Adnan Aydiner
Abdullah İğci
Atilla Soran
Editors

Breast Disease

Diagnosis and Pathology

Volume 1

Springer

Adnan Aydiner • Abdullah İğci
Atilla Soran
Editors

Breast Disease

Diagnosis and Pathology

Volume 1

Springer

Editors
Adnan Aydiner
Medical Faculty
Istanbul University
Istanbul
Turkey

Abdullah İğci
Institute of Oncology
Istanbul University
Istanbul
Turkey

Atilla Soran
Magee-Womens Hospital of UPMC
Pittsburg, CA
USA

ISBN 978-3-319-22842-6 ISBN 978-3-319-22843-3 (eBook)
DOI 10.1007/978-3-319-22843-3

Library of Congress Control Number: 2015955271

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

The goal of *Breast Disease Diagnosis and Pathology* is to provide a comprehensive, scholarly appraisal of contemporary basic science and diagnosis. Because of advances in molecular medicine and therapeutics, this appraisal requires a more extensive understanding of the basic science of oncology than was required in the past. This book is organized into 16 chapters, and a brief summary of their content is provided below. In addition, we highlight some of the various important points in this book.

The topic of *Benign Breast Diseases* covers a wide variety of conditions, both common and unusual, that may require additional work-up, excision, or surveillance. In addition, some benign conditions may confer an increased risk for future disease, and this risk should be explained to the patient during treatment for these entities. This section attempts to provide a basic understanding of some of the most frequently encountered benign breast conditions and various rare types, including current recommendations for work-up, management, differential diagnoses, and future surveillance. The specific conditions that are explored in this chapter include fibroadenomas, intraductal papillomas, lipomas, hamartomas, radial scars, and gynecomastia in males.

Age, family history, and both endogenous and exogenous ovarian hormone exposure have important effects on risk and have been incorporated into models that predict the individual *risk of breast cancer*. Diet, alcohol use, and other factors play smaller roles. BRCA mutation-associated breast cancer differs from sporadic breast cancer in that BRCA mutation carriers exhibit an increased risk of breast and ovarian cancer and differential sensitivity to chemotherapeutic agents. Because BRCA genetic testing is readily available, BRCA mutation status should be evaluated in high-risk women, including women who were diagnosed with breast cancer at an early age and women with a strong family history or triple-negative tumors. Given the high rate of contralateral breast cancer and ovarian cancer, mutation carriers with newly diagnosed breast cancer may choose to undergo contralateral prophylactic mastectomy or bilateral salpingo-oophorectomy. In addition, two selective estrogen-receptor modulators, tamoxifen and raloxifene, and aromatase inhibitors can be used to decrease the incidence of invasive breast cancer in women who are at high risk of this condition.

Breast imaging is an essential component of breast cancer diagnosis and guides surgery and treatment options. Imaging techniques, such as mammography, ultrasound (US), and magnetic resonance imaging (MRI), enable the

detection of breast cancer at earlier stages. Mammography remains the standard screening examination; however, additional imaging studies are useful in evaluating the breast. US is utilized primarily in the diagnostic setting to characterize mammographic or palpable findings and assess axillary lymph nodes. Supplemental US screening may also be useful in patients with an intermediate risk for developing breast cancer and dense breasts to increase cancer detection. In addition to mammography, high-risk patients may also have annual MRI or US screening if they are unable to undergo MRI. MRI is also performed to evaluate the extent of disease, the response to neoadjuvant chemotherapy, and silicone implant integrity. In addition, these imaging modalities are also used to guide percutaneous biopsy, enabling minimally invasive tissue diagnosis.

Lobular carcinoma in situ (LCIS) is a high-risk indicator lesion for and a non-obligate precursor of the development of invasive breast carcinoma. Loss of E-cadherin is the hallmark pathological feature of lobular entities. Effective clinical management of LCIS requires good communication among the radiologist, surgeon, pathologist, and medical oncologist and entails surgical excision, subsequent surveillance, and systemic and surgical strategies to reduce the risk of future invasive cancer.

Ductal carcinoma in situ (DCIS) is defined as abnormally proliferating malignant cells confined to the breast milk ducts by the basement membrane. DCIS is diagnosed most commonly as a mammographic abnormality but can occasionally present as a palpable breast mass. Overall survival after breast-conserving therapy is equivalent to that observed for mastectomy. Patients undergoing mastectomy for DCIS should have sentinel lymph node biopsy (SLNB). Immediate breast reconstruction should be considered for patients undergoing mastectomy. Endocrine therapy, such as tamoxifen, is offered for 5 years to women with estrogen receptor-positive DCIS.

The topic of *Biology and Genetics of Breast Cancer* covers a wide variety of molecular studies. Understanding the mechanisms of DNA alterations leading to carcinogenesis can provide crucial insights for resolving the development of malignant processes, such as growth, invasion, and metastasis. This chapter reviews hereditary and somatic genetic alterations, epigenetic misregulations, and miRNA signatures associated with breast cancer. This chapter also emphasizes the molecular profiles of breast cancer and critical signaling pathway alterations.

Human breast cancers depend on estrogen and/or progesterone for growth, and these effects are mediated through *estrogen receptors* (ERs) and *progesterone receptors* (PRs), respectively. The *human epidermal growth factor receptor 2* (HER2) gene encodes a member of the epidermal growth factor receptor family of receptor tyrosine kinases, and its amplification with resultant overexpression plays a major role in sustaining multiple pathways in cancer growth. ERs, PRs, and HER2 status are the most important molecular markers in the standard care of all primary and recurrent/metastatic breast cancer patients and play both predictive and prognostic roles. The responsiveness of a tumor to hormone therapy is an important parameter in breast cancer management in both the adjuvant and metastatic settings. Only breast cancers with HER2 amplification or overexpression respond to HER2-directed therapies. Tumor hormonal status

is prognostic for patient outcome and potential sites of metastasis. Hormonal receptor-positive disease represents an indolent and slowly growing tumor with longer time to disease recurrence. HER2 is a poor prognostic factor in the absence of HER2-directed therapies. Assessment of the ER/PR/HER2 status is an essential factor in the evaluation of every newly diagnosed breast cancer, and the standardization of assay methods is crucial.

Invasive breast carcinomas comprise a heterogeneous group of lesions that differ in their molecular and pathologic features and clinical behavior. Some patients experience long periods of disease-free survival, whereas others experience the rapid development of recurrence and metastases that are fatal within a few years of the initial diagnosis. Numerous factors in individual tumors can be evaluated to stratify patients into subsets with varying risks of recurrence and response to different therapy modalities. The *Prognostic and Predictive Factors of Invasive Breast Cancer* chapter describes the current standard prognostic and predictive factors of invasive breast carcinoma and discusses emerging data on molecular markers that can be considered in clinical practice.

Adjuvant chemotherapy and endocrine treatment decrease the mortality of early breast cancer. However, not all early breast cancer patients benefit equally from adjuvant endocrine treatment and/or chemotherapy. High-risk patients are classically identified based on clinicopathological factors, such as age, tumor size, histopathological grade, nodal status, hormone and HER2 receptor positivity, and menopausal status. However, for patients with early breast cancer, the use of these standard clinicopathological factors might not thoroughly reveal the individual risk of disease recurrence and the benefits from adjuvant systemic chemotherapy. Many patients with early breast cancer do not derive benefit from adjuvant systemic chemotherapy. Quantitative approaches for defining prognoses and individualizing treatments are required. In recent years, *molecular signatures of gene expression* have been correlated with breast cancer recurrence risk. Several tests for genomic expression have been developed and validated on specimens from previous phase III studies to improve the prognostication of early breast cancer patients and/or the prediction of adjuvant systemic treatment.

In clinical practice, although local recurrence or distant metastasis develops in some individuals who have been assessed as low risk despite treatment, some individuals with high-risk disease do not relapse despite systemic and local therapy. Therefore, oncologists must determine objective prognostic factors to identify early recurrence and metastasis in patients with breast cancer. Based on the presumption of residual disease, clinicians have recently attempted to identify micrometastases using *disseminated tumor cells* (DTCs) in the *bone marrow and circulating tumor cells* (CTCs) from the peripheral blood. DTCs are known as epithelial cells in the bone marrow, and they are also considered to be micrometastases in the bone marrow. DTCs are observed in approximately 30 % of early-stage breast cancer patients. Tumor cells that circulate in the peripheral blood of patients with cancer are referred to as CTCs. CTCs are cells that have entered the peripheral blood circulation after having detached from an existing primary tumor or its metastases. DTCs and CTCs can be used to predict progression-free and overall survival as well as response to treatment.

In the *Pathology of Breast Cancer* chapter, classification is based on the recent WHO classification of breast carcinoma, and specific gross and microscopic features of in situ and invasive breast carcinomas are explained. Morphological groups, grading of DCIS, and the necessary information that should be included in a surgical pathology report are discussed. Recent information regarding columnar cell lesions and flat epithelial atypia of the breast are discussed along with their clinical importance. Common forms of invasive carcinomas, such as invasive ductal carcinoma and invasive lobular carcinoma; special types; and rarer forms are also discussed along with their clinical consequences.

Intraoperative pathological examination may be performed for the rapid diagnosis of breast malignancy, the assessment of the surgical margins of breast-conserving excision specimens, and the pathological analysis of sentinel lymph nodes. The most commonly used methods for intraoperative pathological examination of breast lesions are cytological and frozen section examinations in addition to gross analysis. The pathological examinations of sentinel lymph nodes necessitate careful gross examination and serial and/or step sectioning. Immunostaining using antibodies against pancytokeratin can also be performed. Sentinel lymph node metastases should be clearly defined as macro- or micrometastases or isolated tumor cells. The differential diagnosis of subtypes of metastasis and mimickers is detailed.

Fibroepithelial tumors of the breast represent a heterogeneous group of biphasic tumors composed of a proliferation of epithelial and stromal components. Fibroadenomas and phyllodes tumors constitute the major entities. These tumors are among the most challenging diagnostic lesions for pathologists. It can be difficult to make a clear microscopic distinction between fibroadenomas and benign phyllodes tumors. No reliable morphological features or immunohistochemical markers that predict phyllodes tumors are available.

A variety of reactive and neoplastic lesions of the breast are characterized by spindle cell proliferation. The pathologist must be aware of the clinical, radiological, and morphological overlap between reactive and *neoplastic spindle cell lesions* of the breast. In addition, metaplastic (spindle cell) carcinoma is far more common than spindle cell sarcoma in the breast. Among the vascular lesions of the breast, angiosarcoma is more common and may appear very bland, simulating a hemangioma. Core biopsy samples must be evaluated very carefully to interpret spindle and vascular lesions. In general, excision is recommended due to morphological overlap, and clinicopathological correlation is necessary for a correct diagnosis.

We would like to dedicate this book to postgraduate physicians in training to become breast cancer specialists. Some of the recommendations are controversial and the subject of ongoing trials. We hope this book stimulates today's young doctors to contribute to the research on which future books will be based.

Istanbul, Turkey — Adnan Aydiner, MD
Istanbul, Turkey — Abdullah İğci, MD
Pittsburgh, PA, USA — Atilla Soran, MD

Contents

Contributors

M. Kadri Altundag, MD Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

Cagatay Arslan, MD Department of Medical Oncology, Izmir University, Faculty of Medicine, Medical Park Hospital, Karsiyaka, Izmir, Turkey

Banu K. Arun, MD Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Soley Bayraktar, MD, MBA Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Department of Medical Oncology, Mercy Cancer Center, Ardmore, OK, USA

Zerrin Calay, MD Department of Pathology, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey

Emilia Josefa Borromeo Diego, MD Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

A. Lale Dogan, MD Department of Basic Oncology, Hacettepe Cancer Institute, Hacettepe University, Ankara, Turkey

Marie Ganott, MD Department of Radiology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Brandy Griffith, DO Department of Radiology, University of Pittsburgh Medical Center Hamot, Erie, PA, USA

Breast Imaging Department, Erie, PA, USA

Sennur Ilvan, MD Department of Pathology, Cerrahpasa School of Medicine, Istanbul University, Fatih, Istanbul, Turkey

Saadettin Kilickap, MD, MSc Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

Priscilla McAuliffe, MD, PhD, FACS Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Magee-Women's Surgical Associates, Bethel Park, PA, USA

Kandace P. McGuire, MD, FACS Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Y. Yavuz Ozisik, MD Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

Scott M. Rudzinski, MD Windsong Radiology Group, Williamsville, NY, USA

Aysegul A. Sahin, MD Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Ebru Sari, MD Department of Medical Oncology, Diskapi Yildirim Beyazit Treatment and Research Hospital, Ankara, Turkey

Edward R. Sauter, MD, PhD Oncology and Surgery, Cancer Treatment and Prevention Center, Health Science Center, University of Texas, Tyler, TX, USA

Sitki Tuzlali, MD Department of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Yun Wu, MD, PhD Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Suayib Yalcin, MD Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

Ekrem Yavuz, MD Department of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Breast Anatomy and Physiology

1

Kandace P. McGuire

Abstract

Breast development begins in the 5th and 6th weeks of fetal development and continues through puberty. Errors during development can lead to abnormal development or complete failure of breast development. The breast comprises several structures that are both functional and supportive. Some of these structures do not fully develop until pregnancy and lactation and regress or involute after lactation and at menopause. The anatomy of the breast and axilla are important in oncological surgery and must be considered during surgical planning to ensure the proper treatment of breast cancer.

Keywords

Anatomy • Physiology • Embryology • Development • Lactation • Involution • Poland's syndrome • Axilla • Mastectomy • Sentinel node biopsy

Embryology/Development

During the 5th and/or 6th week of fetal development, the two bands of thickened ectoderm referred to as the ectodermal primitive milk streak develop between the groin and the axilla [1, 2]. This remains in the thorax to become the mammary ridge, whereas the remainder regresses in the human development [2].

The breast develops from an ingrowth of the ectoderm into the mesoderm to form a breast bud [1]. The glandular portion of the breast develops from the ectoderm. During the 12th week of development, 16–24 secondary buds will form off the primary bud [3].

K.P. McGuire, MD, FACS
Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital, University of Pittsburgh Medical Center, 300 Halket St., Pittsburgh, PA 15213, USA
e-mail: mcguirek2@upmc.edu

Sequence of Development

The development of the breast, summarized in Table 1.1, follows a stepwise progression

A. Aydiner et al. (eds.), *Breast Disease: Diagnosis and Pathology*,
DOI 10.1007/978-3-319-22843-3_1

Table 1.1 Embryonic breast development by gestational week

Gestational week	Breast development
5–6	Primitive milk streak develops from the ectoderm
7–8	Thickening of the mammary anlage
	Invagination into the mesoderm
	Growth of breast buds
12–16	Mesenchymal cells differentiate into the smooth muscle of the nipple-areola
	Secondary breast buds develop and branch
16–20	Tips of breast buds become the secretory alveoli
	Secondary mammary anlage differentiates into hair follicles and sebaceous and sweat gland elements
	Apocrine glands develop into Montgomery glands
20–32	Breast buds canalize and become lactiferous/mammary ducts
32–40	Parenchymal differentiation; lobules/alveoli develop
	Proliferation of mesenchyme forms the nipple-areola complex
	Pigmentation of the nipple-areola complex

beginning at the 5th week post-conception and continuing until birth. In weeks five and six, the primitive milk streak develops from a thickened band of ectoderm. Following development of the primitive milk streak in weeks seven and eight, the mammary anlage will thicken, and the mesoderm will invaginate. Simultaneously, the breast buds begin to grow. This process continues until weeks 12 through 16, when mesenchymal cells begin to differentiate into the smooth muscle of the nipple and areola. Secondary breast buds will further develop and branch but remain solid structures during this time period.

At week 16, the tips of the buds become the secretory alveoli. The secondary mammary anlage differentiates into hair follicles and the sebaceous and sweat gland elements. Apocrine glands develop to form the Montgomery glands. Beginning at week 20 of development and continuing until week 32, the breast buds will canalize to form lactiferous/mammary ducts. These ducts open into a shallow mammary pit, which will become the nipple-areola complex. In the final weeks before birth, weeks 32 through 40, parenchymal differentiation occurs. The lobules and alveoli complete development. Finally, the nipple-areola complex develops via proliferation of the mesenchyme and becomes pigmented (Fig. 1.1) [2, 3].

Developmental Anomalies

The development of a normal breast requires perfect adherence to the sequence of development described above. Should development stray from this pattern, anomalies may occur. The three most common developmental anomalies of the female breast are: (1) supernumerary breasts or nipples (polymastia/polythelia), (2) underdevelopment or lack of development of the breast, and (3) nipple inversion.

Supernumerary breasts/nipples (polymastia/polythelia) can occur in both genders and are referred to as accessory if they occur along the milk line (former primitive milk streak). They are referred to as ectopic if they occur elsewhere [3].

Accessory nipples (polythelia) occur in 2.5 % of the population and are much more common than accessory breasts (polymastia). Polythelia most commonly occurs in the thorax, while polymastia most commonly occurs in the axilla [2, 3].

Underdevelopment or hypoplasia of the breast can occur unilaterally or bilaterally and is usually clinically insignificant. However, severe unilateral hypoplasia of the breast can occur and is usually associated with hypoplasia of the pectoral muscle (lacking the lower third of the muscle) and deformity of the rib cage. This defect is termed *Poland's syndrome* because it was first recognized by Dr. Alfred Poland in 1841. Associated abnormalities of the hand (syndactyly and/or hypoplasia of the phalanges) may be present [2].

Amastia or lack of breast development is exceedingly rare. Athelia, a lack of development of the nipple-areola complex, can also occur, as can amazia, a lack of breast development in the presence of a nipple-areola complex [2, 3].

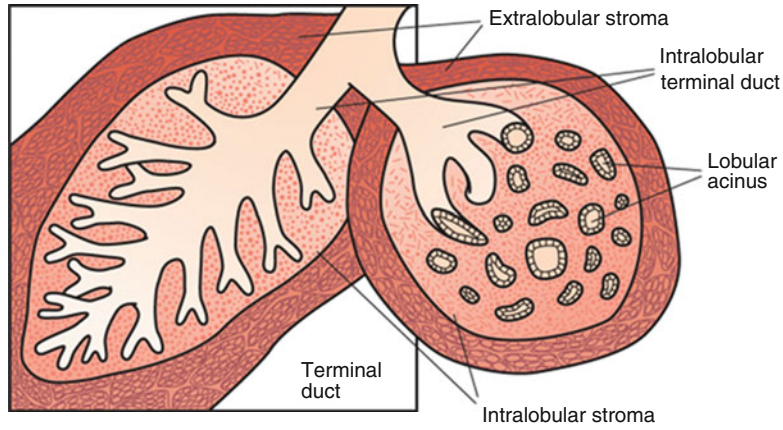

Fig. 1.1 Fully developed breast lobular unit (From Townsend et al. [5]. Reproduced with permission from Elsevier)

Failure of the mesenchyme of the nipple-areola to proliferate and elevate the mammary pit above the skin results in an inverted nipple. This failure can occur unilaterally or bilaterally and occurs in 4 % of infants, both male and female [3].

Anatomy

Breast

The adult female breast lies between the second and sixth/seventh ribs. The base of the breast spans from the sternal border medially to the midaxillary line laterally and is encompassed by the superficial and deep fascia of the chest wall. Two-thirds of the breast lies anterior to the pectoralis major; the remainder lies anterior to the serratus anterior. A prolongation of the upper outer quadrant of the breast, referred to as the tail of Spence, extends into the axilla [3, 4].

Components of the Breast

Skin – The skin is the most superficial layer of the breast. The dermis merges with the superficial fascia [3].

Superficial fascia – This layer lies just beneath the skin. It is continuous with the superficial abdominal and cervical fascia. Along with the deep fascia, it envelopes the breast parenchyma [3].

Breast parenchyma – The parenchyma is composed of three principal tissue types: glandular epithelium, fibrous stroma, and supporting structures and fat.

Glandular epithelium comprises approximately 10–15 % of the adult female breast. It is composed of 15–20 lobes, which are subsequently composed of several lobules. These lobules are referred to as terminal ductules or acini, the milk-producing glands. The major milk ducts are lined with two layers of cuboidal epithelium, while the minor ducts have a single layer. The ductal epithelium is entirely surrounded by myoepithelial cells that serve to propel milk forward through the ducts. These cells are surrounded by a continuous basement membrane. Invasion through this membrane distinguishes invasive cancer from in situ carcinoma. The ducts widen under the nipple-areola complex to form the lactiferous sinuses and then exit through 10–15 orifices in the nipple.

The fibrous stroma and supporting structures are most commonly referred to as the suspensory ligaments of Cooper. These ligaments are fibrous bands of connective tissue that travel through the breast and insert into the dermis. Tumor involvement and contraction of these bands are responsible for the puckering noted at the site of a palpable breast lump.

The remainder of the breast is composed of adipose tissue (fat). The proportion of fat to

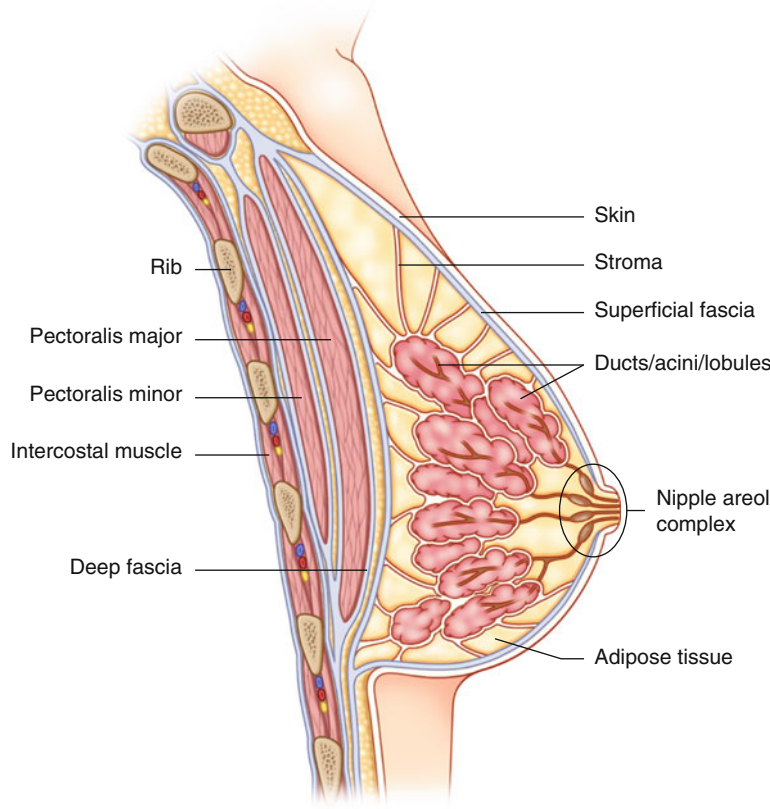

Fig. 1.2 Components of the breast

glandular tissue increases with age and is maximal in the postmenopausal breast (Fig. 1.2) [1, 4, 5].

Nipple-areola complex – As described above, each lobe of the breast leads to a ductal structure that then widens to form a large lactiferous duct (2–4 mm) that continues to form a sinus. The sinus is lined with stratified squamous epithelium. This sinus then narrows as it passes into the ampulla of the nipple (0.4–0.7 mm).

The areola comprises a combination of sebaceous, sweat, and accessory glands that form the Montgomery tubercles. Smooth muscle fibers are contained in the areola and extend into the nipple, and these fibers are responsible for nipple erection. Erection is stimulated by the sensory nerve endings and Meissner's corpuscles, which are located within the dermis of the nipple [1, 3].

Deep fascia – This layer is deep to the breast parenchyma and envelops the pectoralis major. It is continuous with the deep abdominal fascia caudally and spans from the sternum to the axilla laterally and to the clavicle cranially [3].

Neurovascular Structures

Arterial

The arterial blood supply to the breast comes primarily from three sources: (1) anterior perforators of the internal mammary artery (responsible for approximately 60 % of the breast, mostly medial and central); (2) branches from the axillary artery, such as the highest and lateral thoracic, and the thoracoacromial artery (responsible for approximately 30 % of the breast, mostly the upper outer quadrant); and (3) lateral branches of the intercostal arteries (Fig. 1.3) [1–3].

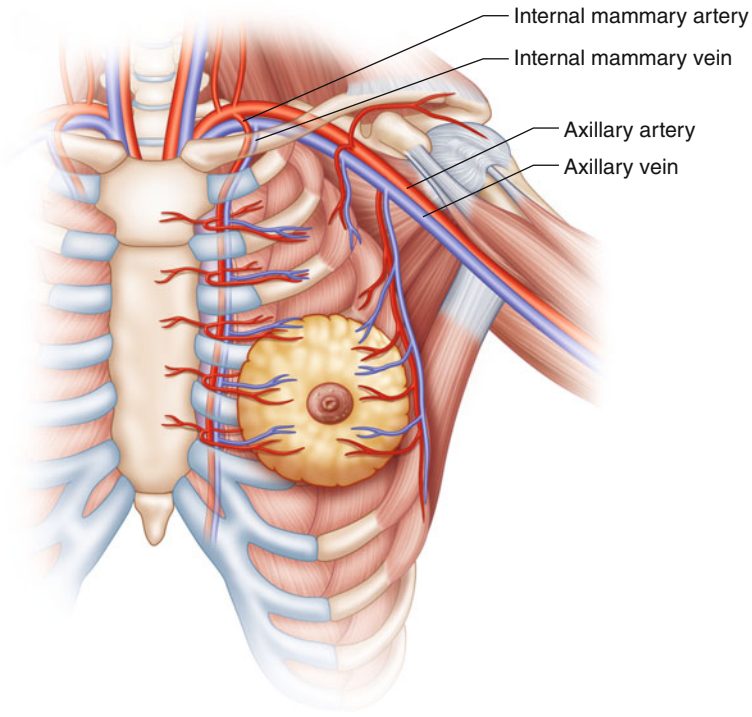

Fig. 1.3 Arterial supply and venous drainage of the breast

Venous

Venous drainage typically mimics the arterial supply. Thus, the primary venous drainage consists of: (1) internal mammary perforating branches, (2) tributaries of the axillary vein, and (3) branches of the intercostal veins (Fig. 1.3) [1].

Nervous

The sensory nerve supply to the breast is principally derived from the lateral cutaneous branches of the third through sixth intercostal nerves. Cranially, some sensory innervation is supplied by cutaneous branches of the cervical plexus. The nipple-areola complex is innervated by the fourth intercostal nerve [1, 3].

Lymphatic Structures

The superficial lymphatic plexus that drains the skin of the breast and the nipple-areola complex is often referred to as Sappey's plexus. Lymph flows from the skin to the subareolar plexus and then into the interconnected deep lymphatic plexus that drains the breast parenchyma via the lymphatic vessels associated with the lactiferous ducts. Approximately 97 % of the lymphatics from the breast drain to the axilla; the remaining 3 % drains to the internal mammary lymph nodes.

The internal mammary chain is located between the first and sixth intercostal spaces along the border of the sternum. The nodes are medial to the internal mammary vessels in the first two intercostal spaces and then become lateral to the vessels in spaces 3–6 (Fig. 1.4) [2, 4, 5]. The anatomy of the axilla and axillary lymph nodes will be discussed in the following section.

Axilla

The axilla is an important component of breast anatomy. Directly contiguous with the breast, the lymph nodes within the axilla provide a rich drainage basin for the breast. The borders of the axilla, which define the extent of axillary dissection, are as follows.

Lateral – The axillary fat pad and the bicipital groove of the humerus

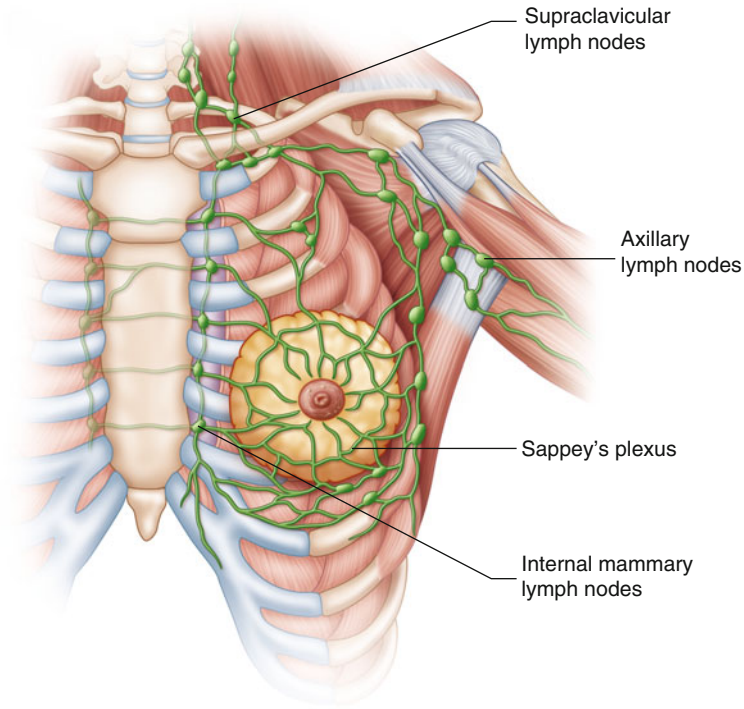

Fig. 1.4 Lymphatic drainage of the breast

Medial – The serratus anterior and the second to sixth ribs

Superior – The apex of the axilla bordered by the clavicle, the scapula, and the first rib

The apex of the axilla can also be defined by the costoclavicular ligament, which is also called Halsted's ligament. The axillary vein is the superior extent of the modified radical axillary dissection. Medial to Halsted's ligament, the axillary vein becomes the subclavian vein.

Anterior – The pectoralis (major and minor) and subclavius muscles and the clavipectoral fascia. The clavipectoral fascia envelops the subclavius and pectoralis minor and is often referred to as the costocoracoid membrane. The lateral band of the clavipectoral fascia between the first rib and the coracoid process is called the costocoracoid ligament.

Posterior – The scapula, the subscapularis, the latissimus dorsi, and the teres major. The axillary fascia lying across the base of the axillary pyramid will envelop the pectoralis major and then the latissimus dorsi. It forms the dome of the axilla. Occasionally, there can be a muscular connection between this fascia and the clavipectoral fascia, which is referred to as the suspensory ligament of the axilla [3, 5, 6].

Axillary Lymph Nodes

There are several groups of lymph nodes within the axilla. These nodes can be grouped as the apical or subclavicular nodes, which are located medial to the pectoralis minor muscle, or the axillary vein lymph nodes, which run along the axillary vein between the pectoralis minor and the humerus. The interpectoral or Rotter's nodes lie between the pectoralis major and minor muscles. The central axillary nodes are found beneath the border of the pectoralis major muscle and below the pectoralis minor. The external mammary nodes lie over the axillary tail of Spence. Intramammary lymph nodes and paramammary lymph nodes can also be found in the fat layer over the upper, outer quadrant of the breast (Fig. 1.5).

For surgical dissection purposes, there are three lymph node levels of the axilla, which are

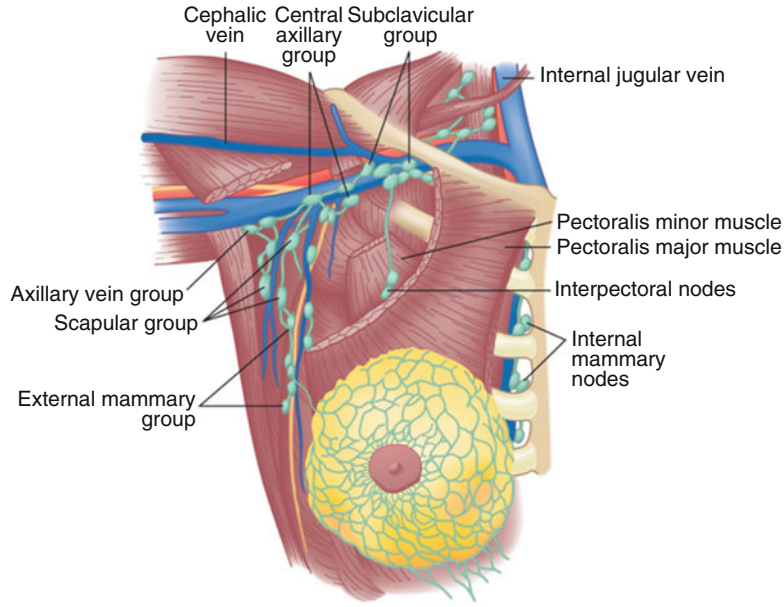

Fig. 1.5 Axillary lymph node groups (From Townsend et al. [5]. Reproduced with permission from Elsevier)

all defined by their relationship to the pectoralis minor muscle. Level I nodes are found lateral to the edge of the pectoralis minor. This level includes external mammary, subscapular, and lateral axillary lymph nodes. Level II nodes are located posterior to the pectoral minor. This level includes the central axillary lymph nodes. Level III nodes are medial and superior to the pectoralis minor. This level includes the subclavicular or apical lymph nodes [2, 6].

Structures Within the Axilla

The *axillary lymph nodes* are divided into several different groups and levels as described above and are variable in number. The maximum number identified and removed during a radical mastectomy is approximately 50, including the level I, II, and III axillary lymph nodes.

The *axillary vein* defines the superior border of the axilla during axillary dissection. It lies posterior and caudal to the brachial plexus. The axillary vein is often paired or branches during its course through the axilla.

The *thoracodorsal nerve/neurovascular bundle* innervates the latissimus dorsi and should be preserved during axillary dissection. It runs posterior to the axillary vein and medial to the subscapular vein.

The *long thoracic nerve/neurovascular bundle* innervates the serratus anterior and should be preserved during axillary dissection. If sacrificed, it will lead to "winging" of the scapula. It runs longitudinally over the serratus anterior and can be found during dissection in the axillary fat pad approximately 7 or 8 cm deep to the lateral edge of the pectoralis minor. As the long thoracic nerve/neurovascular bundle continues caudally, it will become more anterior.

The *intercostobrachial nerves* provide sensory innervation to the medial portion of the upper arm. These nerves run parallel to the axillary vein between the chest wall and the arm. One or more of these nerves run through the axillary fat pad and may be difficult to dissect away from lymph nodes. If sacrificed, either hypo- or hyperesthesia of the posterior axillary web and the medial/upper arm can result [4, 6].

Physiology

Physiological Breast Development

Breast development is stimulated by a variety of hormones that are upregulated during the beginning stages of puberty. Estrogen and

progesterone are the main hormones responsible for breast growth and development during this time. Estrogen stimulates ductal development; progesterone stimulates lobular development and epithelial differentiation.

At the onset of puberty, the hypothalamic-pituitary axis becomes less sensitive to the negative feedback of estrogen. This desensitization leads to an increase in gonadotropin-releasing hormone (GnRH) from the hypothalamus. This increase in GnRH stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary, which in turn leads to an increase in estrogen and progesterone release, thus stimulating breast development, among other developmental changes.

During pregnancy and lactation, prolactin is primarily responsible for upregulating hormone receptors and stimulating epithelial development and lactogenesis in the breast [1].

Abnormal Breast Development/ Gynecomastia

Gynecomastia refers to male breast hypertrophy and can be caused by numerous factors.

1. Physiological gynecomastia: This can occur in the neonatal, pubertal, and senescent periods. Neonatal hypertrophy occurs in response to maternal estrogen. Pubertal hypertrophy occurs due to a relative excess of estradiol to testosterone. Senescent hypertrophy occurs in response to falling testosterone levels associated with aging. The enlargement is usually unilateral in puberty but bilateral in senescence. This usually does not require surgery unless the enlargement is associated with a mass by physical exam or mammogram, fails to regress, or is cosmetically unacceptable.
2. Pathologic gynecomastia: There are a number of pathological causes of gynecomastia, including true hermaphroditism, testicular tumors, adrenal cortical neoplasms, lung or hepatocellular carcinoma, endocrine disorders, cirrhosis, and nutritional deficiencies (estrogen excess states). Hypogonadism, as observed in congenital syndromes such as Klinefelter (XXY) syndrome or ACTH deficiency, can also cause gynecomastia. Secondary testicular failure from trauma, radiation, or untreated cryptorchidism can also cause hypertrophy (androgen deficiency states). Renal failure and other systemic diseases can lead to gynecomastia, as can drugs that provide exogenous estrogen or stimulate estrogen synthesis (e.g., digoxin, estrogens, anabolic steroids, marijuana, and HCG) or that inhibit the activity or production of testosterone (e.g., cimetidine, ketoconazole, phenytoin, spironolactone, antineoplastic drugs, and diazepam). Some drugs, such as reserpine, theophylline, verapamil, tricyclic antidepressants, and furosemide, lead to gynecomastia through idiopathic mechanisms [3, 5].

Physiology of Puberty

As described above, pubertal development of the breast (thelarche) begins with the stimulation of estrogen and progesterone production via the hypothalamic-pituitary axis. At this time, the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. Estrogen stimulates growth of the ductal epithelium. Buds form off the terminal ductules and will eventually become breast lobules. Periductal connective tissue grows and becomes more elastic. Some studies suggest that while estrogen promotes growth of ducts, estrogen and progesterone synergistically promote full ductular-lobular-alveolar development in the breast.

There are three distinct types of breast lobules in the human breast, and the proportion of each is related to a woman's parity and hormonal status. During puberty, the breast develops mostly type I (virginal) lobules, which consist of a cluster of 11 alveolar buds around a terminal duct. These lobules have a much higher rate of proliferation than type 2 or 3 lobules.

Physiology of the Menstrual Cycle

The postpubertal breast contains fat, stroma, lactiferous ducts, and lobular units. The menstrual cycle affects not only the uterus and uterine lining but also the breast. During the follicular phase (days 4–14), levels of estrogen increase, stimulating epithelial proliferation/sprouting and an increased mitotic rate. During the luteal phase (days 15–28), progesterone increases, while estrogen abates. At this time, mammary ducts dilate, and alveolar epithelial cells differentiate into secretory cells. Often, lipid droplets accumulate, and some intraluminal secretion occurs. During this time, estrogen also exerts a histamine-like effect on the breast parenchyma, resulting in increased blood flow and breast edema just prior to the onset of menses.

During this time, type I lobules continue to predominate. The increased rate of cellular proliferation in these lobules may partly explain the differences in breast cancer rates based on parity and age at first live birth.

Physiology of Pregnancy

During pregnancy, there is a decrease in fibrous stroma along with an increase in new acini/lobules. In the first trimester, ducts sprout and branch, and lobules develop as estrogen increases. Breast enlargement is significant, with dilatation of superficial veins and breast edema. The nipple-areola complex darkens and begins to enlarge. Type 3 lobules (with an average of 80 acini) begin to develop during this time and are referred to as alveoli.

In the second trimester, levels of progesterone increase, as does lobular formation. The alveoli begin to form colostrum, which is composed of desquamated eosinophilic cells, plasma cells, leukocytes, and epithelial cells.

In the third trimester, the alveoli continue to produce colostrum. At this time, epithelial differentiation is completed, resulting in the development of secretory cells that produce and secrete milk proteins. Oxytocin increases over the last trimester, resulting in the proliferation of myoepithelial cells surrounding the ductal structures, which propel the milk forward toward the nipple-areola complex.

Physiology of Lactation

After birth, there is a sudden decrease in the levels of estrogen, progesterone, and placental lactogen, coupled with an increase in prolactin, which induces the production and secretion of milk. Hormonal levels reach their lowest levels at about the fifth postpartum day, with a concomitant decrease in prolactin-inhibiting factor (PIF). This decrease results in the secretion of prolactin. Along with additional growth factors, prolactin secretion results in the accumulation of colostrum and, subsequently, milk in the alveoli and ducts. Stimulation of the nipple-areola complex stimulates the release of oxytocin and the contraction of the myoepithelial cells surrounding the ductal system. Upon cessation of breast-feeding (weaning), levels of prolactin and oxytocin fall. Retained secretions are removed via phagocytosis. Atrophy of the glandular, ductal, and stromal elements is observed. The secretory cells responsible for milk production undergo apoptosis. However, the type 3 lobules persist.

Physiology of Menopause

After menopause, the breast parenchyma regresses and is replaced by adipose tissue. This replacement occurs by involution of the ductal, glandular, and stromal elements/connective tissue of the breast. The ductal system remains but undergoes atresia, with collapse of the lobular units. Type 1 lobules again predominate, as in the nulliparous breast. The number of lymphatic channels through the breast parenchyma also decreases [2, 4, 5].

Surgical/Oncological Considerations

Tumor Location Within the Breast

The adult breast develops in a conical form, with epithelial/ductal tissue in each quadrant of the breast. The axillary tail of Spence, as discussed previously, is an extension of the upper outer quadrant of the breast over the axilla. Because of this extension, the upper outer quadrant contains significantly more epithelial tissue than the other quadrants. Thus, this quadrant is the most frequent site of breast neoplasms and harbors more than half of both benign and malignant tumors [3, 4, 7].

The location of the tumor within the breast can also affect the ability to perform breast conservation (segmental mastectomy). In general, segmental mastectomy can be performed with good cosmetic outcome when the tumor volume is less than 20 % of the volume of the breast [8–10]. However, this percentage can vary with tumor location. Tumors in the upper outer quadrant are much easier to resect with good cosmetic outcome because there is a great amount of surrounding tissue in the region. Tumors that lie in the lower quadrants, particularly the lower inner quadrant, have little surrounding parenchyma, and excisions in these regions can lead to significant retraction and poor cosmetic outcome after surgery and radiation are performed. Partial breast reconstruction techniques, such as small latissimus dorsi flaps and local advancement flaps, can replace volume, particularly in the outer quadrants. However, these techniques require more extensive surgery, and the patient may be better served by mastectomy and whole breast reconstruction in this situation [11–13]. Depending on tumor location, volume loss can also be addressed by oncoplastic surgical techniques ranging from simple local advancement flaps to concurrent reduction mammoplasty [14–16].

Borders of Mastectomy

There are three different types of mastectomy, all with different extents of dissection:

1. Simple or total mastectomy – Several skin incisions can be made, including peri-areolar (skin-sparing) or elliptical. Dissection is performed along the superficial fascial plane superiorly to the clavicle; medially to the sternal edge; inferiorly to the inframammary fold, just cranial to the insertion of the rectus sheath; and laterally to the edge of pectoralis major muscle. The deep border of dissection is the deep fascial plane, just superficial to the pectoralis major muscle. This method of mastectomy removes nearly 100 % of the breast epithelial/stromal tissue while preserving the axillary fat pad and axillary lymph nodes.

   This approach is used most often in modern practice and is often combined with immediate reconstruction. When plastic surgery is involved, it is imperative that a multidisciplinary approach to surgery be used and that both oncological and plastic surgeons are involved in incision planning. This is particularly true in the case of nipple-sparing mastectomy, in which several incisions can be used [17–23]. An important anatomic consideration is the blood supply to the nipple and areola, which can vary greatly from patient to patient. Nipples that derive most of their blood supply from the underlying parenchyma are likely to suffer partial or complete necrosis after nipple-sparing mastectomy, whereas the viability of those that derive blood supply from the surrounding skin will be largely unaffected. Blood flow can be assessed either preoperatively or intraoperatively with imaging systems that detect fluorescent dye (usually indocyanine green) injected intravenously. The resulting perfusion patterns can help guide incision planning and also identify candidates for nipple-sparing surgery [24] (Fig. 1.6).

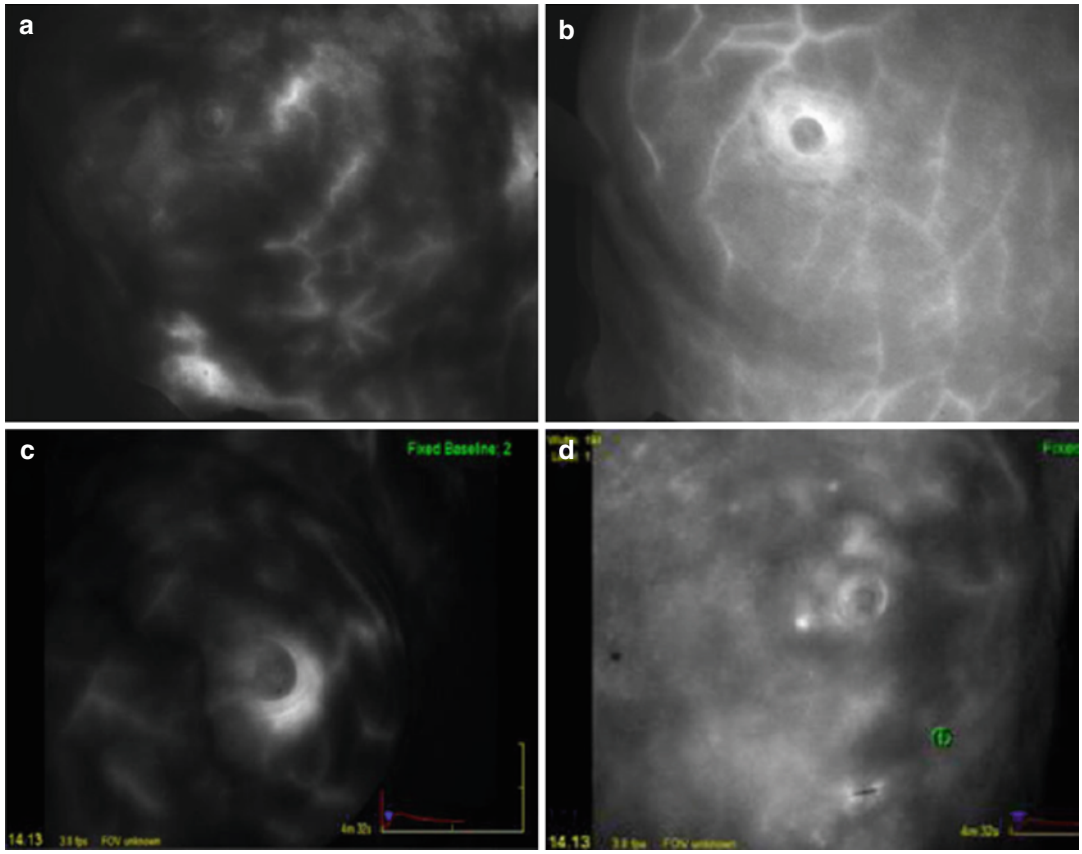

Fig. 1.6 Nipple perfusion patterns

2. Modified radical mastectomy – This operation can be performed through the same incisions as a total or simple mastectomy. The elliptical incision can be extended superolaterally toward the axilla to facilitate axillary dissection. The superior, medial, inferior, and deep borders of the dissection are the same as in a total mastectomy. However, the modified radical mastectomy involves the removal of levels I and II axillary lymph nodes; thus, the lateral border of dissection is the latissimus dorsi extending superiorly to the axillary vein.
3. Halsted radical mastectomy – This operation is rarely performed and very rarely described in current surgical texts and atlases. The superior, medial, inferior, and lateral borders are the same as in a modified radical mastectomy. However, the deep dissection includes the pectoralis major and minor muscles. The axillary dissection includes levels I, II, and III of the axillary lymph nodes and is thus extended superior and medial to the axillary vein. This operation is performed only in the presence of locally advanced cancers that involve one or both pectoralis muscles [6].

Sentinel Node Biopsy

Sentinel lymph node biopsy was originally described as a method for detecting the lymphatic

drainage of melanoma. It has been modified for use in breast cancer using the following method.

1. Isosulfan or methylene blue dye and/or technetium-99 are injected preoperatively into the superficial lymphatic plexus, either into the subareolar plexus or around the tumor.
2. This injection *can* be followed by lymphoscintigraphy to identify the area into which the radioactive dye has drained. Lymphoscintigraphy requires allowing the technetium 1 h or more to travel through the breast lymphatics into the axillary and/or internal mammary lymph nodes. As noted above, 97 % of the breast drains to the axillary region; thus, this step is not necessary. It can be helpful in inner quadrant tumors, which more commonly drain to the internal mammary chain, and in patients with previous breast surgery, which might interfere with the normal lymphatic drainage of the breast.
3. Once in the operating room, the radioactive-sensitive probe can be used to localize the area in the axilla with the highest concentration of technetium colloid.
4. An incision is made in this area through the skin, the subcutaneous tissue, and the clavipectoral fascia. Once the axillary fat pad is identified, the probe can be used to localize the lymph node(s) with the highest concentration of radioactive dye. Those lymph node(s) that are both "hot" (radioactive) and "blue" (have taken up the blue dye) should be removed and sent for pathologic analysis (frozen, touch prep, or permanent). If these "sentinel" lymph nodes show evidence of malignancy, then a full axillary dissection as described for modified radical mastectomy is performed at that time or during a separate operation.

This method is based upon the anatomy of the breast lymphatic system. As described previously in this chapter, the lymph flows from the skin to the subareolar plexus and then into the interconnected deep lymphatic plexus that drains the breast parenchyma via the lymphatic vessels associated with the lactiferous ducts. Therefore, any lymphatic drainage from the breast must travel through both the superficial and deep lymphatic plexuses before leaving the breast, and an injection into the superficial lymphatic plexus will identify the main route of drainage for the breast. This drainage is standard and reproducible. Once the channels reach the axilla, they drain first to the "sentinel" lymph node(s) in either levels I or II of the axilla before draining to the remainder of the axilla. If no cancer is found in the sentinel node, there is a >95 % likelihood that no other cancer exists in the axilla [2, 4, 5, 25].

Sentinel lymph node biopsy has several advantages over axillary dissection in appropriately selected patients, and in fact, axillary dissection has become increasingly rare. Several landmark trials have established the efficacy of sentinel lymph node biopsy in the setting of breast cancer. The great advantage of sentinel lymph node biopsy is the reduction in risk of postoperative arm (and to some extent breast) lymphedema. The rich lymphatic network experiences less disruption. In early studies, most notably NSABP B-32 and ACOSOG Z0010, the lymphedema rates after sentinel lymph node biopsy varied from 8 to 12 %, whereas axillary dissection resulted in lymphedema rates of 14–42 % [26, 27]. However, for patients who require axillary dissection, techniques can identify the lymphatics that primarily drain the arm (outside of the level III lymph nodes, which are excluded in modern axillary dissection if they are not clinically involved due to the low incidence of involved nodes in this region and the high incidence of arm lymphedema after radical mastectomy) [28, 29]. The best-described technique is axillary reverse lymphatic mapping (ARM). This technique involves injecting a small amount of blue dye in the subcutaneous tissue of the volar surface of the upper arm prior to lymphatic surgery. The axillary lymph nodes that drain the arm can be identified and frequently preserved. This can result in a lymphedema rate of 2.4 % after ALND in which the identified arm lymphatics are preserved, much lower than previous reports [30–33].