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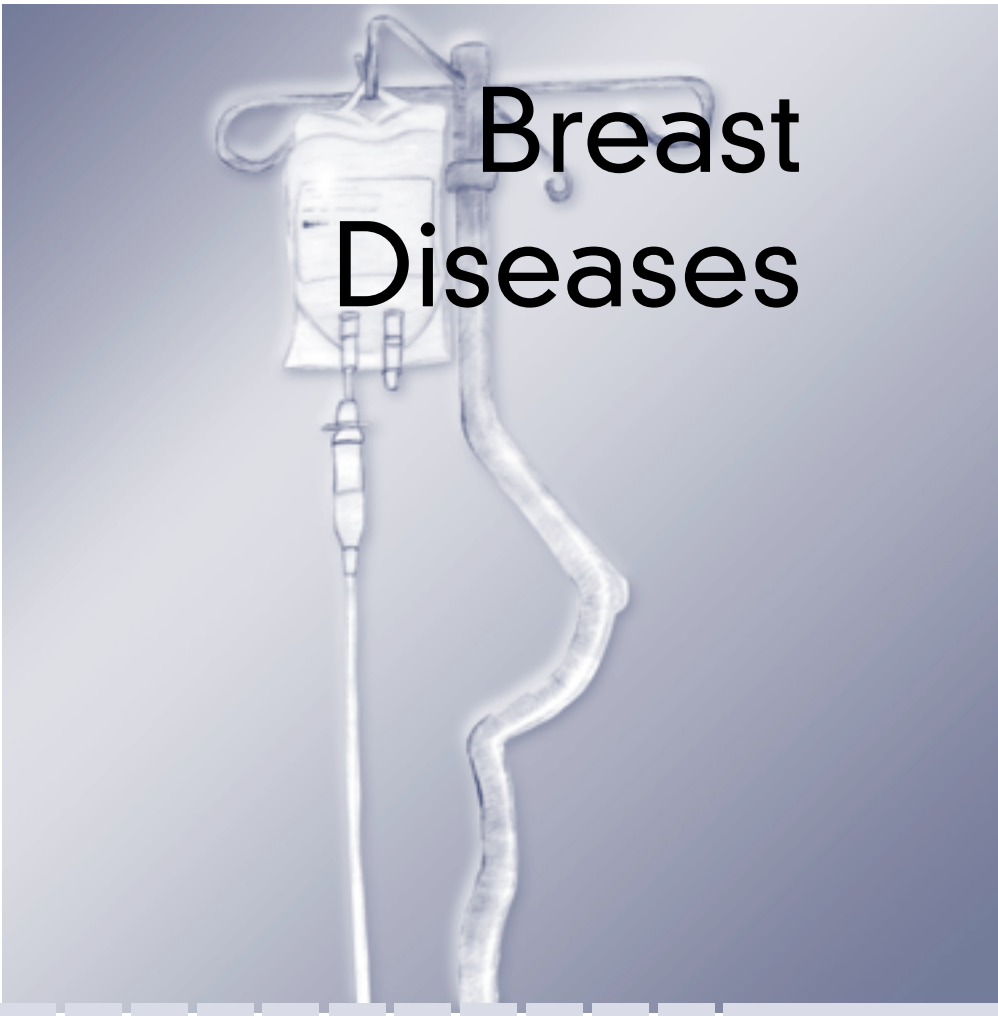
Breast Diseases



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v a d e m e c u m

Breast Diseases

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Dedication

This work is dedicated to the thousands of women fighting breast cancer and to their physicians who have chosen to join them in their battle and to the families of both, whose love and encouragement provides inspiration and strength.

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Preface

Breast cancer remains one of the greatest health threats facing women around the world as we enter the 21st century. In the United States alone, over one million women have died of breast cancer in the past 30 years. The number of American women who have lost their lives to breast cancer outstrips the total number of American lives lost in the Civil War, World War I and II, the Korean War and the Vietnam War combined. Worldwide, many countries continue to document a steady increase in breast cancer incidence rates and a steady worsening of breast-cancer-specific survival rates. By any definition, breast cancer is an epidemic, and its prevention, diagnosis and treatment merit constant updating and reassessment.

To this end, we have assembled leading experts in the field of breast diseases and have compiled herein an up-to-the-minute, concise and practical handbook that encapsulates current thinking on a wide range of topics—from normal breast anatomy through the management of Stage IV breast cancer.

It is worth noting that fully one-third of the chapters in *Breast Diseases* are dedicated to the nonpatient—the woman who has not yet developed breast cancer. This reflects favorably upon the current emphasis on breast cancer prevention and the study of the role of genetics in this disease.

The handbook opens with a thoughtful discourse on the normal anatomy of the breast and the axilla, the understanding of which is crucial to an understanding of malignant transformations in the breast. Chapters 2 and 3 focus on breast symptoms and the ubiquitous benign breast disorders we see in our practices every day. Distinguishing these benign signs and symptoms from those produced by an underlying malignancy is of great importance.

In the fourth chapter, the topics of primary and secondary prevention of breast cancer are discussed, with special emphasis placed on the management of patients at increased risk to develop breast cancer. The Food and Drug Administration's approval of the drug tamoxifen citrate for use in reducing the incidence of breast cancers clearly marks the dawn of the era of breast cancer chemoprevention in the United States.

The breast cancer patient is introduced in Chapter 5, which deals with pathology, prognosis and the staging of breast cancer. This chapter provides a working vocabulary with which to understand the many different types of breast cancer. Practical approaches for prognostic assessment and staging are also presented.

Chapter 6 deals with the all-important field of breast imaging and reports on the current status of breast screening, image-guided biopsy and novel imaging modalities.

Chapter 7 tackles the surgical treatment of breast cancer. Current surgical approaches are discussed in relation to the evolution of the treatment of breast cancer over the past century. Special emphasis is placed on techniques that conserve the breast and the regional nodes, including sentinel node mapping, the most important development in breast cancer surgery of the past 20 years. Chapter 10 provides a separate, detailed discussion of sentinel lymph node mapping.

The most successful treatment approaches to breast cancer involve multimodality therapy integrating surgery, radiation and adjuvant therapy. Chapter 8 addresses adjuvant therapy for breast cancer. The plethora of agents in use today in the treatment of this disease and the patient-selection criteria for those agents have undergone almost continual change over the past 40 years. An up-to-the-minute summary is presented here, complete with a discussion of the current drugs and indications widely accepted as state of the art.

Chapter 9 presents state-of-the-art patient-selection criteria and approaches to radiation therapy. Radiation therapy continues to play an important role in the treatment of even the earliest-stage breast cancers and is, even now, often given to the patient with positive axillary nodes who has undergone mastectomy.

Breast Diseases concludes with a thoughtful and informed summary of our current understanding of hereditary breast cancer and the genes involved therein. We have entered the era of genetic-susceptibility testing for breast cancer, a step forward in the fight against breast disease that promises not only to help us identify those patients at the highest echelon of risk, but also to provide greater understanding of the most fundamental mechanisms involved in breast cancer development and progression.

I am indebted to my coauthors on this book. They have all dedicated their lives to the war on breast cancer. I am grateful for their energy, enthusiasm and expertise, without which this book would not have been possible.

The patient at increased risk for breast cancer development and the patient with a newly diagnosed breast cancer are both forced to choose a course of action from a seemingly infinite list of alternative interventions and therapies. These patients must rely heavily on their physicians to help them navigate this maze and select a reasonable course of action for dealing with this lethal disease. It is my hope that this handbook will prove a useful resource for clinicians as they strive to do so.

Patrick I. Borgen, M.D.

Acknowledgments

Our research activities are supported by major endowments from the W.M. Keck Foundation, the Tow Foundation, the Breast Cancer Alliance and the Breast Cancer Research Foundation. In particular, I would like to thank Mr. and Mrs. Michael Masin, Emily Tow Jackson, Herb and Ann Siegel and Mrs. Evelyn Lauder. Memorial Sloan-Kettering Cancer Center has provided significant institutional support for these activities, and I am particularly grateful to Dr. Murray Brennan, Dr. Lewis Freedman and Mr. Robert Wilkens. This book benefited from the careful editing of K. Alexandra MacDonald, Denise Buckley and Jess Guarnaschelli. Carol Agramonte played an important central role as well. Finally, I am eternally grateful to my family for their love and support. Liz, Emily, Mary Charlotte, Patrick and Slater are the real heroes in my own war against breast cancer.

Patrick Borgen, M.D.

CHAPTER 1

Anatomy of the Breast and Axilla

Mary L. Gemignani

Embryology/Development

The mammary glands develop from ectodermal ridges that form on the ventral surface of the embryo. They extend laterally from forelimb to hindlimb and constitute the milk line. These buds occur in multiple pairs and begin appearing at around 5 weeks of gestation. Most of the pairs regress during fetal development, except for one pair in the pectoral region that eventually develops into the two mammary glands. If buds along the milk line do not completely disappear, they will develop into ectopic glandular tissue. This ectopic mammary tissue is usually seen at the extreme ends of the mammary ridge, usually in the axilla or the vulva in the adult. This can occur as extra breasts (polymastia) or nipples (polythelia). Accessory mammary tissue is found in 2-6% of women.

At midpregnancy, the two fetal mammary buds destined to form breasts begin to grow and divide. Fifteen to 25 secondary buds are formed that are essentially the duct system in the mature breast. Each secondary bud elongates into a cord, bifurcates and differentiates into two concentric layers of cuboidal cells and a central lumen. Secretory epithelium is derived from the inner layer of cells. These cells are responsible for milk production during lactation. The outer layer of cells becomes myoepithelium and is responsible for the mechanism of milk ejection.

In the last 2 months of gestation, canalization of these epithelial cords occurs, as well as development of the branching lobuloalveolar glandular structures. The lactiferous ducts converge to form the mammary pit. Near birth, evagination of the mammary pit forms the nipple.

The earliest stage of fetal mammary gland development does not appear to be dependent on steroid hormones. Testosterone, however, influences actual growth and development after the 15th week of gestation. In the last weeks of gestation, the fetal breast is responsive to maternal and placental steroid hormones and prolactin. Secretory activity may be induced from the fetal mammary ducts. At birth, secretion of colostrum and palpable enlargement of the breast buds can be seen in both sexes. Regression typically occurs during the first 2 months of neonatal life.

Breast Diseases, edited by Patrick I. Borgen and Arnold D.K. Hill.

In the female, adolescent breast development (thelarche) occurs with onset of cyclical estrogen and progesterone. Ductal growth and differentiation of periductal stroma is influenced by estrogen, growth hormones and glucocorticoids. With onset of ovulation, progesterone stimulates development of the alveoli and prepares the breast for possible future lactation.

Adult Breast Morphology

Location/Anatomic Boundaries

The adult breast lies between the second and sixth ribs in the vertical plane and between the sternal edge medially and midaxillary line laterally. The average breast measures 10-12 cm in diameter, and thickness centrally is 5-7 cm. It is concentric with a lateral projection into the axilla, referred to as the axillary tail of Spence.

Structures

The adult breast consists of three major structures: skin, subcutaneous fatty tissue and breast tissue (parenchyma and stroma). The skin contains hair follicles, sebaceous glands and eccrine sweat glands.

The glandular breast is divided into 15-20 segments (lobes) that converge at the nipple in a radial arrangement. These lobes are made up of 20-40 lobules. Each lobule in turn consists of 10-100 alveoli (tubolosaccular secretory units). Collecting milk ducts, measuring approximately 2 mm in diameter, drain each segment. Between five to ten major collecting milk ducts open at the nipple into subareolar lactiferous sinuses, which are about 5-8 mm in diameter. Between the lobes of glandular tissue is subcutaneous connective tissue.

Superficial pectoral fascia envelops the breast and is continuous with the superficial abdominal fascia of Camper. The undersurface of the breast lies on the deep pectoral fascia. Cooper suspensory ligaments provide support for the breast and are fibrous bands connecting the two fascial layers. The retromammary bursa refers to a distinct space on the posterior aspect of the breast between the deep layers of the superficial fascia of the breast and the deep investing fascia of the pectoralis major.

Nipple/Areola

The epidermis of the nipple (mammary papilla) and areola is pigmented and wrinkled and consists of keratinized, stratified squamous epithelium. It is 15-60 mm in diameter. There are bundles of smooth-muscle fibers that are circumferentially arranged in dense connective tissue and are responsible for the contractile function and erection of the nipple. Two receptor-type nerve endings (Ruffini-like bodies and end bulb of Krause) are present on the nipple and are associated with the tactile reception of stretch and pressure.

Neuronal plexuses around hair follicles in the skin peripheral to the areola are also present. The areola has no hair follicles. It has sebaceous glands (at its margin), apocrine sweat glands, and accessory areolar glands (Montgomery glands). Montgomery glands are intermediate between true mammary glands and sweat glands and open on the surface of the areola as small elevations called Morgagni tubercles. Figure 1.1 is a tangential view of the breast on the chest wall and a sectional view of the breast and chest wall.

Blood Supply of the Breast

The blood supply of the breast is mostly from superficial vessels. The principal blood supply is derived from the internal thoracic (mammary) and lateral thoracic artery. Enlarged lateral branches of the anterior perforating arteries originating from the internal thoracic artery run to the breast as medial mammary arteries. The lateral mammary arteries are often multiple in origin and are derived from the lateral thoracic artery. The posterior intercostal arteries of the second and fourth intercostal spaces also give off mammary branches. The superficial veins follow the arteries and drain through perforating branches of the internal thoracic vein, tributaries of the axillary vein and perforating branches of posterior intercostal veins. The veins anastomose circumferentially around the nipple, the circulus venosus. Figure 1.2 illustrates the blood supply to the breast.

Innervation of the Breast

Sensory innervation is supplied primarily by the lateral and anterior cutaneous branches of the second through sixth intercostal nerves. Branches of the supraclavicular nerve supply a limited portion of the skin in the upper breast.

Secretory activity is under pituitary and ovarian hormonal control. Oxytocin released in the neurohypophysis stimulates myoepithelial cells that in turn stimulate contraction and release of milk from the mammary glands.

Thoracic Wall

The thoracic wall is composed of the 12 thoracic vertebra, 12 ribs and costal cartilages, sternum and associated muscles. The external, internal, innermost intercostal muscles, intercostal vessels and nerves lie in the intercostal spaces. All three are thin sheets of muscles whose fibers run from one rib to the next. The external intercostal muscles begin posteriorly, lateral to the tubercle of the rib, and extend anteriorly, past the costochondral junction. Between the costal cartilages, the muscle is replaced by the external intercostal membrane. The fibers slant downward and forward from one rib to the other. The internal intercostal muscle fibers run in the opposite direction, upward and forward from the upper border of one rib to the lower border of the next one. The muscle fibers of this layer reach the sternum anteriorly.

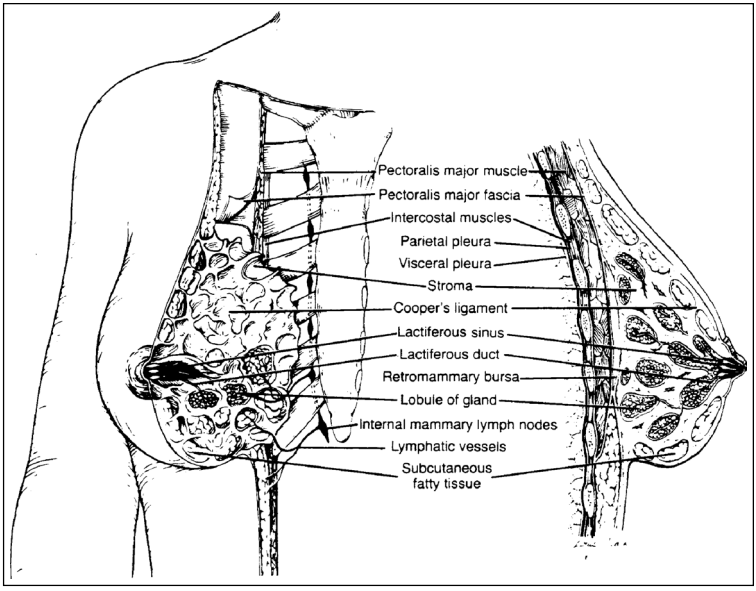

Fig. 1.1. Anatomical structures of the breast and underlying chest wall. Reprinted with permission from: Bland KI, Copeland III EM, eds. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 9-36. ©1998 W.B. Saunders Co.

Posteriorly, they extend only as far as the costal angles and continue as the internal intercostal membranes. The innermost intercostal muscles lie internal to the internal intercostals and occupy chiefly the middle part of the length of each intercostal space. They are less well developed and are separated from the intercostal muscles by the intercostal nerves and vessels. The subcostal and transversus thoracis muscles are located on the internal surface of the thoracic wall. The subcostal muscles are variable fiber bundles posteriorly placed that span two to three intercostal spaces. The transversus thoracis is a thin layer of muscle whose fibers arise from the posterior surface of the lower part of the sternum to the neighboring costal cartilages. The thoracic wall is innervated by the ventral rami of T1 to T12 spinal nerves. T1 to T11 are the intercostal nerves, and T12 is the subcostal nerve. These nerves innervate all the muscles and give branches to the overlying skin as lateral cutaneous nerves. The upper six terminate as the anterior cutaneous nerves, superficially. The lower six terminate as the thoracoabdominal nerves, innervating the anterior abdominal wall. The nerve lies below the vein and artery. In each intercostal space, there are two sets of intercostal arteries, posterior and anterior, that anastomose with each other. The posterior intercostal arteries, except for the

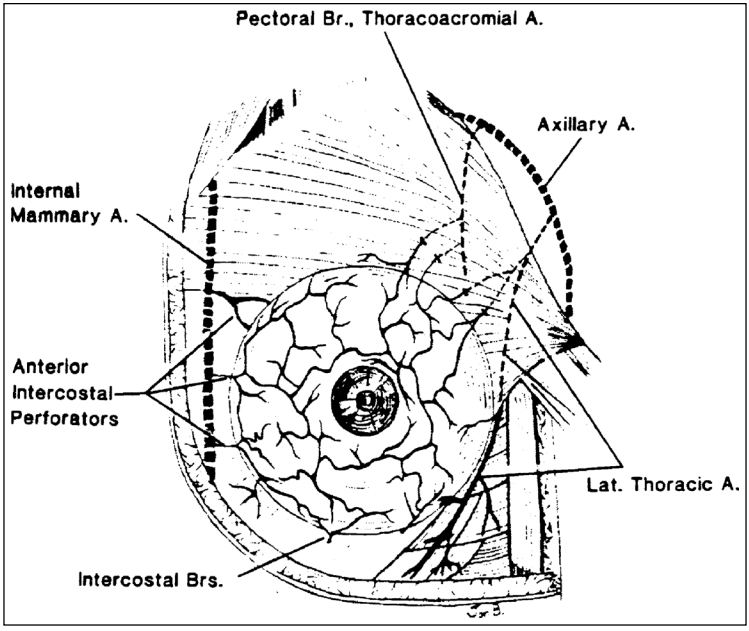

Fig. 1.2. Arterial blood supply to the breast. The main blood supply is from the internal mammary artery and lateral thoracic artery. Reprinted with permission from: Bland KI, Copeland III EM, eds. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 9-36. ©1998 W.B. Saunders Co.

first two spaces, are branches of the descending thoracic aorta. The first two originate from the supreme intercostal artery that is a branch of the costocervical trunk of the subclavian artery. The upper five anterior intercostal arteries are branches of the internal thoracic (mammary) artery. The lower six arise from the musculophrenic artery, one of the terminal branches of the internal thoracic. The intercostal veins follow similar patterns. The first two anterior intercostal veins drain into the brachiocephalic vein and the remainder into muscolophrenic and internal thoracic veins. The posterior intercostal veins drain into the azygos and hemiazygos veins. Figure 1.3 is a cross section of the breast and chest wall illustrating the layers of the thoracic wall and paths of blood vessels and nerves.

Muscles and Associated Structures

Table 1.1 lists muscles of the chest wall that comprise the anatomic boundaries of the axilla, their origin, insertion, action and nerve innervation. The nerves are discussed in the section on the brachial plexus.

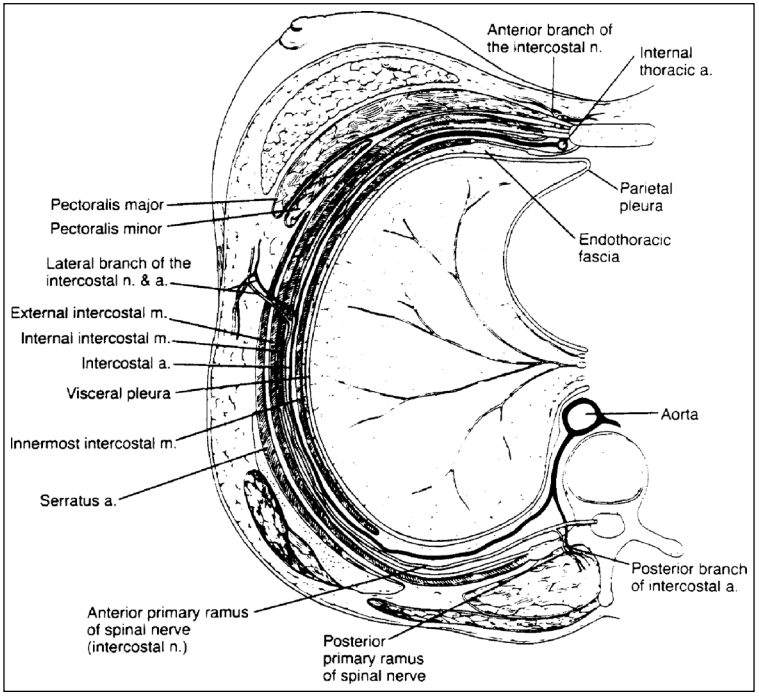

Fig. 1.3. Cross section of the breast and chest wall. The intercostal muscles occur in three layers. The intercostal vessels and nerves pass between the internal and innermost layers. Reprinted with permission from: Bland KI, Copeland III EM, eds. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 9-36. ©1998 W.B. Saunders Co.

Muscular Abnormalities

Cases of complete or partial absence of the pectoralis major have been reported on occasion. Most commonly, congenital absence of the sternocostal head of the pectoralis major has been noted as an anatomic variant. The pectoralis minor may or may not be absent when the pectoralis major is absent. The pectoralis minor inserts into the head of the humerus as well as into the coracoid process of the scapula in 15% of cases. Variations in the origin from the latissimus dorsi have also been reported. The latissimus dorsi can cross the base of the axilla superficially and pass deep to the pectoralis major muscle to join its insertion or to continue to the coracoid process. This is called a Langer's axillary arch, and can cause compression of the axillary artery or difficulty in orientation during axillary dissection. This has been noted in approximately 3-6% of cases.

Table 1.1. Muscles of the thoracic wall and axilla

Muscle	Origin	Insertion	Action	Nerve
Pectoralis major	1. Clavicle 2. Sternum 3. First 6 ribs 4. External abdominal oblique muscle	Humerus	Flexion, adduction, medial rotation of arm	Medial and lateral pectoral
Pectoralis minor	Ribs 3-5	Scapula	Draws scapula down and forward	Medial pectoral
Subclavius	First rib	Clavicle	Draws shoulder down and forward	Long thoracic
Serratus anterior	Ribs 1-8	Scapula	Rotation scapula, draws scapula forward	Long thoracic
Subscapularis	Subscapular fossa	1. Humerus 2. Shoulder joint capsule	Medial rotation of arm	Upper and lower subscapular
Teres major	Scapula	Humerus	Adduction, extension, medial rotation of arm	Lower subscapular
Latissimus dorsi	1. Lower 6-upper sacral vertebrae 2. Iliac crest 3. Lower 3-4 ribs	Humerus	Extension, adduction, medial rotation of arm, draws shoulder down and backward	Thoracodorsal

Axilla

1

Location/Anatomic Boundaries

The axilla is a pyramidal space between the arm and the thoracic wall. It contains the axillary vessels and their branches, the brachial plexus and its branches and lymph nodes embedded in fatty tissue. Table 1.2 lists the boundaries and composition of the axilla. In addition, the apex is directed medially and upward and ends in the cervicoaxillary canal leading into the posterior triangle of the neck. The base is formed by axillary fascia and skin.

Fascia

The axillary fascia is an investing layer that extends from the pectoralis major to the latissimus dorsi muscles and encloses the hollow of the armpit. It is continuous with the fascia covering the muscles that make the boundaries of the axilla. The clavipectoral fascia is a deep layer that extends from the clavicle to the axillary fascia in the floor of the axilla. It is separated into two sheets, in front and behind the subclavius muscle. At the lower portion of this muscle, it forms a single layer which extends laterally to the border of the pectoralis minor muscle. Here again it splits to surround the muscle. The upper portion of the clavipectoral fascia, the costocoracoid membrane, lies between the pectoralis minor and subclavius muscles. It is pierced by the cephalic vein, the lateral pectoral nerve and branches of the thoracoacromial trunk. The lower portion of the clavipectoral fascia, located below the pectoralis minor muscle, is often referred to as the suspensory ligament of the axilla, or the coracoaxillary fascia. Here it is continuous with the axillary fascia.

Halsted's ligament is a dense condensation of the clavipectoral fascia. It extends from the medial end of the clavicle to the first rib. The ligament covers the subclavian artery and vein as they cross the first rib. The axillary sheath is found at the apex of the axilla and forms a tubular sheath for vessels and nerves entering the axilla. It is adherent to the clavipectoral fascia under the subclavius and pectoralis minor muscles.

Axillary Artery

The axillary artery may be divided into three parts in the axilla based on its location in relation to the pectoralis minor. Table 1.3 lists the segments of the axillary artery.

Arterial Branches

1. The supreme thoracic artery supplies the thoracic wall over the first and second intercostal spaces.
2. The thoracoacromial trunk divides into the acromial, clavicular, deltoid and pectoral branches.

Table 1.2. Boundaries of the axilla

Anatomic Wall	Structures
Anterior	Pectoralis major and minor muscles, clavipectoral fascia
Posterior	Subscapularis, teres major, latissimus dorsi muscles
Medial	Serratus anterior muscle, 1st–4th ribs and intercostal muscles
Lateral	Humerus, coracobrachialis and biceps muscle

Table 1.3. Axillary artery and branches

Segment	Anatomic Location	Branch(es)
First	Medial to pectoralis minor	Supreme thoracic
Second	Posterior to pectoralis minor	1. Thoracoacromial 2. Lateral thoracic
Third	Lateral to pectoralis minor	1. Anterior circumflex humeral 2. Posterior circumflex humeral 3. Subscapular

3. The lateral thoracic artery passes along the lateral border of the pectoralis minor on the superficial surface of the serratus anterior muscle. It also supplies the lateral mammary branches. The pectoral branches of the thoracoacromial trunk as well as the lateral thoracic artery supply the pectoralis major and minor.
4. Both the anterior and posterior circumflex humeral arteries supply the upper arm and contribute to the collateral circulation around the shoulder.
5. The subscapular artery is the largest branch within the axilla. It is closely associated with the central and subscapular lymph node groups. It branches into the subscapular circumflex and the thoracodorsal artery. The thoracodorsal crosses and supplies the subscapularis. It also gives branches to the serratus anterior and the latissimus dorsi. Figure 1.4 shows the axillary artery and the brachial plexus in situ.

Axillary Vein

The axillary vein begins at the union of the basilic and brachial veins and terminates at the first rib as the subclavian vein. It lies medially and partly overlaps the axillary artery. It receives tributaries (usually paired veins) that correspond to the branches of the axillary artery and the cephalic vein. The cephalic vein lies in the groove between the deltoid and pectoral muscles and pierces the clavipectoral fascia to join the axillary vein.

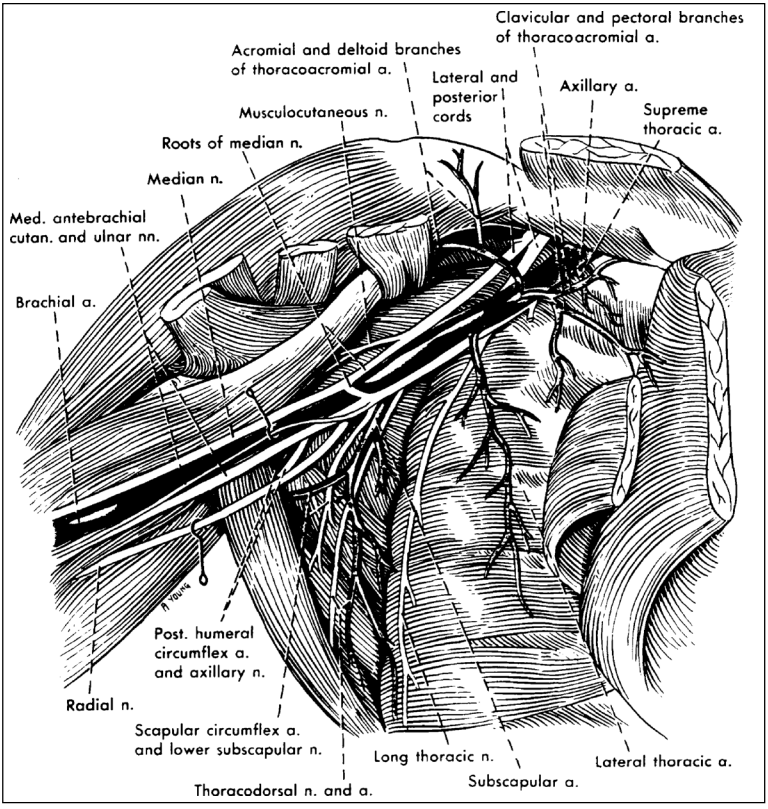

Fig. 1.4. Axillary artery and brachial plexus. The axillary artery, veins, its branches and the brachial plexus are shown in situ. The lymph nodes, veins and the pectoral nerves have been removed. Reprinted with permission from: Rosse C, Gaddum-Rosse. P. Hollinshead's Textbook of Anatomy. 5th ed. 1997; 215. ©1997 Lippincott-Raven

Brachial Plexus

The brachial plexus is formed by the union of the ventral rami of C5-C8 and of most of the ventral ramus of the first thoracic nerve. Often a small part of the fourth cervical nerve also joins the plexus. These nerve eventually form trunks, anterior and posterior divisions and cords. In the axilla, the anterior and posterior divisions form three cords. The three cords of the brachial plexus are named according to their position in relation to the axillary artery. Table 1.4 lists the cords of the brachial plexus, their divisions and terminal branches.

Table 1.4. Brachial plexus

Cord	Nerve Branch	Terminal Branch
Lateral	1. Lateral pectoral	1. Musculocutaneous 2. Lateral root of median
Medial	1. Medial pectoral 2. Median brachial cutaneous 3. Medial antebrachial cutaneous	1. Ulnar 2. Medial root of median
Posterior	1. Upper subscapular 2. Thoracodorsal 3. Lower subscapular	1. Axillary 2. Radial

1. The lateral pectoral nerve supplies the pectoralis major and gives a branch that communicates with the medial pectoral nerve. It pierces the clavipectoral fascia with the thoracoacromial artery and enters the deep surface of the clavicular head of the pectoralis major.
2. The medial pectoral nerve passes between the axillary artery and vein to enter the deep surface of the pectoralis minor and continues into the pectoralis major. It is the main nerve innervation to the pectoralis minor.
3. The thoracodorsal runs downward, crossing the lateral border of the scapula and the teres major to enter the costal surface of the latissimus dorsi.
4. The long thoracic nerve is located on the medial wall of the axilla on the serratus anterior. It arises from the C5-C7 roots and enters the axilla through the cervicoaxillary canal. Injury to this nerve results in paralysis to part or all of the serratus anterior. The functional deficit is inability to raise the arm above the level of the shoulder.
5. The intercostobrachial nerve is formed by the joining of a lateral cutaneous branch of the second intercostal nerve with the medial cutaneous nerve of the arm. This nerve supplies the skin of the floor of the axilla and of the upper medial aspect of the arm. A second intercostobrachial nerve may also form an anterior branch with the third lateral cutaneous nerve of the arm. Injury will cause numbness of the floor of the axilla and of the medial aspect of the arm.

Axillary Lymph Nodes

The primary route of lymphatic drainage of the breast is through the axillary lymph nodes. Axillary lymph nodes can be divided into levels based on location relative to the pectoralis minor muscle. Level 1 lymph nodes include external mammary, axillary vein and scapular lymph node groups and lie lateral to the lateral border of the pectoralis minor muscle. Level 2 nodes include central and some subclavicular lymph node groups and lie behind the pectoralis minor muscle. Level 3 nodes include the subclavicular nodal group and are located medial to the medial border of the pectoralis

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Table 1.5. Nodal groups

Nodal Group	Anatomic Location	Number of Nodes	Area Drained
Axillary vein (lateral group)	Medial or posterior to axillary vein	4 - 6	Upper extremity
External mammary (anterior or pectoral group)	Lower border of pectoralis minor close to lateral thoracic vessel	4 - 5	Major portion of breast
Scapular (posterior or subscapular group)	Posterior axilla, lateral border of scapula Close to subscapular vessels	6 - 7	Posterior neck, Posterior trunk, Posterior shoulder
Central group	Posterior to pectoralis minor	3 - 4	From prior 3 other groups, and breast
Subclavicular (apical group)	Posterior and superior to upper border of pectoralis minor	6 -12	Directly or indirectly from all others
Interpectoral or Rotter's group	Between pectoralis major and minor	1-4	Breast and other groups

minor. These distinctions aid in pathologic examination of surgical specimens. Nodal grouping can also be done based on anatomic location. Table 1.5 is a description of the major nodal groups. Figure 1.5 shows the lymph nodes and veins of the axilla.

Internal Mammary Lymph Nodes

The internal mammary nodes lie in the intercostal spaces in the parasternal region. The nodes lie close to internal mammary vessels in extrapleural fat and are distributed in the intercostal spaces. The number described along the internal mammary chain varies.

Selected Readings

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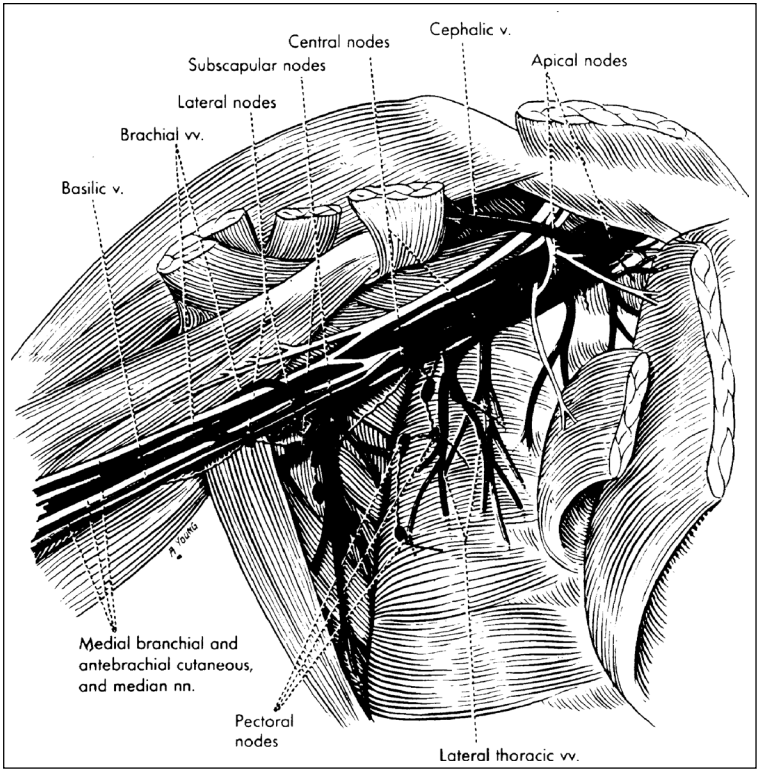

Fig. 1.5. Axillary vein and lymph nodes. The axillary vein, its branches and the lymph nodes are shown in situ. The pectoralis major and minor have been reflected back. Reprinted with permission from: Rosse C, Gaddum-Rosse P. Hollinshead's Textbook of Anatomy. 5th ed. 1997; 217. ©1997 Lippincott-Raven

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CHAPTER 2

Assessment and Investigation of Common Breast Symptoms

Leslie L. Montgomery

Breast-related symptoms are one of the most common reasons prompting women to seek medical attention. The extent of the diagnostic evaluation should be tailored to the age and complaint of the patient. The following chapter hopes to illustrate the more common breast complaints and to elucidate various diagnostic strategies and management options.

Routine Screening for Breast Cancer

In general, an asymptomatic woman over the age of 30 should undergo routine screening for breast cancer as part of her basic health-maintenance regimen. The screening triad includes a monthly self-breast examination, physical examination by a physician and a screening mammogram, if age appropriate.

Breast Self-Examination

Monthly (one week after menses or on the first of the month for postmenopausal women) breast self-examination should be taught and encouraged but not overemphasized. It is important to demonstrate to women the nodular feeling of normal breast tissue and its usual prominent location in the upper-outer quadrant. Women should be instructed that routine self-examination will provide a familiarity with their breasts and that any abnormal area should be evaluated for contralateral symmetry. If an asymmetry exists, premenopausal women should wait one menstrual cycle to see if the abnormality persists. Postmenopausal women should immediately seek medical attention. Woman who are particularly anxious regarding breast cancer or have extremely dense, lumpy breasts will find the breast self-examination to be a fearful experience. In this situation, pressure from healthcare professionals will not increase surveillance but will serve only to increase anxiety and guilt.

Physical Examination

Routine physical examination by internists, family practitioners, obstetricians, gynecologists and nurse practitioners should always include

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an examination of the breasts in women 30 years of age and older. An in-depth review of the breast physical examination follows later in this chapter.

Screening Mammography

The American Cancer Society and the National Cancer Institute now recommend mammography every year for asymptomatic women 40 years and older, regardless of risk group.[1] Women under 40 should not undergo routine screening mammography unless they have risk factors for early-onset breast cancer. It is important to note that the false-negative rate for mammograms is 10-15% and that a normal mammogram does not eliminate the need for further evaluation of a dominant mass in the breast.

Assessment of Common Breast Symptoms

When a woman seeks medical attention for a breast-related symptom, the standardized diagnostic approach with specific modifications can be employed. A thorough medical history with an emphasis on breast cancer risk factors, a complete breast physical examination, appropriate radiological evaluation and, if appropriate, pathologic assessment of cytology or tissue are the mainstays of diagnostic management of the breasts.

Woman with specific complaints should be followed closely until the complaint resolves or the benign nature of the symptom is confirmed.

Medical History

Risk Assessment

Although the majority of women with breast cancer have no identifiable risk factors, the clinician should begin the evaluation with a thorough risk assessment. The reader is referred to the chapter entitled "Risk Factors: Screening and Prevention" for a more in-depth discussion of breast cancer risk.

1. **Age:** As with most cancers, the incidence of breast cancer increases with age.
2. **Family history of breast cancer:** Information on any first-degree relatives with breast cancer, including their menopausal status and whether the disease affected one or both breasts, will impact on breast cancer risk.
3. **Prior breast biopsies:** While the number of breast biopsies does not increase a woman's risk of breast cancer, the resultant pathology of the biopsy might play a significant role in assessing her risk. Atypical ductal or lobular hyperplasia and lobular carcinoma in situ are considered benign markers of increased risk of developing invasive breast cancer in the future.
4. **Prior history of breast cancer:** The risk of developing contralateral breast cancer ranges from 0.5-0.75% per year and is cumulative.[2] A patient's local recurrence rate in the ipsilateral breast is approximately 10% after breast-conservation therapy (lumpectomy/axillary dissection and radiation).[3]

5. **Reproductive history:** The clinician should also obtain information on the patient's parity, her age at first delivery, age at menarche and menopause, use of contraceptive, fertility or hormone replacement drugs and, if appropriate, last menstrual period and the possibility of current pregnancy. In addition, new symptoms suggesting the onset of menopause should be evaluated.
6. **Extensive radiation exposure:** A history of mantle irradiation in childhood, especially for Hodgkin's disease, places women at a high risk of developing breast cancer 10-18 years later.[4]

Symptom Assessment

As with every evaluation of symptoms, the clinician should determine the duration and the severity of the breast symptoms. In particular, the fluctuation of symptoms in response to the menstrual cycle, the onset of menopause or the initiation of hormone replacement therapy should be noted. Any mass in the breast of a postmenopausal woman should be considered cancer until proven otherwise.

Physical Exam

The examination should proceed in both the upright and supine positions and should include both visual inspection and palpation. The clinician should examine the breasts for distortions, asymmetry, masses or nipple retraction. In addition, an assessment of the relative sizes and position of the breasts should be made.

In the upright position, the breasts should be inspected with the patient's arms resting at her sides, up over her head ("the hold-up position") and on her hips (akimbo) to flex the underlying pectoralis major muscle (Fig. 2.1). The lymph node status should then be assessed. The supraclavicular fossa is palpated bilaterally. When the axillary lymph nodes are palpated, the patient should be sitting in the upright position with the ipsilateral arm resting over the examiner's shoulder to relax the shoulder girdle musculature (Fig. 2.2).

The examiner next compresses the breast between his or her hands and bimanually palpates the breast. Care should be taken to palpate the axillary tail of Spence against the chest wall.

The patient should then be asked to lie in the supine position. With the ipsilateral arm of the patient over the patient's head, the examiner then palpates the breast in a circular motion beginning at the axillary tail and spiraling inward toward the nipple (Fig. 2.3). Finally, the nipple is inspected for skin changes or retraction and gently squeezed to reveal any discharge.

The approximate size, location, mobility and texture of any mass or asymmetry should be noted. The false-negative rate for the clinical physical examination is approximately 17% in experienced hands.[5]

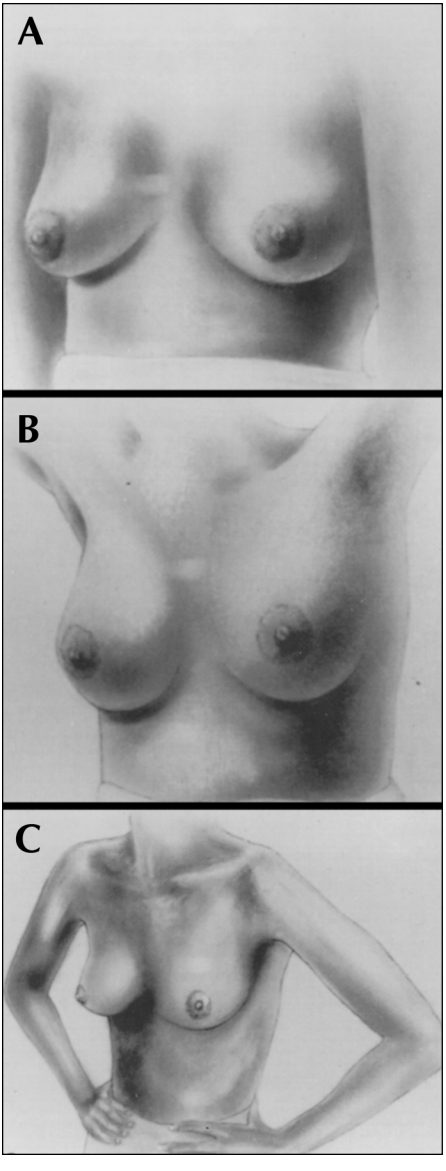

Fig. 2.1. Inspection of the breast: patient's arms at the sides (A), arms straight up in the air (B), and hands on hips (C). Reprinted with permission from: Bland KI, Copeland EM. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 617-618. ©1998 W.B. Saunders Co.

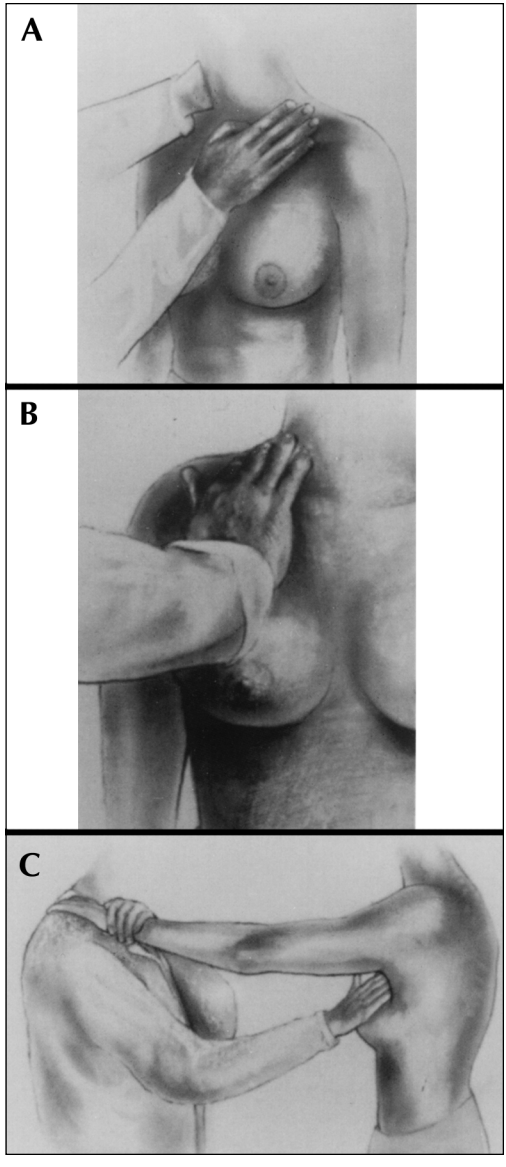

Fig. 2.2. Lymph node assessment: palpation of the infraclavicular area (A), supraclavicular fossa (B) and the axilla (C). Reprinted with permission from: Bland KI, Copeland EM. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 617-618. ©1998 W.B. Saunders Co.

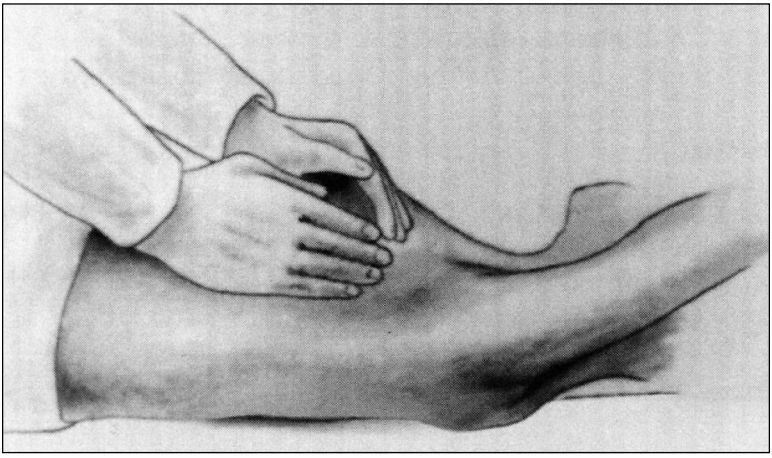

Fig. 2.3. Palpation of the breast in the supine position: ipsilateral arm of patient is raised over the head. Reprinted with permission from: Bland KI, Copeland EM. The Breast: Comprehensive Management of Benign and Malignant Diseases. 2nd ed. 1998; 617-618. ©1998 W.B. Saunders Co.

Diagnostic Evaluation

Radiology

Diagnostic Mammography

The workup of a patient with a dominant mass should include a bilateral mammogram. In addition to providing valuable information about the characteristics of the mass, the use of mammogram in this situation affords an opportunity to screen the normal surrounding breast and the contralateral breast for nonpalpable mammographic abnormalities (densities or calcifications). In general, a routine screening mammogram consists of a mediolateral oblique view (MLO) and a craniocaudal view (CC) of each breast. A diagnostic mammogram will also include compression or magnification views of the abnormal area in the breast.

It is important to note that the false-negative rate for mammograms is 10-15% and that a normal mammogram does not eliminate the need for further evaluation of a dominant mass in the breast.

Ultrasonography

Ultrasound is valuable in distinguishing between cystic and solid masses. With solid masses, benign lesions tend to have well-demarcated edges, while an ill-defined border is the hallmark of malignancy. In addition, ultrasound

can delineate between a simple and a complex cyst (a cyst with intramural nodules). Ultrasound can also complement mammography in young women with dense breasts (which limits the accuracy of the mammogram). Ultrasound, however, should not replace the mammogram as the primary screening modality, as ultrasound cannot detect microcalcifications and is generally less specific.

It is important to note that the accuracy and interpretation of ultrasound is highly user-dependent and subjective; thus adequate training is imperative before relying on this modality.

Other Imaging Techniques

Other imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), are not appropriate for the routine screening and evaluation of breast masses.

MRI is proving useful in the evaluation of scar tissue in the breast following breast conservation as a means of investigating local recurrence. MRI is currently being evaluated as a diagnostic tool in patients with occult breast cancer, multifocal disease or extensive lobular carcinomas, which may preclude breast conservation. In addition, MRI is useful in detecting silicone-implant ruptures, although ultrasound is often just as efficacious and is less expensive.

Pathologic Evaluation

Fine-Needle Aspiration

Fine-needle aspiration (FNA) can be extremely useful in providing a cytological analysis of a palpable breast mass. Many palpable thickenings and all dominant masses should be considered for FNA. The FNA can diagnose and treat simple cysts and provide cellular material for cytological analysis. A FNA requires a cytopathologist experienced in breast pathology. If a cytopathologist is not available, a core-cutting needle biopsy or surgical excision may be appropriate for solid masses. The FNA should be performed after radiological examination because the resultant hematoma could mask an underlying abnormality.

Usually, a 22 g or 25 g needle on a 10 cc syringe is used. Approximately 3 cc of air is aspirated into the syringe to facilitate expulsion of the contents onto the slide following the procedure. The needle is introduced into the lesion and suction is applied on the syringe. Multiple passes (10-15) through the lesion, with changes in direction, allow extensive sampling and create a "feel" for the mass (carcinomas are usually hard and gritty). Sampling should continue until material can be seen in the hub of the needle. The objective is to fill the needle, not the syringe. Care should be taken to release the suction before withdrawing the needle to prevent aspiration into the syringe. The

sample is then ejected onto a glass slide, gently smeared with another slide and placed in sterile jars containing 95% ethanol for transport to the cytology lab.

The false-negative rate can range from 3-35% depending on the expertise of the aspirator and the cytopathologist, the size of the lesion, the location within the breast and the cellular composition of the lesion.[5,6] Negative findings of a FNA in the presence of a suspicious mass mean nothing and should not preclude further diagnostic evaluation and follow-up. A diagnosis of atypical cells following an FNA warrants a surgical biopsy. Any mass remaining after aspiration of a cyst should be excised.

The false-positive rate of an FNA is less than 1%, but in the United States, most surgeons will not perform definitive surgery (i.e., a mastectomy or axillary dissection) without a prior surgical biopsy, core needle biopsy or frozen-section diagnosis at the time of surgery. A FNA that is positive for adenocarcinoma could, however, provide a preliminary diagnosis and guide subsequent management recommendations.

Core Needle Biopsy

In the case where a woman presents with a large palpable breast mass (over 3-4 cm) and an immediate definitive diagnosis is deemed necessary to expedite surgical or chemotherapeutic intervention, a core needle biopsy should be employed.

This technique involves the use of a large-bore cutting needle to obtain a core of tissue that will provide a rapid diagnosis (as well as estrogen- and progesterone-receptor status) with minimal invasion. The skin overlying the mass is cleansed with betadine, and local anesthesia is achieved with 1% lidocaine with 1:100,000 units epinephrine. A small incision in the skin is made to accommodate the needle. A number of needles are available and are usually combined with mechanical devices to facilitate biopsy. The mass is stabilized with one hand and the needle is introduced into the mass with the other. The device is fired and a biopsy is obtained. The needle can then be retracted and the tissue sample retrieved and placed in formalin. Specimens that float in formalin ("floaters") usually consist of nondiagnostic fat. Often, multiple biopsies are required to obtain specimens that sink in formalin ("sinkers") and represent the tumor.

Stereotactic Biopsy

Stereotactic biopsy (a core biopsy under mammographic guidance) should be used to obtain breast tissue in two situations. In the first situation, a stereotactic core biopsy rather than a surgical biopsy could pathologically assess a changing density on mammogram associated with a low suspicion profile (i.e., a probable fibroadenoma or intramammary lymph node). The second situation involves suspicious or indeterminate microcalcifications,

where stereotactic biopsy may rule out cancer or provide a definitive diagnosis of cancer on which further management options may be based. The stereotactic core biopsy has a small but definite false-negative rate, and it is imperative that the mammographic and pathologic findings are concordant. If the findings are not concordant, an open surgical biopsy is recommended. A pathologic diagnosis of atypia or in situ carcinoma (ductal or lobular) following a stereotactic biopsy requires an open surgical biopsy.

Open Surgical Biopsy

The gold standard for complete pathologic assessment of a breast lesion is an open surgical excisional biopsy. The procedure may be performed on palpable masses or on nonpalpable lesions following mammographic or ultrasound-guided localization. The amount of tissue removed depends on the size of the mass and the level of suspicion given the physical exam, the mammogram and the FNA findings. All nonpalpable lesions requiring needle localization preoperatively should have an intraoperative specimen radiograph to document removal of the lesion in question. In addition, a confirmatory postexcisional mammogram should be performed between 6 weeks and 3 months following the procedure.

Evaluation and Management of Common Breast Symptoms

The Triple Test

The triple test should be employed for all breast masses and includes a physician's physical exam, a bilateral mammogram and a fine-needle aspiration of the area in question.[6] A strict principle of the triple test is that if discordance exists between any of the three diagnostic tests, an open surgical biopsy should be done. An extensive review has documented a 99% predictive value for benign disease when all three diagnostic tests are benign.[5] Under these circumstances, a woman can be given the option of close surveillance (an initial 3 month prudence check, then every 6 months if the physical exam remains stable) or surgical excision. A woman's age, risk factors and the reliability of physical exam will also factor into the clinician's recommendation. Close surveillance following a negative triple test has an approximately 1-2% risk of missing a cancer.[5,6] Both the physician and the patient should be aware of the possibility of delayed diagnosis.

Palpable Masses

Solid

Despite the age of the patient, a clinically suspicious lesion should be evaluated completely. A bilateral mammogram is warranted to screen the

rest of both breasts for nonpalpable lesions. All palpable, discrete, solitary or suspicious noncystic masses should be excised unless they undergo percutaneous biopsy and the histopathology is concordant with the physical findings (i.e., fat necrosis or fibroadenoma) (Fig. 2.4).

Any mass that yields equivocal or atypical cells on FNA should also undergo surgical biopsy.

Palpable masses in young women (<30 years) are most likely to be fibroadenomas. A FNA or ultrasound can be diagnostic. If a mass thought to be a fibroadenoma grows rapidly or achieves a size greater than 2 cm, surgical excision is warranted to rule out a phyllodes tumor, which can mimic the radiographic and cytologic features of a fibroadenoma.[7]

Cysts

Cysts usually present in premenopausal and perimenopausal women over the age of 40. Cysts usually regress after menopause. Following a screening mammogram, either an ultrasound or FNA can diagnose a cyst, although an initial FNA is usually more cost-effective.

If the mass does not disappear completely following aspiration, or if the fluid is bloody or guaiac positive, the fluid should be sent for cytological analysis and a biopsy is recommended. If a cyst is aspirated, the patient should be reexamined in 6-8 weeks for recurrence. If the cyst is known to be a simple cyst by ultrasound, painful cysts may be reaspirated and followed closely. If a simple cyst recurs a third time, excision is warranted.

Ultrasound can aid in distinguishing between a simple and a complex cyst (a cyst with intramural nodules). A complex cyst should arouse suspicions of an intracystic carcinoma or carcinoma adjacent to a cyst. Thus, any complex cyst requires ultrasound-guided aspiration followed by cytological examination of the contents. Recurrent complex cysts should be excised (Fig. 2.5).

Finally, cyst formation in postmenopausal women not on hormone replacement therapy is rare and may herald an intracystic carcinoma. Thus, cysts in postmenopausal women are excised.

Vague Nodularity

Often, the premenopausal patient may note an asymmetric breast thickening during the premenstrual phase. If this is the case, examining the patient 1-2 weeks after menses may illustrate resolution of the thickened area.

A vague area of thickening may be watched closely if a negative triple test exists. Specifically, the area must be deemed:

1. clinically negative by an experienced surgeon,
2. negative by FNA (an adequate cellular specimen) and
3. negative by mammogram. An ultrasound may be used to complement the mammogram in particularly dense breasts. This area must be watched closely (biannually or quarterly) by an experienced surgeon until it resolves or is surgically excised.

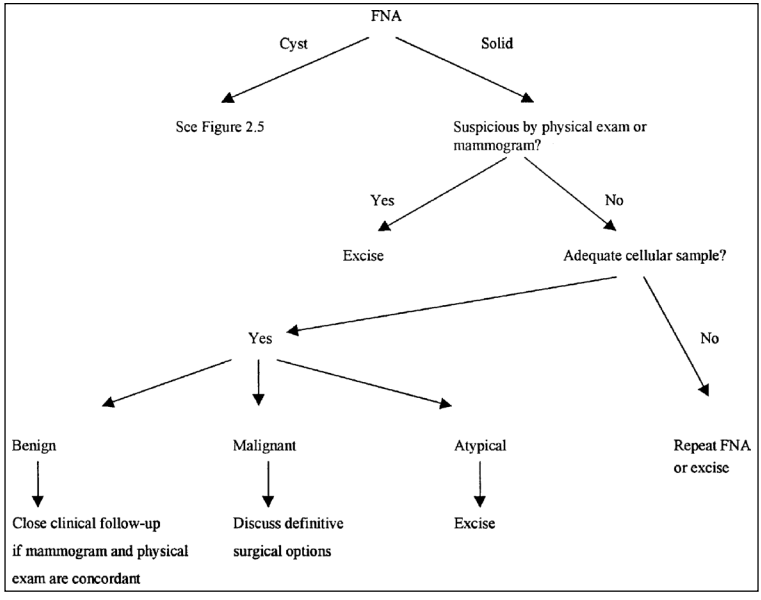

Fig. 2.4. FNA, fine-needle aspiration. Management of breast masses by the "triple test".

Mammographic Abnormality

The Breast Imaging Reporting and Data System (BI-RADS™) uses a terminology and lexicon specified by the American College of Radiology (ACR) to objectively quantify the level of suspicion of the radiologist reading a mammogram (Table 2.1).[8] The patient needs a biopsy if her mammography results are reported as a BI-RADS™ Category 4 or 5. BI-RADS™ Category 0 indicates that further workup is required (compression or magnification views, correlation with ultrasound or obtaining original films if poor quality copies are submitted). BI-RADS™ Category 3 assigns a low level of suspicion but requires an interval mammogram to assess stability of the lesion (usually at a 3 or 6 month interval).

The type of biopsy appropriate for a nonpalpable lesion is based on the level of suspicion of the surgeon, the technical ability of the radiologist and the wishes of the patient. The options include a stereotactic or ultrasound-guided core biopsy versus an open surgical biopsy with preoperative needle localization.

Breast Pain (Mastalgia)

The most common causes of breast pain are cysts or a region of fibrocystic breast tissue. Despite the classic teaching that breast cancer does not cause

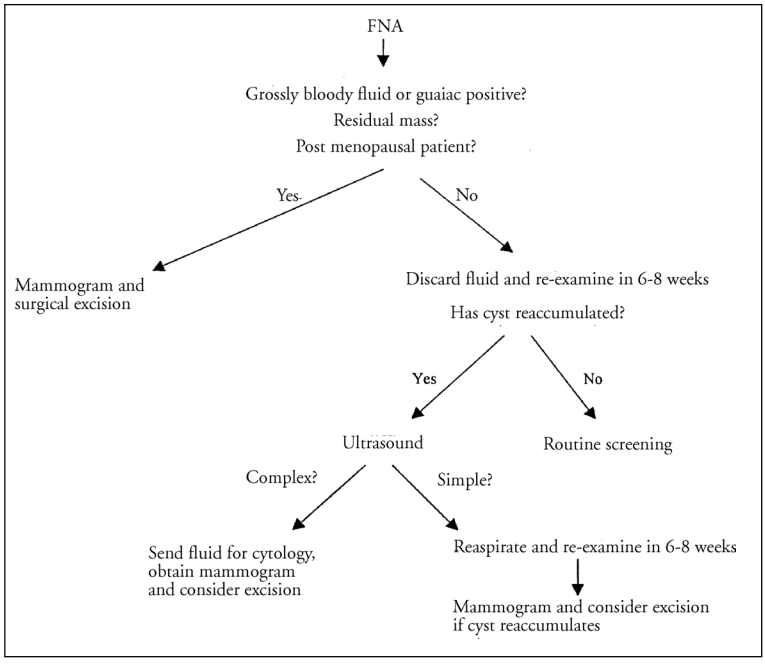

Fig. 2.5. Management of breast cysts

pain, pain associated with a mass does not eliminate the possibility of cancer, and appropriate diagnostic steps should be taken.

After eliciting a history of any cyclical component to the breast pain, a thorough breast exam and screening mammogram should be performed. If the results of the physical examination and mammography are not suggestive of cancer or infection, the most likely explanation of breast pain is fibrocystic changes. Often, an explanation of the hormonal influences on the breast in relation to the menstrual cycle, perimenopausal changes or hormone replacement therapy can greatly reassure the patient.

Symptomatic treatment may be helpful, and the patient should be given a trial of NSAIDS and instructed to wear a good supportive bra. Reducing methylxanthine intake (coffee, tea, chocolate and soda) may be beneficial. Some women find evening-primrose oil (3 gm/day) alleviates symptoms, a controlled trial reported significant improvement in pain and nodularity with evening-primrose oil over placebo after 4 months.[9,10] Given the low incidence of side effects, its over-the-counter availability and relative low cost, evening-primrose oil should be considered as the first-line therapy for women with persistent mastalgia. In the cases of intractable breast pain, tamoxifen (Nolvadex), danocrine (Danazol) and bromocriptine (Parlodel)

Table 2.1. Breast imaging reporting and data system (BI-RADS™) final assessment categories[1]

a. Assessment is incomplete

Category 0

Need additional imaging evaluation:

Finding for which additional imaging evaluation is needed. This is almost always used in a screening situation and should rarely be used after a full imaging workup. A recommendation for additional imaging evaluation includes the use of spot compression, magnification, special mammographic views, ultrasound, etc.

The radiologist should use judgement in to how vigorously to pursue previous studies.

b. Assessment is complete—final categories

Category 1

Negative:

There is nothing to comment on. The breasts are symmetrical and no masses, architectural disturbances or suspicious calcifications are present.

Category 2

Benign Finding:

This is also a negative mammogram, but the interpreter may wish to describe a finding. Involuting, calcified fibroadenomas, multiple secretory calcifications, fat-containing lesions such as oil cysts, lipomas, galactoceles, and mixed-density hamartomas all have characteristic appearances and may be labeled with confidence. The interpreter might wish to describe intramammary lymph nodes, implants, etc., while still concluding that there is no mammographic evidence of malignancy.

Category 3

Probably Benign Finding—Short Interval Follow-up Suggested:

A finding placed in this category should have a very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. Data are becoming available that shed light on the efficacy of short interval follow-up. At the present time, most approaches are intuitive. These will likely undergo future modification as more data accrue as to the validity of an approach, the interval required and the type of findings that should be followed.

Category 4

Suspicious Abnormality—Biopsy Should Be Considered:

These are lesions that do not have the characteristic morphologies of breast cancer but have a definite probability of being malignant. The radiologist has sufficient concern to urge a biopsy. If possible, the relevant probabilities should be cited so that the patient and her physician can make the decision on the ultimate course of action.

Category 5

Highly Suggestive of Malignancy—Appropriate Action Should Be Taken:

These lesions have a high probability of being cancer.

have proven to effectively reduce breast pain but these medications can be associated with significant side effects and are expensive. Luteinizing hormone-releasing hormone (LHRH) analogues are effective in most cases of severe mastopathy but should be reserved for only the most refractory of cases and not used for longer than 3 months.[10]

Vitamin E, progesterones and diuretics have not shown any benefit for patients with mastalgia in controlled trials.

Breast Infection/Abscess

In general, an infection in the nonlactating breast is rare. Breasts that have undergone adjuvant radiation therapy following breast conservation for carcinoma are at risk for spontaneous cellulitis, and care must be taken to distinguish cellulitis from an inflammatory recurrence.

Infection in the lactating/breast-feeding breast is common and results as bacteria (most commonly *Staphylococcus aureus* or a strep species) ascends from the infant's mouth through a fissure in the nipple.

With infection, the patient becomes febrile, and the whole breast becomes hard, reddened and painful. Breast milk should be obtained for culture and antibiotic therapy should be started immediately. Breast-feeding on that breast should cease in order to prevent reinfection but pumping could continue if not too painful for the patient. An obvious infection with an abscess should be treated with incision and drainage or repeated needle aspiration and antibiotics. If there is a residual mass palpable after complete resolution of the abscess (after 6-8 weeks), a mammogram and a surgical biopsy is warranted to rule out a malignancy.

Nipple Discharge

The most common causes of bloody nipple discharge are intraductal papilloma, duct ectasia and carcinoma. Suspicious nipple discharges (pathologic) that require prompt surgical intervention include spontaneous, unilateral or postmenopausal discharges. Any discharge confined to one duct whether it is clear, serous or bloody, should be considered suspicious. The lack of a definable mass on physical exam or mammogram should not delay a surgical biopsy.

Cytologic examination of the nipple discharge is rarely useful and is unnecessary. Galactography (injection of contrast medium into the spontaneously discharging duct to delineate intraluminal abnormalities) may be useful in identifying the precise ductal involvement but has a high false-negative rate. Medical workup of galactorrhea (to rule out a pituitary microadenoma secreting prolactin) is only appropriate when the discharge is milky, persistent and bilateral.

Milky, green or black discharge (if guaiac negative) that is expressed from several ducts can be normal (physiologic) and surgical intervention is not necessary.

Skin or Nipple Changes

An inflammatory appearance in any women older than 40 years should be considered inflammatory carcinoma until proven otherwise. The classic appearance of inflammatory breast cancer includes a red, swollen breast with skin edema ("peau d'orange") that is generally not tender. If the inflammation persists after a short course of antibiotics to rule out cellulitis, a breast and skin biopsy is warranted. Inflammatory breast cancer is often a clinical diagnosis, and further evaluation and treatment should not be dissuaded by a benign skin biopsy.

Any asymmetric skin changes or breakdown on the nipple-areolar complex should arouse suspicion. Paget's disease of the nipple (the presence of intraductal or invasive involvement of the nipple) should be excluded by a nipple biopsy of the abnormal area following a screening mammogram.

Other Problems

Difficult Breast Examination

Any patient with a difficult or unreliable breast examination should be referred to a breast surgeon for evaluation. The breast examination may be difficult due to large or dense breasts, multiple prior biopsies, breast implants, reduction mammoplasty or multiple cysts.

Lactating Breast

A palpable mass in a pregnant or lactating woman should be immediately referred to a surgeon. Approximately 1 in 2,000 pregnant or lactating women has breast cancer. The differential diagnosis (which can be clarified by ultrasound and/or FNA) includes a cyst, a galactocele, a drainable abscess or a solid mass requiring biopsy.

High-Risk Patients

Patients with a history of breast cancer (intraductal or invasive), a strong family history of breast cancer or a diagnosis of atypical hyperplasia or lobular carcinoma in situ on breast biopsy should be referred to a specialized high-risk screening program. These programs often utilize specialized screening regimens and can provide these patients with clinical trial opportunities and emotional support.

Persistently Worried Patient with Negative Workup

If the patient is concerned or anxious, she should be advised to return quarterly for reexamination until she and the examiner are convinced of the benign nature of her symptoms. If she remains persistently worried, she should be referred to a breast surgeon for a second opinion.

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CHAPTER 3

Benign Breast Disease

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The vast majority of women presenting with breast symptoms will have an underlying benign etiology. Only 1 in 10 of all women referred to a specialist breast clinic will have breast cancer.[1,2] After establishing a firm diagnosis of benign disease, reassurance and an appropriate plan of management will need to be instituted. Benign disorders of the breast represent a large proportion of the workload at a specialist breast clinic; therefore, it is important to carefully distinguish these disorders from premalignant and malignant disease of the breast. Understandably, they are a source of considerable anxiety for the patient and a potential source of medicolegal problems. A clear understanding of benign disease of the breast is therefore essential. To ensure uniformity and consistency amongst all members of the specialist breast team, appropriate management protocols are advisable in clinical practice. Our unit has developed management protocols based on available scientific evidence and has adopted a multidisciplinary approach in the management of patients involving surgeons, radiologists and pathologists.

The majority of patients with benign breast disease are premenopausal. With the advent of hormone replacement therapy (HRT), an increasing number of postmenopausal women now present with a similar spectrum of disorders. The simplest approach to benign breast disease is to regard this group of disorders as an aberration of normal development and involution (ANDI).[3] This outlook facilitates an easier understanding of these disorders and consequently makes it easier to reassure patients and treat them appropriately.

General Approach to Patients Presenting with Benign Breast Disease

A detailed history is obtained from each patient. This history should include risk factors for the development of breast cancer. Following this, a thorough clinical examination is performed. It is policy in our unit to perform mammography in all women over the age of 35 years. Women with a discrete lump will undergo ultrasound examination of the questionable area and then either fine-needle aspirate biopsy (FNAB) or core biopsy. Symptomatic discrete cystic lesions will be aspirated. Patients less than 35 years of

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age will undergo ultrasound examination of discrete lesions and a similar management protocol as outlined above. In some rare cases, magnetic resonance imaging (MRI) is performed in addition to mammography and ultrasound in order to establish the diagnosis. Once a firm diagnosis is established and a management plan instituted, the patient is reassured and discharged. It is useful to provide both general practitioner and patient with detailed information leaflets that outline the unit's management protocols. In general, it is our policy not to excise benign breast lumps once a clear diagnosis is established. Instead, our unit practices the philosophy that these lesions have little, if any, premalignant potential and symptoms will most likely improve over the passage of time.

Breast Pain

Due to the increasing awareness of breast cancer, most women now seek advice from their general practitioner about breast pain symptoms. Female patients may present with a variety of symptoms that can range from relatively minor symptoms to severe symptoms significantly affecting quality of life. Heaviness and associated discomfort during the week prior to each menstrual cycle may be associated with tender, lumpy breast areas. Classically, in cyclical mastalgia, these symptoms will regress following the commencement of a period. Due to the fact that mastalgia is a common condition and occurs predominately within the reproductive years, it is best considered an alteration of the normal cyclical pattern. Therefore, a combination of reassurance and medical therapy will most often achieve a satisfactory clinical response in the majority of patients.

Symptoms

A detailed history listing potential risk factors for the development of breast pain (i.e., the use of the oral contraceptive pill (OCP) or HRT, pregnancies, menstrual history, diet and medication) is useful. It is important to define whether mastalgia is cyclical or noncyclical and also from exactly where the pain originates (i.e., from breast tissue or from the underlying chest wall.) Examples of symptoms originating from the underlying chest wall are Tietze's syndrome (costochondritis), herpes zoster and radiculopathy secondary to lower cervical spondylosis.

Signs

Clinical examination may be entirely normal apart from tenderness confined to one area of the breast. Generalized bilateral tenderness may be observed. Associated focal or generalized nodularity may be present. Examination of both axillae is usually normal.

Investigations

In women over 35 years of age, mammography is performed and this may be normal. Women with discrete areas of focal nodularity will undergo ultrasound and if necessary FNAB/core biopsy of the area to confirm its benign nature. No specific histological appearance is associated with this symptom.

Management

Although there is no definitive scientific evidence for it, several features suggest mastalgia is secondary to an underlying hormonal abnormality. The lack of evidence may be due to the difficulty of collecting data in light of daily and circadian variations in plasma hormonal levels. Current recommendations for management of women with mastalgia are based on theories related to possible etiology. The sheet anchor of management of these patients is reassurance of the benign nature of their condition.

Reduction of Caffeine

Recommendations to reduce caffeine intake are based on the hypothesis that methylxanthines cause proliferation of cells in the breast by increasing cyclic adenosine monophosphate (cAMP).[4] Tissue obtained from patients with breast disease has demonstrated increased sensitivity to biochemical stimulation by methylxanthines. Although there is no hard evidence that abstention of methylxanthines is beneficial to women with mastalgia, clinicians continue to recommend this to patients on the basis that anecdotal evidence does exist for improvement of mastalgia on a caffeine-free diet.

Reduced Intake of Dietary Fat

The hypothesis that fat increases endogenous hormonal levels thereby causing breast pain by a direct stimulatory effect, led to the suggestion that fat restriction might relieve symptoms of mastalgia. There is some evidence to suggest that a reduced intake of dietary fat may help cyclical breast tenderness and swelling.[5]

Gamma-Linolenic Acid (GLA)

Studies demonstrate low plasma levels of GLA (an essential fatty acid) in women with mastalgia. It is believed that a higher ratio of saturated to unsaturated fatty acids may alter the sensitivity of breast hormone receptors (both estrogen and progesterone).[6] Based on this hypothesis, administration of GLA in a dose of 320 mg daily for a minimum period of 3 months is recommended. Response rates of up to 58% in cyclical mastalgia and 38% in noncyclical mastalgia were observed in a study conducted at the Cardiff mastalgic clinic.[7] In our experience, GLA is effective and has few side effects and patient compliance is good. It is our next line of management in addition to reassurance and advice regarding reduction in intake of caffeine and dietary fat.

Vitamin B6—Pyridoxine

Vitamin B6 is still prescribed in the United Kingdom, although there is no evidence that it causes significant improvement in women with mastalgia.

Diuretics

There is no evidence that diuretics benefit in the management of mastalgia. It is therefore inappropriate to consider this as a form of treatment for this disorder.

Hormonal Treatment

Danazol

Danazol is a synthetic steroid that competitively inhibits estrogen and progesterone receptors in the breast as well as production of ovarian steroids.[8] Randomized, controlled trials have demonstrated that danazol is beneficial in cyclical mastalgia in relatively low doses of 200 mg causing a reduction in pain and nodularity scores.[9,10] Our current recommendation is to commence therapy with danazol at a dose of 100 mg twice daily for two cycles, maintaining a record of breast pain using a breast pain chart. If the patient fails to respond to this therapy, either the dose may be increased or an alternative drug regimen adopted. Side effects of danazol include weight gain, hirsutism, irregular periods and headaches.

Tamoxifen

Tamoxifen is an estrogen-receptor inhibitor and is widely used in breast cancer. It is therefore not surprising that it has proven itself beneficial in the treatment of mastalgia.[11,12] This drug does not have a product license in the United Kingdom for treatment of mastalgia. In severe cases of refractory mastalgia unresponsive to gamma linolenic acid and danazol, however, it is reasonable to consider this drug, having fully explained to the patient the side effects and in particular the risks it poses to the endometrium. It is sensible to restrict usage of tamoxifen in this context to a maximum period of 6 months.

Luteinizing Hormone-Releasing Hormone Agonist (LHRH Agonist)

LHRH analogues are effective in severe refractory cases of mastalgia but should not be used routinely or for prolonged periods. They act by inducing complete ovarian inhibition, resulting in low blood levels of estradiol or progesterone and prolactin.[13]

Nonhormonal Treatment

Bromocriptine

Bromocriptine acts as a dopaminergic agonist on the hypothalamic-pituitary axis. It has demonstrated itself as effective in cyclical mastalgia but is not as effective as danazol.[9] Severe side effects have been noted with bromocriptine,[14] hence, we do not recommend its use in treating mastalgia.

In summary, it is our experience that the majority of women can be dealt with by reassurance alone. Most of the others can be controlled with a short course of GLA, and it is only in the minority of patients that treatment regimens using drugs like danazol or LHRH agonists are necessary. It is our view that surgery has no place in the management of breast pain, and although anecdotal reports of women undergoing subcutaneous mastectomy for intractable mastalgia have emerged in the past, it is not a mode of practice that we endorse.

Nodularity

Various pathologic terms have been used in the past to describe nodularity. Nodularity in the breast may be focal or generalized. This is such a common finding that it should be regarded as normal or a variation of normal. Terminology such as fibroadenosis and fibrocystic disease of the breast to indicate focal or generalized nodularity has largely been abandoned.

Symptoms

The patient may complain of a lumpy area that may be either confined to a specific quadrant in one breast or alternatively, generalized. There may be associated breast pain, which is usually cyclical in premenopausal women. A history of usage of the OCP or HRT should be obtained.

Signs

Clinical examination may demonstrate focal nodularity that is often present in the upper-outer quadrants of both breasts but equally can be scattered throughout both breasts in the form of generalized nodularity. Localized tenderness may be associated with these areas of nodularity. Examination of the patient at a different phase of the menstrual cycle may demonstrate a fluctuation in pattern.

Investigations

Mammography is performed in patients over 35 years of age, and in addition to this, ultrasound is useful in patients with focal nodularity. At the same time, FNAB or core biopsy may be performed if necessary. In patients less than 35 years of age with focal nodularity, ultrasound examination with or without FNAB or core biopsy may be performed.

Management

Once malignancy has been excluded, patients can be reassured as to the benign nature of their symptoms and informed that they are at no increased risk of developing breast cancer. Treatment of associated breast pain is outlined above. No further follow-up is required.

Fibroadenoma

Fibroadenomas have previously been regarded as benign neoplasms, but should now be considered as an aberration of normal development. The peak incidence occurs in the third decade. An increasing number of newly developed fibroademonas are being detected in the fifth and sixth decade, probably related to increased use of HRT and mammographic screening. Fibroadenomas develop from a lobule in the breast rather than from a single cell, and demonstrate high levels of estrogen and sulfates as well as of enzymes responsible for the formation of estrogen (sulfatase and aromatase), suggesting hormone dependency.[15] Clonal analysis has demonstrated that fibroadenomas are polyclonal lesions.[16] The natural history of fibroadenomas is now better understood, with 72% resolving over a period of 7 years.[17] There is no increased risk of breast cancer in patients with fibroadenomas, apart from a small pathological subgroup (i.e., those with complex fibroadenomas—cysts greater than 3 mm in diameter, sclerosing adenosis, epithelial calcifications or papillary change; relative risk [RR] of 3.1 for breast cancer).[18] Fibroadenomas can undergo vascular infarction during pregnancy and lactation and in their later stages can undergo calcification.

Multiple Fibroadenomas

In a small percentage of patients, multiple fibroadenomas are detected either by clinical examination or screening mammography. The sensible approach in these patients is to investigate each lesion on its merit and perform core biopsies to confirm their benign nature. Excision biopsy is advised for any lesion where the diagnosis is uncertain.

Juvenile and Giant Fibroadenomas

Classically, juvenile fibroadenomas are rare and occur in adolescence. They are characterized by a rapidly growing lesion that usually attains a size greater than 5 cm in diameter causing distortion and asymmetry of the breast. These lesions require surgical excision for cosmetic reasons. Giant fibroadenomas attain a similar size but are usually found in the breasts of pregnant or lactating women and increase under the hormonal environment of these physiological conditions. They frequently diminish in size after the hormonal influences recede. If they remain large, they may be excised for cosmetic reasons. Neither of these lesions have any malignant potential.

Symptoms

Patients present with a discrete lump that may in rare cases be associated with tenderness. Occasionally patients may present with multiple discrete lumps at initial presentation.

Signs

Clinical examination usually demonstrates a well-circumscribed, mobile, firm, discrete breast lump.

Investigations

All clinical fibroadenomas should be investigated by mammography with or without ultrasound and FNAB or core biopsy.

Radiology

Mammography

Fibroadenomas usually appear as oval or round soft-tissue densities with smooth or lobulated margins. They usually have very well-defined borders and may exhibit the "halo" sign, in which a thin dark border is seen around the edge of the mass. Densities with these features are highly likely to be benign in origin. It is only when the typical coarse "popcorn-like" calcification is seen in association with the soft-tissue mass that the appearance is pathognomonic of a fibroadenoma (Fig. 3.1). When multiple fibroadenomas are present, there is usually a mixture of soft-tissue masses with either absent or varying degrees of calcification.[19]

Ultrasound

As the majority of fibroadenomas present as breast lumps in younger women ultrasound is frequently our first-line of investigation. The typical appearance of a fibroadenoma is that of an oval-shaped, well-defined nodule with a uniform internal echo pattern (Fig. 3.2). Deep to the lesion there is no alteration in the echo texture nor is there enhancement ("bright up"). The well-defined borders of a fibroadenoma are frequently illustrated by thin acoustic shadows seen at the edge of the lesion. Variation on such appearances is fairly common. The nodule may appear lobulated or have varying internal echo textures and in rare cases fibroadenoma may cast an acoustic shadow.[20]

Even when presenting with the typical clinical and ultrasound features of a fibroadenoma, the diagnosis should be confirmed by needle biopsy.

Pathology

Macroscopic Appearance

Fibroadenomas are characteristically well-circumscribed round or ovoid masses that are clearly demarcated from the surrounding breast tissue. The

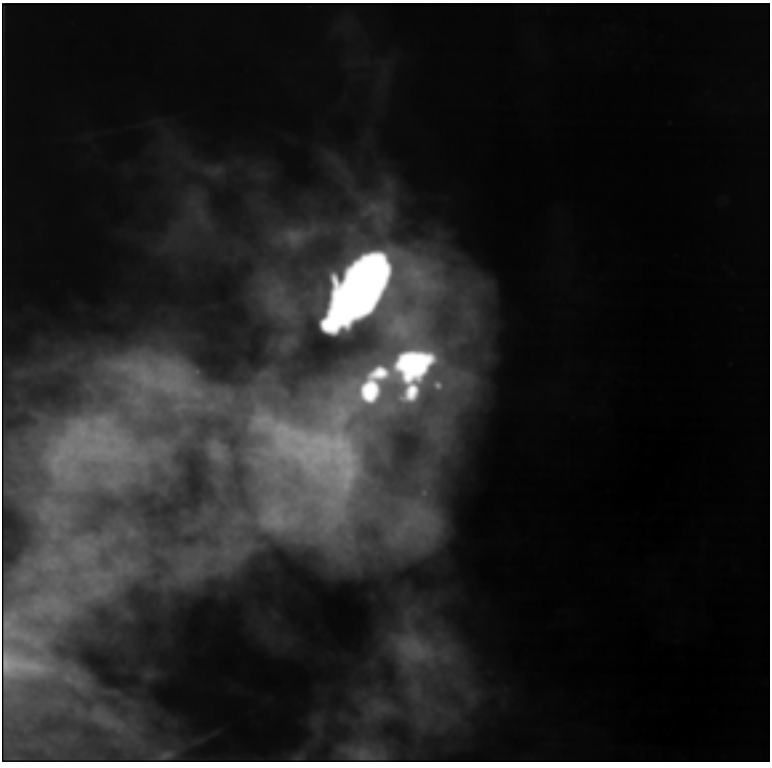

Fig. 3.1. Mammogram showing a well-defined, oval, soft-tissue density with coarse "popcorn-like" calcification characteristic of a fibroadenoma.

texture of the cut surface varies from soft, myxoid through firm, rubbery to very firm depending on the age of the lesion. They have a white or yellow color and a lobulated appearance. Ductal clefts are sometimes apparent.

Microscopic Appearance

As the name implies, there are both stromal and glandular components in fibroadenomas. The stromal component is usually uniformly loose, cellular and intimately related with the epithelium-lined ductal structures that comprise the glandular element. In older lesions, the stroma becomes less cellular and may become densely hyalinised. Calcification of the hyalinised stroma may also occur. The ductal structures are lined by an epithelium, which usually shows mild usual-type hyperplasia (Figs. 3.3, 3.4). Fibroadenomas have traditionally been divided into pericanalicular and intracanalicular types based on the degree of stromal herniation into the ductal structures. This distinction, however, has no clinical relevance, and

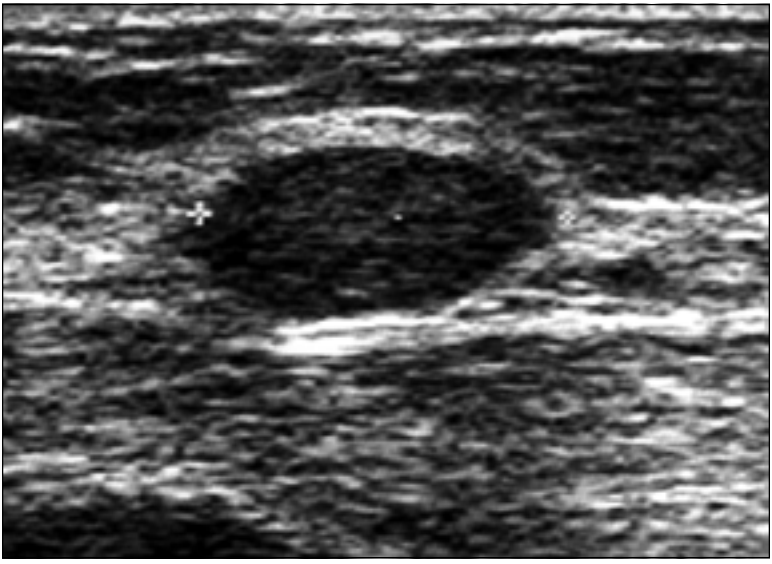

Fig. 3.2. Ultrasound of a typical fibroadenoma appearing as an oval, well-defined nodule with uniform internal echo patterns.

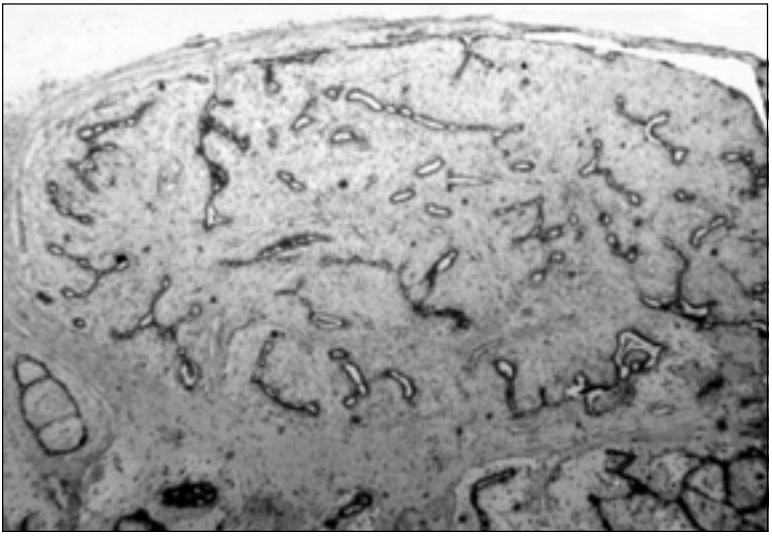

Fig. 3.3. Low-power view of a fibroadenoma showing a well-circumscribed edge at the top of the figure. The stroma stains pale pink, and the purple structures are the ductal clefts.

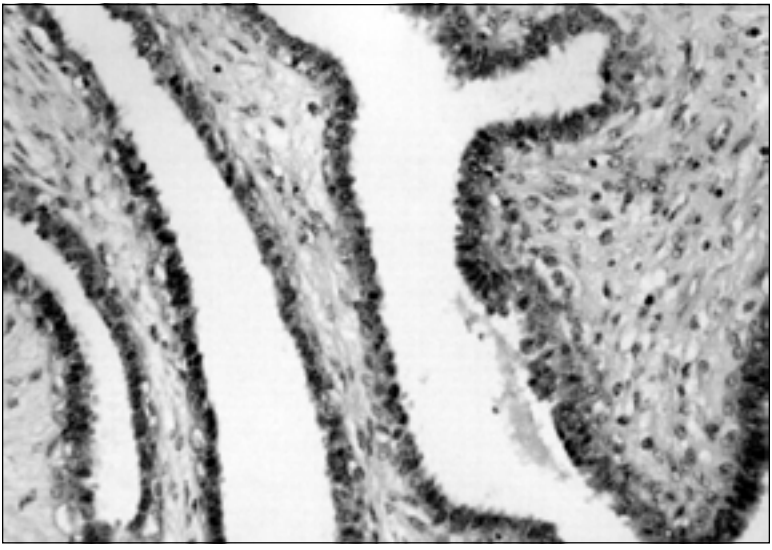

Fig. 3.4. Fibroadenoma (medium-power view) showing loose, cellular, pink stroma and compressed ducts lined by purple-staining ductal epithelial cells.

both patterns are often present in a single lesion. Tubular adenoma is best regarded as a variant of fibroadenoma that has a minimal stromal component and a tubular glandular component lined by regular ductal epithelium. Since fibroadenomas arise from the breast lobule, all changes that occur in the lobule may also be seen in a fibroadenoma namely apocrine metaplasia, sclerosing adenosis and lactational changes. The latter is particularly common in the tubular adenoma variants.

Management

Given the natural history of the disease, and provided triple assessment has demonstrated unequivocally that the lesion in question is a fibroadenoma, our policy is not to recommend excision of these lesions. Some authors recommend excision of all fibroadenomas greater than 3 cm in diameter. The only rationale for adopting such a policy is if fibroadenomas increase in size and there is concern that a delay in surgical excision might result in a greater amount of breast tissue requiring excision, thereby potentially resulting in poorer breast cosmesis. Similarly, in treating these lesions conservatively, we do not adopt a cut-off point as far as age is concerned. There is no scientific basis in recommending surgical excision over the age of 40 years. Despite adequate reassurance following an unequivocal diagnosis based on triple assessment, an occasional patient will request excision based on a deep-seated

fear of cancer. In this exceptional circumstance, it would be reasonable to proceed to surgical excision.

Phyllodes Tumor

Phyllodes tumors range from benign to malignant and often clinically mimic a fibroadenoma. They are, however, distinct neoplastic lesions derived from monoclonal stromal cells[16] and because of their malignant potential are managed by surgical excision.

Symptoms

Patients will present with a single discrete, nontender lump and may provide a history of increase in size.

Signs

Phyllodes tumors are usually unilateral, single, well-circumscribed, mobile and firm in consistency.

Radiology

Imaging features are generally very similar to those of a fibroadenoma.

Mammography

Phyllodes tumors appear as well-defined oval or round soft-tissue densities. They have a lobulated or smooth-outline (Fig. 3.5). Unlike fibroadenomas, calcification is rarely seen. The masses are frequently large and may grow quickly on sequential examinations.

Ultrasound

Phyllodes tumors tend to be well-circumscribed, lobulated or smooth-outlined, hypoechoic mass lesions with a homogeneous internal echo pattern. Cyst-like spaces may be seen within the stroma. Heterogeneity of the internal echo pattern may indicate associated hemorrhage or necrosis. Frequently, phyllodes tumors are highly vascular on color-flow doppler, although this is unreliable in distinguishing benign from malignant change.

Pathology

Macroscopic Appearance

Phyllodes are usually well-circumscribed, firm, lobulated masses. The cut surface is yellowish-white and often has a mucoid consistency with obvious clefts surrounding "leaf-like processes" from which the lesion takes its name. They may be indistinguishable from fibroadenoma.

Microscopic Appearance

Like fibroadenomas, phyllodes tumors are composed of a stromal and an epithelial element. The epithelia component comprises ductal structures with

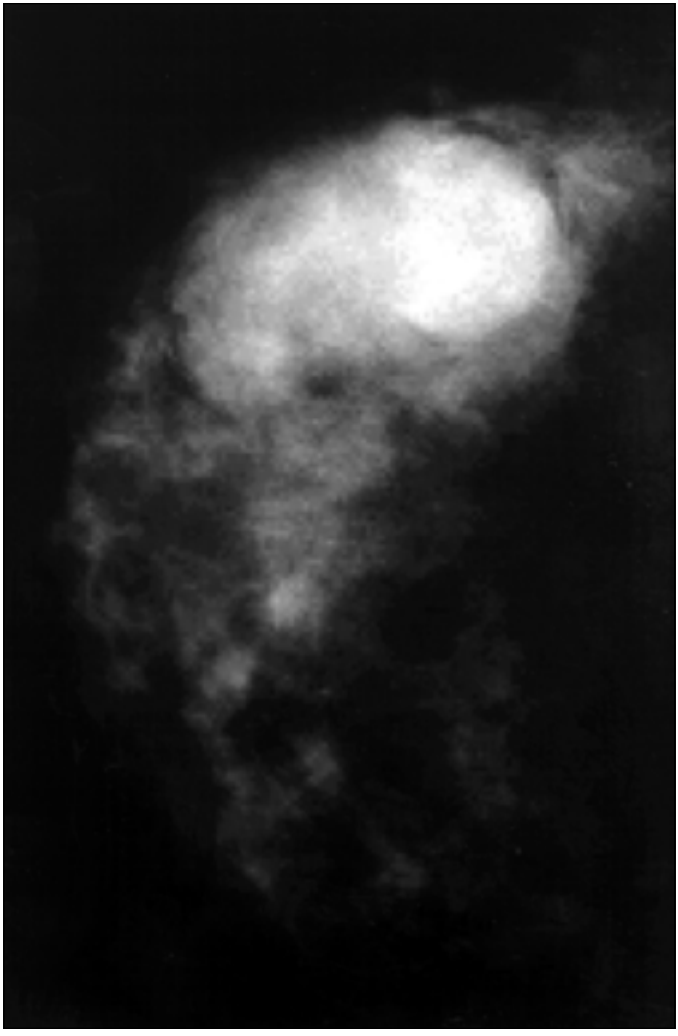

Fig. 3.5. Phyllodes tumor appearing as a large, well-defined soft-tissue mass.

invaginations into the lumina caused by the proliferating stroma (Fig. 3.6). These are the "leaf-like" structures. The epithelial component, like that in fibroadenoma, may show varying degrees of usual-type hyperplasia. The significant component in these lesions however is the stroma which is invariably cellular. The appearance of the stroma ranges from regular cellularity similar to that seen in a cellular fibroadenoma to marked hypercellularity

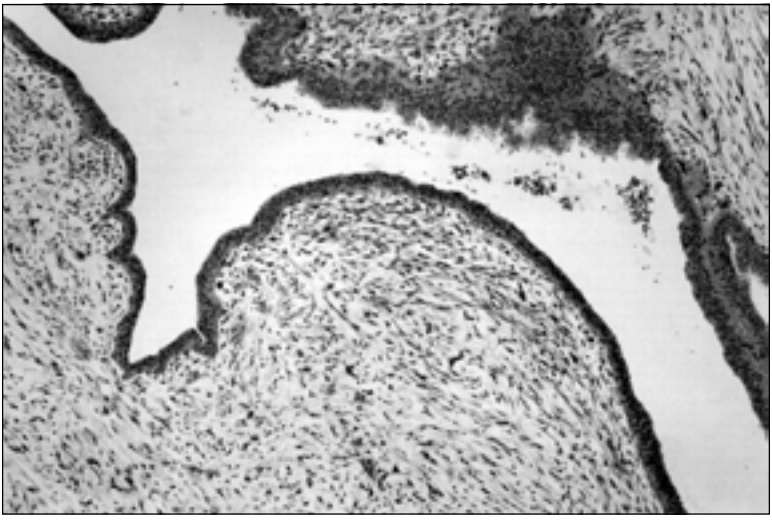

Fig. 3.6. Phyllodes tumor. Note the proliferating stroma invaginating the ductal lumen to produce a blunt leaf-like structure.

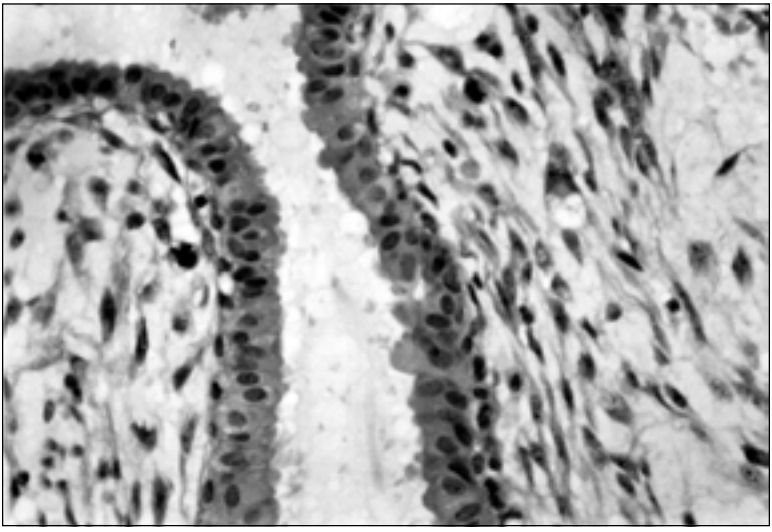

Fig. 3.7. Phyllodes tumor. Higher magnification of the previous field to show prominent stromal cellularity. The stromal cells show moderate pleomorphism. Abnormal mitoses are also present.

including mitoses which may be frequent and may include abnormal forms. The appearance of the stromal cells varies from plump, regular spindle cells to pleomorphic cells with features of sarcomatous change (Fig. 3.7).

These lesions are divided into low-grade, intermediate-grade and high-grade categories based on the presence and degree of stromal overgrowth, the cytologic characteristics of the stromal cells, the number of mitoses per 10 high-power microscope fields and the nature of tumor margin (pushing or infiltrative). No single feature has proved reliable in predicting clinical outcome; however, this constellation of characteristics has been shown by several small studies to be of some use.

Management

All phyllodes tumors must be excised with an adequate margin of excision.[21] These lesions must not be enucleated but excised completely, with a surrounding rim of normal breast tissue. Large tumors may need mastectomy with immediate reconstruction to achieve adequate clearance. Failure to do so will result in an unacceptable local recurrence rate and the potential for malignant transformation.

Hamartoma

Hamartomas are rare and present as well-circumscribed, mobile lesions. They are often impalpable and may be an incidental finding on screening mammography.

Radiology

Breast hamartomas are one of the few breast abnormalities that have characteristic features that allow confident diagnosis without resort to needle biopsy or surgical excision.

Mammography

Hamartomas appear as well-defined lesions containing areas of soft-tissue and fat density—so called "breast within a breast" appearance (Fig. 3.8). There is usually a surrounding capsule present indicated by a thin soft-tissue line demarcated by fat on either side.

Ultrasound

The lesion may be harder to diagnose on ultrasound than with mammography because it tends to blend into the background appearance of the breast. Hamartomas have a well-defined margin and contain varying amounts of hypoechoic fat and echogenic breast tissue.

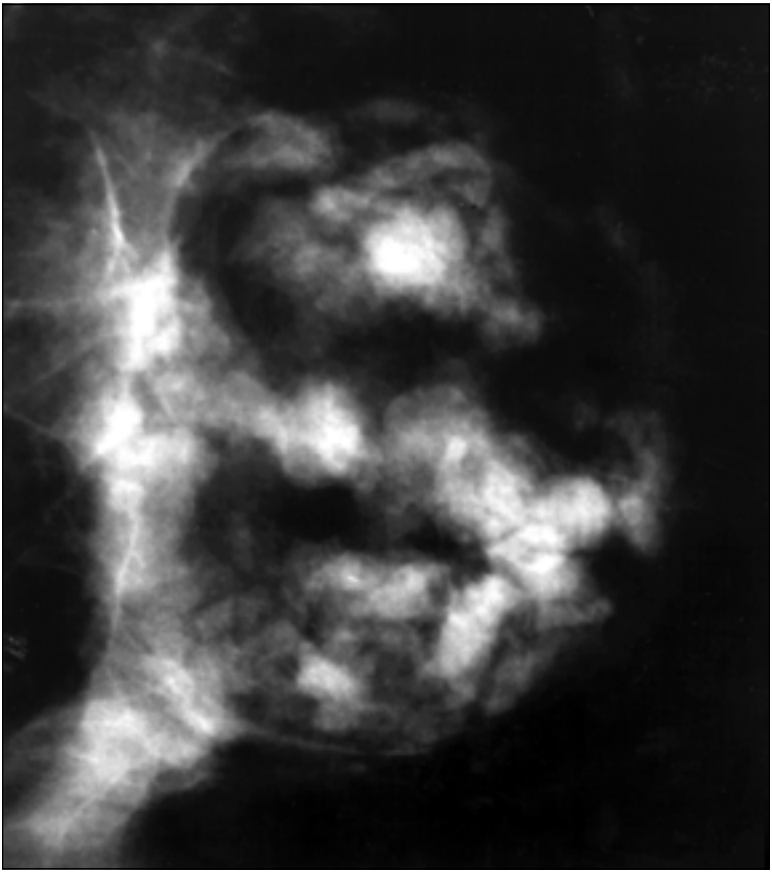

Fig. 3.8. Characteristic appearance of breast hamartoma appearing as a well-defined mass containing areas of soft-tissue and fat density — so-called "breast within a breast" appearance.

Pathology

Macroscopic Appearance

These lesions have a wide size range, with diameters of up to 25 cm having been recorded. The majority, however, are under 4 cm in diameter. They are, like fibroadenomas, well-circumscribed, firm, round or oval masses. The cut surface has a soft or firm consistency and a color that varies from gray to yellow. The consistency and color is dependent on the amount of fat present in the lesion. The lobulation and ductal clefts that characterize fibroadenomas are absent in these lesions. Small cysts are a frequent finding.

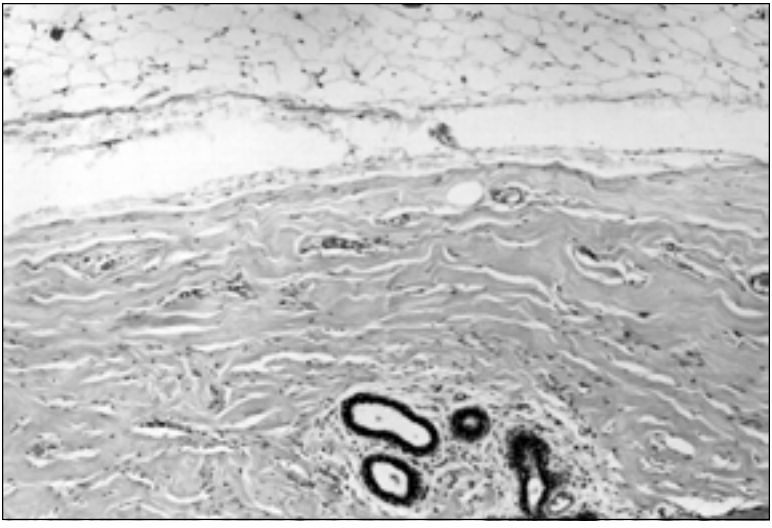

Fig. 3.9. Mammary hamartoma (low-power magnification) demonstrating the well-circumscribed edge of the lesion at the top of the photomicrograph.

Microscopic Appearance

Hamartomas are well delineated from the surrounding breast tissue (Fig. 3.9). They comprise a mixture of breast lobules, connective tissue and fat. The breast lobules may be discrete and histologically normal. Frequently, they lack specialized lobular stroma and may merge to form very large units. Occasionally, ectatic ducts and apocrine metaplasia are seen; however, epithelial hyperplasia is not a feature. The connective tissue stroma is sparsely cellular and densely fibrous. In most cases, the stroma includes areas of pseudoangiomatous hyperplasia. This refers to anastomosing artefactual clefts in the stroma lined by flattened stromal cells. Varying amounts of mature adipose tissue are incorporated into the connective-tissue component. Occasionally, smooth muscle can be demonstrated in these lesions using smooth-muscle actin immunohistochemistry.

Management

These lesions are best left alone.

Cysts

Breast cysts commonly occur in the fifth and sixth decades, with a peak incidence occurring around the age of 50. It can therefore be assumed that their etiology is related to an alteration in the overall hormonal profile of the patient. Cysts can be single or multiple and may be symptomatic or detected on mammographic screening.

Symptoms

Cysts can appear suddenly, grow to any size and may be associated with pain and tenderness. They may be single or multiple, unilateral or bilateral.

Signs

Cysts often appear as well-circumscribed, discrete, mobile lesions that may be fluctuant if they lie superficially in the breast. Alternatively, they may be much firmer if they are tense.

Radiology

Mammography

Cysts appear as well-defined soft-tissue densities. They may exhibit the "halo sign"; however, it rarely encircles the lesion completely. This is due to the fact that cysts are often obscured by surrounding breast tissue (Fig. 3.10). Simple cysts are frequently multiple and bilateral and are seen against a background of dense breast tissue. Calcification in the wall of a cyst (rim calcification) is uncommon and usually follows needle aspiration.

Ultrasound

Ultrasound is the mainstay of diagnosis and is extremely reliable in distinguishing solid from cystic masses. Cysts appear as well-defined, anechoic, thin-walled lesions. As sound travels through liquid with little attenuation, the tissue deep to a cyst appears bright (posterior enhancement). Mural lesions such as intracystic papillomas, which are only very occasionally seen, can be easily visualized using ultrasound. Some simple cysts contain inspissated material, which can make a cyst appear solid. If there is any diagnostic doubt as to whether a lesion is cystic or solid, ultrasound-guided aspiration/needle biopsy should be performed.

Pathology

Macroscopic Appearance

Cysts range in size from a few millimeters to several centimeters in diameter. They are often multiple and may be bilateral. The cyst wall may be smooth, thin and glistening or thickened and fibrotic due to the presence of granulation tissue and inflammation invoked by previous rupture. The cyst contents may be thin, straw-colored fluid or thick green-to-brown material, indicating the presence of inflammatory cells or altered blood within the cyst fluid (Fig. 3.11).

Microscopic Appearance

The cyst lining is usually composed of flattened ductal epithelial cells (Fig. 3.12) or apocrine metaplastic epithelium that may show papillary projections

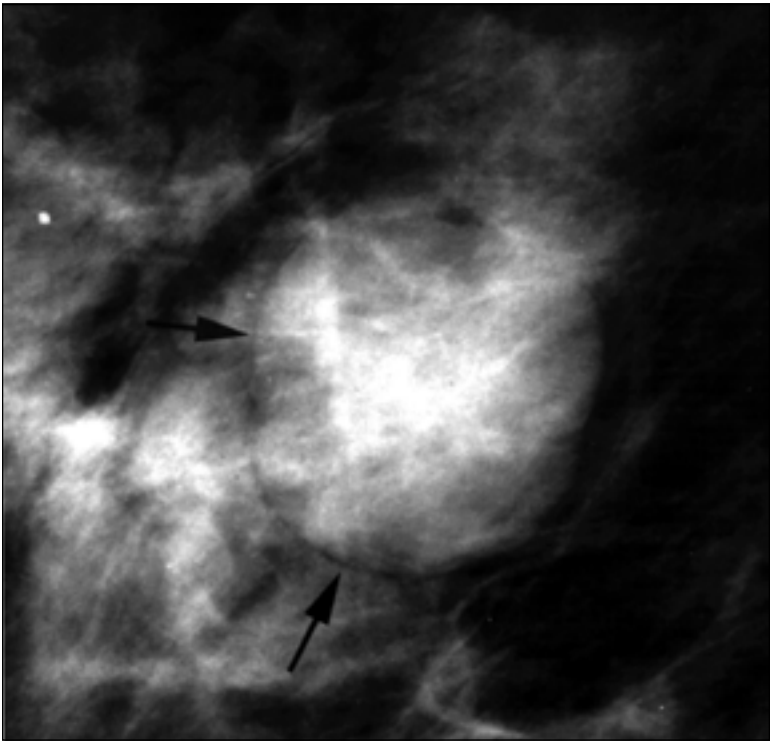

Fig. 3.10. Mammogram of a cyst appearing as a well-defined soft-tissue density exhibiting the "halo sign" (arrows). The edge of the cyst is partially obscured by surrounding breast tissue.

(Fig. 3.13). Foamy macrophages are frequently present in the cyst lumen and may also be seen infiltrating the lining epithelium if it is ductal in type. If the cyst wall is thickened macroscopically, the lining is usually composed of granulation or laminated fibrous tissue with varying amounts of inflammatory cells. Trapped epithelial structures are often seen in thickened cyst walls.

Management

Aspiration of the cyst to dryness is the treatment of choice. Normally, the cyst fluid is discarded. If the fluid is uniformly blood stained, it should be sent for cytology. Following aspiration of a cyst, the patient should be reexamined, and the clinician should confirm that the previously palpable lump has disappeared. Any residual areas of nodularity should be investigated similarly to any other discrete lump (i.e., FNAB or core biopsy). Recurrent

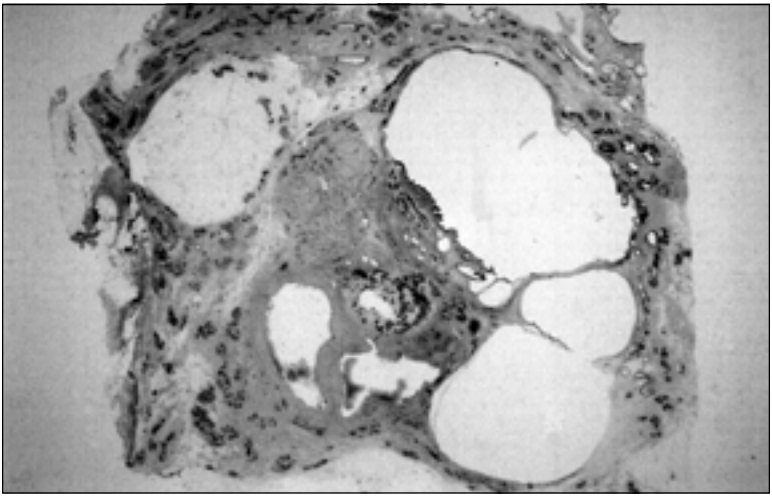

Fig. 3.11. Low-power view of multiple cysts with associated solid areas.

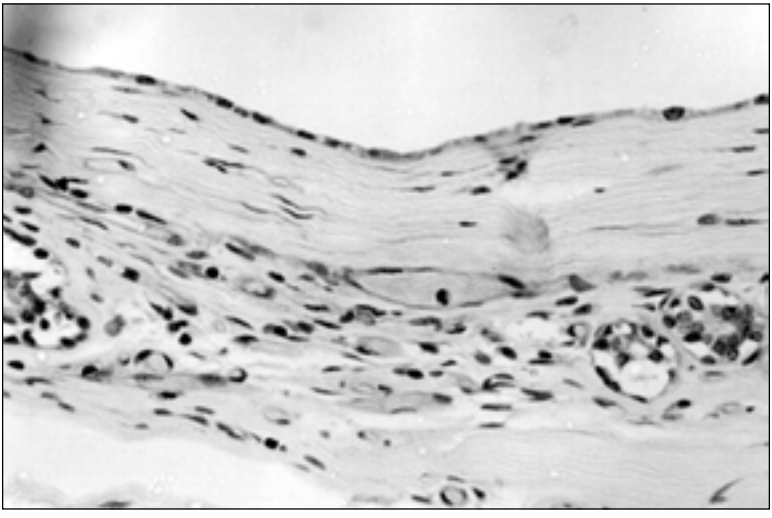

Fig. 3.12. Part of cyst lined by flattened ductal epithelium.

cysts are aspirated as and when they cause symptoms. There is no place for surgical excision.

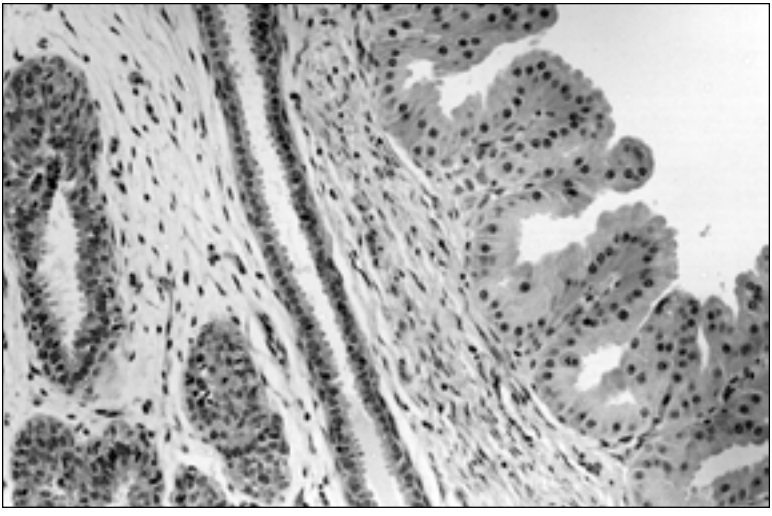

Fig. 3.13. Part of cyst lined by apocrine metaplastic epithelium showing papillary hyperplasia. There are trapped elongated ductal structures in the cyst wall.

Cysts and Risk of Breast Cancer

The relationship between cysts and breast cancer risk is controversial. Based on the potassium:sodium ratio, cysts have been classified into type 1 (apocrine/secretory), type 2 (attenuated/flattened) and mixed cysts (type 1 cysts ratio >1.5; type 2 cysts ratio <1.5). In a large study involving 802 patients with a median follow-up of six years,[22] the incidence of breast cancer in type 1 cysts has been shown to be greater than in type 2 or mixed cysts (RR 4.62). It is not routine practice to analyze aspirated cyst fluid for its electrolyte content. Other studies have demonstrated that, irrespective of cyst type, there is an increased risk of developing breast carcinoma in all women (RR 1.7).[23]

Duct Ectasia

Duct ectasia is a benign condition associated with loss of elastin within the walls of the duct, with an associated chronic inflammatory cell infiltrate.[24] This results in duct dilatation and shortening. Duct ectasia should be regarded as an aberration of normal breast involution affecting older women.

Symptoms

Patients may present with cheesy nipple discharge that may arise from one or multiple ducts. There may be an associated lump representing a dilated duct. Slit-like nipple retraction may be present and is a late feature.

Signs

Pressure on the areola will demonstrate discharge that is usually cheesy and there may be a palpable dilated duct with associated nipple retraction.

Radiology

Mammograms

The majority of patients with duct ectasia have no diagnostic mammographic features. Occasionally the ducts are seen as tubular structures extending from the subareolar area, but this is a nonspecific sign. The purpose of mammography in such instances is to exclude underlying malignancy.

Ultrasound

Duct ectasia can be seen as multiple tubular structures arising from the nipple. The significance of such findings is unclear, however, as it is frequently seen in otherwise normal individuals. Ultrasound therefore has no role to play in the diagnosis of patients with nipple discharge. It should only be performed in patients who are also found to have a palpable mass.

Pathology

Macroscopic Appearance

The large subareolar ducts are predominantly affected. The affected ducts are distended and palpable, and on cross section, they are filled with thick pultaceous material and may contain calcification in rare cases.

Microscopic Appearance

The dilated ducts contain amorphous material and foamy macrophages within them. The lining epithelium also contains infiltrating macrophages and may show reactive hyperplasia or attenuation. The periductal stroma shows varying degrees of inflammation and fibrosis. The fibrosis is usually concentric in distribution but may be irregularly distributed in plaques.

Stromal calcification may also be seen.

Management

Provided assessment confirms the diagnosis of duct ectasia, the majority of patients can be reassured. Patients with troublesome discharge should be treated by total duct excision. The nipple should be everted as part of this procedure.

Periductal Mastitis

Periductal mastitis refers to the inflammatory process occurring around dilated ducts. The etiology and pathogenesis of periductal mastitis is debatable. One theory suggests that the process consists of initial duct dilatation

followed by distention. This results in damage to the duct wall, thereby causing extravasation of lipid material, resulting in an inflammatory reaction. The alternative hypothesis suggests that duct ectasia may be the consequence of an initial periductal inflammatory process, with duct dilatation being a secondary event.[25] Colonization by bacteria may also play a part in the pathogenesis of this condition. Current evidence suggests that smoking is an important contributory factor in the etiology of this condition as it includes damage to the subareolar ducts.

Clinical Features

Pain associated with nipple discharge is a common presenting feature. The pain is usually subareolar, noncyclical and associated with discharge from multiple ducts. There may be associated nipple retraction and an underlying subareolar mass. Patients may give a history of a previous breast abscess. An associated mammary-duct fistula with associated periareolar inflammation may often be noted.

Radiology

Ultrasound may reveal a thick-walled duct with an ill-defined margin due to the presence of inflammation. These appearances are nonspecific, and as a result, imaging has little or no diagnostic role other than excluding malignancy. The long-term sequelae of periductal mastitis may result in calcification that appears as areas of linear, frequently bilateral, crisply-defined calcification.

Pathology

Macroscopic Appearance

There are no specific appearances described in these cases.

Microscopic Appearance

Inflammation appears within and around the involved ducts. It may extend into adjacent breast lobules. Macrophages are almost invariably present. Intense plasma-cell infiltrates (with or without associated noncaseating granulomatous inflammation) are also described.

In these latter cases, the presence of specific pathogens such as mycobacterium tuberculosis need to be considered and, if necessary, excluded.

Management

Initial management is with appropriate antibiotics until the inflammation settles. If there is a history of recurrent episodes of inflammation associated with nipple discharge, treatment should be by total duct excision and eversion of the nipple under antibiotic cover.

Mammary-Duct Fistula

Mammary-duct fistula is a communication between a subareolar duct and skin, usually occurring in the periareolar region. It often occurs spontaneously following underlying periductal mastitis but can also occur following incision and drainage of a nonlactating breast abscess. It occurs predominantly in younger women; the majority are smokers.

Clinical Features

Presence of a fistula in the periareolar region with associated inflammation on a background history of recurrent periductal inflammation is often noted. Patients classically report a long duration of symptoms of recurrent inflammation treated with antibiotics.

Radiology

On ultrasound, the fistulous track may be seen as a linear hypoechoic structure extending from the skin. The main objective of mammography and ultrasound is to exclude underlying abscess or malignancy.

Pathology

Macroscopic Appearance

A thickened fistulous track may be apparent in the specimen.

Microscopic Appearance

Classically, a fistulous track is seen. It is lined with granular tissue that extends from the areolar skin to an underlying duct. Extensive squamous metaplasia is commonly present in the affected duct.

Management

In the presence of acute inflammation, appropriate antibiotic therapy is necessary initially. Surgery is the only means of successfully curing this condition and will involve complete duct excision with excision of mammary-duct fistula. The wound may be left open and allowed to heal by secondary intention. Where the disease is relatively quiescent, it is reasonable to achieve healing by primary skin closure and antibiotic cover.

Duct Papilloma

Duct papillomas can be solitary or multiple. These lesions can present in isolation but are often noted in association with other benign breast pathology. Although papillary lesions are histologically similar, there are different subtypes in terms of clinical characteristics and associated risk of subsequent carcinoma.

Solitary Intraductal Papilloma

Solitary intraductal papilloma is a benign lesion arising in a single central duct.

Clinical Features

A classical symptom is spontaneous nipple discharge, which can be serous or blood stained. The discharge emanates from a single duct, and pressure over the duct at the margin of the areola usually produces copious discharge. There may be an underlying palpable mass that may represent the papilloma itself or a dilated duct proximal to the papilloma.

Radiology

Mammography

Unless the papilloma is large and the breast of predominantly fatty density, papillomas are usually not visualized mammographically. The objective of the mammogram is to rule out underlying malignancy.

Ultrasound

As with mammography, papillomas are not diagnosed reliably with ultrasound. Occasionally, they appear as a solid nodule within a fluid-filled duct.

Galactography

Galactography involves the taking of mammograms following the injection of contrast into a discharging duct. A galactogram reveals an intraductal papilloma as a filling defect either partially or totally occluding a duct. In addition, a galactogram distinguishes between troublesome discharge due to a papilloma and that due to duct ectasia. In our unit, both conditions are treated with surgical excision. The undertaking of a galactogram does not change patient management; therefore, it is not performed preoperatively. Galactography does not reliably distinguish between a benign intraduct papilloma and a carcinoma.

Pathology

Cytologic smears of the nipple discharge may be helpful occasionally in distinguishing between benign intraductal papilloma and a papillary carcinoma.

Macroscopic Appearance

In the majority of cases, no gross abnormality is seen. This is consistent with the small size (<3 mm) of the majority of these lesions. Larger papillomas are evident as pink or deep-red velvety lesions within a dilated duct.

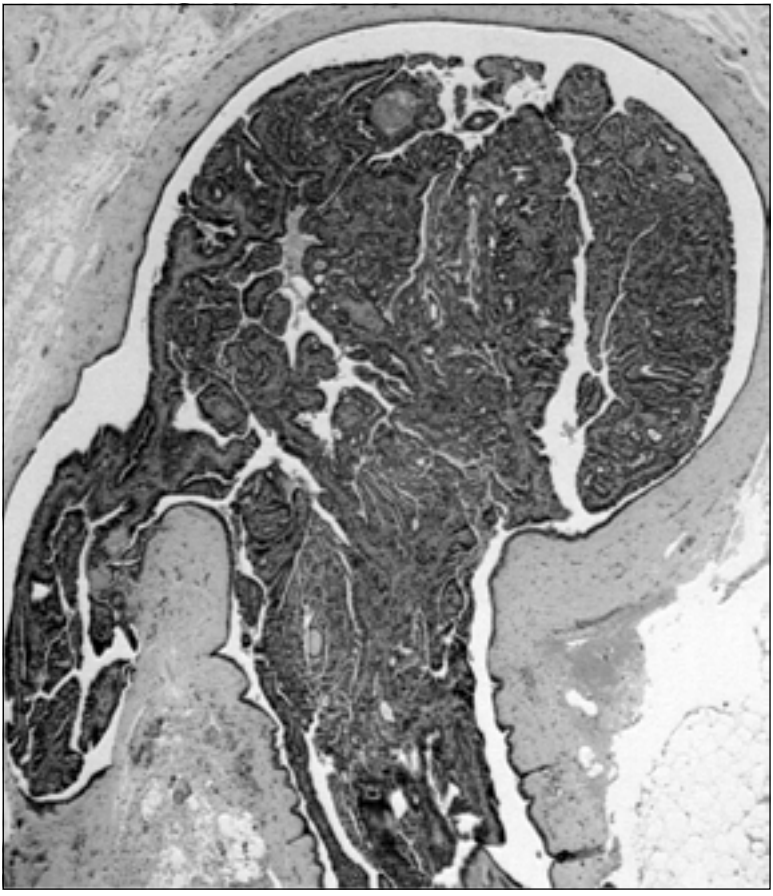

Fig. 3.14. Solitary intraductal papilloma. Duct expanded by a tree-like structure with a pale pink fibrovascular core (higher-magnification view). The stromal core is covered by pink myoepithelial cells with darker, increasingly regular, pink epithelial cells on the free luminal surface.

Microscopic Appearance

Characteristically, these lesions have an arboriform structure containing a central fibrovascular core that is covered by an inner myoepithelial and an outer or luminal epithelial layer (Figs. 3.14, 3.15). The epithelium may show the usual type hyperplasia, apocrine metaplasia and, occasionally, squamous metaplasia. Sclerosis of the fibrovascular core and partial or complete obliteration of the duct lumen may be seen. When these latter changes are present, the lesion is termed a ductal adenoma.

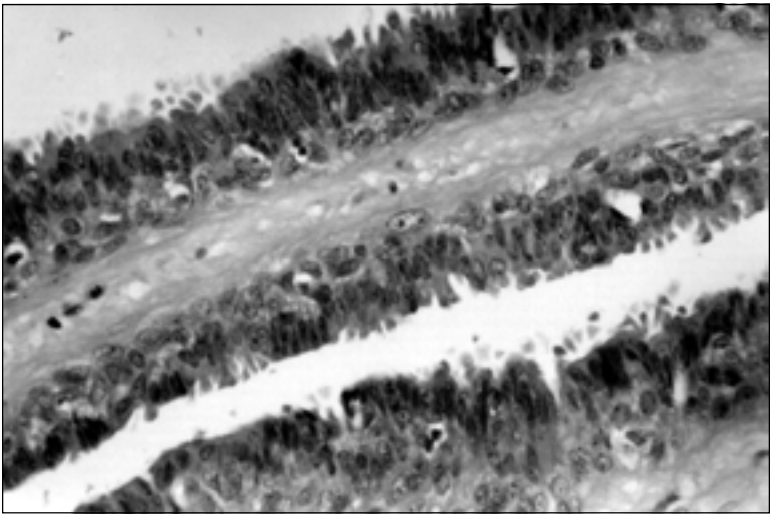

Fig. 3.15. Solitary intraductal papilloma. Duct expanded by a tree-like structure with a pale pink fibrovascular core (higher-magnification view). The stromal core is covered by pink myoepithelial cells with darker, increasingly regular, pink epithelial cells on the free luminal surface.

Management

Surgical treatment consists of offending duct excision through a circumareolar incision. Since the natural history of a solitary intraductal papilloma is that of an isolated benign lesion associated with little risk of subsequent carcinoma, no further follow-up is necessary.

Multiple Peripheral Papillomas

Multiple papillomas tend to occur in peripheral ducts and present with a palpable mass associated in rare cases with nipple discharge. The diagnosis is usually made on core or excision biopsy. Inadequate excision results in a high local recurrence rate. There is a 10-33% risk of subsequent ipsilateral breast carcinoma in patients with multiple peripheral papillomas.[26] Therefore, long-term follow-up with mammographic screening is recommended in these patients.

Juvenile Papillomatosis

Juvenile papillomatosis is a rare, benign, localized proliferative condition encountered mainly in young women (average age of 23 years). Patients usually present with a palpable mass and no associated nipple discharge. The incidence appears to be higher in women with a family history of breast cancer.

Radiology

Mammography

Mammography is very rarely performed, as the majority of patients are under the age of 35 years, and the appearances are likely to be nonspecific and unhelpful.

Ultrasound

Ultrasound can reveal an hypoechoic mass or an area containing multiple small cysts and dilated ducts.

Pathology

Macroscopic Appearance

The excised lesion is a firm, discrete mass and does not have a well-circumscribed outline. The size varies between 1 and 8 cm. The cut surface has the appearance of "Swiss cheese" due to the presence of multiple cysts that measure 1-2 cm. These are separated by firm yellow and white areas (Fig. 3.16).

Microscopic Appearance

These lesions are composed of a constellation of cysts, ducts showing florid epithelial hyperplasia, which occasionally have atypical features, and prominent stroma, which may be sclerotic or cellular (Fig. 3.17).

Management

Complete excision of the underlying area with an adequate margin is the treatment of choice. Inadequate excision will invariably lead to local recurrence. The overall long-term risk of carcinoma remains uncertain; therefore, long-term follow-up is recommended.

Abscess

Lactating Breast Infection

Nursing mothers can develop cellulitis or abscess formation secondary to infection with staphylococcus aureus. The portal of entry is usually an irritated or cracked nipple. It is not known whether poor milk drainage secondary to blockage of a major duct is an initiating event.

Symptoms

Presenting features include pain, swelling and tenderness associated with redness of the overlying skin. There may be associated fever and chills.

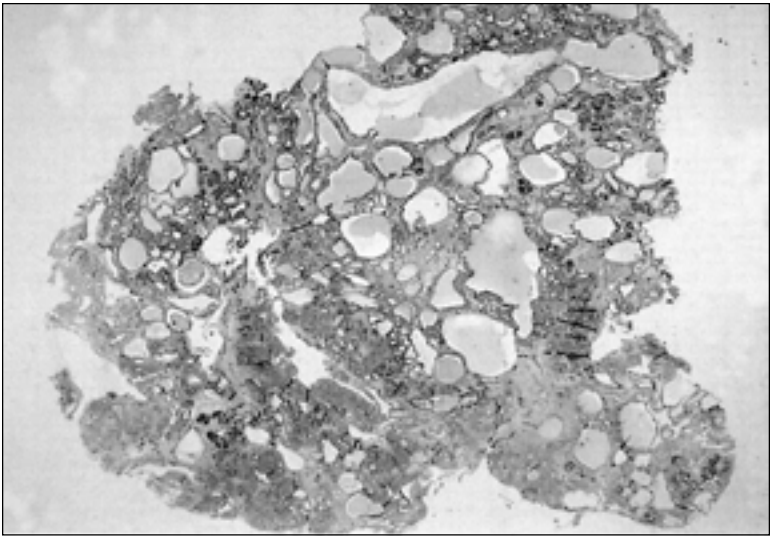

Fig. 3.16. Low-power view of juvenile papillomatosis showing characteristic "Swiss cheese" appearance.

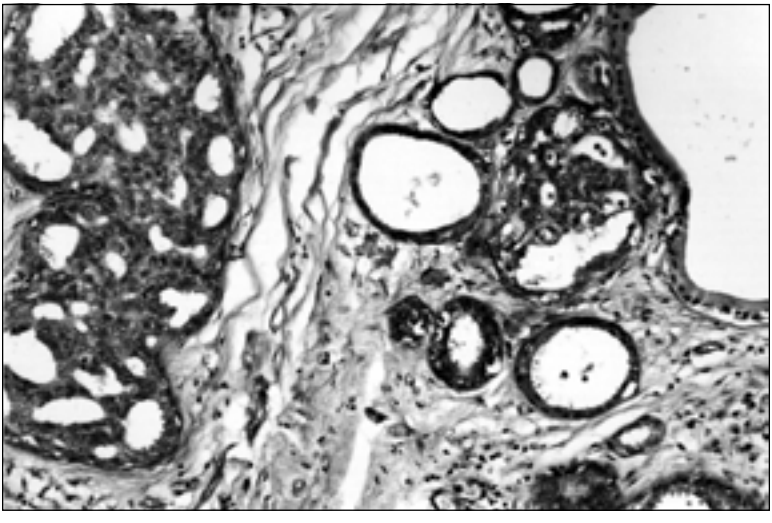

Fig. 3.17. Higher magnification of previous field demonstrating the characteristic triad of florid ductal epithelial hyperplasia adjacent to cysts and associated with a cellular stroma.

Signs

Classically, a segment of the breast is inflamed, with erythema and tenderness present. In some instances, the entire breast is involved. There may be an associated cracked nipple. General signs of infection such as pyrexia and leucocytosis may be present. In the later stages, there may be a fluctuant mass indicating underlying pus.

Radiology

Mammography

This is only indicated if there is clinical uncertainty whether the appropriate diagnosis is an abscess or an inflammatory carcinoma. Often patients will be too uncomfortable to endure the breast compression required to perform a mammogram.

Ultrasound

Ultrasound is very useful in distinguishing between breast inflammation and abscess formation (Fig. 3.18). It also guides needle aspiration, which may need to be repeated on several occasions before infection subsides.

Pathology

Macroscopic Appearance

There are no specific gross features.

Microscopic Appearance

The microscopic features are those of an acute inflammatory process.

Management

In the early phase of lactational mastitis, antibiotics can prevent abscess formation. Emptying the breast as part of treatment can improve the outcome and shorten the duration of symptoms. Topical warmth may provide symptomatic relief. Patients with demonstrable pus either on clinical or ultrasound examination should have needle aspiration in addition to antibiotic therapy. It is our policy to treat these patients with repeated aspiration of pus, prescribe antibiotics and monitor resolution of the abscess by sequential ultrasound examination. If the overlying skin is thinned or necrotic, we subject the patient to incision and drainage, which can be performed as an outpatient procedure under local anesthesia. It is rarely necessary to suppress lactation.

Nonlactating Breast Infection

Periareolar infection occurring in patients with periductal mastitis has already been described. This infection is usually central and subareolar.

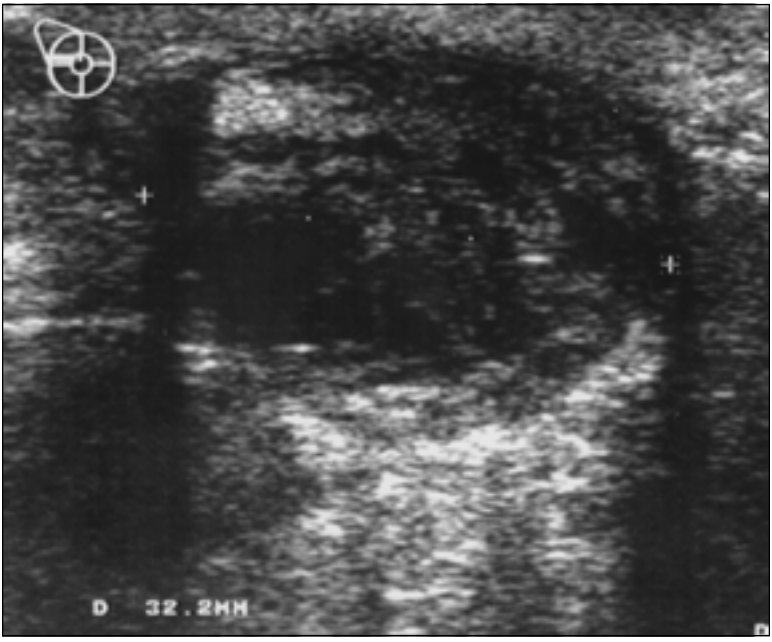

Fig. 3.18. Ultrasound of a breast abscess appearing as a well-defined mass containing mixed echoes.

Peripheral breast abscesses can occur in patients with other systemic conditions such as diabetes, steroid therapy and rheumatoid arthritis. The clinical presentation, diagnosis and management are similar to those for a lactational breast abscess. It should be noted that the organisms cultured from nonlactational peripheral abscesses include alpha-hemolytic streptococci and a variety of gram-positive and gram-negative anaerobic bacteria. It is therefore useful to obtain cultures of aspirated pus and commence the patient on appropriate antibiotic therapy with incision and drainage if necessary.

Hematoma

Breast hematoma can occur secondary to surgical intervention, including FNAB, core biopsy and excision biopsy. The most common cause of postoperative hematoma is inadequate hemostasis. Breast hematoma also occurs after minor trauma to the breast with patients presenting with a tender mass associated with overlying bruising in the early phase following injury. When patients present late, the only clinical feature might be an underlying mass, which should be investigated thoroughly. It should be noted, however, that a history of trauma may not always be present since, often, the injury is trivial.

Pathology

Macroscopic Appearance

A well-circumscribed, thick-walled cystic lesion containing, upon opening, obvious organizing hematoma and brown-stained liquid is usually noted.

Microscopic Appearance

Organizing hematoma appears with or without surrounding fibrosis, granulation or fat necrosis depending on the age and etiology of the lesion.

Management

Postoperative hematomas that are enlarging should be evacuated under general anesthesia. Analgesia and support of the breast with a well-fitting brassiere will provide some relief of symptoms. If the hematoma liquefies, as demonstrated by fluctuation, aspiration may provide some relief. Short-term clinical follow-up to ensure resolution of symptoms may be necessary.

Fat Necrosis

Fat necrosis of the breast may be associated with a history of trauma (35-40%) and is an important clinical entity because it can mimic breast carcinoma. Surgical trauma secondary to biopsy or plastic surgical procedures on the breast, or injection of silicone or narcotics into the breast can cause fat necrosis.

Clinical Features

Patients may present with an irregular, painless mass that may be associated with overlying skin thickening or tethering. Therefore it can sometimes be difficult to distinguish fat necrosis from carcinoma on clinical examination.

Radiology

Mammography

Frequently the mammogram is normal. When present, mammographic changes are often variable. In the early phase, there is usually a soft-tissue density, which may change over a period of weeks to a low-attenuation area with a thin, surrounding capsule. These capsules may undergo subsequent rim calcification.

Ultrasound

Ultrasound is extremely successful at detecting fat necrosis. The appearances vary from superficial hyperechoic, mixed echogenecity or cystic-like structures. Aspiration of such cysts produces oily fluid.

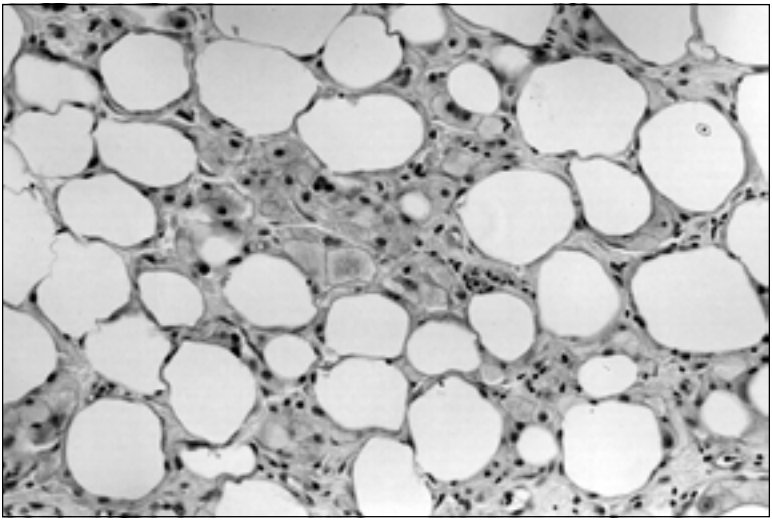

Fig. 3.19. Fat necrosis (high magnification). Note empty fat cells of varying sizes and lack of nuclei. These are surrounded by foamy macrophages and occasional giant cells and lymphocytes.

Pathology

Macroscopic Appearance

Most isolated lesions are small (average <2 cm in diameter). The lesion is usually firm, indurated and may have an irregular or rounded outline. The cut surface in early lesions shows mottled yellow and red areas and in older lesions cystic spaces may be apparent. Eventually, in long-standing lesions, there will be dense fibrosis and sclerosis with possible foci of calcification.

Microscopic Appearance

Foamy macrophages, occasional lymphocytes and foreign-body giant cells are seen infiltrating adipose tissue in the earliest stages. The adipocytes may be uneven in size and lack nuclei (Fig. 3.19). In older lesions, free-lying fat globules surrounded by a rim of foamy macrophages and giant cells are seen. Fibrosis, hemosiderin-laden macrophages and calcification are features of long-standing cases.

Management

In our experience, an unequivocal diagnosis of fat necrosis can be made on core biopsy. Simple observation will result in resolution of the palpable mass. In the absence of a firm diagnosis, open excision biopsy is recommended.

Radial Scar

Radial scars are often detected in screening mammography (0.9 per 1,000 women screened) or as incidental findings in excision breast biopsy for another pathology. Their importance lies in that they may mimic carcinoma.

Radiology

Mammography

Typically, a radial scar will appear as an area of distortion with long radiating strands and a small mixed-density center (compared with a typical carcinoma, which has short spicules and a dense center). Associated fine granular calcification is common. The features of a radial scar and a carcinoma frequently overlap, however, making reliable distinction impossible.

Ultrasound

Radial scars often appear as distorted areas of architecture with no definite mass lesion. Again, distinction from a carcinoma is unreliable.

Pathology

Macroscopic Appearance

The sliced lesion has a stellate outline, firm consistency, often with central puckering, and white color with yellow elastotic foci, which are usually centrally placed. The size can vary from a few millimeters to several centimeters. The larger lesions are sometimes termed complex sclerosing lesions.

Microscopic Appearance

Characteristically the lesion has a dense, sclerotic center with foci of elastosis and scattered flattened and angulated tubules lined by an inner epithelial and an outer myoepithelial layer. Radiating from this central sclerotic area are bands of less dense fibrous stroma that contain ductal and acinar structures (Fig. 3.20) showing a range of changes that include florid epithelial hyperplasia, blunt duct adenosis, sclerosing adenosis, apocrine metaplasia and papilloma formation. In a small number of cases, particularly those larger than 10 mm, atypical hyperplasia of ductal or lobular type may be seen. Very occasionally in situ carcinoma is detected in these lesions.

Management

Surgical excision by mammographic localization of the lesion is recommended in order to exclude an underlying carcinoma. There is no clear evidence for an increased risk of breast cancer in patients who have been treated for a radial scar.[27]

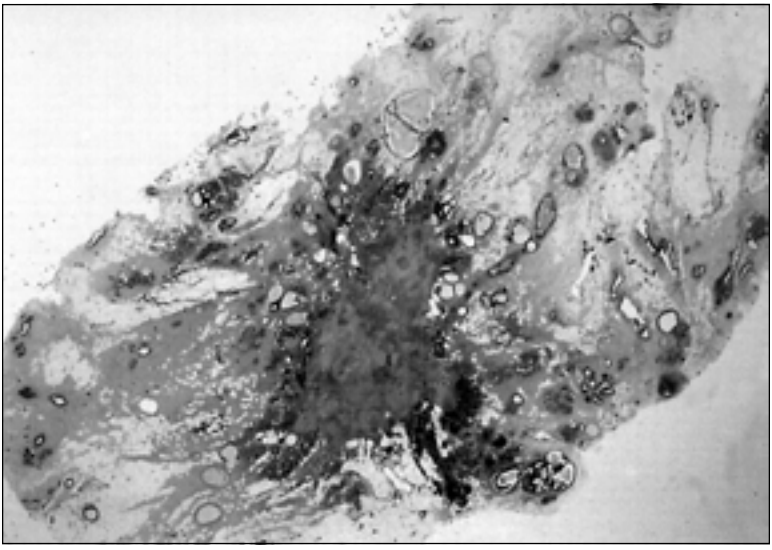

Fig. 3.20. Radial scar (very low power magnification) demonstrating the central dense, pink, hyaline area and paler-pink radiating fibrous bands that give the characteristic stellate or "daisy head" appearance. Within the radiating paler bands of fibrous tissue, expanded purple ductal and acinar structures and occasional cysts are apparent.

Sclerosing Adenosis

Sclerosing adenosis is associated with distortion of the terminal duct-lobular unit and should be regarded as an aberration of breast involution.

Clinical Features

Patients may present with either a breast lump or breast pain, or may be noted to have an area of increased density or clustered microcalcification on mammographic screening.

Radiology

Mammography

Areas of sclerosing adenosis may be indistinguishable from background parenchyma or show as nonspecific areas of asymmetric density. Sclerosing adenosis may be associated with clustered microcalcification. This is usually fine, granular, powderish calcification that may be indistinguishable from low-grade ductal carcinoma in situ (Fig. 3.21). Definitive diagnosis in such cases can usually be reached with stereotactic core biopsy.

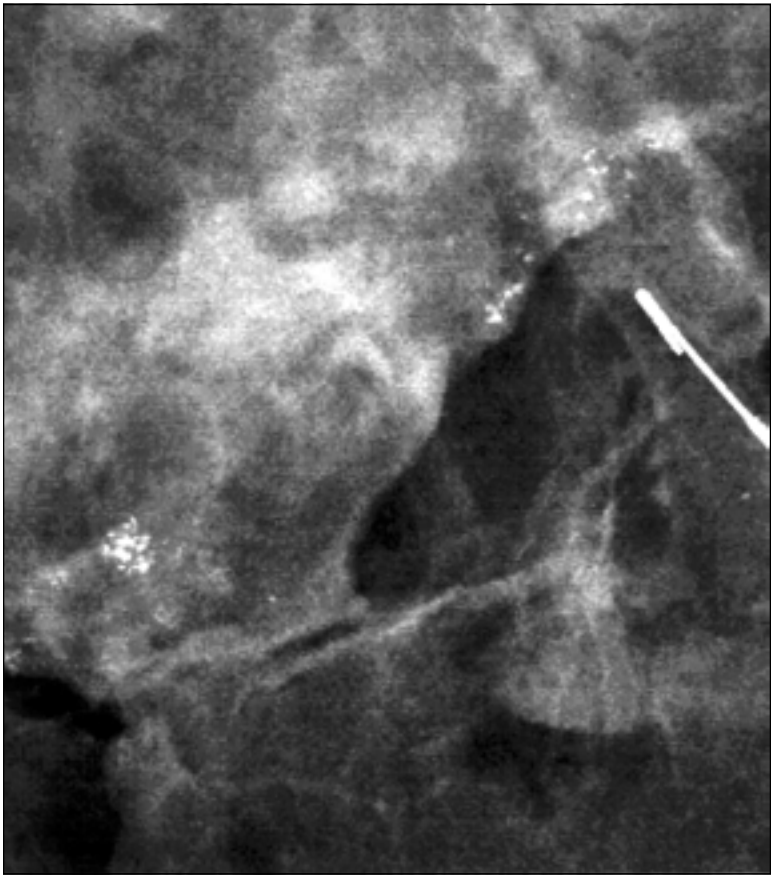

Fig. 3.21. Sclerosing adenosis. Mammogram with multiple clusters of fine granular calcification. The appearances are indistinguishable from low-grade DCIS.

Pathology

Macroscopic Appearance

There are no distinctive macroscopic features.

Microscopic Appearance

Sclerosing adenosis is a disorderly proliferation of lobular epithelial, myoepithelial and stromal cells that leads to an untidy enlargement of the lobule and sometimes to fusion of several involved lobules. The involved lobule or lobules have a crowded cellular appearance. The epithelial acini are usually small and flattened from side to side, with their lumina diminished or obliterated.

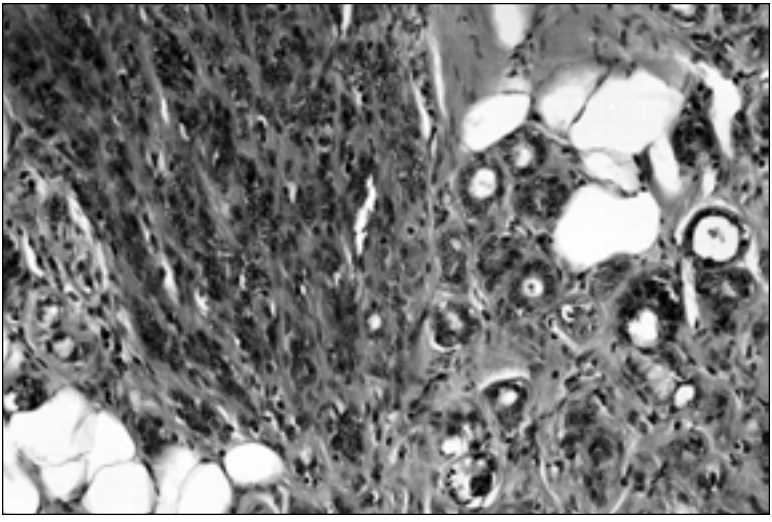

Fig. 3.22. Sclerosing adenosis. On the left is a crowded lobule with elongated, compressed acini that are separated by pink myoepithelial cells. To the right are more rounded acini separated by dense hyaline sclerosis. Two of the rounded acini towards the center and at 6 o'clock of the photomicrograph contain luminal calcification.

The proliferating myoepithelial cells appear plump and eosinophilic and in the early stages fill the spaces between the acini. In older lesions, sclerotic stroma fills the space between the acini (Fig. 3.22). The reduced acinar lumina often contain calcospherites. Apocrine metaplasia may also be present.

Management

If core biopsy is conclusive, no further treatment or follow-up is required. Where there is an area of doubt, excision biopsy is recommended. Impalpable lesions will require preoperative mammographic localization. There is a mildly elevated risk for the subsequent development of breast cancer (RR 1.6).[28,29] This risk is slightly higher in women with a positive family history (RR 2.1).

Epithelial Hyperplasia

Proliferation of epithelial cells lining the terminal duct-lobular unit is known as epithelial hyperplasia. The degree of hyperplasia can be graded as mild, moderate or florid. There may be associated atypical features. The significance of atypia is related to the risk of subsequent development of breast cancer. There is a strong interaction with family history and atypical hyperplasia.[28,30] Three case control studies have demonstrated a relative risk for breast cancer ranging from 3.7-13 in patients with atypical hyperplasia.[30-32]

Clinical Features

Patients with atypical hyperplasia do not present with classical clinical features. They can present with a lump or lumpiness or may be noted to have an abnormality on screening mammography.

Radiology

There are no specific mammographic features associated with hyperplasia, and the most common way to diagnose mammographically is in association with a cluster of microcalcification.

Pathology

Microscopic Appearance

Epithelial hyperplasia of usual type can occur in any part of the breast glandular structure but predominantly affects the terminal duct-lobular unit. Depending on the number of cell layers present, the degree of duct expansion and the presence of secondary lumina, these proliferations can be subdivided into mild, moderate and florid. The cytological inter-relationships of usual-type hyperplasia are haphazard, giving an untidy appearance with irregular and often slit-like secondary lumina where these are present. The cells themselves have regular nuclear chromatin and vary in shape from spindle and elongated to round. An admixture of myoepithelial cells is usually present (Fig. 3.23).

Atypical ductal hyperplasia (ADH) is intermediate between florid epithelial hyperplasia and low-grade ductal carcinoma in situ (DCIS) usually of cribriform type. Thus, at the lower end of the spectrum, ADH includes features of florid epithelial hyperplasia plus small focal areas of more uniform cytology and more even placement of cells (Fig. 3.24). The atypical features give rise to the more rounded, very regular outlines of the secondary lumina characteristic of low-grade DCIS. The cells in ADH also show more nuclear hyperchromasia than those in usual-type epithelial hyperplasia. The distinction of ADH from low-grade DCIS can be extremely difficult and is based on the degree and extent of the atypical features.

Atypical lobular hyperplasia (ALH) is a uniform proliferation of small, monomorphic cells that partially fill most of the acini in one or more lobular units. Some, but not all, of the acinar lumina are obliterated (Fig. 3.25).

Management

Following a pathological diagnosis, the decision to follow up a patient should be based on subsequent risk for breast cancer. Patients with atypical hyperplasia may be considered for entry into breast cancer prevention trials.

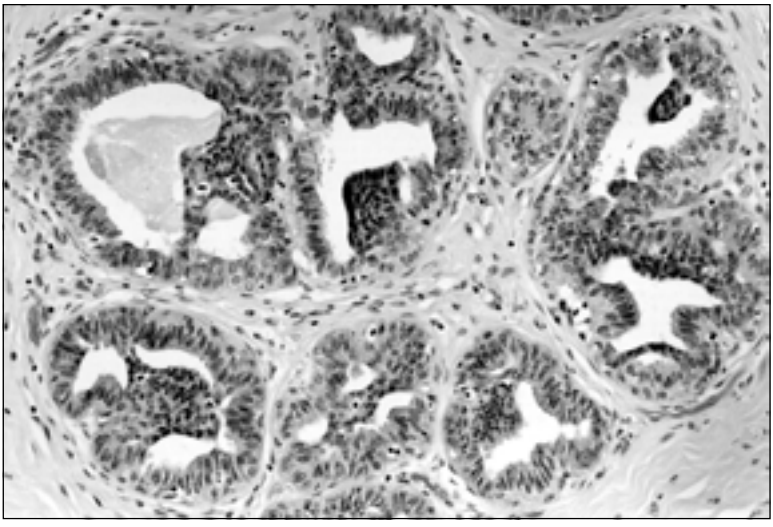

Fig. 3.23. Epithelial hyperplasia of usual type, which is seen expanding a lobular unit. There is irregular heaping up of epithelium towards the center of the lumina, with some secondary lumen formation. The secondary spaces are irregular and slit-like. The cells are of varying shape and size. Scattered clear myoepithelial cells are frequent within the hyperplastic epithelium.

Rare Benign Disorders of the Breast

Granular Cell Tumors

Granular cell tumors are rare but important because they can simulate carcinoma. Patients can present with a palpable mass with associated fixity to skin or underlying muscle.

Radiology

It can be difficult on mammography to differentiate granular cell tumors from carcinoma. Diagnosis is made on histology.

Pathology

Macroscopic Appearance

These tumors may be well circumscribed or appear infiltrative. They are usually creamy white in color and of a firm, sometimes gritty consistency.

Microscopic Appearance

The appearances are identical to those seen in other sites with clusters of plump cells with uniform, dark nuclei and abundant granular, pink cytoplasm (Fig. 3.26). The cell clusters are set in a scanty stroma.

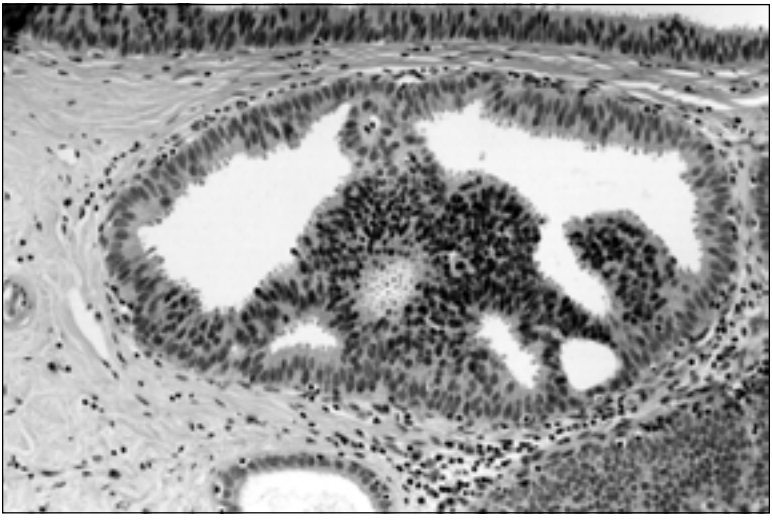

Fig. 3.24. Atypical ductal hyperplasia is seen in the expanded duct at the center of the photomicrograph. The secondary spaces are more rounded and regular, and most of the epithelial cells are more rounded and regular than those in Figure 3.23. There are only very occasional clear myoepithelial cells present.

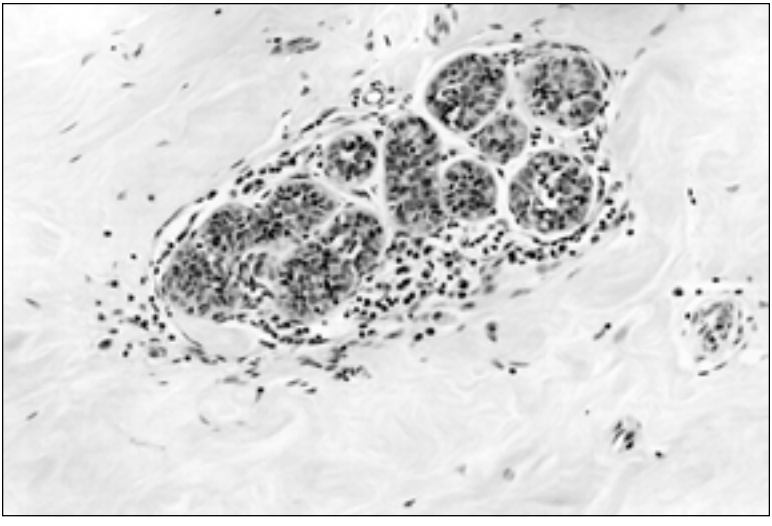

Fig. 3.25. A lobule that is expanded by a uniform population of small epithelial cells that have filled most but not all of the acinar spaces. Occasional acinar lumina are still apparent. These are the features of atypical lobular hyperplasia.

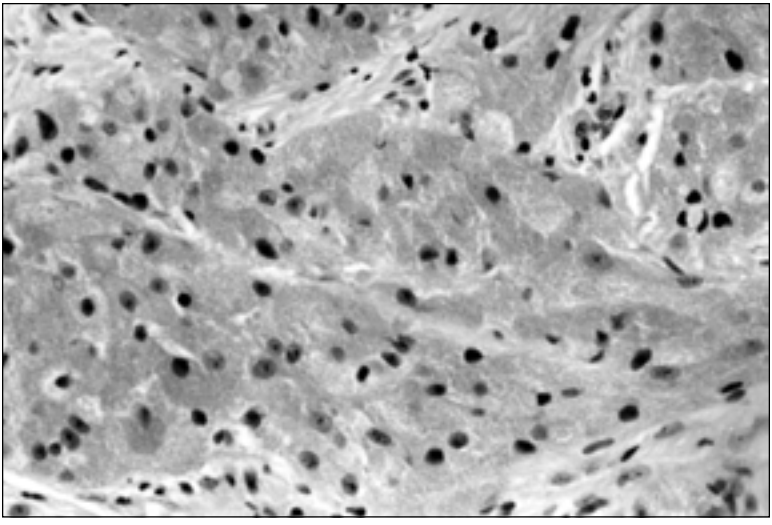

Fig. 3.26. Granular cell tumor. Clusters of cells with characteristic pink, granular cytoplasm and regular, small nuclei.

Management

Wide-local excision is the treatment of choice. Granular cell tumors are invariably benign, but rare cases of malignant granular cell tumors have been reported in the literature.

Fibromatosis

Fibromatosis of the breast is similar to fibromatosis elsewhere in the body (e.g., desmoid tumors).

Clinical Features

Patients can present with a palpable mass that mimics carcinoma and is sometimes associated with skin retraction or fixity to underlying muscle.

Radiology

On mammography, these lesions are indistinguishable from carcinoma.

Pathology

Macroscopic Appearance

These lesions vary in size from 0.7-10 cm. They are poorly circumscribed, vary in color from gray/pink to white and have a fibrous consistency.

Microscopic Appearance

Most lesions are composed of a uniform population of spindle cells that are arranged in interlacing bundles that surround and entrap breast parenchymatous structures. At the periphery, the lesion may have an infiltrative interface with adjacent structures. The cells lack atypical features. Mitotic figures may be present but are uncommon. Collections of lymphocytes are frequently present at the periphery of the lesion.

Management

Wide-local excision is the treatment of choice. Inadequate excision often leads to local recurrence.

Sclerosing Lymphocytic Lobulitis/Diabetic Mastopathy

Sclerosing lymphocytic lobulitis may occur in patients with insulin-dependent diabetes mellitus.

Clinical Features

Patients classically present with a firm to hard, irregular, palpable, breast mass that can be difficult to differentiate from carcinoma.

Radiology

Radiologic features may mimic malignancy.

Mammography

There are a variety of nonspecific appearances, varying from asymmetrical densities to ill-defined mass lesions and distortion.

Ultrasound

Ultrasound reveals areas of distortion with acoustic shadowing.

Pathology

Macroscopic Appearance

The lesions are ill-defined, firm, rubbery, gray-white masses.

Microscopic Appearance

The lesions are characterized by fibrosis and varying degrees of lobulocentric and perivascular lymphoid infiltrates (Fig. 3.27). There is concomitant lobular atrophy of varying degree. In earlier lesions the inflammation is prominent and predominantly lobulocentric, whereas in more long-standing cases there is dense fibrosis, marked lobular atrophy and focal small-lymphoid infiltrates, which are perivascular in location.

Management

If an unequivocal histologic diagnosis has been obtained on core biopsy no further treatment is required.

Granulomatous Lesions of the Breast

Granulomatous lesions of the breast are rare. They can be secondary to systemic conditions (sarcoidosis), infections (mycobacterium, fungal), or reactions to foreign material (silicone, narcotics).

Clinical Features

A detailed history may point in the direction of the diagnosis. Clinical examination usually reveals a palpable, firm mass in the breast.

Radiology

Depending upon underlying etiology, there may be mammographic changes of an ill-defined lesion. Frequently, these are associated with coarse calcification.

Pathology

The pathology of specific granulomatous infections or conditions such as Sarcoidosis or Wegeners granulomatosis is similar to that seen for these conditions in other sites.

Idiopathic granulomatous mastitis and silicone mastitis merit special mention.

Microscopic Appearance

Idiopathic granulomatous mastitis is a granulomatous lesion centered around ducts and lobules. No caseation or noncaseous necrosis is seen and no foreign material or pathogens are present within the lesion. Occasional small microabscesses may be present.

Silicone mastitis has a histologic appearance similar to that of fat necrosis. There are foamy macrophages and occasional multinucleate giant cells arranged in a random fashion, but poorly formed granulomata may be present. The silicone may be apparent as highly refractile, irregular particles both within the phagocytic cells and lying free in the extracellular location (Fig. 3.28).

Management

No active treatment is required once the diagnosis has been established histologically. If in doubt, excision is performed.

Mondor Disease

Mondor disease of the breast is rare and is a superficial thrombophlebitis of the lateral thoracic or superior thoraco-epigastric veins.

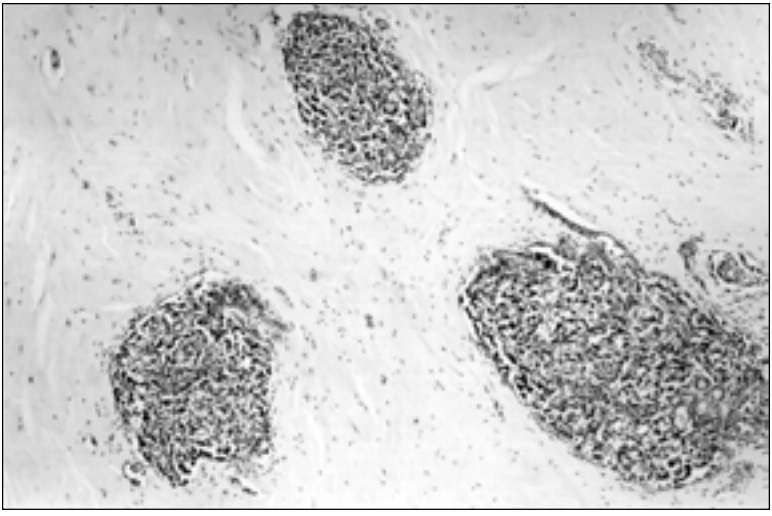

Fig. 3.27. Sclerosing lymphocytic lobulitis. Three lobules are seen in which there is marked acinar atrophy in association with a prominent, well-circumscribed lymphocytic infiltrate. The lobules are separated by uniform acellular fibrous stroma.

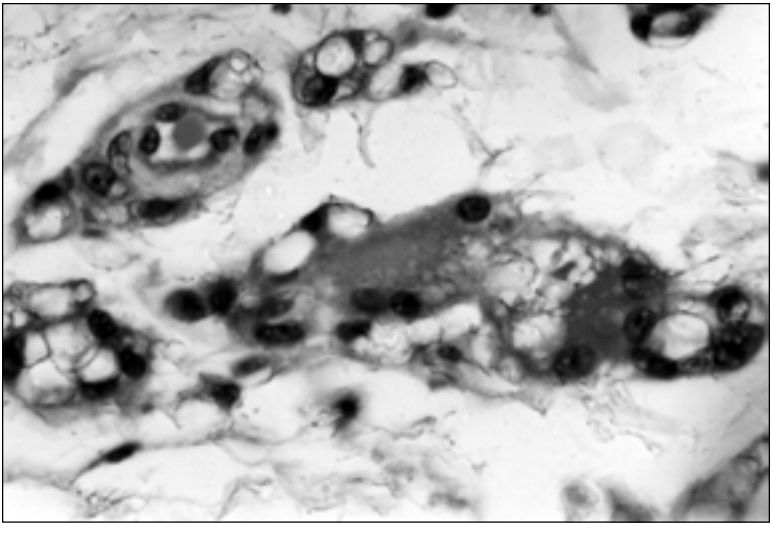

Fig. 3.28. High-power magnification view of a case of silicone mastitis showing highly refractile silica particles that are both present within macrophages and foreign-body giant cells and lying free.

Clinical Features

Patients usually present with a tender subcutaneous cord along the distribution of one or other of these veins, and there may be some dimpling of the overlying skin, particularly on elevation of the arm. It can occur secondary to trauma or excessive physical strain.

Management

Since the condition is self-limiting no intervention is required. Symptomatic relief in the form of topical anti-inflammatory agents may be prescribed.

Gynecomastia

Gynecomastia is a common condition and represents a benign proliferation of glandular tissue of the male breast. Gynecomastia occurs in three different age groups—neonatal, pubertal and elderly. Due to transplacental passage of estrogen, transient stimulation of breast tissue occurs in infancy. Pubertal gynecomastia has a peak incidence in males age 13-14 years and is probably due to an imbalance of estrogen and androgens. Involution generally occurs by 16-17 years. In adult males, gynecomastia increases with advancing age. The degree of gynecomastia is dependent on the hormonal environment, the intensity and duration of stimulation and the sensitivity of breast tissue to hormonal stimulation.[33] There are several pathologic conditions associated with gynecomastia (Table 3.1).

Clinical Features

Patients with gynecomastia present with unilateral or bilateral breast enlargement. There may be associated pain and tenderness. Gynecomastia may also be detected as an incidental finding on physical examination. It may be a source of embarrassment, particularly in young males. Clinical examination will confirm the presence of a firm disc of tissue deep to the nipple and areolar that may be tender. It is usually easy to distinguish gynecomastia from carcinoma of the breast in older men on clinical examination. Associated skin dimpling and nipple retraction with nipple discharge are features suggesting carcinoma. If in doubt, radiologic and histopathologic investigations are mandatory. A thorough history and detailed physical examination of breasts, abdomen and testes is essential. Gynecomastia should be differentiated from pseudogynecomastia in which enlargement of the breast occurs due to fat deposition rather than glandular proliferation.

Pathology

Macroscopic Appearance

The gross appearance is ill-defined. The consistency of the tissue is that of firm breast tissue.

Table 3.1. Pathological conditions associated with gynecomastia

Idiopathic
Drugs (e.g., cimetidine, digoxin, spironolactone, androgens, estrogen agonists)
Alcohol
Cirrhosis
Malnutrition
Primary and secondary hypogonadism
Hyperthyroidism
Renal disease
Testicular tumors
Adrenal tumors

Microscopic Appearance

Classically, there is a ductal and a stromal element. The ducts are enlarged and often flattened and are lined by an insignificant outer myoepithelial layer and an inner, more prominent epithelial layer. The epithelial layer frequently shows mild hyperplasia with luminal tufting or more prominent micropapillary change. The stroma may be loose, myxoid and abundant or acellular and fibrous (Fig. 3.29).

Management

Pubertal gynecomastia does not usually require any treatment since 80% resolve spontaneously. Occasionally, for cosmetic reasons, subcutaneous mastectomy is indicated. Alternatives to excisional surgery include liposuction. Correction of other associated conditions that alter the balance between estrogen and androgens may result in some regression in the early stages. Since the majority of patients improve spontaneously, therapy should be targeted to patients with long-standing gynecomastia. Medical therapy is the first line of treatment in patients with moderate to severe symptoms. Androgens, antiestrogens and aromatase inhibitors have all been tested in patients with gynecomastia. The scientific evidence is in favor of tamoxifen 20 mg daily for 3 months.[34,35] Surgical intervention in the form of subcutaneous mastectomy or liposuction may be necessary for patients in whom other measures have failed.

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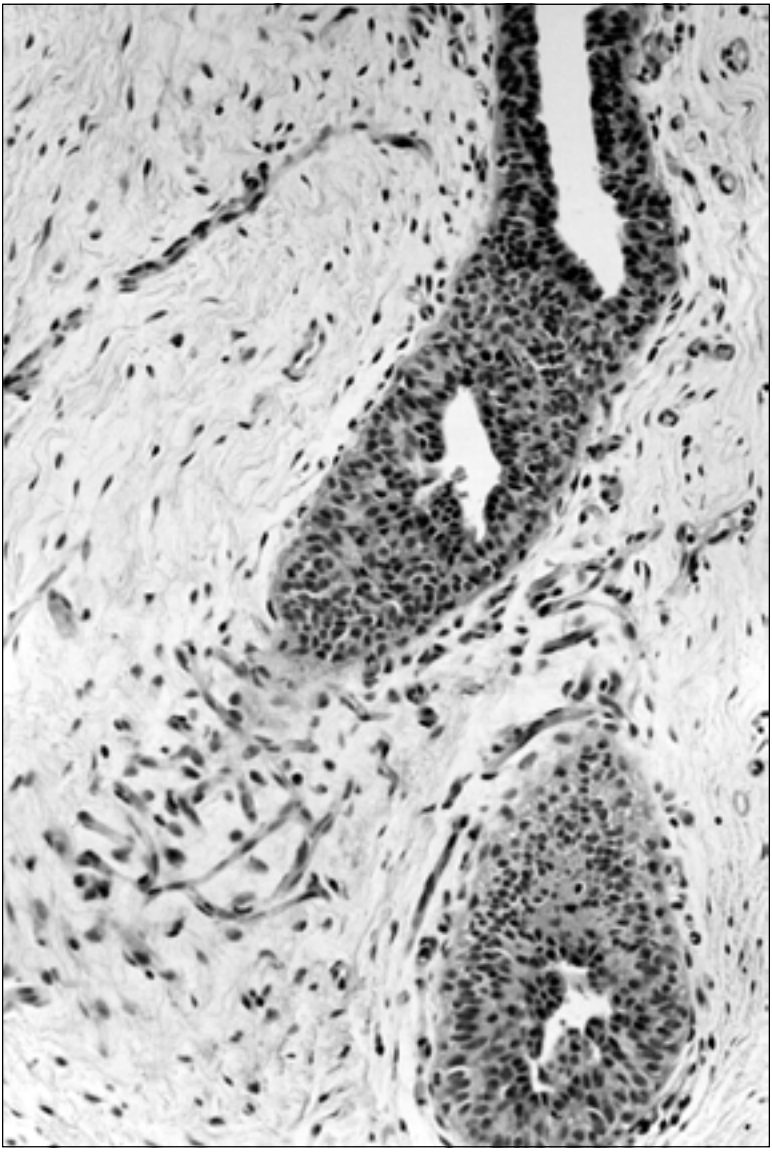

Fig. 3.29. Gynecomastia in which the pale pink stroma is mucoid and vascular and the two ducts present are both lined by hyperplastic ductal epithelium showing luminal tufting.

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CHAPTER 4

Risk Factors, Screening and Prevention

Alexandra S. Heerdt

Each year, over 180,000 females in the United States are diagnosed with breast cancer. Of women living to the age of 90, one in nine will be treated for breast cancer at some point in their lives. These statistics underscore the reality that all women are at risk for developing breast cancer.

Despite these data, it is still important to distinguish certain populations of women who are at higher-than-normal risk for the disease. Defining these populations allows for appropriate screening recommendations to be made. It also helps to determine which patients should be counseled regarding preventive agents. This chapter will serve as a brief outline of risk factors for breast cancer development, the appropriate screening of various populations and the currently available preventive modalities.

Risk Factors

While there are many factors that have been postulated to influence breast cancer risk, only a small number are felt to be significant. Table 4.1 outlines these major risk factors.

Age

Increasing age is associated with an increasing risk of breast cancer. Overwhelmingly, age is the most significant risk factor for breast cancer development. Prior to menopause, the likelihood that a woman will develop breast cancer is relatively low. At menopause, there appears to be a plateau in risk, after which there is again a slow rise in incidence. While it is true that one in nine women will develop breast cancer in their lifetime, it is more helpful to define risk by the actual incidence at a given point in time a woman's life. Table 4.2 summarizes the likelihood that a woman at a particular age will develop breast cancer. While it demonstrates that, even at the age of 80, the risk of breast cancer is not one in nine, it also underscores the fact that breast cancer is much more likely to occur in the postmenopausal years.

Family History

By far, the majority of breast cancer cases are sporadic in nature. Familial or hereditary factors are implicated in the development of only 25% of all breast cancers. Despite this, it is still important to identify the patient who

Breast Diseases, edited by Patrick I. Borgen and Arnold D.K. Hill.

Table 4.1. Major risk factors

Age
Family history
Personal history of benign or malignant disease
Reproductive factors
Environmental exposures

Table 4.2. Risk of breast cancer development at a given age

Age	Incidence
30	1 in 5,900
40	1 in 1,200
50	1 in 590
60	1 in 420
70	1 in 330
80	1 in 290

From Horn JW, Asire AJ, Young JL, et al. SEER Program: cancer incidence and mortality in the United States, 1973. Washington, D.C.: NIH publ. No 85-1837. November 1984

might be at increased risk due to a family history of breast cancer. By documenting the family history of a woman, a physician can determine the magnitude of increased risk that a given patient might experience.

While any family history of breast cancer does increase a woman's risk of future breast cancer development, that increase is often insignificant. If a single first- or second-degree maternal relative of a woman had breast cancer postmenopausally, the absolute increase in breast cancer risk for that woman is negligible. At least one-half of the cases of breast cancer in which family history is documented fall into this category. Table 4.3 illustrates the lifetime risk of breast cancer development when various relatives have a history of breast cancer.

Much more significant in terms of increased risk of breast cancer development is the documented or presumed presence of an inherited susceptibility gene. Approximately 10% of breast cancers develop as a result of a mutation in a gene. Currently, mutations in two genes, *BRCA1* and *BRCA2*, have been identified. Mutations in these two genes are likely to account for approximately 80% of inherited breast cancer cases. This type of mutation is more likely to be present in families in which the breast cancer cases are present in multiple females in multiple generations, are premenopausal and are bilateral. Additionally, a large proportion of families that carry the *BRCA1* mutation, cases of ovarian cancer have also existed. While the clinical scenario associated with these mutations will be discussed in greater detail in another chapter, it is important to be aware of their contribution to risk of breast

Table 4.3. Risk of breast cancer by status of relative's cancer

Relative menopausal status	Risk%
mother, postmenopausal	14
mother, premenopausal	25
mother and sister, postmenopausal	33
sister, premenopausal	25
sister, postmenopausal	14

Claus EB. Genetic epidemiology of breast cancer in younger women. JNCI Monographs 1994; 16:49-53.

cancer. An individual whose mother carries such a mutation has a 50% probability of inheriting that mutation. If a patient carries a mutation, the lifetime risk of breast cancer has been estimated to be anywhere from 60-90%. Furthermore, the likelihood of contralateral disease after an index breast cancer is over 50%.

Personal History

The majority of all breast biopsies are benign. In general, the findings are important only because they provide reassurance for the patient and the physician. The finding of either atypical hyperplasia or lobular carcinoma in situ (LCIS) at biopsy has significant implications, however; women whose biopsies demonstrate either pathologic entity are at increased risk for future development of breast cancer. These two findings are present in approximately 1-5% of breast biopsies, depending on the completeness of the pathologic examination.

Atypical hyperplasia refers to proliferative breast disease in which the appearance of the ductal or lobular epithelium is significantly altered from that of the normal breast epithelium. Several large, retrospective studies have served to define the relative risk of breast cancer in the population of women who have this pathologic finding. Compared to the general population, the presence of atypical hyperplasia in a woman with no family history of breast cancer indicates a relative risk of breast cancer development of approximately 3-4. If there is a family history of breast cancer in a first-degree relative, the relative risk increases to over 8. Perhaps more helpful in counseling women is the absolute risk of breast cancer development over a 20 year period. If atypical hyperplasia is present, a woman has an approximately 15-20% likelihood of developing breast cancer in either breast over that period of time.

Lobular carcinoma in situ in a biopsy specimen also indicates an increased risk of future breast cancer development. Pathologically, this refers to a finding of cytologically malignant cells distending the lobular units. Despite the malignant appearance of these cells, LCIS does not act in a malignant fashion,

neither invading nor metastasizing. While LCIS itself is entirely benign, follow-up studies of patients with this finding demonstrate a risk of between 15-30% for future breast cancer development. As with atypical hyperplasia, the breast in which the LCIS is discovered is not necessarily the breast in which a cancer will develop. One-half of all breast cancers will be identified in the contralateral breast.

A woman's future risk of breast cancer may be altered not only by the findings of a benign breast biopsy but also by a personal history of breast cancer. Once a patient has been treated for a breast cancer, her risk for future breast cancer is significantly increased over that of the general population. Due to the increased use of lumpectomy and radiation therapy for the treatment of early breast cancers, many women continue to be at risk for the development of disease in the same breast in which their initial breast cancer was diagnosed. By 10 years, this risk could be 10% or higher. Additionally, all women who are treated for breast cancer, whether with mastectomy or with breast-conservation therapy, are at risk for the development of a contralateral cancer. Various studies have shown this risk to be between 0.5-1% per year. Thus, by 20 years postdiagnosis of her initial breast cancer, a woman has up to a 20% risk of disease in the opposite breast. Table 4.4 summarizes the risks associated with a woman's biopsy history.

Reproductive Factors

Epidemiologic data clearly demonstrate that reproductive factors influence a woman's risk of breast cancer. There is a slight but consistently evident increase in the incidence of breast cancer in women who have early menses and late menopause. Additionally, an early age at first full-term pregnancy appears to be somewhat protective of breast cancer risk.

The mechanism by which these factors influence breast cancer risk appears to be the cyclical hormonal stimulation of the breast. Continuous, uninterrupted stimulation of the breast tissue on a monthly basis promotes proliferation of breast cells. The greater the number of cycles the breast experiences, the more likely there is to be uncontrolled proliferation of cells and eventual breast cancer cell growth. Any decrease in the absolute number of cycles should theoretically decrease the risk of breast cancer. Likewise, an interruption of the normal cycling should also be protective.

Data regarding natural menopause indicate that women who undergo menopause after the age of 55 have twice the risk of breast cancer of women undergoing menopause before the age of 45. Early oophorectomy (before the age of 50) also appears to have a protective effect on breast cancer risk. Additional studies indicate that a full-term pregnancy by the age of 30 may reduce risk by up to 30 % and that a full-term pregnancy by the age of 20 reduces risk by 50%.

Table 4.4. Relative risks associated with pathologic biopsy findings

Atypical hyperplasia	
- family history (FH)	3-4
+family history (FH)	7-8
LCIS	11

While data regarding endogenous hormonal factors are fairly consistent, the data regarding the role of exogenous estrogens in the promotion of breast cancer risk are somewhat less well established. Studies of oral contraceptives and of hormone replacement therapy (HRT) have yielded conflicting results. It is likely, however, that long-term use of either agent does increase the risk of breast cancer slightly.

Recent studies of HRT and breast cancer risk indicate that women who are currently using HRT are at increased risk for breast cancer development. A meta-analysis of the largest studies, however, suggests that the increased risk is only about 10% and is of questionable statistical significance. Those women who have taken HRT in the past but are not currently using it are not at increased risk. Interestingly, multiple studies have now shown that the risk of death from breast cancer is lower in women diagnosed while taking hormonal therapy. It is unclear what biologic event is responsible for this finding.

In the past, almost every study investigating oral contraceptive use and breast cancer risk concluded that there was a significant increase in risk associated with their use. The majority of recent studies regarding oral contraceptive use and breast cancer risk, however, have shown that their use has little impact upon breast cancer incidence rates. Even in women who have used oral contraceptives for extended periods of time (greater than 10 years), there is only a minimal, nonsignificant increase in breast cancer cases. This increase is seen most commonly in the group of women who begin using oral contraceptives at a young age (<20 years). Mortality from breast cancer is not affected by the use of oral contraceptives, either at the time of diagnosis or prior to diagnosis. Furthermore, in studies evaluating risk of breast cancer and either oral contraceptive or HRT use, the presence of a family history of breast cancer does not appear to increase the risk of breast cancer further.

Radiation Exposure

Significant radiation exposure at certain times in a woman's life has been shown to increase the risk of subsequent breast cancer. The initial studies relating to this risk were performed after the atomic bomb was used in Hiroshima and Nagasaki, Japan. Subsequent to the bombings, survivors who were in adolescence or early adulthood at the time of the bombing were

noted to have an increased risk of breast cancer. In contrast, women over the age of 40 at exposure had a decrease in the incidence of subsequent breast cancer. These findings suggest that breast tissue exposed to radiation during particularly active periods of growth is most sensitive to radiation exposure. The decreased incidence in women nearing menopause most likely occurred because of an induction of premature menopause in this population.

More recent studies of radiation exposure and subsequent breast cancer risk have corroborated the early findings. In a study of patients undergoing fluoroscopic examinations for tuberculosis treatment during adolescence, the risk of breast cancer was double that of the general population. The statistics for increased risk in women having undergone mantle radiation therapy for the treatment of lymphoma during adolescence and early adulthood are even more staggering. In one review performed at Stanford University, the relative risk of breast cancer development was 136 for women irradiated prior to the age of 15. Even women who underwent radiation between the ages of 20 and 30 had relative risks of breast cancer ranging from 7-19. Thus, all women who receive radiation therapy during adolescence and early adulthood should be considered to carry an increase risk for breast cancer.

Diet

Breast cancer occurs with a greater frequency in countries in which the intake of dietary fat is higher. Additionally, women who move from environments in which there is a low dietary fat consumption to areas with higher dietary fat consumption eventually increase their risk for breast cancer development. These findings have led to the assumption that dietary fat intake must be a significant risk factor for the development of breast cancer.

Despite these findings, case-control studies in which dietary habits of women with breast cancer are compared to those of women without a history of breast cancer have not been able to show a direct relationship between dietary fat consumption and the subsequent risk of breast cancer. Further studies evaluating this relationship are ongoing. It appears that, if dietary fat contributes in any way to breast cancer risk, it is likely to be through its role in altering hormonal regulation.

The relationship of alcohol intake to subsequent risk of breast cancer is less controversial. Almost every study that has investigated this relationship has demonstrated a dose-related increase in breast cancer risk. Even in women drinking approximately one drink per day, the risk of breast cancer is slightly elevated when compared to that of nondrinkers. With increasing alcohol intake (two to five drinks per day), the risk of breast cancer may double.

The effect of antioxidants and vitamins on breast cancer risk is currently of considerable interest. While it is believed that cruciferous vegetables and fruits may play a role in protection from breast cancer risk, studies investigating

high-dose vitamin and antioxidant intake have not demonstrated significant reductions in breast cancer risk with their use. Thus, the appropriate role for these agents continues to be controversial.

Screening

The ultimate goal of widespread screening for breast cancer is a reduction in mortality from the disease. Toward this end, appropriate screening for breast cancer involves both the physician and the patient. In general, the approach should include a clinical exam by a healthcare provider, monthly breast self-examinations by the patient, and routine screening mammography. Schedules for both clinician examinations and mammography will vary depending on the risk of an individual woman.

The data regarding the impact of breast self-examination on mortality from breast cancer are inconsistent. While many retrospective studies have indicated earlier stage of diagnosis and a reduction in the risk of mortality in women who perform routine monthly self-examinations, the only randomized trial addressing breast self-examination has not been able to demonstrate an impact upon stage of diagnosis. Because of these contradictory findings, further research is warranted. It is, however, still appropriate for women in all risk categories to practice self-examination. Not only does this have a potential impact upon stage at diagnosis, it allows the woman to be involved in her own medical care.

In addition to practicing monthly breast self-examination, all women over the age of 20 should have a clinical breast examination by a healthcare provider at least yearly. In most instances, women who have a normal risk for breast cancer development can be seen by their gynecologist or internist for this examination. Some women with normal risk may be referred to a breast specialist, however, simply because of difficulty with examinations. This occurs almost exclusively in women who have extremely dense, fibrocystic breast tissue.

Women who are at moderately increased risk of breast cancer (less than two times the normal risk of breast cancer development) may benefit from seeing a clinician more often. While no data exist to indicate that more frequent examinations will have a significant impact upon breast cancer mortality, studies have documented the ability of trained professionals to detect breast lesions and subtle skin and nipple changes at an earlier point than those who do not specialize in this area.

A family history consistent with a hereditary breast cancer syndrome, the presence of a *BRCA1* or *BRCA2* mutation or the presence of atypical hyperplasia or LCIS places a woman in the highest risk category. In this population, consideration of more frequent examinations should always be entertained. Often, these women will be examined by a healthcare provider two to four times per year. These examinations allow for the detection of

early lesions that may present between mammographic studies. It is especially useful in the very young patient, in whom mammographic screening is sometimes less helpful due to the density of breast tissue.

Mammography continues to be the most significant component of breast cancer screening for the majority of the population. Every study that has evaluated this modality has demonstrated a reduction in mortality from breast cancer with yearly screening exams in women over the age of 50. Although it is somewhat more difficult to demonstrate a statistically significant impact upon breast cancer mortality when routine mammography is employed in women between the ages of 40 and 50, there is a trend toward a decrease in mortality in this age group. Therefore, women in all risk categories should begin yearly mammographic screening at the age of 40.

For women at increased risk for breast cancer development, it may be appropriate to begin mammographic screening at an earlier age. A study performed at Memorial Sloan-Kettering Cancer Center demonstrated a downward shift of 8-10 years in the age of diagnosis of breast cancers in consecutive generations of women in the same family. While earlier diagnosis had a small impact upon this, it was not the only factor. Thus, it is appropriate for women with family histories of breast cancer to begin mammographic screening 10 years earlier than the age at which the youngest family member developed breast cancer or at the age of 25, whichever is later. Once screening has been initiated, it is appropriate to perform exams yearly unless a woman is pregnant or breast-feeding.

Newer imaging techniques for screening are currently being studied in the high-risk population. The hope is that they will provide additional information that mammography is currently unable to provide. Whether ultrasound or magnetic resonance imaging on a routine basis will be beneficial in this population remains to be determined.

Prevention

The screening that was discussed in the previous section is actually considered a form of prevention. By definition, secondary prevention refers to any modality that leads to the earlier detection of a breast cancer, thereby resulting in a potential decrease in mortality from the disease. Both breast examinations and screening mammography fall into this category.

In addition to current efforts at secondary prevention, primary prevention of breast cancer (elimination of or significant delay in clinical appearance of disease) remains an important goal. Currently, the two methods of primary prevention that exist are prophylactic surgery and chemoprevention.

Prophylactic bilateral mastectomies may be considered in women with the diagnosis of lobular carcinoma in situ, in women with a significant family history of breast cancer and in women who are known carriers of a genetic mutation. Data regarding the actual numbers of patients who undergo this

procedure are lacking, however, over 1000 women responded to a national inquiry concerning prophylactic mastectomy. Based on the tremendous response to a single advertisement in one publication, it is likely that prophylactic mastectomies are performed more commonly than is thought.

In order to validate this method as appropriate for primary prevention, it is important to know the rate of subsequent breast cancer development after such a procedure. In an analysis of these patients by Memorial Sloan-Kettering Cancer Center, the incidence of subsequent breast cancer was approximately 3%. Additional data from a single-institution study at the Mayo Clinic suggest that subsequent breast cancers may occur in 10% of patients. In that study, all of the cancers developed in women who had undergone subcutaneous mastectomies rather than total mastectomies. Thus, it appears that, if the goal of prophylactic surgery is to reduce the risk of subsequent cancer by the greatest amount, total mastectomies are more appropriate than subcutaneous mastectomies.

Despite the risk reduction associated with bilateral total mastectomy, for obvious reasons it will not be the preventive option of choice in most instances. Chemoprevention should therefore be considered for all women with significant risk for future breast cancer development. Currently, the only FDA-approved medication for prevention of breast cancer is tamoxifen. Tamoxifen acts as an antiestrogen and has been used for many years for the treatment of both metastatic breast cancers and early-stage breast cancers. As patients with breast cancer taking tamoxifen had significantly reduced numbers of contralateral breast cancers, it was felt to be an ideal agent to use in trials of chemoprevention. The largest trial to determine tamoxifin's role in chemoprevention was performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP). In this randomized, double-blind trial, women with a projected risk of breast cancer of greater than 1.66% over a 5-year period received either tamoxifen or a placebo for a period of 5 years. When an independent reviewing agency verified a 50% reduction in both invasive and noninvasive breast cancer cases in the population taking tamoxifen, the trial results were unblinded earlier than expected. Shortly thereafter, its use for chemoprevention was approved.

Raloxifene, an agent considered to be a selective estrogen-receptor modulator, will soon be investigated in an attempt to define its role in breast cancer chemoprevention. In studies in which raloxifene was used for treatment of osteoporosis, a secondary finding was the reduction of breast cancer risk of 50-70% in the population taking the medication. While the results were promising, the women in those trials were at fairly low risk of breast cancer development. A randomized, double-blind trial to compare raloxifene with tamoxifen in a population of postmenopausal women at increased risk for breast cancer development is currently being organized. This medication may hold promise for chemoprevention in the future.

Conclusion

Screening for breast cancer is clearly indicated for all women at the appropriate age. Determining a woman's unique risk factors will help to determine both the age at which that screening should begin and also the intensity of that screening. It will also help to identify those women who need to be counseled regarding options for prevention of breast cancer. By correctly identifying high-risk populations and then applying appropriate screening schedules and chemopreventive agents, the hope is that many cases of breast cancers will be averted completely and that those that still occur will be found at the earliest stages.

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CHAPTER 5

Pathology, Prognosis and Staging of Breast Cancer

Laura Weldon Hoque

Pathology

Breast cancer arises in the terminal duct-lobular unit. The most common type of breast malignancy is invasive ductal carcinoma not otherwise specified (NOS), which comprises about 85% of breast cancers. Carcinoma that is confined to the terminal duct-lobular unit and the associated lobules and ducts is known as in situ carcinoma. Lesions of this type are completely local and are therefore confined by the basement membrane. Abnormal proliferative lesions that do not yet qualify as carcinoma in situ are called atypical hyperplasia. It is generally accepted that hyperplasias progress to carcinoma in situ, which progresses to invasive carcinoma. The exact sequence and timing is not fully understood.

Atypical Hyperplasia

Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are proliferative lesions of the breast that are abnormal but do not possess all of the qualities of carcinoma in situ. In 1985, Dupont and Page studied the eventual risk of developing breast cancer once a diagnosis of atypical hyperplasia had been rendered. The relative risk of developing breast cancer was four times that of the general population. If the patient also had a family history of breast cancer, her relative risk rose to nine times that of the general population. A landmark study by Rosai in 1991 compared the readings of five experienced breast pathologists of proliferative breast lesions. None of the pathologists agreed on a diagnosis for any of the specimens, and the range of diagnoses spanned from hyperplasia to carcinoma in situ. The diagnosis of atypical hyperplasia should correlate with the clinical presentation, and these patients should be followed closely for the possible development of breast cancer.

Carcinoma In Situ

Lobular carcinoma in situ (LCIS) is a proliferative lesion confined to the lobules and/or the terminal duct-lobular units of the breast. It lacks clinical

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or mammographic signs and is usually an incidental pathologic finding. Lobular carcinoma in situ is considered a marker for increased risk of breast cancer and is multicentric. Once diagnosed, it is not treated surgically and negative margins on a biopsy are not needed. The risk of developing breast cancer is distributed equally between the two breasts and is approximately 1% per year (relative risk [RR] is approximately 9). The most common histology in subsequent cancers is infiltrating ductal carcinoma. There are three treatment strategies one can offer these women. The first is close follow-up by a breast specialist, frequent breast exams and yearly mammograms.

There are two other options for the prevention of breast cancer in the high-risk patient. The first comes from the recent NSABP-P1 trial, which concluded that when tamoxifen was administered for 5 years to women at high risk (strong family history, ADH/ALH or LCIS) their risk of breast cancer was cut in half over the placebo group. Another alternative is bilateral prophylactic mastectomy, which reduces risk by about 90%. Physician and patient must be aware that neither of these prevention strategies lowers the risk to zero; therefore, these patients must continue to be followed closely.

Ductal carcinoma in situ (DCIS) represents the abnormal proliferation of mammary epithelium within the duct. Ductal carcinoma in situ is a heterogeneous group of lesions varying in their malignant potential. The most common types include comedo (with necrosis), cribriform, micropapillary, papillary and solid. Ductal carcinoma in situ is considered a precursor to invasive ductal carcinoma and as such is distinctly different from LCIS. The most common presentation is either abnormal microcalcifications on a mammogram or a mammographic mass. The recurrences usually occur in the ipsilateral breast at or near the prior excision. Treatment options include excision (with negative margins), excision with radiation or mastectomy. Lymph nodes are usually not evaluated except in cases of extensive DCIS, in which microinvasion is more common. The NSABP B-17 trial compared excision alone to excision with irradiation; the radiated group experienced a 75% reduction in the risk of an invasive recurrence. Treatment options must be individualized based on the histologic subtype, age of the patient, size of the breast or the presence of residual calcifications. Randomized trials (NSABP B-24) assessing the efficacy of tamoxifen in reducing the local recurrence rates are ongoing.

Invasive Mammary Carcinoma

Invasive ductal carcinoma comprises about 75% of all breast cancers and is often referred to as invasive ductal carcinoma not otherwise specified (NOS). This type of breast cancer usually forms a solid mass and is easily measured on bisection of the tumor (the largest diameter is taken). There have been many studies correlating the size of the tumor and rising incidence of axillary nodal metastases along with a decreasing survival. Breast carcinomas are graded based

on their level of differentiation. Nuclear grading examines the cytologic features of the nuclei and compares them to the nuclei of normal epithelial cells in the breast. There are three categories for nuclear grading: well differentiated (grade 3), intermediate (grade 2), and poorly differentiated (grade 1). Histologic grading measures the amount of tubule formation, nuclear hyperchromasia and the mitotic rate of the tumor. This is also classified into three categories and is reported in reverse sequence from nuclear grade: well differentiated (grade I), intermediate (grade II) and poorly differentiated (grade III).

Grading of tumors is generally considered important for Stage I tumors only. The prognosis of node-positive tumors is determined by the number of positive nodes and not by tumor characteristics. It has been shown in a number of studies that nuclear and histologic grade are predictors of prognosis in Stage I (and possibly Stage II) cancers. Other poor-prognostic indicators are lymphatic and/or vascular tumor emboli. In Rosen's long-term study of T1N0M0 cancers, those with lymphatic tumor emboli had a 33% chance of dying of disease at 10 years versus a l0% chance in those with no lymphatic tumor emboli. There have been a number of studies correlating poorly differentiated tumors, those with lymphatic emboli or those with vascular space invasion with an increased rate of breast tumor recurrence and eventual death from disease.

Special Types of Breast Carcinomas

The special types of breast cancer have been described by many pathologists, who vary in their estimation of the exact percentages these tumors encompass. Cancers of the breast were initially described as ductal (arising from the epithelial lining of the duct) or lobular (arising from the epithelial lining of the lobule.) This proved to be too broad a categorization because only 10% of breast cancers were found to be lobular; therefore, the ductal terminology was too broad. Out of this arose the characterization of the special types of breast cancers, which, depending on the series, comprise 20-30% of all breast cancers. The variation in the percentage of breast cancers these represent is mainly a problem in diagnosing and categorizing these tumors appropriately. It is generally agreed upon that at least 90% of the tumor needs to contain the subtype to be called pure. This obviously allows a considerable amount of judgement on the part of the pathologist, which probably accounts for the variation in survival by each study. In general, a diagnosis of a special type carries a better prognosis than NOS-type ductal carcinoma and the various special types include lobular, tubular, medullary and mucinous, metaplastic, apocrine and adenoid cystic.

Invasive Lobular Carcinoma (ILC)

Invasive lobular carcinoma (ILC) is a malignant transformation of the lobular epithelium of the breast that has invaded into the stroma of the breast. There is a classic desmoplastic stromal reaction and a linear arrangement of tumor cells (known as "Indian filing"). Invasive lobular carcinoma has a propensity to circumferential growth around ducts and adjacent lobules (targetoid growth). In its pure form, it accounts for no more than 5% of all breast cancers. Clinically, it can present as a mass or merely a vague thickening, usually in the upper-outer quadrant. Mammography frequently underestimates the size of the lesions. Most ILC tumors are visible on mammography, but those cancers that are not mammographically apparent are more likely to be ILC.

Synchronous Bilateral Cancers

The incidence of synchronous bilateral cancers has been reported to be anywhere from 6-30%, and subsequent synchronous contralateral cancers have been reported in another 10%. Much has been written on the value of a contralateral "mirror image" breast biopsy at the time of definitive ipsilateral surgery. It is an area of controversy, but most agree that there will be a yield of about 10% in those with an incident of ILC. Although ILC is also more likely to be multicentric, it can be treated with breast-conservation therapy if negative margins can be obtained. Patterns of dissemination are distinctly different from NOS and include more common hematogenous spread, spread to the ovaries and uterus and metastases to the meninges and peritoneum. Prognosis varies among reports but appears to be very similar to NOS, stage for stage.

Tubular Carcinoma

Tubular carcinoma is a variant of invasive ductal carcinoma and is characterized by a proliferation of tubules that closely resemble normal breast ducts. Pure tubular carcinomas represent between 2-18% of all breast carcinomas. There is no universal consensus on the definition, and thus the reported frequency varies. The prognosis of pure tubular carcinomas is generally favorable and is dependent on the tumor having greater than 75% of tubular elements. In a pure tubular cancer, excision with adequate margins is the only treatment needed. Axillary dissection is not indicated for pure tubular cancers as their rate of lymph node metastases is very low. Overall survival is excellent. Medullary carcinoma is a histologically high-grade tumor of the breast. Tumors are usually large, unifocal and occur in younger women. The average size is about 2-3 cm and has been often confused with a fibroadenoma. Lymph nodes are frequently enlarged, even in the absence of lymph node metastases. Overall, the survival from medullary carcinoma

is much improved over nonmedullary breast cancer. Ten year survival for medullary carcinoma is over 90%, even in the presence of axillary lymph node metastases.

Pure Mucinous Carcinoma

Pure mucinous carcinoma is a low-grade form of mammary carcinoma, constituting 1-4% of breast cancers. These tumors are most common in the elderly and are of average size. They are usually estrogen-receptor positive and have circumscribed margins. The distinguishing feature of these tumors is the extracellular mucinous secretions mixed with invasive duct carcinoma. Pure mucinous tumors have the best prognosis. Mucinous carcinoma mixed with NOS is called NOS with mucinous features. This variant of invasive ductal carcinoma carries a more favorable prognosis than a pure NOS tumor, but the best survival is in patients with pure mucinous cancers. This subgroup of patients has a greater than 90% 10 year survival.

Papillary Carcinoma

Papillary carcinoma of the breast occurs in a noninvasive and invasive form, representing no more than 1-2% of all breast cancers. There is considerable variation in the terminology regarding papillary carcinoma of the breast. The World Health Organization Histological Classification of Breast Tumors defines it as a "rare carcinoma whose invasive pattern is predominantly in the form of papillary structures." They may be either intracystic or noncystic, but either diagnosis is associated with nipple discharge in about one-third of patients. Patients with papillary carcinomas tend to be older, with an average age at onset of 65. Overall survival, stage for stage, is better than for NOS-type cancers. The incidence of lymph node metastases ranges in the literature from 20-35% depending on the size of the tumor.

Metaplastic Carcinoma

Metaplastic carcinoma is a variant of adenocarcinoma of the breast in which the epithelial component undergoes changes to a nonglandular epithelium. There is considerable variation in the percentage of cancers with this classification because the amount of metaplasia required for this diagnosis is not uniformly agreed upon. The exact etiology of the metaplastic change is not well understood either. The subtypes include squamous or pseudosarcomatous. The clinical presentation and gross pathology does not differ significantly from other cancers of the breast. Treatment in the literature is predominantly by mastectomy, usually with an axillary lymph node dissection. Overall, metaplastic carcinoma does not have an especially different prognosis from other breast cancers. When there is a predominance of spindle-cell components or sarcomatous elements, the prognosis may be poor.

Squamous Carcinoma

Squamous carcinoma of the breast is an extremely uncommon breast neoplasm. The hallmark of this lesion is keratinizing epithelium. This is present in both pure squamous carcinoma of the breast and in the metaplastic variant of adenocarcinoma in which some of the glandular epithelium has undergone metaplasia to squamous epithelium. The diagnosis of a breast primary can only be established after excluding an extramammary site as the primary. Metastatic squamous carcinoma to the breast has been reported from a variety of primaries including skin, lung, cervix, bladder and esophagus. Histologically, these lesions are often cystic, although they can have a solid pattern of growth. The diagnosis is best confirmed using immunohistochemical stains for keratin. Stage for stage, these lesions are similar to invasive ductal histology of the NOS variety.

Secretory Carcinoma

Secretory carcinoma is a very unusual subtype of breast carcinoma, having been first described in 1966 and with only a handful of reports in the literature. It usually presents as a small well-circumscribed mass, most often under 3 cm. Histologically, one sees a papillary growth pattern and abundant secretions in both the intra- and extracellular spaces. Most of the cases in the literature are in women, and it is described in women of all ages, although it was first described in children. The treatment has traditionally been modified radical mastectomy, although in children, the preferred treatment should be a wide excision and possible axillary lymph node dissection. The role of postexcision radiotherapy has not been fully evaluated and should be individualized. The incidence of axillary lymph node metastases is under 20%; and their prognosis is favorable.

Apocrine Carcinoma

Apocrine carcinoma is a variant of invasive duct carcinoma with apocrine differentiation in a significant portion of the tumor. These carcinomas represent between 1% and 4% of all breast carcinomas and do not have a prognosis that differs appreciably from conventional forms of invasive duct carcinoma. In prior reports, these have been grouped with "sweat-gland carcinoma." This large subtitle is considered too broad to have any prognostic significance and the terminology is not used today.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is a very unusual breast cancer, representing less than 0.1% of all mammary carcinomas. Histologically, it is identical to those tumors with the same name originating in the salivary glands. It spawns considerable interest because of its relatively favorable prognosis. Rarely does this lesion have lymph node metastases (most patients have been treated with mastectomy).

Inflammatory Carcinoma

Inflammatory carcinoma, a rare variant of breast cancer, represents less than 5% of all cases and is commonly misdiagnosed. It is one of the most aggressive subtypes and implies a dismal prognosis. This cancer is characterized by diffuse edema and brawny erythema of the skin, with or without an underlying breast mass. If there is a mass, it is often a large central, indiscreet area of thickening. The histopathology of the underlying cancer is most likely to be infiltrating ductal but may be of another subtype. The pathognomic feature of this disease is "dermal lymphatic invasion" in a skin biopsy; however, this is not necessary for the diagnosis. By definition, an inflammatory breast cancer is a T4 tumor and falls into the classification of a Stage IIIB breast cancer. One-quarter to one-half of all patients present with distant metastases (compared to 5% in noninflammatory breast cancer), and almost all have axillary nodal involvement. It is more likely than noninflammatory breast cancer to have *HER2* overexpression and more likely to be ER negative. Combined modality treatment (induction multidrug chemotherapy, radiation and surgery) results in a 5 year survival of 40%, compared with 25% for surgery or radiation therapy alone.

Sarcomas and Lymphomas of the Breast

Sarcomas of the breast represent less than 1% of all breast tumors. These tumors are histologically comparable to sarcomas from other parts of the body and are specifically nonepithelial tumors. The most frequently diagnosed tumors include fibrosarcoma, desmoid tumors, malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, osteogenic sarcoma, angiosarcoma (including angiosarcoma of the breast, postmastectomy angiosarcoma and angiosarcoma after breast-conservation surgery) and cystosarcoma phyllodes. Treatment includes a wide excision to obtain negative margins (a total mastectomy, if needed to achieve negative margins) and no axillary lymph node dissection. In general, these tumors are not sensitive to cytotoxic chemotherapy and radiation therapy is used for recurrences. Their prognosis is dependent on cell density, mitotic activity, differentiation and degree of cellular pleomorphism.

Mammary Angiosarcoma

Mammary angiosarcoma is an especially aggressive sarcoma; however, it accounts for less than 10% of sarcomas of the breast. It usually presents with a painless mass in the breast with a bluish discoloration of the skin. It is a proliferation of endothelial cells that form an anastomosing array of vascular channels. Treatment consists of obtaining negative margins (usually requiring a total mastectomy) and overall survival at 5 years is about 30%.

Stewart-Treves Syndrome

Stewart-Treves syndrome is an angiosarcoma of the ipsilateral upper extremity, occurring in the setting of chronic postmastectomy lymphedema. The average time of onset is 10 years postmastectomy and has the appearance of small bruises on the arm. Histologically, these are the same tumors that arise de novo in the breast and the same as those seen postradiation. The treatment is a four-quarter amputation, which results in a 5 year survival of 10%.

Angiosarcoma

Angiosarcoma after breast-conservation therapy develops an average of 6 years postradiation and is similar to de novo angiosarcoma of the breast. Treatment should include a total mastectomy; however, the overall prognosis is very poor, most women dying of distant disease.

Phyllodes Tumors

Phyllodes tumors (cystosarcoma phyllodes) is fibroepithelial tumor of the breast that occurs in both a benign and malignant form. It represents less than 1% of all breast tumors and occurs in a younger population than breast cancer (mean age 45). It is usually a solitary, large mass of the breast that is visible on mammography. Prognostic features include tumor size, stromal cellularity, mitotic activity, presence of necrosis and margin status. Treatment is wide excision to obtain negative margins (total mastectomy, if negative margins cannot be achieved otherwise) and prognosis is generally good. Five year survival for malignant tumors is about 80% and for benign above 95%.

Primary Breast Lymphoma

Primary breast lymphoma is very rare. These usually present with a large painless mass (average 4 cm) and most have axillary nodal involvement. Histopathology is described as a uniform population of malignant lymphoid cells infiltrating the mammary lobule. Treatment should include a modified radical mastectomy with chemotherapy for systemic or regional disease (those agents used in non-Hodgkin's lymphomas). Overall 5 year survival is 74%.

Metastases to the Breast

Metastatic tumors to the breast usually present as well-circumscribed, superficial masses and are usually visible on mammogram. The most common primaries are the contralateral breast, leukemia, melanoma, lymphoma, lung cancers (oat-cell carcinomas), ovarian cancer, intestinal carcinoids, thyroid cancers, renal cancer, cervical cancer, bladder cancer and various intra-abdominal malignancies. An infrequent breast metastasis has been seen in patients treated for neuroblastomas in childhood. In men who died from prostate cancer, metastases to the breast have been found in up to 25% at autopsy. Clinically, it is described infrequently. Since one of the treatments

for prostate cancer is estrogen therapy, when one sees a breast mass in a man with a history of prostate cancer, an excisional biopsy is warranted. When faced with a new breast mass in a patient previously diagnosed with another neoplasm, it is essential that the pathologist have both the clinical information and slides from the prior tumor.

There should be a relatively high suspicion for metastatic disease when there are multiple masses, no associated intraductal component, no benign proliferative changes in the surrounding breast tissue and a sharp transition from tumor to breast parenchyma.

Prognosis is poor overall, with a mean survival of less than 1 year. Therefore, treatment should be excisional biopsy only and treatment of the primary tumor.

Male Breast Cancer

The pathology of male breast cancer is predominantly ductal. The normal male breast is devoid of lobules; however, in patients with Kleinfelter's syndrome or other cases with excessive circulating estrogen, lobules can exist. Eighty-five percent of cases are invasive ductal, with the remainder being ductal carcinoma in situ. Paget's disease can also occur in males. Male breast cancer is staged with the same system as female breast cancer and, stage for stage, carries the same prognosis.

Pathologic Examination of Breast Specimens

The pathologist should receive the specimen from the surgeon as quickly as possible. Excisional biopsies should be oriented in the operating room by the operating surgeon. Our convention is to use a short stitch on the superior aspect of the biopsy and a long stitch on the lateral aspect (S-S, L-L). If a biopsy cavity is being excised for positive margins and the cavity is entered during the procedure, the edges of the biopsy cavity should be reapproximated with an invisible suture so that, during the inking, none of the ink enters the inside of the cavity. Masses found at surgery should not be incised by the surgeon and should be sent to pathology fresh for inked margins. After the margins are inked, the specimen is fixed in formalin and then embedded in paraffin wax. Mastectomy specimens should also be oriented with a suture on the axillary tail. When axillary dissections are performed, each level that is dissected needs to be marked with a separate suture or axillary tags indicating the levels.

Routine processing of a specimen should report on the presence of invasive cancer, carcinoma in situ and the size of each. Margin status also must be reported, specifically if there is invasive cancer or carcinoma in situ at or near a margin. Other proliferative lesions should be noted as well, and estrogen and progesterone receptors should also be commented on. Nodal status should be reported as the number of nodes positive/number of nodes excised (for each level).

Staging of Breast Cancer

Once patients have been diagnosed with breast cancer, they must be staged. Accurate staging of patients with breast cancer has two main objectives: it allows appropriate treatment and it determines prognosis. In addition, it allows for standardization of treatment and results. Clinical staging is based on all known information prior to any treatment and is used to select patients for therapy. Pathologic staging is inclusive of the surgical specimen and axillary contents and is best used to estimate prognosis.

There are five stages in the current version of the TNM staging system. This system is detailed and can be cumbersome; however, it provides the most detailed information about prognosis that we have.

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
  Intraductal carcinoma, lobular carcinoma in situ, Paget's disease with no tumor
- Tl Tumor dimension less than or equal to 2 cm
  - Tlmic Microinvasion less than or equal to 1 mm
  - Tla Tumor greater than 1 mm and less than or equal to 5 mm
  - Tlb Tumor greater than 5 mm and less than or equal to 1 cm
  - Tlc Tumor greater than 1 cm and less than or equal to 2 cm
- T2 Tumor dimension greater than 2 cm and less than or equal to 5 cm
- T3 Tumor dimension greater than 5 cm
- T4 Any size tumor
  - T4a Extension to chest wall
  - T4b Edema (peau d'orange), ulceration of the skin or satellite skin nodules
  - T4c Both T4a and T4b
  - T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastases
- Nl Metastases to ipsilateral axillary lymph nodes, movable
- N2 Metastases to ipsilateral axillary lymph nodes fixed to one another or other structures
- N3 Metastases to ipsilateral internal mammary lymph nodes

Pathologic Lymph Node Classification (PN)

- PNX Regional lymph nodes cannot be assessed
- PN0 No regional lymph node metastases

PNl Metastases to ipsilateral axillary lymph nodes, movable
- PNla micrometastases (less than or equal to 2 mm)
- PNlb metastases larger than 2 mm
  - PNlbi 1-3 lymph nodes positive for tumor (less than 2 cm)
  - PNlbii greater than 4 lymph nodes positive for tumor (less than 2 cm)
  - PNlbiii extranodal extension (less than 2 cm)
  - PNlbiv metastases in a lymph node greater than 2 cm

PN2 Fixed ipsilateral axillary lymph nodes with metastases
PN3 Metastases to ipsilateral internal mammary lymph nodes

Distant Metastases (M)

MX Distant metastases cannot be assessed
M0 No distant metastasis
Ml Distant metastasis present (includes ipsilateral supraclavicular lymph nodes)

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Extent of Disease

There is a very low incidence of metastatic disease in patients with Stage I breast cancer. It is our practice in Stage 0 and I cancers to limit the extent of disease workup to a physical exam, liver-function tests, blood counts and a chest x-ray. In patients with clinical Stage II or III, the above is performed along with a chest/abdominal and pelvic computed tomography (CT) and a bone scan. Nonspecific tumor markers are not used for the workup of the patient with breast cancer.

Prognosis

In summary, Stage 0 cancers are in situ only and are curable in 99% of cases with surgery alone. Stage I cancers are node-negative cancers under 2 cm in greatest dimension. TlA or TlB tumors are treated by local measures only, as these patients enjoy a 20 year survival of 90%. Node-negative TlC

patients have a decreased 20 year survival to about 80% and are generally offered multidrug chemotherapy. Stage II breast cancer is divided into Stage IIA (tumors less than 2 cm with axillary nodal involvement or a node-negative patient with a T2 tumor) and Stage IIB (either a T2 tumor with positive axillary nodes or a node-negative T3 tumor.) Ten year survival for all Stage II cancers is about 60%; multidrug chemotherapy is routinely given as well as postmastectomy radiation to selected patients. Stage IIIA encompasses all cancers (T0, Tl, T2, T3) with fixed axillary lymph nodes, and their l0 year survival is about 50%. Stage IIIB tumors included locally advanced (T4a, T4b, T4c) or inflammatory cancers and also those tumors that have metastasized to the internal mammary lymph nodes. These patients are usually treated with induction chemotherapy, breast irradiation and surgery, in that order. Ten year survival for Stage IIIB cancers is approximately 30%. Stage IV breast cancer has already metastasized either to distant sites or to the supraclavicular nodes. These patients do poorly and have a 10 year survival of about 10%.

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CHAPTER 6

Breast Imaging

Laura Liberman and Timothy L. Feng

Breast imaging plays an integral role in breast cancer screening and diagnosis. Screening mammography is performed in an asymptomatic woman in order to detect clinically occult breast carcinoma. Diagnostic mammography is performed to evaluate a questioned abnormality, detected either on clinical evaluation or on mammographic screening. This section will review screening and diagnostic mammography, the role of additional mammographic views and other imaging modalities, the mammogram report using the terminology of the Breast Imaging Reporting and Data System (BI-RADS™) lexicon,[1] needle localization and image-guided percutaneous breast biopsy.

Screening Mammography

As breast cancer increases in size, there is a higher frequency of axillary metastases and a higher mortality rate. Tumor size for infiltrating breast carcinomas has been classified as T1 (<2 cm), T2 (2-5 cm), or T3 (>5 cm).[2] The frequency of axillary metastases is 24-31% for T1 carcinomas, 44-49% for T2 tumors, and 60-70% for T3 carcinomas.[3-7] If breast cancers are detected when they are smaller, breast cancer mortality can be decreased. This is the basis for screening mammography.

Technique of Screening Mammography

The standard screening mammogram consists of two views of each breast: the craniocaudal view (the view from the top) and the mediolateral oblique view (the view from the side).[8] Performance of both views is essential in order to determine the location of a lesion in three dimensions. It is important to include the posterior tissues of the breast on the films. On the mediolateral oblique view, the pectoral muscle should be identified to approximately the level of the nipple. On the craniocaudal view, the pectoral muscle is often not identified, but there should be approximately the same amount of tissue (as measured by dropping a perpendicular line from the nipple to the chest wall) as on the mediolateral oblique view. The breast is compressed during mammography in order to eliminate motion that could

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cause blurring of the image, to create a more uniform thickness of breast tissue to allow better quality images, and to minimize radiation dose.[8]

Radiation Dose of Screening Mammography

Although excess breast cancers have been detected in women exposed to high doses of radiation (0.25-20 Gy) related to atomic-bomb radiation, multiple chest fluoroscopies, or radiation therapy, there is no direct evidence of a carcinogenic effect of mammography. The Biological Effects of Ionizing Radiation (BEIR) V Report of the National Academy of Sciences estimates a mean glandular dose of 4mGy for a two-view bilateral mammogram.[9] Kopans[10] has stated that the excess risk of death incurred by undergoing screening mammography is comparable to risks of daily life that are undertaken routinely, such as breathing Boston or New York City air for 2 days, riding a bicycle 10 miles, driving in a car 300 miles, flying 1,000 miles by jet, or eating 40 tablespoons of peanut butter.

Even among the youngest women who undergo screening mammography, the risk-benefit ratio favors the use of mammographic screening. Feig[11] estimated that annual mammography of 100,000 women for 10 consecutive years from age 40 to 50 could theoretically result in eight breast cancer deaths during their lifetime. Assuming the demonstrated 24% mortality reduction due to biennial mammographic screening in this group, the benefit-to-risk ratio will be 48.5 lives saved per life lost. An assumed mortality reduction of 36% from annual screening would result in 36.5 lives saved per life lost. Feig[11] concludes that the proven benefit from screening mammography far outweighs the theoretical radiation risk.

Efficacy of Screening Mammography

The efficacy of screening mammography in decreasing breast cancer mortality has been demonstrated in numerous studies. In the 1960s, The Health Insurance Plan (HIP) of Greater New York performed a study of physical examination and mammography in a study group of 30,756 women and a control group of 30,239 women age 40-64 years.[12-14] The study consisted of an initial screening with a two-view mammogram and physical examination plus three annual follow-ups. In the study group, 132 breast cancers were detected. Of these, 33% were detected by mammography alone, 45% by physical examination and 22% by both methods. At 10 year follow-up, the study had a 30% decrease in breast cancer mortality compared to the control group.

The Breast Cancer Detection Demonstration Project (BCDDP) screened 283,222 women from 1973-1981 in 27 cities in the US with an initial physical examination and two-view mammogram and four subsequent examinations.[15-16] No control group was used, but data were compared to the data from Surveillance, Epidemiology, and End Results (SEER) of the National Cancer

Institute. Of the cancers detected in the BCDDP study, 42% were detected by mammography alone, 9% by physical examination alone and 47% by both methods. Of the in situ cancers found in the BCDDP study, mammography alone found 59%. Minimal cancer (in situ or infiltrating cancer <1 cm) made up 33% of the tumors found by mammography. These data, and those of numerous subsequent studies, support the ability of screening mammography to detect early breast cancers and save lives.

There has been recent controversy regarding the use of screening mammography in women under the age of 50. Kopans[17] has pointed out that this controversy has no biological basis, since none of the screening parameters change abruptly at age 50. Individual screening studies have not had sufficient numbers of women to demonstrate a statistically significant decrease in mortality in women under the age of 50. When the data from multiple trials are pooled in a meta-analysis, however, a statistically significant decrease in mortality from screening mammography is demonstrated in women in their 40s. Hendrick et al[18] analyzed eight randomized controlled trials of mammographic screening and found a statistically significant 18% reduction in mortality in women in their 40s; combined data from five Swedish trials yielded a statistically significant mortality decrease of 29%.

Guidelines for Screening Mammography

Currently, the American College of Radiology[19] and the American Cancer Society[20] recommend annual mammographic screening to begin at age 40. The National Cancer Institute[21] recommends mammographic screening every 1 to 2 years for women between the ages of 40 and 50 and annual mammography for women age 50 and older.

Annual screening mammography can commence earlier than age 40 in a few special circumstances.[22] Women who have had breast cancer or a biopsy diagnosis of lobular carcinoma in situ (LCIS) are screened annually from the time of diagnosis. For women with a first-degree relative (mother or sister) who developed premenopausal breast cancer, annual screening mammography may begin at an age 10 years younger than the age at which her relative developed breast cancer, but no younger than age 25.[23] For women under age 40 who received mantle irradiation for Hodgkin's disease, it has been suggested that screening mammography should begin approximately 8 years following completion of radiation.[24] For women with positive genetic testing for the breast cancer genes *BRCA1* or *BRCA2*, annual mammography is suggested beginning at age 25-35 years, with the specific age chosen based on individual preferences, the adequacy of mammographic imaging in the first study and the feasibility of breast examination.[25]

Diagnostic Mammography

Abnormalities found on mammographic screening may need further evaluation with additional mammographic views or other imaging modalities, such as ultrasound or magnetic resonance imaging (MRI). In some screening programs, the mammograms are reviewed by the radiologist as they are performed, and if additional views are needed, they are performed on the same day. In other settings, the initial two-view screening mammogram is performed, and if additional studies are required, the patient is called back for them at a later date. In several studies, the frequency of "call-backs" has ranged from 5-11%.[26-32]

A variety of diagnostic views can be performed to evaluate breast lesions. Coned compression views, mammographic images of a limited area, are useful in distinguishing a mass from a confluence of normal glandular structures or in separating out a mass from overlying parenchymal tissue. They may be helpful in assessing an area of concern on the mammogram or an area of questioned palpable abnormality. Special projections can be used to image certain areas: exaggerated craniocaudal views image the axillary tail, cleavage views image the medial breast, and 30° oblique views image the axilla. Rolled craniocaudal views may help localize a lesion seen on only the craniocaudal projection, and a 90° lateral view may help determine the location of a lesion seen only on the mediolateral oblique projection. Magnification views are helpful to assess the margins of masses and to evaluate the morphology of calcifications.

Ultrasound is used primarily in three settings:

1. to evaluate a focal mass identified on the mammogram that has circumscribed (smooth), obscured or indistinct borders
2. to evaluate a palpable lump
3. to guide interventional procedures[33]

Ultrasound can distinguish a cyst, or fluid-filled mass, from a solid lesion. The criteria for a simple cyst include a round or oval shape, a thin wall, the absence of internal echoes and the presence of posterior acoustic enhancement. Although previously the primary use of ultrasound was in distinguishing cystic from solid lesions, recent work has suggested that ultrasound may also be helpful in characterizing solid masses in the breast.[34]

The role of magnetic resonance imaging in the evaluation of breast lesions is still evolving. At the current time, MRI is used primarily in selected settings, such as in the identification of the primary carcinoma in women with breast carcinoma in an axillary node with a normal mammogram and physical examination.[35] Early work suggests that MRI may be useful in women with known or suspected breast cancer to assess for the presence of multifocal or multicentric disease, to evaluate for involvement of the skin or chest wall and to distinguish scar tissue from recurrent carcinoma.[36-39]

Screening with Other Imaging Modalities: Early Investigations

Ultrasound

Several investigators are evaluating the use of ultrasound to detect breast cancer that cannot be seen with mammography. Because ultrasound cannot reliably identify microcalcifications, which are mammographically evident in approximately one-half of breast carcinomas and are the sole method of diagnosis of the majority of ductal carcinoma in situ (DCIS) lesions, ultrasound cannot replace mammography in breast cancer screening. Some have suggested, however, that it may be used in addition to mammography in some groups of women, such as those at high risk who also have dense breasts.

Gordon and Goldenberg[40] performed 12,706 whole-breast ultrasound examinations in women who had a palpable or mammographically evident mass (the "index lesion"). Ultrasound revealed 1,575 incidental solid masses, of which 279 underwent fine-needle aspiration (FNA) biopsy. Ultrasound detected 44 carcinomas that were not evident on mammography or physical examination. Cancer was found by ultrasound in 44 (16%) of the 279 solid masses that had biopsy, in 44 (3%) of the 1,575 solid masses that were found by ultrasound and in 44 (0.35%) of 12,706 screening ultrasound examinations. These 44 cancers were in 30 women, in whom the index lesion was benign in 15 and carcinoma in 15. The mean size of these sonographically detected cancers was 1.1 cm (median, 1.0 cm; range, 0.4-2.5 cm).

Kolb et al[41] performed a study of 11,220 consecutive patients. Screening ultrasound examinations were performed in all 3,626 women with normal mammograms, normal physical exams and dense breasts. They found 11 surgically proven cancers. Ultrasound revealed cancers not identified on mammography or physical examination in 11 (0.3%) of 3,626 women. The rate of cancer detection by ultrasound alone was six (0.58%) per 1,043 high-risk women and five (0.19%) per 2,583 normal-risk women. The size and stage of sonographically detected cancers were not significantly different from those of 61 nonpalpable, mammographically detected cancers and were smaller than the 64 palpable cancers diagnosed in the rest of their population. In women with dense breasts, screening ultrasound increased breast cancer detection by 17% (from 63-74 tumors), and the number of tumors revealed only by imaging increased by 37% (from 30-41 tumors).

Additional work is needed to confirm and expand upon the work of these intriguing early studies. At the current time, however, ultrasound is not part of the standard of care in breast cancer screening.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) has a high sensitivity in the diagnosis of breast cancer, ranging from 86-100%.[35] Many studies have confirmed the

ability of MRI to detect breast cancer not identified with mammography or physical examination. Slanetz et al[42] performed bilateral breast MRI in 42 patients scheduled for biopsy of a mammographically visible or palpable abnormality, of which 17 proved to represent invasive cancer. Magnetic resonance imaging identified all 17 invasive cancers in the breast of concern. In addition, eight (19%) of 42 patients had 14 contralateral lesions found on MRI, of which nine (64%) were malignant. This is one of the first reports of breast MRI in an otherwise normal breast, and the authors suggested that their data support the use of breast MRI as a screening technique.

There are several limitations with breast MRI as a screening method. First, it has poor specificity, ranging from 37-97%.[35] Second, it is an expensive examination and requires injection of intravenous contrast. Third, the technology for performing biopsy under the guidance of MRI is not widely available, making it difficult to sample lesions identified only with MRI. Refinement in the technology for MRI-guided localization and biopsy is essential if MRI is to be helpful as a screening technique. Currently, breast MRI is most useful in a problem-solving setting, and is not part of the standard of care for screening.

The Mammogram Report: The Breast Imaging Reporting and Data System (BI-RADS™) Lexicon

The Breast Imaging Reporting and Data System (BI-RADS™) lexicon was developed by the American College of Radiology (ACR) in an effort to standardize terminology used in reporting mammograms.[1] The lexicon includes specific terminology for reporting breast composition, mammographic findings, such as masses and calcifications, and overall assessment of the likelihood of malignancy.

Breast Composition

Breast composition may be one of four patterns of increasing density:

1. almost entirely fat
2. scattered fibroglandular densities
3. heterogeneously dense
4. extremely dense

The higher the breast density, the lower the sensitivity of mammography.

Masses

A mass is defined as a space-occupying lesion seen in two different projections. If a possible mass is seen on only one view, it is called a density until its three-dimensionality is confirmed. The lexicon includes specific terms to describe masses and calcifications. Possible mass shapes are round, oval, lobular or irregular. Architectural distortion is a special case of shape, in which there are radiating spicules with no central mass visible. Mass margins

can be circumscribed (well defined or sharply defined), microlobulated (undulant with short cycles), obscured (hidden by adjacent fibroglandular tissue), indistinct (ill defined) or spiculated (with lines radiating from the margins of the mass, which suggests a lesion that is invading surrounding tissue or inciting desmoplastic reaction). Special cases of masses include solitary dilated ducts (usually of minor significance), intramammary lymph nodes (of a reniform shape, with radiolucent notch due to fat in the hilum), asymmetric breast tissue (may be important when it corresponds to a palpable asymmetry), and focal asymmetric density (visible as asymmetry with similar shape on two views, but lacks the borders and conspicuity of a true mass). Density of masses can be high, equal (isodense), low, or fat-containing/radiolucent (e.g., oil cyst, lipoma, galactocele or mixed lesions such as hamartoma).

The frequency of carcinoma as a function of mass shape and margins in a study by Liberman et al[43] of lesions that had surgical biopsy is demonstrated in Table 6.1. The highest frequency of carcinoma was observed in masses that had irregular shape or spiculated borders.

Calcifications

The BI-RADS™ lexicon describes calcification morphology (shape) and distribution. Calcification morphology is divided into three groups: typically benign, intermediate level of concern and higher probability of malignancy. Typically benign morphologies include skin (lucent centered), vascular (parallel tracks), coarse or "popcorn-like" (fibroadenomas), large rod-like (secretory disease), round (often in acini of lobules; when under 0.5 mm, called "punctate"), lucent-centered, eggshell or rim (fat necrosis), milk of calcium (within tiny cysts), suture (may have knots) or dystrophic (after trauma or irradiation). A morphology that is of an intermediate level of concern is amorphous/indistinct (round or "flake shaped," small or hazy in appearance). Morphologies that have a higher probability of malignancy are pleomorphic or heterogeneous (granular) calcifications (often varying in size and shape, usually less than 0.5 mm in diameter) and fine/linear or fine/linear/branching (casting) calcifications (appear linear but discontinuous, suggests irregular filling of a duct lumen by breast cancer).

Calcification distribution can be described as grouped or clustered (multiple calcifications in less than 2 cc of tissue), linear (arrayed in a line that may have branch points), segmental (suggests deposits in a duct and its branches, raises possibility of multifocal breast cancer in a lobe or segment of the breast), regional (scattered in a large volume of tissue but not necessarily conforming to a duct distribution) or diffuse/scattered (random in arrangement). The term "multiple" is used to indicate more than one group of calcifications similar in morphology and distribution.

The frequency of carcinoma as a function of calcification morphology and distribution in a study by Liberman et al[43] of lesions that had surgical

Table 6.1. Mass shape and margins: frequency of carcinoma

Mass Margins	Mass Shape: Irregular	Round	Lobulated	Oval	Distortion	TOTAL
Spiculated	45/54 (83)	6/6 (100)	–	1/1 (100)	4/8 (50)	56/69 (81)
Indistinct	20/35 (57)	5/14 (36)	3/9 (33)	1/8 (13)	– –	29/66 (44)
Obscured	–	2/3 (67)	1/3 (33)	0/3 (0)	– –	3/9 (33)
Microlobulated	–	0/2 (0)	1/2 (50)	0/2 (0)	– –	1/6 (17)
Circumscribed	1/1 (100)	0/6 (0)	1/4 (25)	0/11 (0)	– –	2/22 (9)
TOTAL	66/90 (73)	13/31 (42)	6/18 (33)	2/25 (8)	4/8 (50)	91/172 (53)

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Note: Data refer to lesions that were subject to surgical biopsy. Numbers in parentheses are percentages. Dash (-) indicates there were no lesions with the specified combination of features.

biopsy is shown in Table 6.2. The highest frequency of carcinoma was observed in calcifications that had linear morphology or segmental or linear distribution.

Associated Findings

The mammogram report should describe associated findings, including skin or nipple retraction, skin or trabecular thickening, skin lesions, axillary adenopathy and the presence of architectural distortion.

Lesion Location

Lesion location should be indicated by the breast (left, right or both), depth (anterior, middle, or posterior one-third of the breast) and location in relation to the nipple (as if you are using a clock face, facing the patient with 12:00 up, 6:00 down, 3:00 to the patient's left, and 9:00 to the patient's right: thus, 9:00 is lateral in the right breast and medial in the left breast).

Assessment Categories

Every report should include an overall summary impression and give one of the BI-RADS™ assessment categories as listed in Table 6.3.[1] In

Table 6.2. Calcification morphology and distribution: frequency of carcinoma

Calcification Distribution	Calcification Morphology: Linear	Pleomorphic	Amorphous	Punctate	Coarse	TOTAL
Segmental	10/10 (100)	7/12 (58)	0/1 (0)	–	–	17/23 (74)
Linear	6/8 (75)	7/9 (78)	–	0/2 (0)	–	13/19 (68)
Multiple	1/1 (100)	4/6 (67)	0/2 (0)	–	–	5/9 (56)
Regional	0/1 (0)	4/9 (44)	2/3 (67)	–	–	6/13 (46)
Clustered	9/12 (75)	76/204 (37)	7/29 (24)	1/9 (11)	0/1 (0)	93/255 (36)
Diffuse	–	0/1 (0)	–	–	–	0/1 (0)
TOTAL	26/32 (81)	98/241 (41)	9/35 (26)	1/11 (9)	0/1 (0)	134/320 (42)

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general, additional imaging evaluation is suggested for BI-RADS™ Category 0 lesions. Routine screening mammography is appropriate for BI-RADS™ Category 1 (normal mammogram) or 2 (benign finding). For BI-RADS™ Category 3 (probably benign) lesions, the recommendation is 6 month follow-up of the ipsilateral breast, followed by bilateral mammograms at 1 year, 2 years, and 3 years following the initial screening study. Biopsy is suggested for lesions classified as BI-RADS™ Category 4 (suspicious abnormality) and 5 (highly suggestive of malignancy).

Appropriateness of Short-Term Follow-Up Mammography for "Probably Benign" Lesions

The use of short-term follow-up mammography for BI-RADS™ Category 3 ("probably benign") lesions has been well supported in the literature. Examples of such lesions include single or multiple circumscribed masses

Table 6.3. Breast imaging reporting and data system (BI-RADS™) final assessment categories[1]

a. Assessment is incomplete
Category 0
Need additional imaging evaluation:
Finding for which additional imaging evaluation is needed. This is almost always used in a screening situation and should rarely be used after a full imaging workup. A recommendation for additional imaging evaluation includes the use of spot compression, magnification, special mammographic views, ultrasound, etc.

The radiologist should use judgement in to how vigorously to pursue previous studies.

b. Assessment is complete—final categories
Category 1
Negative:
There is nothing to comment on. The breasts are symmetrical and no masses, architectural disturbances or suspicious calcifications are present.

Category 2
Benign Finding:
This is also a negative mammogram, but the interpreter may wish to describe a finding. Involuting, calcified fibroadenomas, multiple secretory calcifications, fat-containing lesions such as oil cysts, lipomas, galactoceles, and mixed-density hamartomas all have characteristic appearances and may be labeled with confidence. The interpreter might wish to describe intramammary lymph nodes, implants, etc., while still concluding that there is no mammographic evidence of malignancy.

Category 3
Probably Benign Finding—Short Interval Follow-up Suggested:
A finding placed in this category should have a very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. Data are becoming available that shed light on the efficacy of short interval follow-up. At the present time, most approaches are intuitive. These will likely undergo future modification as more data accrue as to the validity of an approach, the interval required and the type of findings that should be followed.

Category 4
Suspicious Abnormality—Biopsy Should Be Considered:
These are lesions that do not have the characteristic morphologies of breast cancer but have a definite probability of being malignant. The radiologist has sufficient concern to urge a biopsy. If possible, the relevant probabilities should be cited so that the patient and her physician can make the decision on the ultimate course of action.

Category 5
Highly Suggestive of Malignancy—Appropriate Action Should Be Taken:
These lesions have a high probability of being cancer.

and single or multiple groups of rounded or punctate calcifications. In previous studies, the frequency of carcinoma for BI-RADS™ Category 3 lesions has ranged from 0.5-2.0%.[44-46]

Sickles[44] recommended short-term follow-up mammography in 3,184 "probably benign" lesions; cancer was subsequently discovered in 17 (0.5%). Fifteen of the 17 cancers were diagnosed by means of interval change at follow-up mammography before they were palpable; all 17 were Stage 0 or Stage I at the time of diagnosis (one positive axillary lymph node was present in two patients). These data support the utility of the short-term follow-up mammogram in the management of "probably benign" lesions. The likelihood of cancer in this setting is extremely low, and if present it is likely that it will be diagnosed at an early and treatable stage.

More recently, Sickles[45] has extended his work to address the question of whether patient age or lesion size should prompt immediate biopsy of nonpalpable, circumscribed, solid nodules. Of 1,403 circumscribed masses included in this study, cancer was found in 19 (positive predictive value [PPV]=1.4%). Only small differences in PPV were found for various patient age and lesion size subgroups. Even in the group of women age 50 and older, the ratio of benign to malignant was 60:1 (PPV=1.7%). These data suggest that lesion size and patient age should not deter the clinician from recommending short-interval follow-up mammography for "probably benign" lesions.

Positive Predictive Value of BI-RADS™ Categories

The BI-RADS™ categories are useful predictors of malignancy. The frequency of carcinoma is 29-34% for BI-RADS™ Category 4 (suspicious abnormality) and 81-94% for BI-RADS™ Category 5 (highly suggestive of malignancy).[43-47] Biopsy is generally recommended for BI-RADS™ Category 4 and Category 5 lesions. For nonpalpable masses, biopsy can be performed with needle localization and surgical biopsy or image-guided percutaneous breast biopsy.

Needle Localization

The goals of needle localization are to assist the surgeon in removing a nonpalpable breast mass that is suspicious or highly suggestive of malignancy and to minimize the amount of tissue that must be sacrificed in the process.[48] Although a variety of techniques can be used for needle localization, today it is most commonly performed with hook wires or retractable curved wires. Imaging guidance for localization may be provided by mammography or ultrasound.

To perform mammographic-guided hook-wire localization, the patient usually sits with the breast in a fenestrated compression paddle with an alphanumeric grid. An image is obtained, coordinates of the lesion in two dimensions are determined, and a needle is placed to the appropriate depth as

determined from review of the films taken prior to the procedure. Following needle placement, two orthogonal views are obtained. When the needle is in good position, the wire is deployed and the needle is removed. Two orthogonal views are obtained, labeled and sent with the patient for use in the operating suite. Removal of the lesion should be confirmed with specimen radiography.[48]

The most common complication of needle localization is vasovagal reaction, which occurred in 27 of 370 (7%) patients who underwent needle localization or fine-needle aspiration in a series by Helvie et al.[49] Vasovagal reactions may range from lightheadedness to syncope (the latter occurred in 2 of 370=1% cases in the study of Helvie et al[49]). Prolonged bleeding occurred in 3 of 370 (1%) cases and pain in 2 of 370 (1%). Pneumothorax is exceedingly rare in localizations performed parallel to the chest wall. Other complications such as migration of wire fragments are also extremely unusual.[48] Retention of wire fragments following localization has been reported but is thought to be of no clinical consequence.[50]

The incidence of "missed lesions" at needle localization has ranged in published series from 0-18%.[51] Jackman et al[51] recently reviewed findings in 280 consecutive nonpalpable breast lesions that underwent needle localization. Biopsy failed in 7 (2.5%) of 280 lesions. Unsuccessful needle localization was more likely with two lesions per breast, small lesions, small specimens and microcalcifications. Removal of more than one tissue specimen converted failure to success in 14 (67%) of 21 initially missed microcalcification lesions.

Image-Guided Percutaneous Breast Biopsy

Percutaneous image-guided breast biopsy is being used increasingly as an alternative to surgical biopsy for the evaluation of lesions that can be seen with mammography or ultrasound.[52] Percutaneous biopsy methods differ with respect to the method of imaging guidance (most commonly stereotaxis or ultrasound) and the tissue-acquisition device (fine needle, automated core needle, directional vacuum-assisted biopsy probe, biopsy cannula, and others).

Stereotactic Biopsy

Stereotactic biopsy uses specialized mammography equipment to calculate precisely the location of a lesion in three dimensions. Stereotactic biopsy can be performed with the patient prone on a dedicated table or with the patient sitting in an upright unit. Digital equipment is available for stereotactic biopsy, which dramatically decreases the amount of time necessary to perform the procedure. Stereotactic biopsy can be used for all types of mammographic lesions (i.e., masses and calcifications).

To perform stereotactic biopsy on a dedicated table, the patient is positioned prone and the lesion is localized with a scout image. Two

mammographic images are obtained (usually at 15° oblique angles from the scout film). The same point is identified on both views and communicated to the computer, usually by means of a hand-held mouse or cursor, allowing the computer to calculate the coordinates of the lesion in three dimensions. The skin is cleansed with iodinated soap and anesthetized with local anesthesia. A skin nick is made with a scalpel, the tissue acquisition device (e.g., automated core needle or directional vacuum-assisted biopsy probe) is inserted, and its positioning confirmed on two angled stereotactic images. Multiple tissue specimens are obtained and sent in formalin for pathologic analysis.[53]

Ultrasound-Guided Biopsy

Ultrasound can be used to guide biopsy of mass lesions that can be identified with ultrasound examination. Advantages of ultrasound include the multipurpose use of the equipment, lack of ionizing radiation, the lack of breast compression during the procedure, accessibility of all areas of the breast and axilla, multidirectional sampling and ability to observe the needle in real time.[54-55]

To perform ultrasound-guided 14-gauge automated biopsy, the patient is positioned in the supine oblique position, the area is localized with real-time sonography and anesthetized with lidocaine, and a skin nick is made with a scalpel. The 14-gauge automated needle is inserted and its accurate position confirmed with real-time imaging. Multiple samples are obtained and sent for pathologic analysis.

Previous studies have reported excellent results with ultrasound-guided 14-gauge automated core biopsy. Parker et al[54] reported 100% concordance between results of ultrasound-guided 14-gauge automated core biopsy and surgery in 49 lesions that went to surgery, and no carcinomas at 12 to 36 month follow-up in 132 lesions for which ultrasound-guided core biopsy yielded benign results. Liberman et al[55] found that ultrasound-guided core biopsy obviated a surgical procedure in 128 (85%) of 151 lesions, resulting in a decrease in the cost of diagnosis by 56%. In that study, the investigators found that both ultrasound-guided core biopsy and stereotactic core biopsy were less expensive than surgery, but cost savings were higher if the biopsy was performed under ultrasound guidance.

Choice of Guidance Modality

Stereotactic guidance is preferable for lesions evident as calcifications, as well as for masses that cannot be identified with ultrasound. For masses that can be seen with ultrasound, ultrasound-guided biopsy is faster, less expensive and does not use ionizing radiation; therefore it may be the method of choice, in such cases if the appropriate equipment and expertise are available.

Tissue-Acquisition Devices

Available tissue-acquisition devices include fine needles, automated core needles, directional vacuum-assisted probes and biopsy cannulas. Although early work with image-guided biopsy was performed using fine needles, many centers have turned to larger tissue-acquisition devices because of the lower frequency of insufficient samples and the better characterization of benign and malignant lesions that is possible when a larger volume of tissue is obtained.

Previous studies of stereotactic core biopsy with a 14-gauge automated needle showed 87-96% concordance between results of stereotactic core biopsy and surgery.[52] Complications were rare, with the frequency of hematoma and infection each approximately 1 in 1000.[56] A directional vacuum-assisted biopsy instrument is now available for performing imaging-guided biopsy, most often used with stereotactic guidance. Compared to the automated needle, the vacuum device acquires larger samples of tissue, has a higher frequency of retrieval of calcifications and may provide more accurate characterization of complex lesions such as those containing atypical ductal hyperplasia or ductal carcinoma in situ.[52]

Choice of Tissue-Acquisition Device

Excellent results have been obtained using the 14-gauge automated needle for biopsy of masses under ultrasound or stereotactic guidance. For calcifications, several investigators have demonstrated a higher rate of calcification retrieval and more accurate lesion characterization using the directional vacuum-assisted biopsy probe than the automated needle.[52] The directional vacuum-assisted biopsy instrument may also be preferable for small lesions (e.g., ≤0.5 cm), because technology is available that allows accurate placement of a localizing clip through the biopsy probe to facilitate subsequent localization, if necessary. Further work is needed to determine if there is any benefit to the use of the larger biopsy cannulas that are now available.

Role of Imaging-Guided Biopsy in Diagnosis of Breast Disease

There are many patientcare advantages from using image-guided percutaneous breast biopsy.[52] Percutaneous biopsy is less invasive and less expensive than surgery. Less tissue is removed, so there is less resulting deformity in the breast and less scarring on subsequent mammograms. The biopsy can be performed rapidly, so there is less time lost from work or other activities. Percutaneous biopsy is less expensive than surgery. Women who have percutaneous biopsy undergo fewer operations, regardless of whether the diagnosis is benign or malignant. Continued improvements in the technique for percutaneous biopsy will allow more women to take advantage of this alternative to surgery for the diagnosis of breast lesions.

Summary

Breast imaging plays a critical role in breast screening and diagnosis. Screening and diagnostic mammography allow the detection and evaluation of clinically occult breast cancer. The mammogram report should be worded in accordance with the terminology of the Breast Imaging Reporting and Data System (BI-RADS™) lexicon,[1] so that the findings and recommendations are clearly communicated. Percutaneous imaging-guided breast biopsy can allow expeditious diagnosis of early, nonpalpable breast cancers. Close communication between the clinical staff and the breast-imaging radiologist allows optimal utilization of the excellent technology available for early detection and diagnosis of breast cancer.

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CHAPTER 7

Breast Cancer Treatment—Surgery

Patrick I. Borgen and Bruce Mann

Surgery is the most effective treatment option ever employed against breast cancer. Halsted's radical mastectomy (RM), which dates from the turn of the century, revolutionized the local control of the disease and demonstrated that a subset of patients could be cured by surgery alone. Halsted viewed breast cancer as a principally local-regional disease that spread in a centripetal fashion. Fifty years later, Bernard Fisher would hypothesize that breast cancer is primarily a systemic disease and state that the surgeon's knife had little impact upon outcome. Today, we would argue that they are both right and both wrong – breast cancer begins as a local disease and, at some point in its evolution, becomes systemic. Local control cannot cure all patients, but no patients are cured without it. Surgery remains the mainstay of local control at the turn of the millennium, and recent trends towards earlier stage at diagnosis will undoubtedly increase its role.

Surgery for Invasive Breast Cancer

The treatment options for patients with early-stage (Stage I and II) invasive breast cancer today are breast-conservation therapy (BCT) with adjuvant radiation therapy and modified radical mastectomy (MRM) with or without breast reconstruction.

Until the late 19th century, there was no effective treatment for breast cancer, and most patients died within a relatively short time from uncontrolled local disease or complications of surgery. The first major advance was the development and popularization of the radical mastectomy. The operation, described by William Halsted and Willy Meyer in 1894, removed the breast and the pectoral muscles and removed lymph nodes from levels 1, 2 and 3 of the axilla. The operation reduced the local recurrence rate from 60-70% to about 6%, establishing radical mastectomy as the standard treatment for breast cancer for three-quarters of a century. In the 1950s, Patey modified the radical mastectomy by sparing the pectoralis major muscle. The MRM was equally effective in terms of local control and overall survival, and became the standard operation for breast cancer. Today the most common reasons that modified mastectomy is performed include patient choice, extensive local disease or an inability to receive radiation therapy.

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Conservative breast surgery was introduced for small breast cancers in the 1970s. There was a gradual trend towards earlier stage at diagnosis and more appreciation of the systemic health threat breast cancers can pose. The logical extension of both was to reduce the magnitude of the local surgery and attempt to preserve the organ.

Throughout the 1970s and 1980s, large numbers of patients participated in trials in the USA and Europe to evaluate the safety and efficacy of breast-conservation therapy. Participants were randomized to either wide excision of the tumor and radiation therapy or mastectomy. These studies demonstrated that BCT was as safe as mastectomy in selected patients but was preferred because it is less disfiguring. The first trial reported was from the National Tumor Institute in Milan, Italy, by Veronesi.[1] Their trial compared radical mastectomy with 'quadrantectomy' (excision of one-quarter of the breast) followed by radiation therapy (QUART) for clinically T1N0 breast cancers. There was no difference in survival and little difference in local recurrence rates between the two treatment approaches. The major US trial was the NSABP-B06 trial, which ran from 1976-1984 and was first reported in 1985 by Fisher.[2] Over 1,800 patients with tumors up to 4 cm in size were randomized to total mastectomy or tumorectomy with or without adjuvant radiation therapy. Negative histologic margins were required, and any patient with positive margins went on to total mastectomy. The incidence of recurrence within the breast at 5 years was 8% in the tumorectomy-and-radiation-therapy group, and 28% in the tumorectomy-alone arm (10% and 39%, respectively, at 8 years). There was no significant difference in overall or distant disease-free survival between the arms of the trial. As a result of these and further trials, BCT is now possible in about two-thirds of patients presenting with breast cancer.

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Risk of Recurrence

After BCT or mastectomy, there is a risk of breast cancer recurrence. Trials of partial mastectomy have shown an incidence of breast recurrence of between 1% and 4% per year, depending on the amount of breast tissue excised and patient selection criteria. Factors associated with an increased likelihood of breast recurrence include positive surgical margins, ductal carcinoma in situ (DCIS), the presence of lymphovascular invasion and young age of the patient. Borgen et al[3] have published a review of this issue.

Surgical Margins

Surgical margins, defined as the presence of normal (unaffected) tissue between the tumor and the path of the surgeon's knife, are important and controversial. Pathologic assessment of tumor margins is often imprecise, however. Interpreting the literature regarding local recurrence after BCT is complicated by the lack of standardization of margin determination. The

NSABP-B06 trial accepted a margin as negative if the cancer was not incised. The Milan trial involved quadrantectomy, with a widely clear margin. Other studies have considered a 3 mm margin as a clear negative margin. Some retrospective studies have found that positive histologic margins are associated with increased local recurrence, but others have not found this relationship.

Radiation-therapy techniques that boost the tumor bed may compensate for microscopically positive margins, but it is worth noting that the tumoricidal effect of radiation therapy is quite variable. It is our practice to insist upon clear margins, both in DCIS and invasive cancers. Centrally located tumors may be suitable for BCT. To avoid a positive margin at the nipple, BCT may require excision of the nipple/areola complex, but this does not preclude a good cosmetic result. Nipple removal with radiation therapy provides a cosmetic result that is superior to virtually all attempts at breast reconstruction after mastectomy.

Ductal Carcinoma In Situ (DCIS)

The presence of DCIS in and around the invasive tumor has been associated with increased likelihood of breast recurrence. Extensive intraductal component (EIC) is a term used to describe situations in which at least 25% of the primary mass consists of DCIS and in which DCIS is seen in ducts extending beyond the primary tumor. Extensive intraductal component is more common in young patients and is associated with a higher incidence of positive margins and residual tumor in the surrounding grossly normal breast. Subsequent studies revealed that EIC is likely to represent a margin question and is no longer considered a contraindication to BCT if margins are acceptable. Extensive intraductal component is not radioresistant, nor does it represent a variation of the disease spectrum that must be treated uniformly with mastectomy.

Pathologic Features of the Tumor

Tumor size is not a risk factor for local recurrence with T1 and T2 lesions, although it is possible that very small lesions might have a lower recurrence rate. Some studies suggest that tumors with lymphovascular invasion may be more likely to recur than those without this finding. Infiltrating lobular carcinoma is no more likely to be associated with local recurrence if the margins are negative. Due to the more diffuse growth characteristics of infiltrating lobular carcinoma, it is more difficult to obtain negative margins. The grade of the tumor (state of differentiation) has not been associated with local recurrence.

Age

Young age, defined variably as less than 35 and up to 50 years of age, is a risk factor for breast cancer recurrence. This has been reported in series from both the US and Europe in which younger patients, particularly those below

age 30 at diagnosis, have a consistently higher local-regional relapse rate than older patients. This is unfortunate, as younger patients are often most interested in breast conservation. While young age should not be a contraindication to breast conservation, it is an important part of the informed consent process. Kim et al at Memorial Sloan-Kettering Cancer Center demonstrated that young women had a higher local and a higher systemic failure rate than did matched older patients but that the two appeared to be independent of one another. Mastectomy with reconstruction may be appropriate in selected patients.

Adjuvant Radiation Therapy

Adjuvant radiation therapy reduces the incidence of local recurrence and is an essential part of BCT. Trials are ongoing to define the group in whom radiation can be safely omitted, but the current standard of care is to include radiation as an integral part of BCT. Alternative methods of radiation-therapy administration, including breast brachytherapy, have been proposed by Kuske and his colleagues at the Ochsner Clinic and bear further study. The standard dose to the breast itself is 50 Gy, and many institutions give a boost dose of 12 Gy to the tumor bed. The value and/or necessity of the boost dose remains unknown. Two contraindications to the administration of radiation therapy include advanced connective-tissue disease, such as scleroderma, and a prior history of ionizing radiation to the breast.

Adjuvant Chemotherapy and Breast-Conservation Therapy

In general, cytotoxic chemotherapy is felt to have a minimal impact upon local relapse rates in the breast. A notable exception, the NSABP-B13 trial of chemotherapy versus no adjuvant systemic therapy for node-negative patients, included many patients treated with BCT, and the incidence of local recurrence was significantly lower in the group receiving chemotherapy. Trials are underway to further define the issue. Neoadjuvant chemotherapy has been shown to increase the proportion of patients suitable for BCT without any effect on overall survival.

Patient Selection Criteria for Breast-Conservation Therapy

The patient's choice regarding BCT or mastectomy must be informed. There are only two contraindications to BCT: inability to excise the local disease completely and inability to complete radiation therapy to the breast. Patients considered poor candidates include patients in the first two trimesters of pregnancy, patients with widespread multifocal breast cancer and patients with cancer arising in an irradiated area. Patients with collagen vascular or autoimmune disease, such as scleroderma, respond poorly to radiation and should not undergo BCT. Cosmetic concerns are a relative contraindication to BCT. If the tumor is large relative to the size of the breast, the result of

conservation is likely to be poor, and so BCT may be contraindicated. The fundamental issue for the patient is the psychological benefit of breast preservation, compared with the requirement for radiation therapy and the subsequent risk of breast cancer recurrence.

Surgery for Pure DCIS

Historically, DCIS comprised about 3% of breast cancers, and most cases were large palpable tumors. Recently, an increasing portion of patients present with impalpable DCIS. Up to one-third of breast cancers found on screening mammography are DCIS. Consequently, 20-25% of breast cancers seen in a population where screening is widespread will be DCIS.

In the past, the standard treatment for DCIS was total mastectomy. The local recurrence and mortality rates have been uniformly low after mastectomy, and mastectomy remains the gold standard against which lesser treatments are compared. Today, total mastectomy remains the standard treatment for extensive or multifocal DCIS. Despite the paucity of prospective trials for DCIS, the treatment has altered as the pattern of disease has changed. Most surgery for DCIS now comprises wide excision with or without radiation therapy.

The major problem with BCT for DCIS is the risk of local recurrence; specifically, up to 50% of recurrences are invasive. Various factors contribute to the risk of recurrence. Important tumor-related factors are the size and histologic features of the tumor. Positive surgical margins are also associated with recurrence. Young patients may have higher recurrence rates, although it is not certain that age is an independent risk factor.

The NSABP-B17 trial compared wide excision alone to wide excision with postoperative adjuvant radiation therapy in patients with DCIS who were treated conservatively. This trial reported that the addition of adjuvant radiation therapy reduced the incidence of overall recurrence by about 50% and the incidence of invasive recurrence by about two-thirds.[4] There does not appear to be a survival advantage associated with adjuvant radiation therapy. In the US, most patients with DCIS are treated with surgery and radiation, while in Britain, the lack of survival effect has been frequently interpreted as meaning that radiation is not mandatory.

Attempts have been made to predict the risk of local recurrence in order to help patients and clinicians decide between treatments. The Van Nuyes Prognostic Index is perhaps the best known such attempt. This system rates the grade of DCIS, the size of the tumor, and the excision margin to produce an overall score. Tumors with a low score may be appropriate for wide excision alone, those with an intermediate score may be appropriate for wide excision with radiation therapy, and those with a high score are at high risk of recurrence, even with radiation therapy, and so might be better treated with mastectomy. The major obstacle to the widespread adoption of the Van Nuyes Prognostic Index lies in the fact that it is very difficult to accurately assess the size of the tumor and to quantify the precise size of the margin of excision.

Breast Reconstruction

Breast reconstruction is an integral part of the surgical treatment of breast cancer. Reconstructive options are part of the discussion with a patient if mastectomy is being considered. It is a central component of the discussion if prophylactic mastectomy is being considered.

The options for reconstruction are

1. autologous tissue reconstruction
2. reconstruction with a subpectoral implant or
3. a combination of both.

Reconstruction can be performed immediately or can be delayed until oncologic treatment is complete. Tissue options include using the latissimus dorsi muscle or the transverse rectus abdominus myocutaneous (TRAM) flap, comprising skin, fat and muscle transferred from the abdominal wall. Tissue flaps can be either pedicled or "free" with a microvascular anastomosis.

Implants are usually placed in a subpectoral position after a pocket has been fashioned and progressively enlarged with a tissue expander. Now most implants are saline implants, following concerns about the safety of silicone-filled devices. Recently, the moratorium on silicone implants has been lifted, and they are gaining favor, as they have been deemed safe and certainly are capable of achieving a better cosmetic result than saline implants. Subsequent nipple reconstruction can result in an excellent cosmetic outcome. Immediate reconstruction with tissue generally gives the best cosmetic result and can have psychological benefits.

It is now possible to remove the breast tissue with a very small incision around the nipple (skin-sparing mastectomy), greatly facilitating the quality of the reconstruction by minimizing evident scars. The skin-sparing mastectomy relies on improvements in fiberoptic illumination technology and is gaining popularity. Breast cancer is rarely a disease that involves the skin; therefore, leaving considerable skin behind will have little impact on local control rates.

Axillary Surgery

Axillary dissection (AD) has been part of breast cancer surgery from the time of Halsted. The status of the axillary nodes remains the most powerful prognostic indicator in the treatment of invasive breast cancer. Debate exists concerning the therapeutic value of AD; however, intuitively, removing lymph nodes containing metastatic breast cancer should have a small but identifiable survival benefit. Historically, this was the rationale for the inclusion of a full axillary dissection in the radical mastectomy. Adair[5] reviewed 1,458 patients who had had radical mastectomy as sole treatment in the 1940s and showed that there were many women among them whose breast cancer had included lymph node involvement who were long-term survivors (all levels of lymph

node involvement were represented among them). Presumably, removing the disease was curative in these patients.

The NSABP-B04 trial challenged the rationale for axillary dissection. It compared radical mastectomy, total mastectomy with radiation therapy to the axilla and total mastectomy alone, with subsequent axillary dissection for isolated axillary recurrence. There was no statistically significant survival difference between the three arms of the study.[6] This has been interpreted as showing that axillary dissection does not confer a survival benefit. Many clinicians, however, are uncomfortable with this interpretation. Close examination of the NSABP-04 study shows that it was not powerful enough to detect a 5-10% difference between the treatment arms; furthermore, surgeons were allowed to remove nodes in the total-mastectomy arm, greatly confounding trial results. It is worth noting that even the NSABP continued to mandate a full axillary dissection in all subsequent trials involving invasive breast cancer. Recently, an important analysis of a large number of patients from the National Cancer Registry showed a clear survival benefit in women in whom axillary nodes were removed compared with those in whom nodes were not removed. Other studies have found a survival advantage for axillary dissection over both axillary sampling (removal of a small number of nodes) and observation. Currently, the issue remains unresolved.

Axillary dissection is not necessary for pure DCIS. With invasive carcinoma, if the patient is clinically node positive, axillary dissection is the most effective method of gaining local control and offers the best chance of cure. It also provides staging and prognostic information. In clinically node-negative disease, the main objectives of dissection are to obtain information used to guide the selection of adjuvant therapy and to gain prognostic information. About one-third of clinically nonsuspicious axillae will contain lymph node metastases, and in these patients, the dissection provides local control and, possibly, a survival benefit.

Nodal status remains the most significant prognostic factor in breast cancer, and the incidence of nodal metastases is closely related to the size of the tumor. As greater numbers of small breast cancers are being diagnosed, the wisdom of routine axillary dissection has been called into question. There has been considerable debate over the true incidence of axillary nodal disease in invasive breast cancer less than 5 mm in size (T1a lesions). One study found an incidence of nodal metastases in these patients of 3%, and consequently, some have advocated omission of axillary surgery in these patients. A large series from Memorial Sloan-Kettering Cancer Center found that the incidence of nodal metastases in T1a tumors was 10% and 15% in T1b tumors, with no subgroup having an insignificant incidence. Other series have also found an incidence of about 10%.

The problem with axillary dissection is that the incidence of morbidity is high. This is discussed in detail later in this chapter. Sentinel node mapping

has been developed and introduced in response to the problem of the "unnecessary" morbidity of a negative lymph node dissection. A later chapter is devoted to this topic.

In the absence of sentinel node biopsy, it is reasonable to tailor the extent of axillary dissection to the individual situation, such as in the case of an elderly woman with a small ER-positive tumor. In the case of a T1 or T2 tumor with clinically negative nodes, a level 1 and 2 dissection should be performed. The incidence of level 3 nodal involvement in this case is low. In cases involving gross disease within the axilla, a full, three-level dissection should be performed.

Surgery for Locally Advanced Breast Cancer

Surgery plays a less important role in Stage III breast cancer. A large majority of patients with Stage III breast cancer will have axillary lymph node involvement, and a significant proportion will have distant metastases present at the time of diagnosis. The primary aim of surgery in this setting is to achieve local control. Surgery alone has a high failure rate for locally advanced breast cancer, and the long-term survival rate is dismal. Features predicting poor outcome with surgery alone include skin edema, fixation and ulceration, and chest-wall fixation. The diagnosis is usually made using core needle biopsy. Occasionally, incisional biopsy is needed, and skin biopsy will confirm the diagnosis of inflammatory breast cancer. Currently, the usual treatment involves the use of induction chemotherapy with an adriamycin-based regime, followed by surgery. Primary chemotherapy has the advantage that the response to treatment can be monitored. In addition, BCT may become possible after tumor downstaging. Further chemotherapy is used following the surgery if there was good response to the chemotherapy, and once the chemotherapy is complete, adjuvant radiation therapy may be used. The best local control rates are seen with surgery and radiation therapy following induction chemotherapy.

Surgery for Recurrent Disease

Local Recurrence

Local recurrence after BCT may be detected on mammography, physical examination or both. Signs of recurrence are often subtle and difficult to distinguish from effects of surgery and radiation. Any changes that occur, especially changes occurring more than 2 years after the end of radiation therapy, must be considered suspicious.

The overwhelming majority of patients who present clinically with an isolated breast recurrence after BCT have no evidence of systemic disease and are therefore candidates for salvage treatment. Breast recurrence after BCT carries a 5 year systemic disease-free survival of about 50%. Factors

influencing the prognosis are the initial node status at BCT and the interval between BCT and recurrence. Patients who were initially node positive have a significantly worse prognosis after failed BCT than those patients who were node negative. Patients who recur in the breast in less than 24 months also have a significantly worse prognosis than do those with a disease-free interval of greater than 4 years. The standard treatment for isolated operable local recurrence after BCT is salvage mastectomy. If radiation therapy has not been used previously, it may be possible to repeat a wide-local excision with adjuvant radiation therapy. For recurrence after wide excision and radiation therapy, repeat local excision is generally not advisable.

Chest-Wall Recurrence

Chest-wall recurrence after total mastectomy usually presents as a painless lump in the scar or on the chest wall. Diffuse chest-wall recurrence sometimes occurs early after mastectomy for locally advanced disease. Most chest-wall recurrences occur within 5 years of the mastectomy. Up to one-half of patients with chest-wall recurrence have had prior or have simultaneous distant metastatic disease.

Chest-wall recurrence is an ominous finding. Nevertheless, at least 50% of patients will live 5 years disease free; therefore, isolated recurrence should be treated for cure. Node-negative patients with a disease-free interval of more than 2 years have an approximately 60% 5 year survival after curative resection of localized chest-wall recurrence, whereas node-positive patients with a short disease-free interval do very poorly.

Distant Metastatic Disease

Surgery has a negligible role in the management of distant recurrences. There have been few series looking at the rate of cure with lung or liver resection. In general, such procedures would only be considered in otherwise well patients who have no evidence of other metastatic disease and a long disease-free interval. With solitary lung lesions, the alternative diagnosis of primary lung cancer must be considered.

Surgery is occasionally required for the palliation of recurrences. The most common situation is in the management of bony metastases, where internal fixation of long bones can prevent pathologic fractures, or may be needed in their treatment.

Surgical Approach

Preoperative mammography is essential prior to treatment of any patient with suspected malignancy. The mammogram may show the extent of the lesion, or additional lesions or microcalcification elsewhere in the breast that alter the operative approach. It may also show lesions in the other breast. Preoperative cytology or histology must also be reviewed.

Technique of Breast Biopsy/Partial Mastectomy

The incision for breast biopsy or wide excision is placed to allow an adequate biopsy with a good cosmetic result, which does not compromise future treatment (i.e., it fits within usual mastectomy flaps). Extensive tunneling is avoided. For central lesions, a periareolar incision is very satisfactory, but for peripheral lesions, the incision is placed close to the lesion in Langer's lines. In the inferior part of the breast, a radial incision has been advocated (Fig. 7.1), although we have had better cosmetic success with the curved skin-line incision used elsewhere in the breast. To avoid tunneling when needle localization is used the incision is placed over the lesion, rather than close to the site of needle entry. If axillary dissection is required, a separate incision is used unless the lesion is located in the axillary tail.

Local anaesthetic is infiltrated prior to making the incision, and the skin and subcutaneous tissue are retracted (Fig. 7.2). The breast tissue overlying the mass is grasped with Allis clamps, and the mass is excised with sharp dissection (Fig. 7.3). Electrocautery is not used for the excision, as it makes pathologic assessment of the margins more difficult. The mass itself is not grasped with clamps, as this risks tumor disruption and dissemination.

The amount of tissue removed depends on the indication. A fibroadenoma is removed with little if any surrounding breast tissue. For a small suspicious lesion, it is wise to take a margin of about 1 cm so that the diagnostic excisional biopsy might also be adequate local surgery. Diagnostic biopsy of an equivocal area should remove the lump if it is discrete, or consist of a representative sample if it is less well defined. For a breast cancer diagnosed on percutaneous biopsy, a 1cm margin of grossly normal breast tissue is removed. An ellipse of skin can be included with a superficial tumor. The specimen should be oriented with clips or sutures to allow the pathologist to assess the margins. After needle-localized biopsy, specimen radiography is essential to ensure complete removal of the mammographic abnormality. If cancer is suspected, it is valuable to place titanium clips in the tumor bed to facilitate radiation targeting. In cases of inflammatory or locally advanced cancer, incisional biopsy may be needed for diagnosis and treatment planning.

Meticulous hemostasis is obtained with electrocautery and interrupted absorbable sutures if needed. Deep breast tissue is not usually reapproximated, as this leads to later distortion. Interrupted sutures to the superficial breast tissue or subcutaneous tissue followed by a subcuticular skin suture produce an optimal cosmetic result (Fig. 7.4). Breast support is needed for at least 48 hours postoperatively.

Technique of Mastectomy

The first step is the creation of skin flaps. These are marked preoperatively (Fig. 7.5), the skin is incised with a scalpel, and flaps are raised with either scalpel or electrocautery. Traction is maintained on the breast with the

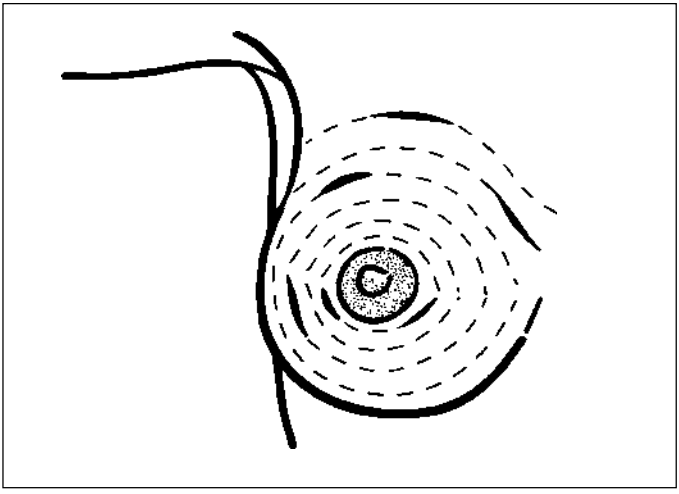

Fig. 7.1. Position of incisions for breast biopsy/wide excision. Incisions are in Langer's lines, except for lesions below the nipple. The incisions should fit within the flaps for a mastectomy, in case this is subsequently required.

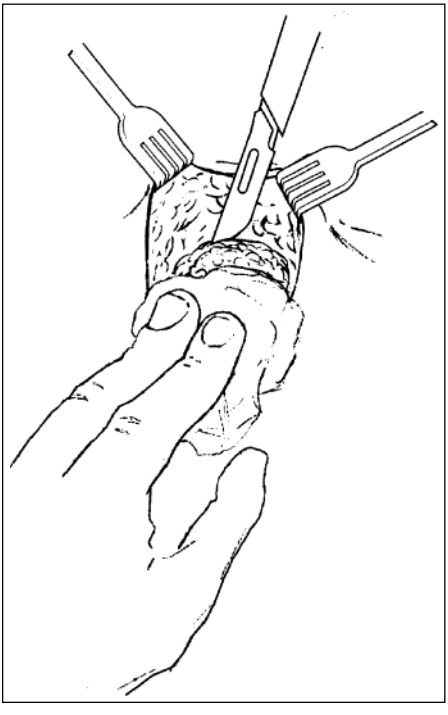

Fig. 7.2. The skin and subcutaneous tissue is incised down to the vicinity of the mass.

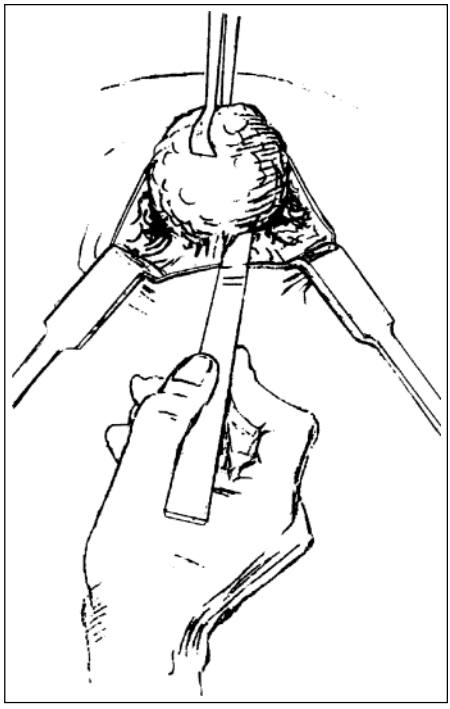

Fig. 7.3. The mass is grasped with a clamp and excised using sharp dissection.

nondominant hand, and even, upward counter-traction is applied to the skin flaps (Fig. 7.6). The flaps are developed just outside the envelope of superficial fascia around the breast. The superior extent of dissection is the position where the superficial fascia fuses with the pectoralis fascia. The inferior flap is raised in a similar manner, with the surgeon controlling the skin and the assistant retracting the breast. The inferior extent of the dissection is the fusion of the breast fascia with that over the rectus abdominus.

The breast is then removed from the pectoralis major muscle. Electrocautery or a scalpel is used to divide the fascia over the muscle. The fascia is removed with the breast; this is easier if the dissection proceeds downwards from above (Fig. 7.7). Medially, there are perforating vessels from the internal thoracic artery. In the second and third intercostal spaces, these vessels are large and may require ligation. If an axillary dissection is part of the treatment, the mastectomy is carried to the lateral edge of the pectoralis major, then the clavipectoral fascia is excised to enter the axilla. If the operation is a total mastectomy (i.e., for DCIS), the mastectomy is continued superficial to the clavipectoral fascia to the anterior border of latissimus dorsi. The axillary tail of the breast continues around the lateral border of the pectoralis

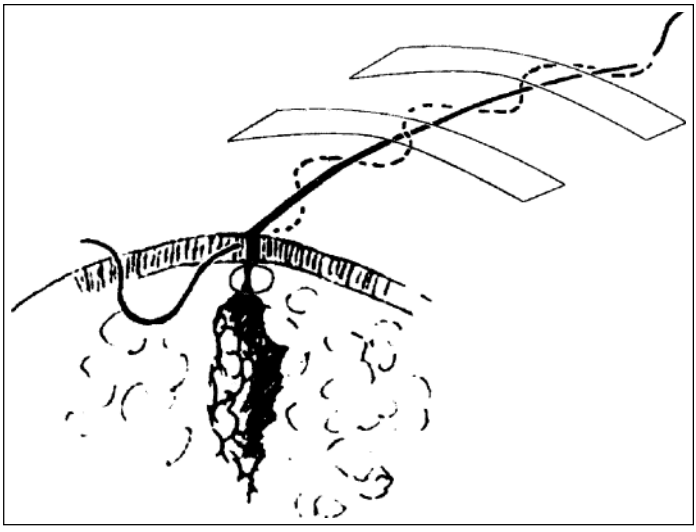

Fig. 7.4. The wound is closed with a subcuticular suture and steri-strips. The cavity is not closed.

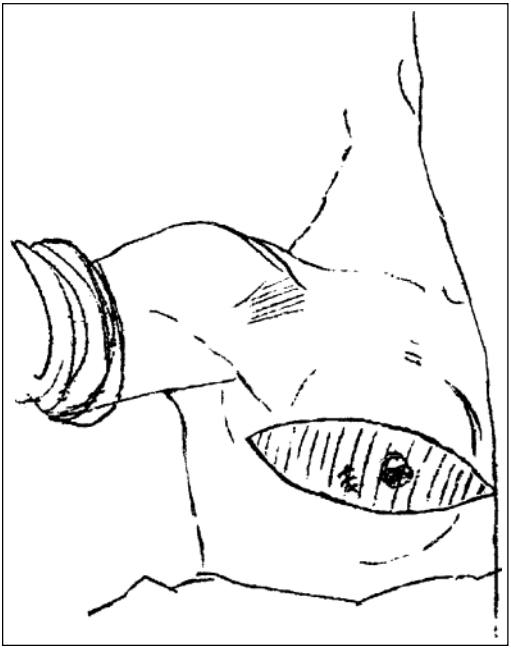

Fig. 7.5. Skin flaps are marked to include the biopsy site. Enough skin is removed to result in a flat scar.

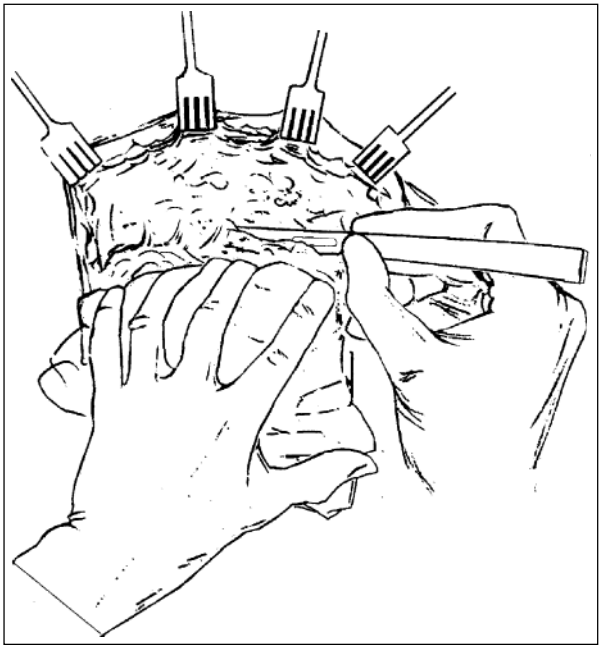

Fig. 7.6. Skin flaps are developed with upward traction on the skin, and countertraction on the breast. The breast is removed with its fascial envelope.

major, and this must be removed to ensure near complete excision of all breast tissue. During this phase of the dissection, the medial pectoral nerve is at risk but may be sacrificed with no ill sequelae.

After hemostasis is confirmed, the wound is irrigated and a closed suction drain placed over the pectoralis major. The wound is approximated with interrupted subcutaneous sutures, and the skin is closed with a subcuticular suture (Fig. 7.8).

Technique of Axillary Dissection

The arm is draped free and rests on an arm board for most of the procedure. During dissection of the apex of the axilla, the arm can be flexed and abducted to relax the pectoralis major muscle and allow better access. Care is taken to avoid stretching the brachial plexus.

For axillary dissection as an independent procedure, the incision is planned to maximize exposure while allowing for an excellent cosmetic result. A transverse or somewhat u-shaped incision extending from the lateral margin of the pectoralis major to the anterior border of the latissimus dorsi meets these requirements (Fig. 7.9). It is important to avoid a radial incision extending

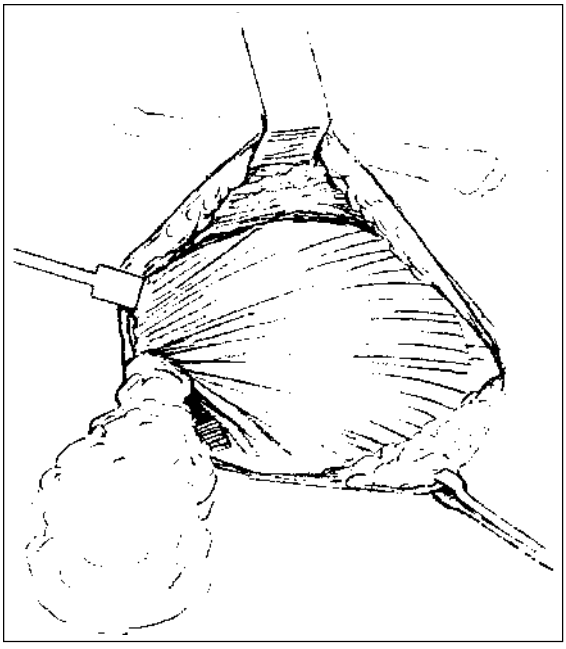

Fig. 7.7. The breast is removed along with the pectoralis fascia in a superomedial to inferolateral direction.

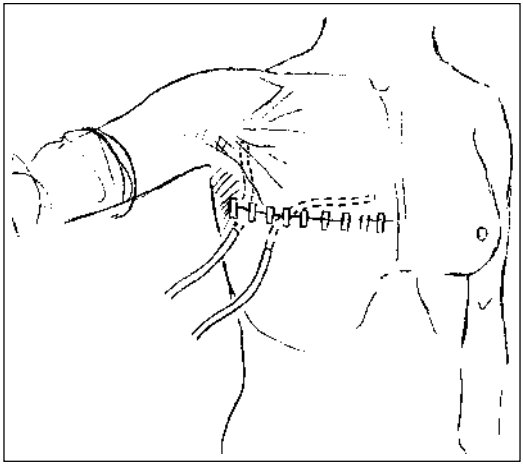

Fig. 7.8. The wound is closed over a suction drain (illustration shows a second drain in the axilla) using a subcuticular suture and steri-strips.

from the breast to the axilla. While this does provide excellent exposure, scar shortening produces significant distortion, especially after breast irradiation. During modified radical mastectomy, axillary exposure is excellent after removal of the breast.

Skin flaps are elevated at the level of the axillary fascia. There are no lymph nodes superficial to this; therefore, it is unnecessary to excise the subcutaneous fat. The superior flap is elevated to the level of the transverse skin crease. A medial flap is elevated to expose the lateral margin of the pectoralis major. A lateral flap is raised to expose the anterior border of the latissimus dorsi. The extent of the inferior flap is arbitrary, as there are no bony or muscular landmarks. It is usually extended to about the fifth or sixth intercostal space (Fig. 7.9).

The lateral edge of the pectoralis major is exposed. The clavipectoral fascia is then excised along the lateral margin of the pectoralis minor, from the vicinity of the axillary vein to the costal origin of the pectoralis minor. In the upper part, a neurovascular bundle containing the medial pectoral nerve and branches of the thoracoacromial vessels is found, and the nerve is preserved if possible. The incision is carried laterally, in front of the estimated position of the axillary vein (Fig. 7.10). At this time it is important to limit the dissection to the area below the axillary vein. Vigorous traction during dissection can easily lead the surgeon to remove a pad of fat from the front of the vein as well.

For a more extensive nodal clearance, the pectoralis minor muscle can be excised or divided. Unless there is extensive nodal disease, it is not usually necessary to do this. Retraction of both pectoral muscles after flexion and abduction of the arm usually allows adequate access to the apex of the axilla.

The upper level of dissection is individualized. The axillary lymph nodes are then dissected from the lateral chest wall and from below the axillary vein. Small arteries and tributaries of the vein are ligated. There is usually one large tributary of the axillary vein requiring individual ligation. The second intercostal nerve (the intercostobrachial nerve) traverses the axilla about 2 cm below the axillary vein. It supplies the skin of the axilla and the medial aspect of the upper arm. It is possible to preserve this nerve in most cases, although many surgeons routinely divide it. The long thoracic nerve passes straight down the chest wall in a position about 2 cm posterior to the intercostobrachial nerve. It lifts off the chest wall with the axillary fat and must be deliberately separated from the specimen and placed back on the chest wall (Fig. 7.11). As the dissection of the specimen from the axillary vein progresses, the subscapular vessels appear. The thoracodorsal nerve lies deep and usually medial to these vessels. The nerve and vessels are usually spared, but if there is suspicious nodal disease in the area, they can be sacrificed. Once the long thoracic and thoracodorsal nerves are identified, the tongue of tissue lying between them on the subscapularis muscle is then

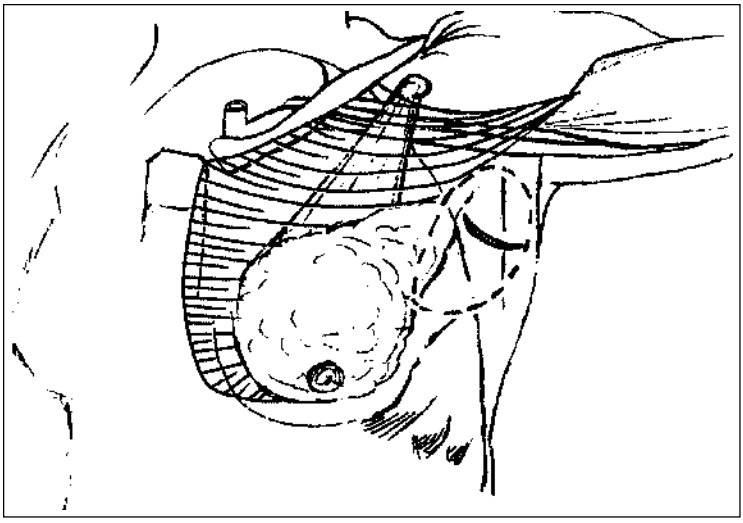

Fig. 7.9. Schematic diagram showing the incision for an axillary dissection and the extent to which flaps are elevated.

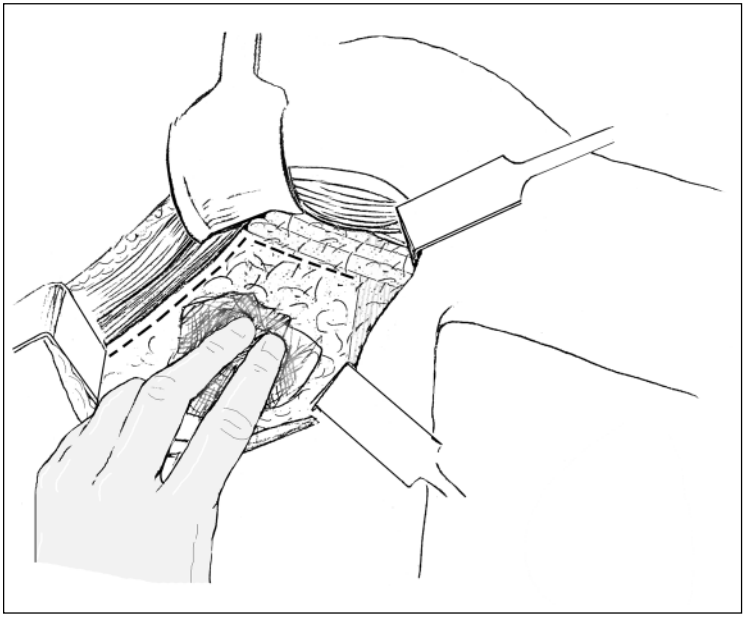

Fig. 7.10. Incision of the clavipectoral fascia along the lateral edge of the pectoralis minor and below the axillary vein. The position of the vein is outlined.

removed (Fig. 7.12). The thoracodorsal nerve is finally dissected free from the specimen. This requires ligation of a few small vessels.

The specimen is marked to identify the apical nodes. Hemostasis is secured, a suction drain is placed, and the wound closed with an absorbable subcuticular suture. Postoperatively, the drain should remain in place until the daily drainage is less than 30 cc.

Complications of Axillary Dissection

The axillary surgery causes the bulk of postoperative discomfort for breast cancer patients, and minor complications are frequent. Seromas are frequently seen, especially if the drain is removed early. These can be managed by aspiration in the outpatient clinic. In the long term, numbness in the medial aspect of the arm is universal if the intercostobrachial nerve has been divided.

Lymphedema and recurrent cellulitis are the most feared and potentially disabling of the complications. The reported incidence of lymphedema varies from 7-60% according to the methods used to assess the arm and the interval between surgery and follow-up. Many recent studies have reported a 15-20% incidence after treatment with axillary dissection or axillary irradiation. The incidence is much higher if both surgery and radiation therapy are used. The extent of axillary surgery and the use of axillary radiation therapy are the only factors that have been consistently associated with the formation of lymphedema. Older age, obesity and infection are other likely risk factors.

Lymphedema can appear years after the surgery. It is routine to advise patients to avoid arm swelling and infection by taking special care not to suffer cuts and scrapes on the operated side, to avoid injections, blood-pressure monitoring, and blood draws, to avoid constricting clothing and jewelry, etc.

Warmuth[7] reported a survey of 330 patients who were disease-free 2-5 years after surgery for early-stage breast cancer. Thirty-five percent reported numbness, 30% reported pain, 15% reported arm swelling, and 8% reported limitation of arm movement. Most of the symptoms were mild and did not interfere significantly with daily activity.

Selected Readings

1. Veronesi U, Saccozzi R, Del Vecchio M et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiation therapy in patients with small cancers of the breast. N Engl J Med 1981; 305:6-11.
This is the landmark report of the first randomized prospective trial of breast-conservation therapy.
2. Fisher B, Bauer M, Margolese R et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985; 312:665-73.
This is the first report of the major North American trial of breast-conservation therapy from the NSABP.

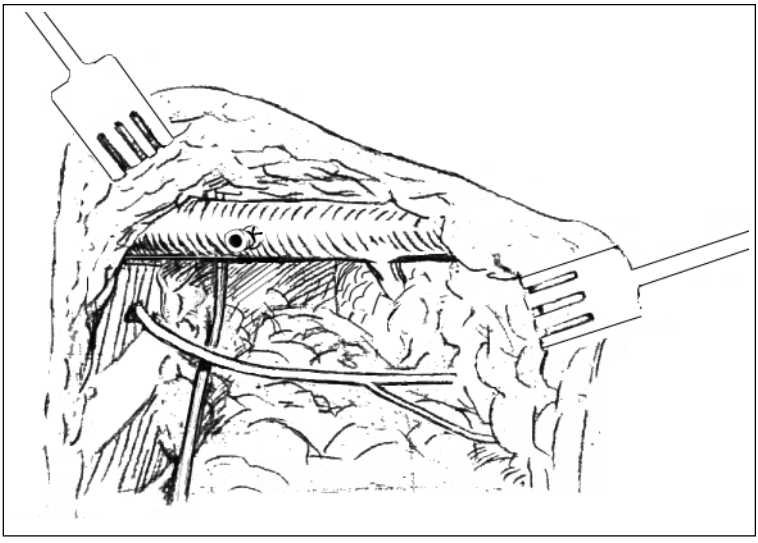

Fig. 7.11. Axillary dissection in progress. The anterior tributary of the axillary vein has been divided, the intercostobrachial nerve has been preserved and the long thoracic nerve identified.

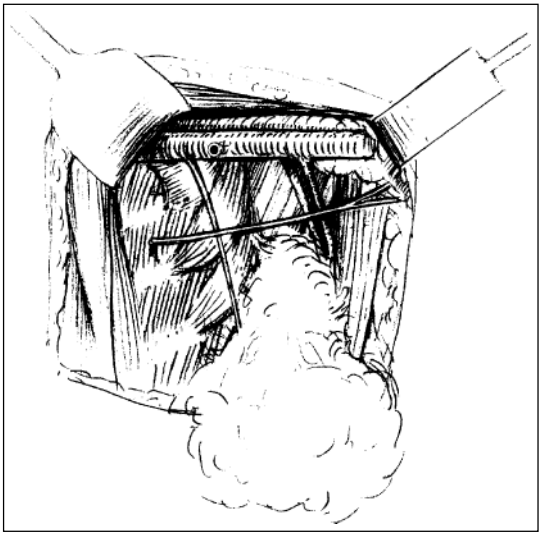

Fig. 7.12. Advanced stage of axillary dissection. The thoracodorsal nerve has been preserved, and the tissue between the long thoracic and thoracodorsal nerves has been removed.

3. Borgen PI, Heerdt AS, Moore MP et al. Breast conservation therapy for invasive carcinoma of the breast. Current Problems in Surgery 1995; 33:189-256.
This is a review of all aspects of breast-conservation therapy.
4. Fisher B, Costantino J, Redmond C et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993: 1581-6.
This is the major trial of conservative therapy for DCIS
5. Adair F, Berg J, Joubert L et al. Long-term follow-up of breast cancer: the 30-year report. Cancer 1974; 33:1145-50.
This is an older report from the days before adjuvant therapy that demonstrates the effectiveness of surgery in node-positive disease.
6. Fisher B, Redmond C, Fisher E et al. Ten year result of a randomized clinical trial comparing radical mastectomy and total mastectomy with of without irradiation. N Engl J Med 1985; 312:674-81.
This is a very influential trial that showed that less-extensive surgery had similar results to radical mastectomy.
7. Warmuth MA, Bowen G, Prosnitz LR et al. Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey. Cancer 1998; 83:1362-8.
This report gives a good idea of the range of complications after axillary dissection.

CHAPTER 8

Adjuvant Therapy of Breast Cancer

Maura N. Dickler

Breast cancer is the most common malignancy among women in the United States and is second only to lung cancer as the most common cause of cancer-related mortality. In 2000, it is estimated that 182,800 new cases of invasive breast cancer will be diagnosed, as well as 42,600 new cases of ductal carcinoma in situ (DCIS). Although mortality rates from breast cancer declined by approximately 1.8% per year between 1990 and 1996, 40,800 women are still expected to die from breast cancer in 2000. Widespread screening and improvements in treatment, particularly with the use of post-operative adjuvant chemotherapy and hormonal therapy, have contributed to this declining mortality.

In women with "early-stage" breast cancer, all detectable disease is limited to the breast and, in women with lymph node-positive disease, to the axillary lymph nodes. Advances in surgery have provided local control with goals towards removing less tissue, and patients are now offered several surgical options including modified radical mastectomy, lumpectomy with axillary lymph node dissection, and lumpectomy with sentinel lymph node mapping and selective lymphadenectomy. Adjuvant radiation therapy has reduced the incidence of local recurrence after breast-conservation therapy. Despite adequate local control, undetected deposits of micrometastatic disease will remain in some patients, and if left untreated, may develop into recurrent disease. In the late 19th century, Halsted proposed the theory of the orderly spread of cancer, which traveled from the breast through the axillary lymph node "filter" to distant metastatic sites. It is now thought that metastases can occur much earlier in the natural history of the disease. Therefore, the treatment of breast cancer requires a "systemic" approach with the use of therapies that will treat the "distant" microscopic disease that has already escaped the breast and lymph nodes by the time of initial surgery. Systemic postoperative treatment, referred to as "adjuvant therapy," has been the focus of numerous clinical trials over the past 25 years, representing an effort to reduce this risk of recurrence in these women.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was formed in 1985 to perform systematic overviews (meta-analyses) of all of the randomized trials of treatment of early-stage (resectable) breast

Breast Diseases, edited by Patrick I. Borgen and Arnold D.K. Hill.

cancer including chemotherapy and hormonal therapy. The EBCTCG continues to meet every 5 years to update the worldwide prospective experience with adjuvant therapy. The results of the most recent 1995 overview analysis were published in 1998. Because of the large number of women included in these trials as well as the long duration of follow-up, these overviews provide a powerful tool with which to analyze the worldwide randomized data. The results of these analyses will be the focus of this review, as they provide the foundation on which medical oncologists base their selection of adjuvant therapy.

Tamoxifen for Adjuvant Therapy

The largest group of women in the 1995 analysis included almost 37,000 women randomized in 55 trials, all of which were designed to look at whether tamoxifen was an active agent in the postoperative setting. Women who were randomized to tamoxifen were found to have a highly significant reduction in the annual risks of both recurrence and death compared with women who received no adjuvant tamoxifen. This was seen for women who were randomized to tamoxifen for a median duration of 1, 2 or 5 years. This effect was most pronounced for women who received 5 years of adjuvant tamoxifen, with a reduction in the risk of recurrence of 42% (standard deviation [SD]) and a reduction in the risk of death of 22% (SD 4). A longer duration of tamoxifen is currently being explored; however, at the present time there are no data to suggest an advantage to more than 5 years of tamoxifen. The dose of tamoxifen that was administered in most of these trials was 20-40 mg each day, and there was no evidence of a dose-response relationship within this range.

Most of the benefit of tamoxifen was noted for women with estrogen-receptor (ER)-positive tumors rather than for patients with ER-poor tumors (Table 8.1). After 5 years of tamoxifen, women with ER-positive tumors had a reduction in the risk of recurrence of 50% (SD 4), compared with a risk reduction of only 6% (SD 11) for women with ER-poor tumors. Within this "receptor-poor" category, some of the receptors must have been low receptor-positive, which partially accounts for the small positive effect. The benefits of tamoxifen were most significant in women with the highest estrogen-receptor expression (>100 fmol receptor per mg cytosol protein). The 1995 analysis was the first overview to provide convincing evidence of a lack of a substantial benefit for the effect of tamoxifen in the ER-poor population, and the hormone-receptor measurement is considered an important determinant of the response to treatment. Although the number of women was small, patients with ER-negative and progesterone-receptor (PR)-positive tumors appeared to benefit from tamoxifen; therefore, this subgroup most likely represents a tamoxifen-responsive population.

Table 8.1. Benefits of adjuvant tamoxifen by hormone-receptor status and age

	(% ± SD)	
	Recurrence	**Death**
ER-poor	6 (SD 11)	– 3 (SD 11)
ER-unknown	37 (SD 8)	21 (SD 9)
ER-positive	50 (SD 4)	28 (SD 5)
Total	43 (SD 3)	23 (SD 4)
Age		
< 50	45 (SD 8)	32 (SD 10)
50-59	37 (SD 6)	11 (SD 8)
60-69	54 (SD 5)	33 (SD 6)
> 70	54 (SD 13)	34 (SD 13)

Percentage decrease in the annual odds of recurrence of breast cancer or death from any cause for women randomized to tamoxifen (versus no tamoxifen) for a median duration of 5 years
ER=estrogen receptor; SD=standard deviation

The proportional benefits of tamoxifen are similar for women with both lymph node-positive and node-negative disease. The absolute benefits, however, from the use of tamoxifen are related to each woman's risk of recurrence. Women with lymph node-positive disease have a higher annual risk of recurrence and mortality from breast cancer and therefore derive a greater absolute benefit from the use of tamoxifen (Fig. 8.1). The effects of tamoxifen are apparent on the risks of recurrence after the first year of treatment, with most of the benefits seen during the initial 5 years of therapy. The effects of tamoxifen on mortality, however, continue to increase even after the completion of 5 years of therapy, with a significant difference noted at 10 years.

In previous overviews, the benefits of tamoxifen appeared limited to postmenopausal women (defined as age >50); however, with longer follow-up and a greater number of premenopausal women included in the analysis, the 1995 overview has extended the benefits of tamoxifen to women less than and greater than 50 years of age (Table 8.1). Therefore, age and menopausal status should no longer represent a barrier to the use of tamoxifen, and the majority of women with ER-positive tumors should be offered tamoxifen as part of adjuvant therapy.

Although tamoxifen was shown to reduce the risk of recurrence and mortality in women with breast cancer, tamoxifen was associated with an increased incidence of endometrial carcinoma. The risk of invasive endometrial cancer was increased about 2.5-fold among tamoxifen-treated women, with a higher risk for women who received 5 years of therapy (RR 4.2, 2-sided p <0.0001). Other trials have also demonstrated an increased risk of

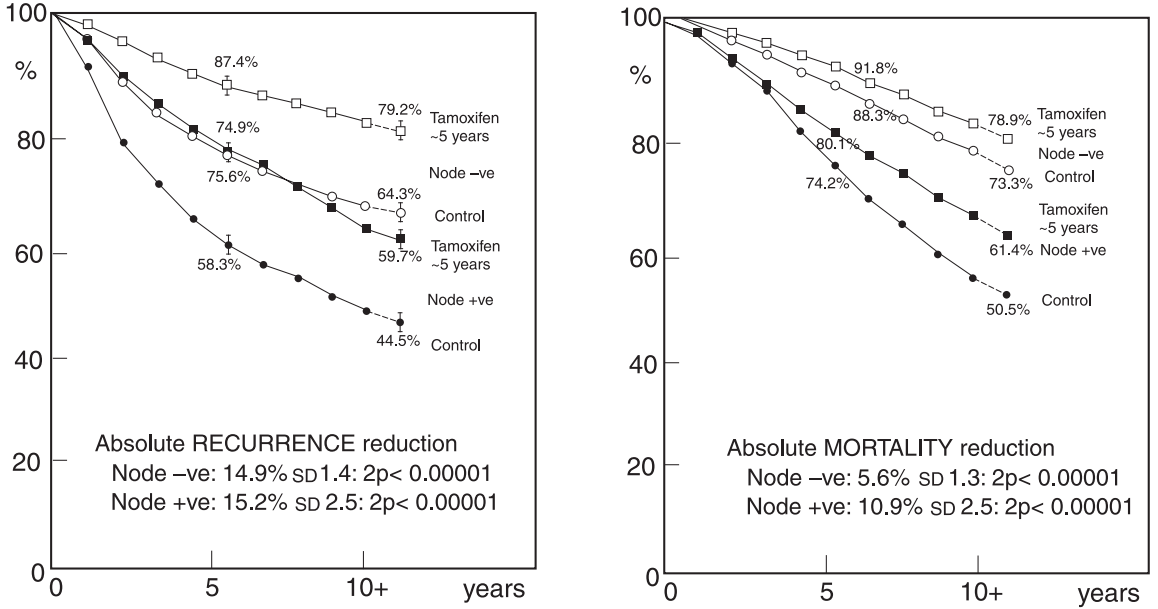

Fig. 8.1. Absolute risk reductions for 5 years of adjuvant tamoxifen during the first 10 years, subdivided by nodal status (after exclusion of women with ER-poor disease). In these generalized Kaplan-Meier curves, the values for the tamoxifen and control patients at 5 years and at 10 years are given beside each pair of lines. Differences in 10 year outcome, together with their standard errors, are given below the lines. Reprinted with permission from Lancet 1998; 351:1451-1467. © 1998 Lancet.

endometrial cancer with the use of tamoxifen. In NSABP-B-14, a randomized adjuvant trial of tamoxifen, 23 cases of endometrial cancer were reported in women receiving tamoxifen compared with two cases in the control group (both of whom had subsequently required tamoxifen due to a change in medical status). This translated into a relative risk of 7.5 (95%, CI 1.7-32.7) for the tamoxifen-treated patients, and a 5 year cumulative hazard rate of 6.3 per 1,000. The vast majority of cases (21 of 24) were International Federation of Gynecology and Obstetrics (FIGO) Stage I, with most cases of good to moderate histologic grade.

Tamoxifen is considered the first choice of adjuvant therapy for postmenopausal women with ER-positive tumors as it is well tolerated with minimal toxicity. Tamoxifen also adds to the benefits of chemotherapy in all women with receptor-positive disease. The combination of chemotherapy with tamoxifen will be discussed further below. Other hormonal therapies, including the aromatase inhibitor anastrozole, are presently being compared to tamoxifen in adjuvant clinical trials.

Tamoxifen and the Risk of Contralateral Breast Cancer: Role as a Chemopreventive Agent

Women randomized to 5 years of tamoxifen in the overview analysis were found to have a 47% (SD 9) reduction in the risk of contralateral breast cancer. In light of these promising results, large-scale trials were initiated in Europe and North America to definitively evaluate tamoxifen as a chemopreventive agent in healthy high-risk women.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently reported results from the Breast Cancer Prevention Trial (BCPT), a randomized double-blind, placebo-controlled trial of tamoxifen involving 13,388 high-risk women. Women were eligible for this trial if they were over the age of 60, or if their risk of breast cancer was calculated to be that of a 60-year-old woman (equivalent to a risk of breast cancer of 1.67 % over 5 years). For women under age 60, the modified Gail model calculated this risk. This model took into account several risk factors including number of first-degree relatives with breast cancer, current age of the participant, age at menarche and at time of first delivery, parity, number of breast biopsies and history of atypical hyperplasia. Women with a history of lobular carcinoma in situ were eligible based on their risk of breast cancer after this biopsy result alone.

After a median follow-up of 4.5 years, a 49% reduction in the risk of invasive breast cancer was observed among the participants randomized to tamoxifen, with a relative risk of 0.51 (range, 0.39-0.66). This number closely approximates the risk reduction in the overview analysis, supporting the benefits of tamoxifen as a chemopreventive agent. In addition, there was a significant reduction in the risk of noninvasive breast cancer, including ductal

carcinoma in situ. Tamoxifen was also shown to reduce the number of fractures in the hip, wrist and spine; however, there was no difference in the risk of ischemic cardiac events between the treatment groups. As expected, there was an increased risk of thromboembolic events, including pulmonary emboli and deep vein thromboses in the tamoxifen group, with a relative risk of 3.01 (range, 1.15-9.27) and 1.60 (range, 0.91-2.86), respectively.

The results of two European studies evaluating tamoxifen as a chemopreventive agent have failed to confirm the positive results that were reported by the NSABP. These European trials differed from the NSABP trial with respect to trial design, size and populations of women enrolled, such that a valid comparison between the three trials is difficult to perform. In addition, these trials allowed the use of hormone replacement therapy, which may have confounded the results. The negative European trials remain blinded, and will be updated after follow-up analyses.

Ovarian Ablation

Ovarian ablation is among the oldest treatments for metastatic breast cancer. Beatson first described the method in 1896 when he reported the dramatic shrinkage of tumor in three women with locally advanced disease. Surgical oophorectomy was used extensively for the treatment of advanced disease in premenopausal women, and in 1922 radiation-induced ovarian ablation was also introduced. The EBCTCG reported the results of a meta-analysis of 12 trials of adjuvant ovarian ablation, published exactly 100 years after Beatson's original report.

For women under the age of 50 (most of whom were premenopausal at the time of diagnosis), ovarian ablation (either surgical or radiation-induced) was found to improve disease-free and overall survival significantly. For women who received ovarian ablation as their only adjuvant therapy, there was a 25% (SD 7) reduction in the risk of recurrence. For women who received adjuvant chemotherapy in addition to ovarian ablation, the benefits were much less (10%, SD 9). By contrast, there was no significant benefit of ovarian ablation in older women, as would be expected based on their perimenopausal/postmenopausal status. Although the numbers of patients were small, there was no difference in the incidence of contralateral breast cancer in these women.

Chemotherapy in the Adjuvant Setting

In a similar fashion to tamoxifen, the EBCTCG performed an overview of the worldwide randomized data for the use of adjuvant chemotherapy in early-stage breast cancer (almost 18,000 women randomized in 47 trials). The chemotherapy regimen used in the majority of trials was CMF (cyclophosphamide, methotrexate and 5-fluorouracil [5-FU]). Chemotherapy significantly reduced the annual risk of recurrence and

mortality compared with no chemotherapy, and trials that used a combination of several agents (polychemotherapy) were superior to those of single-agent chemotherapy. The use of prolonged chemotherapy (regimens of typically 1-2 years) did not improve upon the efficacy of shorter regimens (3-6 months).

The benefits of chemotherapy were greatest in women younger than age 50; however, the reductions in the risk of recurrence and death were still significant for women in all age groups (Table 8.2 and Fig. 8.2). Some have argued that the benefits of chemotherapy in younger patients (typically premenopausal women) are secondary to the actions of chemotherapy on ovarian ablation. Chemotherapy, however, appears to have the greatest impact in the youngest group of patients (age <40), who are least likely to experience drug-induced amenorrhea. Unfortunately, few women greater than age 70 were randomized in these trials, and therefore insufficient data exist to comment on the benefits of chemotherapy in this age group. With that said, there is little reason to believe that women over age 70 do not benefit from chemotherapy; however, the proportional benefits in this age group are not known. Age alone should not be the only determinant for the use of adjuvant chemotherapy in women who are at substantial risk of recurrence.

Chemotherapy has a proportional reduction in the risk of recurrence and death among women with lymph-node positive and node-negative disease similar to that seen with tamoxifen. The absolute benefits of chemotherapy are dependent upon the underlying risk of recurrence, and therefore women with lymph-node positive disease derive the greatest benefit. This concept is best illustrated in Figure 8.3, in which the proportional reductions in mortality

Table 8.2. Benefits of adjuvant chemotherapy

	(% ± SD)	
	Recurrence	**Death**
CC vs. no drug	23.5 ± 2.1	15.3 ± 2.4
CC vs. no drug, stratified by age		
<40	37 ± 7	27 ± 8
40-49	34 ± 5	27 ± 5
50-59	22 ± 4	14 ± 4
60-69	18 ± 4	8 ± 4
Age 50-69		
CC + tamoxifen vs. tamoxifen alone	19 ± 3	11 ± 4
Anthracycline-containing chemo vs. CMF	12 ± 4	11 ± 5

Percentage decrease in the annual odds of recurrence of breast cancer or death from any cause for women randomized to chemotherapy
CC=chemotherapy; SD=standard deviation; CMF=(cyclophosphamide, methotrexate and 5-FU)

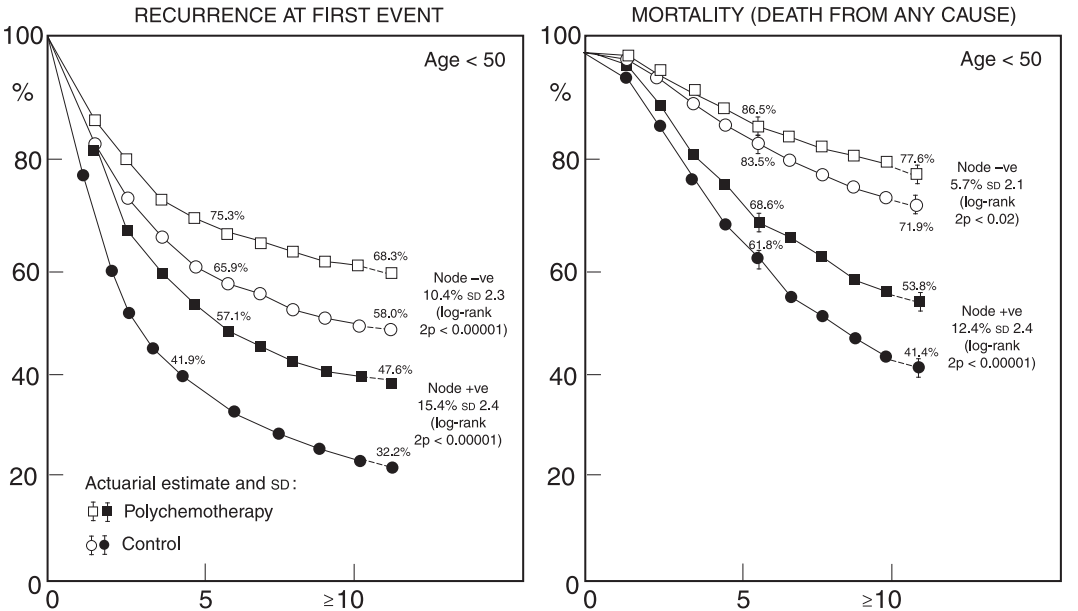

Fig. 8.2. Absolute risk reductions with polychemotherapy during the first 10 years of follow-up, subdivided by age at randomization and nodal status. Values for polychemotherapy and control patients at 5 and 10 years and absolute differences at 10 years (with SDs, and log-rank *p*-values for whole period) are given beside each pair of lines. Reprinted with permission from Lancet 1998; 352:930-942. © 1998 Lancet.

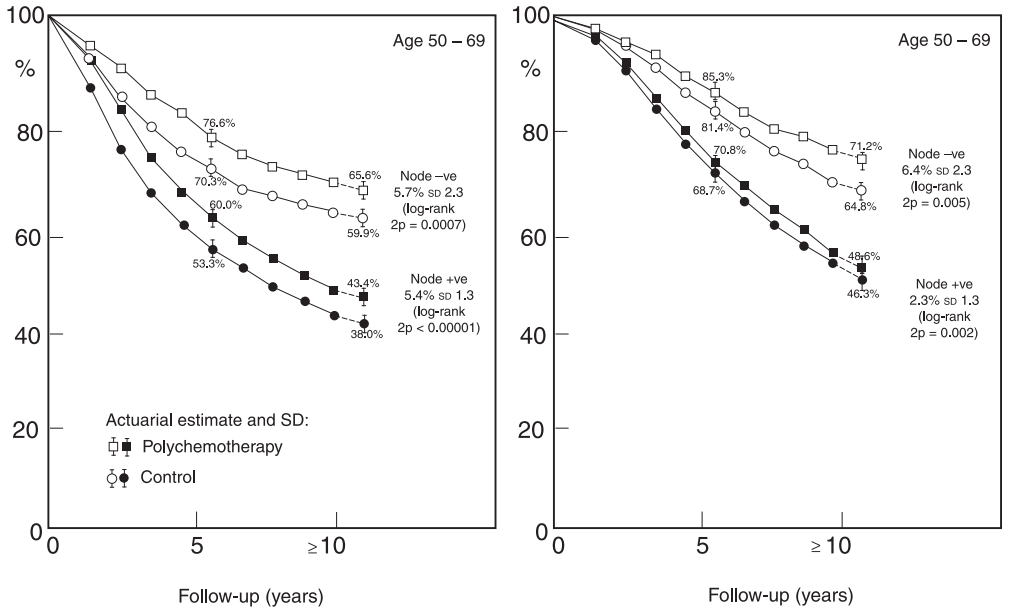
100
%
80
60
40
20
0
Age 50 – 69
76.6%
70.3%
60.0%
53.3%
65.6%
59.9%
43.4%
38.0%
Node –ve
5.7% SD 2.3
(log-rank
2p = 0.0007)
Node +ve
5.4% SD 1.3
(log-rank
2p < 0.00001)
Actuarial estimate and SD:
Polychemotherapy
Control
0
5
≥10
Follow-up (years)
100
%
80
60
40
20
0
Age 50 – 69
85.3%
81.4%
70.8%
68.7%
71.2%
64.8%
48.6%
46.3%
Node –ve
6.4% SD 2.3
(log-rank
2p = 0.005)
Node +ve
2.3% SD 1.3
(log-rank
2p = 0.002)
0
5
≥10
Follow-up (years)

Fig. 8.2, cont'd.

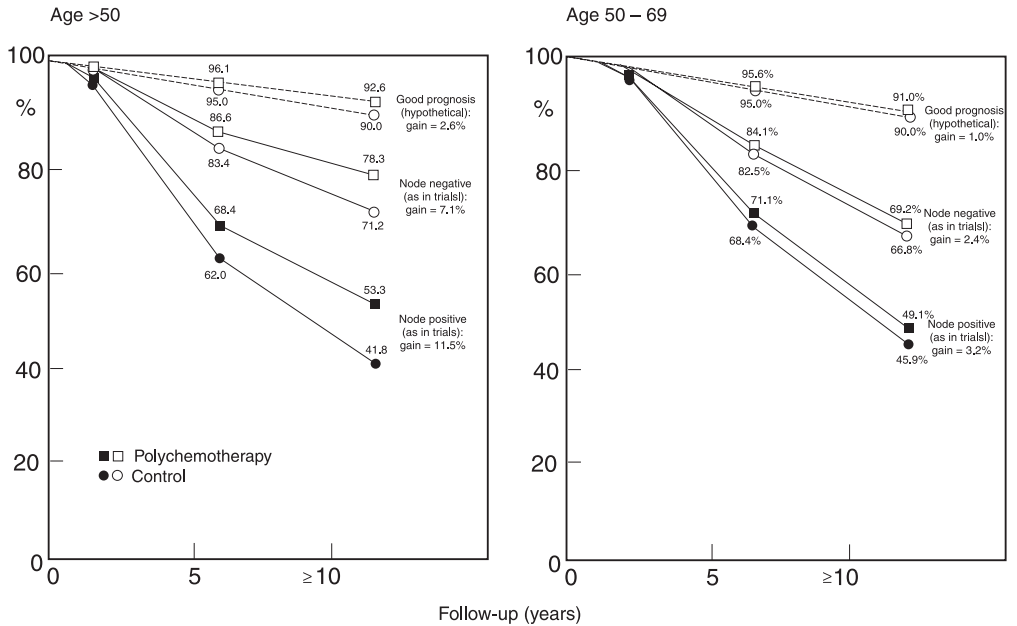

Fig. 8.3. Estimated absolute survival advantages with prolonged polychemotherapy for populations of women with good, intermediate and poor prognosis, subdivided by age (calculated by having the proportional risk reduction unaffected by prognosis). Reprinted with permission from Lancet 1998; 352:930-942. © 1998 Lancet.

are applied to three groups of patients at different risks of recurrence (node-positive, node-negative, and "good prognosis" node-negative with small tumors found on screening mammography). For women under 50 years of age, absolute improvements in 10 year survival are approximately 11% in the "poor prognosis" lymph-node-positive patients, whereas the "moderate" and "good" prognosis node-negative groups experience smaller improvements in survival of 7% and 2.6%, respectively. For women over age 50, the absolute improvements in 10 year survival are approximately 3.2% for women at the highest risks of recurrence, and 2.4% and 1.0%, respectively, for women with moderate-and good-prognosis disease. Although the absolute percentages are small, when these improvements in survival are applied to the large number of women who develop breast cancer around the world, the potential number of lives saved is quite large.

Some of the trials included in the overview analysis addressed chemotherapy plus tamoxifen versus tamoxifen alone. In women of all ages, the addition of chemotherapy to tamoxifen further reduced the risk of recurrence as compared to treatment with tamoxifen alone. As mentioned previously from the tamoxifen overview, tamoxifen has been shown to add to the benefits of chemotherapy. Therefore, each treatment appears to contribute independently to improving disease-free and overall survival, and should be considered complementary and not competing adjuvant treatments (Table 8.2).

Beyond CMF: The Use of Doxorubicin and Taxane-Containing Regimens

In the chemotherapy overview analysis, 11 trials included women who were randomized to receive CMF versus an anthracycline-containing regimen (either doxorubicin or, in European trials, epirubicin). There was a small but significant reduction in the risk of recurrence with the anthracycline-containing regimen (12% ± 4) as compared to CMF, which translated into a small benefit in overall survival (Fig. 8.4). The use of doxorubicin-containing chemotherapy is now commonly employed for the treatment of patients with lymph node-positive disease. Doxorubicin is generally more toxic, such that women experience more frequent side effects, including alopecia, nausea, vomiting and mucositis. In addition, women can develop symptoms of congestive heart failure which occurs in approximately 1% of patients in the adjuvant dose range (<300 mg/m^2). Recently, a link has been established between doxorubicin use and an increased incidence of acute myelogenous leukemia. Patients with anthracycline-induced AML typically have a specific chromosomal translocation (11q23), which is characteristic of drugs that inhibit the enzyme topoisomerase II. Thus, the benefits of doxorubicin in improving disease-free and overall survival must be carefully weighed against the side effects of these regimens.

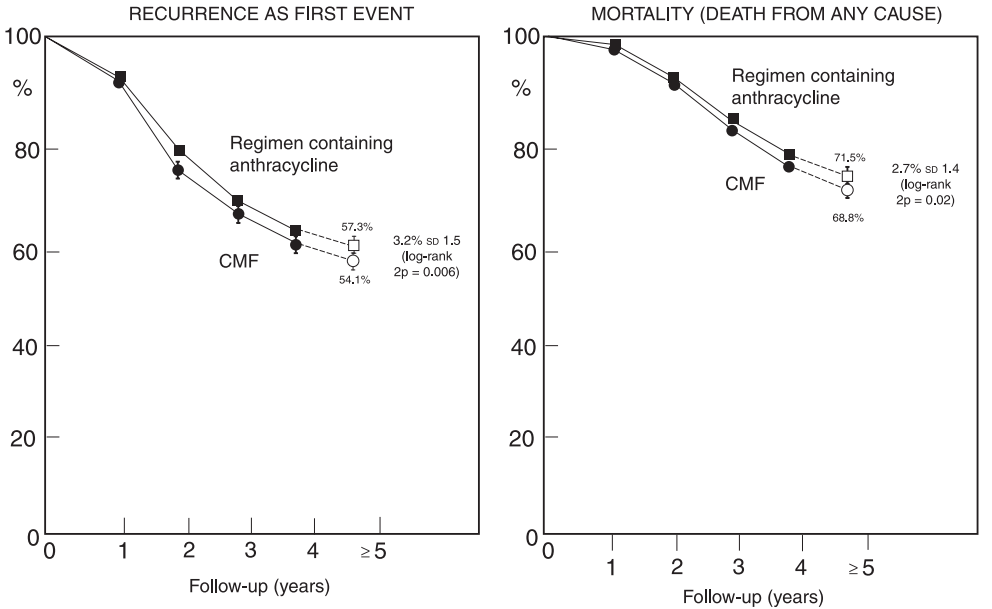

Fig. 8.4. Absolute effects of anthracycline-containing regimens compared with CMF. Values at 5 years and absolute differences in outcome (with SDs, and log-rank *p*-values for whole period) given beside each pair of lines. Years 0-4 include 90% of all recurrences and 81% of all deaths in these trials. Reprinted with permission from Lancet 1998; 352:930-942.

The use of escalating doses of doxorubicin (60, 75 and 90 mg/m^2) in combination with cyclophosphamide (referred to as AC) and the sequential addition of paclitaxel (Taxol®) to this regimen (AC followed by T) has recently been tested in the adjuvant setting. Paclitaxel is a chemotherapeutic drug that causes stabilization of the microtubule assembly and has proven to be an effective agent in the treatment of metastatic disease. After a median follow-up of 18 months, no differences in either disease-free or overall survival were seen with increasing doses of doxorubicin; however, the addition of paclitaxel to AC was slightly but significantly superior to AC alone in both disease-free and overall survival (improved disease-free survival from 86 to 90%, RR 22%, p=0.0077 and overall survival from 95 to 97%, RR 26%, p=0.0390). Additional follow-up is required to confirm these early results, which have recently been reported in abstract form. The use of taxanes, however, appear to be promising additions to adjuvant treatment, and ongoing trials are investigating the use of both paclitaxel- and docetaxel-containing (Taxotere®) regimens.

Role of High-Dose Chemotherapy for High-Risk Breast Cancer

The investigation of high-dose chemotherapy for the treatment of women with breast cancer was supported by laboratory findings that suggested a dose-response relationship for alkylating agents. Medical advances to support patients through the intensive high-dose therapy permitted the initial investigation of this principle in women with metastatic disease. The use of autologous bone-marrow support with the aid of hematopoietic growth factors and, more recently, peripheral blood-progenitor stem-cell support, has allowed high-dose chemotherapy to be administered with improved safety and reduced morbidity.

Subsequently, small uncontrolled trials of high-dose chemotherapy in high-risk patients with extensive axillary lymph node involvement (10 or more lymph nodes) reported an improved disease-free and overall survival as compared with historical controls. These patients underwent an extensive screening evaluation prior to receiving high-dose chemotherapy to exclude patients with occult metastatic disease. Such pretreatment testing introduces selection bias, which may explain the favorable results of these uncontrolled trials when compared with historical controls.

Several Phase III randomized trials have been reported recently evaluating the role of high-dose chemotherapy in both the adjuvant and metastatic settings. The trials reported to date have not been shown to improve overall survival in either the high-risk adjuvant or metastatic group. One of the adjuvant trials was initially reported to show a benefit in both relapse-free and overall survival for patients randomized to the high-dose arm. Unfortunately, the results of this trial have been invalidated due to the discovery of

scientific misconduct. Therefore, the role of high-dose chemotherapy with stem-cell support remains an investigational question and should not be offered to women outside of a clinical trial. Future trials are planned to evaluate the efficacy of tandem transplants, as well as the addition of biologic treatments for consolidation.

Assessment of Risk and Choice of Adjuvant Therapy

In order to decide which patients will benefit from the addition of adjuvant therapy, it is important to assess each woman's risk of developing recurrent disease. Competing comorbid conditions must also be considered. The overview analysis then provide an estimate of the reductions in the risk of relapse that can be expected from the administration of the drug therapies. With this information, the absolute benefits of therapy can be estimated for each patient. These benefits must be balanced by consideration of the toxicities of the treatment, as well as of the expense and relative inconvenience of the drug administration.

By far the most important predictor for estimating the risk of recurrence is the number of ipsilateral axillary lymph nodes involved with metastatic carcinoma. A patient with even one positive lymph node has a risk of relapse of approximately 30%. An adjuvant therapy that reduces the odds of recurrence by at least 30% at 10 years would improve a woman's chances of disease-free survival by approximately 9%. Therefore, adjuvant therapy should be strongly considered for these patients.

For patients with negative lymph nodes, the risk of recurrence is lower, and the benefits of therapy must be weighed carefully against the side effects of treatment. Approximately one-quarter of such patients will eventually relapse with recurrent metastatic disease. This supports the concept that local control with surgery and radiation does not prevent the early dissemination of distant metastatic disease. Although all patients are not destined to relapse, it is difficult to select definitively which patients will recur, thereby sparing other patients the unnecessary treatment.

The ability to predict the biological behavior of breast tumors has been an active area of investigation, and potential prognostic factors, including hormone receptor status, S-phase fraction, DNA ploidy and cathepsin D, may help to select a group of patients who would benefit from adjuvant therapy. These variables often correlate with already proven factors such as tumor size and histopathologic features such as degree of differentiation and lymphovascular invasion. For node-negative patients, tumors measuring less than or equal to 1 cm have an excellent prognosis with a risk of relapse of only 12% at 20 years. The risk of relapse and mortality, however, increases

Table 8.3. Five year breast cancer survival rates by tumor size and lymph node status

Size / Lymph node status	Number	Relative survival (%)
<2.0 cm		
Total	8,319	91.3
Negative nodes	5,728	96.3
1-3 positive nodes	1,767	87.4
4 + positive nodes	824	66.0
2-5 cm		
Total	13,723	79.8
Negative nodes	6,927	89.4
1-3 positive nodes	3,622	79.9
4 + nodes	3,174	58.7
>5 cm		
Total	2,698	62.7
Negative nodes	809	82.2
1-3 positive nodes	630	73.0
4 + positive	1,259	45.5

Data on 24,740 cases recorded in the Surveillance, Epidemiology, and End Results (SEER) Program of the NCI were used to evaluate the breast cancer survival in a representative sample of women in the United States. From Carter CL, Allen C, and Henson DE. Relation of Tumor Size, Lymph Node Status, and Survival in 24,740 Breast Cancer Cases, Cancer 1989;63:181-187.

with greater tumor size and axillary lymph node involvement (Table 8.3). Tumors with favorable histologies (including tubular, mucinous, papillary and colloid) have a better outcome, with a low risk of recurrence for tumors up to 3 cm in diameter.

Recently, attention has focused on specific molecular genetic changes as indicators of prognosis. Overexpression/activation of genes that promote cellular transformation, tumor growth and tumor dissemination has been detected in a significant proportion of breast tumors. HER-2/*neu* is a growth factor receptor that is overexpressed in approximately 20-30% of breast cancers, and HER-2/*neu* overexpression may predict for a more aggressive tumor biology and natural history of disease. Retrospective analyses of prospective trials have recently suggested that tumors that overexpress the HER-2/*neu* gene may be more responsive to anthracycline-containing chemotherapy regimens. Therefore, molecular genetic changes may play an increasingly larger role in the future selection of adjuvant therapy for patients with lymph node-negative disease.

New Approaches for Adjuvant Therapy

Historically, adjuvant chemotherapy has been tested in combination regimens, in which one multiagent regimen is cycled over time to allow recovery

of normal tissues (in particular, hematologic recovery). The doses of each agent in the combination must be reduced from full single-agent doses to permit for acceptable toxicity. Recently, the use of full-dose single agents administered in a sequential fashion (e.g., doxorubicin for 4 cycles, followed by paclitaxel for 4 cycles, followed by cyclophosphamide for 4 cycles) to increase the dose intensity of the regimen has been explored. In addition, the concept of dose density has also been investigated, in which similar doses of drugs are administered over shorter intervals of time (every 2 weeks as compared with every 3 weeks), with the use of colony-stimulating factors (G-CSF) to promote faster hematologic recovery between cycles. The concepts of dose intensity and dose density are being investigated in ongoing cooperative group trials, and answers to these questions should be available in the next few years.

A new approach to therapy that has been investigated in patients with metastatic disease is the use of trastuzumab (Herceptin®), a monoclonal antibody that is directed against the HER-2/*neu* receptor. When added to chemotherapy, trastuzumab has been shown to increase the efficacy of single-agent paclitaxel and doxorubicin in the metastatic setting in women with tumors that overexpress the HER-2/*neu* gene. Presently, trials are underway to evaluate trastuzumab in the adjuvant setting, both in combination with chemotherapy and as single-agent maintenance therapy. Since this drug was found to increase doxorubicin-associated cardiotoxicity, careful cardiac monitoring will be an important component of these trials.

The EBCTCG will continue to perform overview analyses every 5 years, with the next planned analysis in the year 2000. At that time, there will be additional follow-up of trials addressing the duration of tamoxifen (10 vs. 5 years) and the addition of doxorubicin and paclitaxel to adjuvant regimens. Although adjuvant therapy has contributed to the declining mortality of our patients, new strategies for the treatment and prevention of breast cancer are needed if mortality is to continue to be significantly reduced in the future.

Selected Readings

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2. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet 1998; 352:930-942.
3. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: Overview of the randomized trials. Lancet 1996; 348:1189-1196.
4. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for the prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst, 1998; 90:1371-1388.
5. Gianni Bonadonna, Guest Editor. Breast Cancer. Seminars in Oncology 1996; 23:413-532.

CHAPTER 9

Treatment—Radiation

Karen D. Schupak

Breast cancer was the first major malignancy demonstrated to be adequately treated with organ preservation. The impact of the randomized trials performed in the United States and Europe to investigate the effectiveness of radiation in securing local control in patients who had undergone lumpectomy for early-stage breast cancer cannot be underestimated. Not only has this influenced the treatment of this very prevalent disease, it has also motivated investigators of malignancies of other sites to explore the now popular concept of organ preservation.

Moderate doses of radiation are extremely effective at controlling subclinical populations of cancer cells. Over the past two decades, a better understanding of the nuances of breast cancer histology that impact on local control and refinements in radiation-therapy techniques have maximized the likelihood of control with minimal consequences to normal tissue. This parallels the refinement of surgical and pathologic techniques that are a necessary component of the procurement and analysis of the tumor to guide further therapy.

Further refinements in surgical technique, such as sentinel lymph node biopsy, are gaining in popularity and will further challenge practicing oncologists to refine their treatment approaches in order to deliver the greatest likelihood of tumor control with the least likelihood of morbidity.

Among all malignancies, breast cancer investigations stand as a paradigm of multimodality collaboration to advance knowledge and patient care.

Radiation Therapy for Early-Stage Breast Cancer

Six randomized trials, both in the United States and Europe, demonstrated conclusively that lumpectomy followed by radiation therapy to the conserved breast tissue was as effective as modified radical mastectomy in controlling breast cancer and in achieving commensurate survival.[1-6] The ideal candidate for breast-conservation therapy is a patient who has a unifocal tumor 5 cms or smaller in size that is excised with a negative margin. Although the definition of a negative margin is somewhat open to interpretation, several institutional retrospective reviews have indicated that a margin of 2 mm or greater,

Breast Diseases, edited by Patrick I. Borgen and Arnold D.K. Hill.

plus postoperative radiation, is sufficient to achieve control within the breast at a rate of approximately 93-95%.

Ordinarily, when surgery is performed to remove a breast malignancy, a 1 cm gross margin of normal tissue is considered desirable. In fact, tumors are often seen to extend beyond the initial anticipated size of the tumor. The analysis of mastectomy specimens performed by Roland Holland has revealed that subclinical foci of cancer frequently exist up to 4 cms from the periphery of the tumor.[7,8] Therefore, the value of removing a 1-2 cm rim of normal tissue along with the primary tumor is to eliminate a significant burden of subclinical disease. Given the limits of pathologic sampling, it stands to reason that a patient who undergoes lumpectomy with a resultant positive margin will have a commensurate large residual tumor burden that will decrease the patient's likelihood of local control with moderate doses of radiation. The desire to achieve tumor excision with a negative margin will commonly require the patient to return to the operating room for a second excision of the tumor bed. Occasionally, the cosmetic outcome is degraded by further surgery, highlighting the importance of collaboration between the radiologist, pathologist and surgeon to achieve excellent localization, tissue excision and margin analysis at the initial surgery.

A further element in the selection of ideal candidates for breast-conservation therapy is the ability to follow the patient mammographically. Those patients who have tumors detected mammographically, particularly by virtue of microcalcifications, must undergo postexcision mammography to assess the status of the breast tissue in the region of excision. Specimen radiography simply does not substitute for postexcision mammography with magnification views of the operated site in providing the level of security that all abnormal findings have, indeed, been removed. This study should be performed prior to embarking upon a course of postoperative radiation. Patients who have multicentric breast cancer, particularly in different quadrants of the breast, are poor candidates for breast-conservation therapy as local control in these patients is demonstrably lower.[9,10] Lastly, patients with collagen vascular diseases are reputed to tolerate radiation poorly, with several series reporting very serious and exaggerated normal-tissue consequences from radiation.[11,12] Thus, patients with collagen vascular disease should be approached with caution if breast-conservation therapy is being considered. Patients with a history of prior therapeutic radiation, such as those previously treated for Hodgkins Disease with mantle radiation therapy, are not considered candidates for breast-conservation therapy.

Currently, most patients with early-stage breast cancer, that is any patient with a T1N0 tumor 1.0 cms or greater in diameter, will ordinarily receive systemic chemotherapy. If the above criteria of wide-local excision with a negative margin have been satisfied, our policy has been to postpone radiation until the completion of all chemotherapy. This permits adequate and

uncompromised dosing of chemotherapy agents. We have found that the toxicity of combining chemotherapy and radiation is deleterious to the cosmetic result from local radiation as well as to the adequate and full dosing of current chemotherapy regimens. As Adriamycin takes an increasingly central position in the treatment of even early-stage breast cancer, the possibility of combined modality treatment is eliminated because concurrent administration of Adriamycin with radiation is contraindicated.

The patient usually commences radiation therapy 3-6 weeks after completion of the last cycle of chemotherapy. Longer intervals are associated with decreased local control.[13] Therapy must be custom-planned for each patient prior to commencing actual radiation treatments. At Memorial Sloan-Kettering Cancer Center, this includes fabricating a custom upper-body mold to assure reproducible torso, head and arm position on a daily basis. A liquid styrofoam substance is utilized that expands and conforms to the patient's desired body position and hardens to permit daily utilization of this mold for radiation setup. We feel that this type of immobilization is superior to devices that are interchanged between patients. Slight variations in arm position and rotations in the torso can dramatically alter the position of the breast upon the patient's chest wall.

Once the custom mold has been fabricated, the radiation oncologist will thoroughly examine the patient to determine the periphery of the breast tissue. We utilize solder wire to mark the periphery of the breast tissue. Similarly, the lumpectomy scar and axillary scar are wired to permit their visualization on x-rays taken within the simulator suite. Suitable beam trajectories are chosen such that the medial and lateral entry points encompass all of the breast tissue and limit the exposure to the lung and, in the case of left-sided lesions, to the heart. Furthermore, the beam trajectories must be evaluated closely to assure that the medial aspect of the contralateral breast is not being irradiated. Final beam trajectories will satisfy the requirement to treat all breast tissue and minimize the dose to lung, heart and contralateral breast. Permanent tattoo marks are placed to be utilized in coordination with calibrated laser beams, both in the simulator and treatment suites, to assure accurate daily treatment setup.

A customized plan is generated to modify the distribution of radiation dose throughout the breast tissue to enhance dose homogeneity. Without such planning and dose homogenization efforts, undesirably high doses in certain areas of the breast will result. Once the above calculations have been finalized and all appropriate beam-modifying devices have been specified, the patient is ready to start treatment. In the future, technological advances in the planning and delivery of radiation therapy, such as intensity-modulated conformal therapy, will permit even greater sparing of surrounding normal tissues.

Ordinarily, the entire breast is treated to 46-50 Gy in approximately 5 weeks of daily treatment, Monday through Friday. Ordinarily, the primary site is boosted so that it receives a total dose of 60 Gy.

The placement of small surgical clips within the lumpectomy cavity greatly enhances the ability of the radiation oncologist to completely cover the biopsy cavity with the boost. Utilizing the scar as an external landmark and the clips to define the biopsy cavity, a boost field can be designed to assure that the proper dose is being delivered thoroughly to the region that clearly has the highest risk of microscopic residual disease. Investigators have shown that the spatial correlation between the external scar and the biopsy cavity is imperfect and unreliable.[14] Other investigators have utilized ultrasound to localize the biopsy cavity.[15] The placement of small surgical clips in the biopsy cavity not only enhances the design of radiation therapy treatments. It is very helpful to the breast radiologist in directing attention, once again, to the area that will in the future be the most complicated and most in need of careful mammographic analysis.

Side Effects

During the course of therapy, patients commonly experience erythema, irritation and tenderness of the treated breast. Occasionally, there is blistering in the inframammary and anterior axillary region. Our policy on skin care is to utilize emollients copiously from the first day of therapy. Patients are carefully evaluated with regard to the fit of their bras and areas of constriction, and irritations are carefully monitored so that the patient may alter the type of undergarment worn, if necessary. Utilizing this type of rigorous attention to skin care, approximately 10% of patients will have small areas of moist desquamation, and treatment will virtually never need to be stopped to permit such areas to heal. In addition, fatigue is a common component of therapy and may last as long as 6 months after the completion of therapy.

Long-term side effects of radiation are uncommon. Radiation pneumonitis is stated to occur in 2-3% of patients and is a transient inflammation of the small volume of pulmonary tissue in the radiation fields.[16] The area of lung that becomes inflamed is that directly beneath the anterior rib cage. Symptoms mimic those of pneumonia or bronchitis: cough, shortness of breath, pleuritic chest pain and fever. This side effect, when it occurs, will occur within 1 month of the completion of therapy. Moderate tapering doses of corticosteroids are adequate treatment for this condition. In patients with normal pulmonary functions prior to treatment, this condition should be self-limiting and of no long-term consequence. It is important to remember that even patients who do not experience clinical pneumonitis may have radiographic changes at the anterior aspect of the ipsilateral lung. Occasionally, radiologists who are called upon to read a chest x-ray or computed tomography (CT) scan in such patients, and who are not provided with a

full clinical history, will misinterpret these changes as other pulmonary disorders. Therefore, it is most important for patients to understand that a small segment of lung tissue will not function properly after radiation, will appear radiographically scarred and, in rare cases, may result in a clinical syndrome of radiation pneumonitis.

Up to 2% of patients are reported to have rib fractures due to accelerated osteoporosis involving the ipsilateral anterior rib cage. Again, this is a self-limiting condition and will usually heal over time. The patient remains at risk for this occurrence over the remainder of her life.

The rate of lymphedema in patients who have had limited axillary dissections is reported to be approximately 5%. Due to the fact that radiation fields need to encompass the axillary tail of breast tissue, a small portion of the axillary contents are usually irradiated, and this will result in a small increase in the rate of lymphedema to approximately 7%. An important component of the long-term follow-up for patients who have undergone breast-conservation surgery utilizing radiation is evaluation for early evidence of lymphedema. When dealt with promptly, while at a subtle stage, this condition can almost always be controlled and, frequently, reversed entirely. If, however, the condition is permitted to advance to a rather dramatic stage, the prospects for complete reversal diminish. The contribution that a patient may make to the avoidance of lymphedema and to its early and aggressive management, should it occur, cannot be underestimated. Our patients are instructed to limit weight bearing to a maximum of 5 lbs on the operated side, and there can be no blood drawing, no IV placement or blood-pressure readings taken on the effected side. Patients are instructed not to hang their handbags over the shoulder on the effected side. Any insect bite or minor cuts or scrapes should be treated promptly with antibiotic ointment, and if the area becomes inflamed, oral antibiotics should be administered without delay. Lymphedema is a lifelong risk and may develop many years after surgery. In its most extreme form, chronic and profound lymphedema after radiation can lead to Stewart-Treves syndrome, where lymphosarcoma, a rapidly fatal soft-tissue malignancy, may occur.

The most dreaded long-term consequence of radiation therapy is the possible induction of a second malignancy. This has been carefully studied and reviewed by many centers.[17,18] The possibility of inducing a primary tumor in the bone or soft tissue of the chest wall is estimated at 1 in 500 to 1 in 1,000. The latency for such tumors is generally between 7 and 14 years time, further highlighting the importance of lifelong follow-up for patients who have undergone treatment for an early-stage breast cancer.

Even the most meticulously planned and delivered radiation treatments will deliver a small "scatter" dose to the contralateral breast. This has been measured and quantified and, theoretically, should increase the risk of contralateral breast cancer slightly. In fact, this correlation has not been

generally found, although there are several studies that suggest that women younger than 40 who have been irradiated for their index tumor have a higher incidence of contralateral breast cancer than those who have undergone mastectomy for their index tumor. [19] In this setting, we omit the medial wedge if at all possible to further decrease the scatter dose of radiation. It is not clear whether such women, who develop their index cancer prior to age 40, have a genetic predisposition to favor initiation of a second tumor with small doses of radiation.

Radiation Therapy for Axillary Control

NSABP-B04 demonstrated that radiation, in lieu of axillary dissection, for patients with clinical N0 or N1 breast cancer was adequate treatment and secured local control in the majority of patients.[20] Currently, most patients require axillary staging to direct systemic therapy. In the case of elderly patients who are not medially fit for chemotherapy, and in cases when the primary tumor, upon excision, is demonstrated to be hormone-receptor positive and, therefore, utilization of hormonal therapy is indicated, axillary dissection is not necessary. For patients who will undergo radiation as a component of their therapy, it is technically quite simple to include levels 1 and 2 of the axilla. In this circumstance, the inferior aspect of the humoral head is the desired superior border of the radiation field. This represents a very minor alteration in the standard radiation field and should be considered as an appropriate alternative to axillary surgery in this select population.

Postmastectomy Radiation Therapy

Among patients who undergo mastectomy for early-stage breast cancer (Stage I and Stage II) the role of postmastectomy radiation is currently in evolution. At one point in time, this was the only adjuvant therapy available and it was clearly effective in diminishing local failure. With longer follow-up on the rather simple radiation techniques from the 1950s and 60s, however, it has become evident that cardiovascular deaths, particularly for patients treated for left-sided tumors, were a significant cause of long-term mortality.[21-23] Therefore, postmastectomy radiation therapy fell out of favor as chemotherapy became more commonly utilized among patients with breast cancer.

It has become evident that chemotherapy alone has little impact upon local failure rates in certain patients with a variety of unfavorable prognostic factors.[24-26] Local control in the chest-wall region clearly benefits from the addition of radiation to combined-modality treatment.

At our institution, patients with primary tumors 5 cm or greater in dimension, four or more positive axillary lymph nodes or positive margins of resection are referred for postmastectomy radiation therapy. Recent randomized studies from Canada and Europe suggest that the indications for postmastectomy radiation should be extended to all node-positive patients.[27,28]

These studies have certain flaws in as much as the local failure rate among patients who underwent mastectomy alone is considerably higher than one would expect. The number of axillary lymph nodes removed is considerably lower than one would expect, and the adequacy of local surgical management in these studies is called into question. Nevertheless, the investigators did demonstrate an improvement in survival among patients who underwent postmastectomy chest-wall radiation and further investigation on this topic is merited.

Currently, postmastectomy chest-wall radiation remains an area of controversy, but patients with positive margins, primary tumors of 5 cm or more in dimension and four or more positive lymph nodes clearly benefit in terms of local control. The impact on survival will have to await further randomized studies.

The radiation-therapy technique for postmastectomy radiation is considerably different than that utilized for the intact breast. Tangential fields may be utilized; however, these do not reliably cover the internal mammary lymph nodes. As local-regional lymphatic permeation is a factor in the high risk of local-regional failure, adequate peripheral lymphatic radiation is considered desirable. Furthermore, the skin dose in this setting is 100% of the prescribed dose, whereas in the breast-conservation setting, the skin dose is approximately 70%. This is felt to be adequate, as skin failures in patients treated with breast-conservation therapy are extremely rare. On the other hand, in patients who have undergone mastectomy, the scar and surrounding skin are the most common area for failure and 100% of the prescribed dose to the skin must be delivered. Therefore, the utilization of dose modifying techniques to assure a 100% dose to the skin is mandatory. This results, logically, in much more severe skin reactions. Again, meticulous attention to skin care is critical from the outset if therapy is to be delivered without interruption. This involves the copious use of emollients, as well as refraining from wearing either restrictive clothing or a breast prosthesis. Between 30-50% of patients will have some element of moist desquamation that will almost always resolve with conservative management.

Rather complicated treatment planning is required to adequately treat the chest wall, skin and peripheral lymphatics without delivering an undesirably high dose to the underlying lung, heart and brachial plexus. Custom electron plans are extremely effective at permitting a conformal dose over the region of the internal mammary lymph nodes while permitting greatest possible limitation of the dose to the lung and the heart, once again, highlighting the importance of a customized approach to each patient's treatment needs. Standard postoperative chest-wall therapy consists of 50 Gy in approximately 5 weeks of daily treatment, Monday through Friday. Under most circumstances, the scar is boosted to a total dose of 60 Gy.

Radiation Therapy for Locally Advanced Breast Cancer

Two important changes have occurred over the last decade in the definition of locally advanced breast cancer.[29] First, T3N0 lesions have now been categorized as Stage IIB disease, reflecting their more favorable prognosis compared with other Stage III breast cancers. Second, the N3 category no longer includes positive supraclavicular lymph nodes. This finding is now considered indicative of Stage IV disease. Numerous older series, however, have included patients with positive supraclavicular lymph nodes, as they were previously categorized as N3, Stage IIIB disease. Therefore, the reporting and analysis of the results of patients who have locally advanced breast cancer is complicated by the fact that many series include patients with a wide variety of presentations.

Locally advanced breast cancer may be considered as three groups of conditions. Patients with 1) operable noninflammatory (T3N1) breast cancer; 2) those with inoperable noninflammatory (T4a,b,c, any N2, any N3) breast cancer; and 3) those with inflammatory breast cancer (any T4d).

All patients with locally advanced breast cancer have a high local tumor burden and a high likelihood of systemic metastases. Therefore, aggressive systemic chemotherapy plays a central role in their management.[30] Both local-regional radiation therapy and mastectomy, when possible, are useful in securing local control. Most patients with Stage III breast cancer will receive chemotherapy as their first therapeutic maneuver. This permits the earliest treatment of micrometastatic disease, assessment of response to therapy and, in many cases, conversion of inoperable or nearly inoperable disease to operable disease. For operable noninflammatory (T3N1) lesions, surgery as the primary therapeutic modality is perfectly reasonable. In this situation, mastectomy is customary. Comprehensive chest-wall radiation is indicated for all patients with this stage breast cancer. Investigators have looked at utilizing neoadjuvant chemotherapy to assess response and to permit breast conservation.[31] In this situation, postoperative radiation therapy to 60 Gy to the entire breast has been utilized.

For inoperable noninflammatory lesions, neoadjuvant chemotherapy is considered the standard of care. In patients who have attained a suitable response to therapy, mastectomy is then added. There is no established role for breast-conservation therapy in this group. Completion of adjuvant chemotherapy followed by chest-wall radiation is standard practice. Alternatively, patients who are not candidates for chemotherapy may do well with hormonal management and may achieve a dramatic result. Radiation therapy alone as the local management for this entity has been reported, and reasonable local control may be anticipated.[32] With such a high tumor burden, however, significantly higher doses of radiation are indicated. Doses up to

80 Gy have been used in this setting with good results in terms of local control. Naturally, cosmesis in this situation would be anticipated to be very poor, with dense fibrosis, atrophic skin changes and contraction of the breast tissue being common.

For patients with N2 disease, radiation alone is undesirable. Unfortunately, the tolerance of the brachial plexus will not permit adequate treatment of significant volumes of gross disease in the regions of the axilla or supraclavicular fossa. Therefore, the use of systemic agents as the initial management of this group of patients is highly desirable. If a good response is obtained, a mastectomy is performed and followed by comprehensive chest-wall radiation.

In the case of inflammatory breast cancer, neoadjuvant chemotherapy is considered the standard of care.[33] Among patients who have an excellent response, which is quite common, mastectomy is added. Chemotherapy is then completed and comprehensive chest-wall radiation is added. This previously dire condition is now associated with approximately a 50% survival among patients who respond well to neoadjuvant chemotherapy.

Local Recurrence

Among patients who experience failure within the treated breast after breast-conservation therapy, mastectomy is the standard of care. When there has been a considerable disease-free interval between the treatment of the primary tumor and the recurrent breast tumor and, assuming systemic disease has been ruled out, chest-wall radiation may be considered. When there are high-risk features (pectoralis/skin invasion/positive margin), postmastectomy chest-wall radiation can be utilized following previous irradiation of the intact breast. This is a very unusual circumstance in our experience. The cumulative dose to the bone and soft tissue of the chest wall will be approximately 100 Gy. Again, cosmesis in this situation would be anticipated to be very poor, with dense fibrosis, atrophic skin changes and osteonecrosis being common.

Patients who have undergone mastectomy and who never received chest-wall radiation are candidates for comprehensive chest-wall radiation if they experience a local-regional failure. In this situation, a full extent-of-disease workup is performed and other prognostic factors, such as the interval between the initial mastectomy and chest-wall recurrence and the number and size of recurrent lesions, are considered.[34] Commonly, such patients will receive systemic chemotherapy and, thereafter, local-regional radiation is indicated. For such patients, local-regional failure may be a repetitive problem if not dealt with thoroughly at the outset. Simple excision of a chest-wall recurrence in a patient who has never had chest-wall radiation is not adequate treatment. The likelihood that subclinical disease remains within the chest wall or peripheral lymphatic system is extremely high and can usually be

effectively controlled with moderate doses of radiation. Among patients who manifest local-regional failure solely at the supraclavicular fossa, we offer neoadjuvant chemotherapy to effect tumor shrinkage in this area, and if a suitable response has been obtained, comprehensive chest-wall radiation is utilized. Although these patients are believed to have systemic disease, a small percentage are candidates for curative management and, particularly in cases involving a long disease-free interval, a radical approach to therapy should not be excluded.

Palliation

Among the sites of systemic failure most prevalent in patients with breast cancer, brain and bone metastases are very adequately treated with brief courses of radiation. In certain circumstances, surgical excision of a solitary brain metastasis followed by whole-brain irradiation can prolong survival compared with that of patients who do not undergo surgical resection.[35,36] Therefore, for the patient who appears to have a solitary metastasis on CT, a gadolinium-enhanced MRI would be indicated to evaluate the patient's candidacy for craniotomy. The patients who do the best, with median survivals as long as 21 months, are those who have systemic disease under control. Therefore, this radical approach to brain metastases, particularly solitary metastases, should not be eliminated from consideration.

For patients with bone metastases, radiation can provide very reliable palliation. We usually employ a fractionation scheme of 30 Gy in 10 fractions, which permits the completion of therapy in 2 weeks time. Ordinarily, patients do not begin to feel any meaningful improvement until halfway through the course of radiation, and the maximal effectiveness is expected approximately 1 month after therapy is completed. Bone metastases from breast cancer are a significant cause of morbidity. Palmidronate therapy is a valuable adjunct to prevent fractures.[37] When an impending fracture is identified in a weight-bearing bone, either prophylactic pinning or irradiation with limited weight bearing is indicated. In this situation, the early involvement of an orthopedic consultant to evaluate the need for prophylactic surgical fixation is mandatory.

In the case of vertebral metastases causing spinal-cord compression, there appears to be no advantage to approaching these patients with surgical intervention at the time of diagnosis.[38, 39] Patients are pretreated with dexamethasone, then commence with radiation utilizing a dose fractionation scheme of 30 Gy in 10 fractions. The patient's neurologic status must be carefully monitored and the dexamethasone tapered as tolerated. The majority of patients with spinal-canal compromise can be adequately managed and have neurologic disability averted utilizing this technique. The practitioner must be vigilant for early signs of spinal-cord compression that may initially manifest as back pain. An MRI is invaluable in the evaluation of

these patients. It is also extremely valuable in the planning of radiation fields to include other nearby sites of subclinical disease.

Paradoxically, planning palliative radiation fields for bone metastases requires restraint as numerous subclinical lesions that are unlikely to cause symptoms during the patient's lifetime are frequently visualized. Fields that are designed significantly larger than is necessary to achieve the goal of palliation will compromise the patient's ability to tolerate systemic chemotherapy. All areas of irradiated bone will have a severely diminished ability to support hematopoiesis after irradiation. Therefore, careful consideration must be utilized when designing palliative fields for bone metastasis.

Conclusion

Breast cancer is one of the most prevalent malignancies among women in the western world. Well-designed scientific trials in the diagnosis and management of this disease remain paradigms for investigators in all fields. The value of a multimodality approach to each patient's care cannot be overemphasized. Radiologists, pathologists, surgeons, medical and radiation oncologists have all contributed to the improvements that have been achieved in the rates of survival from this disease. Their continued collaboration will assure further advances and, ultimately, the conquest of breast cancer.

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CHAPTER 10

Sentinel Lymph Node Mapping

Arnold D.K. Hill

The role of regional lymph node dissection in the treatment of breast cancer remains controversial. Currently, standard surgical management comprises resection of the primary tumor (whether by mastectomy or breast-conservation surgery) and axillary lymph node dissection.

There is overwhelming evidence that axillary lymph node involvement is the most important prognostic factor in patients with breast cancer.[1-5] Thus, axillary dissection will always be an important staging procedure, yielding information for the planning of adjuvant therapy.

Morbidity of Axillary Dissection

There is potentially a significant morbidity attached to the procedure of axillary dissection.[6] Arm lymphedema is one of the principal complications of axillary surgery,[7-9] although one randomized trial has reported that lymphedema was not a prominent problem following either axillary sampling or dissection.[10] While it has been suggested that the risk of lymphedema increases with the extent of surgery,[11] the Edinburgh study[10] did not confirm this finding nor did a nonrandomized study from Yorkshire.[12] It has been repeatedly demonstrated, however, that axillary surgery plus radiation therapy increases the risk of lymphedema,[7,8,12,13] although this difference was not significant in the Edinburgh study.[10] Lymphedema may predispose the patient to cellulitis and has been shown to have psychological side effects.[14] Potentially the most significant, but extremely rare, complication of arm edema is the development of lymphoangiosarcoma, also known as the Stewart-Treves syndrome.[15]

Neuropathies can also occur following axillary surgery. "Intercostobrachial nerve syndrome" (paraesthesia of the axilla, shoulder and upper arm) has been reported.[16] In a series by Lin et al,[11] 78% of patients complained of paraesthesia in the distribution of the intercostobrachial nerve, and 47% also complained of pain.

After axillary dissection, shoulder movement may be restricted,[6] and this problem may be compounded by radiation therapy.[10] Seromas may occur in 10-52% of women following surgery, despite the use of suction drains.[17] Finally, early postoperative complications such as hematoma, wound infection and delayed wound healing may also be seen.[18-20]

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Given this morbidity, there is clearly an incentive to avoid axillary surgery in women who are lymph node negative. Currently, the only accurate method of identifying women with positive axillary nodes is histopathologic examination of all lymph nodes removed at axillary dissection. Clinical examination has been shown to be unreliable in demonstrating the presence of axillary metastases.[21] Ultrasound examination has also been employed to determine axillary nodal status,[22] but although more accurate than clinical examination, its reported sensitivity of 73% means that it remains an inaccurate method of noninvasive staging. Computed tomography (CT) scanning has not been shown to be clinically useful in predicting axillary nodal status.[23] Magnetic resonance imaging (MRI) has also been studied in assessing the axilla, but with a reported sensitivity of 90% for axillary metastases,[24] it remains inferior to surgical staging. Positron emission tomography (PET) scanning is a technique that has been used with some degree of success in the detection and staging of breast cancer;[25-27] however, this is an expensive technique and is currently a research tool.

The Sentinel Lymph Node

Recent techniques have been developed to allow the identification of positive regional lymph nodes without clearing the whole lymphatic basin. The concept of the sentinel lymph node was originally introduced in 1977 in the management of penile carcinoma.[28] This concept states that the first lymph node to receive lymphatic drainage from the site of a tumor should be the first site of lymphatic spread. Therefore, a tumor-free sentinel lymph node implies the absence of lymph node metastases in the entire lymphatic basin. In penile carcinoma, lymphatic mapping to identify the sentinel lymph node was performed using lymphangiography. The concept of sentinel lymph node biopsy was then introduced to patients with cutaneous melanoma by Morton and colleagues.[29] The approach in this study consisted of the injection of 0.5-1.0 ml of blue dye intradermally at the site of the melanoma. This allowed intraoperative identification of blue-stained lymphatic vessels leading away from the primary tumor to the blue sentinel lymph node.

The techniques used for intraoperative lymphatic mapping in this study were based on previous work in a feline model by the same group.[30] This study examined several vital blue dyes and concluded that isosulfan blue dye was the most useful for lymphatic mapping. Isosulfan blue dye is a monosodium salt of a 2,5-disulphonated triphenyl methane dye. It is weakly bound to albumin and is selectively taken up by the lymphatics.[31] Other dyes were examined by Wong et al[30] but were abandoned as they gave unsatisfactory results. Methylene blue, a water-soluble dye, proved to have poor lymphatic uptake and caused background staining of the tissues. Cyalume, a fluorescent dye, was also examined and allowed good visualization of the lymphatics, but leaked out into the interstitial tissue space, resulting in marked background

fluorescence. For this reason, isosulfan blue dye was chosen as the best agent for lymphatic mapping as it rapidly enters the lymphatic vessels and is readily visualized in the vessels and sentinel lymph node, with minimal diffusion into the soft tissues.

In studies of the technique in patients with melanoma, Morton et al[29] compared isosulphan blue dye with patent blue-V dye. Patent blue-V dye is a triphenyl methane dye similar in structure to isosulfan blue dye. Morton et al found that patent blue-V dye gave optimum results in visualizing the lymphatics and postulated that this may be due to its greater concentration: 2.5% in aqueous solution compared with the 1% concentration of isosulfan blue.

In this initial report,[29] Morton et al commented that injection of large volumes of dye resulted in extravasation in the subcutaneous tissues with consequent movement of dye through separate lymphatic channels and therefore advocated the use of small volumes of dye (0.5-1.0 ml). Furthermore, they noted that if dissection was not performed promptly, dye would pass through the sentinel nodes up to higher lymph nodes in the regional basin. This caused fading of the color, and to avoid this, repeat injection of the dye was performed every 20 minutes.

In Morton's series of 237 patients,[29] a sentinel node or nodes was identified in 194 cases (82%). In all, 72% of patients had a single sentinel lymph node, 20% had two sentinel lymph nodes, and 8% had three sentinel lymph nodes. This study also showed that there is a learning curve associated with this procedure; as surgeons become more experienced, their rate of sentinel lymph node detection increases significantly. Of the 194 patients who had a sentinel node identified, 40 (21%) had lymph node metastases. In two patients in this group of 194, there were metastatic deposits in nonsentinel nodes in the absence of tumor in the sentinel lymph node; i.e., the false-negative rate was 1%. It is of interest that in the 40 patients with lymph node metastases, 23 (12%) were detectable using hematoxylin and eosin (H&E) staining techniques, but a further 17 (9%) were only detectable using immunohistochemistry. In all cases, the sentinel lymph node was the only site of metastatic disease.

Further work has validated this approach in patients with melanoma.[32] By demonstrating in a series of 42 patients that none had skip metastases, Reintgen et al provided evidence for the theory that nodal metastasis in melanoma occurs in an orderly fashion. In addition, in the eight cases where there were nodal metastases, seven of these were only in the sentinel node—further evidence in support of the sentinel node hypothesis.

It is clear from this study that the use of vital blue dyes such as isosulfan and patent blue-V dyes in lymphatic mapping for melanoma has its drawbacks. It may be difficult to visualize or to dissect out the blue-stained lymphatic vessels and nodes in the lymphatic basin. The site of the sentinel lymph node is unknown prior to surgery, and it may be difficult to accurately

site the incision for exposure of the sentinel lymph node. Furthermore, dye may pass rapidly to nonsentinel nodes, resulting in the staining of several nodes and preventing the true sentinel node from being found. In an attempt to avoid these pitfalls, some groups have advocated the use of radionuclide techniques.[33-36]

The use of lymphoscintigraphy to identify lymphatic drainage patterns and to identify the sentinel lymph node in melanoma has been described in several studies.[33-38] Preoperative scintigrams allow identification of the sentinel lymph node and marking of its position on the overlying skin. The gamma probe can then be used intraoperatively to identify the "hot" sentinel lymph node during dissection. Initial studies in a feline model found that the sensitivity of sentinel lymph node identification was the same as that for vital blue dye.[39] The reliability of the technique was verified in a small study of 10 patients with melanoma, and the use of preoperative lymphoscintigraphy and intraoperative use of the gamma probe was considered to allow accurate identification of the sentinel lymph node and verification of its removal.[36] Further work by the same group combined the use of the gamma probe with vital blue dye in a larger group of patients,[35] and in this study, all the nodes that were stained blue were also radiolabeled with the colloid. Further studies have confirmed that the combination of preoperative lymphoscintigraphy and intraoperative use of the gamma probe can identify the sentinel lymph node.[33,34]

Recently, Giuliano et al provided histologic validation of the sentinel lymph node hypothesis for breast cancer.[40] To determine whether the sentinel node was the node most likely to harbor an axillary metastasis from breast carcinoma, Giuliano et al used cytokeratin immunohistochemical staining to examine sentinel and nonsentinel lymph nodes in 103 patients.[40] In 60 patients whose sentinel nodes were metastasis-free by H&E staining and immunohistochemistry, 1,087 nonsentinel nodes were examined at two levels by immunohistochemistry and only one additional tumor-positive lymph node was identified. Therefore, if the sentinel lymph node is negative by H&E staining and immunohistochemistry, it is most likely that the rest of the axillary lymph nodes are negative for tumor.[40]

Results of Clinical Studies in Breast Cancer

Giuliano et al[4,41,42] have published their experience with the sentinel lymphatic mapping in breast cancer using isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Richmond, VA). In a landmark paper, Giuliano et al[41] reported successful localization of 207 sentinel lymph nodes in 114 of 174 patients (65.5%). Sentinel lymph nodes accurately predicted axillary nodal status in 109 of 114 patients (95.6%); the five false negatives were all in the first 87 cases. In retrospect, three of these were lymphoid collections in fat tissue incorrectly identified as lymph nodes by the pathologist, one was negative for metastasis by histology but was found to be positive by immunohis-

tochemistry, and one remained false negative. There was a definite learning curve for this technique. Sentinel lymph nodes were localized in 51 of the first 87 patients (59%), and in 63 of the second 87 (72.4%); in the next 50 patients, sentinel nodes were localized in 39 (78%).

Giuliano et al[4] subsequently reported 259 patients with T1 invasive carcinomas, 114 of whom had sentinel node biopsy followed by completion axillary lymphadenectomy. Sentinel lymph nodes were identified in 73 (64%), and there were two false negatives, both in the first half of the study. On retrospective review, one of these proved to have a micrometastasis missed by the pathologist, and the other was positive by immunohistochemistry. In the discussion of these results, the authors noted that in their more recent experience, the sentinel lymph node localization rate had improved to 85% with only one false negative in the previous 150 sentinel lymph node biopsy procedures.[4]

In 1997, Giuliano published a further series of 107 patients in which he reported a 93% success rate in identifying the sentinel node.[42] The technique of using blue dye alone for identifying the sentinel lymph node is successful in experienced hands but the learning curve remains too long for the widespread adaptation of this technique alone.

Investigators at other institutions have verified the lymphatic mapping and sentinel lymphadenectomy concept for breast cancer (Table 10.1). All groups have confirmed the hypotheses that lymphatic drainage of a breast cancer can be identified and traced to the sentinel node intraoperatively and that the histologic status of the sentinel node accurately predicts the pathologic status of the entire axilla. These studies differ in several aspects of patients selection, injection technique and type of lymphatic mapping agent used (Table 10.1).

Krag and associates[43] utilized unfiltered technetium sulfur colloid alone as a mapping agent, with a range of 1-4 hours between colloid injection and sentinel node excision. The sentinel node was identified in 18 patients of 22 (82%), and it predicted the pathologic status of the axilla in each. In a more recent update of their experience of 157 patients, Krag reported a similar success rate with a false-negative rate of 4.5%.[44]

Albertini and colleagues[45] utilized isosulfan blue dye and filtered technetium sulfur colloid as lymphatic mapping agents. Sixty-two patients were included and the sentinel node was identified in 57 (92%) of these. Forty-five sentinel nodes were identified by both blue dye and radiolabeled colloid and 12 were identified by colloid alone. Metastases were found in 18 sentinel nodes, all of which were identified by both blue dye and colloid. There were no patients with negative sentinel nodes and positive nonsentinel nodes (false negatives).

Albertini and associates concluded that the combination of dye and colloid, increase identification of the sentinel node and that this method is superior

Table 10.1. Sentinel node biopsy for breast cancer

Authors/year	Technique	Number of Patients	Successful Mapping # (%)	Accuracy
Krag/93[43]	Tc-99 SC	70	50/70 (71)	50/50 (100)
Giuliano/94[41]	Blue dye	174	114/174 (66)	109/114 (96)
Albertini/96[33]	Blue Dye + Tc-99m SC	62	57/62 (92)	57/57 (100)
Pijpers/96[86]	Tc-99m CA	37	34/37 (92)	34/34 (100)
Meijer/96[93]	Tc-99m CA	30	28/30 (93)	28/28 (100)
Nieweg/96[94]	Blue Dye	22	11/22 (50)	22/22 (100)
Folscher/97[92]	Methylene blue dye	79	32/79 (40)	27/32 (84)
Roumen/97[58]	Tc-99m CA	83	27/83 (32)	56/57 (98)
Borgstein/97[48]	Blue Dye + Tc-99m CA	33	33/33 (100)	33/33 (100)
Giuliano/97[42]	Blue Dye	107	100/107 (93)	100/100(100)
Veronesi/97[49]	Tc-99m CA	163	160/160 (100)	156/160 (97)
Guenther/97[95]	Blue Dye	145	103/145 (71)	100/103 (97)
Borgstein/98[48]	Tc-99m CA	130	122/130 (94)	103/104 (99)
O' Hea/98[50]	Blue Dye + Tc-99m SC	59	55/59 (93)	52/55 (95)
Galimberti/98[96]	Tc-99m CA	241	238/241 (99)	232/238 (97)
Barnwell/98[97]	Blue Dye + Tc-99m SC	42	38/42 (90)	38/38 (100)
Krag/98[43]	Tc-99m CA + other agents	157	119/157 (76)	117/119 (98)
Offodile/98[98]	Tc-99m Dex	41	40/41 (98)	40/40 (100)
Cox/98[99]	Blue Dye + Tc-99m SC	466	440/466 (94)	439/440 (99)

Tc-99m SC, technetium 99m sulfur colloid; Tc-99m CA, technetium 99m colloidal albumin; and Tc-99m Dex, technetium 99m Dextran.

to either colloid or dye alone. Although it is clear that more sentinel nodes were identified with both techniques, no sentinel nodes identified by colloid alone contained metastases. The same group recently reported their updated experience with 466 patients.[46] Although this is the largest experience reported to date in the literature, it is lacking in critical information such as the details on the patients who had a conventional axillary dissection in order to establish the true false-negative rate. Their success rate with blue dye remains low at only 60%; however, the strongest point to be made by the paper is that the combination of blue dye and radioisotope increases the success rate of lymphatic mapping compared to either technique alone.[46]

Borgstein et al[47] from the Netherlands reported their experience of lymphatic mapping in 33 patients comparing intradermal injection of blue dye with intramammary injection of radioactive technetium 99 m colloidal albumin. There was 100% concordance between the two techniques of

localizing the sentinel node. Borgstein concluded that the lymphatics of the overlying skin drain to the same axillary sentinel node as the underlying glandular breast tissue. In a more recent report, Borgstein et al reported using technetium 99 m colloidal albumin alone in 130 women to identify the sentinel node, with a 94% success rate and a 1.7% false-negative rate.[48]

Veronesi et al[49] reported a consecutive series in 163 women using technetium-labeled human serum albumin as a tracer to identify the sentinel node. This technique allowed an accurate prediction of the axillary lymph node status in 97.5% of patients. Veronesi et al[49] found that all of their four false-negative sentinel nodes occurred in patients with tumors larger than 1.5 cm. This inaccuracy may be due to alternate lymphatic drainage pathways, to inexperience with the procedure of sentinel node biopsy, or simply to the increased prevalence of axillary metastases in patients with larger tumors.

O'Hea et al[50] reported the initial experience at Memorial Sloan- Kettering Cancer Center in 60 patients in whom both blue dye and radiolabeled technetium sulfur colloid were used to identify the sentinel node. They reported a 93% success rate at identifying the sentinel node and concluded that the blue dye and radioisotope are complementary techniques. The overall success of the procedure was maximized when the two techniques, blue dye and radioisotope, were used together.

It appears that many techniques can be used to identify the sentinel node in breast cancer patients. It would appear that blue dye alone is associated with a long learning curve and that the use of radioisotope complements the blue dye.

Axillary Staging and the Sentinel Node

It seems clear from these studies that the concept of the sentinel node is a valid one. Indeed, histopathologic evidence has recently been produced to validate this concept.[40] This study confirms that the sentinel node is the axillary node most likely to contain metastasis. If the sentinel node is tumor-free using both H&E staining and immunohistochemistry, the probability of nonsentinel node involvement is less than 0.1%. This would tend to suggest that axillary nodal metastasis in breast cancer occurs in the same orderly fashion as nodal metastasis in melanoma, according to the lymphatic anatomical drainage, as proposed by Reintgen et al.[32] Thus, what has previously been described as "skip metastasis" may be a consequence of variations in local lymphatic anatomy rather that a nonsequential spread of tumor cells. The incidence of skip metastases in several studies ranges from 1.3-42%.[21,51-57] The variation in reported incidences of skip metastases may be due to differing techniques of axillary dissection, individual anatomical variations or possibly failure to identify micrometastases in lower level nodes. Where lymphatic mapping has been performed, the sentinel lymph node has been found in

level 2 in 18% of cases by Roumen et al[58] and in 23.2% of cases by Giuliano et al.[41] Allowing for the above variables, this would be roughly in keeping with the quoted figures for skip metastases.

There seems little doubt that the use of histologic techniques in addition to the staining of a single section of lymph node with H&E will improve the rate of detection of lymph node metastases. It has been known for some time that serial sectioning of resected nodes and staining of these sections with H&E will detect additional occult metastases.[59-64] The use of immunohistochemical techniques has also been demonstrated in several studies to increase the diagnostic yield of occult nodal metastases in patients who were classified as "node-negative" on standard histologic examination.[65-71] In addition, there is evidence to suggest that the use of the reverse-transcriptase polymerase chain reaction may be even more sensitive in the detection of occult disease.[72-74]

More important, however, than the detection of such micrometastatic disease is the extent to which it influences the patient's prognosis, if at all. This is a more controversial topic and has been the subject of great debate. Initial studies suggested that micrometastases detected on serial sectioning did not have an adverse effect on prognosis.[60,61,75,76] More recently, however, larger studies have shown a reduction in both disease-free survival and overall survival in patients with micrometastases.[62,62,68-72,77] It has been shown that if patients with micrometastases are followed up for 6 years, their survival is similar to that for node-negative patients;[78] however, this study shows that at 10 years, survival rates in this group are significantly poorer than for node-negative patients. The long follow-up period required, the small patient populations used in the early studies and the use of immunohistochemistry in more recent studies together almost certainly account for the differing results. A recent review article concludes that the use of conventional techniques will underestimate the presence of metastases in axillary lymph nodes, and that patients with micrometastases have a clear survival disadvantage.[79]

Although the pathologic methods detailed above allow for more accurate nodal staging of the axilla, they are impractical for use in patients undergoing a standard axillary clearance. The majority of pathology departments do not have the resources to perform serial sections, immunohistochemistry and rt-PCR on all the nodes retrieved from an axillary clearance. Sentinel lymph node biopsy may allow for more accurate staging of the axilla by allowing histopathologic examination to concentrate on one or two nodes only. Recent work by Giuliano et al[80] confirms this hypothesis. In this study, evaluating the sentinel node using serial sections and immunohistochemistry, metastases were found in 42% of patients, as opposed to in 29% when the specimen from a full axillary dissection was analyzed in a routine fashion.

A detailed analysis of one or two sentinel nodes using serial sections and immunohistochemistry may offer an accurate, cheaper and simpler method of staging the axilla. The implication of this is that if a patient were to be truly node-negative based on a thorough examination of the sentinel lymph node, no further axillary treatment would be necessary. Clearly, this hypothesis will require validation by means of a randomized, controlled trial with prolonged follow-up comparing patients treated by sentinel node biopsy and no further treatment if the axilla is negative with patients treated by standard axillary dissection, taking axillary recurrence and overall survival as outcome measures.

Internal Mammary Lymph Nodes

One further issue of note in discussing the role of sentinel node biopsy in breast cancer is that of internal mammary node metastases. It has been shown that metastases to the internal mammary nodes occur in approximately 20% of breast cancer patients.[81,82]

Interestingly, in one of these studies,[82] the site of the tumor within the breast had no impact on the presence or otherwise of internal mammary node metastases. Another study from the same center suggests that the internal mammary node involvement has a bearing on prognosis, with patients who had positive nodes in both the axilla and the internal mammary chain having the worst overall survival.[83]

A multicenter, prospective, randomized clinical trial has shown that the addition of routine internal mammary node dissection to the procedure of radical mastectomy does not improve outcome.[84] Overall survival rates were very similar, and the internal mammary recurrence rate was very low without dissection of the nodal chain. In light of this, Veronesi et al suggest that although there is no benefit to be gained from internal mammary dissection, a biopsy of the internal mammary chain could be carried out via the second or third intercostal space. This would allow prognostic information regarding involvement of the chain to be obtained,[82] while avoiding the morbidity of internal mammary dissection.

Clearly, this may be relevant to sentinel lymph node biopsy where it is performed with lymphoscintigraphy. The blue-dye technique will not allow visualization of the internal mammary nodes, but where preoperative lymphoscintigraphic images are taken, a sentinel node may be visualized in the internal mammary chain. This has in fact been described in studies on sentinel lymphadenectomy.[58,85,86] In one study involving 37 patients, drainage to the ipsilateral internal mammary chain was seen in five patients (in one of whom no axillary nodes were visualized).[86] In a further study, nine out of 34 patients had a sentinel node in the internal mammary chain.[85] Finally, Roumen[58] identified internal mammary sentinel lymph nodes in two of 83 patients. In none of these studies were the internal mammary

nodes removed at operation, however; therefore, the presence or absence of metastases in the chain could not be documented. It may be difficult to detect internal mammary nodes lymphoscintigraphically due to the "hot spot" from the tumor obscuring any "hot" internal mammary nodes. One study had noted that although it was simple to pinpoint the surface marking of internal mammary nodes, they were not visible in the lateral view, as the primary tumor obscured them; hence, it was difficult to measure the depth of these nodes.[85]

Clinical Issues in Lymph Node Mapping

Blue Dye and Isotope

With the patient under local or general anesthesia and positioned for axillary dissection, either isosulfan blue (Lymphazurin, Zenith Parenterals, Rosemont, IL)[12] or patent blue-V[47] is injected into the breast. Methylene blue should not be used because the particle size within methylene blue is too small to allow it to be trapped in the lymph nodes.[13]

Radiopharmacologic properties of different radioparticles and their kinetics have been reviewed by Strand and Persson.[87] Many radioparticles have been studied, including radiolabeled antibodies and different albumin preparations. Krag et al[44] reported that unfiltered technetium sulfur colloid was the best radiopharmaceutical agent to selectively label the sentinel node among six agents evaluated. Particle size of unfiltered sulfur colloid ranges from 50-100 nm (average size 200 nm).[87,88] In Europe, the preferred isotope is technetium-99m-labeled human albumin colloid particles whose particle size range from 50-200 nm. The use of technetium-labeled nannocolloid has also been reported in lymphatic mapping for breast cancer.[89]

Safety of Radioisotopes

In the United States, there are no limitations on bodily contact with an individual having a body burden of less than 1110 MBq (30 m Ci). The dose of radiation used for lymphoscintigraphy is 0.8 m Ci, which is only a fraction of the threshold for imposing radiation restrictions. Physiologic excretion significantly decreases the body burden to a much lower level. Operating-room contamination is also minimal with 99 m Tc, as it has a half-life of 6 hours. Many studies have indicated that there is minimal radiation exposure to the surgeons, operating room personnel and pathologists.[90,91]

Training Issues

Training in sentinel node biopsy should include participation in a comprehensive hands-on training program and intraoperative proctoring by a colleague with experience in sentinel lymphatic mapping. The initial period of training in sentinel node biopsy should be validated by a formal axillary

dissection. The specific number of cases that need to be done with a backup axillary dissection remains unresolved. Both blue dye and radioisotope should be used to maximize the yield of successful localizations. Whenever the procedure is in any way unsatisfactory, sentinel node biopsy should be abandoned in favor of a standard axillary dissection.

Conclusion

Sentinel node biopsy in patients with early-stage breast cancer has established itself as a safe and effective alternative to routine axillary dissection. This minimally invasive axillary staging procedure represents a major advance in the surgical treatment of breast cancer.

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CHAPTER 11

Hereditary Breast Cancer

Mark E. Robson

Familial Breast Cancer

A family history of breast cancer has been consistently recognized as one of the most important risk factors for the disease. Various studies have suggested that between 15-25% of women with breast cancer have at least one first- or second-degree relative who also has breast cancer. A woman with an affected first-degree relative has from 1.5-2.5 times the breast cancer risk of a woman without a family history of breast cancer. Within the group of women with a family history of breast cancer, those with multiple affected relatives are at higher risk, as are those with relatives affected at younger ages. Risk is also higher in some, but not all, series if one or more of the affected relatives has had bilateral disease. Because relative risk figures may be difficult to translate in a meaningful way when performing clinical risk counseling, empirical models have been developed that can be used to provide women with an estimated percentage risk of developing breast cancer over a defined time period. The best known models are the "Claus tables" and the Gail model. The "Claus tables" derive from the Cancer and Steroid Hormone Study (CASH) dataset, and only use family history data to generate risk figures. The Gail model, generated from the Breast Cancer Detection Demonstration Project dataset, incorporates reproductive and clinical variables in addition to a history of breast cancer in first-degree relatives (mothers and sisters). Both models are useful, but have significant limitations when used to estimate individual cancer risks.

Hereditary Breast Cancer and the Identification of *BRCA1* and *BRCA2*

There are several possible explanations for the observed tendency of breast cancer to cluster in families. Chance may cause a common disorder such as breast cancer to afflict more than one member of a kindred. Alternatively, shared environmental risk factor exposures or common sociocultural practices (e.g., late age at first childbirth) may be responsible. A common genetic background may increase familial risk by modulating sensitivity to environmental or reproductive risk factors in a similar fashion among members of a kindred. None of these hypotheses satisfactorily explain the 5-10% of breast

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cancer cases that occur in families that appear to be transmitting a predisposition to breast cancer in an autosomal dominant pattern (Fig. 11.1). In such families, breast cancer occurs in women of each generation, and approximately 50% of the female offspring of an affected woman are themselves affected. The disease tends to occur at an earlier age than in the population at large and is not infrequently bilateral. There may be other types of cancer within the pedigree, especially ovarian cancer. Male breast cancer is not prominent in most families, but either males or females may transmit the predisposition. Early investigators suggested that the passage of a single autosomal dominant susceptibility allele could explain these uncommon families, if one accepted the assumption that expression of the susceptibility would be largely restricted to females. Unfortunately, until modern epidemiologic and molecular biologic techniques became available, this hypothesis was not proven. In 1988, Newman et al provided the first formal demonstration (through segregation analysis) that one or more low-frequency, highly penetrant autosomal dominant alleles were responsible for a small proportion of breast cancers. Subsequent studies indicated that one such locus was linked to the region of chromosome 17q21, and the term *BRCA1* was coined to describe the putative gene. Clinical investigators observed that this locus was not only linked to hereditary breast cancer, but also to hereditary ovarian cancer. This demonstration validated earlier clinical descriptions of an increased prevalence of ovarian cancer in families with an apparent predisposition to breast cancer. Families with an apparent predisposition to male breast cancer were not linked to the putative *BRCA1* locus.

After an intensive multinational effort, *BRCA1* was isolated by Miki et al in October of 1994. Shortly thereafter, germline mutations were detected in individuals from hereditary breast- and breast-ovarian cancer families. The wild-type allele was shown to be lost in tumor tissue from patients with germline mutations, supporting the hypothesis that *BRCA1* was a tumor-suppressor gene, analogous to *P53* and *RB*, among others. In contradistinction to other tumor-suppressor genes, *BRCA1* mutations could not be demonstrated in sporadic breast cancers. A number of hereditary breast and breast-ovarian cancer families could not be attributed to *BRCA1* by either linkage or direct mutational analysis. Some of these families manifested an apparent predisposition to male breast cancer. By studying these families, a second susceptibility locus, called *BRCA2*, was mapped to chromosome 13q12. In December 1995, the gene was cloned by Wooster et al and shown to be mutated in members of some, but not all, non-*BRCA1* families.

Functions of *BRCA1* and *BRCA2* and the Mechanism of Hereditary Susceptibility

The functions of *BRCA1* and *BRCA2* are incompletely defined. The genes share little sequence homology, although there are some similarities in exon

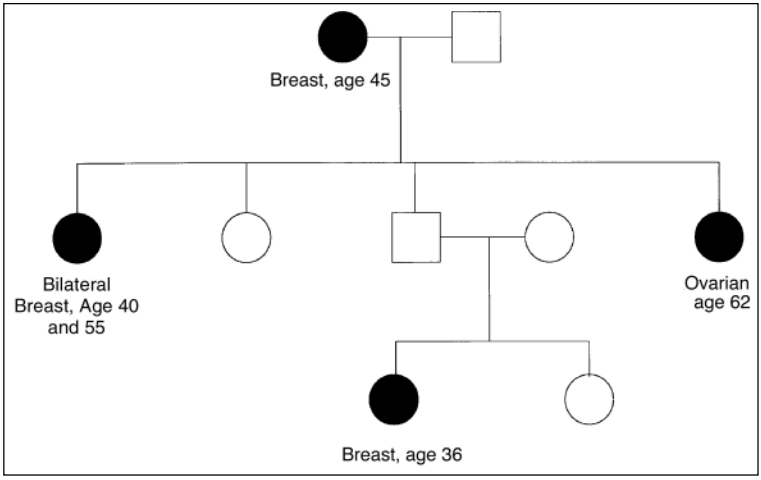

Fig. 11.1. Hereditary breast-ovarian cancer pedigree demonstrating autosomal dominant inheritance.

structure. The susceptibility conferred by a germline mutation appears to follow the classic tumor-suppressor model, in that the normal copy of the gene must be mutated or lost before the predisposition can be expressed. Current evidence suggests that the products of these genes function in a DNA-damage repair pathway (reviewed in ref. 8). Cells lacking *BRCA1* or *BRCA2* function appear to be defective in their ability to resolve double-stranded DNA breaks. Such cells appear to be prone to accumulate additional genetic damage, and are sensitive to the effects of DNA-damaging agents such as ionizing radiation and certain chemotherapeutic agents. The two gene products appear to participate in a common pathway and have been reported to physically coexist in a biochemical complex. The exact mechanism by which loss of *BRCA1* or *BRCA2* function produces the observed predisposition to cancer is not known. One hypothesis suggests that loss of gene function is an early event, with cells lacking *BRCA1* or *BRCA2* being prone to acquire the additional genetic changes that lead to the malignant phenotype. The restricted tissue expression of this predisposition is currently unexplained.

Probability of Detecting Mutations in *BRCA1* or *BRCA2*

The probability of detecting a *BRCA* mutation in a given individual varies greatly with the clinical scenario. In two population-based series of unselected

breast cancer cases, the rate of *BRCA1* mutation was 2.6% overall and 6.2% in women affected before the age of 35 (2.9% if the young woman had no family history of breast cancer). Although no *BRCA1* mutations were found among women of African descent in these series, several groups have observed mutations among African-American families presenting to cancer risk assessment clinics. Population-based prevalence data are not currently available for *BRCA2*, but the contribution to early-onset breast cancer appears to be less than that of *BRCA1*. In one series, only 2.7% of women with breast cancer at or before age 32 were found to have *BRCA2* mutations. In part, this under-representation of *BRCA2* mutations in early-onset breast cancer may be due to a later age of onset in *BRCA2* heterozygotes, rather than to a lower lifetime penetrance. The probability of detecting a *BRCA* mutation in unselected series of ovarian cancer patients is approximately 4.6% for *BRCA1* and 1.8% for *BRCA2*.

While *BRCA* mutations are infrequent in unselected breast and ovarian cancer patients, they are more often observed in individuals presenting to familial cancer clinics. In a series of reports describing various high-risk ascertainments around the world, the probability of detecting mutations in either gene ranged from 21-73% (reviewed in ref. 14). These ascertainments are clearly not uniform and include families from differing ethnic backgrounds at higher and lower levels of risk. In the most striking families, such as those participating in the Breast Cancer Linkage Consortium effort to isolate *BRCA1* and *BRCA2*, the probability that the predisposition is linked to *BRCA1* or *BRCA2* is up to 87%. Factors such as lower average age at onset of breast cancer or the occurrence of bilateral breast cancer, ovarian cancer or male breast cancer in a pedigree increase the likelihood of linkage to *BRCA1* or *BRCA2* (Table 11.1). Unfortunately, current technology fails to detect mutations in a significant proportion of families that are attributable to *BRCA1* or *BRCA2* by traditional linkage analysis. This may be due in part to the presence of so-called regulatory mutations, or to the presence of large deletions/insertions. *BRCA1* mutations have only been detected in approximately 64% of the strongly linked families that have undergone direct mutation testing. Similar data regarding sensitivity are not available for *BRCA2*.

Ethnic Status and Mutation Prevalence

Ethnic status strongly influences the probability of detecting a mutation in *BRCA1* or *BRCA2*. In the United States, Jewish women do not, as a group, manifest a significantly increased risk for breast or ovarian cancer; however, Jewish women who have a close relative affected with breast or ovarian cancer appear to be at greater risk than non-Jewish women with an affected relative. It has been suggested that the increased familial risk of breast or ovarian cancer among Jewish women is related to an increased prevalence of *BRCA1*

Table 11.1. Indicators of increased probability of detecting BRCA mutations

- Multiple cases of early-onset breast cancer
- Bilateral breast cancer
- Ovarian cancer and breast cancer in the same family
- Ovarian cancer and breast cancer in the same woman
- Male and female breast cancer in the same family

or *BRCA2* mutations in this population. In 1996, Tonin et al described a recurring *BRCA1* mutation (185delAG, also known as 187delAG) in breast cancer patients of Ashkenazi (Central and Eastern European Jewish) descent (reviewed in ref. 16). Several groups quickly demonstrated that up to 20% of Ashkenazi women with early-onset breast cancer carry this mutation. Soon thereafter, a recurring *BRCA2* mutation (6174delT) was identified in an additional 8% of Ashkenazi women with early-onset breast cancer. The high prevalence of these specific mutations among young breast cancer patients of Ashkenazi descent is a reflection of a remarkably high prevalence of these same changes in the Ashkenazi population as a whole. Population studies have indicated that 2.5% of unselected individuals of Ashkenazi descent carry one of three recurrent mutations (the two described above or a third, *BRCA1* 5382insC, also known as 5385insC). This high population prevalence is presumably the result of a "founder effect" in the ancestral European population. Unpublished series of Ashkenazi women with breast cancer (not selected for age at onset or family history) indicate that approximately 10% of women from this population have one of these three germline mutations. Founder mutations are even more common in women of Ashkenazi descent with ovarian cancer. In unselected series, nearly 28% of Ashkenazi women with ovarian cancer (all ages) have one of the two *BRCA1* mutations, and approximately 12% of those tested have *BRCA2* 6174delT. Collaborative series have shown that families of Ashkenazi descent with two or more breast cancers (at least one occurring before age 50) have a 29% likelihood of transmitting a founder mutation. If there is at least one case of ovarian cancer in the family, the probability of finding one of these mutations rises to 73%. Interestingly, mutations appear to be less common in Ashkenazi women with DCIS (although still greater than in the general Ashkenazi population) and do not appear to occur with increased frequency in women with borderline ovarian tumors. Although these specific mutations are responsible for the majority of *BRCA1* or *BRCA2* alterations identified in this population, it is important to note that other mutations have been described in individuals of Ashkenazi descent. Hence, Ashkenazi families with pedigrees that are strongly suggestive of a hereditary breast or breast-ovarian cancer syndrome, but who do not appear to transmit one of the three founder mutations, should be offered more complete analysis of *BRCA1* and *BRCA2*.

Other Causes of Hereditary Breast Cancer

It is important to bear in mind that not all families with a pedigree suggestive of hereditary breast cancer are linked to *BRCA1* or *BRCA2*. Alterations in other genes, such as *P53* (Li-Fraumeni syndrome) and *PTEN* (Cowden's syndrome) may account for a proportion of such families (Table 11.2). These additional syndromes are quite rare. Most families with an apparent predisposition to breast cancer that cannot be attributed to either *BRCA1* or *BRCA2* remain unexplained.

The Li-Fraumeni syndrome (LFS) is characterized by the occurrence of multiple different tumor types within a kindred, often arising at very early ages. The syndrome is most commonly attributable to germline mutations in *P53*. Soft-tissue sarcoma and osteosarcoma, adrenocortical carcinoma, brain tumors and leukemias are the tumors most often associated with LFS, but early-onset breast cancer is actually one of the most common component tumors.

Cowden's syndrome (also known as Cowden disease) is associated in at least some families with germline mutations of *PTEN*. The original syndrome was characterized by the presence of multiple hamartomatous lesions, papillomas of the lip and tongue and acral keratoses. An increased risk of early-onset breast cancer (and also thyroid cancer) has been reported to be associated with the syndrome.

Several other conditions have been reported to be associated with an increased risk of breast cancer. These include the Muir-Torre syndrome and the Peutz-Jegher syndrome, both of which are more commonly associated with gastrointestinal tumors. Rare associations have been described with a constitutional translocation of chromosomes 11 and 22, as well as with alterations in the androgen-receptor gene. Finally, there have been reports that the carrier state for ataxia telangiectasia, an autosomal recessive neurologic disorder caused by mutations in the gene *ATM*, is associated with an increased breast cancer risk.

Cancer Risks in Individuals with a *BRCA1* or *BRCA2* Mutation

The identification of unaffected women with *BRCA1* or *BRCA2* mutations provides an opportunity to reduce cancer mortality by enrolling such individuals in intensive surveillance and prevention programs. Such programs would appear to be justified by the significantly increased cancer risks faced by these women. Unfortunately, the exact degree to which risk is elevated remains a topic of active investigation. Current estimates of cancer risks among *BRCA1* or *BRCA2* heterozygotes are shown in Table 11.3. The lifetime breast cancer risk for a woman with a mutation in either gene is estimated to be 50-85%. The higher estimates are generated by the study of families with

Table 11.2. Syndromes associated with increased breast cancer risk

Syndrome	Responsible Gene(s)
Hereditary breast and breast-ovarian cancer	*BRCA1, BRCA2*
Li-Fraumeni syndrome	*P53*
Muir-Torre	*PTEN*
Peutz-Jegher syndrome	*SKT11*
Ataxia-telangiectasia (heterozygote)	*ATM*
Unnamed	*AR*
	t(11;22)-gene unknown

dramatic pedigrees, such as those included in the Breast Cancer Linkage Consortium effort. Lower estimates arise from the study of less highly selected families. Risk estimates range widely due to differences in methods of ascertainment and penetrance calculation. In addition, unidentified genetic or environmental factors may exist that may be distributed differently in the reported study populations. Factors modulating cancer risks in this population are not well described but may be different from those that are operative in populations that do not have an inherited predisposition. It is crucial to recognize that the Gail model or "Claus tables" may substantially underestimate breast cancer risk in hereditary breast-ovarian cancer families, and such models should not be used for this purpose.

Although there are few data, the contralateral breast cancer risk by age 70 in women with *BRCA1* mutations who have undergone mastectomy for one breast cancer is estimated to be as high as 65% and is likely to be similar for *BRCA2* heterozygotes. Male *BRCA2* heterozygotes are estimated to have an up to 6% lifetime risk of breast cancer. The estimated risk of ovarian cancer ranges between 15% and 65% for *BRCA1* heterozygotes and between 10% and 20% for those with mutations in *BRCA2*. Women with mutations in either gene also appear to be at increased risk for fallopian tube cancer and primary peritoneal carcinoma, but the level of this risk is undefined. As with breast cancer risk, estimates of ovarian cancer risk may vary as a result of ascertainment biases, or as a consequence of unidentified environmental or genetic factors. Other cancers that may occur with increased frequency in hereditary breast cancer families include colon (*BRCA1*), prostate *(BRCA1* and *BRCA2*), pancreas (*BRCA2*) and larynx (*BRCA2*).

Clinical Aspects of *BRCA*-Associated Breast and Ovarian Cancer

From a clinical perspective, it is important to determine whether or not *BRCA*-associated malignancies are distinct, either in appearance, biology or outcome. *BRCA*-associated breast cancers are usually infiltrating ductal carcinomas (NOS), with some series reporting a modest increase in medullary

Table 11.3. Estimated lifetime cancer risks associated with germline BRCA mutations

Site	*BRCA1*	*BRCA2*
Female breast	50-80%	50-85%
Contralateral breast	Up to 65%	Presumed similar
Ovary	15-60%	10-20%
Fallopian tube	Unknown, presumed increased	Unknown, presumed increased
Primary peritoneal carcinoma	Unknown, presumed increased	Unknown, presumed increased
Male breast	Not increased	6%
Other sites (suggested)	Prostate Colon	Prostate Pancreas Larynx

and atypical medullary types. These tumors are usually poorly-differentiated, although there may be subtle differences in appearance between *BRCA1*- and *BRCA2*-associated cancers. Difficulties in obtaining concordance among pathologists with respect to the components of histologic grade preclude using these differences to judge the probability of detecting a mutation in either *BRCA1* or *BRCA2*. Mucinous histologies and low-grade tumors are under-represented among *BRCA*-associated ovarian cancers. From a biologic standpoint, *BRCA*-associated breast cancers tend to be aneuploid with high proliferative rates (by mitotis counts, flow cytometry or Ki-67 staining). The proportion of *BRCA1*-associated breast tumors that are hormone-receptor negative appears to be greater than expected, even accounting for the young age at onset of these cancers. The distribution of hormone-receptor status in *BRCA2*-associated cancers is less clearly defined, but may be more similar to that of nonhereditary cases of comparable age. Although few data are available regarding other biologic parameters, *P53* overexpression (and somatic mutation) appears to be common in *BRCA*-associated breast and ovarian cancer. Interestingly, HER2/*neu* overexpression appears to be quite uncommon in *BRCA*-associated breast cancers.

The prognosis of *BRCA*-associated cancers is a matter of some controversy (reviewed in ref. 21). Most published series have failed to demonstrate inferior survival for breast cancer patients with germline *BRCA1* mutations when compared to population controls or women without mutations from the same ascertainment (e.g., early-onset breast cancer). Two series, however, one from Canada and one from France, have suggested that the presence of a *BRCA1* mutation may be an adverse prognostic factor for survival. Most of the published series suffer from a systematic survival bias in that only living women were tested. This bias could obscure an adverse effect of *BRCA* mutations on survival. In addition, other prognostic features (e.g.,

nodal status, hormone-receptor status, age) are not routinely taken into account in any of these series. It is important to note that few data are available specifically regarding the impact of *BRCA2* mutations on outcome, and the impact of the two genes may not necessarily be the same. To date, then, there is no conclusive evidence that women with *BRCA*-associated breast cancer have an inferior outcome when compared to women without mutations with a similar distribution of traditional prognostic factors. The matter requires further study, however, preferably in large groups of unselected, incident cases. As regards ovarian cancer, an early report suggested that women with *BRCA*-associated ovarian cancer had a superior survival when compared to controls. Although other small series failed to confirm this observation, a large incident series demonstrating a significantly improved survival for *BRCA*-associated ovarian cancer has recently been reported. The biologic reason for the improvement in survival remains to be elucidated, and at this time there are no data to indicate that *BRCA* heterozygotes with ovarian cancer should receive less intensive treatment than women without mutations.

Based on the above data, there is presently no indication that systemic therapy of either breast or ovarian cancer should be modified on the basis of germline *BRCA* status. Concern has been raised, however, that *BRCA* heterozygotes with breast cancer might not be appropriate candidates for breast-conservation therapy. While there are few series specifically addressing this issue, 37 heterozygotes at our institution have undergone breast-conservation therapy for 41 breast cancers. With a median follow-up of 77 months for surviving patients, the projected 5 year ipsilateral failure rate is 11.9%. While this rate of ipsilateral recurrence is comparable to that reported in other series of young women undergoing breast-conservation therapy, it will be extremely important to verify these data on an unselected series of women with mutations. Until such information is available, current data do not support denying *BRCA* heterozygotes the opportunity to undergo breast-conservation therapy because of fears about a prohibitive rate of local recurrence. The contralateral breast cancer risk, however, is significant in all women with *BRCA1* or *BRCA2* mutations, and those women who would consider risk-reducing mastectomy need to be made aware of the impact that radiation therapy may have upon options for reconstruction. Whether radiation therapy influences the contralateral breast cancer risk in these women is presently unknown.

Surveillance Options for Individuals with *BRCA1* or *BRCA2* Mutations

Surveillance options for individuals with germline *BRCA* mutations are necessarily built on expert opinion. Unfortunately, there has been no formal demonstration that any approach will impact cancer-specific mortality in this population. Nonetheless, the ability to identify an at-risk population

presents an opportunity to apply proactive, potentially life-saving programs for primary and secondary cancer prevention. Such programs have been proposed by the ELSI consortium in the United States and by the French National Ad Hoc Committee in Europe. The surveillance program currently recommended at Memorial Sloan-Kettering is outlined in Table 11.4. For management of female breast cancer risk, women should be educated in the practice of monthly breast self-examination between the ages of 18 and 20. Clinical breast examination should be performed three to four times a year, beginning at age 25. Annual mammography should also be performed beginning at age 25, although breast density may preclude satisfactory examination in the youngest women. The utility of other breast screening modalities (e.g., ultrasound, MRI) is unclear, and these procedures should currently be considered investigational. There are no published recommendations for screening of males at inherited risk for breast cancer. It is rational, but unproven, to suggest self-examination and periodic clinical examination by an experienced provider. The utility of screening mammography in such men is undefined.

For management of ovarian cancer risk, biannual transvaginal pelvic ultrasound should be performed beginning at age 35. Biannual measurement of serum CA-125 is also suggested. Ovarian screening can be deferred until slightly later than breast screening as few hereditary ovarian cancers occur before the age of 35.

It is reasonable to consider screening for some of the other tumor types that have been reported to be part of the spectrum of malignancies associated with *BRCA* mutations. In particular, screening for colon and prostate cancers should be considered, beginning at age 40.

Prevention Strategies for Women with *BRCA1* or *BRCA2* Mutations

Given the uncertain utility of screening programs (secondary prevention) in this high-risk population, some women consider undergoing surgical procedures in an attempt to manage their risk. Bilateral risk-reducing mastectomy appears to be approximately 90% effective in reducing breast cancer incidence and mortality in women with a significant familial risk. Unfortunately, failure can occur as the result of the development of breast cancer in residual breast tissue. This is a particular issue after subcutaneous mastectomy, but even women undergoing total (simple) mastectomy may develop cancer in ectopic rests of breast tissue (e.g., in the axilla). The effectiveness of mastectomy in women with germline *BRCA* mutations has not been defined. Despite its presumed effectiveness, the uptake of risk-reducing mastectomy by such women in the United States appears to be quite low.

Table 11.4. Suggested surveillance program for individuals with BRCA mutations

Site	Modality	Frequency	Age to begin
Female breast	Self-examination	Monthly	18-20
	Clinical examination	3-4 Per year	25
	Mammography	Annual	25
Ovary	Transvaginal ultrasound	Biannual	35
	Serum CA-125	Biannual	35
Colon	Fecal occulat blood +	Annual	40-50
	sigmoidoscopy OR	Every 3-5 years	40-50
	colonoscopy	Every 3-5 years	40-50
Prostate	Digital rectal examination	Annual	40-50
	Serum PSA	Annual	40-50

Laparoscopic risk-reducing salpingo-oophorectomy is performed more commonly, particularly in women who have completed child-bearing and are nearing menopause. There are few data regarding the effectiveness of this procedure in reducing ovarian cancer risk. Oophorectomy cannot be considered completely protective, as cases of primary peritoneal carcinoma have been described after surgery. Nevertheless, because of uncertainties regarding the effectiveness of ovarian cancer screening and the perceived high case-fatality rate of ovarian cancer, a significant fraction of women at defined hereditary risk choose to undergo the procedure. On a policy level, two separate decision analyses have demonstrated that risk-reducing surgery (mastectomy and/or oophorectomy) is a cost-effective way to manage cancer risk in this population. While these analyses are encouraging, it is difficult to translate these population benefits in a meaningful way to an individual patient.

There has been considerable interest in the use of chemoprevention as a means to reduce cancer risk. In particular, the encouraging results of the NSABP-P1 trial have provided a springboard for investigating the use of antiestrogens in *BRCA* families. At this time, it is unknown whether this strategy will be as effective as it is in the wider population. Of particular concern is the fact that many *BRCA*-associated breast cancers are hormone-receptor negative, and neither tamoxifen nor raloxifene substantially affect the incidence of such tumors. Further analysis of the P1 study is ongoing to determine the impact of antiestrogen therapy on breast cancer risk in *BRCA* heterozygotes. Until these results are available, the use of tamoxifen and other antiestrogens should be considered investigational in this group.

Oral contraceptives have been known for some time to reduce ovarian cancer risk in the general population. A recent study has indicated a similar beneficial effect in *BRCA* heterozygotes. Specifically, heterozygotes who took oral contraceptives for any period of time had a relative risk for ovarian cancer

of 0.5 (95% CI 0.3-0.8) when compared to controls. Benefit seemed to accrue particularly to women who took oral contraceptives for over 3 years. Although the results of this study are encouraging, methodological limitations mandate confirmation of the results before these agents can be routinely recommended to women with *BRCA* mutations. This is particularly the case as the impact on breast cancer risk was not described in the aforementioned study, and at least one publication has suggested an increased risk of breast cancer among heterozygotes taking oral contraceptives when compared to controls.

Summary

In summary, the identification of a germline *BRCA* mutation in a woman with breast or ovarian cancer should not, at present, influence her local or systemic treatment. The recognition of a hereditary breast or ovarian cancer, however, indicates the need for specialized surveillance and prevention strategies to manage subsequent cancer risk in that woman and in her female relatives. Males in such families may also benefit from heightened surveillance for colon, prostate and possibly breast cancer. The choice of whether or not to undergo genetic testing is a difficult one and should only be made after genetic counseling by a qualified professional. Such professionals should also be involved in the interpretation of genetic test results. Such expertise is necessary because the integration of test results into a cancer risk assessment is a complex endeavor, particularly if results are "negative" in the setting of a strong family history or if the results are ambiguous (genetic variants of uncertain significance). Although the feared social risks of genetic testing appear not to have materialized in any systematic way, the psychosocial consequences and impact upon family dynamics are important considerations that are still being defined. Finally, the medical management of individuals at highest hereditary risk is being continuously refined. A new era of genetically targeted risk management has dawned, and much research is required to maximize the benefits of this technology for families at risk.

Note

We have recently published an evaluation of 305 unselected women of Ashkenazi descent undergoing breast-conservation therapy for a total of 329 invasive breast cancers.[29] Using an anonymized design, outcomes of 28 women with founder mutations in *BRCA1* or *BRCA2* were compared to those of women without mutations. Overall, women with mutations fared poorer than those without, with 10 year breast-cancer-specific survival of 71.9% compared to 87.2% in those without. After adjustment for tumor size and nodal status, however, mutation status was not an independent predictor of worse survival. These results, using a study design that avoids the survival biases inherent in other series, suggest that women with certain specific *BRCA* mutations tend to present at a more advanced stage than women without

such mutations, although it remains unclear if this tendency for more advanced presentation is a result of a lack of screening among younger women or a consequence of a more aggressive biology.

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