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Hossein Gharib *Editor*

Thyroid Nodules

Diagnosis and Management

Humana Press

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This book is dedicated to our families who deserve deep, enduring gratitude; to our patients who see us for care and continue to teach us; and to our residents, fellows, and younger colleagues who inspire and keep us humble.

Series Editor Foreword

Evaluation of a thyroid nodule remains one of the most common, and yet one of the most challenging, problems facing a practicing endocrinologist. Difficulties and uncertainties persist, particularly in assessing the likelihood of malignancy and determining the most appropriate management strategy.

Even as significant new information about the molecular markers in thyroid nodules has become available for clinical use, the final decision about the likelihood of malignancy, the extent of surgery (if any) and the nature of post-surgical surveillance and therapy ultimately rests with the clinician rather than with any particular test. Thus, the opinion of an experienced thyroidologist is invaluable.

For the current volume, Dr. Hossein Gharib, one of the world's most prominent thyroidologists, has assembled a group of authors with unmatched collective expertise. All relevant issues of diagnosis and management of thyroid nodules are addressed using the most up-to-date information from both basic science and clinical studies. This book is likely to become an important tool to be used by all those who are tasked with advising and managing patients with this common, but not simple, problem.

New York, NY, USA — Leonid Poretsky, MD

Foreword

It is a pleasure and honor to introduce this extremely timely textbook exploring all aspects of the clinical and laboratory evaluation and therapy of thyroid nodules edited by Dr. Hossein Gharib, a leader for many years in the clinical and laboratory evaluation of goiter and, in particular, thyroid nodules. The book begins with chapters devoted to the epidemiology, history, and laboratory and clinical evaluation of the thyroid nodules followed by the use of radioactive isotopes, ultrasound, and CT scanning to further define the thyroid nodule. Interpretation of thyroid cytology following fine-needle aspiration biopsies of nodules deemed suspicious for malignancy under ultrasound evaluation and the use of molecular markers in those nodules which are indeterminate by cytology are discussed in detail including the potential pitfalls in techniques. Whether thyroxine therapy is useful in the therapy of benign thyroid nodules is certainly controversial and is appropriately discussed. The surgical approach to thyroid nodules, including newer minimally invasive techniques, is reviewed as is the diagnostic and therapeutic to thyroid nodules in children.

This textbook will be extremely helpful to a wide range of physicians, both specialists and primary care physicians in the diagnosis, therapy, and follow-up of thyroid nodules which have become extremely common worldwide with the use of ultrasound, CT, and MRI scans for non-thyroid-related procedures.

Boston, MA, USA — Lewis E. Braverman, MD

Preface

There are compelling reasons to dedicate a book to the topic of thyroid nodules. First, although many books about thyroid disorders have been recently published, none deals specifically with thyroid nodules and nodular goiters. Second, thyroid nodules are very common in clinical practice, and we hope those who take care of these patients, endocrinologists, internists, general surgeons, ENT surgeons, pediatricians, primary care physicians, radiologists, nurses, and physician assistants, find it useful. Third, conventional approach to diagnosis and management of thyroid nodules has undergone considerable change during the past several decades, with an ever-increasing number of published reports (Fig. 1). Finally, to provide optimal care, it is essential to understand new developments and advancing technology in molecular genetics, novel cytologic classifications, US techniques, and evolving surgical approaches.

We are extremely fortunate to have contributions from an outstanding group of international experts who provide up-to-date recommendations for diagnostic evaluation and management of patients with nodular thyroid disease. Each author, the best in the field, was selected for her/his expertise and contributions to the topic

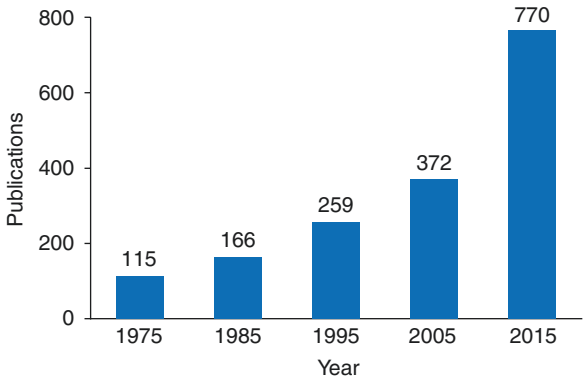

Fig. 1 Increasing thyroid nodule publications between 1975 and 2015 in PubMed

area. Chapter length and book size limitations notwithstanding, I believe the subject matter has been thoughtfully and thoroughly covered.

This book is intended for those who look for a state-of-the-art update on management issues important to the care of patients with thyroid nodules.

Rochester, MN, USA Hossein Gharib, MD, MACP, MACE

Acknowledgments

I am indebted to all contributors, my friends and colleagues, for their chapters, expertise, and on-time submission of manuscripts. They are indeed the best examples of exemplary teachers who freely offer their time and expertise to teach, hoping to improve care of patients with thyroid disease.

My special thanks also to two Springer Publishing Company editors: Mr. Kristopher Spring, who initially suggested the idea of this book some 2 years ago, and Ms. Mariah Gumpert, whose continuous, regular emails kept us on schedule and without whose support, expert assistance, and useful advice, this project could not have been completed.

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Chapter 1
Epidemiology of Thyroid Nodules

Alan A. Parsa and Hossein Gharib

Introduction

The prevalence of nodular thyroid disease has increased over time predominantly due to advances in imaging techniques. Epidemiological studies have reviewed possible environmental factors influencing nodular formation.

Iodine, a key component of thyroid hormone production, is known to effect thyroid function. It is estimated that around 30% of the world's population is deficient in iodine intake which can lead to goiter/nodule formation [1–3]. For instance, in Jutland, Denmark, an area of longstanding low iodine intake, a 12% female prevalence of goiter exists, compared to around 2% in the iodine-sufficient Iceland [4]. Other studies have shown similar trends with low iodine intake areas having a higher prevalence of goiter compared to iodine-sufficient regions (Table 1.1) [5, 6]. One hypothesis is that iodine deficiency may lead to monoclonal somatic mutations causing goiter and nodule formation [7, 8]. Replacement of iodine to areas of insufficiency has a positive effect leading to goiter and nodule regression.

A Danish investigation, the DanThy study, evaluated thyroid function before and after the mandatory iodine fortification of table salt and salt in bread in Denmark [9, 10]. Prior to the introduction of iodine, the prevalence of thyroid nodules >1 cm increased with age from 15% in wo me n aged 40–45, to 25–30% in those aged 60–65 [9]. Eleven years after initiation of the iodization requirement, the DanThyr study showed that among the 618 subjects with thyroid nodules at baseline, 24% had no evidence of

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Table 1.1 Prevalence of thyroid nodules and goiters in iodine-deficient areas

Investigation	Number of subjects	Age (years)	Iodine deficient	Prevalence (%)	Country
Laurberg et al. (1998) [4]	423 100	68 66–70	Yes No	12 (female) 2 (female)	Denmark
Laurberg et al. (2006) [9]	4649	40–45 60–65	Yes	15 25–30	Denmark
Karger et al. (2010) [6]	736	Adult woman	Yes	45	Germany
Aghini-Lombardi et al. (2013) [12]	1411	Adult	Yes No	46 26	Italy

nodules in follow-up [10] indicating reversal of nodular disease with normalization of iodine levels. In a survey of 1411 subjects in Pescopagano, an iodine-deficient village in Southern Italy, goiter prevalence was 16% in children and 59.8% in adults [11]. Dietary iodinated salt incorporation decreased the overall prevalence of goiter from 46%, in 1995, to 26%, in 2010 ($P < 0.0001$) [12]. Similar changes were noted in an iodine-deficient region of China where schoolchildren aged 8–10 years showed a reduction in goiter prevalence pre- and post-normalization of iodine levels from 18% to 9%, respectively [13]. Iodine repletion leading to the correction of thyroid disorders has been consistent in other studies [14–16]. Table 1.1 shows the prevalence of goiter/thyroid nodules in iodine deficient compared to iodine sufficient areas. This change is not permanent though; if iodized salts are removed from the diet and iodine levels become once again insufficient, goiter prevalence rapidly returns to pre-iodization levels [17].

Radiation exposure, thyroid nodularity, and cancer risk are correlated. Antonelli et al. in Pisa, Italy, evaluated 50 male medical workers occupationally exposed to radiation and compared them to nonexposed workers. Thyroid nodules were detected in 38% of exposed workers compared to 13% of those unexposed, living in the same area [18]. Trerotoli et al. in a cross-sectional study in Bari, Italy, evaluated the prevalence of nodules in an area of mild iodine deficiency in 304 people in work-related "maximum risk category for radiation exposure." Nodules >1 cm were detected in 19% of nonexposed males to radiation compared to 4–9% of exposed males depending on the degree of radiation exposure [19]. The authors concluded that occupational exposure to radiation and iodine deficiency did not correlate with increased nodule risk and the higher numbers of nodules in the nonexposed group was related to this group having a stronger family history of thyroid disease. A similar study evaluated 1247 cleanup workers from Estonia sent to Chernobyl in 1986 for an average of 3 months soon after the nuclear plant accident. The incidence of thyroid nodules measured by ultrasound 8 years post exposure was 10.2%. The authors concluded that Chernobyl cleanup workers from Estonia did not experience an increased risk of nodular thyroid disease associated with exposure to external radiation [20]. These studies suggest that mild to moderate exposure to radiation does not significantly increase risk of nodule formation.

In a more intense radiation exposure setting, Takahashi et al. [21] evaluated 815 subjects present during the atomic bomb test, BRAVO on March 1, 1954, at Bikini

Atoll, Marshall Islands. Their goal was to establish the prevalence of thyroid nodules attributed to fallout radiation. Of the 33% with thyroid nodules, cancer prevalence was particularly high (3.2%) in women who were aged 1–10 at the time of detonation. Papillary type thyroid carcinoma is the most frequently encountered malignancy (92%) in the Marshallese born prior to the 1954 detonation [22]. It is estimated that an overall 20% of Marshallese will develop thyroid cancer as a result of radiation fallout, with the highest estimated lifetime risk of 95% from those from Rongelap Island and Ailinginae community due to these areas having the highest fallout [23].

Suzuki et al. evaluated those under 18 years of age living in Fuskushima, Japan, during the 2011 nuclear power plant accident. While the prevalence of thyroid nodules was not very high (2108 of 300,476 screened), the overall prevalence of thyroid cancer was determined to be 37.3 per 100,000 [24]. This high rate of cancer is thought to be due to the use of highly sophisticated ultrasound techniques rather than a true increase due to radiation exposure [24, 25]. A cohort study survey of 4091 survivors of the Hiroshima and Nagasaki atomic bomb blast of 1945 were evaluated 55–58 years post exposure [26]. Thyroid disease was identified in 45% of participants with the prevalence of solid nodules, malignant tumors, benign nodules, and cysts of 15%, 2%, 5%, and 8%, respectively. A significant linear dose-response relationship was observed for the prevalence of all solid nodules, malignant tumors, benign nodules, and cysts ($P < 0.001$) in those exposed to radiation from the nuclear accident [26].

A cross-sectional analysis attempting to link an association between type 2 diabetes mellitus and thyroid nodules in Zhejiang Province, China, observed a thyroid nodule incidence rate of 81.4% in diabetic patients and 70.7% in nondiabetics. They concluded that though there was a higher incidence of thyroid nodules in the study group, diabetes was not a risk factor for thyroid nodules [27]. This is in contrast to a single-center, prospective case-controlled study in Turkey where 51% of prediabetics and 62% of diabetics possessed thyroid nodules compared to 24% of nondiabetics [28]. The authors suggest an association between impaired glucose metabolism and thyroid nodule prevalence. A possible cause of the difference between the two groups could be that the latter group was studied in a mild-to-moderate iodine-deficient area of Turkey while the iodine status of the first group in China was not revealed.

Volzke et al., in a cross-sectional study of 3662 subjects, evaluated the association between insulin-like growth factor-1 (IGF-1) and goiter risk in those without a history of thyroid disorders [29]. Those with serum IGF-1 levels in the upper tertile had a higher odds for goiter development relative to subjects with serum IGF-1 in the lower tertile [odds ratio (OR) 1.67, 95% confidence interval (CI) 1.24–2.26 in women, OR 2.04, 95% CI 1.55–2.68 in men]. Patients treated with growth hormone (GH), for GH deficiency, developed a high (27%) incidence of thyroid nodules with the primary predictor of nodule development being serum IGF-1 levels ($P = 0.038$) [30]. Patients with active acromegaly, a condition with elevated endogenously secreted GH and subsequent high IGF-1 levels, were shown to have increased thyroid volume of up to 20% [31]. Thyroid volume was reduced with the normalization of IGF-1 by 21.5% in medically controlled ($P < 0.005$) and 24.2% in surgically cured ($P < 0.002$) acromegalic patients [31].

An association between thyroid nodularity and uterine fibroids was described in 925 women of whom 18% had coexisting thyroid nodules with uterine fibroids. A significant association was noted between both fibroids and thyroid nodules ($P = 0.01$) with a closer relationship in premenopausal women ($n = 445$, $P = 0.001$). This suggests that the age and presence of uterine fibroids are independent risk factors for the presence of thyroid nodules [32]. Further, systemic estradiol (E2) levels in premenopausal women showed an inverse correlation with the incidence of thyroid nodules ($P = 0.024$; OR = 0.631; CI, 0.424–0.940) [32].

A cross-sectional study evaluated the association between alcohol consumption and thyroid nodular disease, concluding that increasing levels of alcohol consumption are associated with a lower prevalence of thyroid enlargement as well as a lower prevalence of solitary thyroid nodules [33].

The association between smoking and goiter formation tends to vary depending on the region of the study. In iodine-sufficient areas, smoking tends not to have an impact on thyroid volume or nodular formation as noted in a study in the iodine-sufficient city of Istanbul [34], while, in iodine-insufficient areas such as Copenhagen and Aalborg, Denmark, smokers tend to have thyroid enlargement (OR, 2.9; 95% CI, 2.2–3.7) and palpable goiters (OR, 3.1; 95% CI, 1.6–5.8) compared to ex-smokers and those who never smoked [35]. The fraction of goiter cases attributable to smoking was 49% (95% CI, 29–65%) [35]. This has been shown in another study where smokers had a 30% incidence of goiter compared to 3% of nonsmokers [36].

In an evaluation to better understand the correlation between smoking, iodine status, and nodule formation, Vejbjerg et al. [37] evaluated goiter prevalence before and after mandatory salt iodization in Denmark in 2000. The overall difference in thyroid volume between heavy smokers and nonsmokers was significantly reduced after iodization of salt from 24% to 12%, respectively. A study in Pomerania, Germany, supported the declining risk of goiter formation with better iodine intake in smokers [38]. It is thought that thiocyanate, a competitive inhibitor of iodine uptake, may be the goitrogenic substance from tobacco smoke [39, 40]. Thiocyanate is also found in polluted environments and thought to possess concentration-dependent antithyroid properties [40–42]. The Endocrine Society has recently reported on environmental endocrine-disrupting chemicals [43].

Palpation (Table 1.2)

As the least sensitive method of detecting nodules, palpation identifies the prevalence of nodules of around 4–7% [44–48]. Palpation is a more reliable technique when nodules are greater than 1 cm [49]. Palpation carries a high false-positive rate where up to 68% of palpable nodules may not be identified on high-resolution ultrasound [47]. Palpable nodules appear to be more frequently detected in females (6%) than males (2%) [50]. In a 15-year follow-up study by Vander et al., the incidence of new nodules was 2% in females and 1% in males, with an overall annual incidence rate, by palpation, of 0.1% [50]. A Scandinavian study of a middle-aged woman found a 6.5% prevalence of palpable nodules in females [51]. The Whickham

Table 1.2 Comparison between prevalence of thyroid nodules by palpation versus ultrasound technique

Investigation	Number of subjects	Age (years)	Prevalence by palpation	Prevalence by ultrasound	Country
Wiest et al. (1998) [47]	2441	20–72	6.9%	10.2%	Estonia
Ezzat et al. (1994) [66]	100	Adult	21%	66%	United States
Bruneton et al. (1994) [67]	1000	Adult		34.7%	France
Tunbridge et al. (1977) [52]	1977	Adult	8.6%		United Kingdom

survey in 1977 [52], conducted in Whickham, England, evaluated 2779 people (82% of the available population) and reported that 8.6% of the study group had palpable nodules not visible to the eye and 6.9% had palpable and obviously visible nodules with a higher prevalence in women (5.3%) than men (0.8%).

To compare the accuracy of clinical palpation to diagnose solitary thyroid nodules to ultrasound, Tan et al. noted that the majority of palpable nodules (89%) are greater than 1 cm and around 50% of presumed solitary nodules on palpation turned out to be multinodular by ultrasound [49]. A similar study, evaluating the accuracy of palpation compared to ultrasound showed that, 6.9% of nodules were identified by palpation, while missing 3.3% when subjects were re-evaluated by high-resolution ultrasound (total of 10.2% by ultrasound) [47]. Interestingly, high-resolution ultrasound did not confirm the existence of 68% of nodules found by physical exam, while physical exam missed 79% of nodules detected on ultrasound [47] showing the poor sensitivity and specificity of palpation methods. A systematic review of studies from non-endemic goiter areas found the prevalence of thyroid nodules detected by palpation ranging from 4.7 to 51.0 per 1000 adults and 2.2 to 14.0 per 1000 children [53].

Children have a lower, 0.05–1.8%, prevalence of thyroid nodules [54, 55]. In an evaluation of 4819 school-aged children between 11 and 18 years of age, 4.6/1000 had thyroid nodules. Reevaluation of the same subjects 20 years later noted an increase to 23.2/1000 [56] suggesting an increase in prevalence with age. Though the incidence of thyroid nodules is fairly uncommon in the pediatric age group, it must be noted that the rate of cancer is higher than that seen in adults [57–59] with an overall 18.7–26.4% risk of malignancy in children [54, 60, 61].

Ultrasound (Table 1.2)

When comparing the accuracy of thyroid ultrasound to postmortem pathological review, ultrasound has a sensitivity of 89% and a specificity of 84% [62]. High-resolution ultrasound (US) machines are able to detect impalpable nodules as small as 1–3 mm in size [63]. The reported prevalence of thyroid nodules by

ultrasound is 20–70% in the general population [64–67] with an increase in prevalence with age, peaking in the seventh decade ($P < 0.001$), with a higher prevalence in women than men [68]. There is a 1.6% annual risk for multinodularity (OR, 1.02; $P < 0.001$) in contrast to a decreasing risk of malignancy with age from 22.9% aged 20–30 years to 12.6% aged >70 years (OR 0.972; $P < 0.001$) [69]. The prevalence of thyroid nodules appear to be similar in different areas around the world [70–72] with iodine status remaining as the main determining factor of prevalence differences [4–6].

Other Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), carotid duplex scanning, and 2-^{18}[F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) are used in medicine with variable frequencies. Since they are rarely used specifically to evaluate the thyroid gland, the discovery of thyroid lesions is typically considered incidental. Another chapter describing incidental thyroid nodules can be found in this text, and we refer you to that chapter for details regarding incidental thyroid nodules by another imaging modality.

Autopsy Data (Table 1.3)

Autopsy is the gold standard for identifying the true prevalence of thyroid nodules [73]. In a 1955 study from the Mayo Clinic, thyroid glands considered normal by palpation were removed from 821 cadavers; 12% of glands had one and 38% had multiple nodules, with 36% of glands possessing nodules greater than 2 cm [44]. An autopsy series of 215 cadavers without known thyroid disease had reported 33% prevalence of nodules on pathological review [74]. In Greece, the thyroid glands from 160 cadavers without known thyroid disease were examined; 27% had thyroid nodules of which carcinoma was detected in 7.7% of the nodules and occult papillary carcinoma in 5.6% of the nodules [75]. In 200 cadavers with nodular thyroids prior to thyroid removal, 31% of those with solitary nodules on clinical exam had multiple nodules at pathological review [76]. In a sequence of 1020 autopsies, 22% had goiters and 6.2% of the thyroid glands possessed detectable carcinoma ranging

Table 1.3 Prevalence of thyroid nodule/goiter reported in autopsy reports

Investigation	Number of subjects	Prevalence (%)	Country
Mortensen et al. (1955) [44]	821	38	United States
Furmanchuk et al. (1993) [74]	215	33	United States
Lang et al. (1988) [77]	1020	22	United States
Mitselou et al. (2002) [75]	160	27	Greece

between 0.5 and 10.5 mm in size [77]. Autopsy reports from non-endemic goiter areas collected in a series showed the prevalence of thyroid nodules of 82–650 per 1000 autopsies [73]. These studies on cadavers indicate that thyroid nodules are common in the general population and that, while thyroid cancer is also common, in most cases it remains biologically dormant.

Summary

Thyroid nodules are common in clinical practice. Prior to the use of high-resolution ultrasound, thyroid nodules were identified by palpation in 4–7% of the population. While the incidence via palpation has not changed significantly over the decades, the use of sensitive ultrasound machines has increased the nodular disease prevalence to 50–70% in the general population.

The prevalence of nodular disease and goiters also differs depending on the population screened. For instance, there is a higher incidence of thyroid nodules in areas of low iodine intake, especially in smokers compared to those living in iodine-sufficient societies. Those who consume alcohol tend to have a lower incidence of thyroid nodularity. Thus, environment and medical history should be taken into account when evaluating a patient with an incidental thyroid nodule to avoid over aggressiveness in nodular management when only iodine supplementation may be required initially.

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Chapter 2
History and Examination for Thyroid Nodules

Alan A. Parsa and Hossein Gharib

Introduction

The name thyroid gland, in English, is derived from the Latin *glandula thyreoidea*, meaning shield-shaped gland, named by Thomas Warton in 1656 [1]. As the first endocrine gland to develop embryologically [2], it possesses important functions from fetal development until death.

Embryologically, the development of the thyroid gland begins in the fourth week of development as a depression and epithelial thickening of the floor of the primitive pharynx. Beginning at the base of the foramen caecum, the thyroid primordium descends into the underlying mesenchyme and travels through the neck as a bilobed diverticulum. The gland arrives at its final resting place in front of the trachea in the seventh week [2, 3]. During the descending process, the thyroid gland remains connected to the tongue surface by a thyroglossal duct from which it will eventually detach. The thyroglossal duct typically regresses and disappears; however, in around 50% of the population, the distal portion of the thyroglossal duct persists as a pyramidal lobe of the thyroid (Fig. 2.1) [5]. A thyroglossal duct cyst, the most common congenital neck mass, seen in around 7% of the population, is a remnant dilation of the thyroglossal duct between the foramen caecum and the thyroid gland which did not fully regress [4, 6].

Postpartum: The thyroid gland's final anatomical location is anterior to the trachea and caudal to the thyroid cartilage. The adult thyroid gland consists of a right

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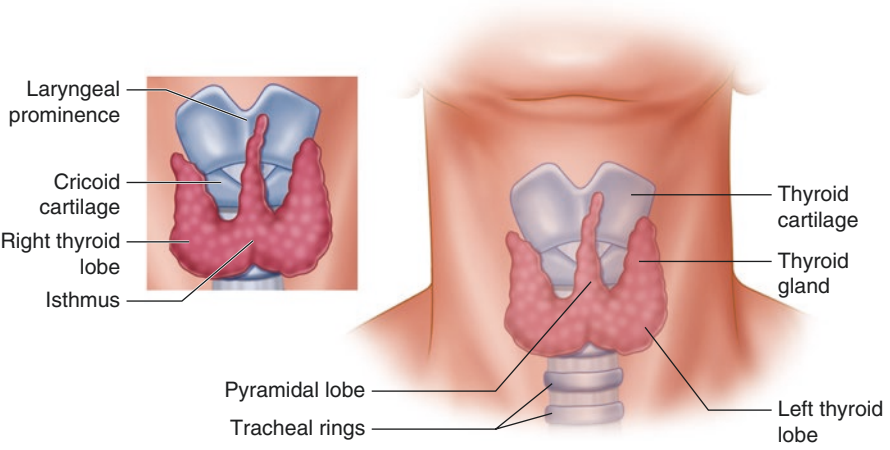

Fig. 2.1 The thyroid gland is inferior to the thyroid cartilage anterior to the tracheal rings. A pyramidal lobe is seen in approximately 50% of the population [5]

and left lobe, bridged together by a thin and often impalpable strip of thyroid tissue called the isthmus.

Thyroid nodules are common in the general population and have a reported prevalence of 70% by imaging studies [7, 8] and 7% by palpation [9–12]. Thyroid nodules are typically nonfunctional, frequently discovered incidentally, with environmental and genetic conditions predisposing them to malignancy. To properly identify malignancy risks, work-up should include a thorough history, a physical exam, and thyroid imaging.

History: Since most thyroid nodules are detected incidentally by exam or imaging and most nodules are benign, directed questions can assist in determining malignancy risk and aggressiveness of follow-up and therapy. For instance, an adult patient with palpitations, heat intolerance, tremor, anxiety, diarrhea, and a thyroid mass is suspect of a toxic nodular thyroid, a benign process. The same findings in a 13-year-old should raise concern of malignancy due to a 26% malignancy risk in those under the age of 17 regardless of the functionality of the nodule [13, 14]. Other risk factors for malignancy in a patient's history include a personal history of head and neck irradiation, family history of thyroid cancer, age of puberty, and history of thyroid disease [15, 16].

A review of systems may also give important information of the aggressiveness of a tumor and the need for immediate surgical, radiotherapy, or chemotherapeutic intervention. For instance, symptoms of dysphagia, odynophagia, hoarseness, or aspiration of liquids are suggestive of recurrent laryngeal nerve involvement [17], while cough, dyspnea, hemoptysis, and stridor are suggestive of tracheal invasion [18]. Though very aggressive thyroid malignancy is rare, it is important to identify these patients as their prognosis is typically poor [19, 20].

A family history identifies genetic conditions linked to thyroid malignancy. These include conditions such as familial nonmedullary thyroid cancer (FNMTC)

Table 2.1 Familial conditions which are associated with thyroid malignancy and the associated risk of malignancy

Condition	Risk of thyroid malignancy	Predominant thyroid cancer type
MEN2 [23]	90%	Medullary
Cowden syndrome [24]	38%	Follicular
FNMTC [21, 22]	3–15%	FCD
FAP [26, 27]	0.4–12%	Papillary
Gardner syndrome [25]	2% (predominantly women)	Papillary

MEN2 multiple endocrine neoplasia type 2, *FNMTC* familial nonmedullary thyroid carcinoma, *FCD* follicular cell derived, *FAP* familial adenomatous polyposis. Risk of developing thyroid cancer and type based on familial syndromes

[21, 22], multiple endocrine neoplasia 2 (MEN2) [23], Cowden syndrome (PTEN hamartoma tumor syndrome) [24], Gardner syndrome [25], and familial adenomatous polyposis (FAP) [26, 27]. The detail of questioning should be determined by the patient's risk factors. For instance, if the patient does not possess a family history of thyroid malignancy, questions related to MEN2 or FNMTC may be excessive. On the other hand, a patient with a family history of colon polyps should be questioned about Gardner syndrome or FAP, due to the increased risk of thyroid malignancy as noted in Table 2.1.

Physical Examination

To our knowledge, studies comparing the efficacy of different palpation techniques to identify thyroid structural disease have not been done. Palpation techniques typically develop through reading or from previous training. Regardless of which method is used, there are three key features of the physical exam: knowledge of neck anatomy, the examiner's training, and the experience and comfort with his/her approach to the exam.

Anatomy: The normal adult thyroid gland is located inferior to the thyroid cartilage and anterior to the second and fourth tracheal rings. The gland is posterior the sternohyoid and sternothyroid muscles (also known as the strap muscles) and medial to the internal jugular vein and carotid artery bound by the pretracheal fascia (Fig. 2.2). Included within the pretracheal fascia is the thyroid gland, trachea, and esophagus. The gland is highly vascularized permitting direct hormone secretion into circulation. The recurrent laryngeal nerve and external branch of the superior laryngeal nerves innervate the vocal cords and are a source of morbidity during surgical thyroidectomy [28]. The four parathyroid glands, typically found posterior to the thyroid gland, are also a source of morbidity during thyroidectomies [29].

The thyroid has two lobes connected in the midline by an isthmus. The average anterior to posterior thickness of each lobe is <20 mm with a superior to inferior length of about 40–60 mm. The average weight of the thyroid gland is between 15 and 30 g in adult males and slightly heavier in females due to enlargement associated

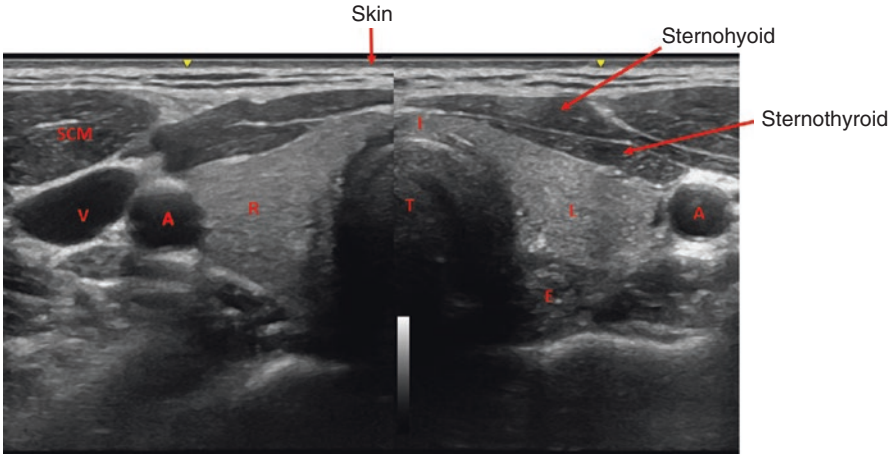

Fig. 2.2 Ultrasound image of the thyroid gland. *T* trachea, *R* right thyroid lobe, *L* left thyroid lobe, *I* thyroid isthmus, *A* carotid artery, *SCM* sternocleidomastoid muscle, *E* esophagus, *V* jugular vein

with menstruation and pregnancy. Thyromegaly is defined when the anterior/posterior or traverse lengths exceed 20 mm or when the parenchyma extends anterior to the carotid arteries.

Inspection: Inspection is typically more useful with large glands. The subject is told to tilt the head slightly upward which will better expose the neck and possible substernal glands. Thyroid size, shape, texture, mobility, and presence of visible nodularity should be observed and documented. A scar superior to the sternal notch, known as a necklace scar, indicates prior thyroid or parathyroid surgery. The gland should be viewed from the front and side of the patient. Shadows cast by light manipulation can exaggerate thyroid borders and texture. Sips of water by the subject cause a cephalad movement of the gland confirming its structure.

Palpation: Two different palpation techniques include thyroid examination facing the patient or from behind the patient. The subject should be warned prior to the procedure that a choking sensation may be felt, while the thyroid gland is palpated. If unable to tolerate, ultrasonography is an alternative to the physical exam.

With the palmar aspect of the fingers, the thyroid isthmus should first be located even though it is frequently impalpable unless enlarged. This is done by initially identifying the laryngeal prominence (the so-called Adam's apple) of the thyroid cartilage. Fingers should slide inferiorly to find the cricoid cartilage, marking the typical location of the superior border of the thyroid isthmus. A sip of water will cause the isthmus to move cephalically under the fingers confirming the structure. If not felt, the thyroid may be further inferior or the isthmus may not be palpable. Once identified, fingers should slide laterally along the isthmus toward the sternocleidomastoid muscle (SCM) along the contour of the trachea wedging the dorsum of the fingers posterior to the SCM. The thyroid gland should now be trapped between the palmer aspect of the fingers and the trachea. A sip of water will cause the thyroid gland to move upward passing under the fingers confirming that the

structure being felt is the thyroid gland. If the structure being felt does not move, it may represent a lymph node, a fixed thyroid malignancy, a prominent neck muscle, or some other neck structure. Asymmetry, size, and any discrete masses should be noted and documented for both lobes. Some thyroid glands are not palpable due to atrophy from levothyroxine therapy, surgical resection, substernal location, or a naturally small gland.

Once the thyroid gland has been examined and findings recorded, the neck should be palpated for lymphadenopathy along the cervical chain with a midline examination for a possible persistent thyroglossal duct, seen in approximately 7% of the general population [4].

Conclusion

A complete thyroid examination includes a careful history, thyroid palpation, appropriate imaging, and lab tests. Thyroid imaging with an ultrasound machine, described elsewhere in this book, is very useful, complements thyroid palpation, and provides information of malignancy risks. Understanding of thyroid anatomy and adjacent neck structures is also critical for a good exam. While different techniques for thyroid palpation are described, no studies have been done to compare accuracy or efficacy of these. We recommend adopting a technique with which the examiner is comfortable and has experience.

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Chapter 3
Laboratory Evaluation for Thyroid Nodules

Alan A. Parsa and Hossein Gharib

Introduction

The basic understanding of thyroid physiology can help in the direct use of laboratory testing to evaluate a nodular thyroid. While patients with thyroid nodules are usually euthyroid, it is essential to determine thyroid status early because it will alter further work-up and therapy.

The cascade of events leading to the secretion of the thyroid hormones, thyroxine (T4), and triiodothyronine (T3) begins in the hypothalamus with the secretion of thyroid-releasing hormone (TRH) produced in the paraventricular nucleus (PVN) of the hypothalamus [1–3]. TRH is carried to the anterior pituitary gland via the hypothalamo-pituitary portal system.

TRH stimulates thyrotroph cells of the anterior pituitary gland, encompassing ~5% of anterior pituitary cellular structure, and secretes thyroid-stimulating hormone (TSH) [4]. TSH is secreted in a non-gender-specific circadian fashion peaking overnight with low (nadir) levels during the day [5, 6]. In circulation, TSH targets and stimulates TSH receptors (TSH-R) on the surface of thyroid epithelial cells while also having effects on other organs (i.e., brain, heart, kidney, adipose tissue, bone) [7, 8]. Once bound, production of the iodine-dependent T4 and T3 begins as detailed in the cited text [9] (Fig. 3.1).

The thyroid gland possesses two different cell lines. Follicular cells produce T4 and T3, while parafollicular cells (C cells) produce calcitonin. T4 and T3 are critical for many bodily functions including the cardiovascular system, linear growth, thermoregulation, nutrient and hepatic metabolism, and fluid balance [10]. While

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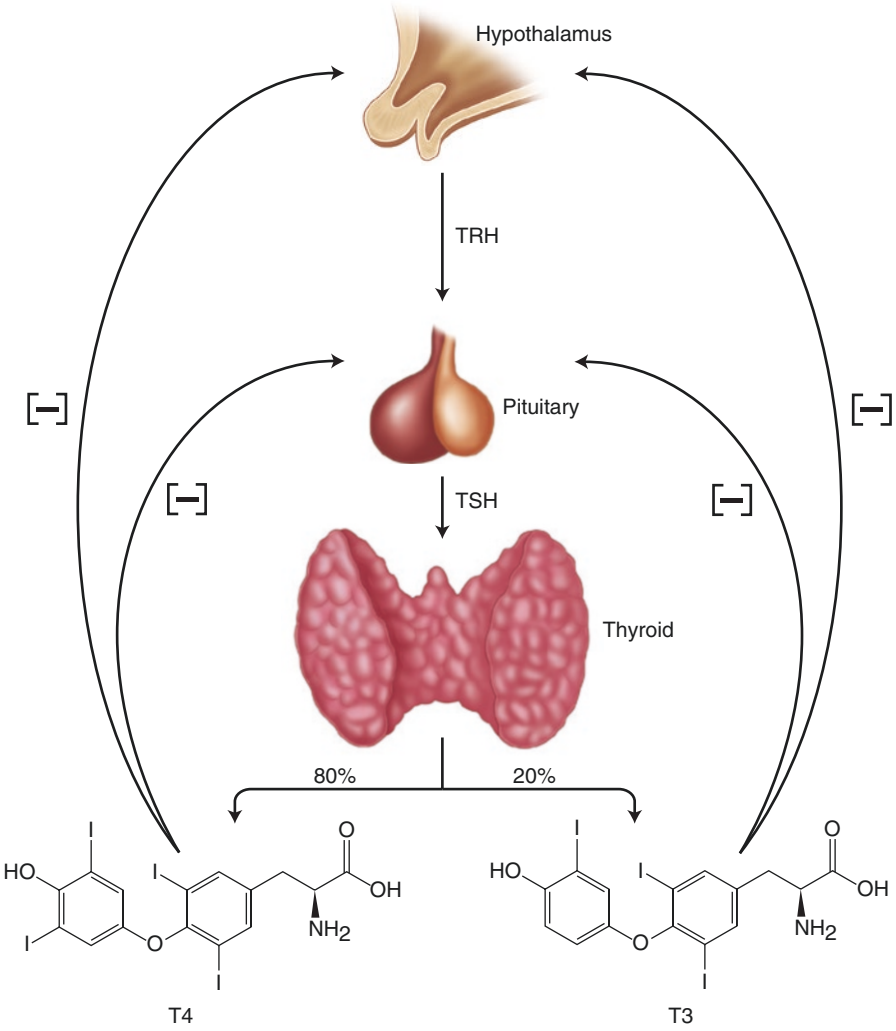

Fig. 3.1 Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus which stimulates thyrotropin-secreting hormone (TSH); TSH secretion by the pituitary gland stimulates thyroid hormone production. The thyroid gland produces thyroxine (T4) and triiodothyronine (T3) in the approximate proportion of 80% and 20% respectively. All circulating T4 is produced in the thyroid gland while most T3 is produced peripherally. T4 and T3 inhibit further secretion of TRH and TSH, by a negative feedback system, preventing excessive production and secretion of these hormones thus maintaining homeostatic balance

T4 is exclusively produced in the thyroid gland, the majority of T3 (~80%), the biologically active form of thyroid hormone, is produced by extrathyroidal tissue by monodeiodination of T4 [11–13]. Serum concentrations of T4 and T3 modulate the secretion of TRH and TSH in a negative feedback fashion leading to a homeostatic balance of circulator hormones (Fig. 3.1).

Calcitonin assists in lowering elevated circulating serum calcium levels by directly inhibiting osteoclastic bone resorption [14] and inhibits intestinal calcium absorption and renal tubular calcium reabsorption [15].

Laboratory Monitoring

TSH

Thyroid hormones, the major determinant of the basal metabolic rate, are tightly regulated [16]. To maintain balance, TSH, which stimulates production of T4 and T3, is steadily secreted with minimal fluctuations in a normal individual [17, 18]. This stable state is known as the "set point" [19, 20] and thought to be genetically linked [21, 22]. While stable within an individual, a wide variability is seen among different individuals with each having his/her own set point [17] explaining the wide TSH reference range seen in laboratories (Table 3.1). A healthy individual will therefore maintain a "personalized" TSH target concentration for optimal metabolic activity [23].

When evaluating patients with thyroid nodules, serum TSH, a sensitive and accurate test of thyroid function, should be the initial test [24]. Assays used to measure TSH have improved significantly over the decades. The original radioimmunoassay (RIA) method [25–27] was unable to measure lower limits of TSH required to identify hyperthyroidism and was abandoned for the newer "ultrasensitive" immunometric assay (IMA), able to detect TSH levels to 0.01–0.02 mIU/L [28]. The IMA method, able to detect the hyperthyroid state, is currently employed in most labs today.

There are different non-thyroid-related medical conditions and drugs which can influence TSH levels. Some of these drugs include glucocorticoids, somatostatin, and dopamine agonist which can suppress TSH secretion, with or without causing changes in thyroxine levels [29, 30]. Table 3.2 gives a list of some medications that affect TSH measurements [29–32]. Medical conditions such as pregnancy can also affect TSH levels in the first trimester due to human chorionic gonadotropin (hCG) stimulation of the TSH receptor, which eventually normalizes later in pregnancy [33–35]. Therefore, knowledge of current medications and medical conditions affecting TSH should be taken into account when evaluating TSH levels.

Table 3.1 Reference rages for thyroid function tests

	Age	Reference limits
TSH	Adult	0.4–4.0 mIU/dL
Total T4	>Or = 20 years	58–160 nmol/L (4.5–11.7 mcg/dL)
Total T3	>Or = 20 years	0.9–2.8 nmol/L (80–200 ng/dL)
Free T4	>Or = 20	10–23 pmol/L (0.9–1.7 ng/dL)
Free T3	>1 year	3.5–6.5 pmol/L (2.8–4.4 pg/mL)

Age-specific limits can be also found in specific labs

Table 3.2 Medications which can suppress thyroid-stimulating hormone (TSH) [30–33, 67, 68]

Drugs	Effect on thyroid-stimulating hormone (TSH)
Glucocorticoid	Suppress TSH stimulation with or without causing clinical central hypothyroidism
Dopamine/bromocriptine	
Somatostatin	
Rexinoid	
Amphetamine	
Metformin	Decreases TSH in those with TSH > 2.5mIU/L
Metyrapone	Leads to increased TSH without effect on T3 or T4 levels
Amiodarone	Increased TSH by up to 2.7× the normal level with and elevation in T4 and slight fall in T3

TSH normal limits are also an area of debate. While many laboratories give a reference range between 0.5 and 5.0 mUI/L, population studies suggest that TSH levels can be affected by ethnicity, iodine intake, gender, and body mass index [36]. The National Health and Nutrition Examination Survey (NHANES) III, a United States (US) population-based study, showed that the serum TSH upper limit of normal was lower in African Americans (3.6 mIU/L) than in Mexican Americans (4.2 mIU/L) [36] and that the upper limit of normal for those 20–29 years old was lower (3.5 mIU/L) than in those over 80 (7.5 mIU/L) [37]. Based on the NHANES III study, it was also suggested that 95% of the US population, without self-history or family history of thyroid disease, had a normal serum TSH concentration between 0.45 and 4.12 mIU/L [36]. The National Academy of Clinical Biochemistry (NACB), on the other hand, states that the upper limit of normal TSH is around 2.5 mIU/L and that values between 2.5 and 4 mIU/L are likely individuals with incipient autoimmune thyroid disease who should undergo ultrasonography to further characterize the thyroid gland [24, 38]. Some recommend using a lower upper limit of serum TSH, as it will better identify incipient hypothyroidism [39], while others feel the current upper limit, while potentially missing incipient disease, does not correspond to adverse health consequences if left untreated, thus not justifying adjusting current limits [40]. While an age-based TSH reference is ideal, in its absence, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommended the use of a normal TSH reference range between 0.4 and 4.0 mIU/L [41, 42] as noted in Table 3.1.

In terms of nodular disease, a patient with a TSH within the normal reference limits does not require further laboratory work-up but will need an ultrasound, possibly followed by FNA to further characterize the nodule. When initial TSH is either elevated or suppressed, further work-up to distinguish between overt disease (free T4 (FT4) above or below normal limits) and subclinical disease (FT4 within normal limits) is necessary. This is accomplished by measuring serum FT4 and, in some instances, serum T3 concentrations.

T4 and T3

In circulation, T4 and T3 are predominantly bound to thyroxine-binding globulin (60–75%) (TBG), transthyretin (15–30%), and albumin (~10%) [43]. These proteins assist in distributing the hormones evenly throughout the body [44, 45], buffer tissues from possible sudden influx or cessation of hormone secretion from the thyroid gland [46, 47], and are capable of increasing or decreasing affinity to thyroid hormone at specific sites depending on tissue demand [48]. While T4 is found in serum concentrations around tenfold higher than T3 [10], the vast majority of T4 is protein bound with 0.02% circulating in the unbound, free form compared to 0.2% of free T3 [47]. Theoretically, it is much easier to measure circulating total T4 (TT4) (free + bound T4) and total T3 (TT3) (free + bound T3) due to higher nanomolar concentrations compared to the significantly lower picomolar concentrations of FT4 and FT3 (Table 3.1) [49–51]. TT4 and TT3, measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, are fairly accurate, precise, and specific [52], but not always reliable as stand-alone tests due to factors disrupting binding protein concentrations [53]; thus, reports may be falsely above or below reference ranges, inaccurately suggesting thyroid disease. A list of different medications and pathophysiologic conditions leading to high or low TBG levels can be found in Table 3.3. For this reason, if measuring TT4, testing should include TBG levels or an estimate of binding proteins to calculate a free hormone index to account for possible binding protein effects [54–56]. For this reason, total T4 is less frequently used nowadays.

Table 3.3 Conditions which may alter thyroid hormone-binding proteins leading to unreliable total thyroxine (T4) and total triiodothyronine (T3) measurements [30, 54, 61]

	TBG increase	TBG decrease
Drugs	Estrogen	Androgen
	Tamoxifen	Anabolic steroids
	Mitotane	Glucocorticoids
	Heroin	Nicotinic acid
	Nicotinic acid	Lithium
		Phenytoin
		Propranolol
Pathophysiologic conditions	Pregnancy	Hyperthyroidism
	Hypothyroidism	Critical illness
	Acute/chronic liver disease	Sepsis
	Adrenal insufficiency	Nephrotic syndrome
	AIDS	Diabetic ketoacidosis
		Chronic alcoholism
		Acromegaly
		Cushing's syndrome
Familial/congenital conditions	TBG excess	Familial TBG deficiency

Table 3.4 Current methods used in different laboratories to measure free thyroxine (FT4) and free triiodothyronine (FT3)

• Estimation FT4/FT3 testing
Two-test index method:
– TBG immunoassay
– Thyroid hormone-binding ratio/"uptake" test
– Isotropic index method
Free hormone immunoassay method:
– Two-step, labeled hormone/back titration FT4 and FT3 method
– One-step, labeled hormone-analog FT4 and FT3 method
– Labeled antibody FT4 and FT3 method
• Direct FT4/FT3 testing
– Equilibrium dialysis
– Ultrafiltration
– Gel absorption

Since the free or unbound hormone is responsible for the cellular biological activity [57], free hormone levels should reflect biological effects better than total hormone levels. Unfortunately, due to very low serum concentrations, accurate testing of FT4 and FT3 has proved technically difficult with modern day testing methods. Currently, two methods are available to measure free hormone levels (Table 3.4): the *direct method* (i.e., equilibrium dialysis, ultrafiltration), which physically separates free hormone from protein-bound hormone [58, 59], and *estimate testing* (i.e., two-test index method, free thyroid hormone immunoassay method), which physically separates free hormone from protein-bound hormone before measuring free hormone levels by sensitive immunoassay, or, antibody is used to immunoextract a proportion of free hormone out of the specimen before quantitation [60–62]. While these tests are widely used, neither method is free of problems. The *direct method* can be influenced by endogenous binding protein inhibitors, dilution, and temperature [63, 64] leading to falsely elevated or suppressed results, while *estimate testing* is protein dependent and prone to over- or underestimation if a significant abnormality exists in binding proteins [61, 60, 65]. Drugs, such as those noted in Table 3.5, can also affect FT4 measurements [66–68]. Thus, a single test method has not been universally validated for all clinical situations. Currently, laboratories use automated immunoassays to estimate FT4 and FT3 levels. Direct free hormone testing methods need special request and should be ordered when FT4 immunoassay reports seem discordant with TSH.

In the ambulatory setting, when evaluating someone with a thyroid nodule, FT4 is more often ordered than TT4 due to the risk of binding protein effects in TT4 measurements (Table 3.3). Thus, a low TSH, suggestive of hyperthyroidism, should be followed by FT4 measurement which, if elevated, suggests thyrotoxicosis. When associated with thyroid nodular disease, diagnosis may include either an autonomous functioning nodule, a toxic multinodular goiter, or a hyperfunctioning gland with non-functional nodules. A radioisotope scan and uptake will help distinguish one from the other [69].

Table 3.5 Drugs which can alter measurements of FT4 in euthyroid patients [67–69]

	Drugs
Increase FT4	Amiodarone
	Salicylate (>2 g/day)
	NSAID
	Biotin
Decrease FT4	Phenytoin
	Carbamazepine

FT4 free thyroxine, *NSAID* nonsteroidal anti-inflammatory drugs

Thyroperoxidase Antibody (TPO)

While an elevated TSH suggests hypothyroidism, FT4 will differentiate between overt (high TSH/low FT4) and subclinical hypothyroidism (high TSH/normal FT4). Thyroperoxidase antibody (TPOAb) is an autoantibody targeting the immunodominant region of the globular glycoprotein, thyroperoxidase, expressed on the apical surface of thyrocytes. TPOAb is helpful in identifying autoimmune-mediated disease and is rarely associated with thyroid malignancy [70]. Thus, TPOAb should be tested in subjects suspected of autoimmune thyroid disease (Hashimoto), especially in the setting of a nodular goiter, and not to assist in determining malignancy risks [71]. Higher values indicate more active and more extensive disease.

An association between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC) has been the subject of long-standing debate [72–79]. More notably, aggressive disease (i.e., regional lymph node metastasis) has been suggested in patients with concurrent HT and PTC [80, 81], but not uniformly reported [82, 83]. One theory behind the connection of HT and PTC is the high expression of oncogenes (i.e., RET/PTC) found in patients with HT [82, 84] and in those with PTC [85]. Recent studies show this to be an unlikely association [86, 87], and we therefore recommend against routine screening of all subjects with nodular disease for HT, unless evidence suggests a concurrent autoimmune thyroid disease.

Some reports show that higher TSH levels are associated with an increased risk of malignancy in thyroid nodules in the absence of autoimmune disease [88–90]. It should be noted, however, that serum TSH tends to increase with age [36, 37, 91] and that approximately 3–16% of individuals over the age of 60 have elevated TSH with normal FT4 (subclinical hypothyroidism) [92]. A US population study showed that those over the age of 80, without thyroid disease, can have a normal upper TSH limit of 7.5 mIU/L [37]. Thus, in the elderly, additional information (i.e., ultrasound features) should be considered when determining malignancy risks and the need for biopsy. It should be emphasized that elevated TSH increases the risk of nodular malignancy in the pediatric population [93], and since this group possesses a higher risk of malignancy [94], an elevated TSH should be followed with biopsy in the setting of a nodular thyroid gland.

Thyroglobulin (Tg)

Serum thyroglobulin (Tg) , a dimeric protein produced by thyroid follicular cells, is measured by automated IMA in many centers (though the older isotopic RIA is still in use) and correlates with iodine intake and thyroid volume rather than the nature or function of a nodule [95]. While a useful marker in patients with differentiated thyroid cancer post-thyroidectomy, it offers no diagnostic value when evaluating malignancy risks of a nodular thyroid and, thus, should not be measured during the routine evaluation of a thyroid nodule.

Calcitonin (Ct)

Serum calcitonin (Ct) , a 32-amino acid linear polypeptide hormone produced by thyroid parafollicular (aka C cells) in response to elevated calcium levels, is a useful marker for medullary thyroid carcinoma (MTC) and correlates with tumor burden [96]. MTC is found in 3–10% of all thyroid malignancies [97, 98]. Studies attempting to show value in routine screening for MTC with Ct have not been convincing. For example, a study screening for MTC by Ct in over 10,800 subjects with nodular thyroid disease identified an MTC prevalence of 0.4% [99]. Another screening study of 5817 subjects found a similar MTC prevalence of 0.3% [100]. Stimulation by pentagastrin, a synthetic polypeptide, was used in these studies to increase specificity but is unavailable in most countries nowadays. Caveats of these studies is that though while they detected MTC at earlier stages of disease, they also detected C-cell hyperplasia (CCH), a preneoplastic lesion in familial forms of MTC, but not shown to undergo malignant transformation in sporadic forms of MTC [100, 101]. The prevalence of CCH in one study of 57 subjects without thyroid malignancy was found to be as high as 50% [102]. Thus, CCH detection increases risks of false positives leading to unnecessary thyroidectomies. Ct has also been shown to be elevated in a variety of nonthyroidal diseases (i.e., pulmonary endocrine tumors, renal failure, hypergastrinemia, alcohol use, and smoking [103, 104]), which should be considered if Ct is used to screen for MTC.

While one report suggests that routine Ct screening may be cost-effective [105], neither the American Association of Clinical Endocrinologists (AACE)/Associazione Medici Endocrinologi (AME) [106] nor the American Thyroid Association [71] recommends routine Ct screening in patients with a nodular thyroid. The European Panel of Experts (EPE) [107], on the other hand, recommends Ct measurements in all patients with thyroid nodules but fails to indicate the role of pentagastrin stimulation testing and how to interpret results. We prefer selective Ct testing in those at risk for MTC, such as patients with a positive family history of MTC, MEN2, and pheochromocytoma, or when FNA suggests MTC.

Conclusions

In summary, TRH, secreted by the hypothalamus, stimulates TSH secretion from the anterior pituitary gland. Serum TSH concentrations are stable in those without thyroid disease. TSH in turn activates follicular cells of the thyroid gland to produce and secrete thyroid hormones, predominantly T4 and small amounts of T3. T4, tightly bound to carrier proteins, acts as a buffer allowing even distribution of hormone throughout the body. A number of conditions can affect laboratory measurements of TT4 and/or TT3 (Table 3.3). FT4 and FT3 are the active functional hormones available for biological activity. However, measurements of free fractions continue to be difficult due to their very low serum concentrations.

In a patient with a thyroid nodule, TSH is the initial test of choice, due to its stability, sensitivity, and availability. While TSH reference limits should likely be both age and ethnicity based, currently accepted limits by the ATA and AACE are 0.4–4.0 mIU/L [42, 41]. If serum TSH is low, FT4 will assist in distinguishing between overt or subclinical hyperthyroidism. Additional testing such as thyroid ultrasound and radioiodine scanning should be performed evaluating for an autonomous nodule or a toxic multinodular goiter. An elevated TSH suggests hypothyroidism and should be followed by FT4 along with TPOAb if autoimmune disease is suspected. It should be remembered that serum TSH can normally increase with age, while an elevated TSH in the young with a thyroid nodule should increase suspicion of malignancy.

Routine serum calcitonin testing may detect unsuspected MTC. Although pentagastrin- stimulated Ct values are more reliable with very few false positives, this agent is unavailable in the USA and in most other countries. Recent guidelines do not recommend Ct screening for those presenting with thyroid nodules, a practice we support.

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Chapter 4
Nuclear Medicine in Evaluation and Therapy of Nodular Thyroid

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Truth is a constant variable—William J. Mayo

Nuclear Imaging and Uptake Measurements in Thyroid Nodular Disease

A Look Back

Iodine-131 (^{131}I, radioiodine) was first produced in late 1930s at the University of California, Berkeley, CA, and at Massachusetts Institute of Technology, Cambridge, MA. Both groups used radioiodine for uptake measurements and treatment of patients with hyperthyroidism and thyroid cancer [1, 2]. At that time, ^{131}I was only available in small quantities. It was so expensive that it had to be recovered from the patient's urine and reused. After the World War II, reactor produced ^{131}I, became available in larger quantities. Thyroid radioiodine uptake and therapy became a routine practice. Introduction of the rectilinear scanners in the 1950s and gamma cameras in the 1960s allowed for imaging of the thyroid in addition to uptake measurements. In the mid-1960s, ^{99m}Tc pertechnetate and ^{123}I became available for thyroid uptake measurements and imaging, as an alternative to ^{131}I.

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For many years, thyroid scintigraphy was routinely used for evaluation of thyroid nodules. The concept was simple: almost all malignant nodules were "cold," while "hot" nodules were almost without exception benign. The problem, however, was that the majority of benign nodules were "cold," as well, and benign nodules were far more common than malignant nodules. Thus, the finding of a "cold" nodule had low positive predictive value for malignancy. Since high-resolution ultrasonography (US) became available, the role of nuclear imaging has dramatically diminished. US became the first test to evaluate thyroid nodules, except for the patients with subnormal TSH.

Current Use of Thyroid Scintigraphy in Evaluation of Thyroid Nodules

In the USA, thyroid scintigraphy is only indicated for initial evaluation of a thyroid nodule if a patient also has subnormal TSH. If TSH is normal or elevated, thyroid scintigraphy should not be performed as the initial imaging evaluation of a thyroid nodule. In a patient with multiple thyroid nodules, scintigraphy may also be considered when TSH is low normal [3]. A recent survey of endocrinologists in the USA (members of the American Thyroid Association, ATA) showed that fewer than 5% of responders would obtain a radionuclide thyroid scan for a clinically euthyroid patient with a 3 cm thyroid nodule [4]. These findings were in contrast with two previous surveys published about 16 years earlier, which found that 23% of ATA responders and 63% of European Thyroid Association (ETA) members would obtain a thyroid scintigraphy in a euthyroid patient with a nodule [5, 6]. The much higher percentage for the ETA members compared to the ATA members is due to lack of nutritional iodine additive in several European countries. Outside of the USA, especially in iodine-deficient regions with higher prevalence of follicular adenomas and hyperplastic nodules, thyroid scintigraphy is still used for the evaluation of nodular disease in euthyroid patients. It helps to select nodules for biopsy and avoid biopsies of iodine-avid follicular adenomas [7].

Thyroid scintigraphy and uptake measurements are used to evaluate eligibility for radioiodine therapy, sometimes regardless of TSH level, for example, when treating a nontoxic multinodular goiter for volume reduction [8]. Occasionally thyroid scintigraphy is used to distinguish nodular retrosternal goiter from other mediastinal tumor or to evaluate for ectopic thyroid tissue. This usually requires hybrid imaging with single photon emission computed tomography with integrated computed tomography (SPECT/CT) for precise localization.

Table 4.1 Radionuclides and radiopharmaceuticals used for thyroid imaging, uptake measurements and treatment, or relevant for incidental finding of nodule with high tracer uptake

Radionuclide	Half-life	Main emission	Radiopharmaceutical	Clinical use or relevance to thyroid nodules
^{123}I	13 h	Gamma	[^{123}I] NaI	Scintigraphy and iodine uptake
^{124}I	4 d	Gamma and positron	[^{124}I] NaI	PET imaging (thyroid cancer)
^{131}I	8 d	Gamma and beta	[^{131}I]NaI	Iodine uptake, therapy (beta emission), imaging thyroid cancer
^{99m}Tc	6 h	Gamma	^{99m}Tc pertechnetate, ^{99m}Tc MIBI ^{99m}Tc tetrofosmin	Scintigraphy (pertechnetate), incidental finding of nodules with high uptake (MIBI, tetrofosmin)
^{111}In	67 h	Gamma	^{111}In penetreotide	Incidental finding of nodule with high uptake
^{18}F	110 min	Positron	^{18}F FDG ^{18}F-choline	Incidental finding of nodule with high uptake
^{11}C	20 min	Positron	^{11}C-choline	Incidental finding of nodule with high uptake
^{68}Ga	68 min	Positron	^{68}Ga SSTR (e.g., DOTATATE) ^{68}Ga PSMA ligand	Incidental finding of nodule with high uptake

Radiopharmaceuticals

Radionuclides and radiopharmaceuticals used for thyroid imaging and uptake measurements and treatment or relevant to incidental findings of nodules with high tracer uptake on nuclear medicine imaging, are listed in Table 4.1.

Iodine-131 (^{131}I) for Uptake and Therapy

In nodular disease, ^{131}I is only used for uptake measurements and therapy. A small amount of ^{131}I in a form of sodium iodide (4–15 μCi/0.15–0.55 MBq) is typically given to measure uptake with a gamma probe [9]. ^{131}I is used for whole-body imaging of thyroid cancer patients after thyroidectomy, but it should not be used for imaging of thyroid nodules [9]. ^{131}I gives much higher radiation dose to the patient and to the thyroid tissue in particular, compared to ^{123}I, and the image quality is inferior. Higher radiation dose is caused by long half-life of ^{131}I (8 days) and its decay by β^--emission (606 keV) with 89% abundance and high-energy γ-emission (364 keV). However, β^--emission makes ^{131}I very useful for therapy (see Section Selection of ^{131}I activity for treatment of nodular disease for the activities recommended for therapy).

Iodine-123 for Imaging of Thyroid Nodules and Uptake Measurements

Iodine-123 (^{123}I) in the form of sodium iodide ([^{123}I] NaI) is the ideal radiopharmaceutical for thyroid imaging with gamma camera. It has favorable energy of gamma rays (159 keV) for imaging with gamma camera compared to ^{131}I (364 keV). A half-life of 13 h is suitable for thyroid imaging, as compared to 8 days for ^{131}I. Images can be done as early as 3–4 h after tracer administration. Usually the images are acquired at 24 h after administration of ^{123}I, and uptake can be measured at the same time. Imaging of acceptable quality and uptake measurements can be performed up to 36 h after administration of ^{123}I. It is given orally in administered activity of 200–400 μCi (7.4–14.8 MBq) [9].

^{99m}Tc Pertechnetate for Imaging of Thyroid Nodules and Uptake Measurements

Technetium-99 m (^{99m}Tc) pertechnetate is a negative ionic compound with similar distribution in the body as iodine. It is transported into the thyrocytes by the sodium iodide symporter. However, it cannot be organified in the thyroid tissue and quickly washes out. When ^{123}I is not available, ^{99m}Tc pertechnetate can be used for thyroid imaging. ^{99m}Tc pertechnetate is eluted directly from a desktop generator and is thus much more easily available compared to ^{123}I, and the cost is substantially lower. The procedure takes less time, but there is higher background uptake in other tissues at the time of imaging. ^{99m}Tc pertechnetate is less avidly concentrated in the thyroid, which results in lower target to background ratio. However, higher administered activity of ^{99m}Tc pertechnetate allows for comparable images, except when uptake is very low. ^{99m}Tc pertechnetate is given intravenously in administered activity of 2.0–10.0 mCi (74–370 MBq). Images are acquired 5–30 min after tracer administration.

Iodine-124 for Thyroid Imaging and Uptake

The positron-emitting radioisotope of iodine, ^{124}I (positron abundance 23%), has been used in research studies for thyroid imaging and radioiodine uptake measurements [10–12]. PET/CT scanners have much better image (spatial) resolution than conventional gamma cameras (~4 mm versus ~10 mm). PET/CT with ^{124}I allows for more precise measurements of tracer uptake compared to planar or SPECT/CT studies; thus radioiodine imaging with PET/CT is an attractive idea. Poor availability, lack of FDA approval, high cost, and lack of reimbursement of ^{124}I make it not yet practical to use. ^{124}I PET/CT has mainly been studied for staging and dosimetry before radioiodine treatment in differentiated thyroid cancer [13].

Thyroid Nuclear Imaging Procedures

Thyroid imaging is typically performed with a gamma camera with a pinhole collimator, and the imaging is often called "thyroid scintigraphy" or "thyroid scan" (Fig. 4.1). The pinhole collimator will magnify the gland when the camera is close to the organ. It allows for better image resolution compared to standard parallel-hole collimator at the expense of some geometric distortion of structures located at different depths. Typically, anterior images with markers on the thyroid cartilage and suprasternal notch, as well as bilateral anterior oblique images, are acquired. Correlation between a palpable nodule and a scintigraphic nodule can be done by placing a radioactive marker on the nodule or even "drawing a contour" on the image with a radioactive marker [14]. SPECT/CT may be used as a supplement to planar imaging (Figs. 4.2 and 4.3) for better anatomical correlation with nodules detected on ultrasound, for volume measurements, or for localization of ectopic thyroid tissue. Much better anatomical information on SPECT/CT allows for better correlation between ultrasound and scintigraphic finding.

Interpretation of Thyroid Scintigraphy

Thyroid scintigraphy is evaluated for the presence of "hot" (tracer uptake greater than the surrounding normal thyroid uptake), "warm" (uptake equal to adjacent thyroid tissue), or "cold" uptake (less than the surrounding thyroid tissue) areas that correspond to palpable nodules or to nodules seen on US.

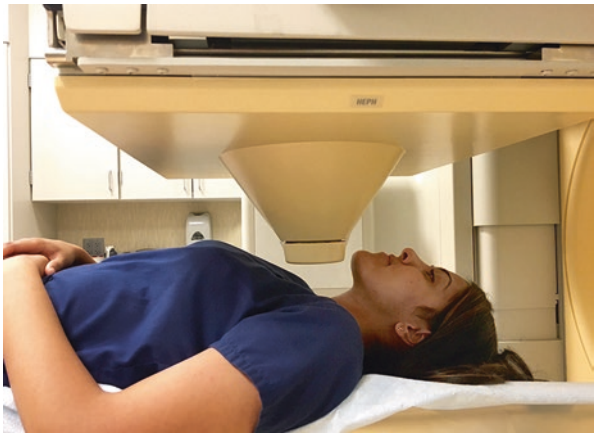

Fig. 4.1 Gamma camera with pinhole collimator for thyroid imaging

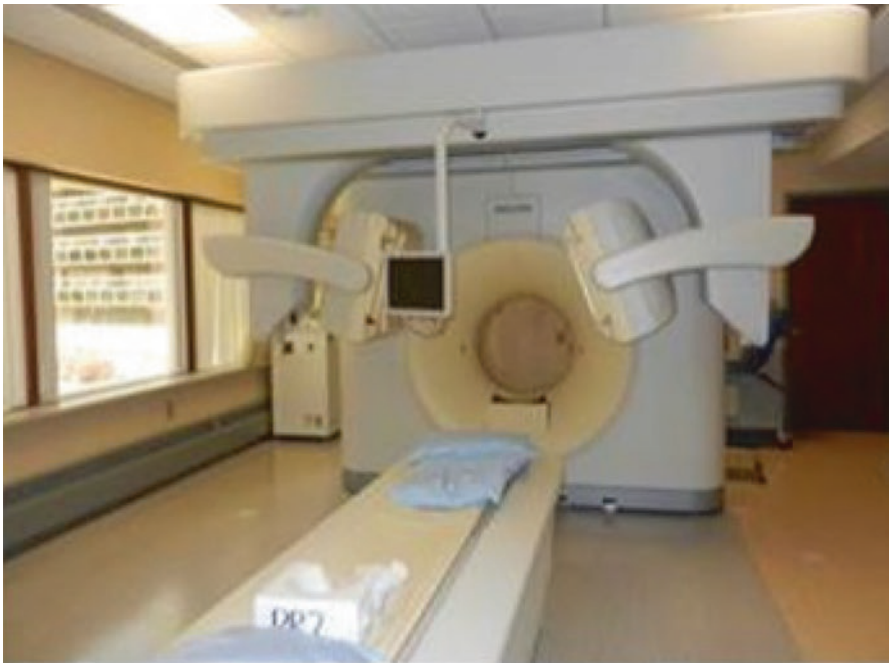

Fig. 4.2 SPECT/CT may be used for better anatomical correlation of nodules with better correlation or to localize ectopic thyroid tissue. It allows for attenuation correction and volume measurements

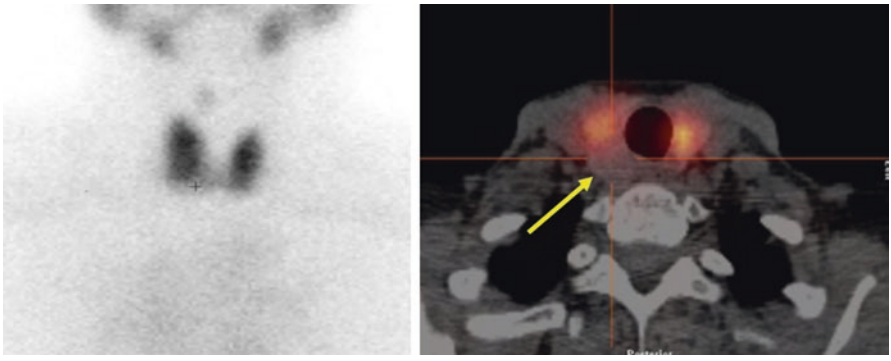

Fig. 4.3 "Cold" nodule on thyroid scintigraphy having benign cytology. Patient with a 1.2 cm thyroid nodule posterior in the right lobe found incidentally on CT. A ^{99m}Tc pertechnetate scan was performed before US-guided FNC. *Left*: Planar scan. No "node," neither "cold" nor "warm," can be seen. *Right*: SPECT/CT transaxial slice shows that the thyroid nodule is "cold" (*arrow*). US-guided FNC was performed and cytology showed benign cells. This case is an example of the usefulness of SPECT/CT supplemental to planar imaging

"Hot" Thyroid Nodules

"Hot" nodules may be solitary or a part of multinodular disease (Fig. 4.4). Occasionally a "hot" nodule may represent normal thyroid tissue surrounded by an area of decreased uptake; however, most "hot" nodules represent follicular adenoma, oncocytic (Hürthle cell) adenomas, or hyperplastic (adenomatous) nodules. They may demonstrate a central area of decreased uptake due to cystic degeneration as will be seen on US. "Hot" nodules usually function independently of TSH stimulation. They may produce sufficient amount of hormones to cause hyperthyroidism and suppress TSH and suppress uptake in normal thyroid tissue, with only the nodule visible on the scan (Fig. 4.5). Autonomous nodule was originally defined as a nodule that does not decrease uptake after administration of thyroid hormones [15]. Thyroid suppression test is not performed in current US practice, and the terms "hot" nodule and autonomous nodule are often used interchangeably. Suppression test is, however, still used in some European practices (per personal communication). Not all patients with "hot" nodules are hyperthyroid, especially in iodine-deficient areas. A European study demonstrated that 49% of 368 patients with

Fig. 4.4 Three patients with toxic multinodular goiter. *Left*: F 31 y. ^{123}I uptake 34% at 24 h. Treated with surgery because of young age. *Middle*: F 83 y. ^{123}I uptake 25% at 24 h. Treated with 45 mCi (1.7 GBq) of radioiodine. *Right*: F 66 y. ^{123}I uptake 23% at 24 h. Treated with 15 mCi (555 MBq) of radioiodine

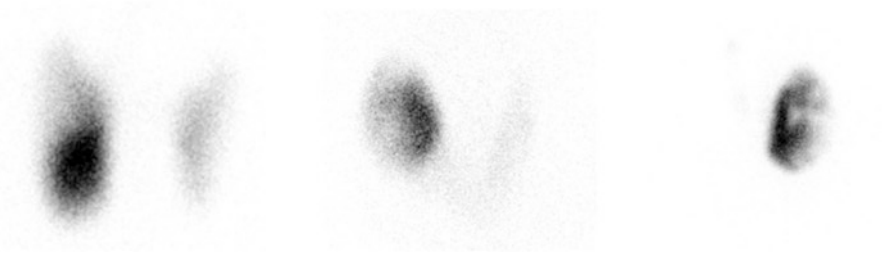

Fig. 4.5 Three examples of autonomous nodule with various degrees of suppression of normal thyroid tissue

autonomous functioning nodules had normal TSH [16]. Cytology from a hyperfunctioning nodule, typically indicating follicular neoplasia, could lead to unnecessary hemithyroidectomy, so scintigraphy is often used, outside of US, to guide FNA from a nodular goiter.

Malignancy in a "hot" nodule is rare. The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (2015 ATA Guidelines) state: "Since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytological evaluation is necessary" [17]. However, malignancy can occasionally be present in a "hot" nodule [18]. A literature search of surgical patients with solitary functioning nodules, managed by thyroid resection, revealed an estimated 3.1% prevalence of malignancy [19]. Of 77 reported cases, 57.1% had papillary carcinoma, 36.4% had follicular thyroid carcinoma (FTC), and 7.8% had Hürthle cell variant of FTC (HTC) (FTC and HTC were more frequent than usual). Compared to individuals with benign hyperfunctioning thyroid nodules, those with malignant hyperfunctioning nodules were younger and more predominantly female.

"Cold" Thyroid Nodules (Fig. 4.6)

The risk of malignancy in "cold" nodules varies between different reports but has been reported as high as 25% [20]. A study of 5637 patients with "cold" nodules demonstrated an overall 4.6% frequency of malignancy [21]. Frequency was higher in iodine-sufficient areas (5.3%) versus iodine-deficient areas (2.7%). The frequency of cancer was significantly lower in female patients with "cold" nodules (4.2%) than in males (8.2%). The proportion of nodules that were malignant was smallest in patients of the fourth decade and was greatest in patients younger than 30 years or older than 60 years. Finally, the frequency of thyroid cancer in patients with a solitary nodule was not different from the frequency in patients with multiple nodules.

In current US practice, where only patients with subnormal TSH undergo thyroid scintigraphy, "cold" nodules are seen much less frequently than in the past, usually in patients with toxic multinodular goiter or patients with Graves' disease and a coexisting nodular disease [22] (Fig. 4.6). Solitary "cold" nodules or dominant "cold" nodules in a multinodular goiter are evaluated with US and US-guided FNA to exclude malignancy prior to radioiodine therapy for hyperthyroidism.

It is important to exclude malignancy in a patient with Graves' disease and "cold" nodule, as patients with Graves' disease tend to have more aggressive thyroid cancer [23]. A European multicenter study of 140 patients with coexistent Graves' disease and thyroid nodules, treated with surgery, showed a 15% rate of malignancy [24]. Another study of 60 patients with Graves' disease and nodules showed 10% of malignancy [22].

Simultaneous existence of autonomous nodules and Graves' disease (Marine-Lenhart syndrome) occurs in 0.8–2.7% among patients with Graves' disease [22, 25, 26]. Even though these nodules are radioiodine avid, they sometimes accumulate relatively less iodine than the remainder of the gland involved with Graves'

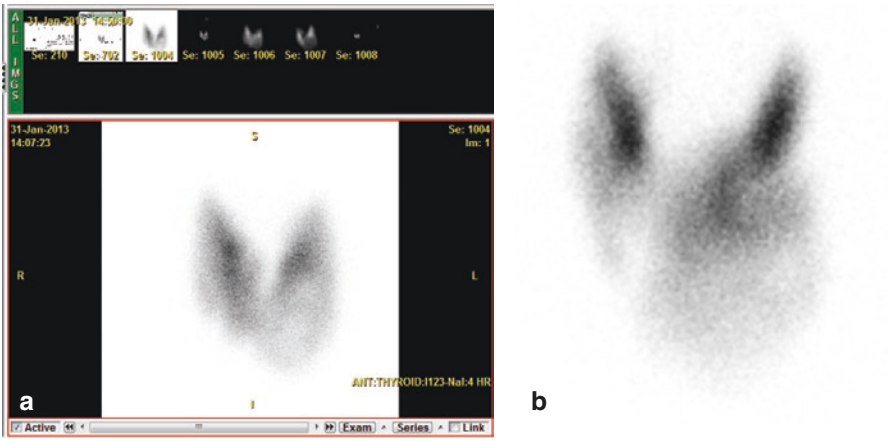

Fig. 4.6 Two hyperthyroid patients with cold nodules. (**a**) ^{123}I uptake 45%. FNA suspicious for follicular neoplasm. Pathology after resection: minimally invasive follicular carcinoma. (**b**) Patient with history of Graves' disease. Fine needle cytology showed a benign lesion. ^{123}I uptake 25%. Treated with 15 mCi (555 MBq) of radioiodine for Graves' disease

disease. They may appear either "cold" or "hot" on the thyroid scan [26]. Radioiodine treatment of these patients may require higher administered activity than used for Graves' disease [26]. There is at least one case report of malignancy in Marine-Lenhart syndrome [27].

Interpretation of Thyroid Scan with ^{99m}Tc Pertechnetate vs. ^{123}I for Imaging of Thyroid Nodules

Since ^{99m}Tc pertechnetate is not handled by the same physiologic mechanism as iodine, ^{99m}Tc pertechnetate scan findings in thyroid nodules may occasionally be discordant from radioiodine imaging findings. The nodules with ^{99m}Tc pertechnetate uptake, but no radioiodine uptake at 24 h, are believed to carry higher risk of malignancy, as the thyroid cancer cells often retain the ability to concentrate iodide without incorporating it into the thyroid hormones. However, no malignancies were found in discordant nodules in a study of over 300 patients with a solitary or dominant palpable nodule, imaged both with ^{99m}Tc pertechnetate and ^{123}I NaI [28]. Discrepancies were found in 5–8% of cases, twice as often in multinodular goiters as in single nodules. There was no correlation between the histopathology and the type of discrepancy. Nodules with higher ^{99m}Tc pertechnetate uptake than ^{123}I uptake were more common than the reverse. Twelve carcinomas were found (4%), but none in the nodules showing discrepancy. However, Reschini et al. found two malignancies in seven patients, who had nodules with ^{99m}Tc pertechnetate uptake at 30 min, but no 24 h radioiodine uptake. It was a prospective study of 140 patients with hot or warm nodules on ^{99m}Tc pertechnetate scan and normal TSH [29].

Measurement of Uptake of Radiopharmaceuticals in the Thyroid Gland

^{123}I and ^{131}I Radioiodine Uptake Measurement

Radioiodine uptake measurement is performed in nodular thyroid disease to help select the amount of ^{131}I activity needed for radioiodine therapy. In some cases, low radioiodine uptake may indicate that the radioiodine therapy would not be indicated, for example, when hyperthyroidism is a result of a thyroiditis coexisting with nodular goiter (Fig. 4.7).

Radioiodine uptake in the thyroid gland of patients with hyperthyroidism caused by nodular disease is often only mildly elevated (lower than typically observed in Graves' disease) and sometimes at the upper range of normal. Normal radioiodine uptake range in the USA is 10–30% at 24 h after administration of radiopharmaceutical. Upper limit of normal uptake is typically higher in areas of iodine deficiency and may be up to 50% [30]. At Mayo Clinic, Rochester, USA, we sometimes do a 4–6 h uptake measurement and extrapolate the 24 h uptake value using the following formula suggested by Hayes et al. [31]:

$$\text{Late}\left(20-28\text{h}\right)\ \text{uptake} = 73.2\ \log\left(\text{early uptake}\right) - 55.7.$$

However, this formula is probably not as accurate for patients with nodular thyroid disease, because Hayes et al. did their study on patients with Graves' disease. When ^{123}I is used for imaging, uptake measurement is done at the same time, typically at 24 h after administration.

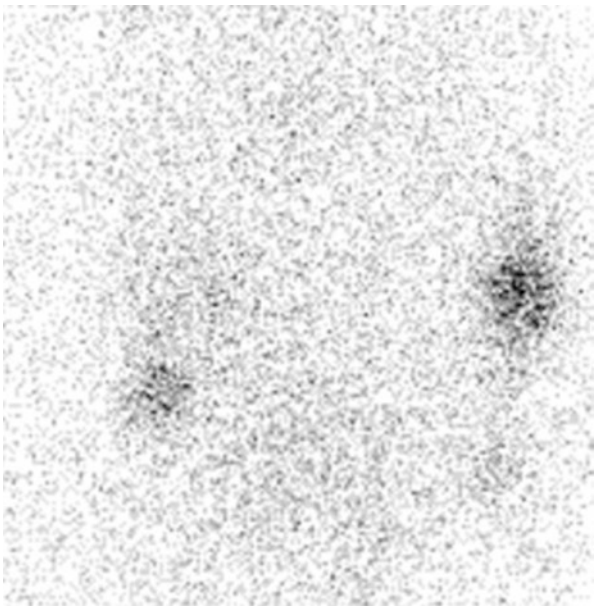

Fig. 4.7 Hyperthyroidism. Nodular gland. Neck discomfort and pain on palpation. ^{123}I uptake 0.5% at 4 h (normal in our institution 3–16%). Diagnosis: subacute thyroiditis. Hyperthyroidism resolved on follow-up. Biopsy of dominant cold nodule was benign

Procedure for Uptake Measurement

Radioiodine uptake in the thyroid gland can be measured using a thyroid uptake probe or a gamma camera. When thyroid probe is used (Fig. 4.8), counts are typically measured over the patient's neck and over the patient's mid-thigh at the same distance and for the same length of time. A source of the same radionuclide of identical activity as given to the patient is placed in a standard neck phantom and measured for the same time with the same geometry, followed by room background activity measurement for the same time. Thyroid uptake is calculated using the following formula:

$$\%\text{Uptake} = [(\text{neck counts} - \text{thigh counts})/(\text{standard counts} - \text{room background counts})] \times 100.$$

When a gamma camera is used for uptake measurement, a known small amount of the tracer is placed in a neck phantom and positioned beside the head of the patient, in the field of view of gamma camera with a parallel-hole collimator (Fig. 4.9). In this method, administered activity has to be corrected for decay during the time elapsed since administration.

Fig. 4.8 Thyroid probe for uptake measurements

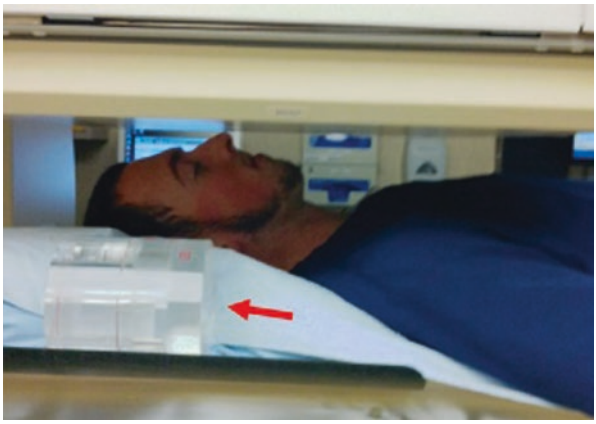

Fig. 4.9 Gamma camera with parallel-hole collimator for imaging and uptake measurements. Neck phantom with standard activity in the field of view (*arrow*)

^{99m}Tc Pertechnetate for Thyroid Uptake Measurement

When ^{99m}Tc is used for imaging, a small amount of ^{131}I in a form of sodium iodide is typically used to measure uptake with a gamma probe. ^{99m}Tc pertechnetate uptake can be used in lieu of radioiodine uptake [32]. It is sometimes used in Europe, but not in the USA. A formula to estimate 24 h radioiodine uptake using a 5-min ^{99m}Tc sodium pertechnetate uptake has been published [33]:

$$24\text{h Iodide Uptake} = \left[17.72 \times \ln\left(5\text{minute}^{99m}\text{Tc pertechnetate Uptake}\right)\right] + 30.40.$$

Normal ^{99m}Tc pertechnetate uptake is 0.5–2% [30, 34]. Individual laboratory validation is recommended, when considering using ^{99m}Tc pertechnetate in lieu of radioiodine, for thyroid uptake. However, radioiodine uptake with ^{123}I or ^{131}I is a preferred method for uptake measurement.

Patient Preparation for Thyroid Scintigraphy and Radioiodine Treatment

- Thyroid medications and iodine-containing products, including iodine-based contrast agents, will interfere with thyroid uptake and should be discontinued or avoided prior to thyroid scintigraphy and radioiodine therapy (Table 4.2).
- Lactating mothers have to refrain from breastfeeding for 3 days after ^{123}I administration [35] and for 12–24 h after ^{99m}Tc pertechnetate injection [35, 36]. Breast milk should be expressed and discarded during the interruption period. Breastfeeding cannot be resumed after administration of ^{131}I [36, 37].

Table 4.2 Thyroid medications and iodide-containing products that will interfere with thyroid uptake and need to be discontinued prior to thyroid scintigraphy and radioiodine therapy (adapted from 2012 SNMMI Procedure Standard)

Type of medication	Recommended time of withdrawal
Water-soluble intravenous radiographic contrast agents	6–8 wk[a], assuming normal renal function
Lipophilic intravenous radiographic contrast agents	1–6 mo[b]
Thyroxine	3–4 wk
Triiodothyronine	10–14 d[c]
Antithyroid drugs (methimazole)	5–7 d
Nutrition supplements containing iodide	7–10 d
Kelp, agar, carrageenan, Lugol solution	2–3 wk, depending on iodide content
Saturated solution of potassium iodide	2–3 wk
Topical iodine (e.g., surgical skin preparation)	2–3 wk
Amiodarone	3–6 mo or longer

[a]wk = weeks
[b]mo = months
[c]d = days

- Thyroid scintigraphy, uptake measurements, and radioiodine therapy are all contraindicated during pregnancy.

Additional preparations prior to radioiodine therapy:

- Radioiodine therapy has to be postponed for at least 6 weeks after cessation of breastfeeding, to allow the hypertrophied breast tissue to involute and avoid unnecessary radiation dose to the breasts. Treatment with lactation-inhibiting medications, such as bromocriptine or cabergoline, has been shown to reduce breast uptake [38].
- Pregnancy test is recommended in all female patients who have a potential to be pregnant, ideally within 24 h prior to radioiodine. Preferably a blood test should be performed, as it is more sensitive than urine test. In addition to a pregnancy test, it has to be assured that a female patient is on adequate contraception. Pregnancy test may remain negative up to 7–10 days after fertilization, so it is best to postpone therapy until the beginning of the next menstrual cycle in patients who may have had unprotected intercourse in the 10 days before treatment. Prior hysterectomy has to be well documented before omitting the pregnancy test. Some institutions perform pregnancy test even if patient has a history of tubal ligation.
- It is usually recommended to avoid getting pregnant for 6 months after radioiodine therapy.
- Patients should be instructed on the therapeutic alternatives, risks, need for follow-up tests, potential hormone supplementation, and a potential for re-treatment.

- Patients have to be asked about urinary incontinence (to limit contamination with radioiodine), nausea, and possibility of vomiting.
- Treating physician has to make sure that the patient is able to follow radiation safety instructions.
- Radiation safety precautions vary depending on the local regulations. SNMMI and ATA have published their recommendations [8, 39].
- SNMMI Guidelines for patients receiving radioiodine treatment are shown in Fig. 4.10.

Guidelines for Patients Receiving Radioiodine I-131 Treatment

What is radioiodine?

Radioiodine (sodium I-131) is a form of radiation therapy that has been used for many years to treat thyroid conditions. It is safe and effective but requires you to observe certain precautions to decrease the small amount of radiation that other people may receive from your body and bodily fluids.

How long does the radioiodine stay in your body?

Radioiodine stays in your body for only a short time. Most of the radioiodine that does not go to thyroid tissue will be eliminated from your body during the first few days after treatment. Radioiodine leaves your body primarily through your urine, but very small amounts can be found in your saliva, sweat and bowel movements.

Ask your doctor for more information. You also may get more information from the Society of Nuclear Medicine at www.snm.org.

How can you reduce radiation exposure to others?

Radiation exposure to other people can be reduced by keeping a reasonable distance between yourself and others and keeping the time you are close to others to a minimum. Your doctor should review the following instructions with you and answer all of your questions. It is important to let your doctor know if you will not be able to follow all of these instructions.

These instructions apply if you are returning to your own home after treatment using private transportation. You should ask your doctor for additional instructions if you are planning to use public transportation or stay in a hotel or other non-private lodging.

First 8 hours:

- Drink one glass of water each hour and use the bathroom as soon as possible when you need to empty your bladder. Men should sit on the toilet while urinating to decrease splashing. Use a tissue to wipe up any urine on the toilet bowl and flush twice. Wash your hands and rinse the sink.
- Maintain a distance of at least 3 feet from all people. If possible, you should drive home alone. If it is not possible to drive alone, you should choose the seat that keeps as much distance as possible between you and the other passengers. You should not use public transportation.

First two days:

- Do not share cups, glasses, plates or eating utensils. Wash items promptly after using. Other people may use items after they are washed.
- Do not share towels or washcloths.
- Flush the toilet twice and rinse the sink and tub after use.
- Wash your towels, bed linens, underwear, and any clothing stained with urine or sweat.

First week:

- Arrangements should be made for others to provide childcare for infants and very young children.
- Sleep alone for 7 days unless otherwise instructed by your doctor.
- Avoid kissing and physical contact with others, and maintain a distance of at least 3 feet from women who are pregnant and children under 18 years old.
- Avoid activities where you may be close to others for more than 5 minutes, for example, movie theaters, sporting events and public transportation.

Additional instructions for women who are breastfeeding

You must stop breastfeeding before you can be treated with radioiodine. If possible, you should stop breastfeeding for 6 weeks prior to treatment. You should not resume breastfeeding after treatment for your current child, but you may safely breastfeed babies you may have in the future. Failure to follow this guidance may result in permanent damage to the thyroid gland of the nursing infant or child.

Pregnancy

Radioiodine treatment should not be given during pregnancy. Tell your doctor if you are pregnant or could be pregnant. If you are planning to become pregnant, you should wait at least 6 months after treatment to ensure your thyroid hormone level is normal and that you do not need additional treatment. Consult your doctor.

Other things you should know during the first week after treatment:

Small amounts of radiation from your body may trigger radiation monitors at airports, border crossings, government buildings, hospitals, and waste disposal sites for up to 3 months after treatment. Ask your doctor for advice if you will be in these areas. Your doctor can provide you with a letter describing your medical treatment if you cannot avoid these areas.

Discarded items that are heavily stained with urine, saliva, nasal secretions, sweat or blood may trigger alarms at waste disposal sites. Ask your doctor for advice on how to safely dispose of these items.

SNM MI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

Fig. 4.10 SNMMI Guidelines for patients receiving radioiodine ^{131}I treatment

Radioiodine Therapy of Benign Thyroid Nodules

Thyroid nodular disease causing clinical or subclinical hyperthyroidism is usually treated with ^{131}I or surgery. The decision is based on multiple factors including patient's age, comorbidities, personal preference, size of goiter, radioiodine uptake, need for rapid correction of hyperthyroidism, history of prior surgery, local expertise, and availability [40]. The degree of reduction of goiter size after radioiodine treatment varies. In a prospective study of 62 patients with solitary toxic thyroid nodules by Nygaard et al., thyroid volume was reduced by 35% within 3 months after radioiodine therapy and by 45% after 24 months [41]. In a European study of 438 patients with borderline hyperthyroidism and multifocal and disseminated autonomy, decrease in thyroid volume ranged between 10 and 60% with a mean reduction of 37% [42].

Toxic Multinodular Goiter

For toxic multinodular goiter, the risk of subsequent hypothyroidism is much lower with radioiodine therapy compared to surgery. A study from Mayo Clinic reviewed records of 253 patients with toxic multinodular goiter treated with an average of 30 mCi (1.1 GBq) of ^{131}I, ranging from 10 to 100 mCi (370 MBq–3.7 GBq) between 1975 and 1993 [43]. Patients had a 28% risk of becoming hypothyroid at 1 year after therapy, compared to 89% of patients treated with surgery. Patients had an estimated probability of radioiodine treatment success of about 90% at 2 years after therapy. Cost of radioiodine therapy is much lower than surgery, and side effects and morbidity are minimal. Patients with toxic multinodular goiter tend to be older with potentially higher immediate risks of surgery. However, surgery is preferred when the goiter is very large and would require high activity of radioiodine or if posttreatment swelling of the goiter could potentially affect adjacent structures. Surgery is also preferred if rapid control of hyperthyroidism or thyroid size is required. It has an advantage of removing incidental foci of malignancy.

Radioiodine Treatment of Solitary Toxic Nodules

For solitary toxic nodules, the choice between radioiodine and surgery is less clear. Unilateral procedure has less surgical risks and much less risk of hypothyroidism compared to total thyroidectomy. For example, in a retrospective study of 630 thyrotoxic patients treated with surgery, 35 patients with solitary toxic adenoma who underwent lobectomy had a 14% incidence of hypothyroidism [44].

A cost-effective analysis showed that for a 40-year-old woman with toxic thyroid adenoma, surgery was most effective, and radioiodine was less costly [45]. This study used a 19% (standard deviation SD 4%) risk of hypothyroidism after radioiodine therapy and a 7.7% (SD 1.7%) risk of failure to control hyperthyroidism, based on literature review. Reported incidence of hypothyroidism after treatment of solitary autonomous nodules varies. For example, a study of 52 patients treated for solitary toxic nodules with 20 mCi (740 MBq) of ^{131}I demonstrated 6% incidence of overt hypothyroidism during the follow-up of 4–17 years (mean 10 years) [46]. A retrospective outcome study by Ceccarelli et al. of 346 patients treated with radioiodine for hyperfunctioning single thyroid nodule, followed for 20 years, demonstrated cumulative incidence of hypothyroidism of 7.6% at 1 year, 28% at 5 years, 46% at 10 years, and 60% at 20 years [47]. This study included patients with subclinical hypothyroidism and had longer follow-up compared to other studies. Pretreatment with methimazole was associated with increased risk of hypothyroidism, probably due to decreased suppression of normal thyroid tissue in these patients. A second treatment was required in 6% of the patients. The patients were treated with approximately 13 mCi (481 MBq) for nodules smaller than 4 cm, 17 mCi (629 MBq) for nodules larger than 4 cm, and a cumulative activity of approximately 27 mCi (999 MBq) for patients requiring multiple treatments.

Radioiodine Treatment of the Nontoxic Multinodular Goiter

Nontoxic nodular disease is sometimes treated with radioiodine to achieve volume reduction without surgery. Uptake in nontoxic multinodular goiter is typically low, especially in non-iodine-deficient areas, so high radioiodine activities would be required to successfully reduce the size of the gland. Recombinant human TSH (rhTSH; Thyrogen, Genzyme Corp., Cambridge, MA, USA) is sometimes used (more commonly in Europe) in patients with nodular goiter with low iodine uptake to increase thyroid uptake. It is an off-label use in both the USA and Europe. Doses from 0.01 to 0.3 mg of rhTSH have been tried. In one European study, a single dose of 0.03 mg of rhTSH, given to patients with large nodular goiter and low radioiodine uptake, increased uptake by 40% allowing for administration of lower therapeutic activity without loss of effectiveness [48]. Braverman et al. found that higher doses of rhTSH (0.1 and 0.3 mg) did not further increase uptake compared to a 0.03 mg dose, but more rise in thyroid hormone levels at higher doses was seen [49]. A study by Nieuwlaat et al. showed that rhTSH increased uptake in the cold areas more than hot areas, making uptake more homogenous, in addition to doubling the 24 h uptake [50]. Volume reduction in patients with nontoxic multinodular goiter is reported to be 30–60% [51].

Selection of ^{131}I Activity for Treatment of Nodular Thyroid Disease

The regimens used for radioiodine treatment of toxic nodular goiter vary. Most centers use either fixed activities or use per gram activities corrected for uptake [52]. Fixed activities are typically between 10 and 20 mCi (370–740 MBq) [40]. The lower fixed activities of 10 mCi have been advised in younger individuals and in patients with mild thyrotoxicosis, with higher activities preferred for older patients and larger goiters [53]. A meta-analysis of the literature done by Rokni et al. demonstrated that calculated therapy may be preferred to a fixed-dose method [54].

The European Association of Nuclear Medicine and Molecular Imaging (EANMMI) Guideline recommends an absorbed radiation dose of 100–150 Gy for either toxic or nontoxic multinodular goiters, which requires about 100–150 microcurie (3.7–5.5 MBq) per gram of thyroid tissue, corrected for a 24-h uptake [55]. The guideline recommends an absorbed dose of 300–400 Gy for treatment of autonomous nodule. The 2016 ATA Guideline recommends 0.15–0.2 mCi (5.55–7.4 MBq) per gram of tissue corrected for 24-h radioiodine uptake [40]. At Mayo Clinic in Rochester, USA, we give 0.2 mCi (7.4 MBq) per gram of tissue corrected for uptake. Therapeutic activity (A) is calculated using the following equation:

$$A = (\text{volume of the nodular thyroid in grams} \times 0.2\,\text{mCi}/g)/\,24\text{h thyroid uptake ratio.}$$

An activity of 0.2 mCi (7.4 MBq) per gram is equivalent to an absorbed dose of approximately 200 Gy, assuming effective half-life of ^{131}I of 6 days. However, radioiodine retention in the avid nodules varies. Reported effective half-lives of ^{131}I in autonomous nodules range from 1.4 to 8 days [56] with a mean value of 6 days [57]. EANMMI published a detailed dosimetry standard procedure in 2013 [58]. Individual effective half-life measurements in the nodules are rarely done, and per gram activities corrected for uptake are usually used for calculating the activities used for therapy. In the USA the volume of the nodular thyroid used for dose calculation is usually estimated by palpation, which introduces a large error. More exact volume measurements can be done by SPECT/CT or by ultrasound when calculated activity is used for therapy.

Even though normal thyroid tissue uptake is suppressed when TSH is low, some uptake is still present, and a prolonged biologic half-life is expected in normal thyroid tissue not stimulated by TSH. Reschini et al. estimated that when an autonomous nodule was treated with 300 Gy, normal thyroid tissue in the ipsilateral thyroid lobe received 34 Gy and contralateral lobe received 32 Gy [56]. Administration of thyroid hormones prior to radioiodine therapy can increase suppression of the normal thyroid tissue and may be used in patients with smaller adenomas with less suppression of the normal thyroid tissue [59]. However, this is rarely needed [60].

A repeat treatment can be done as early as 3 months after unsuccessful therapy, but 6 months is preferred [52]. Iodine-131 can be prepared for intravenous injection for use in patients who cannot tolerate oral administration.

Side Effects of Radioiodine Therapy for Benign Conditions Include

Acute transient:

- Thyroiditis with transient swelling and discomfort in the goiter for approximately a week after therapy is seen in approximately 3% of patients [51]. It is usually treated with over-the-counter nonsteroidal anti-inflammatory medications. Administration of corticosteroids should be considered in patients with large goiter and tracheal narrowing [55].
- Transient change of taste may occur, but with the treatment activities used for benign thyroid disease, permanent injury is uncommon.
- Nausea may occur in a minority of patients (caused by radiation-induced gastritis). It is usually mild and does not require treatment.
- Transient elevation of free T4 and free T3 can happen in the first 2 weeks after therapy. Symptomatic treatment with beta-blockers may be required.

Permanent:

- Hypothyroidism (discussed above), incidence at 15–20% of patients at 1 year [51], varies widely between studies and is increased with longer follow-up.
- Low risk of subsequent autoimmune hyperthyroidism [61]. Nygaard et al. described a de novo development of thyrotropin receptor autoantibodies and simultaneous hyperthyroidism in 6 of 149 (4%) of patients treated with ^{131}I for toxic nodular goiter [62].
- There is no definite evidence of increased risk of malignancy after radioiodine treatment for hyperthyroidism. A retrospective study of 35,593 patients treated for hyperthyroidism between 1946 and 1964 showed no increased mortality from secondary malignancies, except for thyroid cancer [63]. A Swedish study of 10,552 patients treated with ^{131}I between 1950 and 1975 showed possible increase in cancer of the stomach but no increased risk of leukemia or thyroid cancer [64]. A study of 2793 patients from Finland demonstrated increased incidence of several malignancies in patients treated with radioiodine, but there was no control group [65]. A subsequent study from the same institutions analyzed 6148 patients treated with either surgery or radioiodine and compared them to age- and gender-matched controls. Observed increased incidence of cancers of the respiratory tract and stomach was attributable to hyperthyroidism and shared risk factors but was independent of the treatment modality (surgery versus radioiodine) [66].

Role of Nuclear Medicine in Nodular Thyroid Disease in Children

Thyroid nodule in children is uncommon (1–1.5%) compared to adults (19–68%), but the frequency of malignancy is reported as high as 22–26% compared to 5–10% in adults [17, 67]. As for adults, US and US-guided FNA is the method of choice for the evaluation of thyroid nodules. Scintigraphy is indicated only in patients with suppressed TSH, to distinguish autonomous nodules from nodular thyroid coexisting with Graves' disease or thyroiditis. Radiotracer activity administered for the thyroid scan in a pediatric patient should be adjusted based on body mass, body surface, and published formulas (e.g., Webster's formula) [68] or by using pediatric dose calculating tools according to the Society of Nuclear Medicine and Molecular Imaging (SNMMI) or EANMMI available at their respective websites.

Toxic nodular thyroid disease in children is treated with surgery [7, 67], rather than radioiodine due to higher incidence of malignancy in autonomous nodules in this age group (11.3%) [69] and a concern about potential mutagenic effect of radioiodine on the normal thyroid tissue [67].

Potential Value of Nuclear Medicine Studies for Thyroid Nodules with Indeterminate Cytology

Patients with atypia or follicular lesion of undetermined significance (Bethesda Category III), or follicular neoplasm or suspicious for a follicular neoplasm (Bethesda Category IV), typically undergo a diagnostic hemithyroidectomy to differentiate between malignant or benign lesion. After hemithyroidectomy, as many as 85% of the follicular tumors are found to be benign, so there is a need for improved diagnostic tools to reduce the high number of futile hemithyroidectomies.

The Potential Value of ^{123}I Scintigraphy for Thyroid Nodules with Indeterminate Cytology

Scintigraphy, preferably with ^{123}I, can be used to evaluate a nodule with indeterminate cytology [70, 71]. The presence of ^{123}I uptake would indicate a high likelihood of benign adenoma. In iodine-deficient areas, thyroid scintigraphy is sometimes already done prior to biopsy (also see Section Current Indications for Thyroid Scintigraphy in Evaluation of Thyroid Nodules). However, in the USA, only the patients with low TSH undergo scintigraphy prior to biopsy. An adenoma that is not secreting enough hormones to suppress TSH would typically undergo biopsy without scintigraphy, resulting in an indeterminate cytology. If available, scintigraphy with ^{123}I would be preferred to ^{99m}Tc pertechnetate scintigraphy for the evaluation of

indeterminate nodule, because malignant nodules that do not accumulate radioiodine can occasionally accumulate ^{99m}Tc pertechnetate [29] (also see Section Discrepancies in Appearance of the Thyroid Nodules on ^{99m}Tc Pertechnetate versus ^{123}I Scans).

The Potential Value of Sestamibi Scanning of Thyroid Nodules with Indeterminate Cytology

Several groups have explored the possibility of using nuclear imaging with hexakis-2-methoxy-2-methylpropyl-isonitrile (sestamibi or MIBI) to differentiate between malignant and benign follicular tumors.

Saggiorato et al. studied 51 patients with ^{99m}Tc pertechnetate "cold" solitary nodules at least 10 mm in diameter [72]. Using a quantitative measurement of MIBI uptake, the negative predictive value for malignancy was 100% [95% confidence interval, 82.2–100]. In a recently published study, Giovanella et al. have compared genetic mutation analysis and MIBI imaging in 61 patients with follicular neoplasm on cytology [73]. Using a quantitative measurement of the MIBI uptake, a negative predictive value of 100% was found. Giovanella et al. conclude that MIBI scan with quantification of uptake should be the preferred method for differentiating benign from malignant follicular indeterminate nodules. Based on another recent study of 105 euthyroid or hypothyroid patients with thyroid nodules, Campenni et al. also conclude that using quantitative analysis of nodular MIBI uptake improves the diagnostic accuracy of MIBI scanning compared to visual assessment [74].

The Potential Value of FDG PET for Thyroid Nodules with Indeterminate Cytology

Knowing the high sensitivity of FDG PET to localize metastatic thyroid cancer and the high incidence of malignancy in thyroid nodules with increased FDG uptake, several groups have explored the potential possibility of using FDG PET to differentiate between malignant and benign follicular tumors in order to reduce the number of futile diagnostic hemithyroidectomies.

Vriens et al. have performed a systematic review and a meta-analysis on 225 patients from 6 studies on the role of FDG PET in patients with thyroid nodules with indeterminate FNA [75]. They found a negative predictive value of 96% [95% confidence interval, 90–99%]. In a cost-effective analysis, the same group has shown that full implementation of preoperative FDG PET/CT in patients with indeterminate thyroid nodules (Bethesda Categories III and IV) will prevent up to 47% of current futile surgeries leading to lower costs and an increase of health-related quality of life [76]. The authors claim that full implementation of FDG PET/CT could save up to 42,000 futile surgeries annually, 99 million Euro, and 4300 QALYs in the USA only.

In our own retrospective study from the Mayo Clinic, including 51 patients with nodules of indeterminate cytology (all Bethesda Category IV), we found a 95% negative predictive value with a SUVmax cutoff value of 5, supporting the notion that FDG PET/CT may be used to identify low-risk patients for whom surgery can be omitted and surveillance being more reasonable [77]. However, according to 2015 ATA Guidelines [17] and the American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines [7], FDG PET imaging is not recommended to be used routinely for the evaluation of thyroid nodules with indeterminate cytology. FDG PET/CT is recommended to be considered only for preoperative staging of patients with malignant nodules with aggressive features.

MIBI vs. FDG for Thyroid Nodules with Indeterminate Cytology

There seems to be only a few studies that have compared the performance of FDG and MIBI. FDG PET/CT and MIBI using conventional gamma camera with or without supplementary SPECT/CT seem to have comparable performance [78, 79]. Sager et al. suggest that MIBI scan should be the first choice in the preoperative evaluation of patients with "cold" thyroid nodules as an adjunct procedure to FNA because of its low cost and availability. Neither FDG nor MIBI is recommended by any of the American guidelines [7, 17, 67]. Interestingly, MIBI seems to perform comparable to FDG PET despite the far superior image performance of PET scanners compared to gamma cameras. This may indicate that the molecular target of MIBI (mitochondria) may be superior to FDG (hexokinase) for the differentiation of follicular neoplasms, atypia, or follicular lesion of undetermined significance into benign or malignant lesions.

Incidental Finding of Focally Increased Radiotracer Uptake in the Thyroid Gland on Nuclear Imaging

Incidental Finding of a Focally Increased FDG Uptake in the Thyroid Gland on PET

Incidental detection of a focally increased FDG uptake in the thyroid gland is found in about 2% of patients examined with FDG PET [80, 81]. A focal high FDG uptake in the thyroid gland usually corresponds to a distinct nodule on ultrasonography (US). About one-third of these nodules are malignant, most often a primary thyroid cancer [81] (Fig. 4.11). Papillary thyroid carcinoma (PTC), follicular variant of PTC, follicular carcinoma, and medullary thyroid carcinomas are found in about the same proportion as their relative occurrence among thyroid carcinomas. Lymphoma

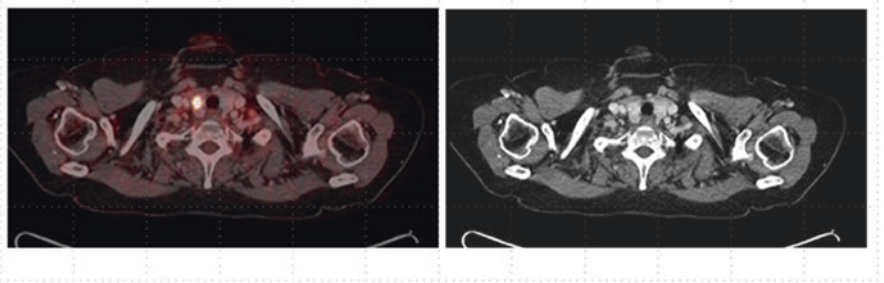

Fig. 4.11 Incidental finding of a thyroid nodule with high uptake of FDG on PET/CT being a classic PTC. FDG PET/CT for cancer indication in a 63-year-old female. *Left*: Fused PET and CT images. Incidental finding of 1 cm nodule with high FDG uptake in the right thyroid lobe. *Right*: Low-dose CT without contrast. Low-attenuation nodule with calcification corresponding to the high FDG uptake. US-guided FNC verified classic PTC

and distant metastases from other cancers constitute about 4% of incidentally detected thyroid nodules with increased FDG uptake [81]. The most common benign etiologies are adenomatous nodule, follicular adenoma, focal lymphocytic thyroiditis, and oxyphilic (Hürthle cell) adenoma [80]. There are some case reports of nodules with increased FDG uptake being solitary autonomous adenomas [82].

As an incidentally detected thyroid nodule with increased FDG uptake has about one-third chance for being malignant, further diagnostic evaluation is needed, and measurement of TSH, US, and US-guided fine needle aspiration (FNA) is the recommended procedure for nodules ≥1 cm [17]. According to Yoon et al., considering the high malignancy rate of thyroid incidentalomas showing increased FDG uptake on PET/CT, US-guided FNA is mandatory even if there are no suspicious features present on US [83]. The American College of Radiology white paper on incidental thyroid nodules detected on imaging also recommends US and FNA, unless the patient has limited life expectancy and comorbidities [84]. Many authors have studied whether a quantification of the FDG uptake in the nodules found incidentally on FDG PET might be helpful to differentiate between benign and malignant nodules. Based on a systematic review of 22 publications from 2000 to 2011, Soelberg et al. found that SUVmax was significantly higher in malignant nodules compared to benign nodules, though the overlap between the groups was substantial [81].

Incidental Finding of Focally Increased Uptake in the Thyroid Gland of Radiotracers Other Than FDG

The tracer ^{99m}Tc-labeled 2-methoxy-isobutyl-isonitrile (sestamibi; Cardiolite™, Bristol-Myers Squibb Medical Imaging, N. Billerica, MA, USA), usually abbreviated MIBI, is extensively used in conventional nuclear imaging, mainly for myocardial perfusion imaging and parathyroid localization. An incidental finding of a

thyroid nodule with increased ^{99m}Tc-MIBI uptake is shown to have a high prevalence of malignancy [85, 86]. Greilsamer et al. found that 44 out of 137 patients (32%) examined with MIBI scan for hyperparathyroidism had a thyroid nodule with high MIBI uptake and as many as 22 of these 44 patients (50%) had thyroid cancer [86].

Carbon-11 (^{11}C)- or fluorine-18 (^{18}F)-labeled choline PET is used to localize residual or recurrent prostate cancer after primary treatment. There are several reports of high uptake of choline in thyroid nodules detected incidentally on PET being malignant or benign oxyphilic (Hürthle cell) lesions [87, 88]. Incidental findings of a thyroid nodule with high choline uptake may also represent a parathyroid adenoma. In fact ^{18}F-choline seems to be a very promising PET tracer for localizing parathyroid adenomas [89, 90].

Gallium-68 (^{68}Ga) DOTATATE was approved by FDA on June 1, 2016, as a diagnostic imaging agent to detect neuroendocrine tumors. Many malignancies including differentiated thyroid carcinomas express somatostatin receptors. Gallium-68 DOTATOC uptake is seen in normal thyroid glands, while increased uptake has been reported in patients with multinodular goiter, Graves' disease, Hashimoto thyroiditis, autonomous adenoma, papillary thyroid carcinoma, and radioiodine-negative metastatic differentiated thyroid carcinoma [91, 92]. Nockel et al. found focal thyroid uptake in 14 out of 237 patients imaged with ^{68}Ga DOTATATE PET/CT. Three of the ten patients who underwent follow-up studies were found to have differentiated thyroid cancer. The authors suggested that patients with incidentally detected focally increased thyroid uptake on ^{68}Ga DOTATATE PET/CT should have further evaluation with US and FNA [93].

Thyroid nodules incidentally found on imaging studies are further discussed in Chap. 12.

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Chapter 5
Imaging for Thyroid Nodules

Tara L. Henrichsen

Thyroid imaging has been performed since the first time tracheal deviation and calcifications were identified in the thyroid bed on a chest radiography which began in 1900. Thyroid masses could also be identified on barium sulfate contrast esophagrams after this practice began in 1910. However, the largest step forward came in the late 1960s when ultrasound became the first cross-sectional imaging modality to enable us to look into the soft tissues of the body and see the internal structure of the thyroid. Today high-frequency ultrasound remains the workhorse of thyroid imaging. However, the thyroid and any associated nodules are now often seen on multiple cross-sectional imaging exams where the thyroid was not the organ intended for imaging including computed tomography (CT), magnetic resonance imaging (MRI), and even ultrasounds of the neck performed for vascular indications where incidental note is made of the thyroid nodules. In addition, the functional imaging of nuclear medicine studies with sestamibi and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) or ^{11}C-choline demonstrates thyroid nodule avidity. Thyroid imaging has been the target of many articles and opinions as the purported cause of overdiagnosis of thyroid malignancy. It is, however, important to remember that thyroid imaging by ultrasound has also allowed many patients to avoid surgery and fine needle aspiration (FNA) secondary to the imaging appearance of the nodule in question. Much has been published about pattern recognition of thyroid nodules on ultrasound as well as more recently a Thyroid Imaging Reporting and Data System (TI-RADS) categorization process. Both of these will be discussed in this chapter as well as how to handle incidental detection of thyroid nodules on other imaging studies.

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Ultrasound Technique

The value of a diagnosis from an ultrasound of the neck depends on the quality of the technique used to obtain the images. Technique encompasses training of the individual obtaining the images, patient positioning, quality of the equipment, and the use of the most appropriate imaging parameters. All healthcare practitioners obtaining diagnostic clinical images of the thyroid should have documented training in the use of ultrasound. This includes not only understanding the anatomy but also understanding the physics of ultrasound, the equipment and resultant images.

All patients should be scanned in the supine position with the neck hyperextended to fully image the entire thyroid gland. Hyperextension assists in bringing the inferior thyroid lobe up above the level of the sternoclavicular junction and may assist in decreasing the thickness of the soft tissues anterior to the thyroid gland. This positioning is best achieved with the use of a sandbag or small pillow under the scapulae. Ultrasound equipment has a large range of sensitivity and quality from small handheld units to larger multifunctional diagnostic units. The most important scanning parameter for the thyroid is the use of a high-frequency transducer with a range extending to at least 15 mHz, and most vendors have a small footprint linear array transducer used for the scanning of the thyroid with an 8–18 mHz range. This allows for the highest resolution and definition of small superficial structures. However, in the case of a larger neck and subsequently deeper thyroid glands, the frequency may need to be dropped significantly to penetrate deep enough into the tissues to adequately see the thyroid and any nodularity, with the knowledge that this decreases the resolution. Adequate imaging of the thyroid gland includes both transverse and longitudinal of both lobes of the thyroid. Any nodules that require mention should have orthogonal images with three measurements (anterior posterior × transverse × longitudinal) to assess volume. Movie or cine loops of each lobe are extremely helpful to get an overview of the entire gland and a better sense of the entire nodule to evaluate for calcifications and margins. All images should be saved in an archival system for comparison purposes. In addition, careful evaluation of the cervical jugular chain lymph nodes should be performed and documented.

Pattern Recognition

Pattern recognition has been well published as a method to categorize thyroid nodules into typically benign and typically malignant [1, 2]. The American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) have also incorporated some patterns in its recommendations. There are patterns for both benign and malignant nodules which have shown to be helpful in selecting nodules for biopsy and can be utilized to avoid biopsy [2].

The first example is the simple cyst or predominately cystic nodule as seen in Fig. 5.1. These are believed to be nonneoplastic hyperplastic nodules that have undergone degeneration resulting in a large cystic component. Importantly, any associated soft tissue echogenicity should be interrogated to rule out a solid component with

worrisome features. While the vast majority of thyroid malignancy is solid or less than 5% cystic, 2.5% of thyroid carcinomas can have greater than 50% cystic change [3]. Closely related is the colloid cystic nodule which is anechoic but contains brightly hyperechoic foci with comet tail or ring down artifact within the cyst as shown in Fig. 5.2. This is understood to be secondary to abundant colloid that has condensed. The presence of colloid comet tail artifact in a cystic nodule has been shown to be benign [4].

Another pattern to recognize as a benign nodule is the "spongiform nodule" also described in the literature as honeycomb or puff pastry appearance. All of these descriptors refer to the multiple small cystic spaces separated by thin septations which is shown in Fig. 5.3. These are considered highly likely benign and occur secondary to hyperplasia. Occasionally, bright echogenic foci may be found in these nodules. This finding needs to be closely interrogated, as the small cystic areas may have a bright linear interface at the posterior back wall of the cystic area which is benign and not to be confused with the malignant microcalcifications found within the stroma of a solid thyroid nodule.

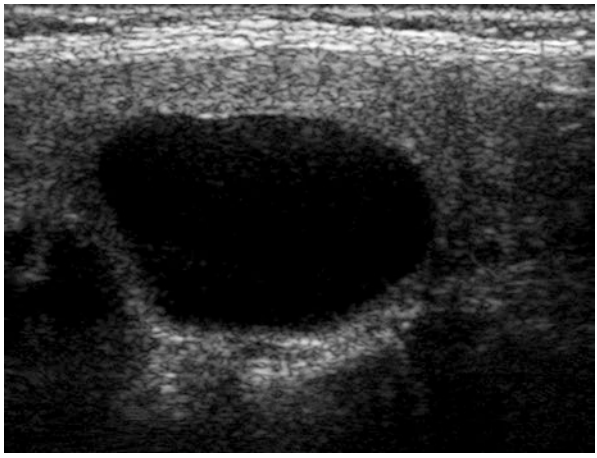


Fig. 5.1 Simple thyroid cyst

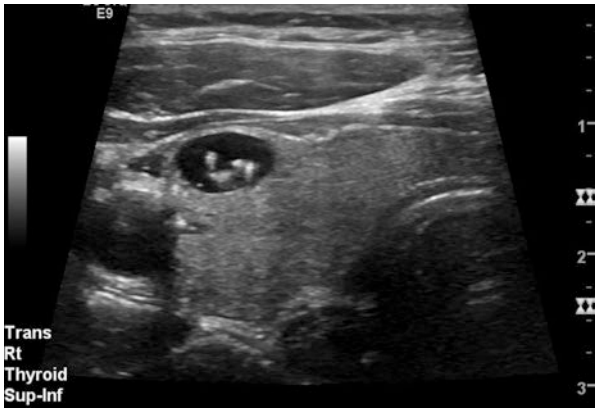


Fig. 5.2 Colloid cystic nodule

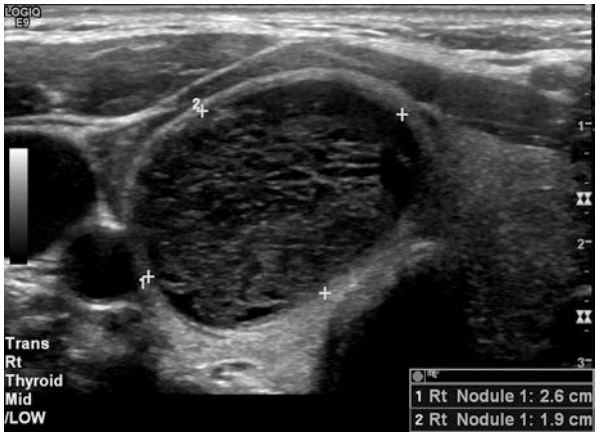


Fig. 5.3 Spongiform nodule

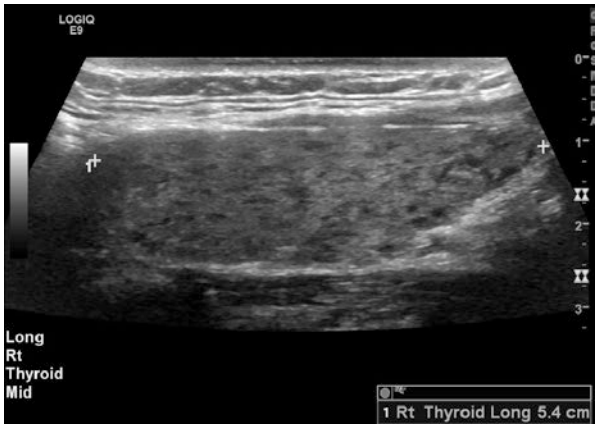


Fig. 5.4 Diffuse tiny hypoechoic nodule pattern

Another classic benign pattern is diffuse tiny hypoechoic nodules. Figure 5.4 demonstrates this classic appearance of Hashimoto's thyroiditis also known as chronic lymphocytic thyroiditis. These nodules range in size from 1 to 6 mm which pathologically is related to a lymphoplasmacytic infiltrate and lymphoid follicles and may have intervening echogenic bands of tissue, which correspond to fibrosis pathologically. The gland is usually symmetrically involved. This appearance has a 95% positive predictive value for Hashimoto's thyroiditis [1, 5]. Vascularity is not helpful as it may be normal, increased, or decreased. Nodules are also commonly associated with Hashimoto's thyroiditis. Careful evaluation of each nodule is warranted as studies have shown an increased risk of papillary thyroid carcinoma around 16% as well as an association with primary thyroid lymphoma [6, 7]. Figure 5.5 demonstrates a widely accepted, but rarely seen, benign nodule pattern found in Hashimoto's thyroiditis the giraffe pattern or giraffe hide. This is described as geographic areas of increased echogenicity which are bounded by thin intervening bands of hypoechogenicity similar to the color pattern seen on giraffes. The echogenic nodule seen in Fig. 5.6 is a variation of this benign process. Sometimes referred to as a "white

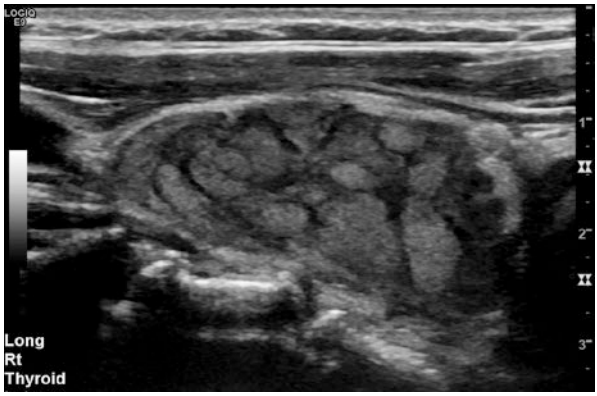


Fig. 5.5 Giraffe pattern

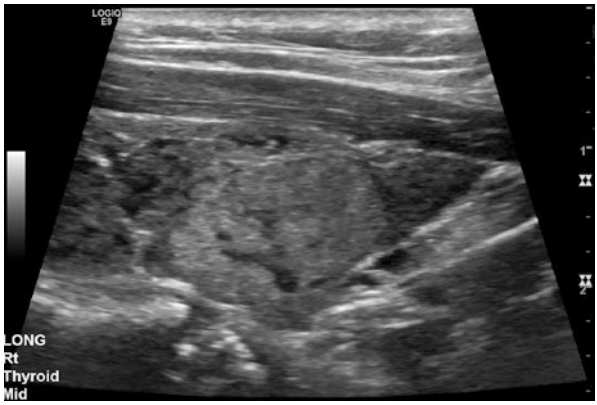


Fig. 5.6 Echogenic nodule

knight," this nodule pathologically represents a benign regenerative nodule of Hashimoto's thyroiditis [2].

There are also a few patterns associated with malignancy. The most common and well-known malignant pattern is that of a hypoechoic solid nodule with microcalcifications or punctate echogenic foci. This is shown in Fig. 5.7. The vast majority of papillary thyroid cancers are hypoechoic with a high sensitivity but low specificity as many benign nodules are also hypoechoic. Microcalcifications have a low sensitivity but high specificity. This has been shown in several meta-analyses [8, 9]. Combining these two features yields a combination that increases specificity for papillary thyroid carcinoma. The echogenic foci are secondary to tiny calcifications which may be psammoma bodies and/or amorphous calcium deposits. The psammoma bodies are likely secondary to necrotic cells causing calcium to laminate around this nidus. The amorphous calcifications may occur secondary to degeneration or fibrosis. Both are present in papillary thyroid carcinoma.

Another pattern associated with malignancy is a hypoechoic solid nodule with coarse calcification centrally as seen in Fig. 5.8. This example demonstrates a

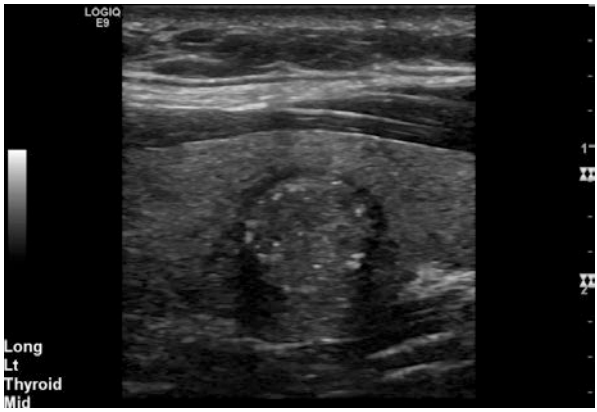


Fig. 5.7 Hypoechoic solid nodule with microcalcifications or punctate echogenic foci

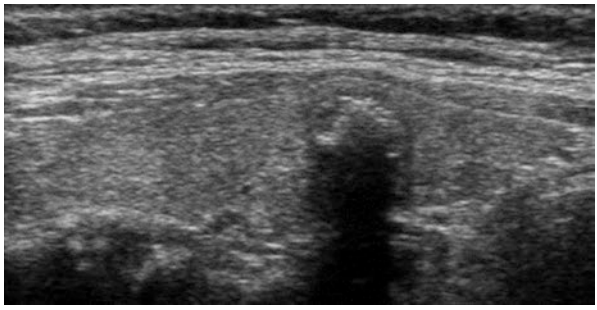


Fig. 5.8 Hypoechoic solid nodule with coarse calcification centrally

well-demarcated rim of a hypoechoic nodule with central dense calcification felt to be suggestive of medullary carcinoma. [1] However, as medullary carcinoma accounts for only 3–5% of all thyroid carcinoma, macrocalcifications are more commonly seen in papillary carcinoma, and this is likely secondary to conglomeration of microcalcifications [10]. It is important to note that the coarse calcification is also common in benign nodules and multinodular goiter which is dystrophic in etiology. Therefore, this combination of a hypoechoic nodule with coarse calcification is the worrisome pattern, and coarse calcification alone is not worrisome on its own.

These patterns have been shown to be specific when present, but not sensitive enough to pick up all malignancies or stratify all nodules. Therefore, many groups have sought to implement classification schemes to include more appearances and characteristics which have been called thyroid imaging reporting and data systems (TI-RADS).

Thyroid Imaging Reporting and Data Systems

Multiple papers have been written on proposed TI-RADS. While there is no consensus statement on the use of these systems, many health systems are beginning to use variations. The primary impetus was to standardize thyroid nodule imaging and

reports to yield dependable and reproducible malignancy risk stratification. These systems have been modeled after the Breast Imaging Reporting and Data System (BI-RADS) from the American College of Radiology (ACR). These vary from having specific descriptors fall into certain risk categories to assigning a point value to each description that are then added up to the sum that falls into a risk category. All of the proposed models use similar terminology for categorizing thyroid nodules using the numerical system or a risk descriptor For example, TI-RADS 1 is equivalent to normal/benign, TI-RADS 2 is equivalent to benign/probably benign, TI-RADS 3 is equivalent to probably benign/indeterminate, TI-RADS 4 is equivalent to suspicious/probably malignant, and TI-RADS 5 is equivalent to highly suggestive of malignancy [11, 12]. These categories have been divided differently in different studies but correspond to a risk of malignancy in the range of 0–2% in TI-RADS 1, 2–10% in TI-RADS 2, 2–30% in TI-RADS 3, 5–92% TI-RADS 4, and 80–100% in TI-RADS 5 [11, 12]. The ACR is expected to release TI-RADS within the next year after a meta-analysis of the many proposed systems already published. This should increase consistency across radiology departments. In 2015 the ACR expert committee started the process by producing a thyroid ultrasound reporting lexicon to begin standardizing the reporting process.

Thyroid Ultrasound Reporting Lexicon

The American College of Radiology (ACR) published a thyroid ultrasound reporting lexicon in 2015 [13]. This lexicon divides the reporting lexicon into six categories. A summary of these categories follows.

Category 1 is for composition. The recommended terminology includes cystic described as completely fluid filled, predominately cystic where the soft tissue component is less than 50% of the volume, predominately solid where the soft tissue component occupies greater the 50% of the volume, solid described as nearly completely solid with only a few tiny cystic spaces, and spongiform, which has been previously discussed in this chapter, composed of multiple tiny cystic spaces. Figure 5.9 demonstrates these five composition descriptors.

Category 2 provides four options for echogenicity, all of which are compared to surrounding tissue. Hyperechoic is increased compared to thyroid parenchyma, isoechoic is similar compared to thyroid parenchyma, hypoechoic is decreased compared to thyroid parenchyma, and very hypoechoic is decreased compared to neck musculature. Examples are demonstrated in Fig. 5.10. Category 3 is shape of the nodule, of which the only shape identified in several meta-analyses to have a significant sensitivity and specificity is taller than wide as seen in Fig. 5.11.

Category 4 is the size of the nodule. Thyroid nodules should be measured in three planes: longitudinal, transverse, and anteroposterior. Measuring is more important for follow-up comparison than a criterion to determine biopsy. Category 5 has six margin descriptions, all of which are demonstrated in Fig. 5.12. Smooth is found on spherical or elliptical nodules with a well-defined edge. Irregular describes spicu-

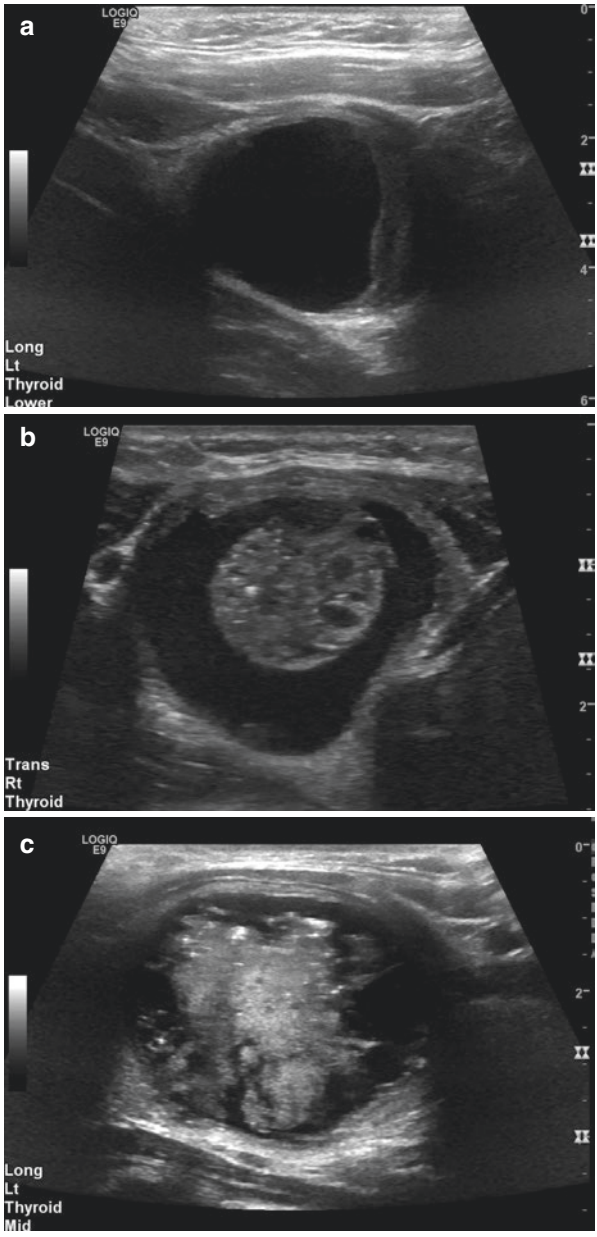
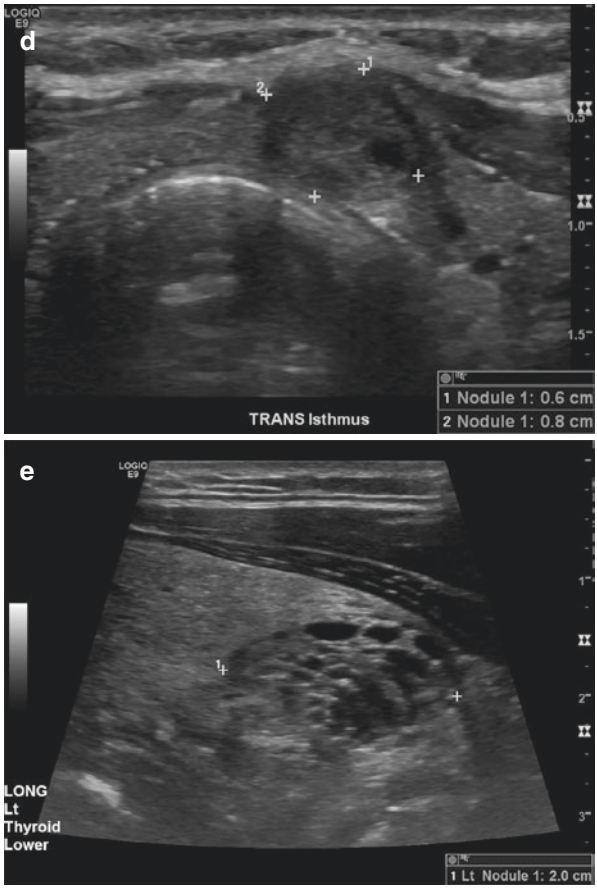


Fig. 5.9 Category 1: composition. (**a**) Cystic; (**b**) Predominately cystic; (**c**) Predominately solid; (**d**) Solid; (**e**) Spongiform

Fig. 5.9 (continued)



lated, jagged, or sharp angles with protrusions into the surrounding parenchyma. Lobulated margins are rounded protrusions into the surrounding parenchyma. Ill-defined margins are those where it is not possible to clearly define the margin. Halos are a dark border at the periphery of the nodule and may be incomplete. The last margin descriptor is extrathyroidal extension where the nodule has broken through the thyroid capsule.

Category 6 is echogenic foci. Punctate echogenic foci are "dot-like" and less than 1 mm. Macrocalcifications are large enough to generate a posterior acoustic shadow. Peripheral calcification encompasses the majority of the nodule. Comet tail artifacts are reverberation artifacts that are triangular in shape. Examples of these various types of echogenic foci are shown in Fig. 5.13 [13].

It is expected that each of these category descriptors will be assigned a point value in which the summation of points leads to a recommendation of benignity with no further action, probably benign with a follow-up recommendation, and lastly a recommendation for biopsy.

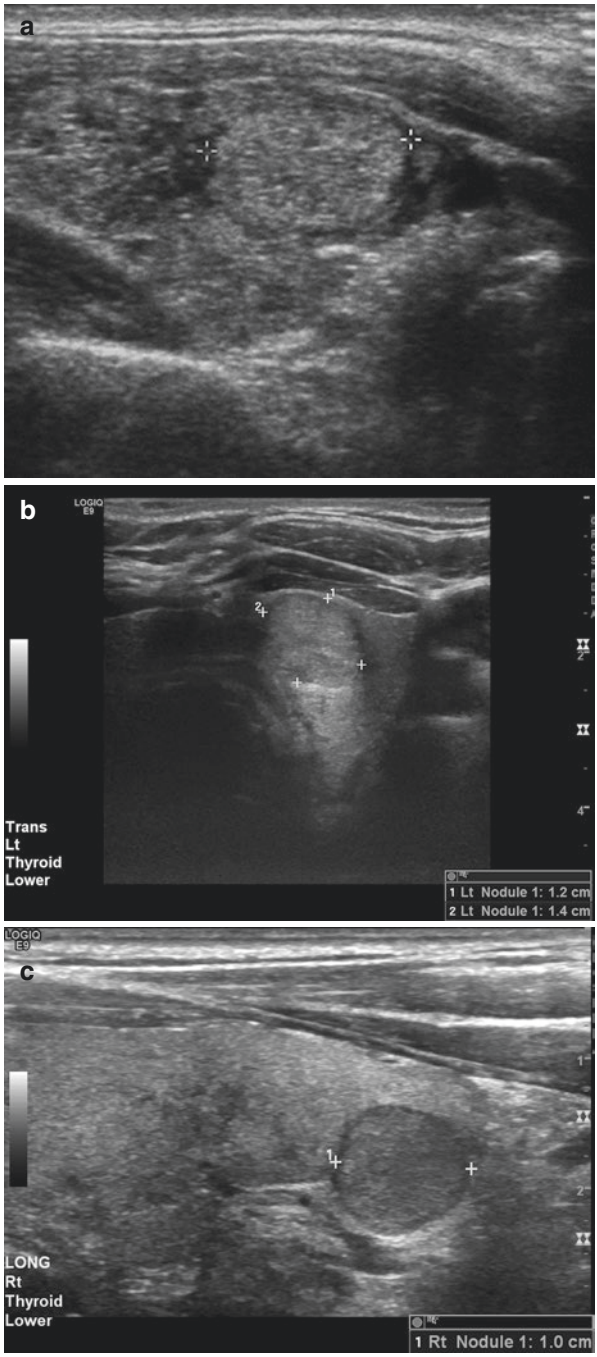


Fig. 5.10 Category 2: echogenicity. (**a**) Hyperechoic; (**b**) Isoechoic; (**c**) Hypoechoic; (**d**) Very hypoechoic

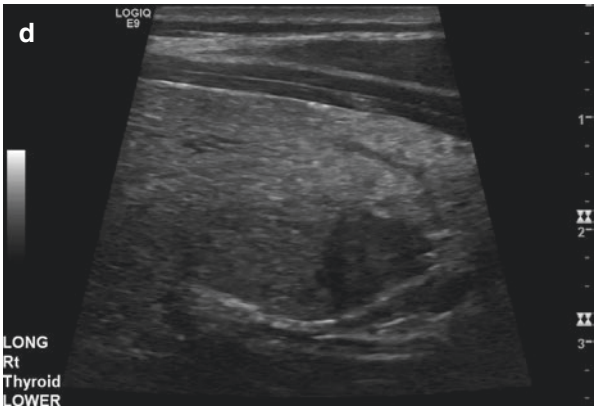


Fig. 5.10 (continued)

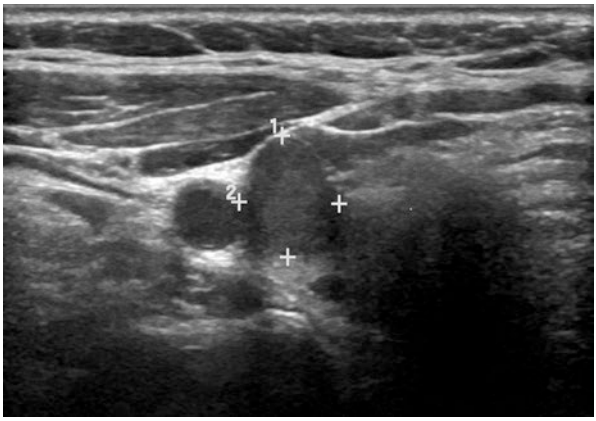


Fig. 5.11 Category 3: shape taller than wide

Other Medical Imaging Techniques

PET-CT

^{18}F-FDG PET-positive nodules are detected on 4% of PET scans and have a 15–50% risk of malignancy [14, 15]. SUV studies have a wide range and a reliable cutoff point, while trend to higher values for thyroid carcinoma, has not been determined. A recent study comparing ^{18}F-FDG PET-positive nodules to one version of TI-RADS from South Korea showed higher sensitivity and specificity of ^{18}F-FDG PET leading to a recommendation to biopsy all focally PET-positive nodules in patient without limited life expectancy or significant comorbidities [14, 16–18]. C-Choline PET/CT has also shown papillary carcinoma to be intensely avid, and ultrasound evaluation with guided FNA is recommended, again with the disclaimer of incorporating life expectancy and comorbidities into the decision [19].

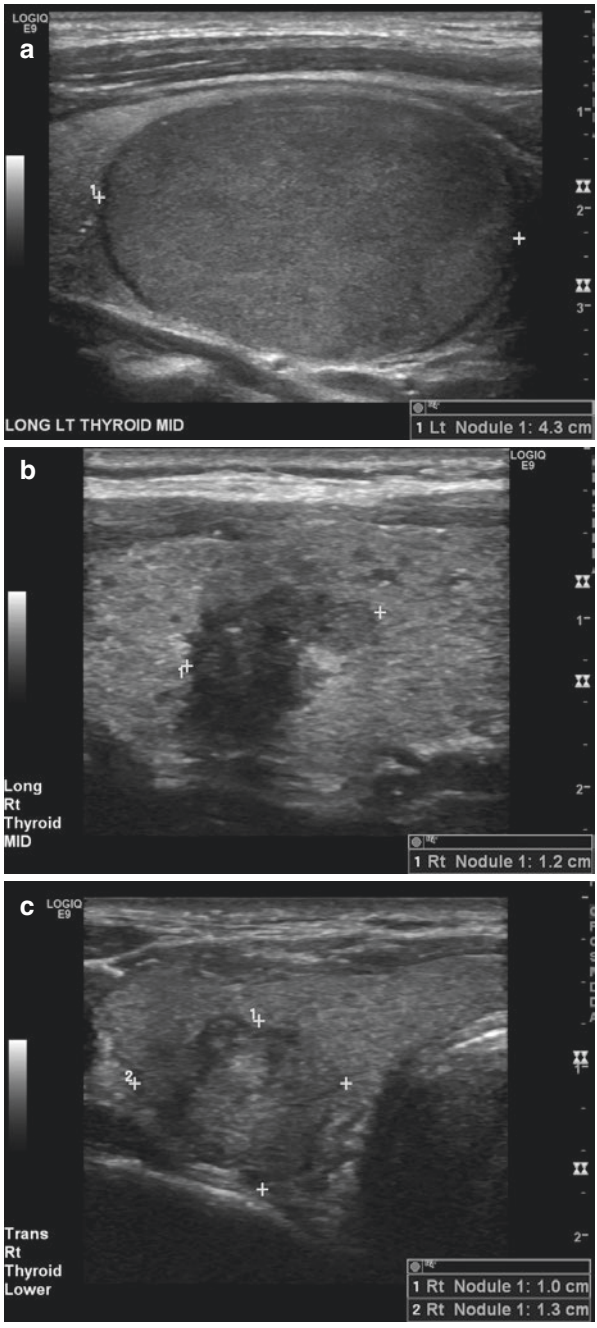


Fig. 5.12 Category 5: margin. (**a**) Smooth; (**b**) Irregular; (**c**) Lobulated; (**d**) Ill-defined; (**e**) Halo; (**f**) Extrathyroidal extension

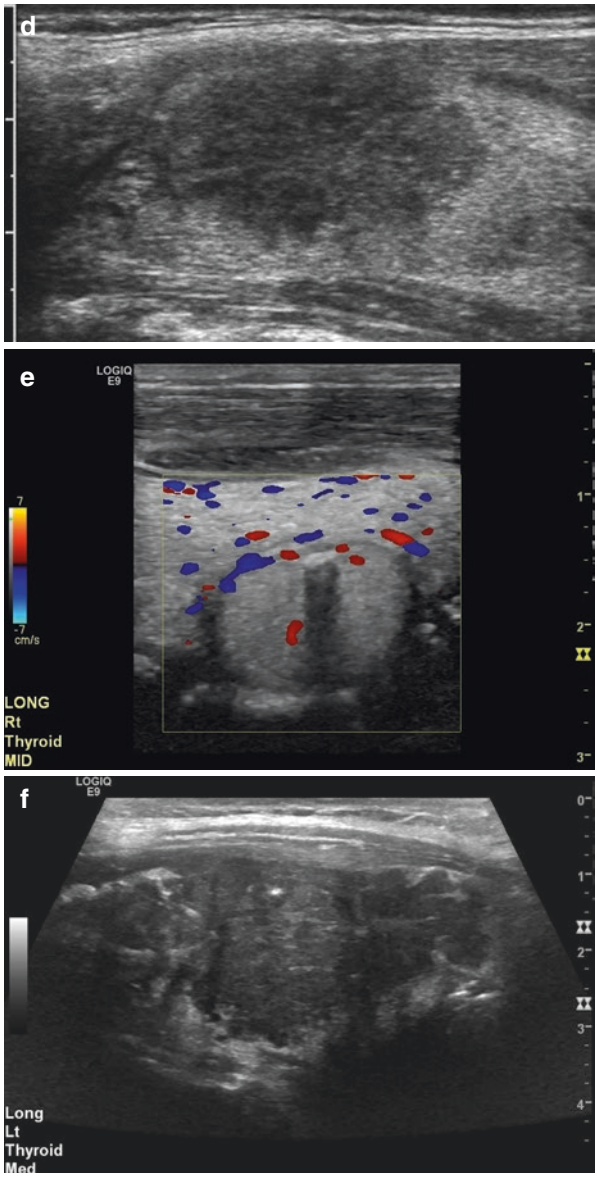


Fig. 5.12 (continued)

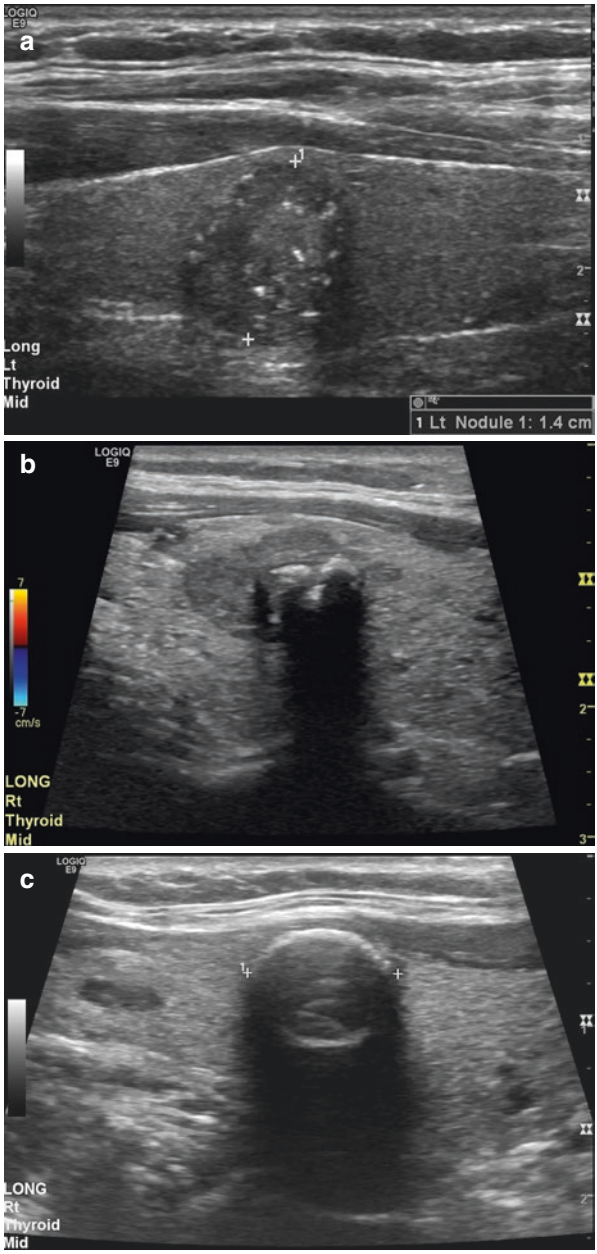
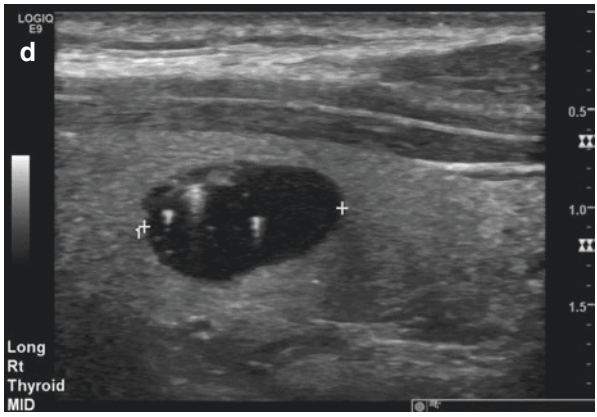


Fig. 5.13 Category 6: Echogenic foci. (**a**) Punctate echogenic foci; (**b**) Macrocalcifications; (**c**) Peripheral calcification; (**d**) Comet tail artifacts

Fig. 5.13 (continued)



Nuclear Medicine

Thyroid scintigraphy may utilize ^{99m} technetium pertechnetate or a radioisotope of iodine such as ^{123}Iodine. Iodine radioisotopes are preferred as there are higher false negatives with pertechnetate. The primary purpose of these tests is to assess whether a nodule is functioning. Hyperfunctioning nodules are rarely malignant; therefore, FNA is not recommended. However if a nodule is hyperfunctioning on pertechnetate scanning, this should be repeated with iodine-based scanning as a small percentage of these have been shown to be malignant when they are hypofunctioning on iodine-based scanning [20]. Nonfunctioning nodules are also referred to as cold nodules and should be further evaluated with ultrasound and possibly FNA. Any indeterminate examination should also go to ultrasound to determine if FNA is recommended. Thyroid carcinoma can uncommonly be detected on ^{99m}technetium-methoxyisobutylisonirile (MIBI) and ^{111}Indium-octreotide scans. However, this uptake is indeterminate, and further evaluation with ultrasound is recommended to determine whether FNA is warranted [21].

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are both considered advanced cross-sectional imaging; however, neither is adequate for determining fine detail that clears or implicates intrathyroidal thyroid nodules. Thyroid nodules are found in up to 25% of chest CTs and 18% of neck CTs and MRIs [17, 22]. Both of these modalities excel in evaluating extrathyroidal extension of malignancy and evaluating regional metastases. Recently several institutions have begun

using a three-tiered flow chart system to determine the need for FNA. A combination of these was published by the ACR incorporating life expectancy, age of the patient, and size of the nodule with the intent of decreasing FNAs and surgery for nonmalignant lesions. Research has shown that this decision tree process does decrease FNAs by 35–46% but had a false-negative rate of 13% [18]. This translates to missing 1.2% of papillary thyroid carcinomas measuring less than 1 cm in the less than 35 age group and those measuring less than 1.5 cm in the greater than 35 age group.

Advanced Ultrasound Techniques

Elastography and contrast enhanced sonography are both actively being studied and have shown some promise. It is important to note that there are different types of elastography examinations. Both techniques measure the elasticity of the thyroid nodule tissue compared to the surrounding thyroid parenchyma; however, the forces applied to measure change in the tissue elasticity are different. The traditional real-time elastography (RTE) techniques require pressure in the form of external compression from the ultrasound probe, and the degree of tissue distortion is measured. This technique is very operator dependant. Research has been published which ranges widely from demonstrating excellent results to inferior performance when compared to gray-scale ultrasound [23, 24]. Shear wave elastography (SWE) also known as acoustic radiation force impulse imaging (ARFI)-generated SWE is another technique for measuring elasticity of the nodule using acoustic force where the resulting speed of shear wave propagation is measured. Several meta-analyses have been published demonstrating high sensitivity 0.80–0.84 and specificity 0.81–0.93 and high negative predictive values [25–28]. Few studies have been performed directly comparing these two types of elastography techniques.

Contrast enhanced ultrasound (CEUS) of thyroid nodules was first reported in 2006 [29]. Studies have shown a pattern approach with ring enhancement being more common in benign nodules and heterogeneous enhancement more common in malignant nodules [30]; however, there is overlap and therefore not a dependable finding. Current research is looking at quantification of contrast enhancement and maximum intensity of peak enhancement, but these are not yet ready for clinical use [31–33].

Imaging of the thyroid gland has been performed since the early 1900s; however, the examination of choice has been ultrasound for the last few decades. While there are multiple new cross-sectional imaging and nuclear medicine techniques available, none have proven superior to ultrasound. The new TI-RADS categorization schemes and lexicons recently published support ultrasound as the standard for thyroid imaging. In addition, advanced ultrasound techniques are actively being studied and may become helpful adjuncts to diagnostic ultrasound.

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Chapter 6
Fine-Needle Aspiration for Thyroid Nodules

Tara L. Henrichsen

Fine-needle aspiration (FNA) is a critical component of thyroid nodule evaluation. This minimally invasive test was initially performed with palpation guidance; however, today the vast majority of these procedures are performed with ultrasound guidance. The introduction of ultrasound-guided FNA techniques to thyroid nodule evaluation has increased the percentage of thyroidectomies with malignant nodules from 14% to more than 50% [1]. Therefore, fewer patients are going to surgery for benign disease as the diagnosis of benignity made at FNA precludes the necessity of surgical resection in the operating room. Ultrasound guidance is recommended, as this technique has a lower false-negative rate and lower nondiagnostic rate [2]. This is secondary to ultrasound allowing for real-time guidance and accurate targeting of the nodule.

Preprocedural Planning

The selection of nodules that warrant FNA may be determined by guidelines and recommendations available from the Society of Radiologists in Ultrasound, the American Thyroid Association, the American Association of Clinical Endocrinologists, the National Comprehensive Cancer Network, recently published Thyroid Imaging Reporting and Data Systems (TI-RADS), or individual institutional care processes. Planning the biopsy includes pre-scanning to determine the best position of the neck for the shortest unobstructed distance to the nodule requiring cytological assessment. Typically, the optimal positioning is with the neck slightly hyperextended, which is accomplished with a sandbag or

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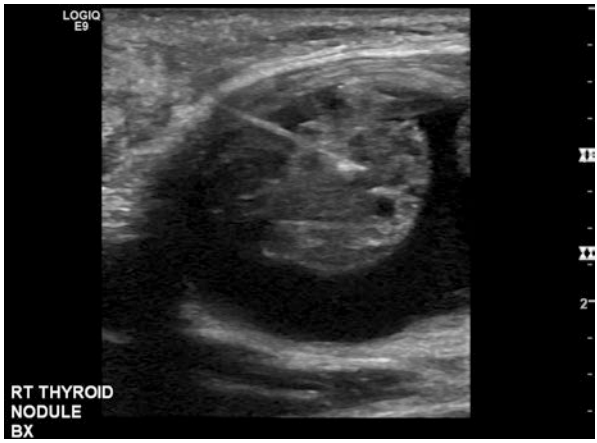

Fig. 6.1 Needle placement into the solid portion of a partially cystic thyroid nodule during FNA

rolled towel under the scapulae. This initial assessment also allows for selection of the best ultrasound probe. In the thyroid, the high-frequency (8–18 mHz) probes are preferred for the higher resolution in superficial tissue. These probes are usually linear arrays and may have a larger footprint which works well in moderate-sized neck. A smaller footprint, high-frequency linear probe is available that often has a "hockey stick" or "L shape" that lends itself to better contact in smaller necks. In instances where the neck is larger or the nodule is deep in the posterior thyroid, a lower frequency probe (5–10 mHz) may be used to optimize visualization at that depth, although with less resolution. It is also important to optimize the ultrasound parameters of zoom, depth, focus, and time-gain compensation to insure visualization of the targeted nodule and the entire length of the FNA needle during biopsy.

In addition, the portion of the nodule to be biopsied needs to be planned; specifically in mixed cystic and solid nodules, the solid portion should be the target of the FNA as seen in Fig. 6.1. While FNA can be performed with other imaging modalities for guidance, ultrasound is the preference secondary to the benefit of real-time visualization. Real-time ultrasound guidance assists in needle tip placement around structures such as vessels, which minimizes procedure-associated hemorrhage and allows for documentation of needle tip placement within the nodules during the FNA passes.

Setup

The setup for FNA includes preparation of the ultrasound probe for use. There are several options for ensuring a clean and sterile probe. Sterile probe covers are commercially available and widely used, as are soaking systems designed for probe sterilization. Additional probe preparation procedures include cleaning with high-level disinfectant wipes which remain in contact with the probes for 3 min resulting in a sterilization level acceptable for ultrasound guidance. This process

is shown in Fig. 6.2. Skin preparation includes washing the neck with chlorhexidine gluconate, iodine, or alcohol-based products, many of which are available in single-use packaging as seen in Fig. 6.3. Sterile draping also assists in keeping the field sterile.

Fig. 6.2 Ultrasound probe wrapped with a high-level disinfecting wipe in preparation for FNA

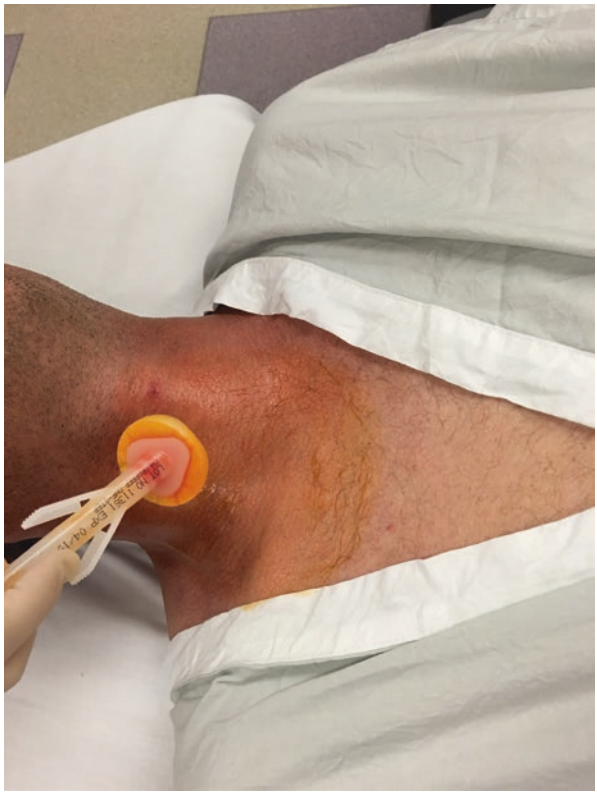

Fig. 6.3 Skin preparation for thyroid nodule FNA

Technique

FNA may be performed with or without local anesthesia. The type of FNA obtained may have a role in determining utility of anesthesia. If only a single suction-assisted pass is being performed, many institutions do not use local anesthesia. However, local anesthesia results in the increase of the patients' comfort level and decrease of anxiety during the procedure [3]. Local anesthesia may be achieved with topical lidocaine cream, injected lidocaine, or lidocaine buffered with 8.4% sodium bicarbonate. Topical lidocaine requires application 30 min prior to the procedure and results in excellent anesthesia of the dermis. Injected lidocaine is performed immediately prior to FNA and allows for anesthesia of the dermis with a skin wheal and deeper anesthesia through the overlying strap musculature and into the perithyroidal soft tissues as seen in Fig. 6.4. Optimal anesthesia requires a 1 min wait time with lidocaine and 2 min wait time with buffered lidocaine. Buffering of lidocaine increases the pH of the solution and decreases pain associated with subcutaneous infiltration. Buffered lidocaine is available prepackaged, prepared in the hospital pharmacy, or mixed in the room with 10 parts 1% lidocaine and 1 part 8.4% sodium bicarbonate. Multiple studies from the emergency medicine, anesthesia, surgery,

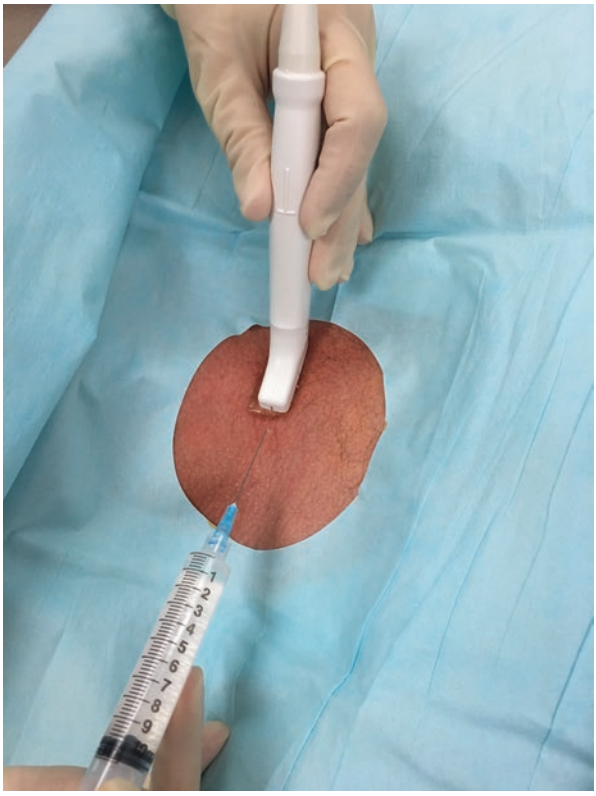

Fig. 6.4 Local anesthesia administered prior to FNA

and dermatology literature have demonstrated less pain associated with percutaneous procedures with buffered lidocaine [3–6]. The speed at which the lidocaine is injected is thought to have an effect on patient pain with initial infiltration. However, Krause et al. found that while there was a decrease in perceived patient pain with slower infiltration, it was not statistically significant [7]. Complications with local anesthesia are uncommon. The topical preparations have been shown to irritate skin and cause pruritus. Allergies to lidocaine are reported and patients should be should be questioned about known drug allergies prior to biopsy.

Ultrasound-guided FNA is usually performed using a long-axis technique with the needle lined up at the center of the short axis of the ultrasound probe as seen in Fig. 6.5. This long-axis technique allows for complete visualization of the needle from the dermis to thyroid nodule shown in Fig. 6.6. Targeting of the nodules may be performed with needle guides or with a freehand technique. Many vendors have a needle-directing device which can be attached directly to the ultrasound probe to assist in needle guidance. Although the freehand ultrasound guidance technique requires skilled eye-hand coordination, it allows for intra-nodule needle tip redirection to more solid and less vascular portions of the nodules to increase adequacy of aspirations. The needle size selected for FNAs ranges from 23 to 27 gauge; however the 25 g needle is the most often utilized. FNAs may be suction assisted or capillary

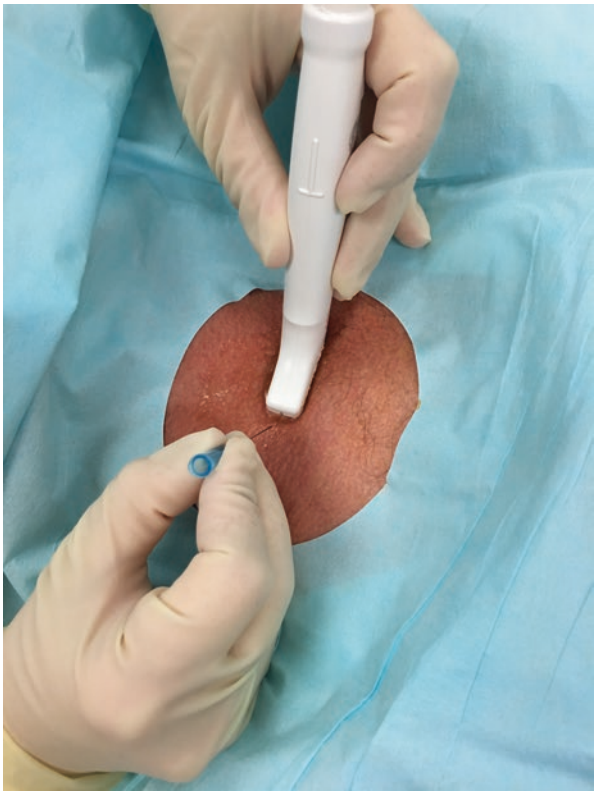

Fig. 6.5 Needle position for long-axis visualization during FNA using capillary technique

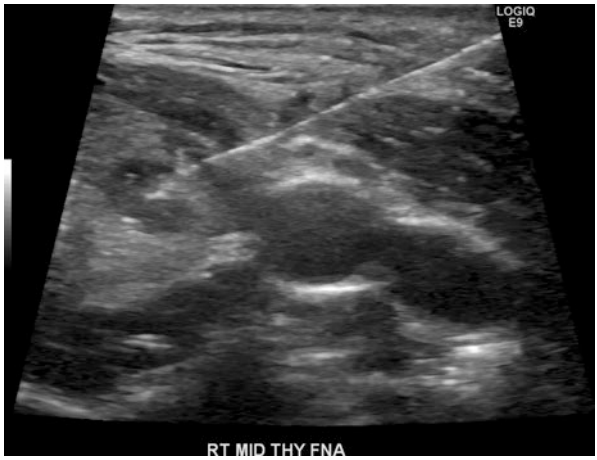

Fig. 6.6 Ultrasound image showing complete visualization of the needle from the skin to the nodule during FNA

technique, which is sometimes referred to as fine-needle capillary sampling or FNC. Slide preparation from capillary sampling is performed by direct smear onto slides that are immediately fixed in alcohol and sent to the pathology department for staining and interpretation. If suction is used, the samples are usually placed into liquid preservative which is made into thin prep slides or spun down into cell blocks for interpretation in the pathology department. The capillary technique has been shown to yield fewer nondiagnostic samples [8]. This is felt to be secondary to the negative pressure from aspirations causing more tissue damage and bleeding. Core needle biopsy (CNB) is also an option for pathologic diagnosis; however it has higher rates of bleeding complications and pain. Therefore, CNB is typically reserved for repeat biopsy after a nondiagnostic FNA.

Complications

As with any percutaneous intervention, there are associated risks. Technically, infection post procedure is a potential complication although rarely reported. The most common post procedure complication is hemorrhage; however, the complication rate for thyroid FNA is extremely low with the literature reporting between 1.9 and 6% hemorrhage rates following FNA per an article by Polyzos and Anastakis [9]. Hemorrhage may be intrathyroidal, usually within the nodule targeted for biopsy, perithyroidal, or subcutaneous. Bruising at the skin entry site is most common. Localized pain is also possible but usually short in duration. Rare complications including thyroid swelling, tracheal injury, and recurrent laryngeal nerve damage have been reported.

Thyroid nodule FNA has made a profound impact on the care of patients with thyroid nodules, by assisting in directing care and preventing unnecessary surgery. Like all procedures, attention to the details of technique is imperative to ensure quality outcomes.

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Chapter 7
Description and Classification of Thyroid Cytology

Michael Rivera, Jennifer L. Sauter, and Michael R. Henry

Introduction

Fine needle aspiration (FNA) of the thyroid plays a key role for the evaluation of thyroid nodules. FNA has been in common use in the United States since the 1970s; however, its use in Europe reaches two decades earlier. The purpose of thyroid FNA is to distinguish between benign and malignant disease. The incidence of thyroid carcinoma is approximately 2.5 cases per 1000 persons [1]. However, in autopsy studies, 10–26% of patients have been reported to have incidental papillary microcarcinoma [2–4]. Given the incidental and clinically innocuous nature of many microcarcinomas, the term well-differentiated papillary microtumor has been suggested as an alternative nomenclature but is not widely used by pathologists in practice [5].

The reported sensitivity and specificity of thyroid FNA ranges from 43 to 100% and 47 to 100%, respectively [6–10]. The false-negative rate ranges from 1.5 to 11.5%, and the false-positive rate ranges from 0 to 8% [11–14]. The overall accuracy has been reported to be about 90% for a single aspiration session, analyzed by the use of receiver operator characteristic curves [15]. These measures are important to guide the uses of FNA and which clinical scenarios may require re-aspiration in the face of a negative or indeterminate aspirate. However, it should be kept in mind that the classification of some excised thyroid tumors is subject to disagreements of classification, including whether the tumor is benign or malignant. This is best exemplified by the example of encapsulated follicular variant of papillary thyroid carcinoma. A panel of experts diagnosed the follicular variant of papillary thyroid carcinoma with a concordance of 39% on excision specimens [16]. This variability in the histological diagnosis would naturally lead to differing measures of accuracy of thyroid cytology studies from one institution to another and also may affect the

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reported risk of malignancy [17, 18]. Indeed, in light of recent data showing an indolent biology for the noninvasive follicular variant of papillary carcinoma and its differing molecular featured from classic papillary thyroid carcinoma, a change in nomenclature to noninvasive follicular tumor with papillary-like features (NIFTP) has recently been proposed [19]. Other factors that may influence the reported accuracy of FNA include sampling issues related to the nature of the lesion, such as if the lesion is solid and cystic. The frequency of malignancy for cystic nodules is measured up to 25% and is more common with larger cysts and cysts with solid components [20, 21].

The risk of primary thyroid malignancy in patients with thyroid nodules depends on several factors including age, gender, nodule size, and imaging characteristics. Some of the aforementioned features also have great importance in predicting the prognosis of patients with established thyroid carcinoma. The presence of Hashimoto's disease has been linked to an increased risk for developing thyroid carcinoma, but this assertion remains controversial [22]. Prior exposure to radiation is a well-established risk of thyroid carcinoma [23, 24]. Proper patient selection is an important step to determine which patient's would benefit most from FNA. In general, patients with solitary nodules with worrisome or indeterminate features measuring ≥1.0 cm are candidates for FNA [25]. In some cases, patients will undergo some form of thyroid surgery regardless of the fine needle aspiration results, based on clinical and imaging features. However, FNA can still provide useful information that may guide the extent of surgery in such cases. For instance, in patients with a large circumscribed thyroid mass occurring in the background of hyperplasia, some possibilities to consider would include a dominant hyperplastic nodule, follicular neoplasm, and papillary thyroid carcinoma. If the FNA shows an exclusive population of oncocytic cells, suspicious for Hurthle cell neoplasm, the clinician may decide to offer subtotal or total thyroidectomy, as the likelihood of malignancy for Hurthle cell neoplasms measuring over 4.0 cm is 65% [26–28]. Alternatively, if the FNA shows only macrofollicles and colloid consistent with a benign nodule, then a less aggressive surgery or observation may be suggested.

The importance of having a uniform reporting system for thyroid fine needle aspiration is underscored by the complex variables that influence which patients are ultimately referred to surgery. The Bethesda system for reporting thyroid cytopathology (TBSRTC) was introduced in 2007 to address the need for a uniform reporting system [29]. The system contains six tier: I, nondiagnostic or unsatisfactory; II, benign; III, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); IV, follicular neoplasm or suspicious for a follicular neoplasm; V, suspicious for malignancy; and VI, malignant. Uncommon diseases that may involve the thyroid such as intrathyroidal paraganglioma are not specifically addressed by the TBSRTC and can be reported using traditional cytology reporting categories. For an FNA of the thyroid to be called benign, at least six clusters of benign follicular cells are needed. Each cluster should be comprised of at least ten cells. The nondiagnostic category is reserved for cases containing too few cells or cases that are hampered by obscuring artifacts such as bloody smears, excessive air-dry artifact, or overly thick smears. However, in cases containing

abundant colloid, allowance can be made for fewer follicular cells being present. Naturally, this conclusion is ideally made in conjunction with knowledge of the imaging characteristics and clinical impression of a colloid nodule. In cases of diminished or absent follicular cells present in a background of histiocytes (rather than colloid), greater caution needs to be exercised, and the use of category I (non-diagnostic or unsatisfactory) may be more appropriate. The risk of malignancy associated with category I aspirates is between 1 and 4%. Category III (AUS and FLUS) encompasses a group of lesions that does not fit into benign, suspicious, or malignant lesions. There are a few scenarios outlined by the TBSRTC for the use of AUS/FLUS category. For instance, the category could be applied to aspirates showing follicular cells with some grooves and nuclear membrane irregularities in the background of an otherwise benign aspirate. AUS/FLUS could also be applied to sparsely cellular aspirates that show a predominance of Hurtle cells with scant colloid in the background. It also has been suggested that the category of AUS could be used for an atypical lymphoid population that falls short of suspicious (category V). Therefore, the AUS/FLUS category includes concern for heterogeneous, and sometimes unrelated, entities including follicular neoplasm, papillary thyroid carcinoma, and even lymphoma. The use of this category frequently mandates the use of additional comments on the part of the pathologist, to elaborate on the nature of the concern and/or differential diagnosis.

Benign Thyroid Diseases

The majority of thyroid nodules are benign. The most common scenarios in which benign thyroid nodules are encountered are nodular hyperplasia and chronic lymphocytic thyroiditis or other inflammatory conditions of the thyroid. These two disease processes are not mutually exclusive and frequently occur together. The most common cause of chronic lymphocytic thyroiditis is Hashimoto's disease; however, various medications and other immune-mediated diseases can also cause a similar cytomorphologic and histological appearance. Aspirates of nodular hyperplasia produce variably cellular smears comprised of macrofollicular clusters. The cells of macrofollicular clusters are containing small, uniformly spaced nuclei with dark, homogenous chromatin. The appearance has been compared to a honeycomb (Fig. 7.1). Microfollicles can also be seen and in some cases may predominate making distinction from a follicular neoplasm difficult. Usually, fairly abundant colloid is present in the background of aspirates from benign thyroid nodules in contrast to follicular neoplasms (Fig. 7.2). Histiocytes may be present in the background of cystic or degenerated nodules (Fig. 7.3). Aspirates of chronic lymphocytic thyroiditis show numerous bland-appearing, small lymphocytes admixed with clusters of follicular cells (Fig. 7.4) [30]. The nuclei of lymphocytes may have a streaked appearance on smears. The follicular cells in chronic lymphocytic thyroiditis are mostly macrofollicles; however, scattered microfollicles may be present. In some cases, mild nuclear enlargement and grooves may be seen simulating the

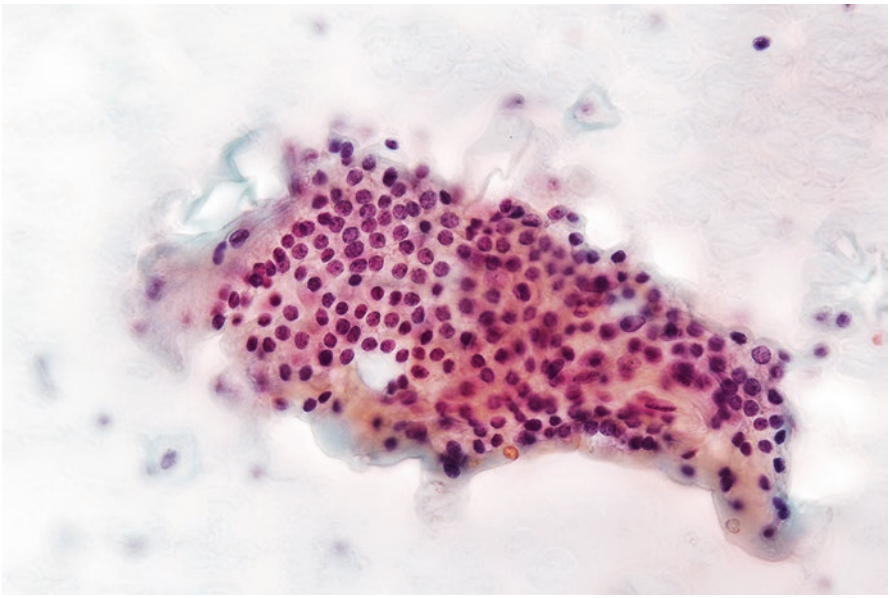

Fig. 7.1 Benign macrofollicular cluster with uniform, evenly spaced nuclei

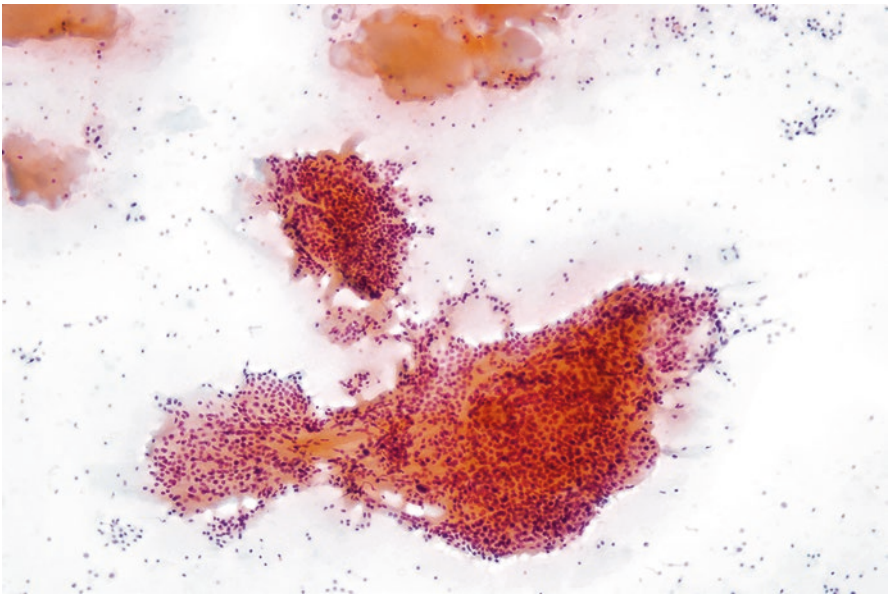

Fig. 7.2 Benign macrofollicular clusters and pools of colloid from a benign thyroid nodule aspirate

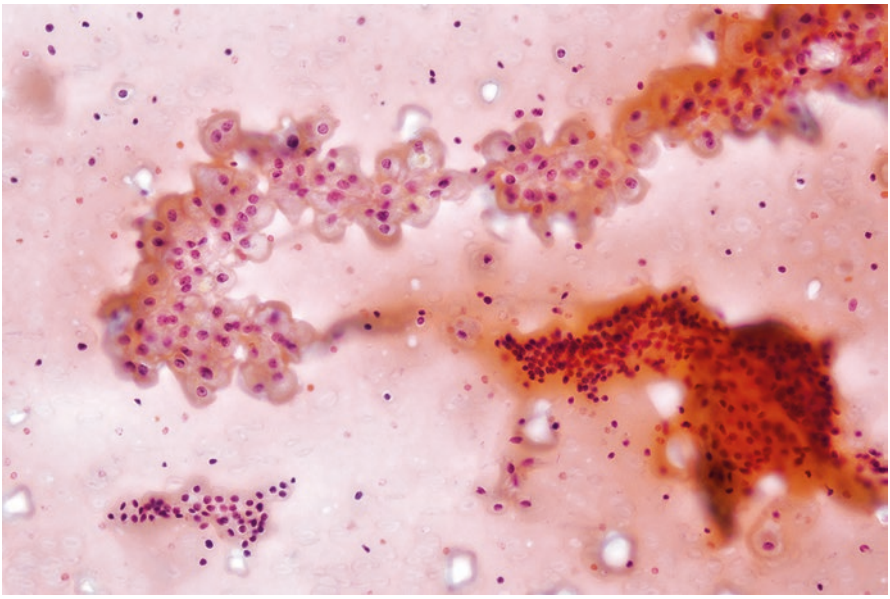

Fig. 7.3 Mixture of histiocytes and macrofollicular clusters in benign cystic thyroid nodule

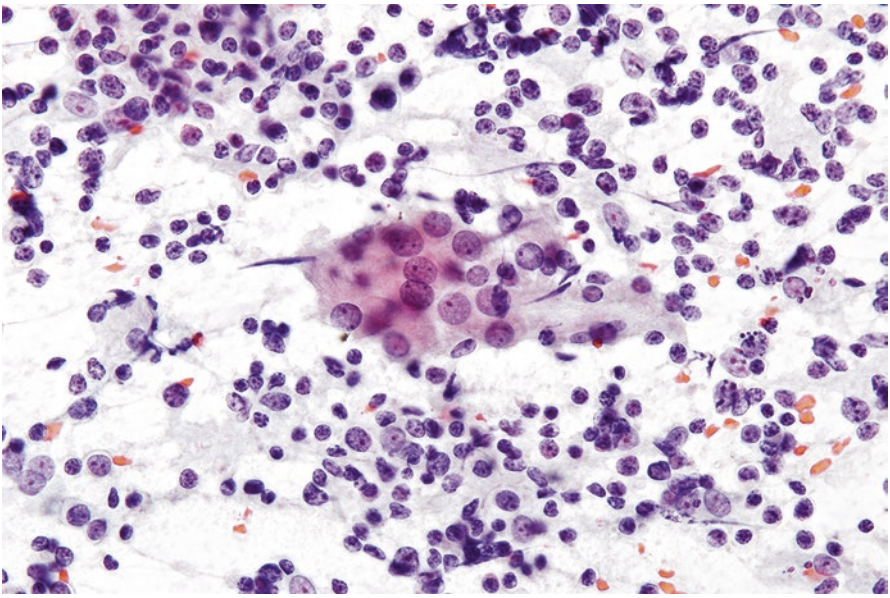

Fig. 7.4 Benign lymphocytes mixed with cluster of benign follicular cells in chronic lymphocytic thyroiditis

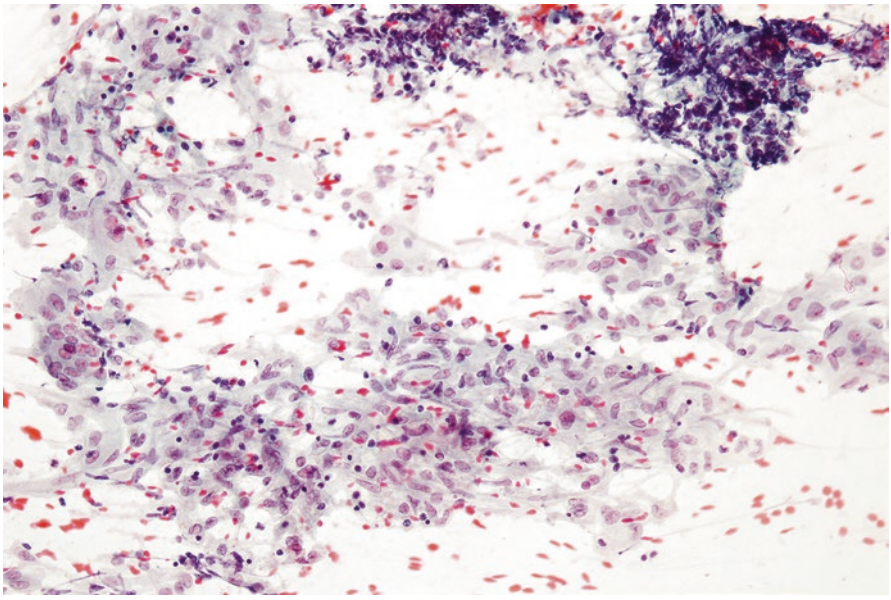

Fig. 7.5 Granulomatous inflammation characterized by clusters of epithelioid histiocytes

appearance of papillary thyroid carcinoma. An abundance of lymphocytes usually merits caution when observing this degree of atypia which may represent reactive changes. Clusters of Hurthle (oncocytic) cells can be seen in chronic lymphocytic thyroiditis and are typically seen in aspirates of Hashimoto's thyroiditis. A variety of granulomatous diseases can involve the thyroid including de Quervain's thyroiditis or infection by *Mycobacterium* or fungal organisms (Fig. 7.5). When a predominance of histiocytes is seen, careful attention should be given to exclude rare histiocytic neoplasms such as Langerhans cell histiocytosis and Rosai-Dorfman disease (Fig. 7.6). Abscesses can occasionally involve the thyroid, which show an abundance of neutrophils on smears (Fig. 7.7).

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) is the most common malignant thyroid tumor representing approximately 80% of all thyroid malignancies. PTC is the most common pediatric thyroid malignancy and among adults occurs mostly in women. Histologically, papillary thyroid carcinomas may show papillary, solid, or follicular architecture. Some forms of papillary thyroid carcinoma may contain abundant granular and eosinophilic cytoplasm such as tall cell, oncocytic, and hobnail variants of PTC. Lamellar calcifications called psammoma bodies may be present and are more frequent in cases showing classical papillary architecture. While relatively

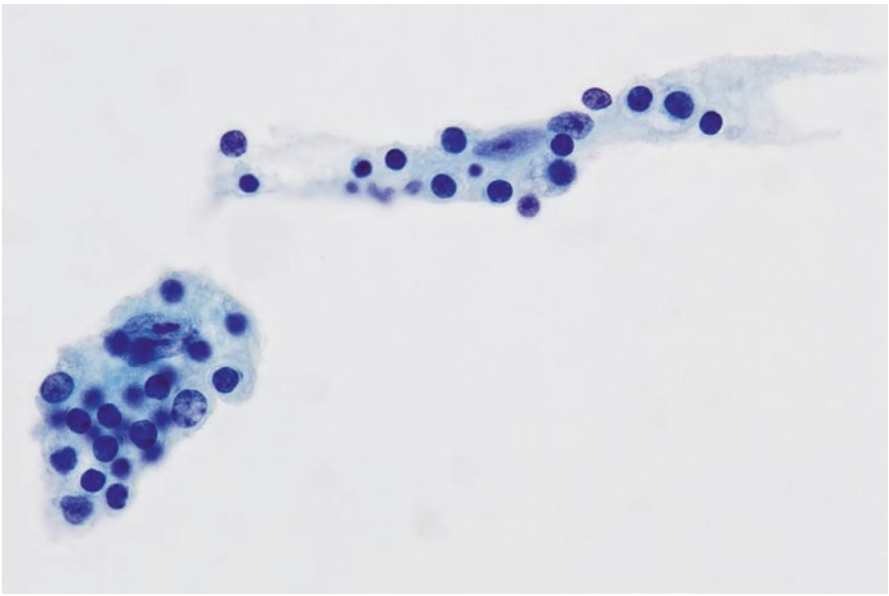

Fig. 7.6 Histiocytes in Rosai-Dorfman disease showing emperipolesis

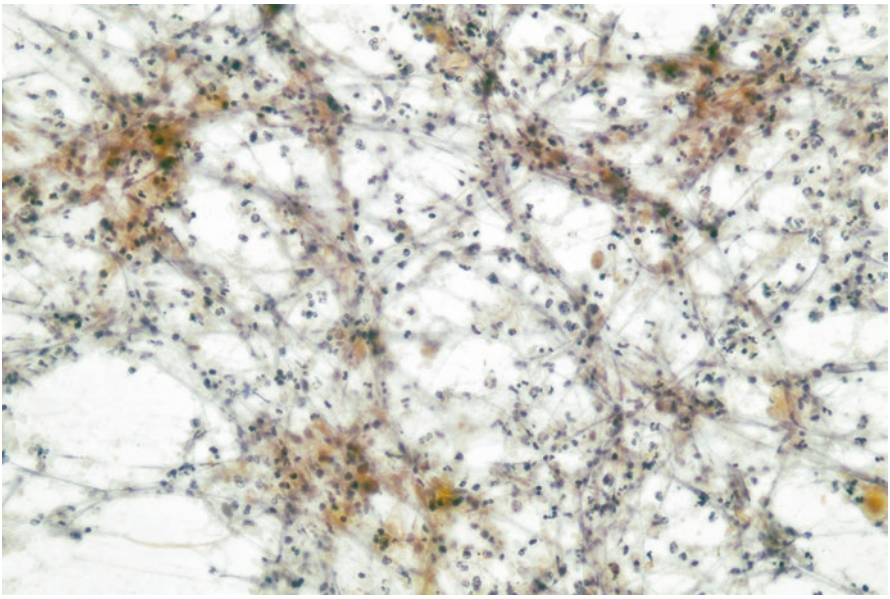

Fig. 7.7 Abundant neutrophils from an abscess of the thyroid

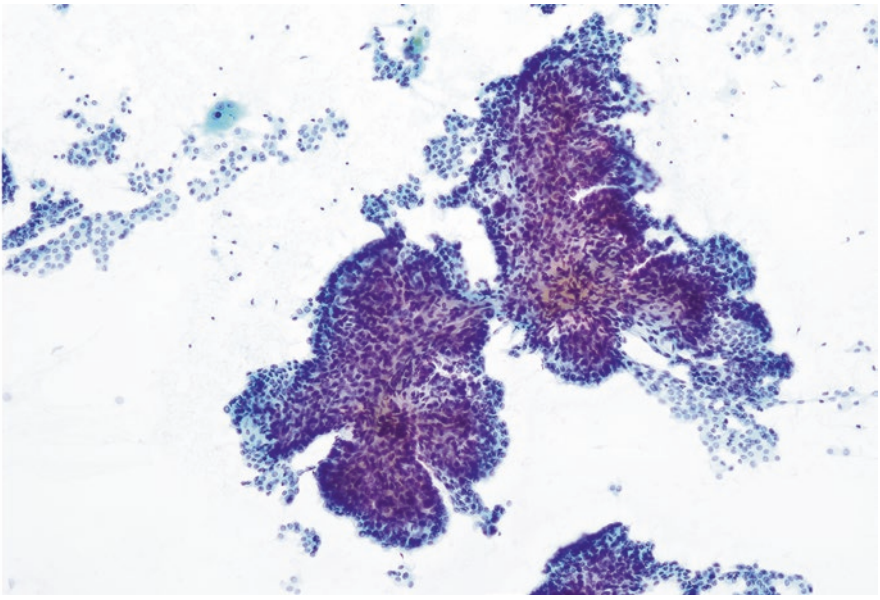

Fig. 7.8 Papillary clusters of papillary thyroid carcinoma

diverse architectural patterns can be seen among papillary thyroid carcinomas, greater unity can be seen in its cytologic features. In particular, characteristic nuclear features are seen in most cases of papillary thyroid carcinoma.

Aspirates of papillary thyroid carcinoma usually produce cellular smears. Colloid is usually sparse or absent. The cellularity can even be appreciated before microscopic examination while the smears are being prepared. The smears of papillary thyroid carcinoma are frequently granular, producing a gritty sensation when the smears are being made. This contrast with FNAs is predominated by colloid in which the aspirated material spreads smoothly on the slides and shows a glistening quality. Microscopically, a well-sampled papillary thyroid carcinoma shows numerous clusters of follicular cells spread across the slide. Single cells can be seen, but numerous other diagnostic possibilities should be excluded such as medullary thyroid carcinoma. When colloid is present, it may have a dense "bubblegum"-like quality. Care should be taken to not confuse dense colloid with amyloid which would raise the possibility of amyloidosis or medullary thyroid carcinoma. Clusters in PTC may appear flat or rounded and may show a trabecular or branched appearance. Papillae may be seen with a characteristic central fibrovascular core (Fig. 7.8). In some cases the tips of the papillae may become detached having the appearance of caps. Small follicular groups can also be seen and may predominate simulating the appearance of a follicular neoplasm. Histiocytes and multinucleated giant cells may also be seen. Giant cells with a twisted appearance or scalloped edges are frequently associated with papillary thyroid carcinoma. In cases where follicular cells are infrequent or absent, the presence of such giant cells may merit a comment in

the report to alert the clinician about the possibility of papillary thyroid carcinoma. Psammoma bodies, when identified, are a worrisome feature for papillary thyroid carcinoma. However, the presence of psammoma bodies alone is not specific for PTC and can also be seen in nodular hyperplasia, chronic lymphocytic thyroiditis, and Hurthle cell neoplasms [31, 32]. The tumor cells of PTC can show a variety of shapes including polygonal, cuboidal, or columnar contours. The cytoplasm varies from delicate and histiocytoid to dense and squamoid. Squamous metaplasia may be seen in papillary thyroid carcinoma, especially after prior biopsy or as a result of infarction. Squamous metaplasia may be accompanied by larger and more irregular nuclei than seen in typical PTC. This can sometimes create confusion with anaplastic thyroid carcinoma or metastatic squamous cell carcinoma from other sites. Knowledge of the clinical history including any prior biopsies performed in the thyroid may assist in raising the possibility of squamous metaplasia. In addition, while squamous metaplasia in PTC may have more cytologic atypia than usual PTC, the level of pleomorphism and nuclear atypia is usually far less than seen with anaplastic thyroid carcinoma or squamous cell carcinoma. The nuclei in squamous metaplasia may retain some similarities to usual PTC such as fine chromatin, grooves, or rare pseudoinclusions. It should be noted that squamous metaplasia can also involve benign thyroid follicles, especially in the setting of a cyst or after prior FNA.

The nuclei in papillary thyroid carcinoma have shared features across most of the variants of PTC. On low power, the nuclei of PTC usually overlap, departing from the honeycombed appearance seen in benign thyroid aspirates. In some cases, the nuclei have an ovoid appearance, overlapping along the tips of the long axis of the nuclei (head-to-tail). This may create the appearance of nuclear streaming. In the most dramatic examples, the streaming nuclei form distinctive whorls (Fig. 7.9). The chromatin may appear fine and powdery or may have a ground-glass appearance. Nuclear membranes frequently show irregularities that manifest as nuclear grooves and pseudoinclusions (Fig. 7.10). In addition, rather than having a smooth appearance, the nuclear membranes may show clefts or sawtooth-like irregularities. The nuclear membranes usually appear thicker compared to the nuclei in benign follicular clusters due to margination of the chromatin. While it should be noted that grooves and pseudoinclusions are characteristics of PTC, they are not completely specific for PTC. Pseudoinclusions can sometimes be seen in other benign and malignant thyroid tumors and rarely can occur in nonneoplastic thyroid conditions [33]. Therefore, the diagnosis of PTC rests on a collection of observations and not on any one single criteria alone. Numerous pseudoinclusions can be seen in hyalinizing trabecular tumor. Aspirates of this benign tumor can have clusters showing enlarged overlapping nuclei with fine chromatin, grooves, and pseudoinclusions [34]. The number of pseudoinclusions usually far exceeds what is usually seen in PTC which can be a clue to the diagnosis. Other features include cells with fusiform contours containing oncocytic cytoplasm arranged in trabecular aggregates. Fragments of hyalinized stromal tissue (best seen on Diff-Quik), closely associated with the abovementioned clusters, are an additional useful clue.

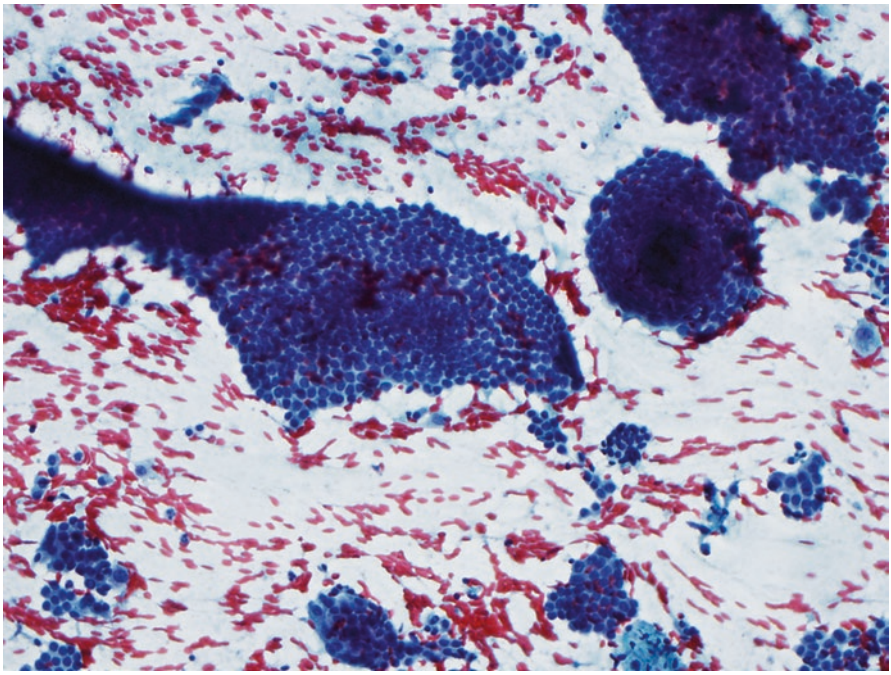

Fig. 7.9 Papillary thyroid carcinoma showing whorled clusters of follicular cells

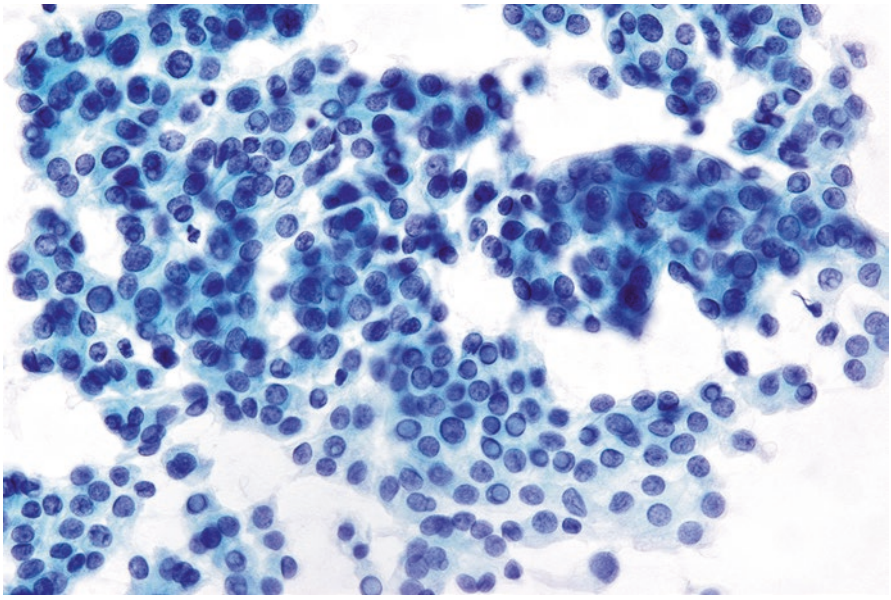

Fig. 7.10 Clusters of follicular cells from papillary thyroid carcinoma showing several nuclear pseudoinclusions

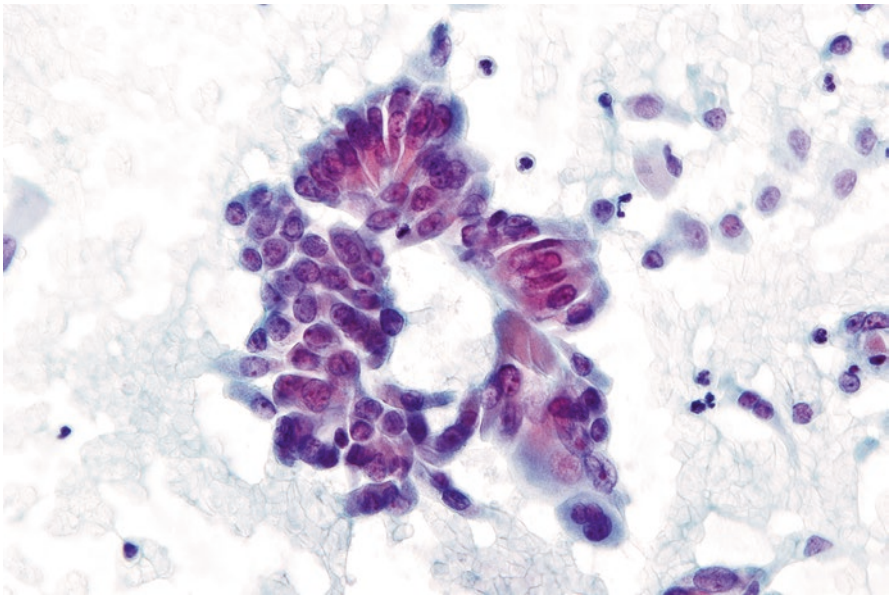

Fig. 7.11 Cluster seen on the edge from tall cell variant of papillary thyroid carcinoma

Variants of papillary thyroid carcinoma have features that may be discernable by FNA. The cells of the tall cell variant of papillary thyroid carcinoma contain abundant granular cytoplasm and distinct cell borders. When seen on the edge, the abundant apical cytoplasm can be observed (Fig. 7.11). The tall cell variant of PTC may appear similar to Hurthle cell neoplasms. The presence of typical PTC nuclear features can help discriminate these two possibilities [35]. The columnar cell variant (CMV) of papillary thyroid carcinoma shows features that can resemble endometrioid or colorectal adenocarcinoma. Aspirates of CMV can show pseudostratified nuclei resembling a picket fence arrangement [36]. However, nuclear grooves are infrequent, and pseudoinclusions are usually absent. The diffuse sclerosing variant (DSV) of papillary thyroid carcinoma is observed mostly within the pediatric age range. Cytologically, in addition to the classic nuclear features seen with classical PTC, clusters of tumor cell showing squamous metaplasia are frequent in DSV. In addition, numerous psammoma bodies are observed. Many lymphocytes can be seen in the background of aspirates from DSV, which may cause diagnostic confusion with reactive changes associated with chronic lymphocytic thyroiditis. The follicular variant (FV) of papillary thyroid carcinoma can be difficult to diagnose on fine needle aspiration. For infiltrative types of FV, the cytological features are usually indistinguishable from classic PTC. However, the encapsulated follicular variant of PTC often shows less obvious nuclear features. Pseudoinclusions are usually absent, and nuclear grooves are less frequent than classical PTC. Aspiration specimens from the encapsulated follicular variant of PTC can mimic the appearance of follicular neoplasms or have atypical features that might be ascribed to the AUS/

FLUS category. As mentioned earlier, a recent consensus has suggested that the noninvasive encapsulated FV be renamed the noninvasive follicular thyroid neoplasm with papillary-like features (NIFTP). Indeed, the encapsulated noninvasive follicular variant of PTC (now NIFTP) has more similarities to follicular neoplasms than PTC on both a molecular and clinical level. The new proposed nomenclature will most likely affect the risk of malignancy associated with class III and IV FNAs to some degree.

Follicular Neoplasms

Assessment of follicular nodules is one of the most diagnostically challenging areas in thyroid pathology. The histological distinction between a hyperplastic nodule and follicular neoplasm is based on whether the tumor has a capsule as well as distinct cytology and architecture from the surrounding. However, these features are somewhat arbitrary as all the abovementioned features have broad zones of overlap between follicular neoplasms and hyperplastic nodules. The distinction between follicular adenoma and follicular carcinoma is based solely on the presence or absence of invasive features. For the cytopathologist, this means there are no reliable features to distinguish between follicular adenoma and follicular carcinoma. The diagnosis of suspicious for follicular neoplasm or suggestive of follicular neoplasm is usually the greatest level of certainty that cytopathologist can render for this tumor type. Patients with this diagnosis may be referred to surgery in order to determine if the tumor is benign or malignant histologically.

Aspirates of follicular neoplasms can be hypercellular compared to hyperplastic thyroid nodules. However, the suspicion of follicular neoplasm should not rest on cellularity alone as cellular hyperplastic nodules can also produce hypercellular smears. If the increased cellularity is accompanied by the absence of colloid, this usually raises the concern for a neoplasm, and the possibility of a follicular neoplasm can be considered. In aspirates of follicular neoplasms, the follicular cells may be arranged in small ringlike clusters of 6–12 follicular cells called microfollicles (Fig. 7.12). When the smears are comprised of mostly microfollicles with absent or only spare colloid in the background, the risk of a follicular neoplasm is higher. Care should be taken to avoid overdiagnosing macrofollicles disrupted by shearing forces in smears as microfollicles. This artifact can be detected by observing the presence of the smaller clusters appearing to trail behind larger macrofollicular clusters. The disruption of macrofollicles into small microfollicle-like clusters is a relatively common artifact. If ample colloid is seen in the background, attention should be given to the possible presence of this artifact in order to avoid overcalling hyperplastic nodules as suspicious for follicular neoplasm. As some follicular neoplasms are hypervascular, abundant blood may herald the presence a follicular neoplasm. However, if the cellularity of the specimen is low, caution should be exercised as bloody aspirates may also signal poor aspiration technique or even the presence of a hematoma or vascular tumor.

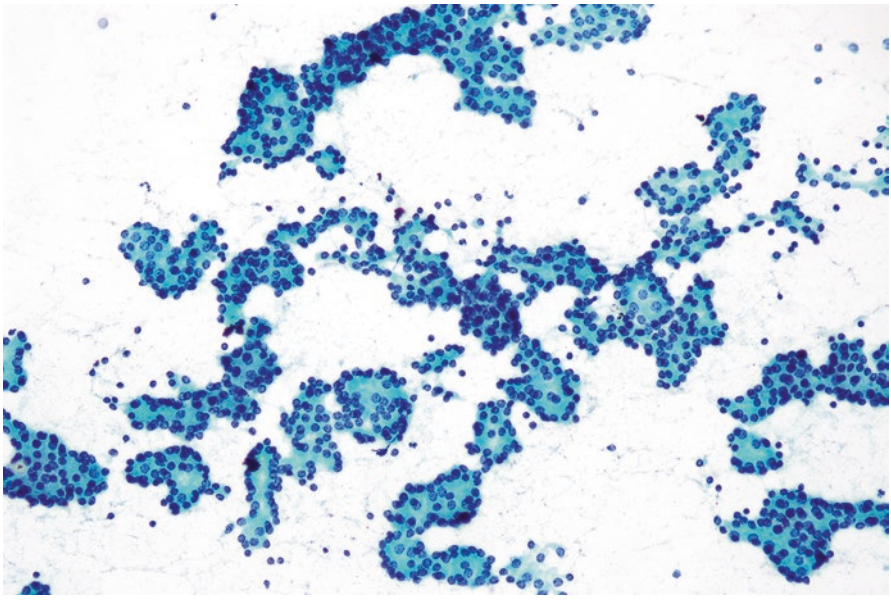

Fig. 7.12 Clusters of microfollicles, suspicious for a follicular neoplasm

Hurthle Cell Neoplasms

Hurthle (oncocytic) cell neoplasms are considered as a subtype of follicular neoplasms by the 2004 WHO. However, Hurtle cell carcinomas show distinct molecular abnormalities that may separate these tumors from follicular carcinomas [37]. In FNA specimens, Hurthle cell neoplasms are either exclusively or predominantly comprised of cells with abundant granular cytoplasm [38]. On Papanicolaou stains, the granularity imparts a deep blue color. The nuclei are enlarged and usually contain prominent central nucleoli. At times, the nuclei have relatively monomorphous shapes indicating a clonal appearance. However, significant nuclear size variation may be seen. Nuclear pleomorphism is not a sign of malignancy but rather can be seen in benign Hurthle cell neoplasms as well as nodular hyperplasia accompanied by Hurthle cell metaplasia. The nuclei may be eccentrically displaced imparting a plasmacytoid appearance (Fig. 7.13). Binucleated cells may be seen. The cells may be arranged as large clusters or microfollicles. Large clusters may have a three-dimensional appearance or appear as flat sheets. The cell clusters of Hurtle cell neoplasms show a tendency for less cohesion, with single cells present in the background. Moreover, some Hurtle cell neoplasm aspirates are dominated by single cells. When numerous single Hurthle cells are present, care should be taken to exclude the possibility of the oncocytic variant of medullary thyroid carcinoma, which can also show many single cells. In some cases the distinction can be subtle, and correlation with serum calcitonin levels may be required. Thin-walled blood vessels coursing through the tumor clusters, termed “transgressing vessels,” can be

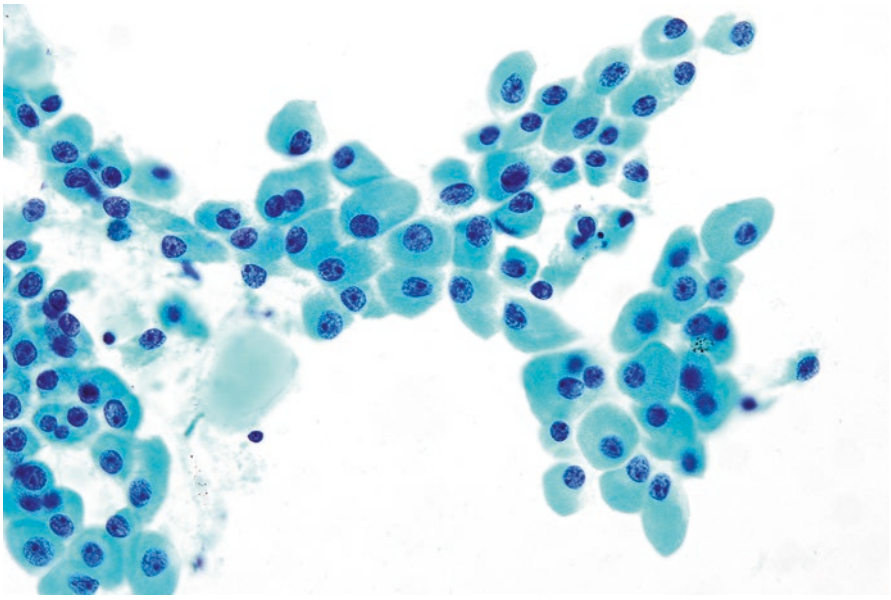

Fig. 7.13 Hurthle cells with abundant granular cytoplasm

seen. When present, transgressing vessels are considered relatively specific for Hurthle cell neoplasms [39]. Several authors have attempted to determine the distinguishing features of benign and malignant Hurthle cell neoplasms. However, as with follicular neoplasms, no reliable cryptologic features separate Hurthle cell adenomas from Hurthle cell carcinoma.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) represents approximately 10% of all thyroid malignancies. It arises from parafollicular C cells which maintain serum calcium homeostasis by the secretion of calcitonin. Medullary thyroid carcinoma can occur sporadically or in association with heritable genetic syndromes such as familial medullary thyroid carcinoma and multiple endocrine neoplasia types 2A and 2B. Fine needle aspirates of MTC can show a great degree of variability that can mimic other thyroid tumors. Smears usually show loosely cohesive aggregates and single cells. Single cells frequently predominate. The cells may have a variety of shapes including rounded, spindled, and triangular. Multinucleated tumor cells can also be present. All these shapes may be represented on a single aspirate. This variability can be an important clue to the diagnosis of MTC in conjunction with other findings [40]. Microfollicle-like clusters may be seen that can be mistaken for a follicular neoplasm. The cells contain moderately dense cytoplasm with granules

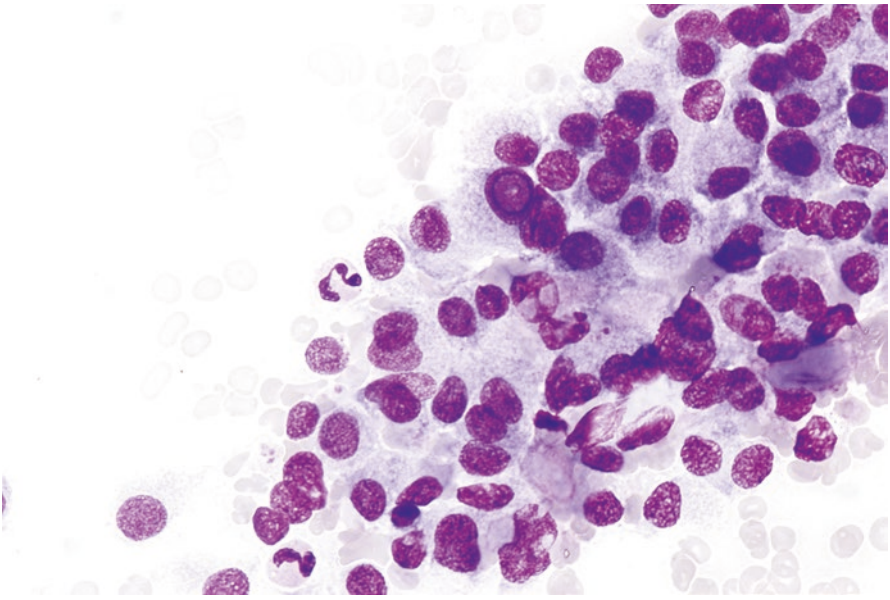

Fig. 7.14 Cells of medullary thyroid carcinoma showing stippled chromatin. Note the presence of a cell with a nuclear pseudoinclusion

that appear metachromatic on Diff-Quik stains. The nuclei are generally oval and may appear monomorphous; however, it is not uncommon to see at least scattered cells with markedly enlarged nuclei. This feature, called endocrine anaplasia, may cause confusion with higher-grade tumors such as anaplastic thyroid carcinoma. The nuclear chromatin of MTC appears granular which is commonly referred to as "salt-and-pepper chromatin." Nuclear pseudoinclusions can be observed in MTC, mimicking the appearance of papillary thyroid carcinoma (Fig. 7.14). As many MTCs are dominated by single cells, or loosely cohesive aggregates, the low power pattern of the smear can assist in avoiding this pitfall. Up to 80–85% of medullary thyroid carcinomas are associated with amyloid production composed of calcitonin or calcitonin-related peptide in most cases [41]. In aspirates this is seen as amorphous globular deposits that may be intimately associated with the tumor cells (Fig. 7.15). In most cases it is useful to have additional material for a cellblock preparation in order to perform immunohistochemical testing for calcitonin.

Poorly Differentiated Thyroid Carcinoma

Poorly differentiated (PD) thyroid carcinoma is a follicular cell-derived malignant thyroid neoplasm with a prognosis between well-differentiated thyroid carcinoma and anaplastic thyroid carcinoma. Histologically, PD thyroid carcinoma typically

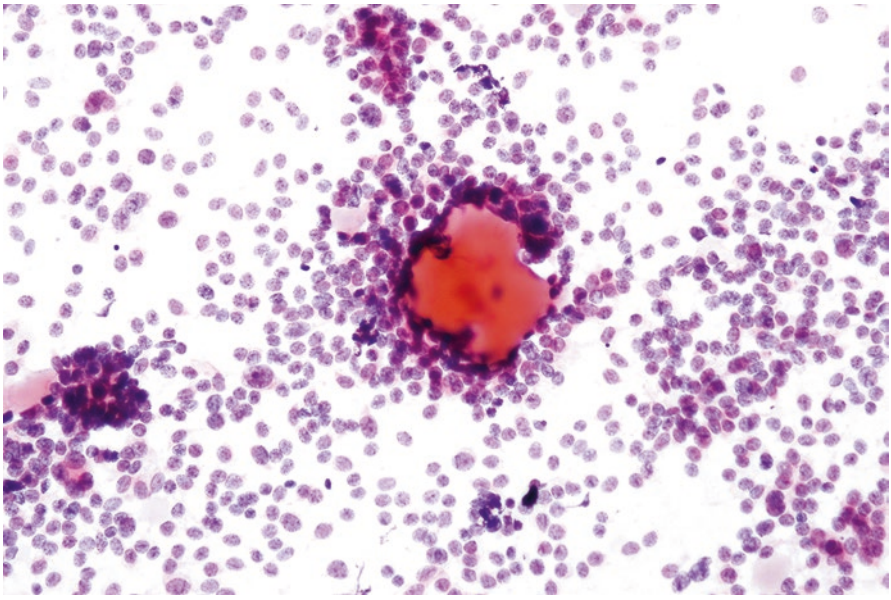

Fig. 7.15 Amyloid deposit seen centrally in the photograph

has an infiltrative growth pattern, solid architecture, and proliferative features including mitotic activity and necrosis. The classic form of PD is known as insular carcinoma. Smears from PD are highly cellular. Crowded groups of follicular cells are seen that can be arranged as large rounded clusters, microfollicles, and trabecular-appearing aggregates [42]. Many single cells can also be seen [43]. The cells contain enlarged, round, and dark nuclei imparting a high N/C ratio. The chromatin may appear granular or homogeneous. Nucleoli are inconspicuous. Mitotic figures and necrosis may be seen and when present can help distinguish PD from a follicular neoplasm. However, PD thyroid carcinoma may be difficult to distinguish from a follicular neoplasm, especially when microfollicles are numerous.

Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma (also called undifferentiated thyroid carcinoma) is a highly aggressive tumor that affects primarily people over the age of 60. Nearly all patients with anaplastic thyroid carcinoma succumb to the effects of extensive local invasion or metastasis within 1 year of the diagnosis. The clinical history of a rapidly enlarging thyroid-based mass in an older patient should raise concern for anaplastic thyroid carcinoma. Smears prepared from anaplastic thyroid carcinoma may be highly cellular; however, as many anaplastic thyroid carcinomas contain

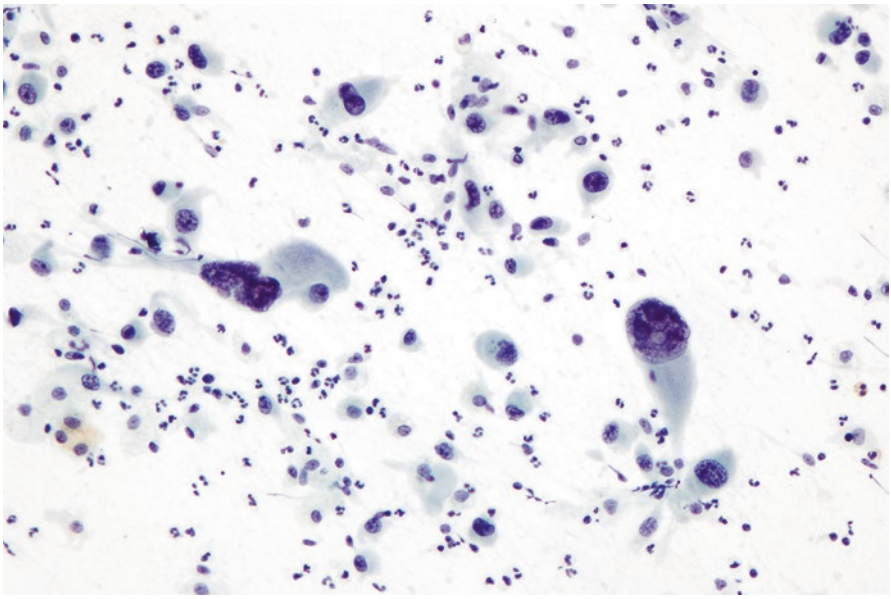

Fig. 7.16 Tumor cells showing marked nuclear pleomorphism and coarse chromatin characteristic of anaplastic thyroid carcinoma

abundant fibrosis, it may be difficult to obtain a cellular specimen. The tumor cells contain highly pleomorphic nuclei with prominent nucleoli (Fig. 7.16). The tumor cells may be arranged as irregular clusters or may appear as single cells. Mitotic figures, including atypical forms, may be seen. A variety of cell types can be seen in anaplastic thyroid carcinoma including epithelioid, epidermoid, giant cell, and spindled. Osteoclast-like giant cell may also be identified. Karyorrhectic nuclear debris, when identified, indicates the presence of necrosis. Frequently anaplastic thyroid carcinoma is associated with neutrophils that are intimately admixed with the tumor cells [44].

Lymphoma

Lymphoma accounts for 5% of all thyroid malignancies. Most lymphomas involving the thyroid are of non-Hodgkin B-cell lymphoma, the most common being diffuse large B-cell lymphoma (DLBCL). The second most common lymphoma occurring in the thyroid is extranodal marginal zone lymphoma. DLBCL lymphoma produces cellular smears comprised of mostly single cells with enlarged nuclei demonstrating coarse chromatin prominent nucleoli [45] (Fig. 7.17). Multiple irregular nucleoli may also be seen. As the cytoplasm of the tumor cells are delicate, fragments of cytoplasmic debris called lymphoglandular bodies are frequently present in the

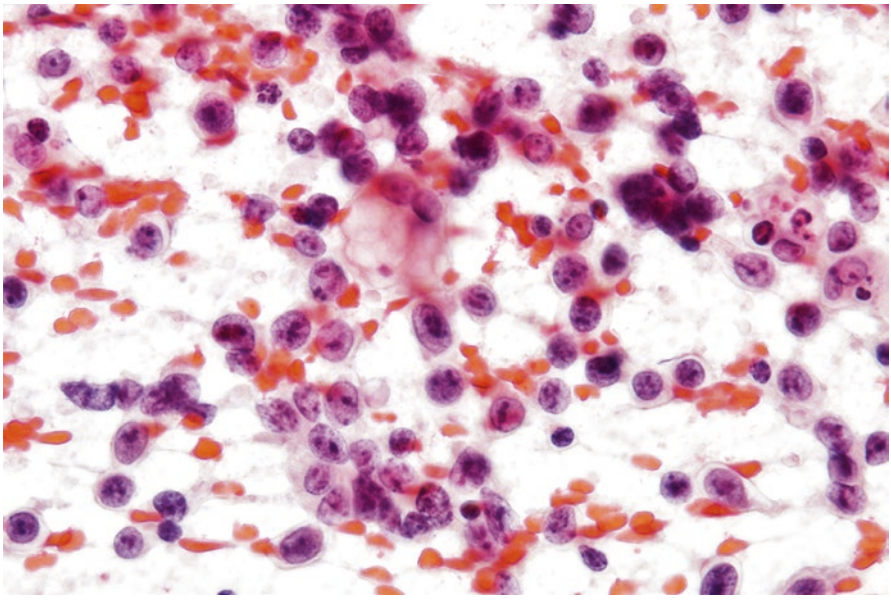

Fig. 7.17 Cells from diffuse large B-cell lymphoma with coarse chromatin and multiple nucleoli

background. Extranodal marginal zone lymphoma can be difficult to appreciate on cytology specimens since aspirates tend to show a more heterogeneous population of lymphocytes that overlaps with the appearance of a reactive lymph node or chronic lymphocytic thyroiditis. A clue to the diagnosis of extranodal marginal zone lymphoma is the predominance of small- to intermediate-sized lymphocytes with a monocytoid- or centrocyte-like appearance [46]. Variable numbers of plasma cells can be seen in the background, which, when numerous, can mimic plasmacytoma [47]. A diminished number of tangible body macrophages are usually observed in contrast with chronic lymphocytic thyroiditis. Cellblock or core biopsy material is usually required to confirm the diagnosis of lymphoma and for classification. Submission of material for flow cytometry may also be of great diagnostic utility.

Metastases

Metastases to the thyroid represent 5.7–7.5% of all malignant tumors involving the thyroid [48]. Many different types of malignancies can metastasize to the thyroid including carcinomas from various sites and sarcomas. In addition, direct spread of

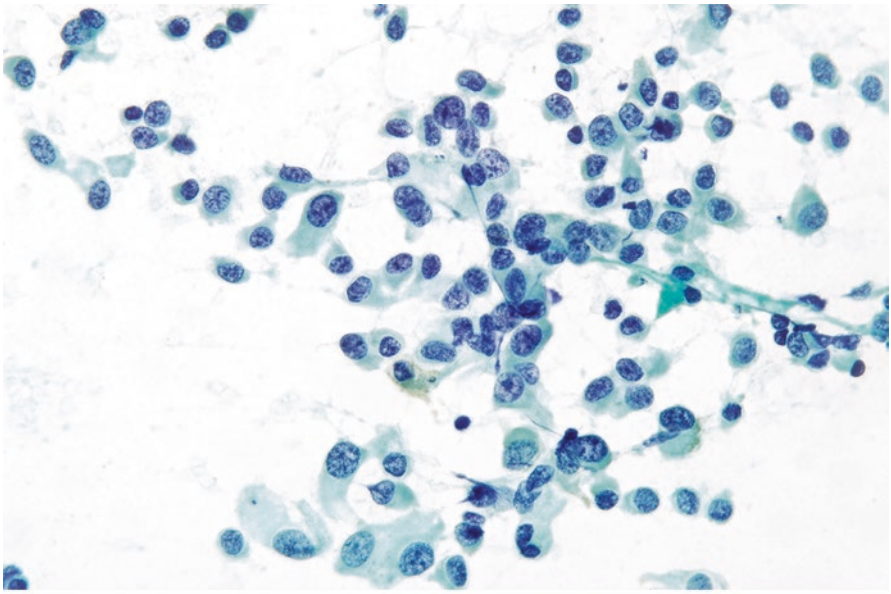

Fig. 7.18 Metastatic melanoma with rare pigmented cells

malignant tumors secondarily involving the thyroid can also occur. For instance, advanced laryngeal squamous cell carcinoma frequently invades into the thyroid gland. In FNA specimens, the presence of overtly malignant tumor cells mixed with clusters of benign follicular cells can serve as a clue to recognizing a metastasis. Metastatic malignant melanoma is relatively straightforward to recognize when melanin pigment is present. However, metastatic melanoma that lacks pigmentation can be mistaken for primary thyroid tumors. As some melanomas produce cells with a plasmacytoid appearance, the morphology can be confused with medullary thyroid carcinoma (Fig. 7.18). Usually, medullary thyroid carcinoma shows at least some cells with characteristic "salt-and-pepper" chromatin. In addition, immunostains performed on cellblock material (if available) will reliably identify melanoma in most cases. Metastatic renal cell carcinoma represents 22% of all metastases to the thyroid gland in a large series from the Mayo Clinic [49]. The presence of cells with abundant pale to clear cytoplasm may be a clue to the diagnosis; however, renal cell carcinoma may be difficult to distinguish from primary thyroid neoplasms (Fig. 7.19). Knowledge of the clinical history and ancillary immunohistochemical testing may be required to confirm the diagnosis of metastatic renal cell carcinoma.

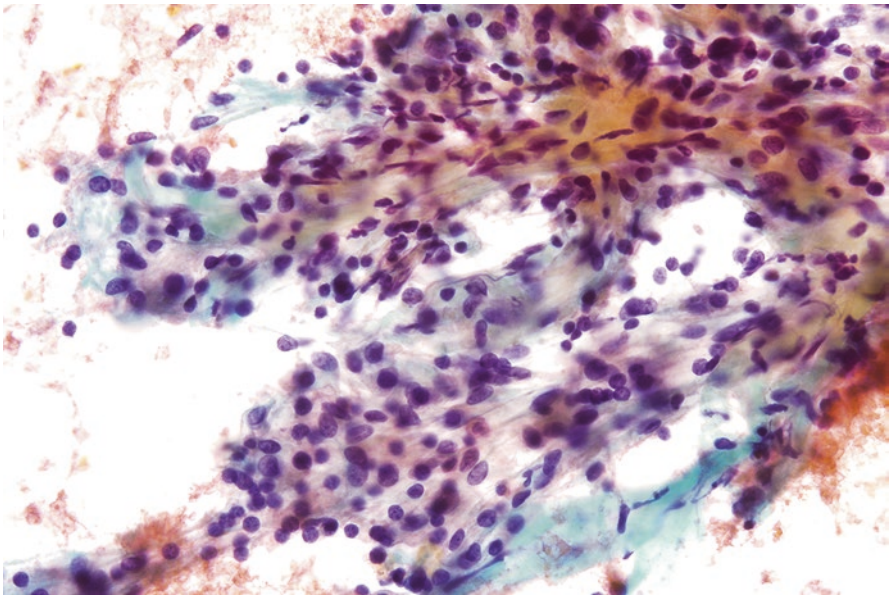

Fig. 7.19 Metastatic renal cell carcinoma showing cells with clear cytoplasm

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Chapter 8
Molecular Markers and Thyroid Nodule Evaluation

Trevor E. Angell, Matthew I. Kim, and Erik K. Alexander

Introduction

Thyroid nodules are common, and incidental detection is increasingly prevalent. While nodules are most often asymptomatic and benign, the guiding clinical concern is the risk of possible thyroid carcinoma. Numerous studies from large nodule populations confirm the risk of malignancy to be approximately 8–15%. Thus, the principle goal of thyroid nodule evaluation is to accurately, efficiently, and safely determine which nodules are benign and which are cancerous, ideally through a simple and cost-effective process. Over the past 30 years, this clinical care paradigm has evolved to address limitations while seeking to improve care.

The approach to thyroid nodule evaluation is multidisciplinary, integrating radiologic, cytologic, clinical, and molecular analysis. No single means of evaluation can effectively determine if a nodule represents benign or malignant disease with high accuracy. However, an integrated approach provides a more accurate means of cancer detection. Most recently, this accuracy has been improved through our understanding that specific molecular markers or molecular profiles of thyroid nodules correlate with benign or malignant disease. The clinical application of these markers has reduced unnecessary surgery while enhancing understanding of individualized prognosis.

Molecular analysis is a broad term, encompassing many different types of molecular testing. Specific mutations in cellular DNA reflect a base pair change or gene translocation that affects the function of an oncogenic pathway. Messenger RNA (mRNA) expression profiles identify patterns of multiple expressed genes that

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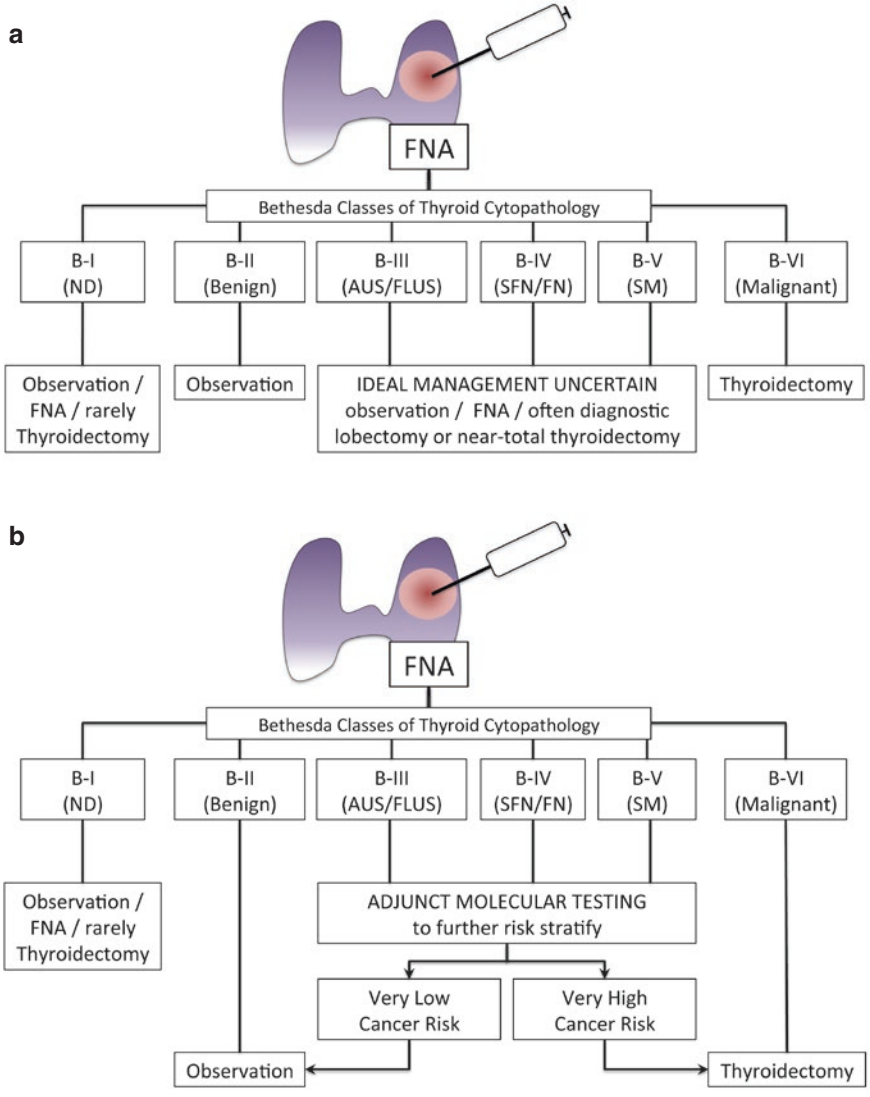
correspond to benign or malignant processes. MicroRNA are small non-translated modifiers of mRNA expression and translation, and individual or groups of microRNA may show differential levels of expression in benign or malignant processes. Finally, evaluation by immunohistochemistry (IHC) can determine the presence (or absence) at the cellular level of expressed proteins that are associated with benign or malignant disease. These four categories represent diverse and distinct mechanisms of molecular diagnostic testing, and each has shown the ability to assist in the clinical care of affected patients.

This chapter will review the typical approach to thyroid nodule evaluation. In euthyroid individuals, ultrasound (US) evaluation and ultrasound-guided FNA (UG-FNA) remain the principle first step of evaluation. However, a substantial limitation to this approach surrounds the 20–25% of nodules that prove to have indeterminate cytology. Traditionally, this finding has most often led to diagnostic surgery. The use of molecular markers has significantly addressed this shortcoming, allowing improved preoperative risk assessment (shown in Fig. 8.1). Through this, unnecessary surgery for benign nodules has been reduced. This chapter will conclude with discussion of forward-looking areas of necessary research, as we seek to expand our knowledge of this increasingly common disease.

Fig. 8.1 Management of a thyroid nodule based on fine needle aspiration biopsy results. (**a**) Historical management decisions for thyroid nodules: fine needle aspiration (FNA) biopsy provides a thyroid tissue specimen for cytopathologic evaluation and placement into one of six categories according to the Bethesda system for reporting thyroid cytopathology, which imply specific risk of malignancy. Benign and malignant cytologies are considered sufficiently accurate to recommend nodule observation or thyroidectomy, in these two situations, respectively. For nodules that are indeterminate, considered to be Bethesda classes III (AUS/FLUS), IV (SFN/FN), and V (suspicious for malignancy), the optimal management remains uncertain. In the former two categories, malignancy risk is low but not excluded, and observation may miss a clinically relevant malignancy, while surgical resection may be unnecessary. For nodules with Bethesda V cytology, malignant risk is often sufficiently high to warrant surgical resection (60–70%), but the extent of surgery (lobectomy versus near-total thyroidectomy) is uncertain. Nodules with non-diagnostic (ND) cytology are low risk (1–4% cancer risk) and can typically be managed non-operatively, though a subset of repeatedly ND nodules will be removed. (**b**) Current recommended schema of thyroid nodule management using adjunct molecular testing: for nodules with indeterminate cytologies, further evaluation with molecular testing allows for classification as low or high risk for malignancy. When test performance has been shown in prospective, multicenter, blinded validation studies to have a sufficiently high negative predictive value (NPV), indicating a very low chance of a "false-negative" or missed cancer, nodule observation can be selected in lieu of diagnostic lobectomy avoiding an unnecessary surgery. Conversely, when a test with very high positive predictive value (PPV) indicates the presence of cancer, thyroidectomy is indicated, and near-total thyroidectomy as initial surgery rather than diagnostic lobectomy may be appropriately performed. The management of ND, benign, and malignant nodules is unchanged with current molecular testing. *B* = Bethesda classification. *Dx* = diagnostic. *AUS/FLUS* = atypia of undetermined significance/follicular lesion on undetermined significance. *SFN* = suspicious for follicular neoplasm/follicular neoplasm. *SM* = suspicious for malignancy

The Approach to Thyroid Nodules

Most thyroid nodules are asymptomatic except as a palpable mass detected by the patient or medical practitioner, and may be discovered incidentally by cross-section imaging [1, 2]. Most recent large series of consecutive nodules suggest that approximately 8–15% of thyroid nodules will prove to be malignant [3–5]. Clinical factors such as sex, age [6], childhood exposure to ionizing radiation [7], and rarely symptoms or palpable lymphadenopathy are present that increase the possibility that a



thyroid nodule will be malignant. Thus, a full medical history and physical examination should be obtained on all patients who present for evaluation of a thyroid nodule.

Ultrasound is the optimal imaging technique for thyroid nodule evaluation. Beyond measurement of nodule size, sonographic features can assist with nodule risk assessment [8]. However, low to moderate inter-rater reproducibility of findings limits the precision and accuracy of interpretation [9]. For this reason, UG-FNA to obtain material for cytopathologic evaluation is recommended for most thyroid nodules larger than 1–2 cm [10]. Although there is high diagnostic accuracy of benign and malignant cytology, ~20–25% of aspirates will be cellularly sufficient but cytologically indeterminate. The Bethesda classification system effectively subdivides indeterminate cytologic findings into distinct categories associated with escalating risk of malignancy that improve the ability of clinicians to stratify the risk of thyroid malignancy [11–14], but inter-rater and intra-rater reliability of cytologic interpretation remains poor [15].

Because the risk of thyroid malignancy is generally low but not excluded in these cases, key considerations are whether such a nodule can be monitored conservatively or should be surgically removed and what extent of surgery (thyroid lobectomy or near-total thyroidectomy) is most appropriate [10, 16, 17]. These options carry risks and benefits, and the optimal management remains uncertain, in part, because of the limitations inherent to the clinical, sonographic, and cytologic assessments described above, indicating the need for synergistic forms of assessment, such as molecular testing, for such nodules.

Molecular analysis of nodular tissue has proved highly valuable. As price points for these diagnostic tests have fallen, cost-effectiveness analyses also suggest that the use of diagnostic molecular tests may reduce cost while improving quality-adjusted life years [18, 19]. Thus, the approach to cytologically indeterminate thyroid nodules is increasingly employing molecular diagnostic testing. Below, we provide a description of the molecular markers thus far evaluated for use in the care of patients with clinically relevant thyroid nodules.

Molecular Markers

A molecular marker assessed on fine needle aspiration material from a thyroid nodule biopsy may target one of many cellular constituents, such as expressed proteins, RNA, or DNA, measured either quantitatively or qualitatively using specific laboratory techniques. Some of the earliest investigations of molecular markers utilized IHC techniques on slides prepared from aspiration material to identify expressed proteins differentiating benign from malignant nodules. The identification of prevalent oncogenic mutations/translocations in thyroid cancer, including *BRAF*, *RAS*, and *RET/PTC*, led to intense focus on the DNA alterations in thyroid cancer, followed closely by advanced nucleic acid sequencing techniques allowing expression profiling of mRNA or microRNA, all of which have been investigated as molecular

markers for thyroid nodule evaluation. Limitations inherent with the use of any single molecular marker have in some cases spawned the use of combinations of molecular tests improving test accuracy.

In each case, the process begins with identifying a possible molecular marker and creating a laboratory test to reliably detect it, which allows understanding of the test's analytic validity. How well the marker discriminates benign from malignant nodules, especially in clinical practice, determines the test's clinical validity. Whether or not knowing molecular marker status changes patient management when incorporated into clinical decision-making establishes its clinical utility and is important for determining the clinical value of the testing. Finally, the cost-effectiveness of using the molecular tests compared to other management requires evaluation within any large healthcare framework. Each of these aspects must be considered in the evaluation of a molecular marker as it is applied to clinical medicine. While the molecular markers described in this chapter (Table 8.1) have largely shown consistent analytic performance, the clinical validity, clinical utility and cost-effectiveness frequently remain unknown.

Galectin-3

Galectin-3 is a lectin that binds to cell surface glycoproteins and interacts with intracellular proteins regulating cellular functioning including cell growth, apoptosis, and malignant transformation [20]. Its presence has been measured by IHC using a monoclonal antibody targeting galectin-3 on formalin-fixed and paraffin-embedded (FFPE) cellblock preparations from thyroid nodule aspires. Early investigations found that galectin-3 expression correlated strongly with thyroid cancers compared to benign specimens [21, 22].

Table 8.1 Molecular markers

Immunohistochemistry
Galectin-3
HBME-1
CK19
Mutations and gene rerrangements
BRAF (V600E)
RAS (H-RAS, K-RAS, N-RAS)
RET/PTC (RET/PTC1, RET/PTC3)
PAX8/PPARγ
Asuragen miRInform™ thyroid panel
ThyroSeq v2 panel
Gene expression and microarray analysis
MicroRNA expression
Afirma® gene expression classifier

Assessment of galectin-3 as a clinical test to improve diagnostic accuracy in cytologically indeterminate thyroid nodules has been performed. In a large multicenter prospective study, galectin-3 expression was assessed in 465 nodules with indeterminate cytology with histopathology available for blinded review and showed a sensitivity of 78% and specificity of 93%, yielding an 82% positive predictive value (PPV) and a 91% negative predictive value (NPV) in this population of patients [23]. While galectin-3 remains a marker of interest, there has not been more extensive validation of the test or robust data on how testing effects clinical care, and its initial performance has not been replicated. For these reasons, as well as the interpreter subjectivity surrounding its use, galectin-3 has shown greater promise in histopathologic assessment as opposed to cytologic assessment.

HBME-1

HBME-1 (Hector Battifora Mesothelial-1) is a monoclonal antibody targeting the microvilli of mesothelioma cells. However, the antigen recognized by HBME-1 has also been detected on differentiated thyroid cancer cells, leading to its development as a molecular marker for assessing malignancy risk. HBME-1 is measured by IHC on FFPE specimens. Preliminary studies evaluating HBME-1 on cytologically indeterminate thyroid nodules have shown moderate test performance, with sensitivity 79–94%, specificity 83–94%, PPV 84–94%, and NPV 80–94% [24, 25], but these have not been reproduced in prospective, multicenter, blinded investigations, and thus, validation of HBME-1 staining in such a population of indeterminate thyroid nodules remains to be seen.

CK19

Cytokeratin-19 (CK19) is a cytoskeleton component of epithelial cells that may be upregulated in well-differentiated thyroid cancer [26]. In one study of cytologically indeterminate nodules, most nodules ultimately proven to be papillary thyroid carcinoma stained positive for CK19; however, there was extensive overlap in CK19 expression between benign follicular adenomas and follicular thyroid carcinomas [27]. There are no high-quality data that support the sole use of CK19 as a single molecular marker at this time.

Combined Immunohistochemical Panels

Because of the limitations of individual protein markers, further studies have evaluated the potential for improved diagnostic accuracy when such markers are combined. An assessment of galectin-3 and HBME-1 together showed a PPV and NPV of 76.9%

and 96.9% when the markers were concordant in their result [28]. Several studies have utilized the combinations of galectin-3, HBME-1, and CK19 [27, 29–31]. The largest of these evaluating 125 thyroid nodule FNA samples demonstrated an increase in sensitivity from 92% to 97% but a decrease in specificity from 96% to 80% compared to the performance of any marker in isolation [27]. Alternative targets have been included in separate panels of protein markers. One retrospective evaluation combining galectin-3, HBME-1, and CXCR4 showed little improvement compared to HBME-1 testing alone [25]. There have been no robust confirmatory data from large-scale clinical trials to validate these findings.

Mutations and Gene Rearrangements

The discovery of oncogenic mutations and gene rearrangements in thyroid cancers revealed that a significant percentage contain one of a small number of "driver" oncogenic events. Assessment of these mutations and translocations as a "rule-in" test for malignancy for indeterminate thyroid nodules soon followed. As our knowledge of the genetic landscape of thyroid cancer has grown, such molecular tests have evolved from detecting single mutations to assessing combinations of known genetic alterations.

BRAF

The *BRAF* gene encodes for the protein BRAF, a serine/threonine protein kinase in the MAPK pathway involved in many cellular processes including cell proliferation, differentiation, and apoptosis [32]. The most relevant *BRAF* mutation seen in thyroid cancers encodes for a mutated protein with a glutamic acid for valine substitution at position 600 (V600E) that causes unregulated kinase activation. BRAFV600E is the most common mutational event in classical PTC and is present in a significant minority of tumors classified as the follicular variant of papillary thyroid carcinoma (fvPTC) [33, 34]. Since this *BRAF* mutation is not present in benign thyroid disease, detection in FNA material essentially confirms the presence of thyroid cancer. *BRAF* mutations are less frequent in fvPTC and have a very low prevalence of 1–2% in follicular thyroid carcinoma (FTC). It lacks sufficient sensitivity to be a sole molecular marker for evaluating indeterminate nodules [35], especially because most BRAF-positive papillary thyroid carcinomas will demonstrate cytology that is "positive" or diagnostic of carcinoma (as opposed to cytologically indeterminate). Thyroid cancers harboring the BRAFV600E mutation are associated with a higher risk of extrathyroidal extension, lymph node metastasis, tumor recurrence, and patient mortality, and therefore, its presence may indicate the need for more aggressive initial therapy, though more data are needed to support specific treatment recommendations [35–37].

RAS

The *RAS* oncogene family is comprised of three genes (*H-RAS*, *K-RAS*, and *N-RAS*) that encode small GTPase proteins involved in signal transduction. Activating mutations of these genes stimulate the MAPK and phosphatidyl-3-inositol pathways that regulate cell growth, proliferation, differentiation, mobility, and survival [38]. *RAS* mutations are detected in up to 40% of differentiated thyroid cancers, occurring most often in fvPTC, noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFT-P), and FTC [30], but are also present in benign thyroid lesions, such as follicular adenomas [39, 40] similarly making *RAS* status suboptimal as a single molecular marker. It may be that the presence of a *RAS* mutation portends a risk of malignant transformation, suggesting that resection of a thyroid nodule on the basis of a *RAS* mutation may still be appropriate [41]. However, data showing the stability and lack of malignant transformation of cytologically benign yet *RAS* mutation-positive thyroid nodules during long-term sonographic monitoring does not support this [42].

RET/PTC and PAX8/PPARγ Translocations

The *RET* proto-oncogene encodes a receptor tyrosine kinase that has been found to undergo intrachromosomal gene rearrangements forming fusion genes in differentiated thyroid cancer. The *RET/PTC1* and *RET/PTC3* gene rearrangements produce constitutively active kinase activity that stimulates the MAPK and phosphatidyl-3-inositol pathways [43]. Because of its relative rarity compared to *BRAF* or *RAS* mutations and the overlap with benign thyroid neoplasms, testing for these translocations has limited value in isolation [44].

Another interchromosomal gene rearrangement linking the *PAX8* transcription factor gene with the nuclear hormone receptor gene *PPARγ* produces the *PAX8/PPARγ* fusion gene, possibly inhibiting the antiproliferative activity of the PPARγ receptor. This gene rearrangement has been detected in 20–40% of follicular thyroid carcinomas and a lower percentage of Hurthle cell carcinomas, as well as follicular adenomas, but has insufficient sensitive or specificity as a molecular marker [45].

Combination Assessment of Oncogenes

Each of these single mutations or translocations has limited diagnostic values, but together genetic alterations in these genes are found in up to 70% of histologically proven thyroid cancers, indicating that if assessed together, better diagnostic discrimination may be achieved. In an early study, *BRAF*, *RAS*, *RET/PTC*, and *PAX8/PPARγ* genes were assessed in 470 consecutive FNA samples with 55 of indeterminate cytology,

showing that while nearly all nodules testing positive were malignant, in some thyroid cancers, no mutations were detected [46]. This indicates potential value as a "rule-in" test to identify cancers but insufficient sensitivity to "rule-out" thyroid cancer.

These and similar results led to continued development and commercialization of a diagnostic test measuring relevant genetic alterations (about 17 in total) in the *BRAF*, *RAS*, *RET/PTC,* and *PAX8/PPARγ* genes (marketed as miR*Inform* Thyroid, Asuragen, Inc.). Independent investigation and use in the larger clinical context have demonstrated positive and negative predictive values that were more variable and less robust than the initial report [47–52].

The results of the integrated genomic characterization of papillary thyroid cancer as part of The Cancer Genome Atlas (TCGA) expanded our knowledge of the somatic genetic landscape present in PTC and identified the driver mutation/translocation in 96% of PTC tumors studied [53]. Inclusion of these additional oncogenes may help identify more thyroid cancers and improve molecular testing of thyroid nodules. Informed by these data, a diagnostic test was produced using next-generation sequencing techniques to assess point mutations in 13 genes and 42 gene fusions (marketed as ThyroSeq v2). This testing involves additional aspiration material that is separately rinsed in a specific processing solution. Two prospective single-center unblinded studies evaluated its performance on FNA material from cytologically indeterminate thyroid nodules. In 143 consecutive FNA samples with cytology of SFN/FN and available histopathology after resection, ThyroSeq v2 showed a high NPV of 96% (CI 92–100%) and moderate PPV of 83% (CI 72–95%) [54]. In a similar study assessing the performance of ThyroSeq v2 on 98 nodules with cytology of AUS/FLUS, the NPV was similar (97.2% [CI 79–100%]) with again moderate PPV (76.9% [CI 61–93%]) [55]. The demonstration of NPV comparable to benign cytology and PPV similar to that found in the Bethesda V category for which surgically is typically recommended suggests this test may provide both "rule-out" and "rule-in" capability; however, confirmatory data from multicenter, blinded studies or broader clinical use remain lacking. There presently are no published data from a prospective, multicenter, blinded validation of this broader panel, thus limiting any understanding of its clinical validation or clinical utility at this time.

Microarray Expression

Microarray platforms are a method to rapidly determine the expression of all transcribed RNA at relative low cost, allowing for the development of diagnostic microarray panels assessing hundreds of expressed genes. Importantly, computational algorithms are necessary to analyze the expression patterns seen. These techniques may be replaced with next-generation sequencing platforms, but it remains a robust form of expression analysis.

MicroRNA

MicroRNA (miRNA) are 21–22 nucleotide segments of noncoding RNA that play a key role in posttranscriptional gene regulation through complementary binding to messenger RNA that regulates translation and degradation [56]. Overexpression of specific miRNAs has been shown in FTC versus follicular adenoma and PTC versus normal thyroid tissues [57, 58], and initial studies using different miRNA expression profiles on tissue and/or aspiration samples showed overall accuracy from 76 to 90% [59–61]. Combining the relative strengths found in miRNA expression classification and oncogene determination, a two-step testing protocol has been developed and studied (marketed as ThyGenX® and ThyraMIR™ combination testing). 10-miRNA panel and 7-gene mutational panel were assessed on FNA biopsy material from 109 Bethesda III or IV nodules with available surgical pathology and demonstrated 94% [CI 85–98%]) NPV and 74% [CI 58–86%] PPV in a population with a 32% rate of malignancy [52]. Confirmation and validation in a large prospective sample representative of the general nodule population are needed.

RNA Gene Expression Classification

Since the majority of indeterminate nodules are referred for surgical resection and are ultimately proven benign, a novel paradigm was proposed to develop a test to identify benignity, thus effectively "ruling out" malignancy and preventing unnecessary surgery. The design of the Afirma® gene expression classifier (GEC) (marketed by Veracyte, Inc.) was based on this idea. This test measures 167 expressed RNAs from FNA tissue and uses trained computational algorithms to identify a profile highly correlated with a benign diagnosis when applied to indeterminate cytology nodules. After RNA expression profiling is completed, the result classifies a nodule as "benign" or "suspicious" [62]. A prospective, multicenter, blinded validation study evaluated the performance and clinical validity of the GEC in 265 indeterminate nodules greater than 1 cm with available histopathology [63]. In this study population with a rate of malignancy of 32%, NPV and PPV were 93% and 47%, respectively. The NPV for Bethesda V nodules was 85% and has generally been considered insufficient for "rule-out" testing. In contrast, NPV was 95% and 94% for nodules with AUS/FLUS and SFN/FN cytology, respectively, which is considered similar to the malignancy risk of a benign cytology and sufficient to recommend conservative management.

In a subsequent retrospective analysis of 339 indeterminate nodules from five academic centers, patients with an indeterminate nodule and "suspicious" GEC result underwent nodule resection in 121 of 148 (82%) cases, with malignancy confirmed in 53 (44%) nodules. By contrast, 4 of 174 patients with a "benign" GEC result were referred for surgery [64]. Taken together, these results show that when applied to clinical care, the Afirma GEC changes management decisions and reduces the need for diagnostic surgery.

The cost-effectiveness of clinical implementation of the GEC has been evaluated in several studies. Cost-effectiveness was demonstrated with statistical modeling [18] and separately by calculations based on rates of surgical resection for GEC-tested patients [65]. One subsequent single-center report did not find routine GEC testing to be cost-effective at a cancer prevalence of 24.5% [66]; however, routine GEC testing was projected to be cost-effective for third-party payers in the United States in a separate analysis [67].

Numerous additional independent retrospective reports have been published regarding the performance and clinical implications of GEC use in various practice settings [66, 68–78]. Assessing the reportedly high NPV and the ability to reasonably "rule out" the presence of malignancy has been difficult, since the vast majority of patients with a benign GEC result do not undergo resection. The small number of patients for whom nodule resection is performed likely represents a biased sample in which there was some additional risk that drove the decision to perform surgery. One study has compared the sonographic follow-up of benign GEC nodules to a large cohort of cytologically benign nodules with similar baseline characteristics and follow-up time [73]. In this analysis, there was no significant difference in nodule growth or suspicious features when reassessed sonographically at a mean of 13 months, suggesting comparable behavior of GEC-benign nodules to cytologically benign ones. To date, there has been no death attributed to a false-negative, GEC-benign, thyroid malignancy that was later detected.

The positive predictive value of the Afirma GEC has been the topic of more extensive study, with single-center, retrospective analyses reporting PPVs for Bethesda category III or IV nodules from 14 to 82%, though most fall within the range anticipated by the original validation trial [66, 68–72, 74–77]. Two studies selecting nodules with Hurthle cell cytologies (AUS with predominantly Hurthle cells and/or suspicious for Hurthle cell neoplasm) have detected a higher than expected rate of suspicious GEC results, and a low risk of malignancy in these nodules [68, 72], but this has not been found in all studies [76]. Whether these observations represent differences in underlying malignancy rate, selection bias in which patients with Hurthle cell cytology receive Afirma GEC testing, assay performance, variability of cytological interpretation, or physician/patient decision-making remains uncertain, but such factors likely contributed to these findings.

It is critical to appreciate that the likelihood of malignancy in a cytologically indeterminate and GEC suspicious nodule is related to the underlying probability of malignancy within the population tested. Differences in the population prevalence of thyroid cancer between institutions, interpretation of sonographic nodule appearance, selection of which nodules undergo FNA biopsy, risk of malignancy implied by an indeterminate result at a given location, selection of which patients undergo resection, and the interpretation of the histopathologic result will all influence the probability that such a nodule will prove malignant. This variability is inherent to the multidisciplinary evaluation of a thyroid nodule [8, 15] and is an immutable limitation of all molecular testing for thyroid nodules. Therefore, it is imperative to understand the PPV of a molecular test in the context of the likelihood that malignancy is present within a thyroid nodule prior to such testing in order to optimally interpret what the test result indicates regarding a patient's risk of harboring thyroid cancer.

Future Directions

The evaluation and management of thyroid nodules due to their inherent risk of thyroid cancer is likely to continue to increase in the future, highlighting the clinical need for continued progress toward adjuvant testing to assess the risk of malignancy when FNA cytology remains indeterminate. Thyroid cancer expression of programmed death ligand-1 (PD-L1), a cell surface protein that promotes inhibition of immune activation when binding to its ligand on effector immune cells, has recently been shown to correlate with aggressive behavior in PTC tumors [79], and IHC assessment of PD-L1 on FNA material may demonstrate value in differentiating benign from malignant nodules. Testing for mutations/translocations, miRNAs, and/or mRNA expression profiles is likely to continue to improve and address limitations in diagnostic accuracy in future iterations of their development. Finally, novel molecular markers, such as measurement of circulating suppressor immune cells, circulating tumor cells, cell-free DNA, and other modalities, will continue to be explored.

Summary

The increasing availability of accurate, reliable, and affordable molecular diagnostic testing is changing the management of indeterminate thyroid nodules. Outcomes and cost-benefit analyses should favor limiting medical interventions to patients likely to obtain greatest benefit while simultaneously reducing test and treatment morbidity. As the number and types of tests continue to expand and their performance continues to improve, the regular use of molecular markers is increasingly becoming a standard practice [10, 16].

At present, there are few widely available options for the evaluation of nodules classified as indeterminate, of which the Veracyte Afirma® gene expression classifier and the 17 gene mutation panels have been the most independently studied and analyzed. Confirmation in large-scale, prospective, and blinded investigations will be critical to the full understanding of test performance of many molecular tests being introduced. Currently, publications are primarily based upon small, single-institution experiences, with suboptimal methodology, and data must be interpreted in the context of these limitations.

With widespread use of these tests, our understanding of their limitations also has become apparent. Population diversity and practice variation lead to substantial differences in test performance from site to site and best explain differences in published experiences. Such variation is a limitation that must be acknowledged and will never disappear. Separately, this field is increasingly seeking to better understand the meaning of all molecular changes. Increased and improved understanding of mutations that exist in benign thyroid nodules will help to expand our knowledge of when genetic alterations (base pair change or translocations) do not necessarily imply malignant transformation.

Ongoing research in this field actively continues with the identification of new potential molecular markers and the publication of clinical trials demonstrating both the utility and limitations of these markers in clinical practice. After discovery, large-scale, prospective clinical validation trials are vitally important. Given the heterogeneity of thyroid cytology and histology, variation in populations, and use of a marker in clinical use, transparent clinical trials provide the optimal means for understanding molecular marker performance in a real-world setting. Indeed, large-scale validation should be viewed as a critical next step after molecular marker discovery.

The current, and future, approach to patients with a clinically relevant thyroid nodule will almost certainly include assessment of clinical, biochemical, radiologic, cytologic—and now molecular—variables as we determine the risk of thyroid malignancy and optimal thyroid nodule management.

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Chapter 9
Thyroxine Therapy for Thyroid Nodules

Alan A. Parsa and Hossein Gharib

Introduction

The administration of thyroid hormones at suppressive doses to shrink thyroid nodules remains controversial. In theory, by suppressing TSH, one removes TSH stimulation to TSH-sensitive receptors on nodules, leading to the atrophy of the nodule. While suppressive therapy may lead to nodular size regression, this is only seen in a small minority of patients and is, importantly, associated with complications caused by chronic low TSH. The most recent American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) guidelines for medical practice recommend against the use of routine thyroxine (T4) therapy in fine needle aspirated (FNA) benign nodules. Here we offer some historical reference to this practice along with recent reports supporting current recommendations not to treat thyroid nodules with suppressive T4 therapy.

History

Throughout antiquity, enlarged thyroid glands (goiter) have been a source of interest, with early descriptions found by the Chinese around 2700 BC [1], in documents by the ancient Greeks [2], in anatomic illustrations by Leonardo da Vinci [3], in

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writings by Hippocrates and Galen [1], and in fine art, as in Jan van Eyck's "Portrait of Margaret van Eyck" or da Vinci's "Madonna of the Carnation" [4]. Its aesthetically altering location in the anterior neck is likely the source of enthusiasm.

In the distant past, burnt sponge or seaweed was an effective method to shrink nodules in Asia and Europe [5–8]. It was not until the Napoleonic Wars, in the early 1800s, and a shortage of saltpeter (potassium nitrate) for gunpowder that led the French saltpeter manufacturer, Bernard Courtois, to accidentally discover iodine in seaweed ash [1]. Iodine proved its place in goiter treatment after an 1820 study showed that using 250 mg of tinctured iodine daily successfully shrank goiters in 150 subjects [9]. For the next half century, iodine was considered the treatment of choice for thyroid dysfunction. Popularity abated eventually with reports of iodine-induced thyrotoxicosis [6, 10], and treatment shifted to using the thyroid gland itself to treat thyroid disorders.

Small, early studies using raw thyroid gland, typically from sheep or pig, to shrink goiters, showed promise [6, 11], while larger studies showed minimal benefits. Burns, in the 1890s, evaluated 326 subjects treated with thyroid extract, 8% showed a full response, 36% had a partial response to thyroid gland administration while 56% did not show any response [6, 12]. It has been suggested that nodular regression is subjective and related to a reduction of blood supply and atrophy of the surrounding normal thyroid gland rather than true nodule shrinkage [13, 14].

Present

In current practice, the efficacy of thyroxine (LT4)-suppressive therapy was initially challenged by Gharib et al. from the Mayo Clinic in 1987 [15]. In a randomized, double-blind, placebo-controlled study, using high-resolution sonography and sensitive TSH testing, they showed that LT4-suppressive therapy failed to significantly shrink benign thyroid nodules. Subsequently, many investigators worldwide published data confirming [14, 16–19], and repudiating [20–24], these observations.

To better evaluate the efficacy of LT4-suppressive therapy, several meta-analyses have emerged. One by Richter et al. in 2002 evaluated nine studies totaling 596 patients [18] and concluded that LT4-suppressive therapy led to a significant decrease in nodule volume in <20% of cases.

Castro et al. [25], in a meta-analysis, reviewed six randomized controlled trials (Table 9.1), and while more than 50% of nodules reduced in size with TSH suppression, the efficacy of therapy was similar to placebo (relative risk (RR) = 1.9; 95% confidence interval (CI), 0.95–3.81). Sdano et al. [26] evaluated nine randomized trials, totaling to 609 subjects. While 88% of subjects were more likely to experience >50% nodule volume reduction compared to placebo, a calculated risk analysis showed that for every one subject to benefit from therapy, eight would be subjected to risks of cardiac and skeletal side effects related to TSH suppression. They reported one long-term study of 5 years noting that volume reductions in sub-

Table 9.1 Review of meta-analysis of the six studies reviewed by Castro et al. (2002)

Study	Study design	Number of subjects	% Response treatment group	% Response in placebo group	Significance
Gharib et al. (1987)	Prospective randomized double blind	53	14	20	NS
Reverter et al. (1992)	Prospective randomized controlled	40	20	15	NS
Papini et al. (1993)	Prospective placebo controlled	101	20	6	NS
LaRosa et al. (1995)	Prospective no placebo	45	39	–	S
Zelmanovitz et al. (1998)	Placebo controlled	45	29	8	NS
Larijani et al. (1999)	Prospective placebo controlled	62	19	13	NS

NS nonsignificant, *S* significant

jects taking placebo versus TSH-suppressive therapy were nonsignificant. In a 2014 Cochrane review [27], 16% of those treated with TSH-suppressive therapy and 10% of those treated with placebo demonstrated a >50% volume reduction, which was considered a minimal difference. Health-related quality of life or all-cause mortality was not mentioned in the studies evaluated. Fast et al. [19] in Denmark, after an evaluation of 822 patients, advocated against the use of TSH-suppressive therapy to treat benign nontoxic nodules, emphasizing risks associated with chronic TSH suppression.

TSH suppression, especially with levels <0.1 mIU/L, can lead to many significant adverse events, including secondary osteoporosis and increased fracture risk from increased mobilization of bone mineral and increased cortical osteoclastic resorption [28–32]. Atrial fibrillation risk can increase by up to 20% [33, 34] with increased risk of cardiomyopathy and heart failure [35–37, 32]. Exercise intolerance with dyspnea and peripheral edema may also occur [38]. Increased morbidity and mortality, from TSH over-suppression, have been described [39, 40] along with decrements in health status, mood, and decision-making [41–43]. Practitioners should be aware of these risk factors when considering therapeutic strategies and goals of therapy when treating benign thyroid nodules.

While the recent literature is against the use of LT4-suppressive therapy to shrink thyroid nodules, clinical practice seems to lag behind recommendations. To evaluate current practice, Bennedbaek et al., surveyed members of the European Thyroid Association (ETA), in 1999 [44], and the American Thyroid Association (ATA), in 2000 [45], asking how to manage a "42-year-old woman with a solitary 2 × 3 cm

thyroid nodule and no clinical suspicion of malignancy." While everyone agreed that FNA biopsy, to rule out malignancy, was the best initial step, 60% of respondents from the ETA and 53% of ATA advocated against TSH-suppressive therapy to shrink a benign solitary nodule. Of note, these studies were conducted more than 16 years ago, and we believe that current practice suggests even less enthusiasm for suppressive therapy. Accordingly, both recent guidelines by the ATA [46] and the American Association of Clinical Endocrinologists (AACE)/Associazione Medici Endocrinologi (AME) [47] recommend against TSH-suppressive therapy to reduce the volume of cytologically negative thyroid nodules.

Conclusion

While controversy continues and treatment should be individualized, we emphasize "first, do no harm." In 1998, Gharib and Mazzaferri, considering risks and benefits of T4-suppressive therapy, stated that "nodule shrinkage for its own sake… is a surrogate outcome that may not be of clinical value to patient or physician" [16]. In a detailed review published in 2003, Hegedus remarked that "In our own country [Denmark], this [LT4] therapy has been abandoned" [48]. We believe this trend to be also true in many other countries. It is our opinion that the recognition of the lack of efficacy of TSH-suppressive therapy, combined with significant potential complications, has been one of the landmark achievements of the twentieth-century endocrine practice.

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Chapter 10
Multinodular Goiter

Sina Jasim and Hossein Gharib

Introduction

The prevalence of goiter can widely differ, depending on the iodine intake, other goitrogens, genetic factors, radiation, etc. Goiter can be seen in endemic areas due to iodine deficiency or sporadically due to many other reasons. Thyroid nodules are common in the United States and Western countries. A detailed description of epidemiology and prevalence is available in Chap. 2 (Epidemiology of Thyroid Nodules).

Etiology and Pathogenesis

Goiter is a complex disease. The pathophysiology and the influence of TSH are still not clear. Increase in thyroid-stimulating hormone (TSH) secretion seems to play an important role in the development of goiter, especially in response to iodine deficiency or chronic autoimmune (Hashimoto's) thyroiditis. However, this does not seem to be the only factor; indeed, most patients with sporadic nontoxic multinodular goiters have serum TSH levels well within the normal range. Several growth factors (TSH dependent or nondependent) can influence the thyroid follicular cell growth and development of goiter. Chronically stimulated follicular cells may lead to thyroid hyperplasia, partially due to TSH stimulation, then a resting face may ensue leading to colloid goiter [1], and long-standing diffuse goiter eventually

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progresses to multinodular thyroid enlargement with the potential of some nodules to develop autonomy. Therefore, multiple factors, including genetic, environmental, and demographic factors, interact in the development and pathogenesis of nodular goiter.

The genetic etiology of goiter, especially nontoxic MNG, is not clearly established. The role of genetic factors is suggested by twin studies, family history, higher predisposition for females in sporadic goiter, and persistence of goiters despite iodine repletion in certain geographic areas [2].

Certain genetic abnormalities have been described as potential culprits in the pathogenesis of goiter. Some of these spontaneous mutations affect the activation of cAMP cascade (e.g., TSH-R mutations) which stimulates growth and function mutation in genes encoding thyroglobulin (Tg), thyroid peroxidase (TPO), dual oxidase 2 (THOX2), the sodium-iodide symporter gene (SLC5A5), Pendred syndrome gene (SLC26A4), the TSH receptor gene (TSHR gene), the iodotyrosine deiodinase (DEHAL 1), and the thyroid oxidase 2 gene (THOX2) [2]. Thyroid nodules in MNG are derived from monoclonal (single ancestor cell) or polyclonal cell (multiple thyroid progenitors) and can be a combination of both [2–5].

Advances were made in genetic studies when familial MNGs were strongly associated with germline mutations in the microRNA processing gene, *DICER1* [6], and MNGs were seen as phenotypic manifestations of the DICER1 syndrome, particularly in female germline mutation carriers [7].

Some environmental factors can play a role in stimulating thyroid cell growth and/or function and possibly aggravating the expression of heterogeneity leading to growth and possibly autonomy of thyroid gland.

There are several naturally occurring goitrogens that work by different mechanisms to impair thyroid hormone synthesis or induce thyroid growth, such as iodine-rich substances like seaweed or substances that impair iodine uptake like cruciferous vegetables and cassava [8]. Protein-caloric malnutrition, iron deficiency, vitamin A, and selenium deficiency may each induce thyroid enlargement if associated with iodine deficiency [8, 9].

Nontoxic MNG may evolve with time from small, nonfunctioning nodules to larger, autonomous nodules with a smoldering state of subclinical hyperthyroidism for years prior to progression to overt hyperthyroidism [10]. Functioning thyroid nodules can be associated with Graves' disease and called Marine-Lenhart disease.

MNG and Risk of Thyroid Cancer

There is some discrepancy between the reported frequency of thyroid cancer in surgical specimens and the reported mortality from thyroid cancer. It is challenging to monitor patients with MNG for the development of malignancy, especially when no reliable markers are available to accurately predict the risk of malignancy [11].

In recent reports, the risk of cancer in MNG is around 2–3% [12–14], but the number is higher if reports include post-thyroidectomy surgical specimens [15, 16]. Certain predictors and prognostic indicators of malignancy in MNG have been suggested, including higher TSH levels [17] and positive serum thyroglobulin antibodies [18]. In general, younger age at diagnosis, male sex, and fixed lesions larger than 4 cm increase the risk of cancer [19, 20]. However, larger or more rapidly growing nodules are not always predictive of malignancy; hence, annual neck ultrasound with fine needle aspiration may not need to be routinely performed. The risk of thyroid cancer is comparable in case of single nodule versus MNG as illustrated in multiple studies (Table 10.1) [21]. Furthermore, in a recent analysis, the prevalence of malignancy in nodules with nondiagnostic FNA was suggested to be around 3% [22].

Table 10.1 Risk of thyroid cancer in MNG versus single nodule (SN)- Modified from Brito et al. [21]

Study (location, year)	MNG		SN		Diagnostic method	OR (CI)
	Events	Population	Events	Population		
Abu-Eshy et al. (Saudi Arabia, 1995)	14	172	16	105	Surgery	0.49 (0.23–1.06)
Belfiore et al. (Italy, 1992)	49	1152	211	4485	Surgery	0.86 (0.62–1.19)
Deandrea et al. (Italy, 2002)	12	174	15	246	FNA	1.14 (0.52–2.50)
Edino et al. (Nigeria, 2010)	24	160	1	13	Surgery	2.12 (0.26–17.05)
Franklyn et al. (UK, 1993)	1	72	19	321	FNA	0.22 (0.03–1.70)
Frates et al. (USA, 2006)	119	804	175	1181	FNA	1.00 (0.78–1.29)
Khairy et al. (Saudi Arabia, 2004)	16	124	24	172	Surgery	0.91 (0.46–1.80)
Marqusee et al. (USA, 2000)	8	90	4	60	FNA	0.37 (0.39–4.75)
Matesa et al. (Croatia, 2005)	15	289	6	117	FNA	1.01 (0.38–2.68)
McCall et al. (USA, 1986)	9	69	16	96	Surgery	0.75 (0.31–1.81)
Papini et al. (Italy, 2002)	13	207	18	195	FNA	0.66 (0.31–1.38)
Rago et al. (Italy, 2010)	411	19,923	446	13,549	FNA	0.62 (0.54–0.71)
Sachmechi et al. (USA, 2000)	9	92	4	50	FNA	1.25 (0.36–4.27)
Taneri et al. (Turkey,2005)	35	237	24	133	Surgery	0.79 (0.45–1.39)
Total	733	23,565	979	20,723		0.80 (0.67–0.96)

Clinical Evaluation

Clinical evaluation includes assessment of symptoms' severity and duration, family history of thyroid disorders or thyroid cancer, and a history of head and neck radiation. Age and gender can influence prognosis.

Clinical picture varies widely based on the location, extent, and function of the goiter. Frequently, small, nontoxic multinodular goiters are asymptomatic and found incidentally on routine physical examination or on imaging done for nonthyroid reasons such as carotid ultrasound, chest X-ray, magnetic resonance imaging, or CT of the neck and chest. Nontoxic MNGs can, at times, present with neck compressive symptoms such as neck pressure, cough, shortness of breath, and swallowing difficulty. Hoarseness of the voice in case of recurrent laryngeal nerve involvement is rare. Large goiters (Figs. 10.1 and 10.2) with retrosternal or mediastinal extension can produce tracheal deviation or compression, positional dyspnea, or thoracic outlet obstruction with certain maneuvers (Pemberton's sign). Pain might be present in case of hemorrhage into a cystic nodule.

The clinical picture in Plummer's disease (toxic MNG) is variable ranging from subclinical to overt hyperthyroidism. Symptoms are associated with increased metabolic and adrenergic responses like heat intolerance, weight changes, nervousness, irritability, diaphoresis, palpitation, and tremor and signs like muscle weakness, tachycardia, increased tendon reflexes, lid lag, and/or retraction. In the elderly, however, the symptoms might not be as evident or may even be "masked" as in "apathetic hyperthyroidism." Hyperthyroidism (subclinical or overt) can be present in up to 25% of patients with MNG [23].

Physical examination can detect thyroid enlargement with nodular irregularities. Neck palpation is imprecise in determining thyroid morphology and size [24]. In retrosternal goiter, fullness in the suprasternal notch can give a hint. There is no

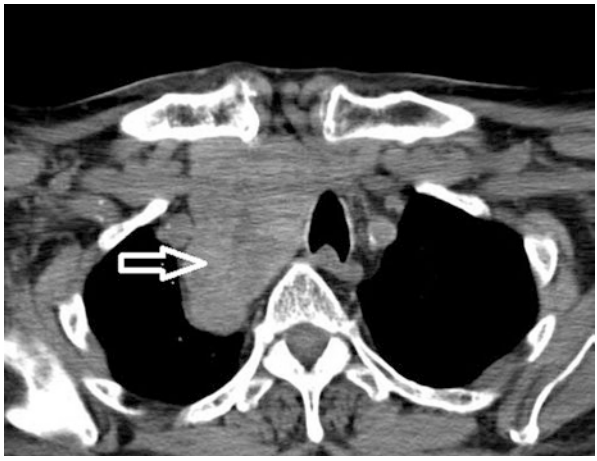

Fig. 10.1 CT scan of the neck and upper chest. Large MNG (*arrow*) deviating the trachea with mediastinal extension

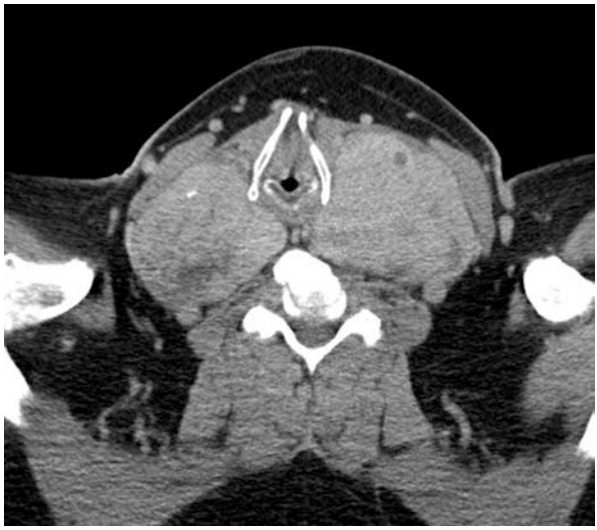

Fig. 10.2 CT scan of the neck. Large MNG compressing the trachea

specific examination finding that can predict malignant nature of a goiter; however, hoarseness, rapid goiter growth, and cervical adenopathy are always concerning features, especially with positive family history or radiation exposure to the neck region.

Radiological characteristics of thyroid nodules should be carefully evaluated in order to select those that require further evaluation or fine needle aspiration.

Laboratory Investigation

There is no specific diagnostic laboratory pattern in patients with MNG. Sensitive TSH should be measured in all patients, and it may be normal, low, or even high. However, in most cases of MNGs, serum TSH is within the normal range [25]. Suppressed TSH (with normal or elevated serum FT4 level) is suggestive of toxic MNG (Plummer's disease); this needs to be supported by diagnostic imaging. Additional testing, such as anti-thyroperoxidase (TPO), has limited value in making the diagnosis of MNG but is helpful as elevated levels indicate autoimmune thyroid disease. Hashimoto disease may be associated with the presence of pseudo-nodules rather than true nodules on thyroid US; these are typically benign. Moreover, it might be associated with bilateral, enlarged, but benign-appearing lymphadenopathy. The routine measurement of serum thyroglobulin (Tg) or calcitonin (Ct) has no value in a patient with MNG. Serum Ct should be measured only with suspicion of MTC or if FNA is abnormal [26]. Measurement of serum TSH and Tg levels to assess malignancy risk of thyroid nodules is discussed later in this chapter.

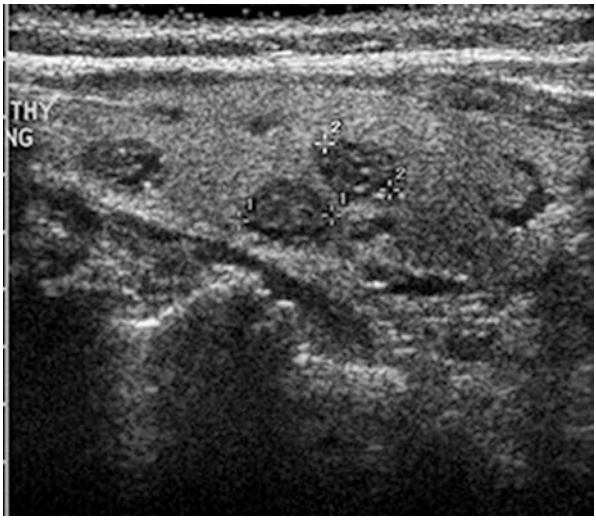

Fig. 10.3 Thyroid US small (sub-centimeter) nonpalpable thyroid nodules

Diagnostic Imaging

Different imaging modalities are available in evaluating toxic and nontoxic MNG, including neck ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), thyroid scintigraphy, and positron emission tomography (FDG-PET), though less frequently used.

Thyroid Ultrasonography (US)

High-resolution US is a widely used, inexpensive, and sensitive (≈95%) method to detect small, nonpalpable thyroid nodules (Fig. 10.3) and to complement neck palpation. Clinical practice has witnessed detection of more thyroid nodules in the United States and elsewhere [27]. An unintended consequence of US sensitivity has been the detection of incidental, and often insignificant, small solid or cystic thyroid nodules.

All patients with suspected or confirmed thyroid nodules should have a full neck US to evaluate location, size, number, and other features of these. US can help identify thyroid nodules that need fine needle aspiration (FNA) and guide the FNA when needed (Fig. 10.4) [26, 28]. The importance of thyroid sonography is underscored by the fact that up to 50% of patients with single nodules on physical examination will show additional nodules [29]. However, the risk of malignancy is similar if nodules are single or multiple [21, 30, 31].

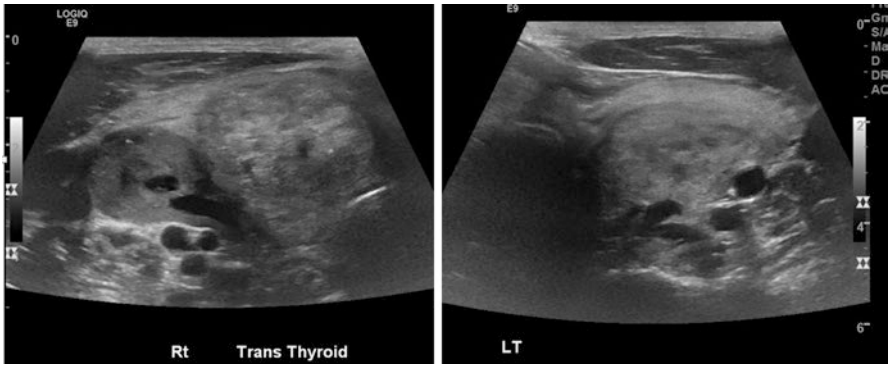

Fig. 10.4 Thyroid US large MNG with multiple heterogenous nodules with cystic changes on both sides

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI)

Computerized tomography (CT) or magnetic resonance imaging (MRI) provides better evaluation of thyroid size and extension in relationship to surrounding structure especially in patients with compressive symptoms and those with large goiter with suspected retrosternal extension (Fig. 10.5). However, these are not used routinely due to high cost. Of note, CT should be preferably used without contrast to avoid possible iodine-induced thyrotoxicosis in the setting of a MNG [23].

Thyroid Scintigraphy (Radioisotope Scan)

This test is not routinely ordered in evaluating MNG except when determining the functional status of thyroid nodule or MNG, associated with low serum TSH [32]. Thyroid scintigraphy can be performed using either technetium 99mTc pertechnetate or I^{123} scanning with sensitivities to detect functioning nodules about 91% and 83%, respectively [33]. Thyroid scan has low specificity (5–25%), due to interference from normal thyroid tissue with the radioisotope uptake. In the setting of a MNG, thyroid scan should always be done together with a neck US to help determine the need for FNA. Functioning nodules are not suspicious for malignancy and need not be subjected to FNA. Hot nodules account for fewer than 10% of all thyroid nodules and are almost always benign [25]. In toxic MNG, hot nodules trap the radioactive iodine (uptake), while this is inhibited in surrounding thyroid tissue giving the "patchy uptake" image suggestive of toxic MNG (Fig. 10.6).

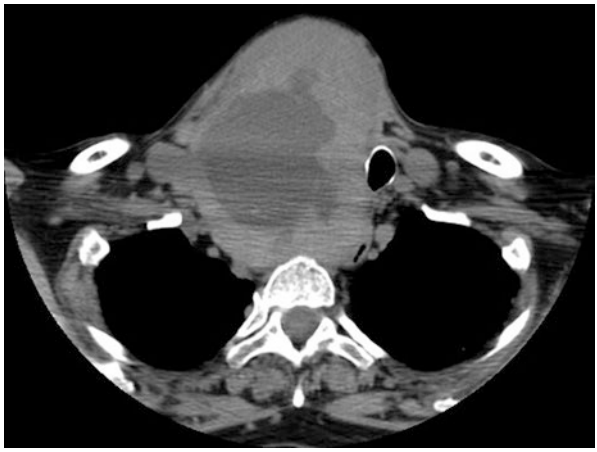

Fig. 10.5 CT scan of the neck and upper chest. Large MNG with huge nodule and central degeneration. There is evident tracheal compression and deviation with mediastinal extension

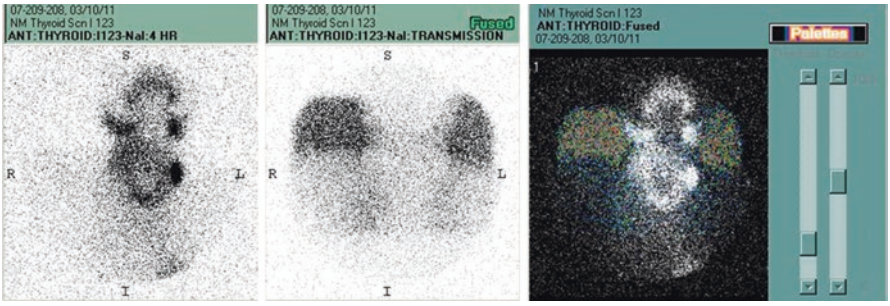

Fig. 10.6 NM thyroid scans I^{123} showing enlarged gland with patchy uptake

FDG-PET-Positive Thyroid Nodule

In recent years, FDG-PET scanning is frequently performed for tumor staging and detection. When FDG-PET scan shows focal uptake in the thyroid bed, the risk of malignancy is high, around 35%; hence nodule warrants FNA [34–36]. On the other hand, diffuse FDG uptake in thyroid bed is suggestive of Hashimoto's thyroiditis, which can be further evaluated with US but may not require FNA.

Fine Needle Aspiration Biopsy: FNA

Thyroid FNA is established as a safe, valuable, and cost-effective test in the diagnosis and treatment of nodular thyroid disease. In current practice, adequate samples should be obtained in 95% of cases [37, 38]. The use of US-guided FNA and on-site

cytological examination can further reduce inadequate sampling [38–40]. Obviously, not all thyroid nodules require FNA. Selecting nodules that require FNA in MNG can be more challenging than in single nodules, because often more than one nodule needs FNA [21, 30, 31, 41]. In general, FNA is recommended for high US-risk thyroid lesions ≥10 mm, intermediate US-risk thyroid lesions >20 mm, and low US-risk thyroid lesions only when >20 mm, associated with high-risk history or increasing in size (Fig. 10.7) [26]. This applies also to glands with multiple nodules; however, it is seldom necessary to perform FNA in more than two nodules in a MNG. Additionally, it is not necessary to biopsy "hot" areas on radioisotope scan in the adult patient [26].

Management

Management is influenced by nodule or goiter growth, size and location of goiter, local and compressive symptoms, functional status, and risk of malignancy [42]. The choice of treatment depends on many issues, including patient's comorbidities. Frequently, benign, small, asymptomatic, and nonfunctional goiters can be monitored with physical examination, TSH, and neck ultrasound without other intervention.

Nontoxic MNG and Toxic MNG

For patients with benign nontoxic MNG, the treatment mostly aims to decrease the size, relieve obstruction, or prevent further growth. Iodine supplementation was used as a therapeutic option in diffuse goiter associated with iodine deficiency in many countries worldwide; however, this has limited effect in treating multinodular goiter. Moreover, iodine load might induce subclinical/clinical hyperthyroidism (Jod-Basedow effect).

The majority of goiters remain stable, while some may even regress [43]. Asymptomatic, euthyroid patient with nonobstructive MNG may require no intervention and can be monitored for further growth, obstruction, or autonomy. This can be done by following TSH, US, and possibly CT scans if indicated.

Surgery

Surgery is preferred to radioiodine therapy in patients with nontoxic, nonobstructive goiters that continue to grow and potentially cause obstructive symptoms or cosmetic concerns.

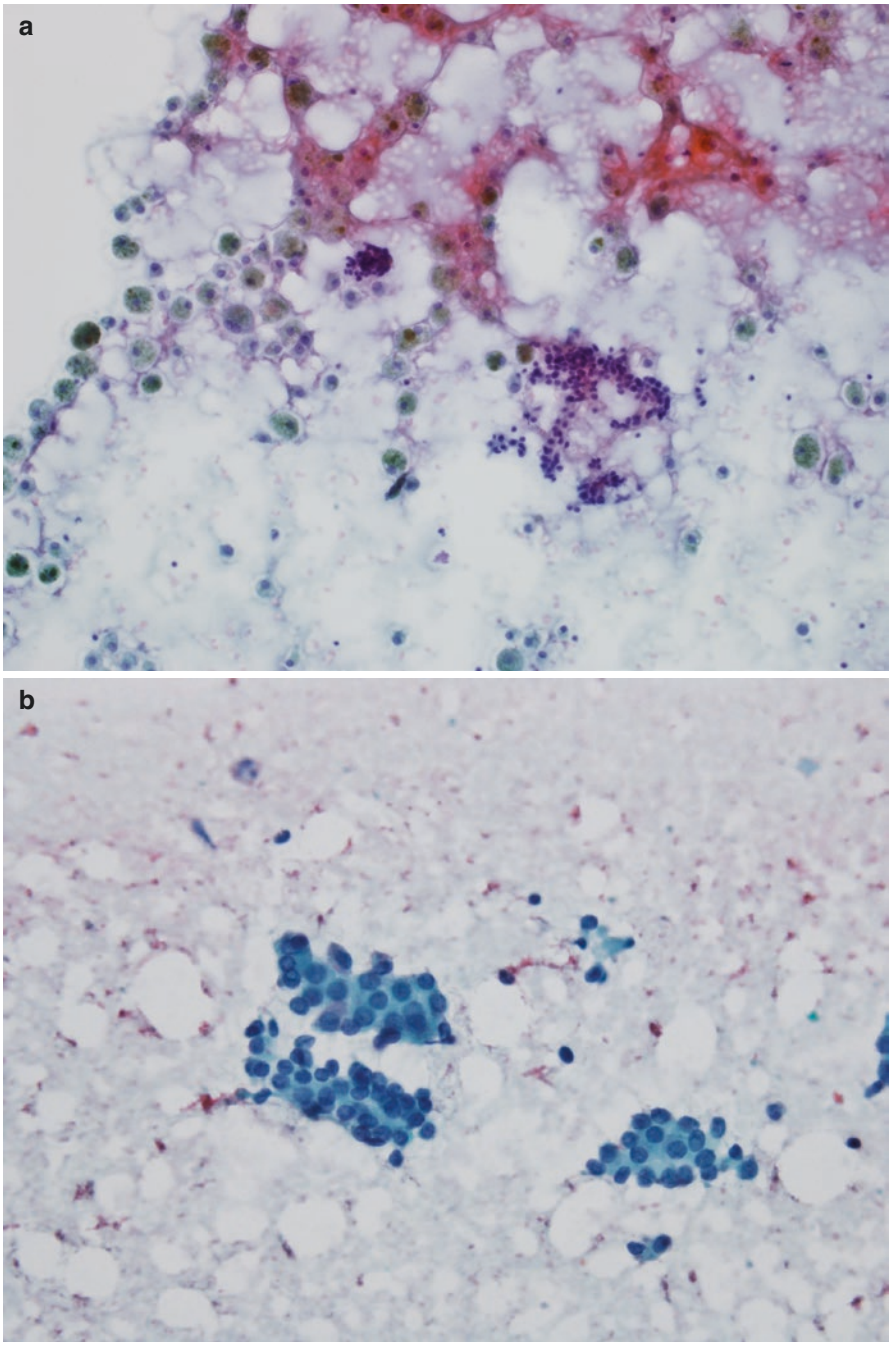

Fig. 10.7 (**a**) Benign thyroid nodule, Papanicolaou stain, 10× magnification: clusters of follicular cells with colloid and histiocytes in the background, suggestive of cystic degeneration (Image is courtesy of Heidi D. Lehrke, D.O.—pathology department-Mayo Clinic). (**b**) Papillary thyroid carcinoma, Papanicolaou stain, 40× magnification: clusters of epithelial cells with jumbled nuclei, nuclear grooves, and occasional pseudoinclusions (Image is courtesy of Heidi D. Lehrke, D.O.—pathology department-Mayo Clinic)

Near-total or total thyroidectomy should be performed for large or retrosternal goiters with obstructive symptoms (Fig. 10.8). After surgery, recurrence is seen in 10–20% in the first decade depending on the size of residual thyroid tissue [44]. Surgical complications are rare in experienced centers, but can be up to 10% since most surgeries are performed by general, low-volume surgeons [45], and include hypoparathyroidism, injury to trachea, or recurrent laryngeal nerves, especially in large and/or retrosternal goiters [46, 47]. When selecting surgery, one should consider risks and benefits in older patients, paying attention to those with significant comorbidities.

Radioiodine Therapy: ^{131}I

RAI is not routinely used in treating nontoxic MNG especially in the United States; however, it has been used with good results in many other countries [48–50]. Reports show reduction of goiter size in up to 40% in 1 year and 55% in 2 years, with 60%

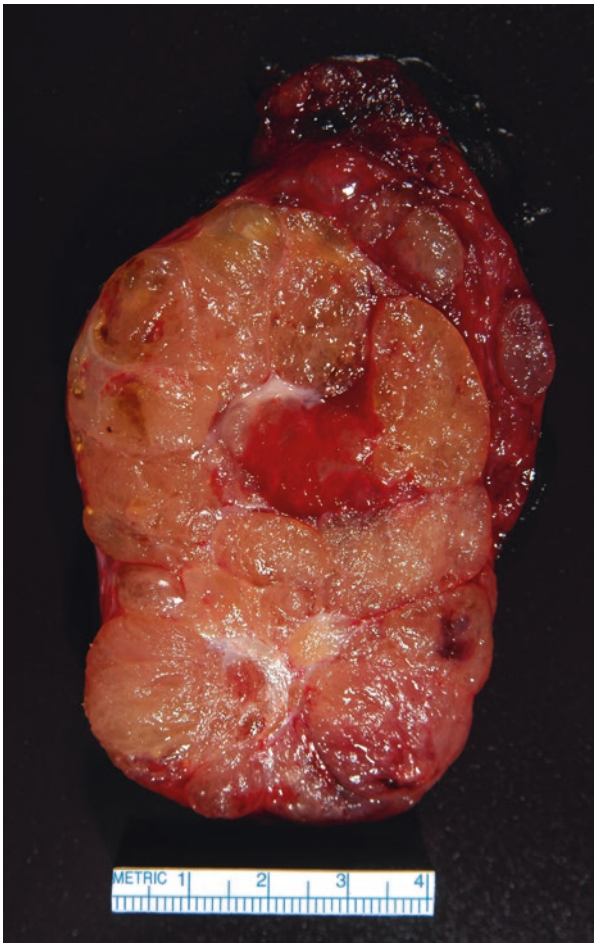

Fig. 10.8 Multinodular goiter, gross image: lobulated, glistening, *tan-yellow* mass forming a multinodular mass within the left thyroid lobe, characteristic of a multinodular goiter (Courtesy of Heidi D. Lehrke, D.O.—pathology department-Mayo Clinic)

volume reduction within just 3 months [51], and improvement in obstructive symptoms in the majority of patients [52, 53]. Painful transient thyroiditis and transient mild thyrotoxicosis [51] may occur within the first month after treatment and subsequent hypothyroidism in about half of the patients [54]. Graves' hyperthyroidism and high TSH receptor antibodies can develop in those with preexisting high thyroid peroxidase antibody (TPO) in some euthyroid patients with MNG treated with RAI [55].

The 24-h thyroid radioiodine uptake is usually lower in patients with nontoxic than toxic MNG; hence, larger dose of radioiodine is needed. Although not approved in the United States, stimulation with low doses of recombinant human TSH (rhTSH) can increase the ^{131}I uptake in the thyroid, which lowers the treatment dose of ^{131}I required but may increase thyroid hormone production; therefore, hyperthyroidism should be excluded before its use [56]. While RAI is not the first choice to treat nontoxic MNG, it is a useful alternative for patients refusing surgery and for high-risk surgical patients.

Thyroid Hormone Suppressive Therapy

Thyroid hormone suppressive therapy was widely used in treating benign goiters, more so in diffuse than in nodular types. It was hoped to reduce nodule size as TSH was presumed to play a role in the pathogenesis of MNG [57, 58]. Its efficacy was questioned since earlier studies showed only a 60% response rate [59], while others suggested no benefit [42].

The variable response probably reflected variability in certain factors such as iodine intake, age, size and duration of goiter, duration of treatment, and degree of suppression. Additionally, suppressive therapy was also reported to be useful in preventing recurrence of goiter after partial thyroidectomy; though, this was not confirmed with large clinical trials [59].

Thyroxine suppressive therapy has important adverse effects, particularly in older men and postmenopausal women, with risks of cardiovascular complications and bone loss [60, 61]. This is especially true with long-term use, since thyroid nodules usually return to original size (pretreatment) after discontinuation of therapy [25]. While this practice remains controversial, neither the recent AACE [27] nor the ATA [62] guidelines recommend it [26, 28].

Others Treatment Options

Percutaneous ethanol injection is a safe and effective alternative option to treating recurrent symptomatic cystic nodules [62, 63]. Other minimally invasive, nonsurgical options include laser ablation, cryoablation, and radiofrequency ablation performed in selected experienced centers and for selected patients when surgery is not an option [63, 64].

Toxic MNG

Surgery and RAI are both effective options for treatment of this condition. The choice between the two depends on patient preference, her/his surgical risk, availability of expert thyroid surgeon, and access to nuclear medicine facility.

Radioiodine Therapy

RAI is more effective and more often used in toxic MNG than in nontoxic MNG. For the majority of patients with toxic MNG, euthyroidism can be achieved in about 2–4 months after a single dose of RAI [50], with a response rate of 50–60% at 3 months, up to 80% at 6 months, and average failure rate around 15% [65–67]. RAI is an effective, alternative treatment for patients who are poor surgical candidates, especially with advanced age, multiple comorbidities, prior neck surgery, and lack of surgical expertise [68].

Typically, larger RAI doses are required, 30–50 mCi in MNG compared to 10–15 mCi, in Graves' disease. There is about a 10–20% failure rate to achieve a euthyroid state after a single RAI dose, and often, an additional dose might be required. Different methods are used to calculate the dose including fixed dose and calculated method, with the goal to maximizing chance of cure and avoiding unnecessary higher radiation exposure.

In a study from the Mayo clinic, in the first 3 months after treatment, 82% of surgically treated patients became euthyroid or hypothyroid, compared to 21% after RAI (^{131}I). Up to 20% of RAI-treated patients required a second treatment dose [65]. After 5 years, a 39% relapse rate and a 24% hypothyroidism were reported with smaller doses of RAI [69]. Absolute contraindications to RAI include pregnancy and breastfeeding or the plan of getting pregnant within 3–6 months.

Surgery

Surgery is a valuable option in large, obstructive goiter and in cases of suspected coexisting malignancy. It is the preferred choice if urgent treatment is needed for relief of airway obstructive or rapid resolution of hyperthyroidism, as euthyroidism is achieved within days to weeks. Both total and near-total thyroidectomy are acceptable, and the risk of treatment failure or the need for reoperation is less than 1% [65, 70]. To minimize complications, it is advisable to perform surgery in centers with high-volume surgeons. Serum calcium level should be checked postoperatively and treated accordingly.

Medical Therapy

Beta-blockers should be used to control the symptoms associated with hyperthyroidism, even before selecting definitive treatment. Thioamides are not first-line treatment for toxic MNG due to higher recurrence rate. Thioamides can decrease thyroid hormone production and restore a euthyroid state but, in contrast to Graves' disease, do not induce lasting remission of hyperthyroidism in patients with nodular thyroid disease resulting in a relapse after disconsolation [71]. They can be used temporarily while waiting for a more definitive therapy with either surgery or RAI or when a patient is not a candidate for ablative therapy or refuses either surgery or RAI.

Other Treatment Options

Ultrasound-guided percutaneous ethanol injection is effective for a solitary hot nodule and when nodule is not very large (<15 mL in volume) [72], although other studies suggest safety even at larger nodular size [73]. Ultrasound-guided laser photocoagulation has also been used in certain cases. In comparison with RAI, both have similar effects on decreasing nodule size, but only 47% achieved a euthyroid state at 6 months after laser compared with 87% in RAI group [74]. Radiofrequency ablation (RFA) of thyroid nodules was found superior to laser therapy as 82% achieved euthyroid state at 20 months [75]. Despite recent encouraging reports, none of these techniques have replaced conventional therapies for toxic MNG.

Post-therapy Monitoring

Monitoring for hypothyroidism or persistent/recurrent hyperthyroidism is necessary after RAI. Early on, measuring TSH may not suffice, and following serum-free T4 and total triiodothyronine (T3) levels is currently recommended in post RAI follow-up every 4–6-week interval for 6 months or until patient is hypothyroid and stable on thyroid hormone replacement [68]. Thyroid hormone replacement with levothyroxine should be started soon after total or near-total thyroidectomy. In patients post-op after partial thyroidectomy for a hot nodule, we prefer follow-up and T4 replacement only when TSH begins to rise.

Not much is known about the impact of hyperthyroidism and its treatment on health-related quality of life (HRQoL). This needs to be kept in mind while treating those patients. A study suggested that hyperthyroidism, including toxic nodular goiter, can cause disease-specific and generic HRQoL impairments which may persist up to 6 months after treatment [76].

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Chapter 11
Thyroid Incidentalomas

Danae A. Delivanis and M. Regina Castro

Introduction

Endocrine incidentalomas are common, and advances in science and technology, especially improvements in the quality of images in ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography [PET] (^{18}FDG-PET) scans, have considerably increased the rate of detection of these incidental findings [1–3]. Thyroid incidentalomas are one of the most common incidental findings on imaging studies of the neck and are defined as nonpalpable, asymptomatic thyroid nodules that are discovered on an imaging study or during an operation performed for reasons unrelated to the thyroid gland. However, clinically unsuspected nodules have been identified in up to 50–60% of patients at autopsy [4, 5]. Thyroid incidentalomas are most commonly detected on US, followed in frequency by CT, MRI scans, ^{18}FDG PET-CT scans [6], and chest X-rays (CXR). The discovery of these nodules raises concern about thyroid malignancy and hypersecretion of thyroid hormones.

Historical reviews document a 5% malignancy rate associated with clinically apparent thyroid nodules [7]. Nonpalpable nodules have the same risk of malignancy as clinical palpable nodules of the same size [8]. The risk of malignancy for a thyroid incidentaloma varies depending on the imaging characteristics of the nodule. Non-thyroid imaging studies such as CT, MRI, and CXR perform suboptimally in characterizing the morphology and echogenicity of the thyroid nodules. As a result, a thorough sonographic evaluation is required for the majority of thyroid

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incidentalomas [9]. The pattern of FDG uptake in the thyroid gland on PET imaging influences the likelihood of malignancy. Focal or unilateral FDG uptake is more likely to be associated with malignancy than bilateral diffuse uptake [10], which is commonly seen in Hashimoto's thyroiditis [11].

As several studies have shown, the increased detection of thyroid incidentalomas and ultrasound-guided FNA biopsies has resulted in an upsurge detection of occult papillary microcarcinoma [12, 13]; this has led to a nearly threefold increase in thyroid cancer diagnosis from 1975 to 2009, with a disproportionate rise in small papillary cancers. However, despite the increase in incidence, the mortality rate has remained unchanged [13], supporting the notion that diagnosing and treating these cancers produced no survival benefit [14].

The increased number of unnecessary investigations and procedures, including diagnostic surgeries, has added to patients' anxiety, has increased morbidity, and finally has increased health-care cost [15], leading clinicians to further question the clinical significance of incidental thyroid malignancy and to debate on the optimal diagnostic evaluation and management of a thyroid incidentaloma.

Prevalence

Thyroid incidentalomas are the most common form of endocrine incidentalomas [3, 4]. The prevalence of thyroid nodules depends on the population studied, level of iodine intake in the population, age, sex, history of radiation exposure, and imaging modality being used [16, 17]. Thyroid nodules are more common in areas with low iodine intake, in women, and in older individuals, as well as in patients with a history of head and neck radiation [18, 19]. Finally depending on the diagnostic modality being used, the prevalence of thyroid incidentalomas can vary from 2 to 67% [20, 21].

Modes of Discovery of Thyroid Incidentalomas

Thyroid Ultrasound

Thyroid nodules identified during sonography of extra-thyroidal structures such as carotid arteries (Fig. 11.1) [22], cervical lymph nodes, parathyroid glands, or other miscellaneous neck masses constitute US-detected thyroid incidentalomas [9].

Older studies report that neck US detects incidentalomas with a prevalence of 10–30% [23–25]. However, with more recent-generation US machines, with improved spatial resolution, the prevalence can be as high as 67%, comparable to that found at autopsy [20]. The malignancy rate of thyroid incidentalomas detected by US varies from 1.3 to 12% in various studies [26, 27].

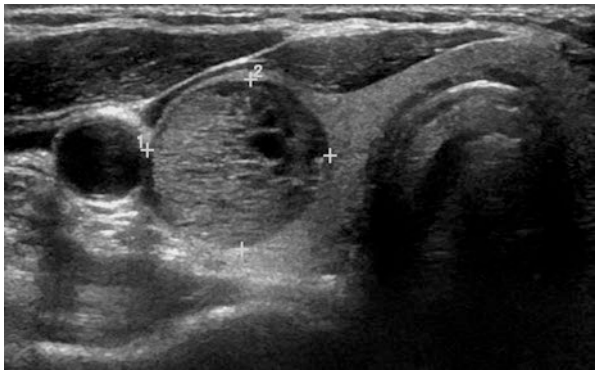

Fig. 11.1 Incidentally discovered thyroid nodule of the right thyroid gland during carotid Doppler ultrasonography

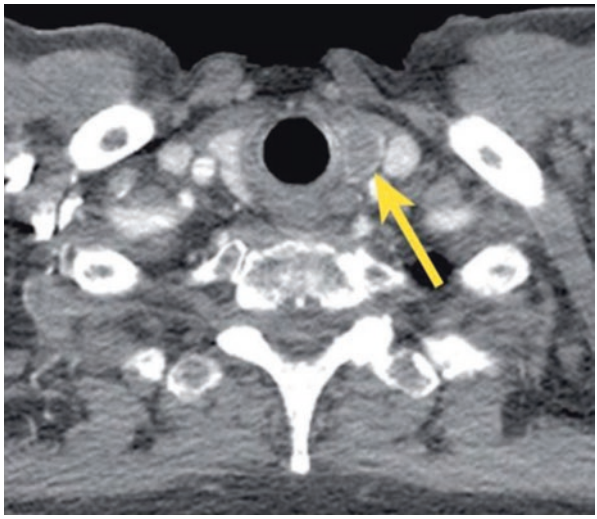

Fig. 11.2 Right thyroid nodule identified on chest CT

CT and MRI Scans

Thyroid incidentalomas are seen in up to 25% of contrast enhanced chest CT scans [28] and 15% of neck CT scans (Fig. 11.2) [29, 30]. CT examinations are not highly reliable in distinguishing benign from malignant thyroid lesions due to the lack of adequate spatial resolution to reveal some findings commonly used in ultrasonography such as cystic changes, microcalcifications, and irregular margins [31, 32]. In a study of Shetty et al., CT findings matched the sonographic characterization in only 53% of patients, correctly identified the dominant nodule but missed multinodularity in 30%, and underestimated the number of nodules in 10% [32]. However, most recent recommendations from the Incidental Thyroid Findings Committee seem to be taking into consideration certain CT and MRI imaging characteristics (e.g., abnormal lymph nodes and/or invasion of local tissues by the thyroid nodule) to

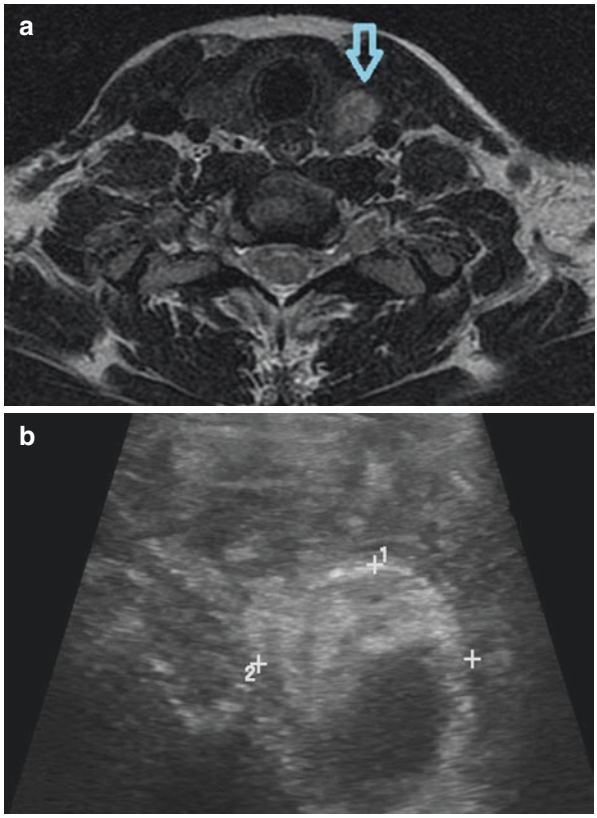

Fig. 11.3 (**a**) MRI of cervical spine identifies an incidental nodule in left lobe of thyroid. (**b**) Corresponding US image of the thyroid nodule incidentally identified on cervical MRI

differentiate patients with thyroid incidentalomas into a high- and low-risk category for thyroid cancer [15].

On MRI, both malignant and benign thyroid nodules can have isointense T1 and hyperintense T2 signals (Fig. 11.3) [33]. The malignancy rate of thyroid incidentalomas detected on CT and MRI ranges from 0 to 11% [30, 34].

^{18}FDG-PET

^{18}FDG-PET is increasingly performed during the evaluation of patients with both malignant and nonmalignant illness. The normal thyroid gland)shows very low-grade FDG uptake and is usually not visualized on the whole-body ^{18}FDG-PET scan [35–39]. Incidental ^{18}FDG-PET uptake in the thyroid gland can be either focal or diffuse (Fig. 11.4). Focal ^{18}FDG-PET uptake in the thyroid is incidentally detected in 1–2% of patients, while an additional 2% of patients demonstrates diffuse thyroid uptake [40, 41]. The overall reported incidence of ^{18}FDG-PET thyroid incidentalomas varies in different studies from 1 to 4% [36, 38, 42], whereas the prevalence of

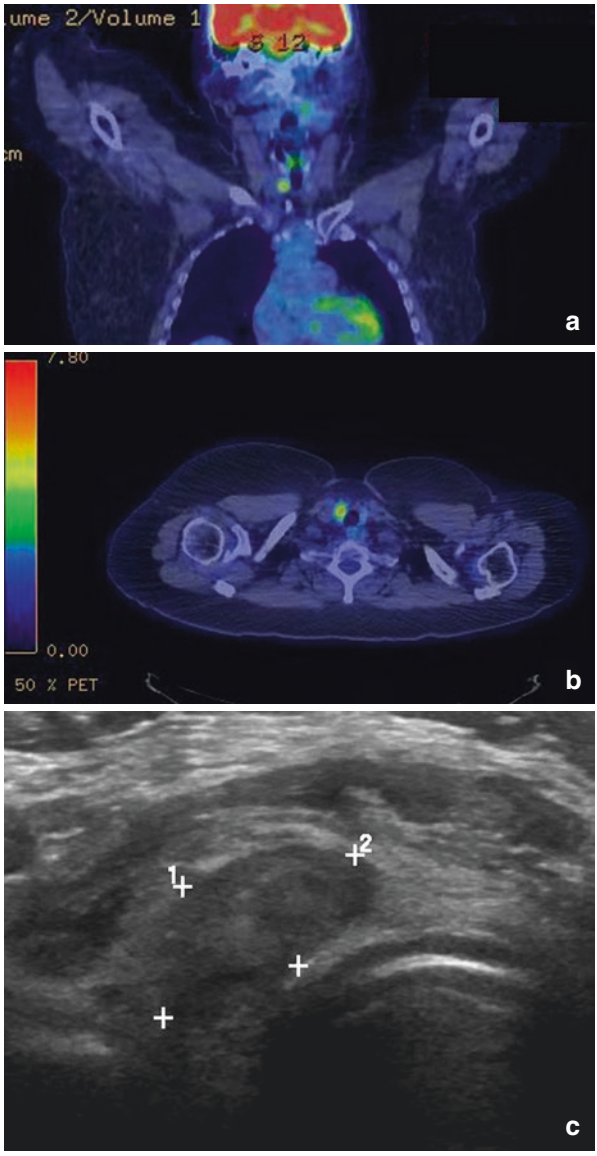

Fig. 11.4 (**a**, **b**) Focal ^{18}FDG-PET uptake of the left thyroid gland. (**c**) Corresponding ultrasonography image of the left thyroid nodule identified on ^{18}FDG-PET

thyroid cancer in these studies is remarkably high, ranging from 14 to 56% [21, 37–39, 42–45].

Diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake in the setting of Hashimoto's thyroiditis or other diffuse thyroidal illness. However, if diffuse ^{18}FDG-PET thyroid uptake is detected, it should still prompt sonographic examination to ensure there is no evidence of clinically relevant underlying nodularity.

Finally, thyroid incidentalomas can also be detected on other nuclear medicine studies such as ^{99}mTechnetium-methoxyisobutylisonitrile (MIBI) and ^{111}Indium-octreotide scans, but these cases are rare [46, 47].

Chest X-ray

Large-in-size thyroid nodules may as well be incidentally identified on chest X-ray, when structural deviation of adjacent organs occurs, as illustrated in Fig. 11.5. This finding should prompt further evaluation with neck ultrasound to better define nodule size, number, and sonographic characteristics and determine need for additional investigation based on these findings.

Diagnostic and Treatment Approach

The major aim when faced with patients with thyroid incidentalomas is to exclude thyroid cancer and to identify those few patients who will benefit from additional investigations and proper management, without incurring in unnecessary tests or causing needless anxiety [48]. Despite the sharp rise in thyroid cancer detection, the mortality of thyroid cancer has not changed. This is not unexpected, considering that we are detecting more cases of thyroid cancer which are most likely clinically

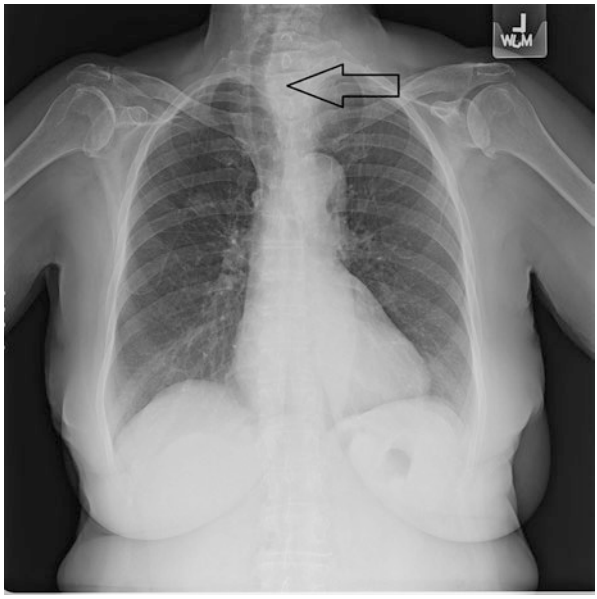

Fig. 11.5 Antero-posterior chest X-ray of a large left side thyroid nodule resulting in tracheal deviation to the right

indolent and/or low-risk disease [13]. The appropriate management of thyroid incidentalomas remains a public health dilemma.

Given that the risk of thyroid cancer in incidentally discovered thyroid nodules is not insignificant, a thorough sonographic evaluation of the thyroid gland should be performed in the majority of patients with a thyroid incidentaloma. Once the nodule is confirmed on US, then management should be identical to a clinically apparent thyroid nodule, since the risk of malignancy is the same [9]. However, particular attention is warranted in the incidentally discovered thyroid nodule with increased ^{18}FDG-PET uptake given that the risk of malignancy in these nodules is higher [39, 42]. The American Thyroid Association (ATA) as well as the Incidental Thyroid Findings Committee are providing guidelines for appropriate management of these patients [9, 15].

History and Physical Examination

All patients with a thyroid incidentaloma should have a complete history and targeted physical exam of the thyroid gland and cervical lymph nodes. Pertinent information in the history that should increase suspicion of malignancy include young age <35 years or older individuals >60 years [34], male sex, a prior history of childhood head and neck radiation therapy, total body radiation for bone marrow transplantation [49], exposure to ionizing radiation from nuclear fallout in childhood or adolescence [50], or a family history of thyroid cancer or other syndromes associated with thyroid cancer (Table 11.1) in a first degree relative.

As already mentioned, patient's age is an important clinical factor to consider. In the study of Shetty et al., patients younger than 35 years of age, with a thyroid incidentaloma, had a significantly higher incidence of malignancy (50% versus 5%) compared to patients older than 45 years of age [32]. Similar data are supported by other studies as well [51]. Two factors that could account for the above difference could be that young patients undergo imaging studies less frequently and that the prevalence of benign thyroid nodules increases with age making the ratio of malignant to benign thyroid nodules higher in young patients [32].

In addition, several studies [51, 52] have shown that there is a slightly higher risk of tumor growth in young patients (age <40 years) with subclinical, low-risk, papillary thyroid cancers compared to older individuals.

Table 11.1 Syndromes associated with thyroid cancer

PTEN hamartoma tumor syndrome (Cowden's disease)
Familial adenomatous polyposis (FAP)
Carney complex
Werner syndrome/progeria
Multiple endocrine neoplasia (MEN) 2

Both observations underline the importance of taking patient's age into consideration during the diagnostic evaluation of thyroid incidentalomas.

Other important elements of the history that should raise concern for malignancy include evidence of rapid growth of a nodule, the presence of hoarseness, dysphagia, dyspnea, and neck pain. Hoarseness can occur due to tumor invasion or compression of the recurrent laryngeal nerve. Dyspnea, cough, and choking spells may occur from tracheal compression and dysphagia from esophageal compression from large thyroid nodules [48].

Physical examination is important to determine if the nodule is palpable and to evaluate the size, location, consistency, and mobility of the nodule. A solitary nodule is more likely to represent carcinoma than a single nodule within a multinodular gland, with an incidence of malignancy from 2.7 to 30% and 1.4 to 10%, respectively [53]. Yet, the overall risk of malignancy within a gland with a solitary nodule is approximately equal to that of a multinodular gland due to the additive risk of each nodule [54].

Physical findings suggestive of possible malignancy include vocal cord immobility, a very firm nodule on palpation, the presence of cervical lymphadenopathy, large size >4 cm [55], and fixation of the nodule to adjacent tissues [7]. Vocal fold immobility is not always adequately assessed by patient's voice, and flexible laryngoscopy may be advised in cases of high suspicion of vocal fold tumor invasion [56]. Neck tenderness appreciated on examination should also raise the concern for acute or subacute thyroiditis.

Physical exam, on the other hand, may be limited by the patient's body habitus and the experience of the clinician on neck palpation, such that obtaining thyroid US becomes an important step in the diagnostic evaluation of these patients [57].

Laboratory Investigation

All patients with a thyroid nodule should have a serum TSH level measured. A serum calcitonin level should be obtained in patients with a family history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) types 2a or 2b, pheochromocytoma, or hyperparathyroidism [58, 59]. An antimicrosomal antibody titer (anti-TPO) should be obtained in patients with an elevated serum TSH level to make a diagnosis of Hashimoto's thyroiditis. In addition, in cases of malignant thyroid nodules, studies have shown that increased levels of TSH are associated with increased likelihood of thyroid cancer and may also be seen in more advanced stages of differentiated thyroid cancer [60, 61].

Patients with suppressed serum TSH levels should have free T4 and total T3 levels measured and an iodine I-123 thyroid scan performed to investigate whether the nodule is hyperfunctioning [62]. Because the risk of malignancy in hyperfunctioning nodules is very low (<1%), cytologic evaluation is unnecessary [48].

Thyroid Ultrasound

Ultrasonography is the imaging study of choice for the assessment of thyroid nodules. It is very helpful to evaluate the thyroid parenchyma (homogeneous or heterogeneous) and gland size, as well as the size, location, and sonographic characteristics of any nodule(s), to evaluate the presence or absence of cervical lymphadenopathy, and to provide accurate measurements of nodule size and volume for interval monitoring [48].

Ultrasonographic characteristics that are associated with an increased risk of malignancy include solid appearance, marked hypoechogenicity, the presence of internal microcalcifications, irregular margins (Fig. 11.6b, c), size >3 cm, increased internal vascularity, an absence of halo, and a shape that is taller than wide measured on a transverse view [27, 63]. Features with the highest specificity for thyroid cancer are microcalcifications, irregular margins, and tall shape [64]. The specificities of the aforementioned features for detecting thyroid cancer vary greatly, from 41 to 95%, but their sensitivities are consistently very low [27, 64, 65]. However, the probability of malignancy increases significantly when two or more suspicious criteria coexist [66].

Although the ATA recommends that a thyroid US be performed in all patients with a thyroid incidentaloma identified on CT, MRI, or FDG-PET [9], the Incidental Thyroid Findings Committee attempts to allow for some exemptions to the rule [15]. Patients with a thyroid incidentaloma and no suspicious CT or MRI findings (defined as normal lymph nodes and/or no invasion of local tissues by the thyroid nodule) that have (1) limited life expectancy due to comorbidities, (2) have a <1 cm nodule and are ≤35 years of age, and (3) have a <1.5 cm nodule and are ≥35 years of age may not necessarily require a diagnostic US, and a patient-centered approach and discussion are instead recommended by this organization. In several studies validating the application of the above criteria, a 35% decrease of the US-guided FNA procedures [47] with only a 1.2% missed incidental malignancies was noted [67].

Fine-Needle Aspiration (FNA) Biopsy

FNA is the most important study in the evaluation of an incidentally discovered thyroid nodule with suspicious sonographic features. Studies have reported lower rates of both nondiagnostic and false-negative cytology from FNA procedures performed using US guidance compared to palpation [68, 69]. Therefore, for nodules with a cystic component, or nonpalpable posteriorly located nodules that are at high risk for nondiagnostic or sampling error, respectively, a US-guided FNA biopsy should be performed [70]. Thyroid US has been widely used to stratify the risk of malignancy in thyroid nodules and to assist in decision-making about whether FNA is indicated. As a result, the pattern of sonographic features associated with a nodule confers a risk of malignancy and, combined with nodule size, guides FNA decision-making.

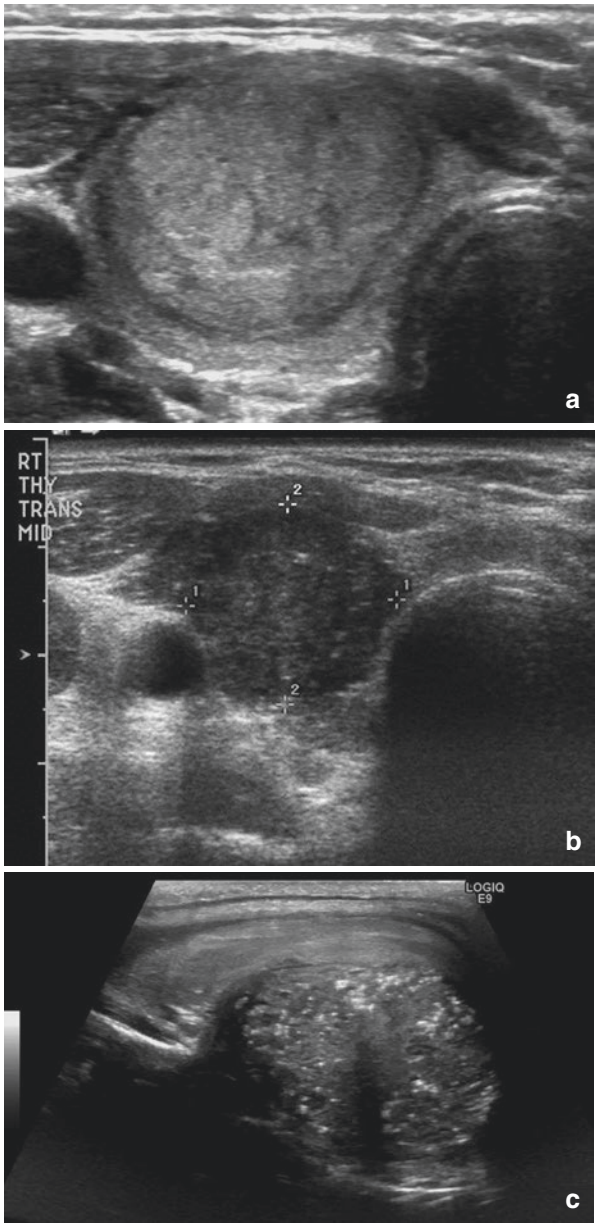

Fig. 11.6 (**a**) Classic sonographic image of a benign thyroid nodule. Note smooth and well-demarcated boarders and isoechogenicity. (**b**) Classic sonographic features of papillary thyroid cancer. Note hypoechogenicity, irregular margins. (**c**) Classic sonographic features of papillary thyroid cancer. Note hypoechogenicity, irregular margins, microcalcifications

Most recent ATA guidelines recommend that only nodules ≥1 cm with a sonographic pattern of high or intermediate suspicion should be evaluated with FNA, since they have a greater potential to be clinically significant cancers [9]. Occasionally, however, there may be nodules smaller than 1 cm that require further evaluation because of the presence of worrisome clinical symptoms or associated cervical lymphadenopathy.

Although FNA for thyroid incidentalomas is a low-risk procedure, for some non-malignant nodules, confirmation of a benign diagnosis may be difficult, e.g., inability of cytology to differentiate between follicular carcinoma and follicular adenoma [59]. This results in a substantial number of patients undergoing diagnostic surgical excision of benign nodules. In a retrospective study, 25–41% of patients who underwent FNA for thyroid incidentalomas proceeded to surgery, and in 36–75% of them, the nodules were benign [46, 63]. Of those who do not undergo surgery, a vast majority are referred for follow-up thyroid ultrasound.

The background incidence of subclinical thyroid cancers at autopsy is estimated at approximately 36% [71]. Compared with other clinically apparent malignancies, incidentally discovered thyroid cancers are more likely to be papillary carcinomas and to be smaller in size and less likely to develop metastases [46, 67]. The prognosis for most small, localized papillary cancers is excellent, even without treatment, as illustrated in an observational study of 340 patients with untreated papillary microcarcinoma. The authors of the study did not find any cancer deaths over a 10-year period, and new nodal metastases were seen in only 3% of patients [72]. Another factor to consider in the diagnostic algorithm of thyroid incidentalomas is the age of patients, with young individuals (<40 years of age) having a higher rate of thyroid malignancy [32, 51] and older individuals with short life expectancy being unlikely to benefit from a diagnosis and treatment of thyroid cancer that would not otherwise alter their quality of life or their life expectancy.

Most patients with diffuse ^{18}FDG-PET uptake demonstrate benign inflammatory disease such as Hashimoto's thyroiditis, and no further intervention or FNA is required. Thyroid function testing in these patients is appropriate; however, one in three thyroid nodules with focal ^{18}FDG-PET uptake is shown to be cancerous. Therefore, all ^{18}FDG-PET-positive thyroid nodules ≥1 cm require cytological evaluation [37, 40].

^{18}FDG-PET-positive thyroid nodules <1 cm that do not meet FNA criteria may be monitored similarly to thyroid nodules with high-risk sonographic patterns that do not meet FNA criteria [9]. Several studies have suggested that ^{18}FDG-PET may be used in the diagnostic algorithm of FNA of cytologically indeterminate nodules because of its high negative predictive value of 95–100% [73, 74]. However, the incremental benefit of ^{18}FDG-PET imaging in these patients was questioned by a later prospective analysis in which no additional diagnostic benefit or improved risk assessment was seen when ^{18}FDG-PET was added to the already obtained thyroid US [75]. ^{18}FDG-PET imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology [9].

Conclusion

Thyroid incidentalomas are frequently encountered in clinical practice. The majority of patients with a thyroid incidentaloma should undergo sonographic examination of the thyroid gland after careful history, physical exam, and laboratory

evaluations have been completed. Patients with suspicious sonographic features should undergo FNA biopsy. However, the majority of thyroid incidentalomas are benign thyroid nodules, and a systematic approach is important to avoid unnecessary procedures that result in increased patient's anxiety and health-care cost.

Conflict of Interest All authors state that they have no conflicts of interest.

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Chapter 12
Surgery for Thyroid Nodules

Randall P. Scheri and Julie Ann Sosa

Introduction

Palpable thyroid nodules are common, with a prevalence of 4–7% in the general population [1]. Subclinical thyroid nodules are even more common and are detected in 19–68% of healthy patients without known thyroid disease [2]. Frequently, thyroid nodules are incidentally identified on imaging studies: 67% of cervical ultrasounds, 16% of computed tomography scans, 9% of carotid duplex studies, and 2–3% of positron emission tomography scans have been reported to include thyroid nodules that were not anticipated based on history and physical examination [3]. The high frequency of incidentally identified thyroid nodules has led to a significant increase in the number of thyroid biopsies and subsequent thyroid surgeries performed in the USA. Indeed, over a 5-year period, there was a 107% increase in the number of fine needle aspiration (FNA) biopsies of the thyroid, such that by 2011, nearly two thirds of all tissue biopsies performed in the USA were on the thyroid. Almost certainly as a result, the number of thyroid nodule-related operations also increased by 31% over the same period. The frequency of total thyroidectomies increased by 12% per year, while lobectomies only increased by 1% per year, such that by 2011, the majority of patients (56%) underwent total thyroidectomy [4].

The incidence of thyroid cancer has increased over the last several decades at a pace faster than any other malignancy in the USA, with 62,450 new cases diagnosed in 2015 [5]. This has almost exclusively been due to an increase in the incidence of papillary thyroid cancer (PTC), as the incidence of other primary thyroid malignancies has remained stable. The increase in incidence of PTC also has been seen in several other high-income countries; most notably, a thyroid cancer screening program in South Korea that was initiated in 1991 ultimately is believed to have led to a 15-fold increase in the incidence of PTC between 1993 and 2011 [6]. This suggests

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that much of the increased incidence in thyroid cancer is due in part to surveillance bias. that is, an increase in (largely radiological) detection of clinically insignificant tumors [7]. However, the number of large thyroid tumors has increased as well [8], suggesting that factors other than improved detection, such as obesity or environmental factors, also may be contributing to the international epidemic of thyroid cancer [9].

Thyroid surgery is the mainstay of treatment for thyroid cancer and nodules suspicious for cancer. Hyperthyroidism and compression from thyroid goiter are the two other indications for thyroid surgery. Treatment guidelines have been created by the American Thyroid Association (ATA) to inform clinicians, patients, researchers, and health policymakers based on published evidence related to the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis (2016) [10], adult patients with thyroid nodules and differentiated thyroid cancer (2015) [11], children with thyroid nodules and thyroid cancer (2015) [12], medullary thyroid cancer (2015) [13], and thyroid disease during pregnancy and postpartum (2011) [14]. These guidelines inform clinical decision-making for the surgical management of patients with thyroid nodules in different clinical settings and are referenced throughout the following chapter.

Preoperative Evaluation

Patients referred for consideration of thyroid resection for nodular disease should have a thorough history to evaluate for symptoms and signs of hyper- and hypothyroidism and local compression, risk factors for thyroid cancer, and a family history of thyroid cancer and/or other endocrinopathies. Symptoms of hyperthyroidism include weight loss, anxiety, hair loss, palpitations, heat intolerance, and insomnia. Symptoms of hypothyroidism include weight gain, fatigue, cold intolerance, and constipation. Symptoms of local compression include a globus sensation, dysphagia, dyspnea, and dysphonia and may be due to goiters or large nodules that compress surrounding structures and especially the aerodigestive tract. In the setting of malignancy, these symptoms are concerning for locally advanced disease and may be due to invasion into surrounding structures. Dysphonia may be due to tumor invasion into the recurrent laryngeal or vagus nerves. Rapid nodule growth or onset of symptoms is concerning for an aggressive malignancy. Risk factors for thyroid cancer include a history of radiation exposure (particularly in childhood or adolescence), family history of thyroid cancer (such as familial medullary or PTC), and history of a familial cancer syndrome, such as multiple endocrine neoplasia (MEN) Type 2.

Physical examination should focus on the thyroid gland and cervical lymph nodes. Firm or irregular nodules are concerning for malignancy. Enlarged cervical lymph nodes are concerning for metastases. Fixed nodules and/or extensive lymphadenopathy are concerning for locally advanced disease. Inability to palpate the inferior aspect of the thyroid gland or a positive Pemberton's sign should raise

concern for thyroid extension into the mediastinum. The patient also should be evaluated for signs and symptoms of hyperthyroidism, including anxiety, tremor, heat intolerance, tachycardia, palpitations, weight loss, lid lag, exophthalmos, orbital edema, and pretibial edema.

The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [11] recommend that all patients with thyroid nodules have a TSH drawn to evaluate thyroid function. If the TSH is suppressed, a radionuclide thyroid scan should be obtained to determine if the nodule is hyperfunctioning. A radionuclide scan is not recommended for patients with a normal or elevated TSH. Fine needle aspiration of hyperfunctioning thyroid nodules is not recommended, since these nodules are rarely malignant. A calcium level should be obtained to evaluate for hyperparathyroidism in the appropriate setting. If hyperparathyroidism is identified, parathyroidectomy should be performed at the same time as thyroid surgery. Patients with medullary thyroid carcinoma (MTC) or a suspicion of MTC should have serum calcitonin and carcinoembryonic antigen (CEA) tumor markers drawn prior to surgery. These levels correlate with extent of disease and provide important prognostic information. Patients with calcitonin levels >500 pg/mL are at risk for distant metastases and should have a neck/chest computed tomography (CT) scan, liver magnetic resonance imaging (MRI), and bone scan to evaluate for distant metastases [13]. All patients with a new diagnosis of MTC should have genetic counseling and testing performed, since 6–7% will harbor an unsuspected RET proto-oncogene germline mutation and MEN2 syndrome [15]. Patients with an unknown or positive RET mutation should have laboratory testing to exclude pheochromocytoma and primary hyperparathyroidism prior to surgery. If diagnosed with pheochromocytoma, adrenalectomy should be performed prior to thyroidectomy.

Preoperative neck ultrasound is essential for all patients with thyroid nodules. The size of the thyroid gland along with the number, location, and size of thyroid nodules and the relationship between the nodules and thyroid and the surrounding cervical structures should be noted. FNA is the diagnostic procedure of choice for thyroid nodules to guide further therapy and inform surgical management. The 2015 ATA guidelines [11] recommend that an FNA be performed for those nodules with high and intermediate suspicion sonographic appearance that are >1 cm, low suspicion sonographic appearance >1.5 cm, and very low suspicion appearance >2 cm. FNA is not recommended for nodules with a benign sonographic appearance. High suspicion features (Fig. 12.1) are solid hypoechoic nodules with one or more of the following features: irregular margins, microcalcifications, taller-than-wide shape, rim calcifications with extrusive soft tissue component, or evidence of extrathyroidal extension. The estimated risk of malignancy for these nodules is 70–90%. Intermediate suspicion features (Fig. 12.2) are hypoechoic nodules with smooth margins without microcalcifications, extrathyroidal extension, or taller-than-wide shape. The estimated risk of malignancy for these nodules is 10–20%. Low suspicion features (Fig. 12.3) are iso- or hyperechoic solid nodules or partially cystic nodules without microcalcifications, irregular margins, extrathyroidal extension, or taller-than-wide shape. The estimated risk of malignancy for these nodules is 5–10%. Very

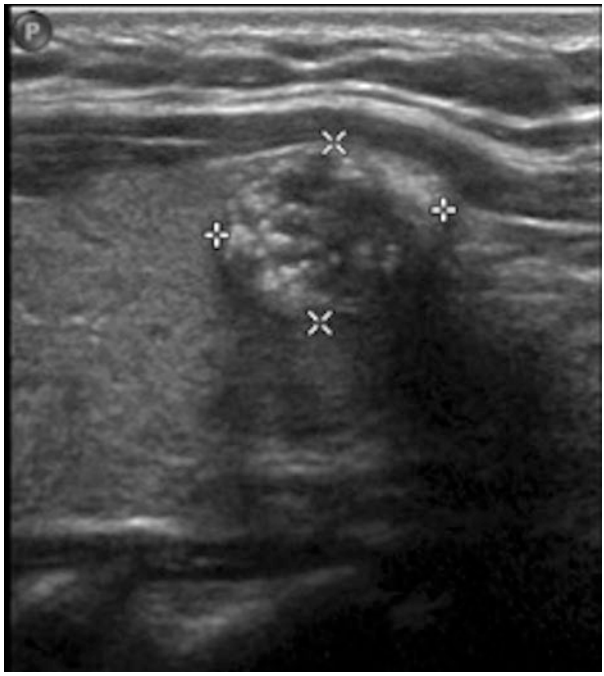

Fig. 12.1 High suspicion thyroid nodule with hypoechoic appearance and microcalcifications

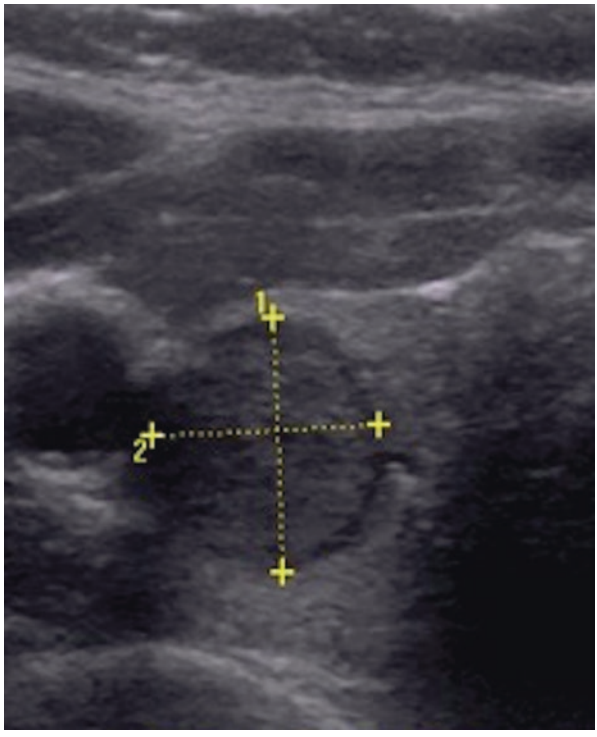

Fig. 12.2 Intermediate suspicion thyroid nodule with hypoechoic appearance and smooth borders

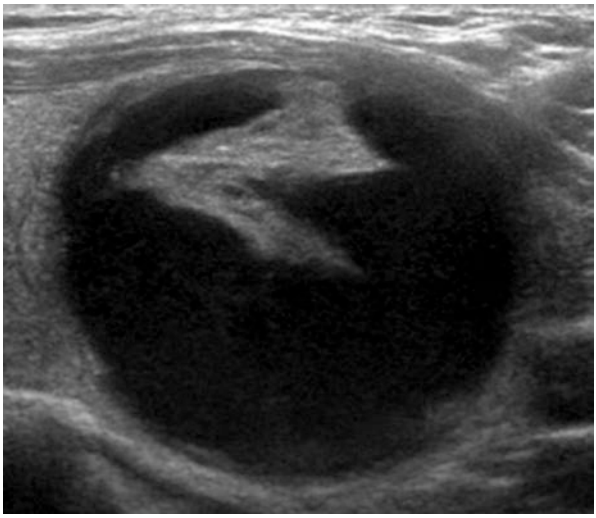

Fig. 12.3 Low suspicion thyroid nodule with partially cystic appearance with an eccentric solid component

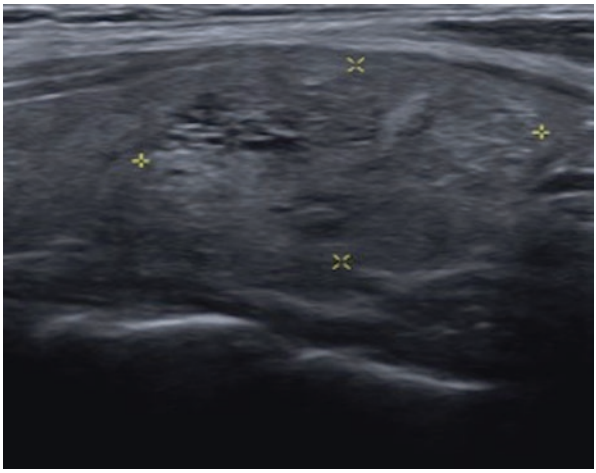

Fig. 12.4 Very low suspicion thyroid nodule with spongiform appearance

low suspicion features (Fig. 12.4) are spongiform appearance and the absence of any of the suspicious features mentioned above. The risk of malignancy is <3%. Benign features (Fig. 12.5) are purely cystic nodules, with a risk of malignancy of <1%.

For patients with known thyroid cancer or cytology and/or molecular findings suspicious for malignancy, lymph node mapping with ultrasound should be performed of the central and lateral neck compartments to evaluate for lymph node metastases. An FNA should be performed on lymph nodes ≥8 mm with any imaging features that are suspicious for malignancy, which include microcalcifications, cystic component, peripheral vascularity, round shape, and hyper-echogenecity (Fig. 12.6). Thyroglobulin washout of the FNA aspirate should be performed for indeterminate cytology to improve the accuracy of FNA for differentiated thyroid cancer. A thyroglobulin concentration <1 ng/mL is reassuring for benign disease,

Fig. 12.5 Benign cystic thyroid nodule with comet tail artifact from colloid

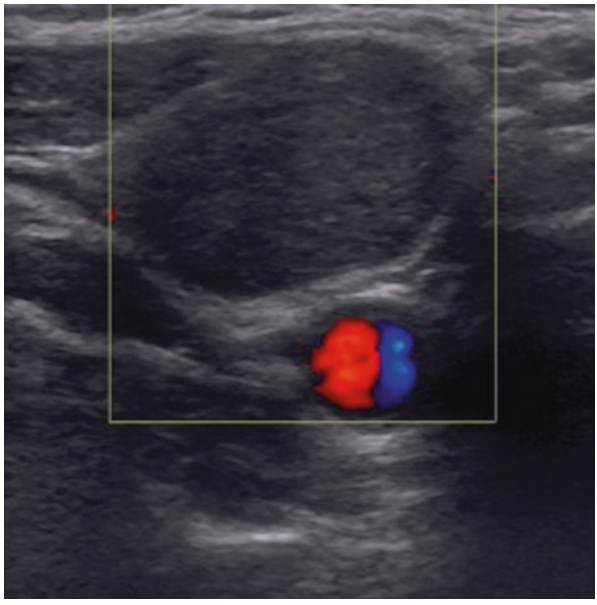

Fig. 12.6 Ultrasound of enlarged hyperechoic lateral compartment lymph node suspicious for metastases

but optimal values for the identification of malignancy are less clear. A meta-analysis by Pak et al. pooling eight studies evaluating the optimal cutoff value for thyroglobulin washout determined that the optimal cutoff was 32 ng/mL for discriminating between benign and malignant lymph nodes [16]. Cross-sectional imaging with CT is not indicated except for goiters that are suspected to extend into the mediastinum or retropharyngeal space where ultrasound is limited or for locally advanced cancers with posterior extension or associated with bulky lymphadenopathy (Fig. 12.7). In these situations, intravenous contrast is essential to evaluate for invasion into the aerodigestive tract, nerves, and major blood vessels and to facilitate operative planning.

All patients with subjective or objective voice changes, a prior history of anterior cervical or chest surgery, or locally advanced cancer should be evaluated with laryn-

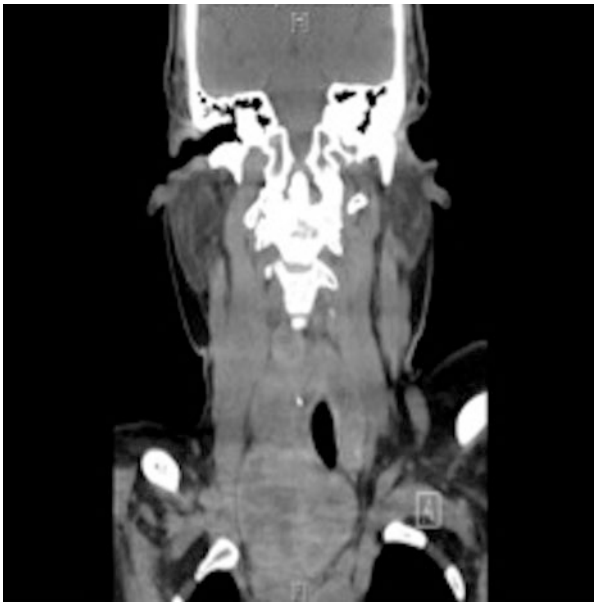

Fig. 12.7 Computed tomography demonstrating substernal thyroid extension

goscopy to assess vocal cord function. A paralyzed vocal cord significantly increases the risk of surgery and may alter surgical planning. Surgery on the side contralateral to the paralyzed vocal cord should be undertaken with caution because the patient is at increased risk for bilateral vocal cord paralysis and subsequent tracheostomy.

Fine Needle Aspiration/Molecular Testing

The management of thyroid nodules is largely directed by the cytologic findings from FNA; however, these results must be considered in the context of ultrasound and clinical findings. Results from FNA should be reported using the Bethesda classification system (Table 12.1), which recognizes six different categories and provides an estimation of malignancy for each category [17]. The risk of malignancy for each Bethesda category may vary between institutions, such that clinicians should be aware of the risk of malignancy at their own institutions for each cytologic category in order to make the most informed decisions for treatment [18]. Generally, the majority of thyroid nodules have benign (Bethesda category II) cytology (75%), a small proportion have malignant (Bethesda category VI) cytology (2–5%), while the remainder (20–30%) have indeterminate cytology. Indeterminate cytology includes atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) (Bethesda category III), follicular neoplasm (FN) (Bethesda category IV), and suspicious for malignancy (SM) (Bethesda category V).

Molecular testing may be performed for indeterminate nodules to supplement clinical and sonographic findings and provide further risk stratification. One option for molecular testing is the use of a gene expression classifier that analyzes 167 genes from

Table 12.1 Bethesda system for reporting thyroid cytology

Diagnostic criteria		Estimated risk of malignancy (%)
I	Nondiagnostic	1–4
II	Benign	0–3
III	Atypia of undetermined significance of follicular lesion of undetermined significance	5–15
IV	Follicular lesion or suspicious for a follicular lesion	15–30
V	Suspicious for malignancy	60–75
VI	Diagnostic for malignancy	97–99

an indeterminate nodule and compares them to the gene signatures of benign and malignant lesions using a proprietary algorithm to classify the nodule as either benign or suspicious. The gene expression classifier test was validated for 265 nodules with indeterminate cytology [19]. The negative predictive value (NPV) for AUS/FLUS and FN was 95% and 94%, respectively, which is similar to benign cytology results; therefore, many argue that it is sufficient to "rule out" malignancy. On the other hand, the NPV for Bethesda V lesions was only 85%, which is thought to be inadequate to exclude malignancy. The positive predictive value (PPV) for suspicious results was only 38% for AUS/FLUS and 37% for FN, making it insufficient to "rule in" malignancy. Another molecular approach is to evaluate the FNA aspirate for a panel of seven gene mutations or rearrangements (including BRAF, RAS, RET/PTC, and PAX8/PPARG translocation) associated with thyroid cancer. A single-center prospective study by Nikiforov et al. [20] analyzed 513 cytologically indeterminate nodes with the seven gene mutation panel and definitive histopathological assessment. The BRAF, RET/PTC, and PAX8/PPARG mutations were associated with 100% risk of malignancy, while the RAS mutation carried an 85% risk of cancer. The nonmalignant RAS-positive nodules were all follicular adenomas. Based on the high likelihood of malignancy, the authors suggested that patients with a positive BRAF, RET/PTC, and/or PAX8/PPARG mutation should undergo definitive thyroid cancer treatment and could avoid a diagnostic lobectomy and two-stage thyroidectomy (lobectomy followed by completion thyroidectomy). However, the low sensitivity for malignancy of the seven gene panel is felt to be inadequate to support surveillance for negative results. More recently, next-generation DNA sequencing for an expanded panel of genes has shown promising results, with a 90% sensitivity and 92% specificity for FN [21] and 91% sensitivity and 92% specificity for AUS/FLUS [22], but this has not yet been validated.

Surgical Management of Papillary Thyroid Cancer

There has been a long-standing controversy regarding the extent of surgery for patients with PTC and whether thyroid lobectomy or total thyroidectomy is superior (Table 12.2). Proponents of thyroid lobectomy argue that PTC is an indolent disease with an excellent prognosis, and the higher risks for recurrent laryngeal nerve injury

Table 12.2 Extent of surgery: reasons for/against total thyroidectomy for papillary thyroid cancer

For	Against
Regional or distant metastases	Localized tumor
Addresses multifocal and/or bilateral disease	Increased risk of RLN injury, hypoparathyroidism
Facilitates surveillance with Tg and/or imaging	Indolent disease that does not imply a significant risk of mortality, recurrence
Need for postoperative RAI	Requires lifelong thyroid hormone replacement

RAI radioactive iodine, *Tg* thyroglobulin, *RLN* recurrent laryngeal nerve

and hypoparathyroidism associated with thyroidectomy are not justified since there is not a clear survival benefit [23, 24]. In many patients, the need for lifelong thyroid hormone replacement may be avoided with lobectomy. Advocates for total thyroidectomy argue that surgery can be performed safely, and complete resection of the thyroid addresses the risks of multifocal and bilateral disease, facilitates treatment with radioactive iodine, and simplifies surveillance [25]. The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [11] recommend that patients with PTC measuring between 1 and 4 cm may be treated with either thyroid lobectomy or total thyroidectomy. Prior versions of these ATA guidelines [26] had recommended total thyroidectomy for PTC measuring >1 cm. This recommendation was based primarily on a study by Bilimoria et al. [27] using the National Cancer Database (NCDB) that included 52,173 patients with PTC demonstrating a slightly higher 10-year survival for total thyroidectomy vs thyroid lobectomy (98.4% vs 97.1%, respectively, $p < 0.05$). Several factors that could impact survival, including extrathyroidal extension, completeness of resection, and patient comorbidities, were not available for this study. A more contemporary NCDB study by Adam et al. [28] that included 61,775 patients with PTC accounted for these and other risk factors and found no survival advantage associated with total thyroidectomy compared to thyroid lobectomy for patients with tumors 1–4 cm in size, suggesting that thyroid lobectomy is an effective treatment for low-risk differentiated thyroid cancer. Another study using the Surveillance, Epidemiology, and End Results (SEER) database that included 22,724 patients with PTC also revealed no difference in survival between thyroid lobectomy and total thyroidectomy [29]. Since PTC is frequently multifocal, some studies have reported a lower risk of locoregional recurrence after total thyroidectomy [30]. However, in a retrospective study by Vaisman et al. [31] of 289 patients treated with thyroid lobectomy ($n = 72$) or total thyroidectomy ($n = 217$), there was no difference in structural recurrence between the lobectomy and total thyroidectomy groups (4.2% vs 2.3%, respectively; $p > 0.05$). There were no patients who died from thyroid cancer. Importantly, 88% of patients who recurred were rendered free of disease with additional therapy, suggesting that locoregional recurrence rates are low after lobectomy with proper patient selection and that recurrences can be treated without detriment to survival.

Based on these studies, the 2015 ATA guidelines recommended a more individualized approach to treatment, taking into consideration tumor features, patient characteristics, patient preference, and surgeon experience. The ATA has devised a risk

Table 12.3 ATA 2015 risk stratification system

ATA low risk	Papillary thyroid cancer with all of the following:
	– No distant metastases
	– No tumor invasion into local structures
	– No aggressive histology (tall cell, columnar, hobnail)
	– No vascular invasion
	– Clinical N0 or ≤5 lymph node micrometastases (<0.2 cm)
	Intrathyroidal encapsulated follicular variant of PTC
	Intrathyroidal well-differentiated FTC with capsular invasion and no/minimal vascular invasion (≤4 foci)
	Intrathyroidal papillary microcarcinoma, unifocal or multifocal
ATA intermediate risk	Microscopic invasion of tumor into perithyroidal soft tissue
	PTC with vascular invasion
	Clinical N1 or >5 pathologic lymph node metastases <3 cm
	Multifocal papillary microcarcinoma with ETE and BRAF mutated
	Aggressive histology (tall cell, columnar, hobnail)
ATA high risk	Macroscopic invasion of tumor into perithyroidal soft tissue
	Incomplete tumor resection
	Distant metastases
	Postoperative serum thyroglobulin suggestive of distant metastases
	Pathologic lymph node metastases ≥3 cm
	FTC with extensive vascular invasion (>4 foci)

PTC papillary thyroid cancer, *FTC* follicular thyroid cancer, *ETE* extrathyroidal extension

stratification scheme that categorizes patients into low-, intermediate-, and high-risk categories for recurrence that should be incorporated into treatment decisions [11] (Table 12.3). Patients with intermediate- or high-risk tumors (tumors that are >4 cm or with gross extrathyroidal extension, clinically apparent lymph node metastases, distant metastases, aggressive histological variants, and vascular invasion) should undergo a total thyroidectomy to enable radioactive iodine treatment and reduce the risk for recurrence and facilitate surveillance [32]. Regardless of tumor size, patients with a history of radiation exposure to the head and neck or familial thyroid cancer, or with bilateral thyroid nodules, should be considered for total thyroidectomy, since they are at risk for multifocal/bilateral cancer [11, 33]. Patients who have tumors between 1 and 4 cm without intermediate- or high-risk features are at low risk for recurrence and unlikely to need treatment with radioactive iodine; therefore, they may be treated with either thyroid lobectomy or total thyroidectomy. The decision for extent of surgery in these patients should be based on the overall treatment plan ideally formulated by a multidisciplinary team taking into consideration the individual risks/benefits of surgery, overall treatment goals, and patient preference. If thyroid lobectomy is selected, the patient should be informed (and consented) that if high-risk tumor features are identified during surgery (i.e., macroscopic extrathyroidal extension or metastatic lymph nodes), total thyroidectomy may be performed. Similarly, if high-risk tumor features are identified on final pathology, completion thyroidectomy should be performed.

If a FNA is suspicious for PTC (Bethesda V), there is a 60–75% risk of malignancy. Due to the high risk, these patients should be treated similarly to patients with a FNA diagnostic of malignancy (Bethesda VI), with either thyroid lobectomy or total thyroidectomy. Alternatively, a diagnostic lobectomy with frozen section/touch prep may be performed to determine if the tumor is malignant. If the intraoperative assessment confirms malignancy, a definitive oncological operation may be performed with either lobectomy or total thyroidectomy. If frozen section/touch prep is not definitive for malignancy, the operation should be terminated and the decision for completion thyroidectomy based on final pathology results.

For tumors <1 cm without lymph node metastases or other high-risk features, thyroid lobectomy is recommended, except if there are other indications for total thyroidectomy (history of radiation exposure to the head and neck, history of familial thyroid cancer, or the presence of bilateral thyroid nodules). Alternatively, active surveillance can be considered for these very low-risk tumors. A study from Japan by Ito et al. [34] evaluated nonoperative management among 1235 patients with papillary microcarcinoma with a mean follow-up of 75 months. At 10 years, only 6.8% of patients progressed to develop clinically significant disease, which was defined as an increase in tumor size to 12 mm or development of lymph node metastases. Disease progression at 10 years was observed in 22.5%, 4.5%, and 2.5% of patients who were aged <40, 40–60, and >60 years, respectively. None of the patients in the study developed distant metastases or died of PTC. Nonoperative management of sub-centimeter PTC with surveillance may be considered as an alternative to surgery for those patients at high risk for surgery due to severe comorbidities, those who have limited life expectancy, or those who are of advanced age.

The relationship between surgeon volume and patient outcomes after thyroidectomy has been extensively studied. Published studies have consistently demonstrated that surgeons who perform more thyroidectomies have superior outcomes, on average, with fewer complications and lower costs. Sosa et al. [35] analyzed the effect of surgeon volume on patient outcomes in 5860 patients who underwent total thyroidectomy in Maryland from 1991 to 1996. After adjustment for case mix and hospital volume, surgeon volume of >100 cases was associated with lower complication rates, shorter hospital stay, and lower cost. In a national study of 16,954 patients who underwent total thyroidectomy, Adam et al. [36] looked for a surgeon volume threshold using multivariate modeling and restrictive cubic spines. The study demonstrated that the likelihood of experiencing a complication decreased with increasing surgeon volume until surgeons performed >25 thyroidectomies per year. Complication rates were on average 51% higher when surgery was performed by low-volume surgeons. Based on these results, the authors defined high-volume thyroid surgeons as those who perform >25 total thyroidectomies per year, which has important implications for quality improvement and identification of criteria for referral. In areas where referral to high-volume surgeons is problematic, a surgeon could be identified to perform all the thyroidectomies in order to concentrate surgeon experience and facilitate improved patient outcomes.

A therapeutic central (Level VI) lymph node dissection (CLND) is recommended for patients with PTC who have clinically involved lymph nodes identified on either

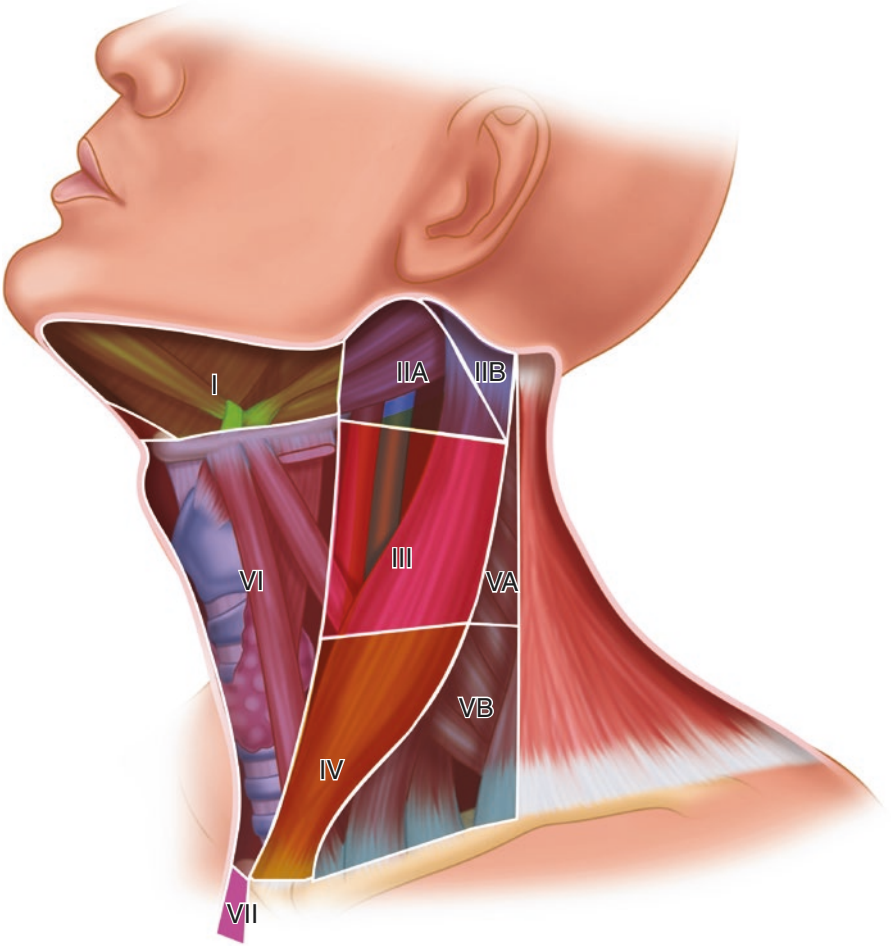

Fig. 12.8 Lymph node compartments in the neck

preoperative imaging or physical examination or intraoperatively. The ATA published a Consensus Statement on the Terminology and Classification of Central Neck Dissection in 2009 to standardize the surgical approach to the central neck [37]. A complete CLND should extirpate all lymph nodes within the central compartment, for which the anatomic boundaries are the hyoid superiorly, innominate artery inferiorly, and carotid arteries laterally (Fig. 12.8). There is no role for "berry picking" of clinically involved lymph nodes, since recurrence after non-compartment-oriented dissection is increased, along with the likelihood of requiring a higher-risk, remedial operation. The role of prophylactic CLND (pCLND) for patients without clinically evident lymph node metastases is controversial. Prophylactic CLND has been suggested to decrease locoregional recurrence and postoperative thyroglobulin levels, provide more accurate staging, and inform

radioactive iodine use [38]. However, pCLND has not been shown to be associated with improved survival, and it is associated with an increased chance of temporary recurrent laryngeal nerve injury and hypoparathyroidism [39]. A meta-analysis by Wang et al. [40] of studies evaluating pCLND revealed no difference in long-term complications or recurrence between patients who underwent total thyroidectomy alone or total thyroidectomy with pCLND. There was a trend toward lower recurrence among patients who underwent pCLND; however, 31 patients would have to be treated with pCLND in order to avoid one recurrence, suggesting that any benefit of pCLND would be small and observed only in high-volume surgical practices. The 2015 ATA guidelines for differentiated thyroid cancer recommend that prophylactic CLND be considered for advanced primary tumors (T3 or T4), or for tumors with clinically involved lateral compartment lymph nodes, and that thyroidectomy without prophylactic CLND dissection is appropriate for low-risk (T1 and T2) tumors [11]. If suspicious lateral compartment lymph nodes are identified on preoperative ultrasound, an FNA is recommended, and if the FNA is positive for malignancy, a lateral compartment lymph node dissection of levels IIa, III, IV, and Vb (Fig. 12.8) should be performed with preservation of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. The ATA published a Consensus Review and Statement Regarding the Anatomy, Terminology, and Rationale for Lateral Neck Dissection in Differentiated Thyroid Cancer in 2012 [41]. There is no role for prophylactic lateral compartment lymph node dissection for PTC.

Indeterminate Nodules

The goal of thyroid surgery for indeterminate thyroid nodules is to establish a definitive diagnosis while minimizing the risk of surgery and, if possible, perform the appropriate oncological operation up front if a diagnosis of malignancy can be established. Patients should be consented for a possible total thyroidectomy if a definitive diagnosis of malignancy is established during surgery and indications for total thyroidectomy are present, including such high-risk tumor features as extrathyroidal extension or lymph node metastases. An up-front total thyroidectomy should be performed for indeterminate lesions if the patient has a prior history of radiation exposure to the thyroid or a history concerning for familial thyroid cancer and if clinically significant nodules are present in the contralateral thyroid lobe. Intraoperative frozen section/touch prep analyses are not routinely recommended for indeterminate nodules as they are seldom helpful. In a study by Chen et al. [42], 120 patients with follicular neoplasms on FNA were treated with thyroid lobectomy with intraoperative frozen section. Frozen section only identified malignancy in 4 patients (3.3%), nondiagnostic in 104 patients (87%), and falsely positive in 6 patients (5%). A cost analysis by Zanocco et al. [43] comparing intraoperative frozen section for follicular neoplasms vs thyroid lobectomy alone revealed that intraoperative frozen section was not cost-effective. Frozen section/touch prep is unable

to evaluate for capsular or vascular invasion to diagnose follicular/Hurthle cell cancer so should be reserved for situations when there are clinical features that are highly suspicious for malignancy, such as extrathyroidal extension or lymph node metastases.

Patients with AUS/FLUS (Bethesda category III) lesions may be treated with a diagnostic lobectomy, repeat cytology with molecular testing, or surveillance. In addition to the cytological results, the decision for management should take into consideration the sonographic appearance of the nodule, clinical context, and patient preference. While the risk of malignancy for AUS/FLUS should range from 5 to 15%, evaluation of the sonographic pattern of the nodules is helpful to further risk stratify AUS/FLUS nodules. In a study of 155 nodules with AUS/FLUS cytology, nodules were classified by ATA sonographic pattern [44]. Only 8% of nodules with very low-risk sonographic features were malignant, while 58% with low or intermediate risk and 100% with high-risk appearances were malignant. This should be taken in the context that the overall risk of malignancy for AUS cytology in this study was 70%. In another study with an overall lower risk of malignancy of 22% for AUS cytology, 70% of nodules with high-risk sonographic appearance were malignant [45]. Based on these data, thyroid lobectomy should be considered strongly for patients with suspicious-appearing nodules on ultrasound. For nodules without high-risk sonographic appearance, repeat FNA with or without molecular testing may be helpful to further risk stratify the nodule and guide treatment, and clinical context and patient preference should be taken into consideration. Alternatively, surveillance with ultrasound may be employed, particularly for nodules with very low-risk sonographic appearance and/or nodules in patients with high surgical risk. Thyroid lobectomy should be considered for nodules that increase in size or take on suspicious ultrasound features during surveillance.

Thyroid nodules with follicular/Hurthle cell neoplasm (FN) (Bethesda category IV) cytology have, on average, a 15–30% risk of malignancy. Thyroid lobectomy has been the long-standing treatment for these patients. However, for patients who would like to avoid surgery and who have tumors with low-risk imaging and clinical features, molecular testing may be performed to provide further risk stratification. If molecular testing is indeterminate, thyroid lobectomy is recommended.

The risk of malignancy for a Hurthle cell neoplasm on cytology is 15–45%. Hurthle cell neoplasms are treated like FN, with a diagnostic thyroid lobectomy. Unlike FN, Hurthle cell neoplasms are more likely to be malignant when they are larger in size. The risk of malignancy for nodules >4 cm exceeds 50%, so up-front total thyroidectomy can be recommended [46]. Molecular testing appears to be less effective for Hurthle cell neoplasms. In a study by Brauner et al. [47], 45 of 71 Hurthle cell neoplasms had suspicious gene expression classifier results. Only 14% (6/43) of the nodules were malignant on final histopathology (4 with Hurthle cell carcinoma and 2 with PTC).

If histopathology from thyroid lobectomy reveals that the tumor is an intermediate- or high-risk thyroid cancer, a completion thyroidectomy is recommended. Completion thyroidectomy is generally not recommended for low-risk thyroid cancers but may be considered based on the overall goal for treatment and patient pref-

erence. Prior to performing completion thyroidectomy, laryngoscopy should be performed to evaluate vocal cord function. A paralyzed vocal cord increases the risk of surgery and may alter surgical planning. The completion thyroidectomy should be performed either within 1 week or 2–3 months after the initial surgery to avoid the worst inflammation.

Benign Nodules

Benign thyroid nodules (Bethesda category II) typically do not require surgical resection but should be followed with ultrasound surveillance. If the nodule increases in size significantly (50% increase in nodule volume or >2 mm growth in 2+ dimensions), FNA should be repeated or diagnostic lobectomy performed based on the unique clinical scenario and patient preference. Surgical resection is recommended for benign nodules that are symptomatic due to compressive symptoms, such as dysphagia or dyspnea. Also, surgery may be considered for large asymptomatic nodules, when FNA may be less accurate. Several studies have shown that 10–12% of thyroid nodules >4 cm with benign cytology on FNA are malignant on final surgical pathology [48]. For nodules with nondiagnostic pathology, a repeat FNA should be performed with ultrasound guidance and on-site cytopathological assessment to increase the likelihood of adequacy. Thyroid lobectomy is recommended for nondiagnostic cytology if the nodule has high suspicion sonographic features or if cytology is repeatedly nondiagnostic.

Medullary Thyroid Cancer

Patients with an FNA suspicious for MTC should undergo immunohistochemical staining of the biopsy for calcitonin/CEA and calcitonin/CEA washout of the FNA aspirate [49], and serum calcitonin and CEA levels should be obtained. If immunohistochemistry or calcitonin washout establishes the diagnosis of MTC, the patients should be treated as if they have MTC. If these results are inconclusive or normal, a diagnostic lobectomy should be performed. Patients with FNA diagnostic for MTC should have a total thyroidectomy with bilateral level VI CLND due to the high frequency of lymph node metastases and lack of effective adjuvant therapy. In a study by Scollo et al. [50] of 54 patients with sporadic MTC, lymph node metastases were present in 30% of patients with tumors <1 cm, 50% of patients with tumors 1–3 cm, and 100% for patients with tumors that were >3 cm. A selective lateral compartment (Level II–V) lymph node dissection is recommended for biopsy-proven lymph node metastases. The role of prophylactic lateral compartment dissection for patients with elevated serum calcitonin levels but without biopsy-proven lateral compartment lymph node metastases is controversial. Some clinicians feel that prophylactic lateral compartment lymph node dissection should be performed

for serum calcitonin levels >20 pg/mL due to the high frequency of occult nodal metastases and improved chance of biochemical cure [51]. However, others feel that lateral compartment lymph node dissection should only be performed for biopsy-proven metastases. The 2015 ATA MTC Guidelines [13] "neither recommend for nor against" prophylactic lateral compartment lymph node dissection in patients with elevated calcitonin without distant metastases. For these patients, an individualized approach is recommended, taking into consideration patient age, comorbidities, overall treatment goals, and patient preference. Younger, healthy patients may be considered for a more aggressive approach with prophylactic lateral compartment dissection, while observation with serial ultrasounds may be preferred for older, less healthy patients and for those patients unwilling to accept the risk of complications from surgery if no metastatic lymph nodes ultimately are identified.

Hyperthyroidism

Patients with thyroid nodules and hyperthyroidism should be initially evaluated by obtaining a thyrotropin receptor antibody level or a radioiodine uptake scan to determine the etiology of hyperthyroidism, which may be Graves' disease, toxic multinodular goiter, toxic adenoma, or thyroiditis. FNA is not recommended for hyperfunctioning (hot) nodules, since these nodules are rarely malignant [52]. Nonfunctioning (cold) nodules should be treated according to the 2015 ATA guidelines for the management of thyroid nodules and should undergo FNA based on the sonographic pattern and size of the nodules. Thyroid cancer in the context of hyperthyroidism appears to be more aggressive compared to thyroid cancer in euthyroid patients [53]. In the USA, the majority of patients with nodular Graves' disease, toxic multinodular goiter, and toxic adenoma are treated with radioactive iodine; however, surgery is the preferred treatment for some patients. The 2016 ATA guidelines for the diagnosis and management of hyperthyroidism [10] recommended surgery for patients who are <5 years, are pregnant, fail alternative treatment, are unable to comply with radiation safety guidelines, have nodules that are concerning or diagnostic for malignancy, need rapid correction of the thyrotoxic state, patients with insufficient radioactive iodine uptake, with large (≥80 g) goiters causing compressive symptoms, with moderate to severe Graves' orbitopathy, or based on patient preference. For patients without clear indications for surgery, treatment with antithyroid drugs (methimazole), radioactive iodine, or surgery should be based on goals of treatment incorporating patient values and preference. Total thyroidectomy is the procedure of choice for Graves' disease or toxic multinodular goiter because subtotal thyroidectomy has similar morbidity but a higher risk of recurrent hyperthyroidism [54]. A thyroid lobectomy is recommended for a toxic adenoma. Prior to thyroidectomy, patients with hyperthyroidism should be rendered euthyroid to avoid thyroid storm during surgery. This can be accomplished with methimazole within 4–6 weeks. Propylthiouracil is no longer recommended due to a higher risk of hepatic failure [55]. Methimazole is typically started at 10–30 mg and titrated based

on response. Beta-blockers may be added to control tachycardia and tremor. Thyroidectomy can be performed safely once T3 and T4 are normal; TSH lags behind and does not need to be normal at the time of surgery. Patients with nodular Graves' disease should be treated with supersaturated potassium iodine (SSKI) with two drops three times daily starting 10 days prior to surgery in order to decrease vascularity of the thyroid gland and reduce blood loss [56]. This is not recommended for toxic multinodular goiter or toxic adenoma, since it may exacerbate hyperthyroidism in these patients. If surgery is chosen, patients should be referred to a high-volume surgeon, since high-volume surgeons on average have superior outcomes compared to low-volume surgeons [35, 36, 57]. The risks of thyroid surgery for hyperthyroidism are higher even than for thyroid cancer. In a nationwide study by Kandil et al. [57] of 46,261 patients between 2000 and 2009 using the Health Care Utilization Project National Inpatient Sample (HCUP-NIS), Graves' disease patients had the highest complication rate (17.5%) compared to patients undergoing total thyroidectomy for other benign (13.9%) and malignant (13.2%) thyroid disease ($p < 0.01$).

Patients with nodular Graves' disease who are treated with thyroidectomy are at higher risk for postoperative hypoparathyroidism and hypocalcemia. Preoperative supplementation with calcium and/or vitamin D may reduce the risk of postoperative hypocalcemia. In a study by Oltmann et al. [58], 45 patients with Graves' disease were treated with 1 g of calcium carbonate three times per day for 2 weeks prior to thyroidectomy and compared to 38 Graves' disease patients who underwent thyroidectomy without preoperative treatment. The rate of symptomatic hypocalcemia was higher in the untreated group (26 vs 9%, $p < 0.05$). In a retrospective study by Kim et al. [59] of 272 patients who underwent thyroidectomy, the incidence of postoperative hypocalcemia was 43.8% for patients who were vitamin D insufficient compared to 30.4% for those who were vitamin D sufficient (p-0.043). Based on such results, the 2016 ATA guidelines recommend vitamin D repletion prior to surgery for patients who are vitamin D insufficient and preoperative calcitriol supplementation in patients at increased risk for hypoparathyroidism.

Multinodular Goiter

Surgery is recommended for goiters that are symptomatic due to local compression, concern for malignancy, or for cosmetic reasons. Large goiters may compress the esophagus or trachea, leading to dysphagia or dyspnea. In select situations when many nodules meet the criteria for FNA, the patient or clinician may prefer surgery rather than surveillance despite benign FNA of select nodules. Surgery may also be performed if the patient is concerned about the cosmetic appearance of a large goiter, although it is rare that a patient with a very large goiter does not have at least some compressive symptoms. Total thyroidectomy is recommended if the goiter/nodules involve(s) both lobes of the thyroid; thyroid lobectomy is appropriate for a unilateral goiter.

Pediatric Patients

Thyroid nodules are less common in children than adults; however, nodules in children are more likely to be malignant (22–26% rate of malignancy for children vs 5% for adults) [60]. The 2015 ATA management guidelines for children with thyroid nodules and differentiated thyroid cancer [12] recommend that the initial evaluation and treatment of children with thyroid nodules should be similar to adults, with several exceptions. The decision to perform FNA should be based primarily on sonographic features (i.e., irregular margins, hypoechoic appearance, and microcalcifications) and clinical context rather than nodule size alone, since the size of the thyroid gland changes with age and absolute size of nodules does not predict malignancy. The risk of malignancy for children with nodules and indeterminate cytology is higher than in adults. In children, 28% of nodules with AUS/FLUS cytology and 58% with FN cytology are malignant on histopathology after surgical resection [61]. Accordingly, thyroid lobectomy is favored over repeat FNA and/or surveillance. Molecular testing to provide further risk stratification for indeterminate nodules has not been validated in children, so it is not recommended [12]. Also, all children with thyroid nodules should have ultrasonographic lymph node mapping and FNA of suspicious lymph nodes to evaluate for metastases, since there is a higher likelihood that these nodules are malignant. Similar to adults, FNA for hyperfunctioning nodules is not recommended; however, thyroid lobectomy is recommended over radioactive iodine due to the possible mutagenic effects of radioactive iodine on thyroid tissue in children [62]. Finally, for children with PTC, total thyroidectomy is recommended, since there is a 60% risk of multifocal disease, and total thyroidectomy has been shown to be associated with a reduction in the risk of recurrence [63]. The risk of postoperative complications after thyroidectomy is higher for children than adult patients. In a nationwide study by Sosa et al. [64] using HCUP-NIS of 1199 pediatric and 96,002 adult patients who underwent thyroidectomy, children were more likely to have endocrine-related complications than adults (9.1 vs 6.3%, respectively; $p < 0.01$). In another nationwide study by Tuggle et al. [65] using HCUP-NIS of 607 children who underwent endocrine neck procedures, high-volume surgeons (>30 cervical endocrine surgeries per year) compared to low-volume surgeons had shorter length of stay (1.5 vs 2.1, $p < 0.01$), lower costs ($12,474 vs $15,662, $p < 0.05$), and trended toward fewer complications (5.6 vs 10%, p = NS).

Pregnant Patients

The ATA published guidelines for the management of thyroid disease during pregnancy in 2011 [14]. Similar to nonpregnant adult patients, the evaluation of euthyroid pregnant patients should begin with a thyroid ultrasound. FNA of nodules with

suspicious sonographic features is recommended, while FNA of benign-appearing nodules may be deferred based on patient preference until the pregnancy comes to term. If surgery is indicated based on a cytology diagnostic for malignancy, the decision to perform surgery during pregnancy or after delivery must be individualized. In a study by Moosa et al. [66], the outcomes of 61 pregnant patients were compared to age-matched nonpregnant thyroid cancer patients. Outcomes were similar for pregnant and nonpregnant patients: recurrence 9 (15%) vs 107 (23%), respectively, distant recurrences 1 (2%) vs 12 (3%), and cancer deaths 0 vs 6 (1.2%) (all p = NS). Patients who had surgery after pregnancy had similar outcomes to patients who underwent surgery during pregnancy (2 [14%] vs 7 [15%] developed recurrences, p = NS). A nationwide study by Kuy et al. [67] using HCUP-NIS compared 201 pregnant patients to age-matched nonpregnant patients. Pregnant patients were more likely than nonpregnant patients to have endocrine-related complications (15.9 vs 8.1, respectively; $p < 0.01$), general complications (11.4 vs 3.6%, $p < 0.01$), and greater length of stay (2 vs 1 day, $p < 0.01$). The overall fetal and maternal complication rates were 5.5% and 4.5%, respectively. Based on this study and others demonstrating no difference in outcomes if surgery is delayed, most patients have surgery after delivery to minimize the risk to the patient and fetus. Elective surgery should be considered during the end of the second trimester for large or locally advanced primary tumors, extensive lymphadenopathy, aggressive histology including MTC, or if the tumor progresses early in pregnancy.

Alternative Access Thyroidectomy

Robotic-assisted thyroid surgery through either a transaxillary or axillo-breast approach avoids a cervical incision. The ideal patients for this approach have a small body habitus, low body mass index (BMI), and a normal-sized thyroid with small nodules (<3 cm) [68]. In addition to the usual complications associated with thyroid surgery, alternative access site surgery can be associated with chest wall numbness, brachial plexus injuries, pneumothorax, and skin flap perforation/necrosis. The vast majority of studies evaluating these techniques are from South Korea. Although there was initial enthusiasm for minimally invasive techniques for thyroidectomy in the USA, the technology has not been embraced outside of select centers. A meta-analysis by Sun et al. [69] included 11 studies with 726 patients undergoing robotic surgery and 1205 undergoing conventional thyroidectomy. The robotic group was younger (40.5 vs 49.2 years, respectively), had a lower BMI (23.1 vs 24.2), and was less likely to undergo total thyroidectomy (58.1 vs 75.1%). The tumors were small, with a mean size of 8 mm. Mean operative time was 77 min longer for the robotic group ($p < 0.001$). There was no significant difference between the groups in the frequency of RLN injury, hypoparathyroidism, postoperative hematoma, or seroma. The robotic group had higher cosmetic satisfaction scores, but follow-up was only 3 months.

Postoperative Management

After thyroidectomy, communication between members of the treatment team is essential to fully integrate care. Thyroidectomy is a well-tolerated procedure, with infrequent complications when performed by an experienced surgeon as measured by the number of thyroid procedures performed. After surgery, patients should be monitored for hematoma, voice changes, and hypocalcemia. Postoperative bleeding and hematoma are rare (<1%) but can be life threatening, with emergent loss of the airway. The presence of new onset hoarseness after surgery may be due to irritation from the endotracheal tube, vocal cord edema/hematoma, or recurrent laryngeal nerve (RLN) injury. Transient RLN injury is seen in 3% of patients, and permanent RLN injury is seen in 0.5–1% of patients after surgery performed by high-volume thyroid surgeons. Patients with significant dyspnea or symptoms concerning for aspiration should be referred for laryngoscopy to evaluate for vocal cord compromise. Hypoparathyroidism leading to hypocalcemia is the most common complication after thyroidectomy. Transient hypoparathyroidism is seen in 10–20% of patients and permanent hypoparathyroidism in 1–2% of patients after total thyroidectomy. Transient hypoparathyroidism usually resolves in 2 weeks but may take up to 6 months. Selective or routine calcium and calcitriol supplementation should be implemented to avoid hypocalcemia. Selective supplementation can be based on ionized calcium or corrected serum calcium values and change in these values between the evening of surgery and postoperative day 1 morning values. Alternatively, selective supplementation can be based on parathyroid hormone (PTH) levels; for example, a serum PTH can be obtained in the recovery room, and if it is >10 pg/mL, patients are given 1000 mg calcium carbonate BID for 1 week; for PTH <10 pg/mL, patients are given 0.25 mcg calcitriol BID in addition to 1000 mg of calcium carbonate TID. Postoperative PTH levels are less accurate for predicting hypocalcemia in hyperthyroid patients. Some surgeons choose to routinely supplement all patients following thyroidectomy with calcitriol 0.25 mcg BID and 1000 mg calcium carbonate TID, since routine supplementation has been shown to be more cost-effective than selective supplementation [70]. Regardless of the strategy, patients should be counseled to contact the surgical team for symptoms of hypocalcemia, such as perioral or distal extremity paresthesias. If these symptoms occur, supplementation may need to be increased. Calcitriol and calcium supplementation are titrated down over 1–2 weeks after surgery, as long as the patient does not experience symptoms of hypocalcemia.

Conclusion

Thyroidectomy remains the mainstay of treatment for indeterminate thyroid nodules, thyroid cancer, and thyroid nodules associated with symptoms of compression; it is an appealing option for some patients with functional thyroid nodules associated with hyperthyroidism. Management of indeterminate thyroid nodules

should take into consideration sonographic features, clinical context, and patient preference. The role of molecular testing continues to evolve and may be used to provide improved risk stratification for indeterminate nodules. For thyroid cancer, the extent of thyroid resection and lymph node management needs to be individualized, taking into consideration risk stratification schema, treatment guidelines, and patient values. Patients should be referred to high-volume thyroid surgeons to minimize their risk of sustaining a surgical complication.

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Chapter 13
Minimally Invasive Treatments for Thyroid Nodules

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Why Is a Novel Approach to the Management of Symptomatic Thyroid Nodules Necessary?

The incidence of thyroid nodules, either solitary or within multinodular goiter, is steadily increasing during the last decades [1]. This epidemic is mostly due to the widespread use of ultrasound (US) and of other sensitive imaging methods, such as color Doppler, CT, MR, and 18FDG-PET, that are employed for cervical or whole-body examination. The majority of thyroid nodules that are incidentally discovered show a benign appearance at US examination and do not need further diagnostic work-up [2]. On the other hand, thyroid nodules that are detected because they are symptomatic or that appear clinically relevant at physical or US examination should be assessed by fine needle aspiration (FNA) biopsy [3–5]. The minority of thyroid lesions which demonstrate suspicious or malignant cytological findings require surgery, while most nodules that are benign at FNA do not necessitate any treatment and should be simply controlled over time [2, 3]. Yet, this apparently uncomplicated approach to the management of nodular thyroid disease reveals some problems. From 5 to 15% of benign thyroid lesions, either solid or prevalently fluid, are symptomatic or progressively enlarge during follow-up controls [6, 7]. For these patients no medical therapy is available, and with the exception of hyperfunctioning thyroid nodules that may be safely treated with radioiodine [2], those benign thyroid lesions that cause local pressure symptoms or induce cosmetic concern are submitted to surgery [3]. Thyroid surgery is a rapid and effective treatment with a low rate of

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permanent complications in high-volume centers. However, thyroid resection is expensive, usually results in a variable degree of hypothyroidism and, sometimes, in an unpleasant cervical scar [8]. Thus, this approach to the management of symptomatic but not harmful thyroid lesions has an unfavorable impact on the quality of life in a nonnegligible number of patients [9]. In accordance with the present trend in the management of thyroid disease that suggests a less aggressive and tailored therapeutic approach also for low-risk thyroid malignancy [10], it seems appropriate to decrease the current use of surgery for definitely benign thyroid lesions. Due to the rather constant rate of growth of enlarging thyroid nodules, an effort should be addressed to change their natural history when they become symptomatic.

Various US-guided, minimally invasive procedures (MIT) are currently available for nonsurgical management of symptomatic or growing thyroid lesions [11]. These techniques offer several advantages when compared to surgery. MIT are low-cost outpatient procedures, do not result in cervical scar nor loss of thyroid function, and are nearly completely devoid of risk of permanent complications [12]. The major limit of MIT is the persistence of viable tissue in the peripheral area of lesion after percutaneous ablation. Thus, a repeat cytological confirmation of the benign nature of thyroid nodules that are undergoing treatment is strongly needed, and all the lesions that are suspicious at clinical or US evaluation should be considered not eligible for MIT [12].

On the basis of the fluid content of the nodule, treatment may be performed with either percutaneous ethanol injection (PEI), a procedure best suited for prevalently cystic lesions [13, 14], or with thermal ablation with laser (LA) [15] or radiofrequency (RF), most effective for solid thyroid nodules [16]. Sound therapy (HIFU) with extracorporeal-focused US is a promising but not yet extensively evaluated ablation procedure [17], while the use of microwaves (MW) should still be considered as experimental [18].

Procedures and Clinical Indications

Percutaneous Ethanol Injection

Procedure PEI is a rapid and nearly painless procedure that does not require local anesthesia. After US assessment of the location and structure of the cystic nodule, a thin needle (usually a commercially available 23-gauge (G) needle) is introduced under US guidance or assistance into the center of the thyroid lesion. In the rare cases in which the colloid is sticky, a larger needle (up to 19G) may be employed [19]. The liquid component of the lesion is first drained through a short plastic tube that connects the needle to the aspirating syringe and prevents the risk of needle displacement during the maneuver. After the drainage of the fluid, the syringe is disconnected and an amount of 95% sterile alcohol that ranges from 25 to 50% of the aspirated liquid volume is slowly injected into the residual cavity. Notably, the fluid component should not be completely aspirated because the persistence of a small quantity of liquid improves the detection of the tip of the needle as a bright spot at US monitoring and prevents the risk of ethanol injection outside the hollow area of the nodule [12]. After a US control of the neck, the treatment is terminated

with the injection of 0.5 mL of xylocaine (or saline solution, in case of anesthetic intolerance) to wash out the remaining ethanol from the needle and to avoid its painful seeping during the withdrawal. A sterile dressing is applied without pressure; no observation nor medical treatment is necessary (Fig. 13.1).

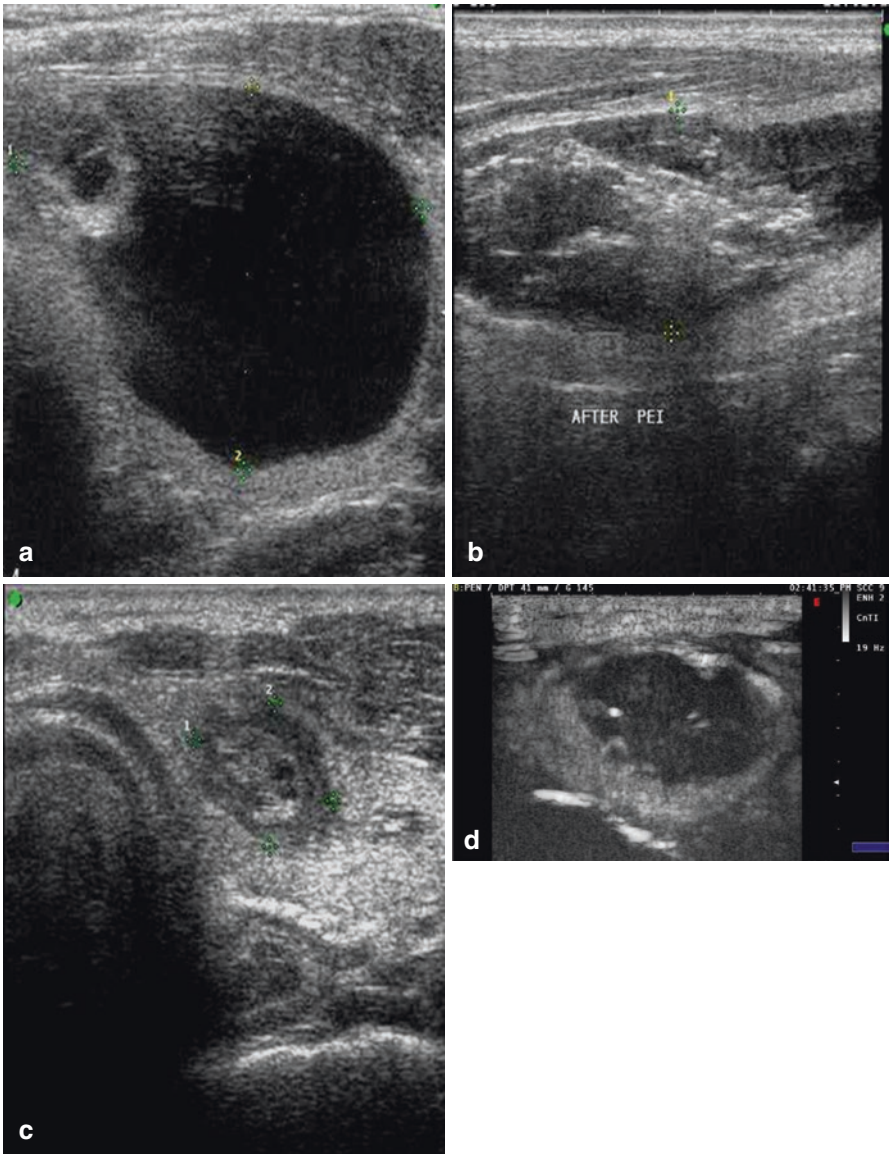


Fig. 13.1 Percutaneous ethanol injection. (**a**) US scan of the left thyroid lobe. The presence of a large thyroid cyst, relapsing after a former percutaneous drainage. Benign cytology. (**b**) Thyroid US scan performed 1 h after the drainage of the fluid collection followed by US-guided injection of ethanol into the cavity. (**c**) The same lesion 6 months after treatment. Complete disappearance of the fluid collection with marked shrinkage of the cystic thyroid nodule. (**d**) Contrast-enhanced US performed 6 h after the procedure. A large area of tissue within the nodule is now ablated, as demonstrated by the absence of blood supply after the intravenous enjection of contrast medium

Indications for Clinical Practice The rare pure cysts, and the more common frequent thyroid nodules with a major fluid component, are treated effectively with PEI [12]. PEI should be performed in cysts and complex nodules that relapse after drainage and gradually increase in size or are symptomatic. Before treatment a repeat cytological evaluation of both the fluid and the solid component of the lesion should be performed to rule out the risk of a cystic carcinoma. The procedure is rapid, well tolerated, and safe, if appropriately performed, and recurrent cystic lesions result in a clinically significant reduction of the size (usually greater than 80% in randomized trials) [20, 21] and improvement of local symptoms [19, 22]. Volume decrease is long-lasting, as demonstrated by the absence of volume changes during long-term follow-up [22, 23].

Complications and Limitations The occurrence of vocal cord paresis is rare and transient and is always due to the incorrect injection of ethanol outside the cystic cavity. No loss of thyroid function nor autoimmune disease occurs after PEI. Of note, in case of large cystic lesions, two or more treatments are generally needed during a 1-month period. The occasional occurrence of a rapid hemorrhagic refilling of the cyst during fluid drainage is associated with a less favorable outcome [12].

Solid thyroid nodules, either cold or hyperfunctioning, are less suitable for PEI [3] even if the procedure may result in a nearly 50% volume decrease [23, 24]. In these lesions ethanol injection is painful, multiple treatments are required, and relevant side effects may follow. Due to the unpredictable distribution of ethanol within solid tissue and its leakage into the thyroid gland and the neck tissues, patients usually complain of a nasty cervical pain that radiates to the jaw and thorax [11]. Complications are much more frequent than in cystic lesions, and the procedure may result in a fibrosis of the neck structures that, if requested, may turn into a difficult surgical approach [12].

Laser Ablation

Procedure Before laser ablation a careful administration of local anesthesia, xylocaine, on the skin, prethyroid muscles, and thyroid capsule should be performed along the planned track of fiber insertion. Usually, from one to two 21G spinal needles are inserted under US guidance into the nodule. A 300 μm optical fiber is then positioned through the needle sheath into the target zone, and the tip is placed in direct contact with the tissue for a length of about 5 mm [25, 26]. A careful US evaluation should be performed to confirm the appropriate positioning of the fiber optic(s) and the presence of a 10 mm safety distance from the vital structures of the neck. Then, laser firing is initiated with an output power from 3 to 5 W, and the energy delivery is usually carried out for 5–10 min, with a total energy delivery from 1800 to 3000 J. Laser illumination is terminated when a cloud of hyperechoic spots, due to the production of gas bubbles, stops enlarging and becomes steady in size. In large volume nodules, a second treatment may be carried out during the same session, after a 1.0–1.5 cm withdrawal of the needle(s) along the longitudinal axis of the lesion (“pullback technique”) [27] (Fig. 13.2).

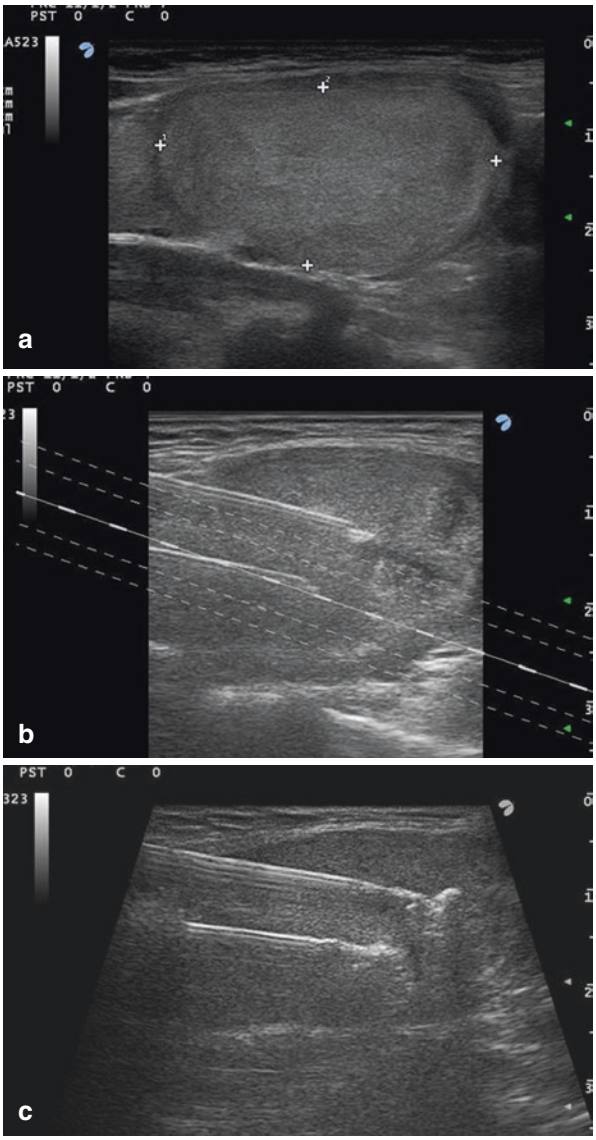


Fig. 13.2 (**a**–**c**) Percutaneous laser ablation. (**a**) US scan of the right thyroid lobe. Presence of an isoechoic nodule with regular margins, 30 mm in its greater diameter, progressively enlarging over the years. A former fine needle biopsy resulted in a benign cytologic sample. (**b**) US-guided insertion of two needles within the lower part of the nodule. (**c**) US detection of the initial hyperechoic spots due to laser firing

Laser treatment is rapid and is usually fairly well tolerated. A mild cervical pain, sometimes radiating to the chest and described by a minority of patients, resolves within an hour and is well responsive to common analgesics. Low-grade hyperthermia is rarely observed after the procedure. No cosmetic damage is induced by the procedure, and cervical bleeding, skin bruising or swelling, and abnormalities of thyroid function are definitely uncommon. The risk of major complications (vocal cord paresis or injury to cervical structures) is well under 1%, is always caused by an incorrect procedure, and was mostly reported during the learning curve of the technique [12, 28].

Indications for Clinical Practice Laser ablation is successful for decreasing the size of large symptomatic thyroid lesions and for preventing further growth of nonfunctioning nodules. A good-quality evidence, due to randomized trials [29, 30] and multicenter retrospective studies [28], demonstrates that a single LA session is consistently followed by about 50% reduction of the size of the ablated nodule. Volume decrease is progressive during the first 12 months after treatment and in most cases persists for several years. These results are quite similar among different centers and are associated with a significant improvement of local symptoms [28].

Laser ablation is employed less frequently nowadays for hyperfunctioning nodules because radioiodine treatment is readily available, safe, and a highly effective alternative to surgery for the control of hyperthyroidism and, to a lesser extent, nodule growth. LA should be considered for patients with small-size autonomously functioning nodules that incompletely suppress normal thyroid tissue and are at risk of hypothyroidism after radioiodine therapy [31]. LA is strongly indicated in subjects for which radiation exposure is inappropriate, due to pediatric age or pregnancy, or radioiodine cannot be used because of an iodine-replete condition caused by drugs or contrast media. Finally, in patients with large toxic nodules that are at surgical risk, the combined management with initial LA followed by radioiodine treatment results in a rapid control of local pressure symptoms [32, 33].

LA may be used for complex lesions with a large solid part to induce with a single-session liquid evacuation and shrinkage of the solid component, but PEI remains the first-line, nonsurgical treatment for relapsing cystic nodules [34].

Radiofrequency Ablation

Radiofrequency devices generate an alternating electric field within the target lesion that is produced by an electrode needle connected to an external radiofrequency generator. The fast movements of the ions are followed by progressive heating of the tissue and, eventually, by thermal necrosis [35].

Procedure Radiofrequency ablation may be performed with local anesthesia or conscious sedation. After the initial trials are carried out in subjects under conscious sedation with large devices, such as multi-tined electrodes with expanding hooks (14-gauge diameter) [36, 37], thinner (18 or 19G) and shorter, internally cooled

electrode needles have been developed and are presently used for thyroid lesions [38]. These tools are more practical and less traumatic and permit a repetitive insertion of the tip of the needle within the target area, according to the so-called "moving shot" technique [38]. The electrode is first placed, through a cervical trans-isthmic approach, in the distal part of the nodule, and after the ablation of the initial zone, it is systematically inserted into the central and more proximal areas of the thyroid lesion (Fig. 13.3).

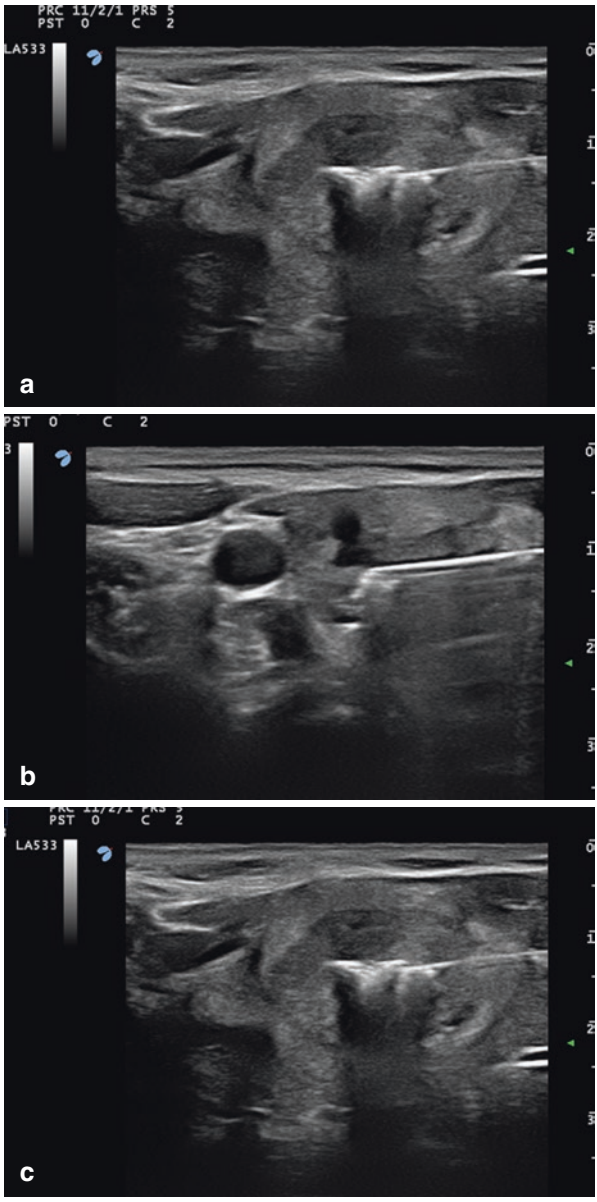
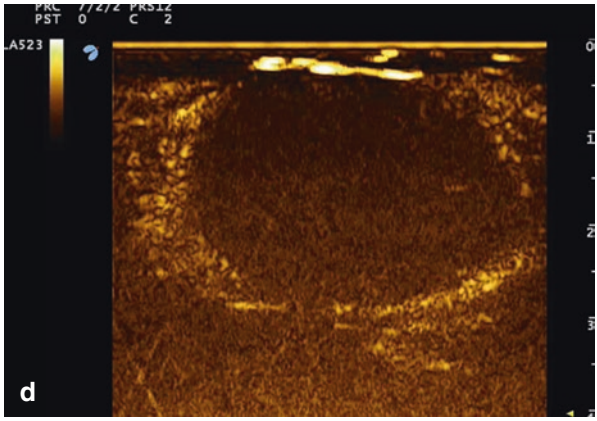


Fig. 13.3 Percutaneous radiofrequency ablation. (**a**–**c**) US monitoring of a treatment with an 18G radiofrequency electrode needle of a symptomatic thyroid nodule, benign at fine needle aspiration biopsy. The tip of the electrode needle is sequentially moved within the nodule producing multiple areas of thermal necrosis. (**d**) Contrast-enhanced US performed 6 h after the procedure. A large area of tissue within the nodule is now ablated as demonstrated by the absence of blood supply

Fig. 13.3 (continued)



Indications for Clinical Practice The "moving shot" RF technique [39, 40] generates multiple confluent areas of thermal necrosis that are followed by a relevant shrinkage of the ablated lesion. Several RF trials report a mean size reduction that 6 months after treatment is about 60–80% and may reach 90% of the baseline volume in complex lesions with a fluid component [40]. Volume reduction is persistent over time, and further treatments may be, anyway, performed in case of nodule regrowth [40]. RF ablation is moderately painful, can be carried out in the outpatient clinic, and does not require major analgesics nor antibiotics. Side effects are rather infrequent (about 3.0% in large retrospective studies) and are usually transient [41]. Rare but serious complications, such as extra-thyroid bleeding, vocal cord palsy, nodule rupture and infection, and skin injury, have been described. Thus, RF ablation requires special and specific expertise with a good knowledge of cervical anatomy that should be obtained with a dedicated training period [41].

Similar to laser ablation, RF may be used for the ablation of hyperfunctioning thyroid nodules [42, 43]. Despite noncontrolled and controlled trials reporting successful results in toxic thyroid nodules [42, 43], RF, like laser ablation, rarely results incomplete destruction of the peripheral areas of the hyperfunctioning nodule. Due to the potential persistence of autonomously functioning tissue and the risk of hyperthyroidism recurrence, RF may, seldom and selectively, be used in patients with contraindications to radioiodine treatment.

RF ablation is rarely used for the treatment of cysts or thyroid nodules that are prevalently fluid. RF may induce with a single procedure a shrinkage of large cystic lesions that is similar to that achieved with multiple PEI sessions [44]. However, due to the efficacy, easiness, and safety of PEI treatment, percutaneous ethanol injection remains the first-line procedure for the management of relapsing thyroid cysts [45].

HIFU

During HIFU treatment several externally generated US beams are focused on a target lesion within the body. Each individual beam passes through the skin with minimal damage, while at the focal point, the union of the multiple beams of ultrasound waves results in tissue heating, denaturation of cell proteins, and coagulative necrosis. Furthermore, focused ultrasound can disrupt the cells through a mechanical action, due to the oscillation of gas bubbles in the US field, that is independent from tissue heating [46].

Procedure The treatment is performed with a real-time US-guided HIFU system that consists of an energy generator, an articulated arm with a treatment head, a cooling system for skin preservation, and a touch screen interface for planning and follow-up of the procedure. The treatment head includes both the imaging transducer and the HIFU transducer that convey energy to the target area. A laser-based movement detector shuts off the power in case of patient movement or swallowing.

Patients are placed in supine position with hyperextended neck and given a mild sedation. After the definition of the treatment volume and of the boundaries of vital structures (carotid artery, trachea, and skin) on a touch screen interface on two axes, HIFU pulses are sequentially delivered to the target lesion. During the procedure the operator controls the beam focus and, if necessary, repositions the treatment head. The applied energy is adjusted according either to the evidence of the hyperechoic marks due to tissue coagulation or to the occurrence of cervical pain [47] (Fig. 13.4).

Indications for Clinical Practice In few small series of patients, the treated nodules showed at the 6-month follow-up a volume reduction of nearly 50% [47, 48]. The procedure was reported as fairly well tolerated, and most patients did not need analgesic drugs after treatment. At the session conclusion, mild skin redness and subcutaneous edema spontaneously disappearing within a few hours or days may be observed. Blistering or severe edema of the cervical tissues is occasionally reported, while serious adverse events, such as dysphonia, tracheal or esophageal damage, or Horner's syndrome, are rare [47].

The use of HIFU has still some limitations in clinical practice. The available evidence is of low quality because it is based on small-size uncontrolled trials, with short follow-up and performed in a limited number of centers. The area to be treated and the beam track should be placed at safety distance from the skin and vital cervical structures, and thus part of the nodules is treated with difficulty with this technique. Finally, when compared to the other MIT procedures, the equipment is more expensive and less accessible, and the treatment time is more protracted. Larger prospective randomized trials, with strict enrollment criteria and appropriate follow-up, are needed for the definition of the role of this potentially innovative procedure.

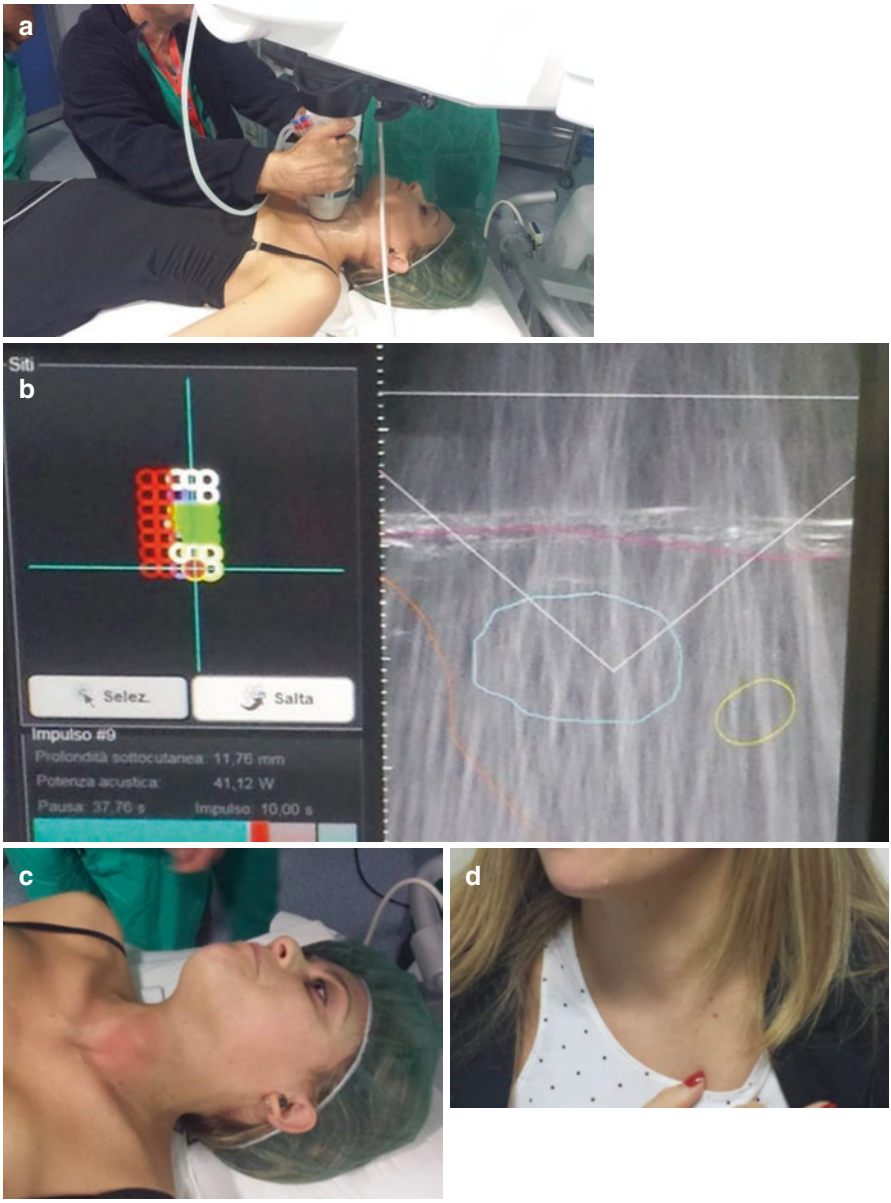


Fig. 13.4 HIFU ablation. (**a**) Positioning of the HIFU robotic arm equipped with the US transducer over the neck of the patient. (**b**) *Left*. Targeting for HIFU treatment of the safe areas (*green*) and of the areas at risk (*red*) of thyroid nodule. *Right*. Monitoring of the shot of high-intensity US waves focused into the central zone of the thyroid nodule. (**c**) At the end of HIFU treatment, a hyperemic area is visible on the skin of the neck, mainly due to the pressure of the cooling device of the US probe. (**d**) Nearly complete disappearance of the skin redness 4 h after treatment

Microwave Ablation (MW)

Microwave ablation is a minimally invasive technique that has been used to treat benign and malignant tumors of the liver, lung, and kidney [48]. Presently, only few studies report the experience on benign or malignant thyroid nodules. A large retrospective study was carried out in China on 254 benign thyroid nodules that were treated with the use of a 16G microwave antenna [49] under local anesthesia. At a 6-month follow-up, the mean decrease in the volume of thyroid nodules was greater than 50% versus baseline. The treatment was reported as well tolerated, but pain and ill-defined voice changes were registered.

Presently, several drawbacks of this technique are unresolved: the large size of MW devices, the insufficiently controlled modality of energy delivery, and the poor quality of the available scientific evidence. Thus, MW ablation is an inadequately investigated procedure and should be still considered as experimental.

Conclusions for Clinical Practice

The incidence of thyroid nodules is steadily mounting, and the number of growing or symptomatic benign lesions is accordingly increasing. In most of these cases, the treatment should be nonsurgical to avoid a negative impact on the quality of life and an inappropriate use of surgical facilities. A timely and appropriate use of MIT may change the natural history of benign thyroid lesions that cause local symptoms or are enlarging over time. Various MIT procedures, characterized by different modalities of action and clinical indications, are now accessible [12]. PEI may be considered as the first-line treatment for recurrent benign cystic lesions and should be performed in all centers with expertise in US-guided FNA. Thermal ablation techniques, performed either with laser or radiofrequency, provide significant volume decrease and improvement of pressure symptoms in nonfunctioning nodules. These procedures require a specific training and may be appropriately performed in high-volume thyroid centers. HIFU, a noninvasive treatment based on the use of high-intensity ultrasound waves, is a promising but not yet fully evaluated treatment. Finally, the ablation with MW should still be considered as an experimental procedure for thyroid lesions.

Minimally invasive procedures are indicated for nonfunctioning nodules and should be used for toxic lesions only when radioisotope treatment or surgery is contraindicated. Both PEIT and thermal ablation are performed on outpatients, carry a very low risk of complications, and do not result in thyroid function abnormalities. The risk of malignancy, however, should be excluded with repeat cytological assessment, and a US follow-up is appropriate after ablation treatment.

In the near future, MIT may redesign the management of cytologically benign but symptomatic nodules and offer, in high-volume centers with specific expertise, the opportunity for a personalized management of benign thyroid lesions that should be centered on the patient quality of life [50].

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Conflicts of Interest The authors declare that there is no conflict of interest.

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Chapter 14
Thyroid Nodules in Children

Siobhan Pittock

Introduction

Thyroid nodules are discrete lesions within the gland, which are radiologically discernible from the surrounding tissue. They present with a mass in the neck, or may be found in non-symptomatic children, discovered during a routine physical examination or in the course of imaging studies of the neck for other reasons.

Thyroid nodules are far less common in pediatric than adult populations. Estimates from ultrasound and postmortem studies suggest that thyroid nodules are present in 1–5% of children [1–6], compared to 19–68% of adults [7, 8]. When present, they are more likely to be malignant, with malignancy noted in 22–26% of children referred for evaluation of nodular thyroid disease, compared to approximately 5–10% of adults [2, 9–13]. By far the most common thyroid malignancy in children and adolescents is papillary thyroid carcinoma (PTC), which accounts for >90% of all childhood thyroid cancer [10, 14–18].

The treatment of thyroid nodules, which consists primarily of surgery, depends entirely on the likelihood of malignancy, and so the priority, in the clinical evaluation of thyroid nodules, is to determine malignancy risk. The diagnostic work-up of nodules in children should include a thorough history to identify any risk factors associated with thyroid malignancy, clinical examination, thyroid function tests, thyroid ultrasound, and fine needle aspiration biopsy when appropriate. Molecular biomarkers of malignancy are different in children compared to adults, and they are typically not used in clinical practice.

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Epidemiology of Thyroid Nodules in Children

A large study by Rallison et al. [2, 19] in the Southwestern United States found that thyroid nodules were present in 1.8% of 5179 school children who were surveyed due to possible radiation exposure [2]. Two thirds of the study's cohort were reexamined in a follow-up study some 20 years later, and 78% continued to have nodular disease [12]. A more recent study from a large Japanese series, which utilized high-resolution ultrasound, showed an incidence of solid nodules of 1.65% in a pediatric population and identified cystic lesions in 57% of children and adolescents [20]. It is unclear whether the rate of thyroid imaging abnormalities would be as high as this in other populations as this highly sensitive technology has not been used in other pediatric studies.

Risk Factors

The risk factors for the development of thyroid nodules in children include radiation exposure, family history of thyroid cancer, iodine deficiency, pre-existing thyroid disease, possibly elevated TSH, and several genetic syndromes.

Radiation: Exposure from Nuclear Accidents

The link between ionizing radiation during childhood and thyroid cancer has been known since 1950 when researchers noted that an unusually large fraction of their childhood thyroid carcinoma patients had a prior history of radiation therapy [21]. A pooled analysis by Ron et al. of seven studies on children irradiated at a young age confirmed a high risk of thyroid cancer in those patients. The increased risk of developing thyroid cancer occurred when the exposure occurred at a younger age (<15 years); it remained present more than 40 years after exposure but peaked between 15 and 30 years post exposure [22].

More evidence for the association between radiation and thyroid cancer formation comes from nuclear accidents, in particular studies after the Chernobyl nuclear accident [23, 24].

Ten years after the accident (in 1996), the incidence rate of childhood thyroid carcinoma in Belarus was 40-fold higher than before the accident; the younger the age at exposure, the greater the risk of cancer. The incidence of new cancers declined progressively after 1996 [16, 25, 26]. No increase in thyroid cancer has been seen after the nuclear accident at the Fukushima Daiichi nuclear power plant in March of 2011 despite extensive screening; ongoing follow-up will be needed to see if we are currently in a latency period [27, 28].

Radiation: Exposure from Medical Interventions

Radiation is used in many pediatric medical, diagnostic, and therapeutic procedures; thyroid exposures to X-rays due to dental radiographic procedures [29] or during CT of the neck during childhood [30, 31] are both associated with low, but not negligible, risk of thyroid cancer. Childhood cancer survivors who receive radiation therapy are at increased risk of thyroid nodules and cancer [32, 33]. Nodules develop at a rate of about 2% annually, with a peak incidence 15–25 years after radiation exposure [34–36]. The risk is highest among patients who received radiation at a younger age and at higher doses (20–29 Gy) [22, 33, 37]. The cumulative incidence for patients with up to 30 years of follow-up after the diagnosis of Hodgkin's lymphoma was 4.4% for thyroid carcinoma (predominantly PTC), with a mean interval after Hodgkin's lymphoma diagnosis of 13.2 years (range 4–29.2 years) [38–40]. While higher-resolution imaging techniques identified smaller thyroid lesions [41, 42] among this cohort, it is unknown whether detection of lesions earlier by these sensitive techniques will have any long-term effect on the quality of life or longevity in these patients, and there are concerns that high-resolution US screening may uncover incidental findings which could confuse the clinical picture and potentially lead to further, unnecessary testing [20].

Family History of Thyroid Cancer

The risk of differentiated thyroid cancer (DTC) is four times higher for children with a family history of differentiated thyroid cancer [43–47] and, when present, has been shown to have a more aggressive course [45]. In a study where first-degree relatives of patients with apparently sporadic differentiated thyroid cancers were routinely screened by ultrasound, thyroid cancer was diagnosed at an earlier stage when it was smaller and had a lower incidence of lymph node metastasis (23.2 versus 65.6%) and extra-thyroidal extension (20.9 versus 56.2%) [48]. However, since the outcome for differentiated thyroid cancer in children is excellent, the current ATA guidelines recommend against routine screening of family members of those with DTC.

Iodine Deficiency

Iodine deficiency is associated with an increased risk of thyroid dysfunction, thyroid nodules, and thyroid cancer. Iodine deficiency results in chronic TSH stimulation of the thyroid cells, which is a plausible potential mechanism for induction of nodules and differentiated carcinoma. Children in areas of Poland with endemic iodine deficiency were found to have higher rates of thyroid nodular disease and

cancer than those in iodine-sufficient areas [49]. A recent review of human and animal studies has shown higher rates of thyroid cancer (especially follicular cancer) in iodine-deficient animals [50]. The presence of iodine deficiency can also influence the morphologic characteristics of thyroid cancer with follicular cancer occurring at higher rates in the setting of iodine deficiency [51] and decreasing in rate after iodine prophylaxis [52–54].

Autoimmune Thyroid Disease

Data is limited and somewhat mixed regarding the risk that autoimmune thyroid disease (AITD) poses for thyroid cancer. Corrias et al., in an Italian study, showed a high prevalence of thyroid nodules in children and adolescents with pre-existing AITD (31.5% of 365 patients), compared to two US studies which found 12–13% prevalence of thyroid nodules among children with goiter, some of whom also had AITD [55–57]. All three studies showed that the majority of the nodules found on ultrasound were non-palpable, yet 8–20% of the nodules showed PTC. Further studies are needed to evaluate this potential association further; some of the differences in frequency between the Italian and US studies may be due to iodine intake since mild to moderate iodine deficiency is more common in Italy.

Despite the higher frequency of both nodules (palpable and non-palpable) and differentiated thyroid cancer in children with AITD, the current ATA guidelines recommend ultrasound in the setting of AITD only if there is suspicion about a nodule or if abnormal cervical lymphadenopathy is noted on physical examination [58].

Abnormal Thyroid Function

Several adult studies show that the presence of a TSH in the upper tertile in a patient with a thyroid nodule confers increased risk of thyroid cancer [59]. A large study in adults showed that elevated TSH (even within the normal range) was an independent predictor of the presence of malignancy and suggested that it should be used as such [60]. However, this link was not shown in the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC), which found that lower TSH levels may have been associated with thyroid cancer onset [61]. While studies in children are more limited, Chiu et al. showed a positive correlation between rising TSH levels $\geq$2.5 mIU/L and malignancy risk in pediatric patients [62]. Mussa et al. also showed a statistically higher TSH level in children with thyroid cancer compared to those with benign nodules but cautioned that this lacked great clinical significance due to significant overlap of TSH levels between the two groups [63].

Genetic Risk Factors

In addition to the well-recognized medullary thyroid cancers associated with germline RET mutations, several genetic syndromes are associated with thyroid nodules and differentiated thyroid cancer. The main genetic syndromes associated with thyroid cancer are outlined in Table 14.1.

Evaluation of a Thyroid Nodule

The evaluation of a thyroid nodule consists of a history, physical examination, thyroid ultrasound, lab evaluation, potentially fine needle aspiration biopsy, and possibly thyroid scintigraphy. The current ATA recommendations are outlined in Fig. 14.1. When a child or adolescent presents for evaluation of a thyroid nodule which they have noticed themselves or which was picked up incidentally on physical examination or

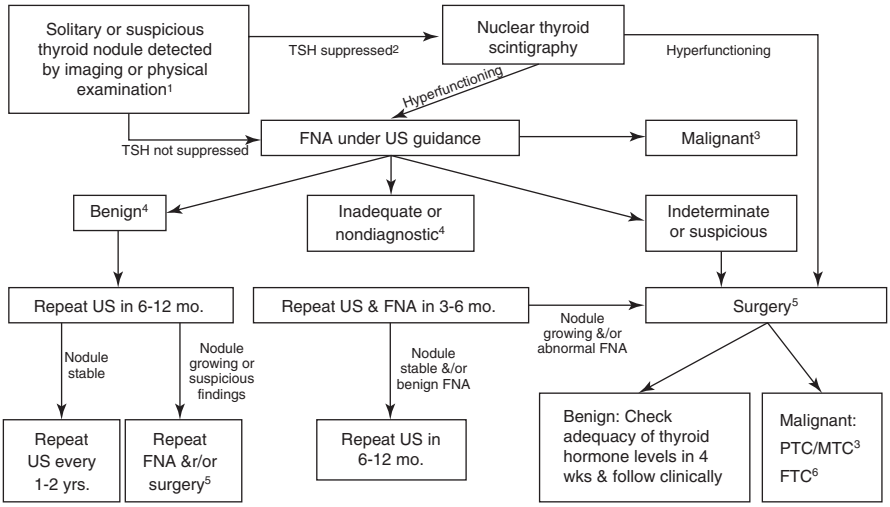

Fig. 14.1 Algorithm for the evaluation and treatment of thyroid nodules in children per the 2015 ATA guidelines (Republished with permission from Mary Ann Liebert, Inc. [71]). [1]Assumes a nodule with suspicious US features in a patient without risk factors for thyroid malignancy. [2]Free T4 may be normal or low. [3]Bethesda category VI on cytology, requires total thyroidectomy and need or extent of neck dissection depends on extent of disease (extrathyroidal spread/cervical lymph node involvement). [4]Bethesda Category I and II, surgery can be considered for compressive symptoms, if US features are suspicious, lesion is >4 cm, or family is uncomfortable with ambiguity of diagnosis and close follow-up. [5]Surgery should consist of at least lobectomy with intraoperative frozen section and completion thyroidectomy if differentiated thyroid cancer is diagnosed. [6]Consider completion thyroidectomy, may require radioactive iodine therapy

Table 14.1 Hereditary syndromes associated with thyroid nodules and cancer

Syndrome	Gene	Chromosomal location	Inheritance	Type of cancer	Other features
Isolated FMTC [151]	RET	10q11.2	AD	MTC	
MEN2A [151]	RET	10q11.2	AD	MTC	Pheochromocytoma, hyperparathyroidism
MEN2B [151]	RET	10q11.2	AD	MTC	Pheochromocytoma, neuromas and ganglioneuromas, marfanoid habitus
Isolated FNMTC [152]		2q21		PTC	
DICER 1 [153]	DICER 1	14q32.13	AD	PTC (only seen after chemotherapy)	Multinodular goiter, pleuropulmonary blastoma, Sertoli-Leydig tumors of the ovaries
Pendred syndrome [154]	SLC26A4	7q31	AR	FTC/PTC	Goiter, hypothyroidism, sensorineural hearing loss
Carney complex [155]	PPRKAR1a	17q23-24 (CNC1 locus) 2p16 (CNC2 locus)	AD	FTC/PTC	Pigmented lesions of the skin and mucosa; cardiac, cutaneous and other myxomatous tumors
Werner syndrome [156]	WRN	8p11-12	AR	FTC/PTC/ATC	A progeroid syndrome: cataracts, thinning of the scalp, premature gray hair and short stature, diabetes mellitus, hypogonadism, osteoporosis, premature atherosclerosis
Intestinal polyposis syndromes: [157]					
Familial adenomatous polyposis [157]	APC	5q21	AD	FTC/PTC	Multiple colorectal adenomas, hepatoblastoma, medulloblastoma
Gardner's syndrome	APC	5q21	AD	FTC/PTC	In addition to FAP features: desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, fibromas, supernumerary teeth, juvenile nasopharyngeal angiofibromas, and adrenal adenomas

Peutz-Jeghers syndrome [158]	STK11	19p13.3	AD	PTC	Pigmented mucocutaneous macules and multiple hamartomatous gastrointestinal polyps
PTEN hamartoma syndromes:					
Cowden disease [159]	PTEN	10q23.2	AD	FTC/PTC	Hamartomatous tumors, trichilemmomas, acral keratosis, facial papules and oral papillomas, developmental delay, breast cancer
Bannayan-Riley-Ruvalcaba syndrome (BRRS) [160, 161]	PTEN	10q23.2	AD	FTC/PTC	Hamartomatous tumors, macrocephaly, penile lentigines, developmental delay, myopathy

MTC medullary thyroid carcinoma, *FMTC* familial medullary thyroid carcinoma, *PTC* papillary thyroid carcinoma, *FNMTC* familial nonmedullary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *ATC* anaplastic thyroid carcinoma, *AD* autosomal dominant, *AR* autosomal recessive

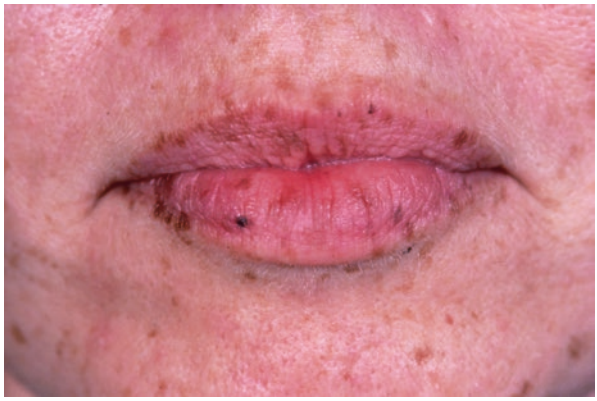

Fig. 14.2 Abnormal pigmentation of the lips seen in Carney complex (Photo courtesy of Dr. J. Aidan Carney, MD, PhD)

imaging, the history should ascertain if there is an increased risk of cancer: thyroid cancer is typically painless and not associated with any inflammation of the neck. The vast majority of patients with thyroid cancer are euthyroid. A prior history of radiation exposure or a family history of thyroid cancer should be sought. The physical exam should include palpation of the thyroid gland and the neck to determine the presence or absence of concerning lymphadenopathy. Although the hereditary syndromes described in Table 14.1 are rare, they need to be kept in mind when performing the physical examination, e.g., abnormal pigmentation in Carney complex (see Fig. 14.2) and Peutz-Jeghers syndrome and hamartomatous lesions in the PTEN hamartoma syndromes. It must also be borne in mind that several non-thyroidal conditions, including abscesses, lymphatic or vascular malformations, ectopic thymus, or thyroglossal duct cysts, can mimic thyroid nodules. Nodular disease of the thyroid may be due to a solitary thyroid nodule, multinodular goiter, or nodules in a goiter due to chronic lymphocytic thyroiditis, or it may be non-palpable found incidentally.

Thyroid Ultrasound

Thyroid ultrasound (US) is the best imaging modality for thyroid nodules. Prior guidelines have recommended against performing a biopsy on any nodules <1 cm unless the patient is at high risk (prior radiation exposure, at-risk genetic syndrome, or pathologic-appearing regional lymph nodes) [13]. In adults, there is growing evidence to support this clinical approach, given the current knowledge regarding the indolent nature of papillary thyroid microcarcinoma (PTMC) (PTC measuring <1 cm); only 3.5% of them grow in adults [64].

The thyroid gland is smaller in children than in adults, and therefore, a tumor <1 cm in a child and in an adult may not be comparable. Thyroid cancer measuring <1 cm is less common in children, and the term PTMC is not typically used. The frequency of papillary thyroid carcinomas in children and adolescents measuring less than 1 cm ranges from 1 to 37% in various studies, and it increases with age, even within the pediatric age ranges [14, 65–70]; when present, it may not be as indolent as in adults.

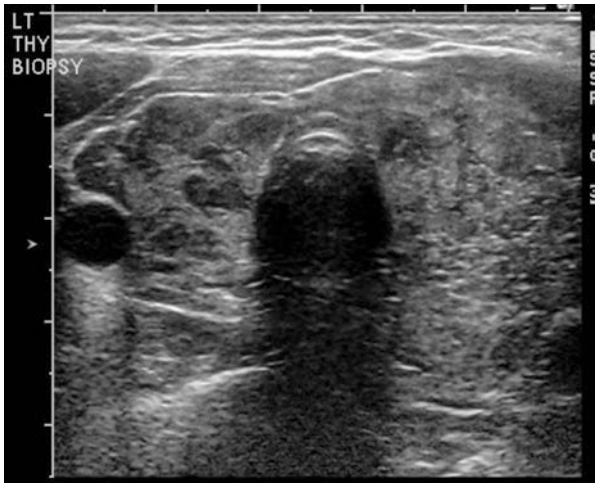

Fig. 14.3 Dominant nodule in the *left* lobe, heterogeneous appearance of the *right* thyroid lobe suggestive of Hashimoto's thyroiditis

Children with PTC ≤1 cm have more frequent lymph node metastases than adults with PMTC of 66.7% (12/18) in one study [69] and 41% (14/34) compared to 19% of adults (85/584) in another study which included adults and children [70].

The most recent pediatric guidelines from the American Thyroid Association [71] have recommended proceeding with biopsy in nodules of any size which have suspicious US characteristics. Hypoechogenicity, irregular margins, increased blood flow, the presence of microcalcifications, and abnormal cervical lymph nodes are all more common in malignancy, and their presence should prompt consideration of biopsy [72, 73] (see Fig. 14.3). A recent meta-analysis and systematic review has shown that the presence of internal calcifications or enlarged cervical lymph nodes were the US features with the highest likelihood ratio (4:46 and 4:96, respectively) for thyroid cancer. A cystic nodule was the feature with highest likelihood ratio for benign nodules at 1:96 [74]. All children with suspicious thyroid nodules should also have a full US evaluation of their cervical lymph nodes. Thyroid nodules can also be detected incidentally on CT or as areas of focal uptake on ^{18}FDG-PET scans performed for other reasons. When nodules are discovered incidentally, they should still be evaluated (with ultrasound) as differentiated thyroid cancer can be discovered in this way and increased uptake on ^{18}FDG-PET is associated with an increased risk of thyroid cancer [75].

Lab Testing

Thyroid function tests should be checked in all patients with thyroid nodules, and in the absence of hyperthyroidism, an US-guided fine needle aspirate should be performed on any nodule with suspicious characteristics. Currently an elevated TSH level is not being used in practice to help predict the presence or absence of malignancy since results from studies conflict as to its clinical benefit [59–62].

Calcitonin levels are elevated in MTC and C-cell hyperplasia; measurement of calcitonin is not recommended in the absence of risk factors for MTC (positive family history of MTC or MEN2, presence of pheochromocytoma); this is mainly because the prevalence of sporadic MTC is very low in children. Thyroglobulin level is often elevated in thyroid disease, but this finding is not at all specific for thyroid cancer [76–78], and therefore, thyroglobulin testing should not be part of the diagnostic work-up of a thyroid nodule.

Thyroid Scintigraphy

TSH suppression may be found in a child with a nodule. In this situation, a radioisotope scan (iodine-123 or 99mTc pertechnetate) should be performed [79, 80]. A toxic adenoma will show increased nodule-specific uptake on the scan (a "hot nodule"). In adults, the presence of an autonomous or "hot" nodule is generally accepted as predictive of benign disease, and these patients do not require biopsy [13]. In children there are fewer studies of hot nodules, and they show some conflicting results: a study by Niedziela et al. in 2002 showed that in an area with iodine deficiency and recent use of iodine supplementation, there was an increased prevalence of hot nodules in children. Thirty-one children with hot nodules were followed, and 9/31 (29%) were diagnosed with differentiated thyroid cancer [79]. A separate study by Hodax found that in patients <21 years of age with thyroid nodules, 17/242 were autonomously functioning; six of these patients had surgery, and only one was diagnosed with papillary thyroid cancer [81]. In a recent study by Ly and colleagues, of 31 children with autonomous nodules (when the strict criteria of autonomy were applied), 21 had either a biopsy or surgical resection with histology, and 0/21 had thyroid cancer compared to 28/125 (22%) of their comparative group of children with non-autonomous nodules [82]. In the absence of long-term follow-up of alternative treatment modalities for children with hot nodules, the current ATA guidelines recommend that all symptomatic children with hyperthyroidism requiring treatment due to autonomous nodules proceed to surgical resection [71]; asymptomatic children or those with subclinical hyperthyroidism can be observed.

Fine Needle Aspiration Biopsy

The most recent ATA guidelines recommend that all FNA in children should be performed under ultrasound guidance [71]; this recommendation is based on the fact that thyroid nodules in children more commonly harbor malignancy than in adults [10] and that biopsies are more difficult to repeat in children. Cytopathology findings for children are classified in the same way as for adults: Bethesda system for reporting thyroid cytopathology [83, 84].

There are six categories, as follows:

I Nondiagnostic or unsatisfactory (the specimen has limited cellularity, absence of follicular cells, or poor preservation of cells)
II Benign
III Atypia or follicular lesion of unknown significance (AUS/FLUS)
IV Follicular/Hürthle cell neoplasm or suspicious for follicular/Hürthle cell neoplasm
V Suggestive of malignancy
VI Malignant

The sensitivity, specificity, and overall accuracy of FNA in children are considered similar to adults [85–90]. Table 14.2 shows the cytological outcomes of thyroid FNA biopsies reported in the pediatric literature over a 21-year timespan. The six Bethesda categories were not consistently used over this time period, and therefore for the purposes of comparison, Bethesda categories III and IV were grouped together into "atypical," and at times III–V were grouped (this grouping is also called indeterminate). The prevalence of Bethesda I ranged from 4–28%, II 46–82%, III–V 3–38%, and VI 3–20%. The wide variation in results likely resulted from geographical differences between studies and variation in clinical assessment algorithms regarding when a biopsy should be performed. When all of the date are pooled (1551 nodules), the prevalence of Bethesda category I was 16%, 57% were Bethesda II, 18% were Bethesda III–V, and 10% were Bethesda VI.

In adults, the risk of malignancy after an inadequate sample is 1–4% [83]; nodules with indeterminate cytology have a 5–30% risk of malignancy (lower in the AUS/FLUS lesions and higher in the follicular neoplasm or suggestive of neoplasm group) [84]. Published pediatric series are outlined in Table 14.3. The prevalence rates of malignancy using pooled data from these studies with a total of 561 histologic diagnoses showed a cancer prevalence of 4% (range 0–10%) after an inadequate(Bethesda I) FNA sample, 8% (range 0–33%) after benign(Bethesda II) cytology, 48% after an indeterminate (Bethesda III–V) FNA sample, and 100% after malignant (Bethesda VI) FNA. Since most nodules with benign cytology on FNA are managed nonoperatively, these retrospective studies of operative cases significantly overestimate the prevalence of malignancy in the benign (Bethesda II) category: cancer prevalence rates vary from 0 to 33% in various studies (pooled data shows a prevalence of 8%). The children reported in these studies were taken to surgery despite negative FNA, presumably because of some concerning features on physical exam or ultrasound; therefore, higher risk nodules are overrepresented in the surgical group. Assuming all nonoperative benign (Bethesda category II) FNA samples are actually benign, the prevalence rate for malignancy in the pooled data drops from 8 to 2%; the true frequency of malignancy in this group likely falls somewhere between these two rates.

In view of these findings, children with suspicious nodules on ultrasound need follow-up even if the FNA is inadequate or benign. When cytopathology results are inadequate, a repeat US and FNA should be performed 3–6 months later; it should not be performed sooner due to the risk that the FNA can change US features of the nodule [91] and result in atypical cellular features during the healing process [92].

Table 14.2 Cytological outcomes of fine needle aspiration biopsy of thyroid nodules in children

Author	Year published	Nodule number	Age, mean (range)	Inadequate (I)	Benign (II)	Atypical (III and IV)	Suspicious (V)	Malignant (VI)
Raab [162]	1995	66	13.1 (1–18)	3 (5%)	51 (77%)	8 (12%)		4 (6%)
Lugo-Vicente [163]	1998	18	14.9 (9–18)	3 (17%)	11 (61%)	2 (11%)		2 (11%)
Khurana [164]	1999	57	16.5		36 (63%)	14 (25%)		7 (12%)
Al-Shaikh [165]	2001	41	13.3	3 (7%)	30 (73%)	6 (15%)		2 (5%)
Arda [166]	2001	46	9 (5–11.6)	2 (4%)	33 (72%)	5 (11%)	3 (7%)	3[b] (7%)
Amrikachi [86]	2005	218	(10–21)	62 (28%)	119 (55%)	20 (9%)		17 (8%)
Hosler [167]	2006	101	14.6 (8–18)	13 (13%)	48 (47%)	13 (13%)	5 (5%)	22[c] (22%)
Altincik [168]	2010	30		4 (13%)	24 (80%)	1 (3%)		1 (3%)
Corrias [169]	2010	104	11.5	7[a] (7%)	77 (76%)	8 (8%)		19 (19%)
Monaco [17]	2012	179	16.5 (4–20)	21 (12%)	82 (46%)	62 (35%)	6 (3%)	8 (4%)
Gupta [10]	2013	136		13 (10%)	86 (63%)	16 (12%)	10 (7%)	11 (8%)
Norlen [170]	2015	66	13.6	7 (11%)	38 (58%)	15 (23%)	3 (4%)	3 (4%)
Lale [171]	2015	282		59 (21%)	136 (48%)	46 (16%)	6 (2%)	35 (12%)
Amirazodi [172]	2015	207	(2–18)	54 (26%)	108 (52%)	17 (8%)	10 (5%)	18 (9%)
Pooled data		1551		251 (16%)	879 (57%)	276 (18%)		152 (10%)

[a]Indeterminate samples were repeated and so were also reported in the other categories
[b]Includes 1 biopsy showing metastatic non-Hodgkin's Lymphoma
[c]Includes 2 non-thyroid malignancies

Table 14.3 Histologic correlation of cytology results in pediatric patients, reported as number of malignancies found for each category

Author	Number of nodules with histology	Inadequate (I)	Benign (II) *Assuming all nonoperative were benign*	Atypia/FLUS (III)	FN/SFN (IV)	Suspicious	Malignant
Raab [162]	25		1/13 (8%) *1/51 (2%)*	4/8 (50%)			4/4 (100%)
Lugo-Vicente [163]	15		2/11 (18%) *2/11 (18%)*	1/2 (50%)			2/2 (100%)
Gupta [10]	63	1/13 (8%)	2/14 (14%) *2/63 (3%)*	4/9 (44%)	6/6 (100%)	4/10 (40%)	11/11 (100%)
Corrias [169]	55		0/30 (0%) *0/77 (0%)*	0/6 (0%)			19/19 (100%)
Khurana [164]	24		1/3 (33%) *1/36 (3%)*	6/14 (43%)			7/7 (100%)
Altincik [168]	5		1/4 (25%) *1/24 (4%)*				1/1 (100%)
Arda [166]	31	0/2 (0%)	0/18 (0%) *0/33 (0%)*	0/5 (0%)		1/3 (33%)	3/3[a] (100%)
Amrikachi [86]	32	0/1 (0%)	0/11 (0%) *0/119 (0%)*	4/9 (44%)			11/11 (100%)
Hosler [167]	45	0/1 (0%)	4/15 (27%) *4/48 (8%)*	3/8 (38%)	2/5 (40%)		13/16 (100%)
Monaco [17]	96	0/8 (0%)	2/30 (7%) *2/82 (2%)*	7/25 (28%)	11/19 (58%)	6/6 (100%)	8/8 (100%)
Norlen [170]	31	0/3 (0%)	0/9 (0%) *0/38 (0%)*	2/9 (22%)	4/4 (100%)	3/3 (100%)	3/3 (100%)
Lale [171]	74	1/10 (10%)	0/17 (0%) *0/136 (0%)*	2/4 (50%)	7/18 (39%)	4/4 (100%)	24/24 (100%)
Amirazodi [172]	65	0/12 (0%)	3/19 (16%) *3/108 (3%)*	6/9 (67%)		5/7 (71%)	18/18 (100%)
Pooled	561	2/50 (4%)	16/194 (8%) *16/826 (2%)*	92/193 (48%)			124/124 (100%)

[a]Includes 1 metastatic non-Hodgkin's Lymphoma

Molecular Genetic Testing

Another modality used in adults to help differentiate between benign and malignant disease is molecular genetic testing [93–98]. This topic is reviewed extensively elsewhere in this book. Multiple studies show that the mutations found in pediatric thyroid cancer differ from those of adults [99] and that the genetics of radiation-exposed and sporadic thyroid cancers are very different [99–101]. Genetic rearrangements including RET/PTC are far more common in children than in adults, especially in children with radiation-exposed thyroid cancers: studies show a pooled prevalence of RET/PTC rearrangements in radiation-exposed pediatric PTC of 58% (range 33–76%) [101–109] and 41% in sporadic pediatric PTC (range 15–65%) [99–101, 107, 108, 110–122], compared to 10–20% of adults [123–125].

BRAF mutations are the most common mutations in adult PTC, seen in 61.7% (range 29–83%) of patients [126–129]; they are less common in children where studies on sporadic papillary cancer show a pooled prevalence of BRAFV600E of 13% [99], albeit with great variation between studies ranging from 0 to 63% [99–101, 107, 108, 110–122]. In radiation-exposed PTC, the prevalence of BRAF mutations in the few studies performed is very low at 3%, with a range of 0–8% [103–111] and no BRAF mutations have been found in a child less than 10 years of age [99].

The goal of using mutational analysis on cytology samples is to help differentiate between benign and malignant disease. Using the Bethesda cytology classification system, pediatric studies show that category VI is highly predictive of malignancy (100% in the pooled studies presented in Table 14.3), while the rate of malignancy was still 48% in the indeterminate categories (III, IV, and V), suggesting that molecular studies in this group could prove useful. Pediatric studies have shown that the presence of a mutation on cytology is highly predictive of malignancy [17, 130]; however, in the largest study to date, mutation-negative FNA samples still had a 48.5% malignancy rate [17]; therefore, molecular analysis of cytology samples is not currently recommended for children [71].

Since thyroid nodules in children are more commonly malignant, follow-up of even benign lesions is important. Follow-up should be by US 6–12 months after the initial benign FNA.

Management of Thyroid Nodules

Management of thyroid nodules depends on the diagnostic work-up and consists of either surgery or potentially levothyroxine therapy. Nodules which are predominantly cystic and have no concerning US features require neither FNA nor treatment.

Surgical Management of Thyroid Nodules

The risks and benefits of surgery for thyroid nodules are based on the risk of thyroid cancer predominantly assessed by the Bethesda category on FNA [71]. The higher the risk of malignancy, the more likely surgery is necessary and the more extensive that surgery should be. Thyroid surgery in children should be carried out by high-volume thyroid surgeons to decrease the potential for complications [131–133]. All children undergoing thyroid surgery should have a full neck ultrasound to determine potential extent of disease and therefore the extent of surgery. Children with papillary thyroid carcinoma (by far the most common thyroid cancer in children) should undergo a total or near-total thyroidectomy due to an increased prevalence of bilateral (30%) and multifocal (65%) disease in children [134–136]. Studies have shown a lower risk of recurrence when a total or near-total thyroidectomy is performed [135–137]. Bilateral lobar resection compared very favorably to lobar resection in a study of 215 children and adolescents followed for 40 years: it improved recurrence risk from 35% to 6% [137]. Children with thyroid cancer may also require central and potentially lateral neck dissections depending on the presence of extra-thyroidal invasion or metastatic lymph nodes [71].

Surgery may be indicated in the absence of confirmed differentiated thyroid cancer; the most recent ATA guidelines recommend surgery (at least a lobectomy and isthmectomy) for any indeterminate cytology on FNA (Bethesda III–V) due to the high risk of cancer in these patients (48% in the pooled data in Table 14.3). We advocate the use of intraoperative frozen section histology to determine the need or not for completion thyroidectomy; this is very beneficial in cases of classic papillary thyroid carcinoma, but it is less helpful for follicular variant PTC and is not helpful for follicular thyroid carcinoma since their diagnosis depend on histologic evaluation of the entire lesion for evidence of vascular or capsular invasion [138–140].

In children with thyroid nodules showing benign cytology, a risk of malignancy remains (estimate 2–8%, see Table 14.3) and close follow-up is warranted; lesions which are growing or have developed suspicious ultrasound features are more likely to be caused by differentiated thyroid cancer and should be removed despite the cytology result [63, 141, 142]. Surgery (lobectomy and isthmectomy) can be considered for benign lesions if there are compressive symptoms, concerning US features or if the family cannot tolerate the uncertainty regarding cancer risk [71].

Since the prevalence of malignancy in inadequate FNA samples is unknown in children, a repeat US and FNA should be performed 3–6 months after the initial sample.

Surgery is usually recommended in large benign lesions (>4 cm) due to the high false-negative rate of FNA in large nodules [10, 143–145]. As discussed previously, thyroid cancers <1 cm in diameter in children are not necessarily as indolent as PMTC in adults [70], and therefore, the cytology rather than the size of the lesion determines the cancer risk and the decision whether or not to proceed to surgery.

The current ATA guidelines recommend that all children requiring treatment for autonomous thyroid nodules, i.e., those with symptomatic hyperthyroidism, proceed to surgical resection rather than an alternative treatment for their hyperthyroidism; however, children without symptoms with subclinical hyperthyroidism can be observed [71]. This recommendation is based predominantly on a lack of follow-up studies on pediatric patients treated with alternative modalities and an Italian study showing a differentiated thyroid cancer in 29% of 31 children with hot nodules [79].

Levothyroxine Therapy

The use of levothyroxine therapy for thyroid nodules in children is controversial; the most recent ATA guidelines neither recommend nor argue against its use [71]. The natural history of thyroid nodules is that some will regress spontaneously; this is likely more common in small cystic lesions [12, 146, 147]. In a retrospective study of 78 children with benign thyroid nodules, 30.6% of those children who received levothyroxine therapy showed a 50% or greater reduction in size of their nodules; the extent of reduction correlated with the extent of TSH suppression [148].

Levothyroxine therapy has been shown to reduce the formation of further nodules when used in pediatric patients with radiation-induced thyroid nodules, but it had no effect on the incidence of thyroid cancer in these patients [149, 150].

Conclusion

Thyroid nodules are less common in children than in adults but, when discovered, are more likely to harbor malignancy. When a nodule is discovered, the goal is to discern if the nodule is malignant and requires surgery. The tools used in this assessment include careful history and physical examination, ultrasound, occasionally thyroid scintigraphy, and fine needle aspiration biopsy.

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