discomfort, flushing of the skin, and occasionally there is a drop in blood pressure. It is wise to conduct all of the stimulation tests with an intravenous line in place and have saline infusion ready if necessary. Blood is drawn at time zero, 2 minutes, and 5 minutes to measure calcitonin [84]. Some investigators obtain additional measurements at 15 minutes and 30 minutes. A stimulated value less than 30 pg/ml is considered normal and a value greater than 100 pg/ml definitely abnormal. One study of seventy-one normal volunteers showed values less than 30 pg/ml in sixty-eight (specificity 96%) [85]. The test was recommended for screening families and for the followup of proven medullary thyroid cancer after thyroidectomy [86]. Pentagastrin is an animal product and is not available, so this test cannot be undertaken in the US because of concern of transmissible diseases.

A third method of stimulating calcitonin release, which did not achieve clinical respectability for reasons that are not altogether clear, was the whisky stimulation test. Fifty (50) ml whisky taken by mouth was shown by one group of investigators to be as accurate as calcium infusion [87]. The alcohol test was found by others to provide inconsistent results [88]. Calcitonin measurements are obtained over 4 hours. How this was discovered and what brand of whisky should be used is widely known.

Some authorities recommend measurement of calcitonin in patients with a thyroid nodule or nodular goiter, and, when the result is high, to consider the likelihood of medullary cancer. In my opinion, because medullary cancer is rare, this is probably not cost effective. However, reports from Europe have suggested that it can be. The first report was by Pacini et al. in 1994, and it has been updated to 10,864 patients with thyroid nodules and nodular goiter [89]. These investigators identified forty-four patients (0.4%) with medullary cancer. Their assay was a two-site immunoradiometric assay with a sensitivity of 14 pg/ml. The upper limit of normal was 20 pg/ml. Patients with measurable calcitonin were subjected to pentagastrin stimulation and had measurements before and at 2 minutes, 5 minutes, 15 minutes, and 30 minutes. (This test cannot be conducted in the United States.) The investigators compared the patients with medullary cancer diagnosed by calcitonin screening to an historic group and demonstrated the former had less advanced disease. The cost of identifying a patient with medullary cancer was $12,500. The FNA was suspicious for medullary cancer or thyroid cancer in twenty-nine of the forty-four patients (66%). The authors continue to recommend calcitonin measurements to screen for medullary cancer. Iacobone et al. measured calcitonin in 7,276 consecutive patients with thyroid problems [90]. They employed an immunoradiometric assay with a sensitivity of 2 pg/ml and accepted that a basal calcitonin above 10 pg/ml was abnormal and obtained a pentagastrin stimulation test when calcitonin was elevated. (Pentagastrin tests cannot be conducted in the United States.) Based on calcitonin values they referred sixty-six patients for thyroidectomy and forty-five patients (0.6% of the total group) had medullary cancer and sixteen (0.2%) had pathological evidence of C cell hyperplasia. A basal calcitonin of 30 pg/ml or more and a stimulated value of 200 pg/ml or more were highly predictive of medullary cancer. The authors do not address how many patients would have been identified using FNA. Using a charge of 23 euros for calcitonin, they state this is cost effective. The cost of calcitonin assay is considerably higher in the United States.

Features of Cushing's syndrome, including moon facies, striae, hypertension, and diabetes might be present in the rare patient whose cancer secretes ACTH [53, 54, 91].

Hypocalcitonemia is not specific for medullary cancer and can occur in patients with chronic lymphocytic thyroiditis, pregnancy, chronic hypercalcemia, and for those on hemodialysis [6, 92]. The values are slightly higher in men. I consulted on a patient with Graves' hyperthyroidism, who for unknown reasons had a calcitonin measurement ordered by another physician. There was no evidence of a nodule by palpation or ultrasound. In one report, an elevated calcitonin was found in four of 161 hyperthyroid patients [93].

The importance of differences in assays and technical difficulties was highlighted by a woman who had sporadic medullary thyroid cancer treated surgically. Post operatively calcitonin was undetectable but on followup a measurement from a different laboratory found a value of 10 pg/ml and she was referred for advice. No evidence of recurrence could be identified. Repeat measurement of calcitonin including calcium stimulated values were undetectable. She remains well.

Treatment

The treatment is based on the clinical presentation. This is discussed first for those diagnosed by genetic testing then in patients who have clinical disease. In the latter case the size of the cancer is important and whether the pathological diagnosis is known prior to surgery. There are published Guidelines and some are available on CD [94, 95].

When the diagnosis is established by genetic testing the main issue is whether there is evidence of pheochromocytoma or hyperparathyroidism (Figure 10.3). The mutation in RET proto-oncogene can help predict the patients

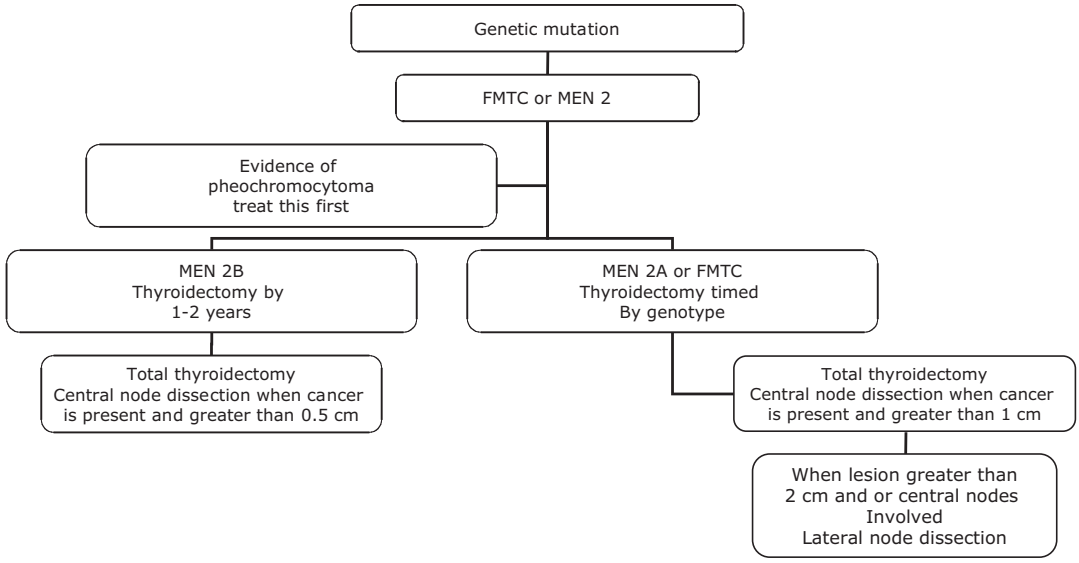

Figure 10.3. Algorithm for management of medullary cancer diagnosed by germline mutation in RET.

most at risk for pheochromocytoma and hyperparathyroidism. Most often these lesions are not present in children and even in older patients the medullary cancer usually is the first manifestation of the syndrome. Nevertheless, biochemical testing should be conducted. When there is a pheochromocytoma, it has to be treated first since untreated hypertensive crisis can occur during stressful situations such as thyroidectomy and cause death. Once that has been excluded or treated, patients with RET mutation who belong to families with MEN 2A should undergo total thyroidectomy by 5 years of age. Some authorities recommend an earlier operation for children with a defect in codon 634. In contrast mutations in codons 609, 768, 790, 791, 804, and 891 have been associated with a more benign course and a better prognosis and annual measurement of a stimulated calcitonin can be used to define the timing of surgery [44, 95]. Basal calcitonin is not appropriate because by the time it is abnormal it can be associated with significant clinical disease [96]. The goal is to remove the gland before there is clinical cancer. Often C cell hyperplasia, which is the precursor of cancer, is diagnosed pathologically. This raises a semantic issue. Some argue that a prophylactic operation should remove the gland because C cell hyperplasia is already evidence of disease. I accept that C cell hyperplasia indicates that there is no evidence of cancer. Of seventeen patients who underwent prophylactic operation at the MD Anderson, twelve patients had C cell hyperplasia, but five had invasive disease [97]. None of the seventeen patients died or had a recurrence. Similarly, Seventy-one patients with a range of age from 10 months to 20 years were operated on prophylactically [96]. Seventy-five percent had abnormal basal calcitonin values and sixty-eight of seventy-one had elevated values after injection of pentagastrin. Five patients had C cell hyperplasia alone, fifty had this plus medullary cancer. Sixty-one of seventy-one (86%) had medullary cancer, and this was bilateral in 67% and greater than 1 cm in 10%. This confirms the poor value of basal calcitonin for determining the best age for surgery. The authors found clinically significant cancer in patients younger than six years and they recommend operating earlier. A recent report analyzed the pathological findings in 207 patients diagnosed by genetic testing and operated on by their twentieth year [42]. The patients came from 145 families of which the phenotypes were 112 with MEN 2A, twenty-nine with familial medullary thyroid cancer, and four with MEN 2B. Development of both C cell hyperplasia and medullary cancer occurred earlier in families with mutations in the extracellular component of RET. In the case

of extracellular defects, the average age for C cell hyperplasia was 8.3 years and for frank cancer 10.2 years. The corresponding ages for those with intracellular mutations were 11.2 years and 16.6 years respectively. Metastases to nodes were found at an average age of 17.1 years when the mutation was extracellular and none of 8 patients with intracellular defects had metastases at age 20 years. Extracellular mutations were much more likely and affected 172 patients versus thirty-one with intracellular defects. It is gratifying that only seven of the patients had nodal disease, strengthening the decision for thyroidectomy at an early age. In patients with the commonest mutation at codon 634, there was an average of 6.6 years between development of the cancer and the occurrence of metastases. The data suggests that surgery could be delayed to age 10 for those with mutations in codons 609, 630, 768, 790, 791, 804 and 891. Data like these, if confirmed by other investigators could allow more precise timing of operations for the individual patient.

Because the onset of cancer and its metastases occur earlier in patients with MEN 2B, total thyroidectomy is recommended before 2 years of age. Some authorities put the age for surgery before the first birthday [95]. This requires a pediatric surgeon skilled in thyroid operations. Since the key for success is the completeness of the operation on the one hand with a low proportion of complications on the other, this procedure should be undertaken by only a few well-trained practitioners. A surgeon who does not normally operate on small children or who conducts one or two thyroidectomies annually should not be entrusted with this procedure. There is disagreement about the need for central node dissection. When there is no cancer in the thyroid there is no chance of nodal metastases. Therefore efforts should be made preoperatively to try and predict whether cancer has developed. In patients with MEN 2A, an elevated basal or calcium-stimulated calcitonin would be indications for nodal dissection. Also when ultrasound demonstrates a mass in the thyroid or lymph nodes that have suspicious characteristics the decision should be for thyroidectomy and central lymph node dissection. A cancer greater than 1 cm and the presence of metastases to the central nodes would be an indication for excision of nodes from level II-VI. Because of the more aggressive behavior of medullary cancer in the MEN 2B syndrome the recommendation for lymphadenectomy is based on a cancer size of greater than 0.5 cm.

Operative complications in young children are problematic since they will persist for the life of the individual. This confirms the importance of having a skilled pediatric endocrine surgeon. In the French series, only one of seventy-one (1.4%) had permanent hypoparathyroidism [96]. When there is concern that the parathyroids have been removed there is a role for auto-transplantation.

In patients with clinical disease, it is accepted that total thyroidectomy and removal of the central neck nodes to level VI is the correct operation (Figure 10.4). The goal is to remove all cancer cells both in the thyroid and lymph nodes. The smaller the primary cancer is, the less likely there are metastases. Unfortunately, one study has shown that patients, some of whom had T1 lesions and no pathological evidence of nodal disease, recurred after all the evidence pointed to a cure [98]. The patients had unmeasurable basal and stimulated calcitonin after surgery that was judged to be curative. After an average of 3.3 years, 3% of the patients were identified to have calcitonin values greater than 10 pg/ml. The authors stress the need for long-term followup. Unfortunately, a proportion of patients with sporadic medullary cancer also have extensive local disease. It can be necessary to conduct extensive surgery [99]. In each case the benefits of an aggressive operation versus complications need to be evaluated and whether a lesser operation followed by palliative radiation would achieve the same outcome should be considered.

The Role of Postoperative Radiation and Chemotherapy

The treatment of differentiated cancer often includes ablation of remnants of thyroid left postoperatively using ^{131}I. It was hoped that this would be effective in medullary cancer by killing C cells that had the potential to become malignant and cause recurrences. Case reports that demonstrated low basal and stimulated calcitonin values after treatment of residual thyroid using ^{131}I were interpreted to mean that

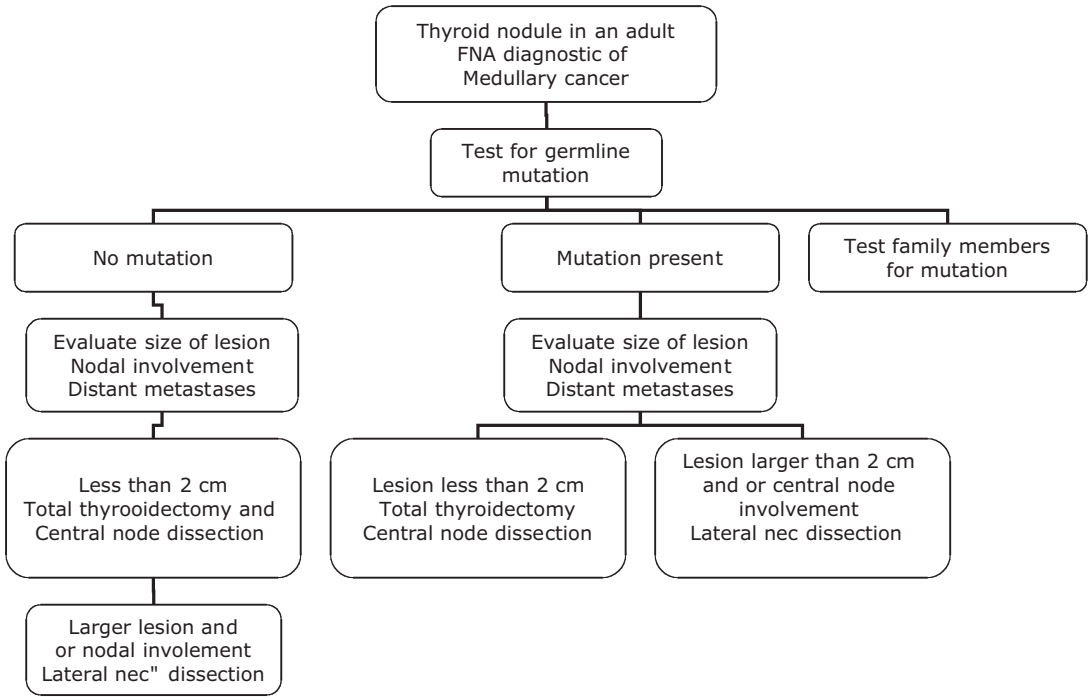

Figure 10.4. Algorithm shows management of medullary cancer diagnosed by FNA of thyroid nodule.

the parafollicular cells were radiosensitive and could be destroyed by β radiation from adjacent follicular cells [100]. This treatment has proven to be ineffective [101]. In one study fifteen patients were treated by operation and ^{131}I and compared to eighty-four treated by surgery. There was no difference in postoperative calcitonin values or 5-year and 10-year survivals.

Treatment of distant metastases is a difficult problem. The cancer is resistant to radiation and to chemotherapy. [102] When radiation or chemotherapy is employed there are several ways of evaluating the outcome. Typically oncologists report on the rate of remission or partial response after the intervention. This is best when there is a treatment and control group and the outcomes can be compared. I have been unable to find any controlled study in the literature. This is not surprising because the number of patients is small and many do not require these therapies and others when hearing the results and potential side effects of external radiation and chemotherapy elect not to be treated. A second method of reporting results is to evaluate the level of cancer markers. For example, do the calcitonin and or CEA levels fall after treatment? Unfortunately a drop in these serum measurements cannot always be equated with improvement. A third method is to determine whether side effects of the disease such as diarrhea improve or not.

When there are large metastases surgical debulking has been shown to prolong survival [103]. This appears preferable to radiation therapy of mass lesions although radiation can help when smaller volumes of cancer are present after surgery [104, 105]. The role of external radiation is limited. Samaan et al. demonstrated no benefit from surgery plus radiation versus surgery alone [106]. Although Tubiana et al. showed the outcome was equivalent in eighty patients who were treated by operation and thirty-five who had radiotherapy after surgery, they concluded that radiation was helpful [107, 108]. This was based on the more extensive disease yet equivalent outcome in the irradiated patients. Other investigators have confirmed that radiation can stabilize disease

judged to be progressive and inoperable [109, 110]. Another French study reviewed the results of radiation in fifty-nine patients. Fifty-five of the fifty-nine had total thyroidectomy and regional node dissection but had residual cancer or nodal metastases. Distant metastases were excluded as far as possible. Fifty-four (54) Gy were delivered and this produced dysphagia in thirty-two (54%) and dyspnea in five (8%). There was a local recurrence within the irradiated field in eighteen (30%) of the group, however twenty-four patients (41%) remained with no evidence of disease. Radiation has a role when there is residual cancer in the neck that cannot be removed by operation. It can also be used in patients with proven metastases to lymph nodes and persistently elevated calcitonin values. It has a definitive place in treating painful skeletal metastases. Investigations to help find sites of cancer are discussed below. These results stress the goal of early diagnosis and definitive surgical treatment before nodal and distant lesions have developed.

A certified radiation oncologist should undertake the planning and delivery of external radiation. It is advisably to have a joint decision including the surgeon, thyroid physician, radiation oncologist and patient to discuss the logistics, benefits and side effects. The radiation port should include known and suspected regions of residual cancer. Usually it will extend from the mandible to the upper mediastinum [111]. The central and lateral cervical nodes should be included in the field. CT simulation and more recently PET/CT can be of value for radiation planning. It is important to ensure the spinal cord does not receive more than 46 Gy to prevent radiation myelopathy.

Trials of internal unsealed radiation therapy have been undertaken. There are several radiopharmaceuticals [112–115]. The therapeutic potential of these should be tested by preliminary diagnostic imaging. When there is good evidence of uptake of a tracer and dosimetry indicates therapeutic advantage a larger treatment dose can be administered. For example, Iodine-123 Metaiodobenzylguanidine (MIBG) whole-body scan can be used as a preliminary to ^{131}I MIBG treatment. Metaiodobenzylguanidine labeled with ^{131}I has been investigated by several groups [114, 116]. Its role in treatment of metastatic pheochromocytoma is more established than its use for medullary cancer [117, 118].

An alternative approach has been the use of radiolabeled antibodies. Iodine-131 monoclonal antibodies to CEA were infused into twelve patients with medullary cancer [119]. The dose was designed to cause myeloablation and the patients received autologous bone marrow transplantation about 2 weeks later. One patient had a partial remission, a second patient a "minor response," and ten remained stable for 1 month to 16 months. The authors conclude "The antitumor responses in patients with aggressive, rapidly progressing disease are encouraging and warrant further research to optimize the effectiveness of this new treatment." The same group has employed the same radiolabeled antibody to treat CEA expressing cancers of the colon, pancreas and breast [120]. Radiolabeled octreotide has been prescribed to treat endocrine cancers including medullary cancer. Some investigators have used ^{111}In-octreotide. The Auger electrons from ^{111}In deliver a high dose over a very short pathlength. Experimental studies have shown a ratio of uptake in the cancer compared to blood of 160:1, suggesting the treatment should be effective [121]. There is increasing evidence that ^{90}Y-octreotide will be effective in selected patients. ^{90}Y is a β emitter, and when a high enough concentration is present in the cancer a lethal dose of radiation can be delivered. Preliminary testing with ^{111}In-octreotide can determine whether this therapy could be successful.

Medullary cancer cells are resistant to chemotherapy [122]. There is no single or combined chemotherapeutic protocol that provides statistically significant benefit. Most conventional protocols include Adriamycin (doxorubicin) alone or in a combination [123–126]. There are reports on small numbers of patients of combinations such as doxorubicin plus streptozocin [126]. 5-Fluorouracil plus dacarbazine was successful in a single patient [127]. This combination produced a partial response in three of five patients [128]. Cyclophosphamide, vincristine, and dacarbazine were used in combination in seven patients with two partial responses. The group from Villejuif, Paris, first used combinations of 5-Fluorouracil/streptozocin and 5-Fluorouracil/dacarbazine in twenty patients [129]. The disease stabilized in eleven

patients, and an additional three had a partial remission. Based on these results, they combined doxorubicin/streptozocin and 5-Fluorouracil/dacarbazine. [130]. Their protocol was doxorubicin 60 mg/m^2 by intravenous infusion over 5 minutes plus streptozocin 500 mg/m^2 by infusion over 4 hours for five consecutive days. After a delay of 4 weeks, this was followed by 400 mg/m^2 of 5-Fluorouracil and 200 mg/m^2 of dacarbazine intravenously for five consecutive days. The cycle was repeated at 8 weeks. Ten patients remained stable and three had a partial remission. In 2001, Orlandi et al. summarized the published data [131]. They identified twenty-nine articles and a total of 144 patients. Three patients (2%) achieved a complete remission and thirty-nine (27%) a partial remission. It is impossible to make a definitive recommendation of the optimal regime for several reasons. The twenty-nine articles include sixteen using a single agent (e.g., doxorubicin, VP 16, methotrexate), six publications describing a combination of two drugs (e.g., doxorubicin and cisplatinum), six with three chemotherapeutic drugs (e.g., doxorubicin, Cytoxan, and streptozocin), as well as the four drug regime described above. They recommend a combination of 5-Fluorouracil and Dacarbazine as the first choice because it is as effective as other combinations and has mild side effects. If that is unsuccessful, the four-drug protocol could be considered.

Because medullary cancer cells exhibit somatostatin receptors nonradioactive analogues of somatostatin have been prescribed. Octreotide has been prescribed by subcutaneous injection in a wide range of doses from 0.1 mg to 1.0 mg daily [132, 133]. Long acting analogues have also been administered [134]. There is some evidence that agents to Type 2 receptor can slow growth of medullary cancers in culture [135]. The answer to the main questions do these pharmaceuticals slow growth of cancer or produce a remission clinically is no. They can stabilize or even lower calcitonin values but the growth of cancer is not slowed. In one study Octreotide was injected subcutaneously in a dose of 0.1 mg every 8 hours or 30 mg lanreotide was injected intramuscularly every 14 days [134]. There was no effect on the growth of cancer and one-fifth of patients had a reduction in serum markers.

The increasing knowledge of the molecular dysfunction in medullary cancer resulting from missense mutations in the RET protooncogene resulting in increases of function in transmembrane tyrosine kinase has led to experimental studies using inhibitors of tyrosine kinase such as Gleevec [136]. The data are conflicting. Cohen et al. reported that tyrosine kinase inhibitors inhibited growth of medullary cancer cells growing in culture. In contrast Skinner et al demonstrated that the doses of Gleevec necessary to kill cells in vitro could not be achieved clinically [137].

The diarrhea can be very problematic. It can be treated by conventional medications including codeine. The benefit can be minimal and side effects annoying. Octreotide and lanreotide can be used and benefit some patients. Several years ago there were case reports on the value of nutmeg [138, 139]. I suggested this to a patient and he obtained excellent benefit. He liked nutmeg and applied it to his cereal in the morning and to various foodstuffs throughout the day. For some years it allowed him to leave the house with some peace of mind.

Cutaneous lichen amyloidosis has been treated with local application of 0.25% Capsaicin [71]. This has produced symptomatic relief in about one-third of patients. The treatment causes a burning sensation and this results in some patients stopping it.

Cushing's syndrome due to ectopic ACTH or its precursors can be helped by removal of the medullary cancer. In patients who have unresectable metastatic disease and severely symptomatic hyperadrenalism it can be necessary to remove the adrenals.

In the rare instance where there are coexisting medullary and differentiated cancers the latter is usually incidental and has been effectively treated by the thyroidectomy. When the differentiated cancer is large, invasive, or has metastasized testing and treatment with radioiodine would follow the principles outlined in Chapter 6.

Followup

Patients should be scheduled for regular followup visits. These should include physical examination of the neck, measurement of calci-

tonin, and thyroid function. The hope is that calcitonin values remain low or undetectable. When the value remains elevated or changes from an undetectable to measurable value, the first decision is whether to try and identify the source of calcitonin production or not. In elderly frail patients who have low values and no abnormality on physical examination, a wait and watch policy is reasonable. In younger patients with a long life expectancy an argument can be made for early identification of residual or recurrent cancer. CEA levels should also be measured for reasons discussed above [52, 140].

Management of Elevated Calcitonin after Primary Treatment

The goal of surgical treatment is to remove all cancer and to have an undetectable level of calcitonin. When there is measurable calcitonin, the patient and physician are both worried. Patients with measurable calcitonin can live for many years but the mortality from medullary cancer is significant accounting for 13.4% of all thyroid cancer deaths [7]. The first decision is how aggressive should the work up be to find the source of calcitonin? The next question is what tests are recommended to find the source of disease? The first decision should depend on the level of calcitonin; minimally measurable values can be followed. One report indicated that calcitonin tended to rise several months after surgery and the investigators were not able to find a source of measurable calcitonin in any of their patients over three years [141]. The age and well being of the patient should be evaluated. The surgical findings and pathology should be reviewed looking at the site of the primary lesion whether there was local invasion and or involvement of regional nodes. These can give a starting point for the workup. In patients who have had a less than complete thyroidectomy some authorities recommend completing the thyroidectomy combined with a meticulous central node dissection. Calcitonin is frequently measurable after reoperation [97]. Because of this and the relatively slow growth of cancer in a proportion of patients, some clinicians advise an expectant policy. They argue that even when a lesion is identified and removed it is unlikely for the calcitonin to become undetectable. This is not always the case. I recommend a discussion with the patient. The presence of the patient's husband, wife, or close family member can be helpful. A consensus about the extent of the workup and the therapeutic decisions that could develop depending on the diagnostic findings should be outlined. Once a consensus decision has been reached to be active in finding the cancer, the plan should start with a careful clinical examination. Then tests should be arranged that define as accurately as possible the exact sites of disease, so they can be excised. Ultrasound of the entire neck is sensitive for identifying enlarged and abnormal looking nodes and residual tissue in the thyroid bed. Computed tomography and MRI can be helpful, but, after extensive surgery, postoperative scarring can be misinterpreted as cancer, reducing the specificity of these tests. Anatomic investigations determine whether lymph nodes are "pathological" are empiric and a transverse diameter of 1 cm or greater is judged to abnormal and smaller nodes benign. This obviously can result in small nodes containing cancer being wrongly classified as normal and large reactive nodes wrongly judged to be malignant. Ultrasound guided FNA can increase both sensitivity and specificity by allowing sampling of small round nodes that do not have a fatty hilum as well as larger nodes. This provides a tissue diagnosis. Computed tomography and MRI of the thorax and upper abdomen, including the liver, can identify disease in these sites. Miliary lesions in either organ exclude surgical treatment.

Scintigraphic Tests

One of several nuclear medicine procedures can help by imaging the entire body with a single test [142]. Medullary cancers do not trap iodine, therefore scanning with radionuclides of iodine is of no value in identifying local or distant metastases. The use of ^{131}I to ablate residual thyroid has been discussed above. It does not improve the outcome. There are several other scintigraphic tests, none is perfect and there is no uniformity of opinion of the single best although my preference is ^{18}FDG PET scan. The

results of conventional scintigraphic tests are summarized, followed by an analysis of PET using ^{18}FDG and finally the results using the newer PET radiopharmaceutical ^{18}F-Fluorodopa are presented. The tests that have been used include MIBG labeled either by ^{131}I or ^{123}I. This has proven value for detecting pheochromocytoma but is less valuable for medullary cancer [115, 143, 144]. Because the cancer cells express somatostatin receptors Indium–111 octreotide (^{111}In-octreotide) has been used for imaging [145]. Pentavalent dimercaptosuccinate labeled with ^{99m}Tc (^{99m}Tc-vDMSA) has been reported to have merit in detecting medullary cancer [146]. Most of the diagnostic potential is for regional involvement in the thyroid bed or lymph nodes, but it has been useful for liver metastases [147]. ^{99m}Tc-vDMSA is not available in the USA. There have been advances in producing vDMSA labeled with β emitters that can be used to deliver local radiation to the cancer [148, 149]. The cardiac agents ^{201}Tl and ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrafosmin are moderately successful [150, 151]. For convenience, the ^{99m}Tc labeled agents will be referred to as DMSA, Sestamibi, and Tetrafosmin.

Adalet et al. compared 740 MBq (20 mCi) DMSA, 740 MBq (20 mCi) Tetrafosmin, and 74 MBq (2 mCi) ^{201}Tl in twenty-four patients, twelve of whom were judged to have thirty-four lesions [151]. DMSA identified thirty sites and the uptake was usually intense. Tetrafosmin was the least effective showing faint uptake in 20 lesions. The authors conclude that Tetrafosmin should not be used. A minor argument in favor of Tetrafosmin or Sestamibi is that they could also identify parathyroid adenomas in patients with MEN syndromes [152]. However that would only need to be considered in patients with elevated parathormone and calcium values. DMSA is valuable for identifying local and some distant metastases [147]. DMSA has also limited success in diagnosing pheochromocytoma and therefore could be used in patients with MEN 2A and 2B. [146] In a separate investigation Tetrafosmin was also judged to be inferior to ^{18}FDG. [153] Tetrafosmin identified eleven of the twenty patients with metastases.

Radiolabeled monoclonal antibodies to CEA were used diagnostically in fourteen patients and therapeutically in two [154]. The sensitivity was 85% for detecting lesions.

Fluorine-18 Deoxyglucose Positron Emission Tomography

More recently PET scanning after intravenous injection of Fluorine-18 deoxyglucose (^{18}FDG) has been investigated for this purpose. The number of patients with medullary cancer who have been studied using PET is considerably less than those with differentiated thyroid cancer. The method is the same. The patient should fast for six hours, and 370 MBq to 550 MBq (10–15 mCi) ^{18}FDG is injected intravenously. The patient should not speak or eat and should be resting in a quiet environment for an hour and then imaging is initiated. Bockisch et al. report that PET is the most sensitive of these investigations with a sensitivity and specificity of approximately 80% [155]. These investigators predict PET/CT will provide further diagnostic benefit.

Adams et al. found that PET was not sensitive for several neuroendocrine tumors [156]. However in a comparison of ^{18}FDG and DMSA in seven patients with recurrent medullary thyroid cancer and rapidly increasing CEA levels, DMSA identified only three lesions in two patients and PET found abnormalities in all seven patients. Twenty-nine cancer sites were identified including one pulmonary, three skeletal, twenty mediastinal, ten cervical, and four liver metastases. Nine nodes containing metastases were surgically excised with a fall in biochemical markers. Twenty patients with suspected recurrent medullary cancer were studied using ^{18}FDG PET by Brandt-Mainz et al. [157]. All had elevated calcitonin and several had abnormal ultrasound findings in the neck. Fluorine-18 deoxyglucose PET identified the cancer in thirteen of seventeen patients, and these were corroborated by other imaging tests or biopsy. There were four false negative results and one true negative. Twelve of fourteen sites of cancer in the neck, six of seven in the mediastinum, and two pulmonary and two bone metastases were diagnosed. In two patients with elevated calcitonin levels, no site of cancer was found by any test. The sensitivity was 76% (95% confidence interval 53%–94%). One hundred ^{18}FDG PET scans were conducted in eighty-five patients with elevated calcitonin or

CEA. Fluorine-18 deoxyglucose PET detected 123 of the 181 lesions (68%) that could be identified by one imaging tests. In fifty-five patients with pathologically proven sites of medullary cancer there were thirty-two true positive, three false positive, eleven true negative, and nine false negative sites. The sensitivity in these fifty-five patients with cancers confirmed by biopsy was 78% and the specificity was 79%. The investigators calculated the sensitivity was 25% for Octreoscan, 33% for DMSA, 25% for Sestamibi, 50% for CT, and 82% for MRI. In a separate investigation in forty patients with elevated calcitonin values after thyroidectomy, ^{18}FDG detected 270 foci, MRI identified 116 lesions, and CT found 141 lesions [158]. For lesions in the neck PET, MRI, and CT found ninety-eight, thirty-four, and thirty-four lesions respectively.

PET was also superior in the mediastinum. ^{18}FDG has been successful in diagnosing pheochromocytoma [159]. Positron emission tomography identifies an occasional adrenal tumor that is not seen on MIBG scan and vice versa. Some authorities accept that PET and MIBG tests are complementary for adrenal pathology. Several investigators use PET for preoperative staging as well as for followup [160]. However, in patients who are diagnosed early and have low calcitonin values, PET is not likely to help. Figure 10.5A shows a PET scan in a woman who had a progressive rise in calcitonin after total thyroidectomy. Computed tomography, MRI, sestamibi, and Octreoscan were all negative. The lesion on PET scan was biopsied using MRI guided FNA and metastatic medullary cancer diagnosed. The lesion was excised surgically with an excellent outcome.

There are several causes for false positive PET scans. Inflammatory lesions take up ^{18}FDG and these include TB and sarcoidosis [161, 162]. Muscle uptake can occur in nervous patients or in those who talk or chew after injection of ^{18}FDG. Benzodiazepam has been used to relax patients and to reduce this potential false positive result [163]. A similar appearance can result from uptake of ^{18}FDG in brown fat, and this is not improved by anxiolytic medications. When one recurrent laryngeal nerve is damaged uptake of ^{18}FDG in the contralateral functioning laryngeal muscles can be misinterpreted as a metastasis [164, 165]. In most cases PET/CT allows the correct interpretation by providing an anatomic correlation for foci of uptake of ^{18}FDG.

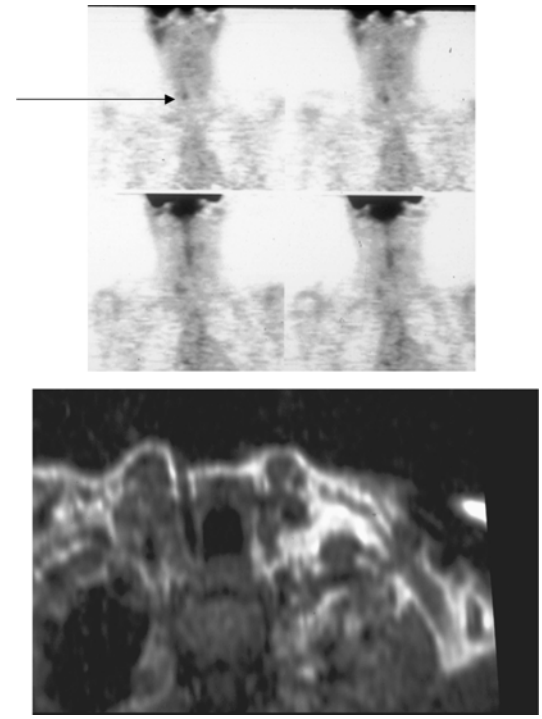

Figure 10.5. (A) is a PET scan showing a lesion in the right cervical area in a patient with medullary cancer treated by total thyroidectomy. Her calcitonin was rising. (B) shows an MRI guided fine needle biopsy that confirmed the hot spot on PET scan was medullary cancer. This lesion was removed and the patient has calcitonin values <2 pg/ml over the last 6 years.

There is evidence that ^{18}Fluorodopamine (FluoroDopa) PET is superior to MIBG and Octreoscan to diagnose pheochromocytoma [166]. A case report confirmed its value in diagnosing recurrent medullary cancer and pheochromocytoma in the same patient [167]. Hoergerle et al. used several imaging tests including ^{18}FDOPA and ^{18}FDG, Octreoscan and CT, and MRI to calculate sensitivity and specificity in detecting twenty-seven known lesions [168]. Three were in the thyroid region, sixteen in lymph nodes, and eight were distant metastases. The tests were complementary. The sensitivity of ^{18}F-DOPA PET was 63%, compared to 44% for ^{18}FDG PET and 52% for Octreoscan. The same authors reported a 100% sensitivity

for ^{18}F-DOPA PET in seventeen pheochromocytomas [169]. This was superior to MIBG. Similar results have been presented by other investigators [170].

After a site or sites of disease have been identified in the neck there is an increasing acceptance that "compartment oriented surgery" should be conducted rather than node picking [97, 103, 171].

Selective Venous Sampling

Selective venous sampling with measurement of calcitonin can help define the site of residual or metastatic cancer [172, 173]. Samples of blood are withdrawn from specific anatomic sites with the aim of finding a "step-up" in calcitonin level. This implies the lesion is upstream and draining into that vein. The technique can help determine which side of the neck is involved or whether the liver rather than the cervical area should be further investigated [173]. Abdelmoumene et al. conducted selective venous sampling in nineteen patients and determined there was residual cancer in the neck or mediastinum in eighteen and five also had distant metastases. [174]. Thirteen were subjected to reoperation and the cancer was found at the expected site in twelve. All of the patients whose tests predicted distant lesions subsequently developed clinical metastases, and only one of fourteen with local disease went on to develop a distant metastasis. The authors conclude this is a sensitive method for identifying cancer sites, but after surgical excision it is unusual to end up with an undetectable calcitonin. In a separate investigation fourteen patients underwent the procedure, and thirteen had surgery [175]. The investigators recommend a microdissection of the central and lateral nodal compartments of the neck and superior mediastinum when there is lateralization of the calcitonin measurement. Three patients had undetectable calcitonin after this procedure. Ben Mrad et al studied seventeen patients, sixteen had surgery, and two had undetectable calcitonin postoperatively [176].

The technique requires a radiologist skilled in venous catheterization. The anatomy can be distorted by prior surgeries. There is debate about what increase in calcitonin is diagnostic, some use a ratio of 1.5:1 but the specificity of the test is better at a ratio of 2.5:1 [176].

Future Directions

How should future generations be "treated?" What happens when a young carrier is treated successfully by thyroidectomy before cancer has developed and then lives a normal life span and has a family? These children are potential patients who have a 50% chance of developing medullary cancer. When the treated carrier is a woman, eggs can be selected for in vitro fertilization. Using polymerase chain reaction to amplify genes ova carrying mutations could be eliminated. Conversely, for male carriers in vitro fertilization and development of blastocysts that could be tested for genetic abnormalities could be considered [50]. There have been substantial advances in this technology, and it should eliminate carriers and potential patients from a family. Arguments against this approach are religious and economic. The economic ones are easier to deal with. It is true in vitro testing and fertilization and implantation are expensive. However, these would be offset by the cost saving of no surgery, the benefit of no complications. There would be no anxiety about cancer, no need for addition testing and treatment, and the 50% chance of pheochromocytoma and 20% to 30% chance of hyperparathyroidism would be eliminated. In addition the genetic abnormality could be transmitted to the next generation. The religious question, as all religious questions, is not easy to answer. I have no difficulty with such a decision but accept that many do. This has to be discussed with the patient and spouse, taking into consideration their personal and religious preferences. For those who have already undergone one or two surgeries, know of relatives who also have had procedures, and who may have died prematurely, the decision to prevent a child having to endure this makes the decision straightforward for me.

Prognosis

The prognosis is described in many reviews as being intermediate between differentiated and anaplastic cancers. Prognosis is usually defined by the percentages of patients surviving or dying at specific times after diagnosis. However, one of the main therapeutic goals is to achieve

Table 10.3. Characteristics of various types of medullary cancers.

Characteristic	Solitary medullary cancer	Familial medullary cancer	MEN 2A	MEN 2B
Age at presentation	40–50	45–55	25–35	5–20
Men/women	1/1.5	1/1	1/1	1/1.5
Medullary cancer	100%	100%	100%	100%
Pheochromocytoma	0	0	50	50
Hyperparathyroidism	0	0	10–25	0
Characteristic phenotype	0	0	0	100
10 year survival	50–70	70–90	50–95	40–80

Extracted from Gimm et al. [171].

an undetectable calcitonin. Some publications address how often this is achieved. This is a simplification, since early identification and treatment of patients with a genetic predisposition to develop medullary cancer results in an excellent prognosis. In contrast the outcome in a patient who already has distant metastases is very poor. Several other factors have a bearing on prognosis. Those factors that are statistically important as judged by univariate analysis are age, the specific syndrome, stage of disease, including the presence of metastases to lymph nodes and distant sites, and the completeness of the surgery. Women have a slightly better outcome. Multifocal cancer does not have an adverse effect. More important are the characteristics that meet statistical significance by multivariant analysis. For example, gender might be an adverse factor when each item is looked at separately. However, if all men have metastatic disease, it is the latter rather than age that dictates outcome, and that is clarified by multivariant techniques.

In the SEER report the 5-year survivals were 83.8% in men and 92.8% in women and for the 10-year survivals the percentages were 74.3 and 89.6 respectively [3]. Many publications demonstrate a better outcome in women. Taken as a whole, patients with familial medullary cancer have the best prognosis followed by those with non familial isolated medullary cancer [8]. Patients with MEN 2B have the worst outcome [177]. MEN 2A patients have a better prognosis than 2B. A mutation in codons 883 and 918 predict a poorer outcome. All reports evaluating prognosis demonstrate that the presence of distant metastases at the time of diagnosis is a bad feature. Cancers that are larger than 4 cm also have a poorer outcome, as do those with nodal metastases. Patients with small cancers (<1.0 cm) have a better outcome. Beressi et al. conducted a retrospective analysis of 80 patients

Table 10.4. Patient characteristics in medullary cancer.

	Gharib et al. [181]	Hyer et al. [184]	Esik et al. [180]	Raue et al. [182]
Number	65	162	91	741
Mean age	–	–	–	45.9 (5–81)
% men	45	46	45	42
% women	55	54	55	58
% neck mass	86	91	–	–
% by screening	–	5	–	–
% with family history	–	32	–	25
% bilateral	–	23	–	–
% extrathyroidal	–	23	–	–
% <1 cm	–	8	8	19
% 1–4 cm	–	52	51	38
% >4 cm	–	10	–	–
% N0	–	31	14	–
% N1	–	63	40* (46 no data)	38
% distant metastases	–	15	54	9

Table 10.5. Overall prognosis for medullary cancer.

Patient characteristic	Bhattacharyya [3]	Raue et al. [5]	Esik et al. [180]	Gharib et al. [181]	Bergholm et al. [185]	Saad et al. [186]
Number of patients	499	632	91	65	249	161
Overall 5 year %	–	81	69	–	80	78
Overall 10 year %	74	64	62	63	68	61
Men 5 year %	83.8	–	–	–	–	–
Men 10 year %	74.3	–	–	–	–	–
Women 5 year %	92.8	–	–	–	–	–
Women 10 year %	89.6	–	–	–	–	–

with small sporadic medullary cancers [178]. The 10-year survival was 93.9%, and 71% had normal basal calcitonin values. The authors point out the importance of trying to establish the diagnosis early and of total thyroidectomy and nodal dissection. Older patients with this cancer do not do well. The preoperative value of calcitonin was not found to be a prognostic factor [179]. This is counter intuitive since the calcitonin value correlates fairly well with the volume of disease. High values can result from intrathyroidal or intrathyroidal plus regional nodal cancer that are amenable to surgical treatment.

Summary and Key Points

Medullary cancer is an uncommon thyroid cancer that arises from parafollicular C cells that secrete calcitonin. About 25% to 30% are part of autosomal dominant familial syndromes that include familial medullary cancer, MEN 2A, and MEN 2B. There is a germline mutation in the RET protooncogene that produces constant function of tyrosine kinase. The majority of these cancers are sporadic and they have the same mutations but these are confined to the cancer cells. Familial cases should be diagnosed early by genetic testing and the carriers treated by thyroidectomy at a young age. When the thyroid is normal or contains only C cell hyperplasia there should be no recurrence. Fifty percent of those with MEN syndromes will develop pheochromocytoma and 10% to 25% of those with MEN 2A hyperparathyroidism. Therefore, followup with biochemical testing is necessary. Sporadic cases should be diagnosed by FNA and treated by total thyroidectomy and central node dissection. The outcome is best in younger patients with small cancers and no metastases. Calcitonin is used to determine the success of therapy.

- Medullary cancer is due to malignant transformation of C cells.
- C cells or parafollicular cells arise from the ultimobranchial bodies and are neuroendocrine cells.
- C cells produce and secrete calcitonin, and serum testing can be used to diagnose and for followup of medullary cancer.
- There are four clinical situations where medullary cancer can be found, one sporadic and three familial syndromes.
- The familial syndromes are familial medullary cancer, MEN 2A in which 50% develop pheochromocytoma and 10% to 25% hyperparathyroidism, and MEN 2B in which 50% develop pheochromocytoma and there are phenotypic features of pectus excavatum, long thin arms, and neuromas of lips and tongue.
- The familial syndromes are due to a variety of mutations in the gene that encodes the protein RET.
- RET is a glycoprotein that dimerizes when the ligand is present and in that form the intracellular tyrosine kinase is activated.
- The mutations allow tyrosine kinase to be activated at all times without the formation of dimers.
- Familial cases can be identified by demonstrating the mutation on the RET gene.
- Carriers of the mutation should have a thyroidectomy at an early age, usually 5 years of age for familial thyroid cancer and MEN 2A.

- Knowledge of genotype and phenotype relations should allow more selective timing of operations with delayed intervention in patients where the cancer is known to be of later onset and slower growth.
- Mutations predicting MEN 2B lead to surgery in infancy.
- Early prophylactic thyroidectomy should lead to a cure.
- Fifty percent of patients with MEN 2 syndromes develop pheochromocytoma.
- Ten percent to 25% of MEN 2A patients develop hyperparathyroidism.
- Sporadic medullary cancer is diagnosed by FNA of thyroid nodule.
- Genetic testing should be conducted to ensure this is not a familial medullary cancer.
- There is some evidence that measurement of calcitonin in all patients with a thyroid nodule helps establish the diagnosis.
- Total thyroidectomy and central node dissection is recommended.
- Calcitonin is used for followup.
- An elevated calcitonin implies residual medullary cancer that could be in thyroid bed, lymph nodes, liver, or other sites.
- Ultrasound, PET scan, and, in some cases, selective venous sampling assist defining sites of disease.
- Focal disease in the neck can be treated by operation.
- Radiotherapy to the neck is of some benefit for treatment of residual disease.
- Treatment of metastases is difficult since the cancer is not responsive to chemotherapy.

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Chapter 11

Primary Lymphoma of the Thyroid

Primary lymphoma of the thyroid is uncommon. The long-term management of lymphomas including lymphoma in the thyroid is generally under the care of an oncologist with expertise in treating these cancers, rather than a thyroidologist. The entity is described here because physicians caring for patients with thyroid diseases will occasionally encounter one with primary lymphoma in the thyroid. In almost every patient the pathology demonstrates non-Hodgkin's lymphoma. Approximately 2% to 4% of cancers of the thyroid are lymphomas and similarly about 2% to 4% of lymphomas arise in the thyroid (1–3). About 65% to 90% of the patients are older women many of whom have previously been diagnosed with Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) (4–8). A small number of reports show a relationship with Graves' hyperthyroidism, which is also an autoimmune thyroid disease with lymphocytic infiltration of the thyroid (9). The onset of symptoms is fast. There is rapid enlargement of the thyroid or a preexisting goiter. Local pressure effects are common. The goal should be to establish the diagnosis quickly and to expedite referral to a specialist in the management of lymphomas.

Pathology

Lymphoma of the thyroid is usually non-Hodgkin's B cell lymphoma (10–14). There has been a new classification of lymphomas and this has impacted on the terminology of primary lymphoma of the thyroid (15). It is now accepted that a significant proportion of these cancers are derived from mucosal associated lymphocytes and known by the abbreviation MALT (16). Most primary lymphomas of the thyroid are intermediate or high grade. The general consensus is that the cancers arise from a low grade B cell lymphoma that with time transforms to a more aggressive form. It is also generally accepted that the low-grade B cell lymphomas arise in or from the lymphocytes of Hashimoto's thyroiditis. The exact sequence of transformation from a benign activated lymphocyte to lymphoma has not been defined. There is a considerably increased risk of a patient with Hashimoto's developing a primary lymphoma of the thyroid (17–21). For example Holm et al. found that four of 829 patients with Hashimoto's thyroiditis that had been confirmed by FNA went on to develop lymphoma (19). Therefore only a small fraction (approximately 1/200) of patients with Hashimoto's thyroiditis develops lymphoma, but this is sixty-seven times the expected incidence. The apparent disparity is due to rarity of lymphoma and the ubiquity of chronic lymphocytic thyroiditis. Using monoclonal antibodies to specific lymphocytes, it is possible to stain specimens and determine whether there is a monoclonal aggregate of lymphocytes that is neoplastic, versus a polyclonal aggregate, which is reactive, or inflammatory as in chronic lymphocytic thyroiditis (22–25).

Table 11.1. Number of patients with different pathological types of lymphomas based on modern classification of primary lymphomas of the thyroid.

Reference	Number	B cell lymphoma	Diffuse large cell	Small cell	MALT	Miscellaneous
Belal et al. (100)	52	52	44	–	–	–
Cha et al. (58)	23	23	19	2	2	–
Derringer et al. (5)	108	108	77	–	30	1 follicular
Lerma et al. (102)	12	6	6	–	2	2 mantle 1 Burkitt 1 Hodgkin's
Sippel et al. (52)	27	27	–	–	27	–
Thieblemont et al. (103)	26	–	13	1	6	3 follicular 2 Hodgkin's 1 Burkitt's

Not all primary lymphomas of the thyroid are MALTOMA or high grade B cell lymphoma (26). There are reports of T cell lymphoma, which have also occurred in association with Hashimoto's thyroiditis. (27–29) Plasmacytoma or extramedullary multiple myeloma and Hodgkin's disease arising in the thyroid have also been reported (30–38). We have described a 37-year-old woman with a thymoma of the thyroid and there are several similar reports in the literature. (39–45) Our patient had a large left sided thyroid mass, and normal thyroid function. Two fine needle aspirations showed predominantly CD4/CD8 dual positive T lymphocytes. A left lobectomy was advised to remove the mass and to obtain a definitive diagnosis. The mass was over 50 grams and had all of the histologic features of a thymoma. Several of the reports cited above indicate that there were malignant characteristics in some of the thymomas (40, 43).

We have also described Burkitt's lymphoma presenting as a rapidly expansile thyroid mass in a 50 year old man (46). In this case flow cytometry and immunological typing of the lymphocytes was necessary for the specific diagnoses. A bone marrow biopsy as part of the staging was also strongly positive for Ki-67. There are a few reports of this lymphoma presenting in the thyroid (47, 48). One of twenty-six thyroid lymphomas analyzed by Thieblemont et al. was a Burkitt's lymphoma (22). Table 11.1 shows the types of lymphomas from several recent publications.

The histological features have been described in chapter 3.

Clinical Features

The patient is usually a woman, aged 60 years or more. Table 11.2 shows the gender and age from several series with twenty or more patients, demonstrating that about 75% are women and the average age is 60 years to 70 years. Primary lymphoma in patients less than 50 years is not common and in the pediatric age group it is distinctly rare (49, 50). The youngest patient I could identify in the literature was seven years (51). There is rapid growth of the thyroid, enlargement of a nodule within the thyroid, or a previously stable goiter of Hashimoto's thyroiditis. This occurs in almost 100% of patients (4, 52). Symptoms have usually been present for only a few weeks in most patients. Pressure effects on the aerodigestive tract occur, commonly causing dyspnea, stridor, and dysphagia as shown in Table 11.3. The voice can become hoarse from entrapment of the recurrent laryngeal nerve. Pain is uncommon. Systemic (B) symptoms of weight loss, fever, and weakness occur in about 10% of patients. The gland is hard and irregular on palpation and there can be fixation to surrounding soft tissues of the neck. Thyroid function is usually normal, but hypothyroidism at presentation is explained by the coexistence of Hashimoto's thyroiditis and can occur in up to 40% of patients. Some of the patients are

Table 11.2. Percentage of patients with primary thyroid lymphoma who are women and have Hashimoto's thyroiditis.

Reference	Number of patients	Proportion women (%)	Average age (years)	Percentage with Hashimoto's
Anscombe and Wright (101)	76	88	63	51 (approximation)
Belal et al. (100)	52	73	60	44
Burke et al. (4)	35	74	65	77
Cha et al. (58)	23	67	–	–
Compagno and Oertel (6)	249	73	62	95
Derringer et al. (5)	108	73	64	96
Devine et al. (14)	57	72	62	36
Hamburger et al. (104)	30	73	61	24
Junor et al. (105)	87	86	72	24
Kapadia et al. (106)	21	75	66	57
Logue et al (92)	87	89	67.5	NA
Matsuzuka et al. (12)	119	67	60	100
Maurer et al.	29	83	64	76
Pedersen et al. (107)	50	80	73 women 63 men	66
Pledge et al. (108)	43	86	68	–
Rasbach et al. (109)	20	86	63	75
Scholefield et al. (110)	22	82	64	23
Sippel et al. (52)	27	93	66	30
Souhami et al. (8)	20	75	64	NA
Thieblemont et al. (22)	26	86	59	42
Tupchong et al. (111)	46	93	64	NA

taking thyroid hormone either because of hypothyroidism or to reduce the size of the gland. Thyrotoxicosis has also been described (53–55). This results from release of stored thyroid hormones by the destructive cancer. Not all of the reports listed in Table 11.3 give a clear definition of the pathologies, symptoms and signs, or thyroid function. This is almost certainly related to the specific expertise of the authors of the publications, some being pathologists, others surgeons, oncologists, or endocrinologists. I have tried to extract the data and compress it as accurately as possible.

Diagnosis

A rapidly growing thyroid mass in an older woman should raise the clinical suspicion of lymphoma. The specific diagnosis of primary lymphoma of the thyroid is based on a tissue diagnosis. In the past this required open biopsy

Table 11.3. Percentage of patients with local symptoms due to primary lymphoma of the thyroid.

Reference	Enlarging mass	Dyspnea (airway obstruction)	Dysphagia	Dysphonia (hoarse)
Belal et al. (1)	75	50	25	42
Derringer et al. (5)	72	10	17	2
Devine et al. (14)	82	17	21	25
Junor et al. (105)	87	59	53	75
Logue et al. (92)	100	50	31	24
Matsuzuka et al. (12)	78	–	7	13
Maurer et al.	76	10	14	10
Sippel et al. (52)	100	70	30	–
Souhami et al. (8)	100	40	60	50

to obtain sufficient tissue for the pathologist to examine histologically (56). The diagnosis is now made by flow cytometry and immunophenotyping of the lymphocytes obtained from a fine needle aspiration (FNA) sample (57). In most patients with a growing nodule, the diagnosis of lymphoma is not anticipated, the cytopathologist can only describe the preponderance of abnormal lymphocytes and suggest the diagnosis of lymphoma and a second FNA can be required to provide enough cells for phenotyping (24). In the case of a high grade lymphoma, FNA can be diagnostic. However the differentiation of a low-grade lymphoma from Hashimoto's thyroiditis is not possible by cytomorphology alone. Until recently there has been concern whether the diagnosis can be established by FNA sample, and Cha et al. found this approach successful in 63% of patients (58). With increasingly improving molecular techniques open biopsy should be used less frequently (57). Takashima et al. described the use of polymerase chain reaction to amplify the immunoglobulin heavy chain gene and establish the diagnosis of lymphoma (59, 60). The presence of the antigen CD 20 and heavy chain clonality establish the diagnosis.

Differential Diagnosis

The main differential diagnoses include goitrous Hashimoto's thyroiditis and anaplastic thyroid cancer (61). The former shows abundant lymphocytes on FNA but they are polyclonal by immunophenotyping. The latter shows typical undifferentiated thyroid cells. Many decades ago, some lymphomas were classified as small cell anaplastic cancers, but immunophenotyping should correctly differentiate lymphoma from anaplastic cancer. This misclassification resulted in the apparent better survival of some patients with anaplastic cancer, but they had lymphoma. Lymphoma has been wrongly interpreted as medullary cancer but the lymphoma cells stain positively with lymphocyte antibodies and are negative for calcitonin. The differential diagnosis includes other benign thyroid conditions such as Reidel's thyroiditis and subacute (de Quervain's) thyroiditis (62). When the lymphoma causes destruction of thyroid follicles and release of thyroid hormone the clinical picture can be similar to subacute thyroiditis but FNA should establish the correct diagnosis.

Workup of the Patient

Routine imaging tests are not helpful in establishing the diagnosis of lymphoma in the thyroid. Thyroid scintigraphy shows reduced uptake at the sites of lymphoma, but this is the pattern for most thyroid lesions. Ultrasound shows hypoechoic lesions at the sites of lymphoma and is therefore nonspecific (63, 64). One report suggests it is possible to differentiate primary lymphoma of the thyroid from anaplastic cancer by CT images (61). There is no calcification in lymphoma; however, there are no specific features of lymphoma, and, in practice, the differentiation is not clear cut. (65). The key is to obtain a tissue diagnosis and ultrasound can be helpful in determining the optimal site for sampling.

Once the diagnosis is established staging should be conducted to define whether the lesion is isolated to the thyroid, involves regional nodes, or is systemic. This should be directed by an expert in the management of lymphoma. Routine investigations include complete blood counts, liver and kidney function tests, and measurement of serum calcium and uric acid. A chest X-ray should be obtained. Oncologists generally rely on imaging by CT scan of the neck, thorax, abdomen and pelvis and examination of bone marrow biopsy. There are reports of Gallium-67 (^{67}Ga) being of value because it was used for staging lymphoma. In one series of patients with Hashimoto's who developed features suggestive of lymphoma ^{67}Ga correctly identified 8 patients with lymphoma and 7 of the patients are described having strong uptake in the thyroid (66). However, ^{67}Ga is concentrated in the thyroid in benign chronic lymphocytic thyroiditis and therefore the test has low specificity (67). Gallium-67 scintigraphy for staging of lymphoma has been replaced by PET using fluorodeoxyglucose (^{18}FDG) (68, 69). Similarly somatostatin receptor imaging with ^{111}In-octreotide is inferior to ^{18}FDG PET for staging lymphoma (70). There are anecdotal reports of thallium-201 (^{201}Tl) demonstrating lymphoma in the thyroid (71). Sestamibi has also been employed for imaging (72, 73). These have little role in practice. Fluorodeoxyglucose

PET is positive in the primary lesion, but it is also positive in uncomplicated autoimmune thyroiditis and can be confused as a cancer (74–76). Therefore PET should not be used to make the diagnosis but for staging the disease by identifying sites of disease outside of the thyroid. Once the diagnosis has been established PET scan can be used accurately to define the extent of the problem (77). The method is standard the patient should be fasted for 6 hours and injected intravenously with 370 MBq to 555 MBq ^{18}FDG. Images are obtained after 1 hour and the patient should be resting in a quiet environment without speaking, chewing or eating during that hour. There is debate of the value of PET in patients with MALT lymphomas with some authorities reporting success and others being less enthusiastic (78, 79). An exception to this dogma is that PET is less sensitive in low-grade lymphoma, but, since these are rare in lymphomas that involve the thyroid, this is not a major issue (80, 81). It should be recognized that the thyroid in Hashimoto's shows intense diffuse uptake of ^{18}FDG (76). Positron emission tomography should not be used to make the diagnosis of intrathyroidal lymphoma, but it is valuable for both staging and followup, as shown in Figures 11.1 and 11.2 (82–84). Positron emission tomography is superior to CT for staging (85). Combined PET/CT has the advantage of combining the functional PET scan with the anatomic CT scan and this allows lesions to be defined with more confidence and to reduce the number of false positive results. Positron emission tomography can accurately determine when the marrow is involved by lymphoma (86). The stage is important for management and prognosis. Because the primary lesion is outside a lymph node it is designated $_{E}$ for extralymphatic. Lymphoma confined to the thyroid is stage I_E. When there are no systemic symptoms it is stage I_{EA}. The presence of systemic symptoms such as fever and weight loss is designated Stage I_{EB}. Stage II_E is the presence of regional nodal involvement as well as the primary lesion. Stage III involves lymph nodes on each side of the diaphragm, and Stage IV is systemic disease.

It is stressed that the clinical features of a rapidly growing nodule or goiter in an older woman should prompt FNA to establish a tissue diagnosis. Treatment should never be based on the imaging findings alone.

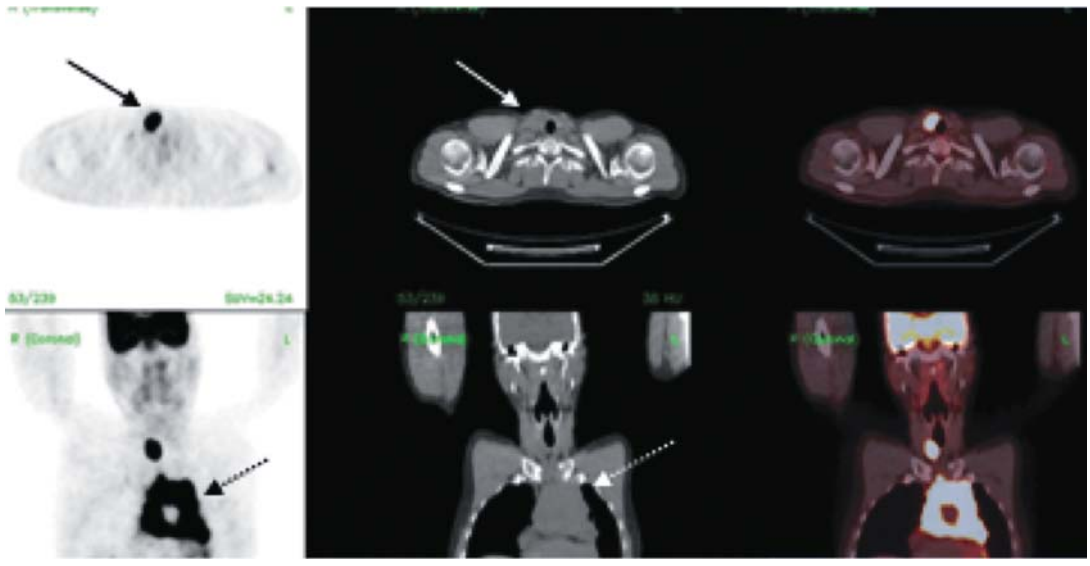

Figure 11.1. PET/CT scan taken of a man with stage IV diffuse large B cell lymphoma involving the thyroid. PET is in the left column, CT in the middle column, and combined PET/CT in the right column. The top row shows transaxial slices through the level of the thyroid, showing intense uptake in a mass in the right lobe of the gland indicated by the solid arrow. The lower row shows coronal sections that demonstrate the thyroid lesion as well as a very large mediastinal mass of lymphoma that has a necrotic center (dotted arrow). The combined PET/CT image shows the relationship of function and anatomy of the lymphoma.

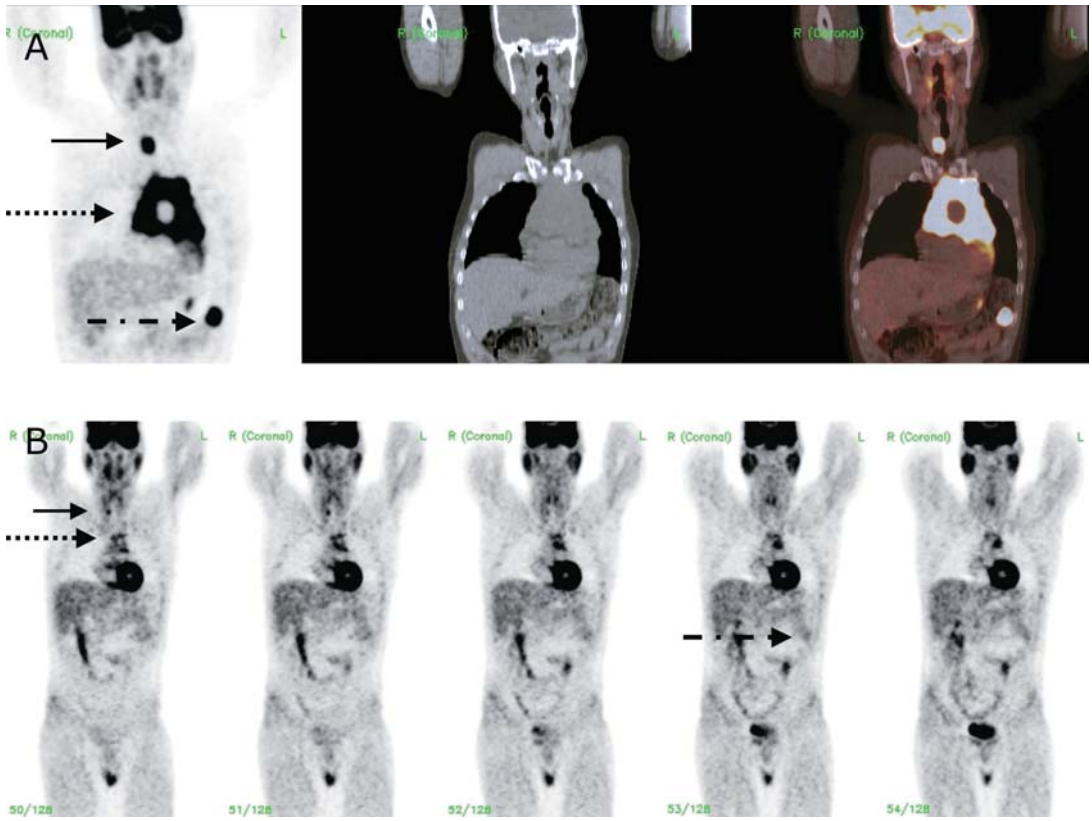

Figure 11.2. (A) is a coronal image of the same patient, and (B) are coronal PET images after 2 cycles of chemotherapy. There is a dramatic reduction in uptake in the thyroid and mediastinal masses, and the lesion in the left side of the abdomen has responded almost completely.

Management

The management should be under the care of a physician trained to treat patients with lymphoma. This will usually be a medical oncologist, but in some cases a radiation oncologist or a team approach. The treatment of diffuse large B cell lymphoma is different from MALT lymphoma involving the thyroid. The fundamentals discussed below are extracted from the guidelines published by the National Comprehensive Cancer Network (87). Stage IE and II MALT lymphoma can be treated by local radiation or surgery provided staging is thorough and shows no evidence of disease outside the neck. When radiation is prescribed the dose is usually in the range of 20 Gy to 36 Gy (2,000–3,600 rad) (88). There could still be a role for surgery to treat Stage IE intrathyroidal lymphoma (89, 90). There are too few patients to mount a trial of surgery versus radiation therapy versus surgery.

Higher stages of disease are treated by chemotherapy, which can be a single agent or a combination. In patients who are likely to have difficulty withstanding systemic chemotherapy antibody treatment such as Rituximab can be administered. When a cardiotoxic agent is part of the regime the patient should have a radionuclide ventriculogram to confirm the function of the left ventricle is normal and this can be used as a base line for testing later.

In the case of B cell lymphoma because the disease presents as a rapidly expansile thyroid mass causing pressure effects, there is frequently the belief that surgery is necessary. Indeed, there are reports of the benefits of thy-

roidectomy (16, 52, 91). In the past, surgery also provided the necessary tissue for pathologic diagnosis as well as symptomatic relief. Rosen et al. suggest a biopsy and removal of operable cancer in patients who do not have a preoperative diagnosis of lymphoma (90). They stress the need to preserve the parathyroids and recurrent laryngeal nerves. Logue et al. treated seventy patients and 62% had surgery such as total thyroidectomy (7%), subtotal thyroidectomy (39%), or lobectomy (16%) (92). Reports from the Mayo clinic have shown that biopsy followed by external radiation is as effective as debulking and radiotherapy (14, 93). However, because the disease can be diagnosed by FNA, because the lesions are very responsive to chemotherapy or radiation, and because the disease can be systemic, there are fewer roles for surgery. As an example, the patient with Burkitt's lymphoma of the thyroid described above had a rapidly growing thyroid mass, which in one week went from unrecognized to causing aerodigestive symptoms. The mass and symptoms disappeared in 36 hours after treatment with systemic chemotherapy. The specific treatment depends on the stage of disease. The chemotherapy is generally a multidrug regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Stage I and II disease is treated with radiation to the thyroid and six cycles of CHOP. Stage II and IV disease in patients with low and intermediate risk factors are treated with six to eight cycles of CHOP and Rituximab. High-intermediate and high-risk patients are treated either with that protocol or an experimental approved by an appropriate group of experts. High-intermediate and high risk patients have three or more risk factors such as age over 60 years (most patients), elevated lactic dehydrogenase, reduced performance status, stage II or IV disease, and more than one extranodal site of disease.

One of the problems in analyzing older publications is the uncertainty of the exact pathological variant of lymphoma that is being treated and the stage of disease. The outcome in localized MALT lymphoma is different from diffuse large B cell lymphoma. In one series, two patients treated by surgery alone who were alive and well after 18 years and 21 years likely had MALT lymphoma that was restricted to the thyroid (93). In a metaanalysis, local radiotherapy plus chemotherapy resulted in fewer relapses than radiotherapy alone (94). This probably is due to unsuspected disease outside the radiation field that was treated by systemic chemotherapy. There are other reports of patients with disease thought to be confined to the thyroid that were treated locally to that site but subsequently died of widespread disease (55). In high-grade disease most oncologists would recommend chemotherapy (95).

Even with the advances in immunophenotyping not every patient has a definitive diagnosis. I am currently following a patient where the diagnosis is either a very low-grade lymphoma or Hashimoto's thyroiditis. Five years ago he was found to have a goiter. Ultrasounds showed a very heterogeneous gland. Fine needle aspiration 5 years ago was consistent with chronic lymphocytic thyroiditis. He had positive antithyroid antibodies. On followup, his physician was not sure if the goiter was stable and requested a second FNA. This was diagnosed as a low grade B cell lymphoma. Oncologists ordered CT scans of neck, chest, and abdomen and all were normal. Positron emission tomography scan showed diffuse uptake in the thyroid and no other abnormality. Ultrasounds have been stable and continue to show an identical heterogeneous pattern. Five years after presentation, his TSH became borderline high 3.5 μ/l to 4.5 μ/l, and he was treated with levo-thyroxine. After 1 year the gland appears unchanged clinically and on ultrasound. The patient does not want an open biopsy, and we have agreed to follow by clinical examination and periodic ultrasound. His mother was recently diagnosed hypothyroid and has elevated antibodies to thyroglobulin (Tg) and thyroid peroxidase (TPO).

The followup should also be under the care of the oncologist. Positron emission tomography can be used for followup after therapy to define that lesions outside of the thyroid have responded to chemotherapy or whether there is residual disease (96). It is superior to anatomic tests such as CT and ultrasound (97). However, there should be caution on interpreting continued uptake in the thyroid as evidence of persistent lymphoma. A recent report showing this finding in a patient who had undergone an excisional biopsy and chemotherapy turned out to be a false positive and only necrotic tissue was identified pathologically when the thyroid was removed (98). Positron emission tomography is valuable in studying the rest of the body

Table 11.4. Prognosis in patients with lymphoma in the thyroid.

Reference	5 year survival overall (percentage)	5 year survival Stage IE (percentage)	10 year survival (percentage)
Junor et al. (105)	43	74	–
Rosen et al. (90)	59	–	–
Logue et al. (92)	49	68	–
Pyke et al. (93)	53	80	46
Dibiase et al. (88)	56	69 (stage I and II)	–
Thieblemont et al. (22)	77	–	54
Sipple et al. (112)	77	–	–
Belal et al. (1)	88	–	–

and defining whether the chemotherapy was a success (99).

Prognosis

The prognosis decreases with extended stage of disease, diffuse large cell lymphoma, rapid clinical growth, lesions greater than 10 cm, vascular invasion, and increasing age of the patient (89). Thieblemont et al. predicted 5-year and 10-year overall survivals of 77% and 54% after treatment with combination chemotherapy (22) Table 11.4. Sippel et al. described a 5-year survival of 77% in their twenty-seven patients who all had palliative surgery first, then ten had combined chemotherapy and radiation therapy, ten had additional radiation treatment, and four additional chemotherapy alone (52). Belal et al. reported a 5-year overall survival of 88% and relapse free survival of 72% (100). These are representative. Patients with stage I_E disease have a 5-year survival of 70% to 90%.

Summary and Key Points

- Lymphoma of the thyroid is uncommon.
- About 2% to 4% of thyroid cancers are lymphoma.
- About 2% of lymphomas arise in the thyroid.
- Women are about five times more likely to have lymphoma of the thyroid.
- Preexisting Hashimoto's thyroiditis is common in patients with lymphoma of the thyroid.
- Most patients are 60 years or older.
- Symptoms and signs include rapid growth of thyroid, dyspnea, dysphagia, stridor and hoarseness.
- Diagnosis is best made by FNA cytomorphology and immunophenotyping.
- The workup of the patient should be by a specialist who is experienced in management of lymphoma in general.
- Treatment of disease restricted to the thyroid can be locoregional radiation or surgery.
- In most patients, treatment is usually combined chemotherapy (CHOP) and is best supervised by an oncologist.

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Chapter 12

Metastases to the Thyroid

The thyroid is a vascular organ and therefore can be the site of blood borne metastases from other cancers. The thyroid, although a small gland, is second to the adrenals with regard to the most arterial flow per gram of tissue. Clinically an increase in the blood flow through the thyroid can be recognized in patients with Graves' disease by a palpable thrill or audible bruit over the gland. It is obvious from clinical practice that most blood borne metastases are found in large organs that receive a significant proportion of cardiac output such as the lungs, liver, brain, and bone marrow. Various cancers have a natural propensity to metastasize to specific sites such as prostate cancer to the skeleton and bowel cancer to the liver. Most of the common cancers seldom metastasize to the thyroid.

The most important issue when a nonthyroidal cancer is diagnosed in the thyroid is how should the patient be managed and will removal of that metastasis improve the prognosis?

Incidence of Metastases to the Thyroid at Autopsy

Nakhajavani et al. and McDougall have summarized the literature on the incidence of metastases at autopsy (1, 2). There is a wide range from 1.25% in unselected patients to 24.2% in selected patients with known metastatic cancer (3, 4). The range is most likely due to the population under consideration and the vigilance and tenacity of the pathologist conducting the study. In some reports 2 mm sections were examined. Willis and Shimaoka et al. reported metastases at autopsy in 5.2% and 8.6% respectively in patients with cancer and these are probably most representative (5, 6).

Metastases to Thyroid in Patients

In practice, the issue relates to the living patient with a metastasis in the thyroid. How should the patient be managed? If the patient is known to have a nonthyroidal cancer with widespread metastases and is found to have a new thyroid mass, the implication is that is also a metastasis. When the patient is terminal, there is no benefit from proving that the thyroid nodule is a metastasis, since the information will not alter the treatment or the outcome. Alternatively, a patient with a known cancer but no evidence of metastases might develop a nodule that on FNA is consistent with a metastasis from the original primary cancer. When a rapidly growing nodule arises in a patient with a previously diagnosed cancer and no prior thyroid disorder, this mass should be suspected to be a metastasis (7). There are reports of the metastasis to the thyroid occurring up to twenty or more years after the diagnosis and treatment of the primary cancer (1, 8). In the Mayo clinic series, twelve

of forty-three patients developed the thyroid metastasis more than 10 years after the original diagnosis of cancer (1). Similarly, three Polish patients were identified to have metastases from renal cancer 5 years, 6 years, and 9 years after nephrectomy (9). The presentation in these patients was a multinodular goiter, which is common in Poland. An elderly Japanese woman presented with a rapidly growing thyroid metastasis 19 years after nephrectomy for renal cancer (10). A separate case report indicated a 14-year gap between nephrectomy and the diagnosis of metastasis to the thyroid (11). In contrast in a report from China, the mean latency time between diagnosis of the primary cancer and the thyroid metastasis was only 9 months (12). In that study only eight of seventy-nine patients presented with a thyroid metastasis after 3 years or more. Finally a patient with a new thyroid nodule who has no history of cancer and unequivocally no other metastases might first be diagnosed to have metastatic cancer on examination of FNA of the nodule. These patients would therefore present as "carcinoma (usually adenocarcinoma) of unknown origin" and would require work-up to confirm the diagnosis and determine management. In this situation the growth of a new nodule containing the metastasis can be the presenting sign and only when the FNA result of the nodule is interpreted does the diagnosis of a nonthyroidal cancer arise (13). This was the case in sixteen of twenty-one patients described by Michelow et al. (14). In a recent report from the Royal Marsden Hospital five of fifteen patients had no prior diagnosis of cancer (15). The nodule containing the metastasis can grow rapidly and cause compression of the aerodigestive tract. Sometimes the metastasizing cancer grows rapidly and invades and destroys normal thyroid causing release of thyroid hormones. This produces biochemical and or clinical thyrotoxicosis (16). When the rapid swelling is also painful, this syndrome is difficult to differentiate from subacute thyroiditis and has been called carcinomatous pseudothyroiditis (16, 17). The differentiation is made more difficult when an radioiodine uptake and or scan are obtained because the uptake is low in carcinomatous pseudothyroiditis and this finding tends to support the diagnosis of subacute thyroiditis in which the uptake of radio-iodine is characteristically low. An FNA is necessary to differentiate these. Because most patients with classic subacute thyroiditis have fever and an elevated white blood count and no history of a prior cancer, an FNA would usually not be indicated. However, when the patient is elderly and the clinical features are atypical, an FNA is indicated. In addition when a patient has a diagnosis of nonthyroidal cancer and presents with a painful thyroid mass and thyrotoxicosis, FNA would be recommended. After a brief period of thyrotoxicosis, hypothyroidism is the expected end result of this syndrome provided the patient lives for several months (18).

Diagnosis

The diagnosis of a metastasis to the thyroid might be suspected clinically because of the prior history of cancer. In some patients there is no such history as was the case in the report of Michelow et al. (see above) and six of forty-three patients from the Mayo Clinic (1). Most of the patients are more than 50 years of age and the genders are about equal. A tissue diagnosis by FNA should be obtained quickly (14, 19–22). Thyroid scintigraphy will usually show a cold area but as discussed in Chapter 4 this test usually does not help establish a diagnosis. Ultrasound findings are not specific because almost all metastases are ill defined, heterogeneous, and hypoechoic (23, 24). Therefore ultrasound is not recommended unless that test would allow more precise localization for FNA (25, 26). When the FNA result indicates a nonthyroidal carcinoma, a review of prior surgeries and pathologies can help clarify whether this is an associated finding.

The vast majority of metastases to the thyroid are from kidney, lung, breast, gastrointestinal tract, and melanoma (1, 27–29). Thyroid metastases in patients dying from melanoma are found commonly at autopsy (13, 30, 31). The types and percentages of cancers reported to metastasize to the thyroid from several publications are shown in Table 12.1 (1, 20, 32, 33). In many of these reports the number of kidney lesions is disproportionate to the incidence of that cancer (1, 9, 15, 32–37). There are also several case reports of this association (38–41). In one patient there were bilateral renal cancers and metastasis to the thyroid (42). The presence of suspected metastatic renal cancer to the

Table 12.1. Percentage of nonthyroidal metastases arising from kidney, breast, lung, gastrointestinal tract, and other sites.

Reference	Number of patients	Kidney %	Breast %	Lung %	G-I Tract %	Melanoma %	Miscellaneous %
Chen et al. (33)	10	50	–	10	20	–	20
Chung et al. (24)	9	–	67	–	–	–	33
Eftekhari et al. (25)	4	25	–	50	–	25	–
Haugen et al. (34)	Compliation of publications	56	12	11	12	3	6
Ivy Mayo Clin 1946–82 (32)	30	40	20	17	–	–	23
Lin et al. (26)	4	–	50	50	–	–	–
McCabe et al. (7)	17	12		24	12	6	46 larynx 29
Michelow et al. (14)	21	5		43	24	10	18 Prostate Larynx Uterus Leukemic deposit
Nakhjavani et al. Mayo Clin 1985–94 (1)	43	33	16	16	9	–	26
Schroder et al. (72)	25	38	20	28		–	–
Watts (20)	6	–	50		17	–	33
Wood et al. (15)	10	27	7	7	7	7	40

thyroid raises an important issue, since clear cell cancer of the kidney cannot always be easily differentiated from clear cell follicular cancer. Can we be sure from which cell the cancer is derived? Therefore staining for organ specific antigens should be part of the diagnostic process. Kidney cancers do not stain positively for thyroglobulin and thyroid cancers do not stain for glycogen (43). Kidney cancers stain positively for diastase-sensitive Periodic-Acid Schiff and Oil Red O. There is a recent report of a thyroid cancer metastasizing to the kidney, and part of the pathological proof was the demonstration of the presence of the sodium iodide symporter (NIS) in the malignant cells (44). However, NIS has also been identified in normal kidney cells so care needs to be taken to ensure the stains, including antibody stains, are specific for only one organ. One patient I have managed for several years first had adenocarcinoma of the lung. After successful lobectomy of the left lung he was found to have a new thyroid nodule. Fine needle aspiration showed an adenocarcinoma that looked like the lung lesion. Immunopathological staining of both the lung and thyroid tissues using antibodies to thyroglobulin (Tg) and lung antigens proved that he had 2 separate primary cancers. The thyroid cancer was treated by thyroidectomy and ^{131}I. He has no evidence of recurrent lung or thyroid cancer after 7 years and has had negative followup scans and undetectable Tg.

There are many single case reports of metastases to the thyroid of uncommon cancers as well as more common cancers described above. These include chromophobe renal-cell cancer (45), choriocarcinoma (46), uterine leiomyosarcoma (47), pancreatic cancer (48), squamous cell cancer of the mouth (49), adrenal cancer (50), bronchioalveolar cancer (51), colon cancer (52, 53), rectal carcinoid (54), sarcoma (55) and malignant fibrous histiocytoma (55–57). Kaposi's sarcoma has been described in the thyroid of patients with AIDS (18, 58). Liposarcoma has metastasized to the thyroid (59). Some evidence points to the metastases being more common in patients with underlying thyroid disorders such as nodular thyroids (60). There are even reports of a nonthyroidal cancer metastasizing to a thyroid cancer. These include a renal cancer and a colon cancer both of which metastasized to Hürthle cell cancers (52, 61).

Management

The management varies depending on the extent of the metastatic disease. In a patient dying from widespread cancer there is no reason to investigate a new thyroid nodule. As a

result, FNA or imaging tests are not advised. On the other hand, a patient with a known cancer who has no evidence of metastases but does have a new thyroid nodule should have an FNA to determine the pathology. Figure 12.1 provides an algorithm. The thyroid lesion might be a benign thyroid nodule, a primary thyroid cancer, or a metastasis. The management of the first two have been described in Chapters 4 and 6. The removal of a solitary thyroid metastasis by operation can result in long-term disease free survival, especially in the case of renal cancer (1, 37, 62). Ericsson et al. also recommend this in the case of an isolated metastasis from melanoma (62). Having diagnosed a thyroid metastasis in the setting of a known primary cancer, staging would be important to ensure there were no other unsuspected lesions. This could involve CT of chest, abdomen and pelvis. This is likely to be an ideal situation for PET (or fused PET/CT) scans, since the body from the base of brain to mid thighs can be evaluated and the sensitivity for most common cancers is excellent (63, 64). Combined PET/CT gives the added value of anatomic and functional imaging. Sometimes focally increased uptake of ^{18}FDG in the thyroid is indicative of a cancer and occasionally this is a metastasis (Figure 12.2).

When the FNA of a thyroid nodule is reported to be a metastatic cancer but the patient is not known to have cancer, it is necessary to identify the primary site. The cytological findings might help direct the appropriate workup. When this does not help, examination of the skin and

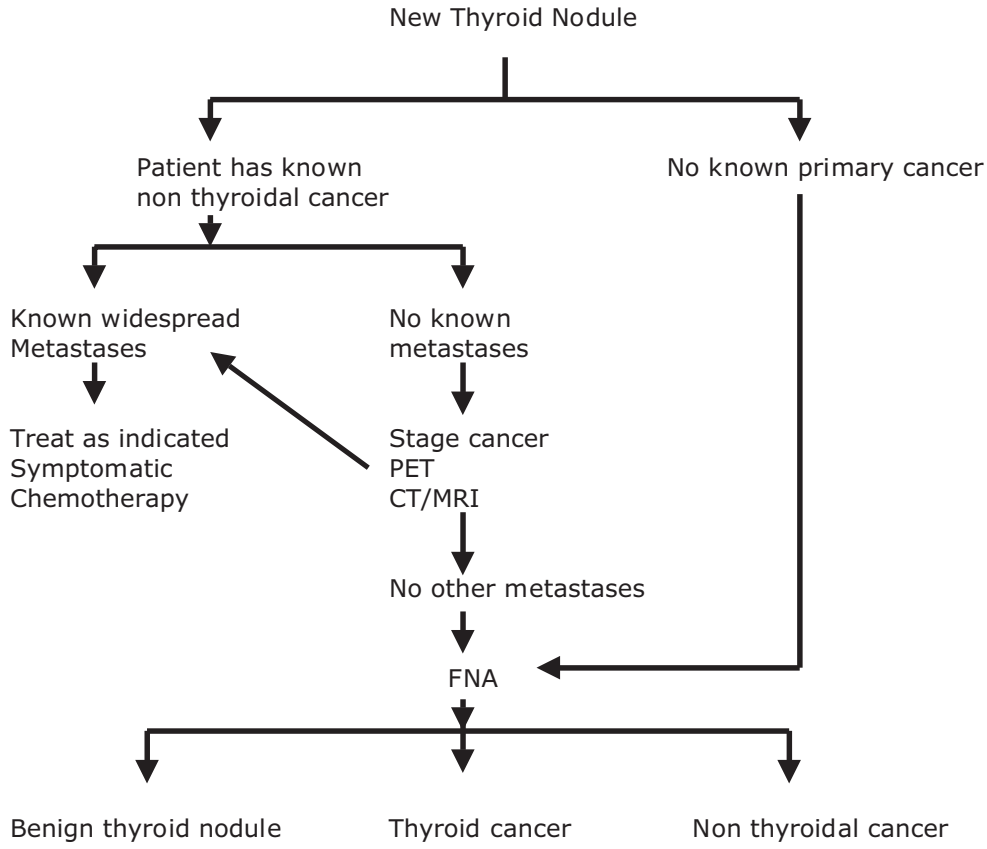

Figure 12.1. Algorithm for work up of patient with a metastasis to the thyroid.

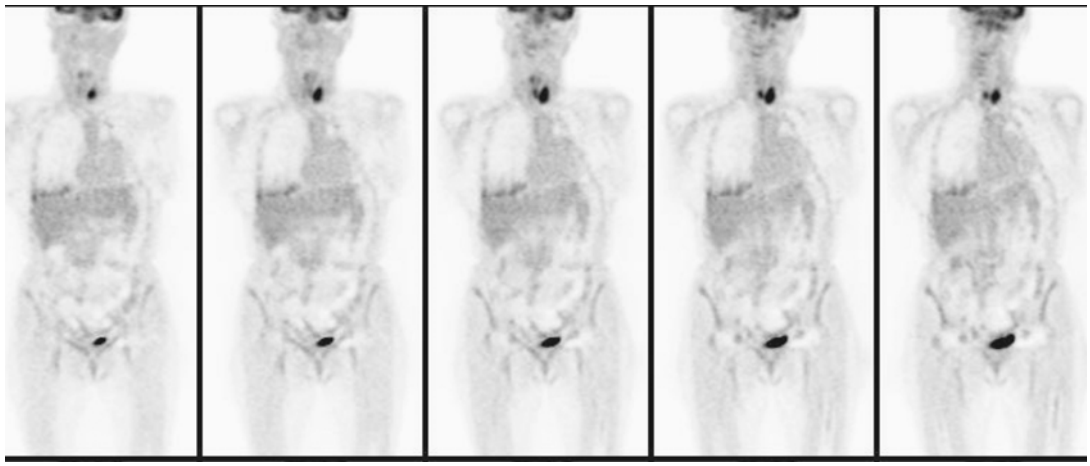

Figure 12.2. Positron emission tomography scan shows intense uptake in the thyroid. This was a metastasis from a squamous cell cancer of the lung.

imaging of the kidneys, lung, and breast would be advised with CT of chest and abdomen and mammography. It is too early to comment definitively on the use of PET in this setting, but intuitively it is likely to be helpful (65, 66). There are preliminary data of the use of PET in patients with carcinoma of unknown origin (67). When the primary cancer is identified and the only metastasis is to the thyroid, removal of the primary cancer and thyroid including the mass might prolong survival and even be curative (68).

There is a report of an expanding metastasis to the thyroid from a rectal cancer that was treated by tracheal and cricoid resection (69). Unless it is clear that there is significant life expectancy hopefully of good quality, the patient, clinicians, and the patient's family must deliberate carefully before major surgery is undertaken (70). Each patient needs to be evaluated as an individual, looking at the site, size, and pathology of the primary cancer, the extent of metastases, the patient's age, state of general health, and so forth. Then a reasoned decision about curative surgery can be made. When the cancer is extensive, systemic chemotherapy appropriate for the primary cancer is administered. Painful or expanding lesions are treated by external radiation therapy. In several of the series of metastases to the thyroid discussed above there are small numbers of patients in whom the primary lesion is not identified. These patients would be treated by protocols for "adenocarcinoma of unknown origin" using a best likelihood of the primary site based on the age, gender, and risk factors in the patient.

Prognosis

The prognosis varies greatly depending on the patient's clinical presentation. Those with widespread metastases are not expected to survive more than a few months. In contrast, those with isolated thyroid lesions, which are amenable to surgical excision, do relatively well. In the Mayo Clinic report by Nakhjavani et al., fifteen patients died out of thirty-seven patients who were followed (1). It was notable that the average survival was 34 months in those who had thyroidectomy versus 25 months in those who did not. The mean survival in 10 patients with renal cell metastases to the thyroid who underwent "metastectomy" was 39 months. Ivy described two patients with renal cancer alive at 3 years and 6 years and two with breast cancer alive after 3 years and 5 years (32). In a different review of seven patients who had thyroid surgery, the average survival was 38 months (71). Most of McCabes' patients survived about 1 year, and one with renal cancer was alive with disease after 45 months (7).

Summary and Key Points

There is considerable range in the reported incidence of metastases to the thyroid. The highest percentages are in patients with disseminated disease whose thyroids are examined carefully at post mortem. In clinical practice this is not common. Cancers that have a propensity to spread to the thyroid are kidney, breast, lung, gastrointestinal tract, and melanoma. Occasionally the thyroidal metastasis is the first evidence of the presence of cancer. The thyroid mass should be investigated by FNA. The cancer should be staged and when the thyroidal metastasis is the only lesion removal of the primary when it has not already been treated and the thyroid can result in long-term survival. This should not be attempted when there is evidence of extensive spread of cancer.

- Metastases to the thyroid are not common in routine clinical practice.
- Thyroid metastases are found in 5% to 10% of autopsies in patients with known nonthyroidal cancers.
- The usual clinical presentation is a new thyroid nodule.
- A new thyroid nodule in a patient with a known primary cancer should raise the suspicion of a metastasis.
- The commonest primary cancers, which metastasize to the thyroid, are the kidney, breast, melanoma, lung, and colon.
- The best diagnostic test is FNA.
- Fine needle aspiration demonstrating a likely nonthyroidal cancer should prompt workup to find the primary and to plan management provided there is not evidence of extensive metastases.
- In some patients, removal of the thyroid metastasis is associated with a good long-term prognosis.
- In patients with widespread metastases, the prognosis is poor.

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