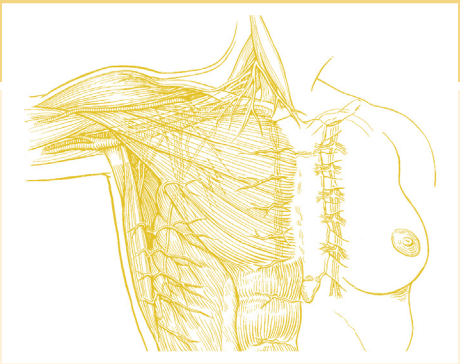

CHAPTER 35

Diseases of the Breast

V. Suzanne Klimberg, Kelly K. Hunt

OUTLINE

ANATOMY

The breast lies between the subdermal layer of adipose tissue and the superficial pectoral fascia (Fig. 35.1). The breast parenchyma is composed of lobes that comprise multiple lobules. Multiple fibrous bands termed the *suspensory ligaments of Cooper* provide structural support and run from the chest wall to the dermis. The retromammary fat pad is a relatively avascular space that lies between the breast and pectoralis major muscle. Located deep to the pectoralis major muscle, the pectoralis minor muscle is enclosed in the clavipectoral fascia, which extends laterally to fuse with the axillary fascia.

The axillary lymph nodes, grouped by location, are shown in Fig. 35.2. Axillary nodes are typically described as three anatomic levels defined by their relationship to the pectoralis minor muscle. Level I nodes are located lateral to the lateral border of the pectoralis minor muscle. Level II nodes are located posterior to the pectoralis minor muscle as well as anterior to the pectoralis minor and posterior to the pectoralis major (Rotter or interpectoral nodes).

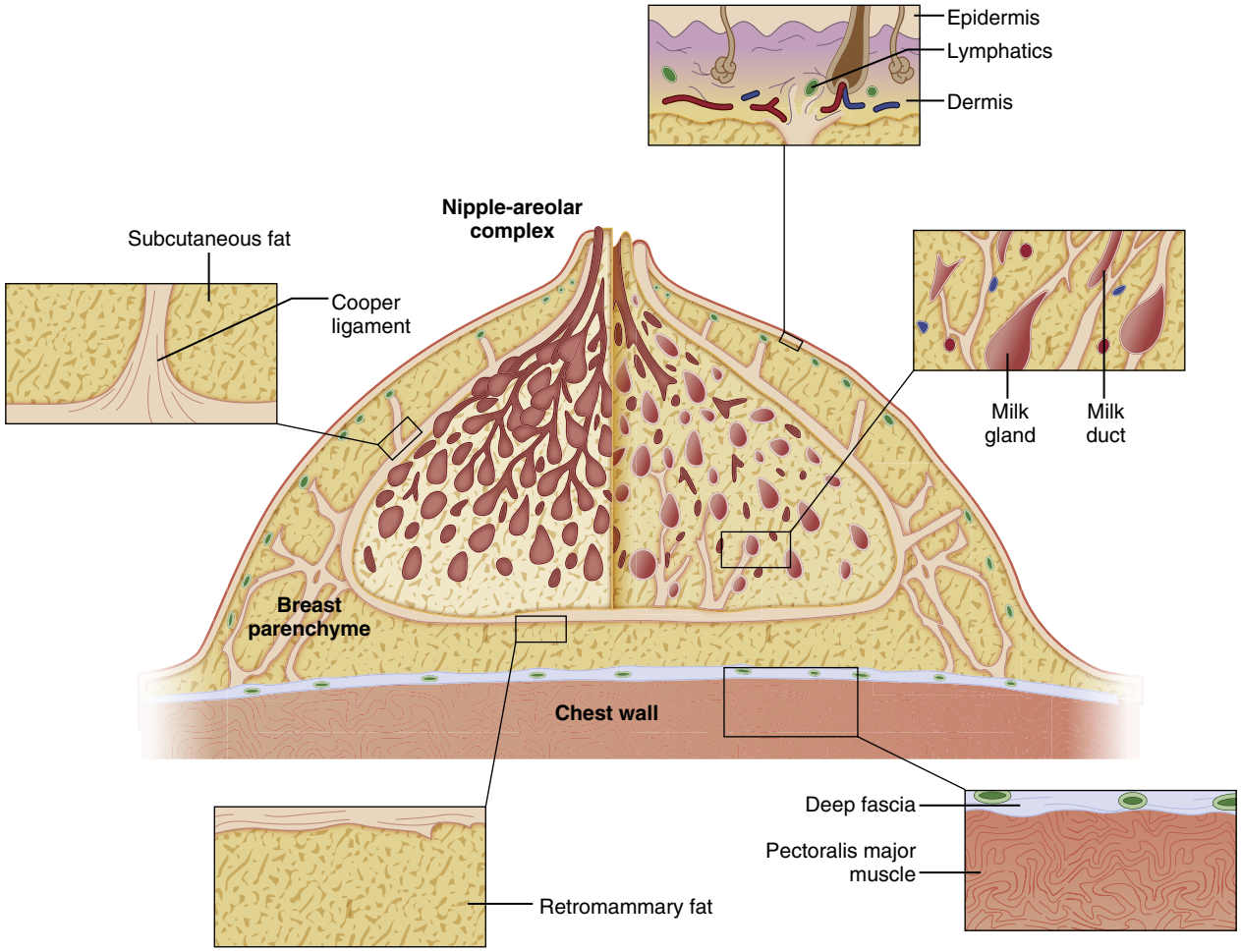

FIG. 35.1 Cut-away diagram of a mature resting breast. The breast lies cushioned in fat between the overlying skin and pectoralis major muscle. The skin and the retromammary space under the breast are rich with lymphatic channels. Cooper ligaments, the suspensory ligaments of the breast, fuse with the overlying superficial fascia just under the dermis, coalesce as the interlobular fascia in the breast parenchyma, and then join with the deep fascia of breast over the pectoralis muscle. The system of ducts in the breast is configured like an inverted tree, with the largest ducts just under the nipple and successively smaller ducts in the periphery. After several branching generations, small ducts at the periphery enter the breast lobule, which is the milk-forming glandular unit of the breast.

Level III nodes are located medial to the pectoralis minor muscle and include the subclavicular nodes. The apex of the axilla is defined by the costoclavicular ligament (Halsted ligament), at which point the axillary vein passes into the thorax and becomes the subclavian vein. However, functionally, the lymph nodes of the axilla are made up of lymphatics from the upper extremity, the back, and the breast. Boneti and colleagues[1] described the anatomic drainage of the lymphatics from the arm within the axilla (Fig. 35.3), including the traditional position just below the vein, above the vein or going directly into the subclavian, a sling pattern that comes well below the axilla, a medial or lateral apron pattern, and a twine pattern. Four percent of the time, the nodes from the breast merge with those draining the upper extremity within Level I. The functional anatomy of these lymph nodes is important in preventing lymphedema during lymphadenectomy for breast cancer.

Lymphatic channels are abundant in the breast parenchyma and dermis. Specialized lymphatic channels collect under the nipple and areola and form Sappey plexus, named for the anatomist who described them in 1885. Lymph flows from the skin to the subareolar plexus and then into the interlobular lymphatics of the breast parenchyma. Appreciation of lymphatic flow is important for performing successful sentinel lymph node surgery (see "Lymph Node Staging" later on). Of the lymphatic flow from the breast, 75% is directed into the axillary lymph nodes. A minor amount of the lymphatic flow from the breast goes through the pectoralis muscle and into more medial lymph node groups (see Fig. 35.2). Lymphatic drainage also occurs through the internal mammary lymph nodes as the predominant drainage in 5% of patients and as a secondary route in combination with axillary drainage in approximately 20% of patients. A major route of breast cancer metastasis is through lymphatic channels; an understanding of the patterns of regional spread of cancer is important to provide optimal locoregional control of the disease.

Coursing deep and close to the chest wall on the medial side of the axilla is the long thoracic nerve (see Fig. 35.2), also known as the external respiratory nerve of Bell, which innervates the serratus anterior muscle. This muscle is important for fixing the scapula to the chest wall during adduction of the shoulder and extension of the arm. Division of this nerve may result in the winged scapula deformity. For this reason, the long thoracic nerve is preserved during axillary surgery. The second major nerve encountered during axillary dissection is the thoracodorsal nerve, which innervates

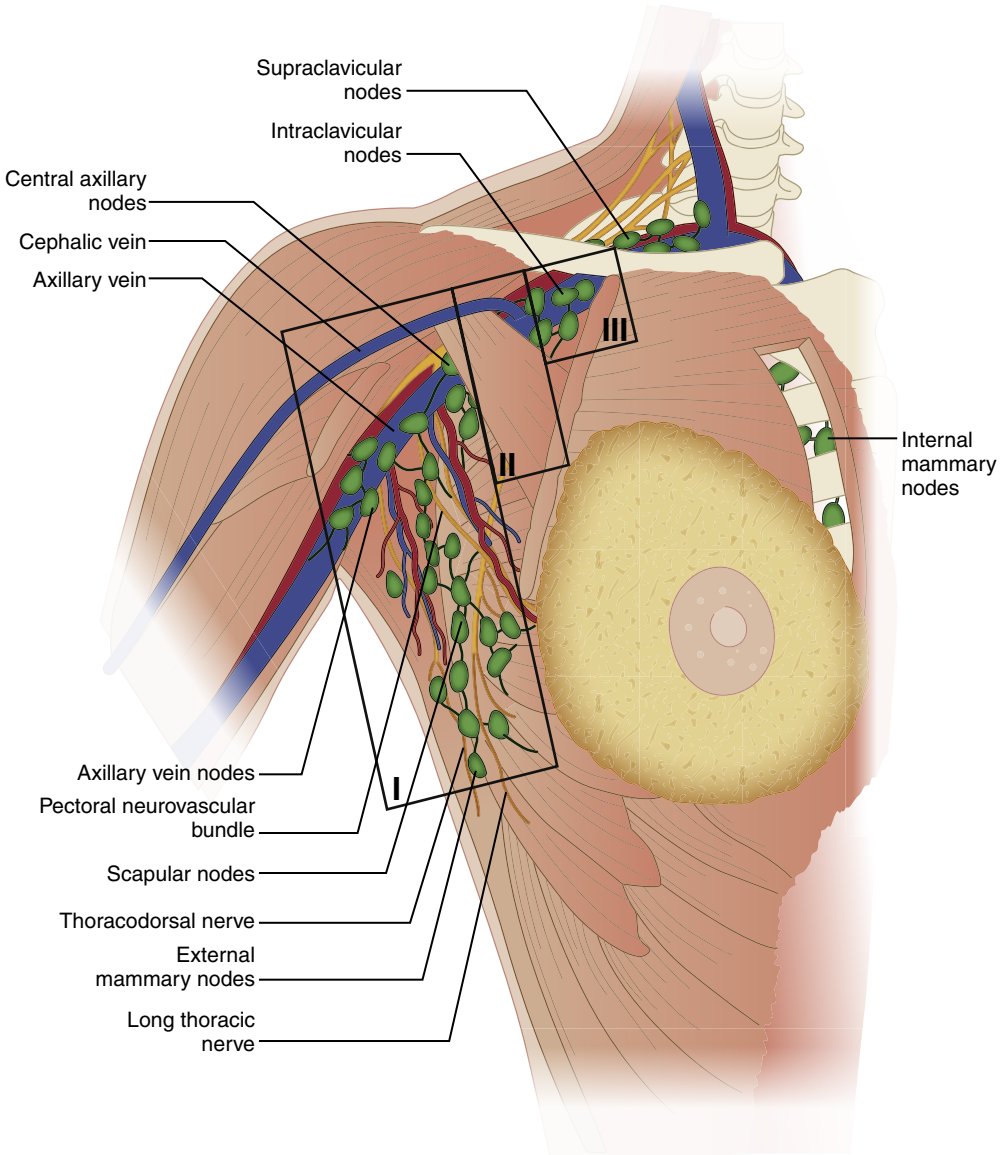

FIG. 35.2 Contents of the axilla. In this diagram, there are five named and contiguous groupings of lymph nodes in the full axilla. Complete axillary dissection, as done in the historical radical mastectomy, removes all these nodes. However, the subclavicular nodes in the axilla are continuous with the supraclavicular nodes in the neck and nodes between the pectoralis major and minor muscles, called the *interpectoral nodes* in this diagram (also known as *Rotter lymph nodes*). The sentinel lymph node is functionally the first node in the axillary chain and, anatomically, is usually found in the external mammary group. The relative positions of the long thoracic, thoracodorsal, and medial pectoral nerves are shown. These major nerves along with the pectoral neurovascular bundle should be preserved during surgery.

the latissimus dorsi muscle. This nerve arises from the posterior cord of the brachial plexus and enters the axillary space under the axillary vein, close to the entrance of the long thoracic nerve. The thoracodorsal nerve crosses the axilla to the medial surface of the latissimus dorsi muscle. The thoracodorsal nerve and vessels are preserved during dissection of the axillary lymph nodes. The medial pectoral nerve, named for its derivation from the medial cord of the brachial plexus, innervates the pectoralis major muscle and lies within a neurovascular bundle that wraps around the lateral border of the pectoralis minor muscle. The pectoral neurovascular bundle is a useful landmark because it indicates the position of the axillary vein, which is just cephalad and deep (superior and posterior) to the bundle. This neurovascular bundle should be preserved, if possible, during any lymphadenectomy.

There are three to five sensory intercostal brachial or brachial cutaneous nerves that cross the axilla horizontally and supply sensation to the undersurface of the upper inner surface of the arm and skin of the chest wall along the posterior margin of the axilla. Lymphatics run along these nerves as well. Dividing these nerves results in cutaneous anesthesia in these areas, and the possibility of this outcome should be explained to patients before axillary dissection. Denervation of the areas supplied by these sensory nerves causes chronic and uncomfortable pain syndromes in a small percentage of patients. Preservation of the most superior nerve maintains sensation to the posterior aspect of the upper part of the arm without compromising the axillary dissection in most patients. Taking these nerves with their associated lymphatics may lead to lymphedema of the chest wall.

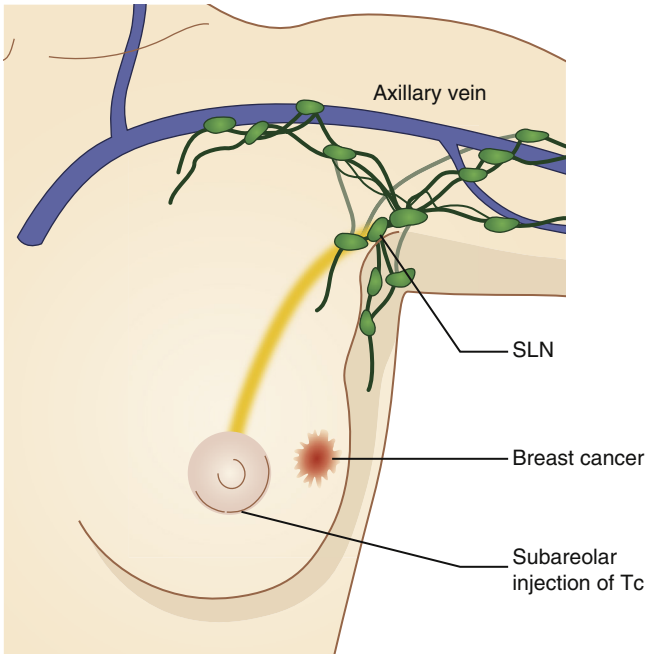

FIG. 35.3 Axillary anatomy of lymphatics draining the arm. (Adapted from Boneti C, Korourian S, Diaz Z, et al. Scientific Impact Award: axillary reverse mapping (ARM) to identify and protect lymphatics draining the arm during axillary lymphadenectomy. *Am J Surg.* 2009;198:482–487.) *SLN*, Sentinel lymph node.

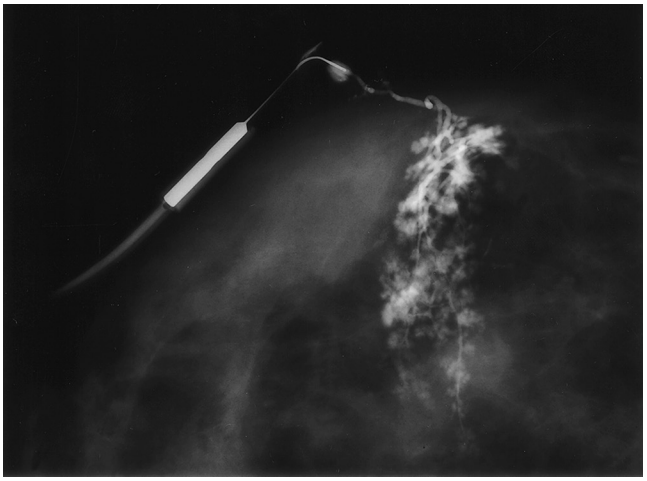

FIG. 35.4 Injection of contrast material into a single ductal system (ductogram). Occasionally used to evaluate surgically significant nipple discharge, ductography is performed by cannulation of an individual duct orifice and injection of contrast material. This ductogram opacifies the entire ductal tree, from the retroareolar duct to the lobules at the end of the tree. It also demonstrates the functional independence of each duct system; there is no cross-communication between independent systems.

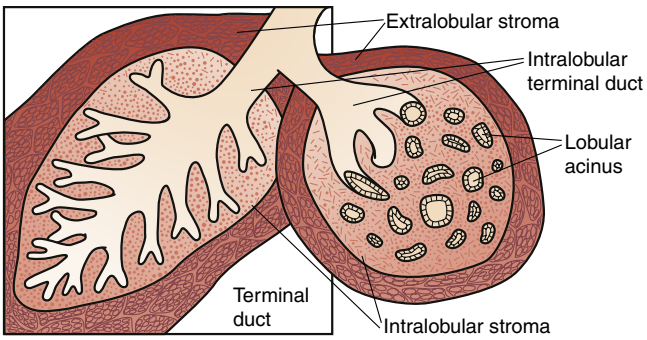

FIG. 35.5 Mature resting lobular unit. At the distal end of the ductal system is the lobule, which is formed by multiple branching events at the end of terminal ducts, each ending in a blind sac or acini, and is invested with specialized stroma. The lobule is a three-dimensional structure but is seen in two dimensions in a histologic thin section, shown in the *lower right*. The intralobular terminal ductule and acini are invested in loose connective tissue containing a modest number of infiltrating lymphocytes and plasma cells. The lobule is distinct from the denser interlobular stroma, which contains larger breast ducts, blood vessels, and fat.

MICROSCOPIC ANATOMY

The mature breast is composed of three principal tissue types: (1) glandular epithelium, (2) fibrous stroma and supporting structures, and (3) adipose tissue. The breast also contains lymphocytes and macrophages. In adolescents, the predominant tissues are epithelium and stroma. In postmenopausal women, the glandular structures involute and are largely replaced by adipose tissue. Cooper ligaments provide shape and structure to the breast as they course from the overlying skin to the underlying deep fascia. Because these ligaments are anchored into the skin, infiltration of these ligaments by carcinoma commonly produces tethering, which can cause dimpling or subtle deformities on the otherwise smooth surface of the breast.

The glandular apparatus of the breast is composed of a branching system of ducts, organized in a radial pattern spreading outward from the nipple-areolar complex (see Fig. 35.1). It is possible to cannulate individual ducts and visualize the lactiferous ducts with contrast agents. Fig. 35.4 shows the arborization of branching ducts, which end in terminal lobules. The contrast dye opacifies only a single ductal system and does not enter adjacent and intertwined branches from functionally independent ductal branches. Each major duct has a dilated portion (lactiferous sinus) below the nipple-areolar complex. These ducts converge through a constricted orifice into the ampulla of the nipple.

Each of the major ducts has progressive generations of branching and ultimately ends in the terminal ductules or acini (Fig. 35.5). The acini are the milk-forming glands of the lactating breast and, together with their small efferent ducts or ductules, are known as *lobular units* or *lobules*. The terminal duct lobular units are invested in a specialized loose connective tissue that contains capillaries, lymphocytes, and other migratory mononuclear cells. This intralobular stroma is clearly distinguished from the denser and less cellular interlobular stroma and from the adipose tissue within the breast.

The entire ductal system is lined by epithelial cells, which are surrounded by specialized myoepithelial cells that have contractile properties and serve to propel milk formed in the lobules toward the nipple. Outside the epithelial and myoepithelial layers, the ducts of the breast are surrounded by a continuous basement membrane containing laminin, type IV collagen, and proteoglycans. The basement membrane layer is an important boundary in differentiating in situ from invasive breast cancer. Continuity of this layer is maintained in ductal carcinoma in situ (DCIS), also termed *noninvasive breast cancer* (see "Pathology" later on). Invasive breast cancer is defined by penetration of the basement membrane by malignant cells invading the stroma. Invasion or infiltration of the wall of the duct gives tumor cells access to the lymphatics and blood vessels that twine around the outside of the ducts.

BREAST DEVELOPMENT AND PHYSIOLOGY

Normal Development and Physiology

In utero, the milk bud develops from the ectodermal thickening in the pectoral area and extends as the milk streak (mammary ridge) from the axilla to the inguinal area. At 9 weeks of gestation, the milk streak begins to atrophy to normally form a single pair of bilateral glands. When less than the normal atrophy of the milk streak occurs, then polymastia and/or polythelia occurs. Rarely, congenital amastia occurs as a result of failure of the milk bud.

Ninety percent of newborns will have a breast secretion that is commonly referred to as "witches milk" that is the result of elevated maternal hormones and prolactin levels. If the secretion sequesters within the nipple, it can cause a mass or lactocele that will resolve on its own in 3 to 4 weeks, as will the discharge.

Before puberty, the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. In the United States, puberty, as measured by breast development and the growth of pubic hair, begins between the ages of 9 and 12 years, and menarche (onset of menstrual cycles) begins at approximately 11 to 14 years of age. These events are initiated by low-amplitude pulses of pituitary gonadotropins, which increase serum estradiol concentrations. In the breast, this hormone-dependent maturation (thelarche) entails increased deposition of fat, the formation of new ducts by branching and elongation, and the first appearance of lobular units. This process of growth and cell division is under the control of estrogen, progesterone, adrenal hormones, pituitary hormones, and the trophic effects of insulin and thyroid hormone. There is evidence that local growth factor networks are also important. The exact timing of these events and the coordinated development of both breast buds may vary from the average in individual patients. The term *prepubertal gynecomastia* refers to symmetrical enlargement and projection of the breast bud in a girl before the average age of 12 years, unaccompanied by the other changes of puberty. This process, which may be unilateral, should not be confused with neoplastic growth and is not an indication for biopsy.

The postpubertal mature or resting breast contains fat, stroma, lactiferous ducts, and lobular units. During phases of the menstrual cycle or in response to exogenous hormones, the breast epithelium and lobular stroma undergo cyclic stimulation. The dominant process appears to be hypertrophy and alteration of morphology rather than hyperplasia. In the late luteal (premenstrual) phase, there is an accumulation of fluid and intralobular edema. This edema can produce pain and breast engorgement.

These physiologic changes can lead to increased nodularity and may be mistaken for a malignant tumor. Ill-defined masses in premenopausal women are generally observed through the course of the menstrual cycle before any intervention is undertaken. With pregnancy, there is diminution of the fibrous stroma and the formation of new acini or lobules, termed *adenosis of pregnancy.* After birth, there is a sudden loss of placental hormones, which, combined with continued high levels of prolactin, is the principal trigger for lactation. The actual expulsion of milk is under hormonal control and is caused by contraction of the myoepithelial cells that surround the breast ducts and terminal ductules. There is no evidence for innervation of these myoepithelial cells; their contraction appears to occur in response to the pituitary-derived peptide oxytocin. Stimulation of the nipple appears to be the physiologic signal for continued pituitary secretion of prolactin and acute release of oxytocin. When breastfeeding ceases, the prolactin level decreases and there is no stimulus for release of oxytocin. The breast returns to a resting state and to the cyclic changes induced when menstruation resumes.

Menopause is defined by cessation in menstrual flow for at least 1 year; in the United States, it usually occurs between the ages of 40 and 55 years, with a median age of 51 years. Menopause may be accompanied by symptoms such as vasomotor disturbances (hot flashes), vaginal dryness, urinary tract infections, and cognitive impairment (possibly secondary to interruption of sleep by hot flashes). Menopause results in involution and a general decrease in the epithelial elements of the resting breast. These changes include increased fat deposition, diminished connective tissue, and the disappearance of lobular units. The persistence of lobules, hyperplasia of the ductal epithelium, and cyst formation all can occur under the influence of exogenous ovarian hormones, usually in the form of postmenopausal hormone replacement therapy (HRT). Physicians should inquire about the menstrual history, age at onset of menses, and cessation of menses and record the use of HRT because all of these factors can influence a woman's risk of developing breast cancer. HRT can lead to increased breast density, which may decrease the sensitivity of mammography.

Fibrocystic Changes and Breast Pain

The condition previously referred to as *fibrocystic disease* represents a spectrum of clinical, mammographic, and histologic findings and is common during the fourth and fifth decades of life, generally lasting until menopause. An exaggerated response of breast stroma and epithelium to various circulating and locally produced hormones and growth factors is frequently characterized by the constellation of breast pain, tenderness, and nodularity. Symptomatically, the condition manifests as premenstrual cyclic mastalgia, with pain and tenderness to touch. This mastalgia can be worrisome to many women; however, breast pain is not usually a symptom of breast cancer. Pain without other signs or symptoms of breast cancer is uncommon, occurring in only approximately 7% of patients with breast cancer. In women with breast pain and an associated palpable mass, the presence of the mass is the focus of evaluation and treatment. Normal ovarian hormonal influences on breast glandular elements frequently produce cyclic mastalgia, pain generally in phase with the menstrual cycle. Noncyclic mastalgia is more likely idiopathic and difficult to treat. Women 30 years and older with noncyclic mastalgia should undergo breast imaging with mammography and ultrasonography in addition to a physical examination. If examination reveals a mass, this should become the focus of subsequent evaluation (see "Biopsy" later on). Occasionally, a simple cyst may cause cyclical or noncyclic breast pain, and aspiration of the cyst usually resolves the pain. In the case of large cysts, which will quickly recur after aspiration, percutaneous excision with a vacuum-assisted device will be definitive. Most patients with simple cysts do not require further evaluation. Patients with complex cysts with solid intracystic components require additional evaluation including biopsy of the solid components. Treatment with danocrine, lupron, and tamoxifen are effective but with significant side effects. Referred pain can be a significant cause of breast pain, the most common source of which is scapulothoracic bursitis. It can be cyclical but is most often noncyclical. Because of the confluence of afferent signals from the shoulder and the dorsal horn of the spinal cord, one can get referred pain from the shoulder in the distribution of the intercostal nerves along the axilla, the breast, and the arm. Trigger point injection along the medial scapular border in order to access the scapulothoracic bursa are both diagnostic and therapeutic for

this malady. Heat and nonsteroidal antiinflammatory drugs will aid in alleviating the inflammation.[2]

Patients with fibrocystic changes have clinical breast findings that range from mild alterations in texture to dense, firm breast tissue with palpable masses. The appearance of large palpable cysts completes the picture. Fibrocystic changes are usually seen on mammography as diffuse or focal radiologically dense tissue. On ultrasonography, cysts are seen in one-third of all women 35 to 50 years old; most of these cysts are nonpalpable. Palpable cysts or multiple small cysts are typical of fibrocystic disease. Cysts with or without fibrocystic disease are uncommon in postmenopausal women.

Histologically, in addition to macrocysts and microcysts, women with fibrocystic changes may have identified solid elements, including adenosis, sclerosis, apocrine metaplasia, stromal fibrosis, and epithelial metaplasia and hyperplasia. Depending on the presence of epithelial hyperplasia, fibrocystic changes are classified as nonproliferative, proliferative without atypia, or proliferative with atypia. All three types of changes can occur alone or in combination and to a variable degree, and in the absence of epithelial atypia, these changes represent the histologic spectrum of normal breast tissue. However, epithelial atypia (atypical ductal hyperplasia [ADH]) is a risk factor for the development of breast cancer. Atypical proliferations of ductal epithelial cells confer increased risk for breast cancer; however, fibrocystic change is not itself a risk factor for the development of breast malignancy.

Abnormal Development and Physiology

Absent or Accessory Breast Tissue

Absence of breast tissue (amastia) and absence of the nipple (athelia) are rare anomalies. Unilateral rudimentary breast development is more common, as is adolescent hypertrophy of one breast with lesser development of the other. Poland syndrome is thought to be a genetic disorder that presents as a unilateral variable loss of the breast tissue, pectoralis major and minor, and serratus anterior muscles as well as several ribs.

Accessory breast tissue (polymastia) and accessory nipples (supernumerary nipples) are common as a result of persistence of the mammary ridge. Supernumerary nipples are usually rudimentary and occur along the milk line from the axilla to the pubis in males and females. They may be mistaken for a small mole. Accessory nipples are usually removed only for cosmetic reasons. True polythelia refers to more than one nipple serving a single breast, which is rare. Accessory breast tissue is commonly located above the breast in the axilla. Rudimentary nipple development may be present, and lactation is possible with more complete development. Accessory breast tissue may be seen as an enlarging mass in the axilla during pregnancy and persists as excess tissue in the axilla after lactation is complete. The accessory mammary tissue may be removed surgically if it is large or cosmetically deforming or to prevent enlargement during future pregnancy. Care should be taken to avoid removing axillary lymph nodes.

Gynecomastia

Hypertrophy of breast tissue in men is a clinical entity for which there is frequently no identifiable cause. Pubertal hypertrophy occurs in boys between age 13 years and early adulthood, and senescent hypertrophy is diagnosed in men older than 50 years. Gynecomastia in teenage boys is common and may be bilateral or unilateral. Unless it is unilateral or painful, it may pass unnoticed and regress with adulthood. Pubertal hypertrophy is generally treated by observation without surgery. Surgical excision may be discussed if the enlargement is unilateral, fails to regress, or is cosmetically unacceptable. Hypertrophy in older men is also common. The enlargement is frequently unilateral, although the contralateral breast may enlarge with time. Many commonly used drugs, such as digoxin, thiazides, estrogens, phenothiazines, theophylline, and cannabis, may exacerbate senescent gynecomastia. In addition, gynecomastia may be a systemic manifestation of hepatic cirrhosis, renal failure, or malnutrition. In pubertal and senescent gynecomastia, the mass is smooth, firm, saucer shaped, and symmetrically distributed beneath the areola. It is frequently tender, which is often the reason for seeking medical attention. Pubertal and senescent gynecomastia may be managed nonoperatively and can be fully characterized with ultrasonography. There is little confusion with carcinoma occurring in the breast. Carcinoma is not usually tender, is asymmetrically located beneath or beside the areola, and may be fixed to the overlying dermis or to the deep fascia. A dominant mass suspicious for carcinoma should be examined with core needle biopsy (CNB). Mammography and ultrasonography can also be useful tools to discriminate between gynecomastia and a suspected malignancy of the breast in older men. A nipple-sparing mastectomy can be performed to remove the enlarged breast. A donut of deepithelized skin around the nipple is then enfolded to remove the excess skin as one would do for a Benelli reduction mammoplasty.[3]

Nipple Discharge

The appearance of discharge from the nipple (Fig. 35.6A) of a nonlactating woman is a common condition and is rarely associated with an underlying carcinoma. In one review of 270 subareolar biopsies for discharge from one identifiable duct and without an associated breast mass, carcinoma was found in only 16 patients (5.9%). In these cases, the fluid was bloody or tested strongly positive for occult hemoglobin. In another series of 249 patients with discharge from a single identifiable duct, breast carcinoma was found in 10 patients (4%). In eight of these patients, a mass lesion was identified in addition to the discharge. In the absence of a palpable mass or suspicious findings on mammography, discharge is rarely associated with cancer.

It is important to establish whether the discharge comes from one breast or from both breasts, whether it comes from multiple duct orifices or from just one, and whether the discharge is grossly bloody or contains blood. A milky discharge from both breasts is termed *galactorrhea*. In the absence of lactation or a history of recent lactation, galactorrhea may be associated with increased production of prolactin. Radioimmunoassay for serum prolactin is diagnostic. However, true galactorrhea is rare and is diagnosed only when the discharge is milky (contains lactose, fat, and milk-specific proteins). Unilateral discharge from one duct orifice is often treated surgically when there is a significant amount of discharge. However, the underlying cause is rarely a breast malignancy.

The most common cause of spontaneous nipple discharge from a single duct is a solitary intraductal papilloma (60%–80%) in one of the large subareolar ducts under the nipple. Subareolar duct ectasia producing inflammation and dilatation of large collecting ducts under the nipple is common (20%) and usually involves discharge from multiple ducts. Cancer is a very unusual cause of discharge in the absence of other signs. However, papillomas that are located away from the nipple-areolar complex are at higher risk of malignancy (20%). A papilloma is the most common benign tumor to develop breast cancer, primarily DCIS.

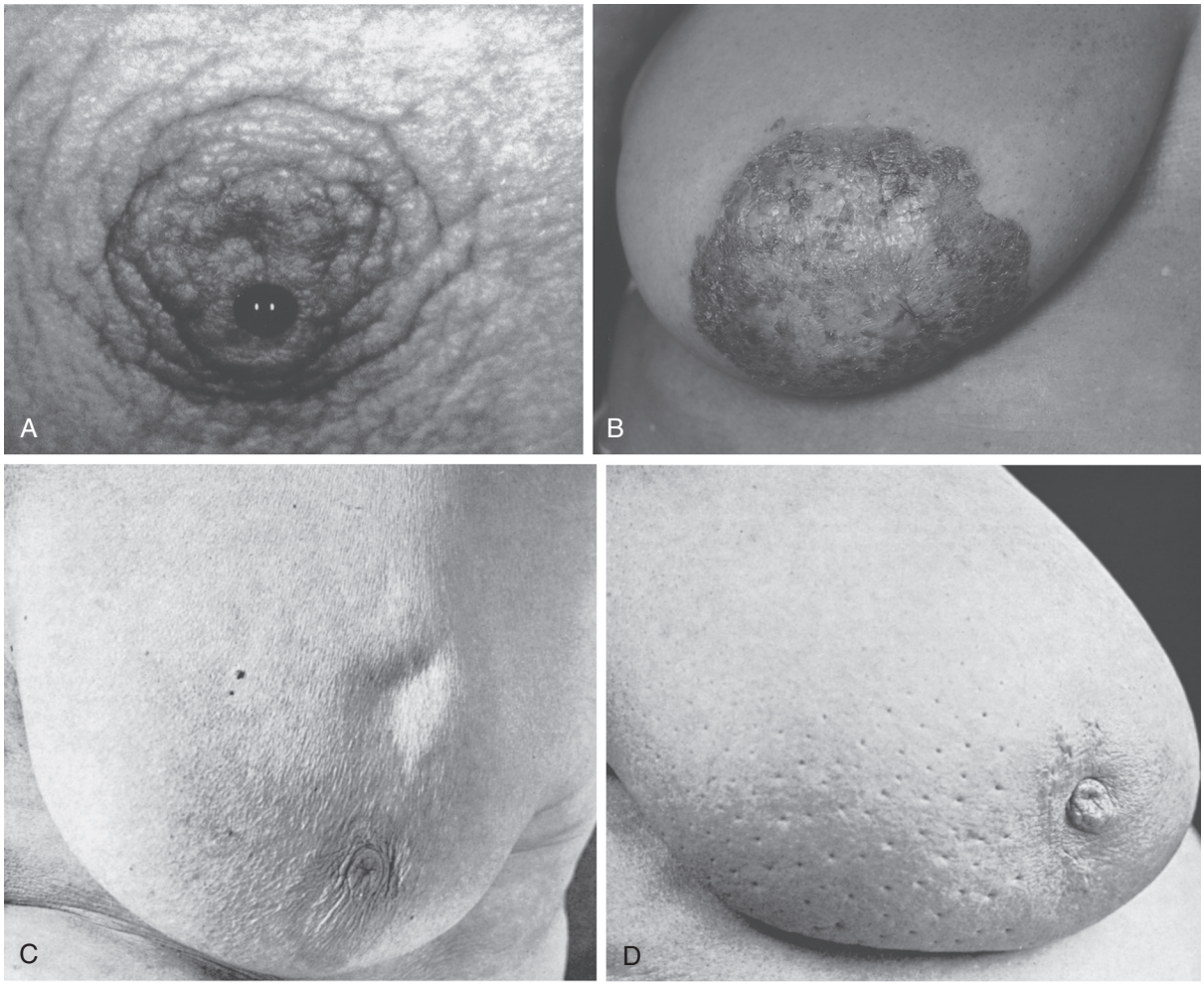

FIG. 35.6 Common physical findings during breast examination. (A) Nipple discharge. Discharge from multiple ducts or bilateral discharge is a common finding in healthy breasts. In the case shown, the discharge is from a single duct orifice and may signify underlying disease in the discharging duct. In this patient, a papilloma was the source of her symptoms. (B) Paget disease of the nipple. Malignant ductal cells invade the epidermis without traversing the basement membrane of the subareolar duct or epidermis. The disease appears as a psoriatic rash that begins on the nipple and spreads off onto the areola and into the skin of the breast. (C) Skin dimpling. Traction on Cooper ligaments by a scirrhous tumor is distorting the surface of the breast and producing a dimple best seen with angled indirect lighting during abduction of the arms upward. (D) Peau d'orange (skin of the orange) or edema of the skin of the breast. This finding may be caused by dependency of the breast, lymphatic blockage (from surgery or radiation), or mastitis. The most feared cause is inflammatory carcinoma, in which malignant cells plug the dermal lymphatics—the pathologic hallmark of the disease.

Nipple discharge that is bilateral and comes from multiple ducts is not usually a cause for surgery. Bloody discharge from a single duct often requires surgical excision to establish a diagnosis and control the discharge. Bilateral bloody spontaneous discharge is likely endocrine in nature and is associated with pregnancy and hypothyroidism.

Galactocele

A galactocele is a milk-filled cyst that is round, well circumscribed, and easily movable within the breast. A galactocele generally occurs after the cessation of lactation or when feeding frequency has declined significantly, although galactoceles may occur 6 to 10 months after breastfeeding has ceased. The pathogenesis of galactocele is unknown, but inspissated milk within ducts is thought to be responsible. The cyst is usually located in the central portion of the breast or under the nipple. Needle aspiration produces thick, creamy material that may be tinged dark green or brown. Although it appears purulent, the fluid is sterile. Treatment is large bore needle aspiration, and withdrawal of thick milky secretion confirms the diagnosis; surgery is reserved for cysts that cannot be aspirated or that become infected.

DIAGNOSIS OF BREAST DISEASE

Patient History

In a woman in whom breast disease is suspected, it is important for the examiner to determine the patient's age and to obtain a reproductive history, including age at menarche, age at menopause, and history of pregnancies including age at first full-term pregnancy. A previous history of breast biopsies should be obtained, including the pathologic findings. If the patient has had a hysterectomy, it is important to determine whether the ovaries were removed. In

premenopausal women, a recent history of pregnancy and lactation should be noted. The history should include any use of HRT or use of hormones for contraception. The family history should detail any known genetic abnormalities as well as any cancer, but especially of the breast and ovaries and the menopausal status of any affected relatives.

With respect to the specific breast complaint, the patient should be asked about history of a mass, breast pain, nipple discharge, and any skin changes. If a mass is present, the patient should be asked how long it has been present and whether it has grown or changes with the menstrual cycle. If a cancer diagnosis is suspected, inquiry about constitutional symptoms, bone pain, weight loss, respiratory changes, and similar clinical indications can direct investigations that could reveal evidence of metastatic disease.

Physical Examination

The physical examination begins with the patient in the upright sitting position. The breasts are visually inspected for obvious masses, asymmetries, and skin changes. The nipples are examined and compared for the presence of retraction, nipple inversion, or excoriation of the superficial epidermis such as that seen with Paget disease (Fig. 35.6B). The use of indirect lighting can unmask subtle dimpling of the skin or nipple caused by a carcinoma that places Cooper ligaments under tension (Fig. 35.6C). Simple maneuvers such as stretching the arms high above the head or tensing the pectoralis muscles may accentuate asymmetries and dimpling. If carefully sought, dimpling of the skin or nipple retraction is a sensitive and specific sign of underlying cancer.

Edema of the skin produces a clinical sign known as *peau d'orange* (Fig. 35.6D). Peau d'orange and tenderness, warmth, and swelling of the breast are the hallmarks of inflammatory carcinoma but may be mistaken for acute mastitis. The inflammatory changes and edema are caused by obstruction of dermal lymphatic channels by emboli of carcinoma cells. Occasionally, a bulky tumor may produce obstruction of lymph channels that results in overlying skin edema. This is not typically the case with inflammatory carcinoma, where there is usually no discrete palpable mass but diffuse changes throughout the breast parenchyma. In 40 patients with inflammatory carcinoma described by Haagensen, erythema and edema of the skin were present in all cases, a palpable mass or localized induration was noted in 19 patients, and no localized tumor was present in 21 patients. Inflammatory cancer also has a rapid onset (less than 3 months) as compared to a similar presentation for locally advanced cancer, which may have been present for years and neglected.

Involvement of the nipple and areola can occur with carcinoma of the breast, especially when the primary tumor is located in the subareolar position. Direct involvement may result in retraction of the nipple. Flattening or inversion of the nipple can be caused by fibrosis in certain benign conditions, especially subareolar duct ectasia. In these cases, the finding is frequently bilateral, and the history confirms that the condition has been present for many years. Unilateral retraction or retraction that develops over weeks or months is more suggestive of carcinoma. Centrally located tumors that go undetected for a long time may directly invade and ulcerate the skin of the areola or nipple. Peripheral tumors may distort the normal symmetry of the nipples by traction on Cooper ligaments.

Paget disease is a condition of the nipple that is commonly associated with an underlying breast cancer. First described by Paget in 1874, Paget disease produces histologically distinct changes within the dermis of the nipple. There is often an underlying intraductal carcinoma in the large sinuses just under the nipple (see Fig. 35.6B). Carcinoma cells invade across the junction of epidermal and ductal epithelial cells and enter the epidermal layer of the skin of the nipple. Clinically, dermatitis occurs that may appear eczematoid and moist or dry and psoriatic. It begins in the nipple, although it can spread to the skin of the areola. Many benign skin conditions affecting the breast, such as eczema, frequently begin on the areola, whereas Paget disease originates on the nipple and secondarily involves the areola.

Visual inspection should be followed by palpation of the regional lymph nodes and breast tissue. While the patient is still in the sitting position, the examiner supports the patient's arm and palpates each axilla from a posterior approach to detect the presence of enlarged axillary lymph nodes. The supraclavicular and infraclavicular spaces are similarly palpated for enlarged nodes. Then the patient lies down, and the breast is palpated. Palpation of the breast is always done with the patient lying supine on a solid examining surface, with the arm stretched above the head. Palpation of the breast while the patient is sitting often leads to inaccurate interpretation because the overlapping breast tissue may feel like a mass or a mass may go undetected within the breast tissue. The breast is best examined with compression of the tissue toward the chest wall, with palpation of each quadrant and the tissue under the nipple-areolar complex. Palpable masses are characterized according to their size, shape, consistency, and location and whether they are fixed to the skin or underlying musculature. Benign tumors, such as fibroadenomas and cysts, can be as firm as carcinomas; usually, these benign entities are distinct, well circumscribed, and movable. Carcinoma is typically firm but less circumscribed, and moving a carcinoma produces a drag of adjacent tissue. Cysts and fibrocystic changes can be tender with palpation of the breast; however, tenderness is rarely a helpful diagnostic sign. Most palpable masses are self-discovered by patients during casual or intentional self-examination. Ultrasonography can be used as an extension of your physical exam delineating normal ridges from worrisome masses and cystic from solid (see Ultrasonography section).

Biopsy

Fine-Needle Aspiration

Historically, fine-needle aspiration (FNA) was a common tool used in the diagnosis of breast masses. FNA can be done with a 22-gauge needle, an appropriately sized syringe, and an alcohol preparation pad. The needle is repeatedly inserted into the mass while constant negative pressure is applied to the syringe. In this way, multiple areas of a mass could be sampled. Suction is released, and the needle is withdrawn. The fluid and cellular material within the needle are submitted in physiologically buffered saline or fixed immediately on slides in 95% ethyl alcohol. The slides are submitted for cytologic evaluation of the aspirated material. A limitation of FNA in evaluating solid masses is that cytologic evaluation does not differentiate noninvasive lesions from invasive lesions if malignant cells are identified. If FNA demonstrates malignancy, a CNB is still required for definitive histologic diagnosis before surgical intervention.

One clinical scenario in which FNA still has utility is in the evaluation of a second suspicious lesion in the ipsilateral breast of a patient with a known malignancy. In this case, FNA can be used to determine if the second lesion is malignant and confirm a diagnosis of multifocal breast cancer. This information can aid in determining the appropriate surgical plan. A second clinical scenario in which

FNA is commonly used is in the evaluation of lymph nodes that are suspicious on either physical examination or imaging, particularly high-resolution ultrasonography of the regional nodal basins. Suspicious lymph nodes can be evaluated by FNA to determine whether metastatic disease is present. In this situation, FNA has a reported sensitivity of approximately 90% and a specificity of up to 100%. Determining whether the tumor has spread to the lymph nodes is an important step in the initial staging of breast cancer that provides prognostic information and helps determine appropriate management strategies. In the setting where neoadjuvant therapy is to be utilized, a clip must be placed in the positive node.

Core Needle Biopsy

CNB is the method of choice to sample breast lesions. Biopsies can be performed with trigger devices requiring multiple entries or with vacuum-assisted devices that require only single insertion. The size of a CNB ranges from 8 to 14 gauge. CNB can be performed under mammographic (stereotactic), ultrasound, or magnetic resonance imaging (MRI) guidance. Mass lesions that are visualized on ultrasonography can be sampled under ultrasound guidance; calcifications and densities that are best seen on mammography are sampled under stereotactic guidance. During stereotactic CNB, the breast is compressed, most often with the patient lying prone on the stereotactic CNB table. A robotic arm and biopsy device are positioned by computed analysis of triangulated mammographic images. After local anesthetic is injected, a small skin incision is made, and a core biopsy needle is inserted into the lesion to obtain the tissue sample with vacuum assistance. There are standards for the appropriate number of core samples to be obtained for each type of abnormality being sampled. A clip should be placed to mark the site of the lesion, particularly for small lesions that may be difficult to find after extensive sampling or when neoadjuvant therapy is to be performed. The specimens should be imaged to confirm that the targeted lesion has been adequately sampled. A similar approach is used for ultrasound-guided and MRI-guided biopsy of lesions.

Specimen radiography of excised cores is performed to confirm that the targeted lesion has been sampled and to direct pathologic assessment of the tissue. A mammogram obtained after biopsy confirms that a defect has been created within the target lesion and that the marking clip is in the correct position. Image-guided localization and surgical excision are required if the lesion cannot be adequately sampled by CNB or if there is discordance between the imaging abnormality and pathologic findings.

The small samples obtained by CNB necessitate proper interpretation of the pathology results. Most patients undergoing CNB have benign findings and may return to routine screening with no other intervention required. If a malignancy is detected, histologic subtype, grade, and receptor status should be determined from the CNB specimen. The patient may proceed to definitive treatment of the cancer if it is an early-stage breast cancer. Patients with aggressive, locally advanced, or inflammatory breast cancer should be treated with systemic chemotherapy before surgical intervention. Depending on the size and grade of the imaging abnormality, approximately one-third of patients with a diagnosis of DCIS on CNB are found to have some invasive carcinoma at definitive surgery.

Excisional Biopsy

Use of a minimally invasive procedure, such as CNB, is the preferred approach for diagnosis of breast lesions. The use of excisional breast biopsy as a diagnostic procedure increases costs and results in delays of definitive surgery for patients with cancer.[4] Less than 10% of patients who undergo CNB have inconclusive results and require surgical biopsy for definitive diagnosis. Biopsy results that are not concordant with the targeted lesion (e.g., a spiculated mass on imaging and normal breast tissue on CNB) necessitate surgical excision. When ADH is found on CNB, surgical excision reveals DCIS or invasive carcinoma in 20% to 30% of cases because of the difficulty of distinguishing ADH and DCIS in a limited tissue sample. A finding of a cellular fibroadenoma on CNB requires excision to rule out a phyllodes tumor.

BREAST IMAGING

Breast imaging techniques are used to detect small, nonpalpable breast abnormalities, evaluate clinical findings, and guide diagnostic procedures. The primary imaging modality for screening asymptomatic women is mammography. During mammography, the breast is compressed between plates to reduce the thickness of the tissue through which the radiation must pass, separate adjacent structures, and improve resolution. On screening mammography, two views of each breast are obtained, mediolateral oblique and craniocaudal and ready at a later time usually in batches. For further evaluation of abnormalities identified on a screening mammogram or of clinical findings or symptoms, diagnostic mammography is indicated, which is read at the time of performance so additional views may be performed. Magnification views are obtained to evaluate calcifications, and compression views are used to provide additional detail for mass lesions.

Sensitivity of mammography is limited by breast density, and 10% to 15% of clinically evident breast cancers have no visible abnormality on mammography. Digital mammography acquires digital images and stores them electronically, allowing manipulation and enhancement of images to facilitate interpretation. Digital mammography appears to be superior to traditional film-screen mammography for detecting cancer in younger women and women with dense breasts. Mammography in women younger than 30 years, whose breast tissue is dense with stroma and epithelium, may produce an image without much definition. As women age, the breast tissue involutes and is replaced by fatty tissue. On mammography, fat absorbs relatively little radiation and provides a contrasting background that favors detection of small lesions. Computer-assisted diagnosis has been shown to increase the sensitivity and specificity of mammography and ultrasonography over review by the radiologist alone.

Screening Mammography

Screening mammography is performed in asymptomatic women with the goal of detecting occult breast cancer. This approach assumes that breast cancers identified through screening will be smaller, have a better prognosis, and require less aggressive treatment than cancers identified by palpation. The potential benefits of screening are weighed against the cost of screening and the number of false-positive studies that prompt additional workup, biopsies, and patient anxiety.

Eight prospective randomized trials of screening mammography have been performed, with almost 500,000 women participating. In these trials, among women 39 to 49 years old, screening mammography reduced the risk for breast cancer death by 15% (relative risk [RR], 0.85; credible interval [CrI], 0.75–0.96). In the six trials that included women 50 to 59 years old, screening mammography reduced the risk for breast cancer death in this age group by 14% (RR, 0.86; CrI, 0.75–0.99). Two trials included

TABLE 35.1 Effect on breast cancer mortality and false-positive mammograms by age group in breast cancer screening trials.

AGE GROUP (YEARS)	NO. TRIALS	BREAST CANCER MORTALITY, RR (95% CrI)	NO. NEEDED TO INVITE FOR SCREENING TO PREVENT ONE BREAST CANCER DEATH (95% CrI)	FALSE-POSITIVE MAMMOGRAMS/ SCREENING ROUND*
39–49	8	0.85 (0.75–0.96)	1904 (929–6378)	97.8
50–59	6	0.86 (0.75–0.99)	1339 (322–7455)	86.6
60–69	2	0.68 (0.54–0.87)	377 (230–1050)	79.0
70–74	1	1.12 (0.73–1.72)	NA	68.8

Adapted from Nelson HD, Tyne K, Naik A, et al, U.S. Preventive Services Task Force: Screening for breast cancer: systematic evidence review update for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2009;151:727.
CrI, Credible interval; *NA*, not available; *RR*, relative risk.
*Per 1000 screened.

women 60 to 69 years old, and screening mammography reduced the risk for breast cancer death in this age group by 32% (RR, 0.68; CrI, 0.54–0.87). Only one trial included women older than 70 years, and data were insufficient to recommend routine screening in this age group. On the basis of these results, the most recent U.S. Preventive Services Task Force report recommended biennial screening mammography for women 50 to 74 years old and recommended against screening for women 40 to 49 years old or older than 75 years.[4] The recommendations were based on the risk reduction, number of women needed to invite for screening to prevent one breast cancer death, and potential for harm from additional testing and biopsies (Table 35.1).

At the present time, the American Cancer Society continues to recommend annual screening mammography for women older than 40 years and suggests that this practice should continue as long as the woman is in good health. Younger women with a previous breast cancer, significant family history of breast cancer, or histologic risk factors for breast cancer equal to a 20% lifetime risk are recommended for screening with MRI. Although the randomized trials of screening mammography did not enroll women older than 74 years, breast cancer risk increases with age, and the sensitivity and specificity of mammography are highest in older women, whose breast tissue has usually been replaced by fat. It is reasonable to continue mammographic screening in older women who are in good general health who would be considered appropriate candidates for surgery.

Recent advances with breast cancer screening include tomosynthesis (three-dimensional [3D] mammography). Tomosynthesis acquired thin sections of tissue with its main advantage being to separate overlapping breast tissues, decrease callbacks, and find smaller significant disease. The Screening With Tomosynthesis or Standard Mammography-2 (STORM-2) prospective trial compared two-dimensional (2D) and 3D mammography. In this trial, 9672 patients were randomized and showed a significantly higher detection of breast cancer but a slightly higher false positive recall.[5] Tomosynthesis excels in delineating small and multiple masses, microcalcifications, and distortion due to ducts and vessels. The question is whether it should be used for screening in a risk-adjusted manner due to the modest increase in radiation dose to the patient.

Ultrasonography

Ultrasonography is useful in determining whether a lesion detected by mammography is solid or cystic. Ultrasonography can also be useful for discriminating lesions in patients with dense breasts. However, it has not been found to be useful as a breast cancer screening tool because it is highly dependent on the operator performing the freehand screening and there are no standardized screening protocols. The American College of Radiology Imaging Network (ACRIN) performed a trial (ACRIN 6666) in high-risk women in whom mammography and ultrasonography were performed and were randomized in order to compare the sensitivity, specificity, and diagnostic yield of ultrasonography plus mammography compared with mammography alone.[6] The investigators found that the combination of mammography plus ultrasonography resulted in detection of an additional 4.2 cancers per 1000 women. However, the use of ultrasonography resulted in more false-positive events and required more callbacks and biopsies. There are no data available showing that the use of screening ultrasonography can reduce mortality caused by breast cancer. Automated breast ultrasound overcomes some of the issues of freehand ultrasonography, but randomized trials are forthcoming.

Magnetic Resonance Imaging

MRI is increasingly being used for the evaluation of breast abnormalities. It is useful for identifying the primary tumor in the breast in patients who present with axillary lymph node metastases without mammographic evidence of a primary breast tumor (unknown primary tumor) or in patients with Paget disease of the nipple without radiographic evidence of a primary tumor. MRI may also be useful for assessing the extent of the primary tumor, particularly in young women with dense breast tissue; extent of residual disease after lumpectomy with positive margins; for evaluating for the presence of multifocal or multicentric cancer; for screening of the contralateral breast; and for evaluating invasive lobular cancers. Some surgeons use MRI preoperatively to determine eligibility for breast conservation; however, there are no high-level data showing that use of MRI to guide decision-making about local therapy improves local recurrence rates or survival. Other diagnostic indications include assessment of treatment response after neoadjuvant chemotherapy. It can also be used for assessing implant rupture or assessing the breast when silicone injections have been used.

The sensitivity of MRI is greater than 90% for the detection of invasive cancer but only 60% or less for the detection of DCIS. The specificity of MRI is only moderate as compared to mammography or ultrasound; there is significant overlap in the appearance on MRI of benign and malignant lesions. A meta analysis of 22 studies reporting the detection of contralateral breast cancer by MRI revealed a mean incremental cancer detection rate of 4.1% and a positive predictive value of 47.9%. This high rate of detection may result partly from selection bias; however, it is of significant concern that more than 50% of the abnormalities detected on MRI represented false-positive findings, resulting in the need for additional imaging studies and biopsies.

BOX 35.1 American Cancer Society

Women at High Lifetime Risk (Risk Criteria for Breast Magnetic Resonance Imaging Screening. ≈20%–25% or Greater) of Breast Cancer

- Known *BRCA1* or *BRCA2* gene mutation
- First-degree relative with *BRCA1* or *BRCA2* gene mutation, but have not had genetic testing themselves
- Lifetime risk of breast cancer of ≈20%–25% or greater
- Radiation therapy to the chest between the ages of 10 and 30
- Li-Fraumeni syndrome or Cowden syndrome or a first-degree relative with one of these syndromes

Women at Moderately Increased (15%–20%) Lifetime Risk

- Lifetime risk of breast cancer of 15%–20% according to risk assessment tools based mainly on family history
- Personal history of breast cancer, ductal carcinoma in situ, lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia
- Extremely dense breasts or unevenly dense breasts when viewed by mammograms

The Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial was a multicenter trial that recruited 1623 women aged 18 years or older with newly diagnosed breast cancer to assess the clinical efficacy of contrast-enhanced MRI.[7] Patients had standard clinical and radiologic examinations and were randomly assigned to undergo MRI or no further imaging. The primary end point was the proportion of patients undergoing another surgical procedure (reexcision or mastectomy) within 6 months. There was no statistically significant difference in reoperation rates between patients who did or did not undergo MRI. The contralateral breast cancer detection rate in the COMICE trial was 1.6%, significantly lower than that reported in other trials. This trial was criticized because MRI-guided biopsy was not available at all centers to assess suspicious findings identified on MRI. This situation led to numerous mastectomies without pathologic verification that the additional findings were malignancy.

With respect to using MRI for routine screening, the American Cancer Society has recommended a risk-adjusted model. Annual MRI screening is recommended beginning at age 30 years for women at high lifetime risk for breast cancer development (approximately 20%–25% or greater) (Box 35.1). Women at moderately increased lifetime risk (15%–20%) are advised to discuss with their physicians the benefits and limitations of adding MRI screening. MRI is not recommended for women with a lifetime risk of developing breast cancer of less than 15%. When MRI is used for screening, it should be used in addition to screening mammography. Although MRI is more sensitive than mammography, it may still miss some malignancies that a mammogram would detect.

Nonpalpable Mammographic Abnormalities

Mammographic abnormalities that cannot be detected by physical examination include clustered microcalcifications and areas of abnormal density (e.g., masses, architectural distortions, asymmetries) that have not produced a palpable finding (Fig. 35.7). The Breast Imaging Reporting and Data System (BI-RADS) is used to categorize the degree of suspicion of malignancy for a mammographic abnormality (Table 35.2). To avoid unnecessary biopsies for low-suspicion mammographic findings, probably benign lesions are designated BI-RADS 3 and are monitored with 6-month interval mammograms over a 2-year period. Biopsy is performed only for lesions that progress during follow-up. Because 75% to 80% of patients for whom diagnostic biopsy of a nonpalpable mammographic lesion is recommended have benign findings, the less invasive and less costly image-guided CNB approach is preferred whenever feasible.

Image-Localized Surgical Excision of Nonpalpable Breast Lesions

Nonpalpable breast lesions should be assessed with image-guided CNB, as appropriate, according to the type of abnormality. If the diagnosis is not concordant with imaging findings or there is ADH in a field of microcalcifications that may represent DCIS, most patients should proceed to excisional biopsy for definitive diagnosis.

To ensure that the abnormality is completely excised, it should be localized with any of a number of different methods. If visible with ultrasonography, then intraoperative ultrasonography can avoid the preoperative pain, vasovagal events and delays of the old standard needle localization breast biopsy. If a wire is used to localize the lesion, it is placed through an introducer needle and has a hook that engages within the breast parenchyma at or near the abnormality to hold it in position after the introducer is withdrawn. Images with the wire in place are made available in the operating room to guide the surgeon. Depending on the size of the breast and length of the localization wire, the hook may be a long distance from the skin entry site. The surgical excision can be performed directly over the lesion or via a number of oncoplastic techniques for better cosmesis. Depending on the size of the lesion and the degree of suspicion of malignancy, some surgeons will excise shaved margins around the resection cavity to ensure a better chance of complete removal with a negative margin.[8] After excision, a specimen radiography confirms that the targeted lesion has been excised. Patients who have a diagnosis of benign findings on excision should undergo new baseline mammogram 4 to 6 months after the surgical procedure.

Other techniques have been developed to facilitate resection of nonpalpable lesions, including radioactive seed localization, which involves positioning a 4.5-mm ^{125}I seed in the breast tissue, most of which require a second procedure. Radioactive seeds are preloaded into needles that are advanced under mammographic or ultrasound guidance into the lesion of interest, after which the seeds are deployed. Images with the seed in place are made available in the operating room to guide the surgeon. In the operating room, a gamma probe, which detects technetium-99m (^{99m}Tc), commonly used for sentinel lymph node dissection (SLND), and ^{125}I can be used to guide the breast resection. After excision, the specimen is sent for specimen radiography to confirm that the targeted lesion and radioactive seed have been excised. A newer technique, fluoroscopic intraoperative neoplasm or node detection, utilizes fluoroscopy to find the radio-opaque clip placed at the time of the original CNB. It avoids any other procedures while the patient is awake and can be used interactively at the time of surgery.

IDENTIFICATION AND CARE OF HIGH-RISK PATIENTS

Risk Factors for Breast Cancer

Identification of factors associated with an increased incidence of breast cancer development is important in general health screening for women (Box 35.2). Risk factors for breast cancer can be

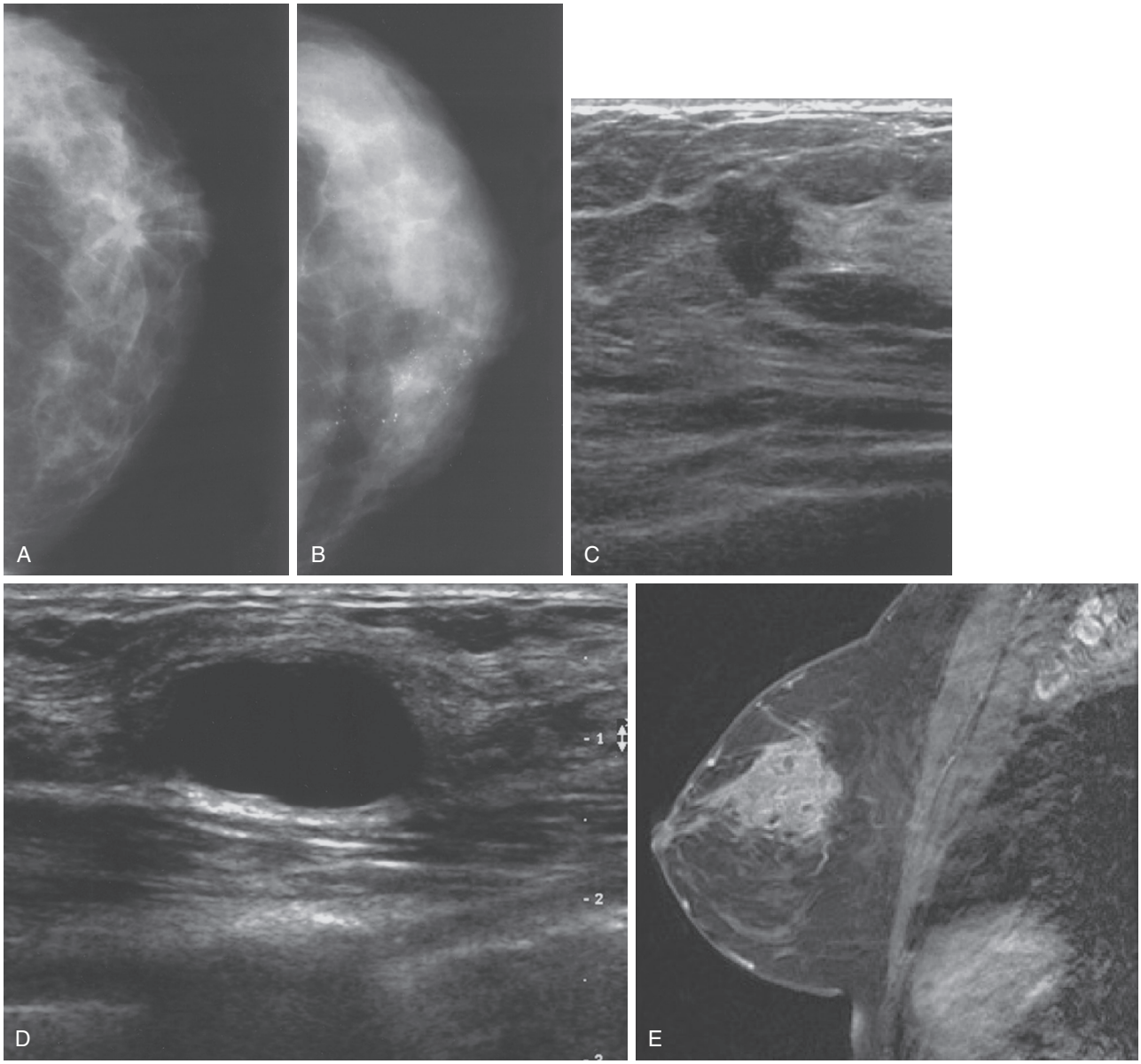

FIG. 35.7 Mammography, ultrasound, and magnetic resonance imaging (MRI) findings in breast disease. (A) Stellate mass in the breast. The combination of density with spiculated borders and distortion of surrounding breast architecture suggests a malignancy. (B) Clustered microcalcifications. Fine, pleomorphic, and linear calcifications that cluster together suggest the diagnosis of ductal carcinoma in situ. (C) Ultrasound image of breast cancer. The mass is solid, contains internal echoes, and displays an irregular border. Most malignant lesions are taller than they are wide. (D) Ultrasound image of a simple cyst. On ultrasound, the cyst is round with smooth borders, there is a paucity of internal sound echoes, and there is increased through-transmission of sound with enhanced posterior echoes. (E) Breast MRI showing gadolinium enhancement of a breast cancer. Rapid and intense gadolinium enhancement reflects increased tumor vascularity. Lesion contour and size may also be assessed by MRI.

divided into seven broad categories—age and gender, personal history of breast cancer, histologic risk factors, family history of breast cancer and genetic risk factors, reproductive risk factors, and exogenous hormone use.

Age and Gender

Age is probably the most important risk factor for breast cancer development. The age-adjusted incidence of breast cancer continues to increase with advancing age of the female population. Breast cancer is rare in women younger than 20 years and constitutes less than 2% of the total cases. Thereafter, the incidence increases to 1 in 225 from ages 30 to 39 years, 1 in 69 from ages 40 to 49, 1 in 44 from ages 50 to 59, 1 in 29 from ages 60 to 69, and 1 in 8 by age 80 years (American Cancer Society, Breast Cancer Facts & Figures). Stated another way, women now have an average risk of 12.2% of being diagnosed with breast cancer at some time during their lives.

Gender is also an important risk factor because most breast cancers occur in women. Breast cancer does occur in men; however, the incidence in men is less than 1% of the incidence in women. Of 235,030 cases of invasive breast cancer anticipated in 2014, 2360 cases were expected to occur in men. Masses in

TABLE 35.2 Breast Imaging Reporting and Data System final assessment category.

CATEGORY	DEFINITION
0	Incomplete assessment—need additional imaging evaluation or prior mammograms for comparison
1	Negative—nothing to comment on; usually recommend annual screening
2	Benign finding—usually recommend annual screening
3	Probably benign finding (<2% malignant)—initial short-interval follow-up suggested
4	Suspicious abnormality (2%–95% malignant)—biopsy should be considered
5	Highly suggestive of malignancy (>95% malignant)—appropriate action should be taken
6	Known biopsy—proven malignancy

Adapted from Liberman L, Abramson AF, Squires FB, et al. The Breast Imaging Reporting and Data System: positive predictive values of mammographic feature and final assessment categories. *AJR Am J Roentgenol*. 1998;171:35; and Liberman L, Menell JH. Breast Imaging Reporting and Data System (BI-RADS). *Radiol Clin North Am*. 2002;40:409.

BOX 35.2 Risk factors for breast cancer.

Risk Factors That Cannot Be Modified
Increasing age
Female sex
Menstrual factors
Early age at menarche (onset of menses before age 12 years)
Older age at menopause (onset beyond age 55 years)
Nulliparity
Family history of breast cancer
Genetic predisposition (*BRCA1* and *BRCA2* mutation carriers)
Personal history of breast cancer
Race, ethnicity (white women have increased risk compared with women of other races)
History of radiation exposure

Risk Factors That Can Be Modified
Reproductive factors
Age at first live birth (full-term pregnancy after age 30 years)
Parity
Lack of breastfeeding
Obesity
Alcohol consumption
Tobacco smoking
Use of hormone replacement therapy
Decreased physical activity
Shift work (night shifts)

Histologic Risk Factors
Proliferative breast disease
Atypical ductal hyperplasia
Atypical lobular hyperplasia
Lobular carcinoma in situ

the breast of a man are more likely to be benign and the result of gynecomastia (see earlier) or other noncancerous tumors rather than breast cancer.

Personal History of Cancer

A history of cancer in one breast increases the likelihood of a second primary cancer in the contralateral breast. The magnitude of risk depends on the age at diagnosis of the first primary cancer, estrogen receptor (ER) status of the first primary cancer, and use of adjuvant systemic chemotherapy and endocrine therapy. In absolute terms, the actual risk varies from 0.5% to 1% per year in younger patients to 0.2% per year in older patients.[6] In patients with other cancers requiring mantle irradiation, especially before the age of 30, the risk of breast cancer is estimated at twofold to fourfold.

Histologic Risk Factors

Histologic abnormalities diagnosed by breast biopsy constitute an important category of breast cancer risk factors. These abnormalities include lobular carcinoma in situ (LCIS) and proliferative changes with atypia. LCIS is an uncommon condition that is observed predominantly in younger premenopausal women. It is typically an incidental finding at biopsy for another condition and does not manifest as a palpable mass or suspicious microcalcifications on mammography. In a report on more than 5000 biopsies performed for benign disease, LCIS was found in 3.6% of cases. In a review of 297 patients with LCIS treated by biopsy and careful observation, it was determined that the actuarial probability of carcinoma developing at the end of 35 years was 21.4%. Using data from the Connecticut Tumor Registry, it was determined that the risk ratio for patients with LCIS (ratio of expected to observed cases of invasive breast cancer) was 7:1. Significantly, 40% of the carcinomas that subsequently developed in patients with LCIS were purely in situ lesions. The invasive carcinomas that developed were predominantly ductal and not lobular in histology, and 50% of the carcinomas occurred in the contralateral breast. LCIS is not considered a breast cancer but rather a histologic marker for increased breast cancer risk, which is estimated at slightly less than 1% per year, longitudinally.

For most patients with a diagnosis of LCIS, a conservative approach is favored. The three options that can be discussed with the patient are close observation; chemoprevention with tamoxifen, raloxifene, or arimidex; or bilateral mastectomy. LCIS predisposes to subsequent carcinoma, and the risk is lifelong and equal for both breasts. A 5-year course of tamoxifen provides a 56% reduction in breast cancer risk.[9] For patients who elect surgery rather than observation, bilateral total nipple skin-sparing mastectomy is the procedure of choice.

Benign breast disease produces a spectrum of histologic lesions that are broadly divided into nonproliferative and proliferative epithelial changes. Nonproliferative changes include mild to moderate hyperplasia of luminal cells within breast ducts; these changes do not significantly increase a woman's lifetime risk for development of breast cancer. Proliferative changes within the breast ductal system are associated with an increased risk of developing breast cancer. Dupont and Page divided proliferative lesions into lesions with atypia and lesions without atypia; proliferative lesions without atypia sometimes are termed *severe hyperplasia*.

TABLE 35.3 Histologic risk factors for development of breast cancer.

HISTOLOGIC DIAGNOSIS	ESTIMATES, RR*
Nonproliferative disease†	1.0
Proliferative disease without atypia‡	1.3–1.9
Proliferative disease with atypia§	3.7–4.2
and strong family history	4–9
LCIS	>7

Data from Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353:229; London SJ, Connolly JL, Schnitt SJ, et al. A prospective study of benign breast disease and the risk of breast cancer. *JAMA*. 1992;267:1780; and Dupont WD, Parl FF, Hartmann WH, et al. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer*. 199371:1258.

LCIS, Lobular carcinoma in situ; *RR*, relative risk.

*Ratio of observed incidence over the incidence in women without proliferative disease.

†Fibrocystic change with no, usual, or mild hyperplasia.

‡Fibrocystic change with hyperplasia greater than mild or usual, papilloma, papillomatosis, sclerosing adenosis, radial scar, and other findings.

§Any diagnosis of atypical ductal or lobular hyperplasia, or both.

Subsequent studies adopted this classification scheme—nonproliferative lesions, proliferative changes without atypia (severe hyperplasia), and proliferative changes with atypia. ADH and atypical lobular hyperplasia (ALH) are categorized as proliferative changes with atypia. The risk for development of breast cancer in women with ADH or ALH is approximately four to five times the risk in the general population. A family history of breast cancer and atypical hyperplasia increases the risk to almost nine times that of the general population. The annual risk for development of breast cancer in a woman with ADH or ALH is 0.5% to 1% per year. The estimates of breast cancer risk according to histologic risk factors are influenced by age at diagnosis, menopausal status, and family history. Histologic risk factors are listed in Table 35.3.

Family History of Breast Cancer and Genetic Risk Factors

Many studies have examined the relationship between family history of breast cancer and the risk for breast cancer. First-degree relatives (mothers, sisters, and daughters) of patients with breast cancer have a twofold to threefold excess risk for development of the disease. Risk is much higher if affected first-degree relatives of the mother or father had premenopausal-onset and bilateral breast cancer. In families with multiple affected members, particularly with bilateral and early-onset cancer, the absolute risk in first-degree relatives approaches 50%, consistent with an autosomal-dominant mode of inheritance in these families.

Genetic factors are estimated to be responsible for 5% to 10% of all breast cancer cases, but they may account for 25% of cases in women younger than 30 years. In 1990, King and colleagues identified a region on the long arm of chromosome 17 (17q21) that contained a cancer susceptibility gene. The *BRCA1* gene was discovered in 1994; it is now known that mutations in *BRCA1* account for up to 40% of familial breast cancers. A second susceptibility gene, *BRCA2*, was discovered in 1995. In addition to being at increased risk for breast cancer, women with mutations in *BRCA1* or *BRCA2* are at increased risk for ovarian cancer (45% lifetime risk for *BRCA1* carriers).

Deleterious mutations in *BRCA1* or *BRCA2* are rare in the general population. The frequency of mutations is approximately 1 in 1000 (0.1%) in the U.S. population. Certain relatively closed populations may have higher prevalence rates and show preference for certain mutations, termed *founder mutations,* including the 185delAG and 5382insC mutations in *BRCA1*, which are found in 1.0% of the Ashkenazi Jewish population (Jews of Eastern European descent), and the C4446T mutation found in French Canadian families. *BRCA1* is a large gene with 22 coding exons and more than 500 mutations; many of these are unique and limited to a given family, which makes genetic testing technically difficult. *BRCA1* is a tumor suppressor gene with disease susceptibility inherited in an autosomal dominant fashion. Germline mutations inactivate a single inherited allele of *BRCA1* in every cell, and this precedes a somatic event in breast epithelial cells that eliminates the remaining allele and causes the cancer. The gene product may provide negative regulation of cell growth and is involved in recognition and repair of genetic damage. If a patient presents with a triple-negative breast cancer, there is a ~20% risk of a BRAC1 mutation. If there is a family history of breast and ovarian cancer in different relatives of a breast cancer patient, then there is ~40% risk of a BRAC gene. If a relative has both breast and ovarian cancer, the risk can be as high as 80%.

The *BRCA2* gene is located on chromosome 13 and accounts for 30% of familial breast cancers; in contrast to *BRCA1*, *BRCA2* is associated with increased breast cancer risk in men. Women with a mutation in *BRCA2* also have a 20% to 30% lifetime risk for ovarian cancer. Founder mutations of *BRCA2* include the 617delT mutation, present in 1.4% of the Ashkenazi population; 8765delAG mutation, present in the French Canadian population, and 999del15 mutation, found in the Icelandic population. In Iceland, 7% of unselected women with breast cancer and 0.6% of individuals in the general population carry the 999del15 mutation.

The penetrance of a gene refers to the chance that carriers of mutations in the gene will actually develop breast cancer. The initial estimates of the penetrance of *BRCA1* and *BRCA2* mutations were high, but the penetrance of *BRCA1* and *BRCA2* mutations more recently has been estimated to be 56% (95% confidence interval [CI], 40%–73%). It is reasonable to quote lifetime rates of breast cancer between 50% and 70% for carriers of *BRCA1* or *BRCA2* mutations.

The histopathology of *BRCA1*-associated breast cancer is unfavorable compared with *BRCA2*-associated cancer and includes tumors that are high grade, hormone receptor–negative, and aneuploid, with an increased S phase fraction. There is a strong association between the basal-like breast cancer subtype and *BRCA1* mutations. Women who carry a *BRCA1* mutation and develop breast cancer are highly likely to have basal-like breast cancer, and 10% of basal-like tumors arise in women with a *BRCA1* mutation. The same is not true for *BRCA2*-associated cancers, which are more commonly hormone receptor–positive. Overall mortality rates in patients with *BRCA1*-associated or *BRCA2*-associated breast cancer are similar to mortality rates in women with sporadic breast cancer. Because the risk for development of breast cancer is high in carriers of a *BRCA* gene mutation, prophylactic surgery is considered to be the most rational approach. MRI is encouraged for women

who prefer intensive screening rather than prophylactic surgery. The efficacy of chemoprevention in *BRCA* mutation carriers is unclear, especially in women with *BRCA1* mutations, who tend to develop ER-negative breast cancers.

Reproductive Risk Factors

Reproductive milestones that increase a woman's lifetime estrogen exposure are thought to increase her breast cancer risk. These include onset of menarche before 12 years of age, first live childbirth after age 30 years, nulliparity, and menopause after age 55 years. There is a 10% reduction in breast cancer risk for each 2-year delay in menarche; the risk doubles with menopause after age 55. A first full-term pregnancy before age 18 years is associated with half the risk for development of breast cancer of a first full-term pregnancy after age 30 years. Induced abortion is not associated with increased breast cancer risk. Breastfeeding has been reported to reduce breast cancer risk, and this effect may be secondary to a decrease in the number of lifetime menstrual cycles. Compared with gender, age, histologic risk factors, and genetics, reproductive risk factors are relatively mild in terms of their contribution to risk (RR, 0.5–2.0). However, in contrast to family history or histologic factors, reproductive risk factors have a large influence on breast cancer prevalence in populations.

Exogenous Hormone Use

Therapeutic or supplemental estrogen and progesterone are taken for various conditions, with the two most common scenarios being contraception in premenopausal women and HRT in postmenopausal women. Other indications for use of exogenous hormones include menstrual irregularities, polycystic ovaries, fertility treatment, and hormone insufficiency states. Studies have suggested that breast cancer risk is increased in current or past users of oral contraceptives but that the risk decreases as the interval after cessation of use increases.

The use of HRT was studied in the Women's Health Initiative, a prospective, randomized controlled trial in which healthy postmenopausal women 50 to 79 years old received various dietary and vitamin supplements and postmenopausal HRT. The study assessed the benefits and risks associated with HRT, a low-fat diet, and calcium and vitamin D supplementation and their effects on rates of cancer, cardiovascular disease, and osteoporosis-related fractures. During the period from 1993 to 1998 at 40 centers in the United States, 16,608 women were randomly assigned to receive combined conjugated equine estrogens (e.g., Premarin, 0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) or placebo. Screening mammography and clinical breast examinations were performed at baseline and yearly thereafter. The study reached a stopping rule at 5.2 years of follow-up, at which time there were 245 cases of breast cancer (invasive and noninvasive) in the combined HRT group versus 185 cases in the placebo group. Compared with placebo, the combination of estrogen and progesterone, specifically Prempro, increased the risk of developing breast cancer in postmenopausal women with an intact uterus. Of greater concern was that breast cancer was more likely to be diagnosed at a more advanced stage in women receiving estrogen plus progesterone, and these women were substantially more likely to have abnormal mammograms.

Also in the Women's Health Initiative, 10,739 women who had had a hysterectomy were randomly assigned to conjugated equine estrogens (e.g., Premarin) at a dose of 0.625 mg daily or a placebo. After 7 years of follow-up, the two groups had similar rates of breast cancer (RR for the estrogen group, 0.80; 95% CI, 0.62–1.04). There was a statistically significant difference between the treatment and control groups in the need for short-interval mammographic follow-up examinations, which was higher in the group that received Premarin (36.2% vs. 28.1%).

These data show that women receiving combination HRT with estrogen and progesterone for 5 years have approximately a 20% increased risk for the development of breast cancer. Women who take estrogen-only formulations (because of previous hysterectomy) do not appear to be at significant increased risk for breast cancer.

Risk Assessment

A model for assessing breast cancer risk, known as the *Gail model*, was developed from case-control data in the Breast Cancer Detection Demonstration Project. (This model is available for clinical use at http://www.cancer.gov/bcrisktool.) In developing the model, factors influencing the risk for breast cancer were identified as age, race, age at menarche, age at first live birth, number of previous breast biopsies, presence of proliferative disease with atypia, and number of first-degree female relatives with breast cancer. The model does not include detailed information about genetic factors and may underestimate the risk for *BRCA1* or *BRCA2* mutation carriers and overestimate the risk for noncarriers. The model should not be used in women with a diagnosis of LCIS or DCIS. The Gail model for breast cancer risk was used in the design of the Breast Cancer Prevention Trial, which randomly assigned women at high risk (>1.67%) to receive tamoxifen or a placebo, and in the design of Study of Tamoxifen and Raloxifene (STAR), which randomly assigned women at high risk to receive tamoxifen or raloxifene.

The Gail model assesses population risk using nongenetic factors, whereas hereditary and familial models assess genetic and familial factors of breast cancer. The Gail model is not accurate for African Americans and a specific model, CARE, was developed. The Claus model is based on assumptions about the prevalence of high-penetrance breast cancer susceptibility genes. The Claus model provides individual estimates of breast cancer risk according to decade of life based on knowledge of first-degree and second-degree relatives with breast cancer and their ages at diagnosis. Many other models have been developed for specific populations, all with similar discriminatory power as compared with the nonspecific traditional models. Mammographic density is associated with high risk for breast cancer. However, models including breast density have only minimal discriminatory power. Other well-known risk factors not included in most if not all risk assessment tools are alcohol consumption, body weight, and physical activity.

Several models have been designed to assess the risk for harboring a mutation in *BRCA1* or *BRCA2*. These models can be useful in determining whether genetic testing is needed. The Couch model predicts risk for a mutation in the *BRCA1* gene. The BRCAPro model, developed by Myriad Genetics Laboratories, estimates the risk of *BRCA1* and *BRCA2* mutations. The Tyrer-Cuzick model incorporates personal risk factors and genetic analysis to give a more comprehensive and individual risk assessment. Such models have estimated that the incidence of clinically significant *BRCA1* or *BRCA2* mutations in the general population is approximately 1 in 300 to 500. Indications for consideration of genetic testing include breast cancer diagnosed before age 50, bilateral breast cancer, breast and ovarian cancer in the same individual, and breast

cancer in men. Other factors that may be indications for testing are a family history (maternal or paternal) of two or more individuals with breast and ovarian cancer, a close male relative with breast cancer, a close relative with early-onset (<50 years) breast or ovarian cancer, and known *BRCA1* or *BRCA2* mutation in the family. Online risk calculators are available.

In addition to BRCA1 and 2, there are many other recognized genes and familial syndromes with lesser but significant risk of breast cancer. The development and reduced cost of multiple gene panel testing make screening for these other genes meaningful. These include evaluation for Li-Fraumeni syndrome (TP53 mutation), Cowden syndrome (PTEN mutation), and PALB2, CHEK2, CDH1, STK-11, NF1, and ATM carriers. The American Society of Breast Surgeons developed recommendations for screening and treatment of the lesser-known genes in the Consensus Guidelines on Hereditary Genetic Testing for Patients With and Without Breast Cancer (https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf, accessed December 27, 2018). In the process of genetic testing, individuals with Variant of Uncertain Significance will be identified but should not be acted upon.

Care of High-Risk Patients

In practice, clinicians assess risk factors and consider the factors that are important to individual patients in making recommendations about breast cancer screening and prevention. Increased risk for breast cancer is defined as a 5-year calculated risk of 1.66% or higher using the National Cancer Institute (NCI) risk calculator, which is based on the Gail model. This is the average risk for a woman who is 60 years old; it has been used in the design of the U.S. prevention trials. This risk calculator is not applicable to women with a history of invasive breast cancer, DCIS, or LCIS or African-Americans. The model does not make adjustments for a first-degree relative with premenopausal or bilateral breast cancer and does not consider genetic mutations. The clinician must understand that risk may be significantly underestimated if these factors are present, and risk should be calculated within the context of the patient's overall personal and family history. However, even with these limitations, the Gail model provides a valuable starting point for the evaluation of breast cancer risk assessment. This risk assessment can provide a context for recommendations for primary prevention strategies and screening appropriate to the individual's risk level. For women found to be at high risk for the development of breast cancer, options include close surveillance with clinical breast examination, mammography, and breast MRI (with a lifetime risk of >20%) and interventions to reduce risk, such as chemoprevention or a bilateral prophylactic mastectomy and/or salpingo-oophorectomy.

Close Surveillance

Surveillance guidelines for individuals at high risk for breast cancer were established in 2002 by the National Comprehensive Cancer Network and the Cancer Genetics Studies Consortium. These guidelines are based primarily on expert opinion; screening guidelines for high-risk individuals are not established by prospective trials. Recommendations for women in a family with a breast and ovarian cancer syndrome include monthly breast self-examination beginning at age 18 to 20 years, semiannual clinical breast examination beginning at age 25 years, and annual mammography beginning at age 25 years or 10 years before the earliest age at onset of breast cancer in a family member. Nonetheless, studies of women with known *BRCA1* or *BRCA2* mutations found that 50% of the detected breast cancers were diagnosed as interval cancers; that is, they occurred between screening episodes and not during the course of routine screening. This observation prompted many groups to add annual screening MRI to screening mammography, with some groups recommending doing the two examinations simultaneously and others recommending staggering the two examinations. For women with a strong family history of early-onset breast and ovarian cancer who have not undergone genetic counseling, genetic counseling is offered; this includes a discussion of genetic testing of multiple gene panel testing.

Chemoprevention for Breast Cancer

Drugs currently approved for reducing breast cancer risk are the selective ER modulators tamoxifen and raloxifene and the aromatase inhibitors (AIs). Tamoxifen has proven beneficial for the treatment of ER-positive breast cancer (see "Endocrine Therapy" later on). Tamoxifen has been used as adjuvant treatment for breast cancer for several decades and is known to reduce the incidence of a second primary breast cancer in the contralateral breast of women who receive the drug as adjuvant therapy for a first primary breast cancer. The largest comprehensive analysis of the benefits of tamoxifen was done by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). This group meets every 5 years to review outcome data from breast cancer trials conducted worldwide. Findings from the EBCTCG overview analysis demonstrated that adjuvant tamoxifen reduces the risk for a second breast cancer in the unaffected breast by 47%. Four prospective randomized trials were completed that evaluated tamoxifen for chemoprevention in healthy women at increased risk for breast cancer.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial, 13,388 women who were 35 to 59 years old and had a diagnosis of LCIS, who had a moderately increased risk for breast cancer (RR, 1.66 over a 5-year period), or who were 60 years old or older were randomly assigned to tamoxifen or placebo. The risk estimates were based on the Gail model of risk (see earlier). In this study, tamoxifen reduced the risk for invasive breast cancer by 49% through 69 months of follow-up; the risk reduction was 59% in women with LCIS and 86% in women with ADH or ALH. The reduction in risk was noted only for ER-positive cancers. Tamoxifen treatment for 5 years was not without side effects and complications. In the tamoxifen treatment arm, endometrial cancers resulting from estrogen-like effects of the drug on the endometrium were increased by a factor of approximately 2.5. Pulmonary embolism (RR, 3) and deep venous thrombosis (RR, 1.7) were also more common in women who received tamoxifen. Data on the efficacy of tamoxifen for reduction of breast cancer risk in *BRCA1* and *BRCA2* mutation carriers were limited because mutation testing was not routinely performed on P-1 study participants. Tamoxifen is most effective at reducing the incidence of ER-positive breast cancers, so its role in *BRCA1* mutation carriers (who more often develop ER-negative breast cancers) is questionable.

Three other tamoxifen prevention trials were conducted approximately the same time as the NSABP P-1 trial, including the Italian Tamoxifen Prevention Study, Royal Marsden Hospital Pilot Tamoxifen Chemoprevention Trial, and International Breast Cancer Intervention Study-I (IBIS-I). The Italian and Royal Marsden studies did not show any benefit of tamoxifen over placebo in terms of reduced incidence of breast cancer.

There were some differences in the study populations and trial designs, which may explain the negative results compared with the P-1 trial. The IBIS-I trial showed a 33% reduction in the incidence of breast cancer with tamoxifen, slightly lower than the risk reduction in P-1 but confirming the risk reduction benefit of tamoxifen. Subsequently, a meta analysis of all the tamoxifen prevention trials found that tamoxifen reduced the risk of breast cancer by 38%. This analysis also confirmed the increased risks of endometrial cancer and venous thromboembolic events seen with tamoxifen use.

The NSABP P-2 trial (STAR trial) compared tamoxifen with raloxifene in postmenopausal women. This comparison was based on the findings from the MORE trial, which included more than 10,000 women who received placebo versus raloxifene for the prevention and treatment of osteoporosis. In the MORE trial, at an average of 3 years of follow-up, there was a 54% reduction in the incidence of breast cancer and no increase in uterine cancer. The STAR trial enrolled 19,747 women at increased risk for breast cancer and demonstrated that tamoxifen and raloxifene each reduced the risk for invasive breast cancer by approximately 50%. Raloxifene had a more favorable toxicity profile. The number of uterine cancers was reduced by 36% in the raloxifene group compared with the tamoxifen group, and women taking raloxifene had 29% fewer episodes of venous thrombosis and a reduced incidence of pulmonary embolism compared with the tamoxifen group.

Because studies showed that AIs prevent more contralateral breast cancers than tamoxifen in postmenopausal women with early-stage breast cancer, AIs have been evaluated for chemoprevention. The NCI of Canada Clinical Trials Group completed the Mammary Prevention 3 (MAP.3) trial investigating the AI exemestane. In this study, 4560 postmenopausal women who had at least one of several breast cancer risk factors (≥60 years old; Gail model 5-year risk score >1.66%; prior ADH, ALH, or LCIS; or prior DCIS with mastectomy) were randomly assigned to exemestane or placebo. After a median follow-up of 35 months, exemestane was associated with a 65% relative reduction in the annual incidence of invasive breast cancer, with 11 invasive cancers detected in the exemestane group and 32 detected in the placebo group. Adverse events occurred in 88% of subjects in the exemestane group and 85% of subjects in the placebo group ($P = 0.003$), with significant differences noted in the development of endocrine, gastrointestinal, and musculoskeletal symptoms. Exemestane has not been approved by the U.S. Food and Drug Administration as a chemopreventive agent; however, it has a category 1 recommendation for breast cancer prevention in the National Comprehensive Cancer Network clinical practice guidelines.

Prophylactic Mastectomy

Prophylactic mastectomy has been shown to reduce the chance of breast cancer development in high-risk women by 90%. Hartmann and colleagues performed a retrospective review of 639 women with a family history of breast cancer who underwent prophylactic mastectomy. The women were divided into high-risk ($n = 214$) and moderate-risk ($n = 425$) groups, with women at high risk defined as women with a family history suggestive of an autosomal-dominant predisposition to breast cancer. For women at moderate risk, the number of expected breast cancers was calculated according to the Gail model. On the basis of this model, 37.4 breast cancers were expected to develop, but only 4 cancers occurred, for an incidence risk reduction of 89%. For women in the high-risk cohort, the Gail model would underestimate the risk for development of breast cancer. The expected number of breast cancers was calculated by using three different statistical models from a control study of the high-risk probands (sisters). Three breast cancers developed after prophylactic mastectomy, for an incident risk reduction of at least 90%.

Several groups reported on prospective studies in *BRCA1* and *BRCA2* mutation carriers treated with prophylactic mastectomy versus surveillance and showed that mastectomy is highly effective in preventing breast cancers. More recently, results of risk-reducing mastectomy and risk-reducing salpingo-oophorectomy were reported in *BRCA1* and *BRCA2* mutation carriers followed in 22 centers as part of the PROSE consortium. None of the participants who underwent risk-reducing mastectomy developed a subsequent breast cancer compared with 7% of the women who did not undergo this surgery. The use of risk-reducing salpingo-oophorectomy reduced the incidence of ovarian cancers from 5.8% to 1.1% and the incidence of breast cancers from 19.2% to 11.4%. Risk-reducing salpingo-oophorectomy was associated with a significant reduction in breast cancer–specific mortality, ovarian cancer–specific mortality, and all-cause mortality. The available data suggest that *BRCA* mutation carriers should be counseled to consider risk-reducing surgeries as a strategy to reduce cancer incidence and improve survival.

Women who undergo annual mammographic screening have an overall 80% chance of surviving breast cancer after it has been detected. Given the penetrance in the range of 50% to 60% for *BRCA1* or *BRCA2* mutation carriers, the chance of a *BRCA1* or *BRCA2* mutation carrier dying of breast cancer is approximately 10% if she chooses not to undergo risk-reducing surgery.

The use of risk-reducing surgery in women who are not known to have deleterious mutations in *BRCA1* or *BRCA2* is controversial. Trends have suggested that more women with newly diagnosed breast cancer are choosing to undergo contralateral prophylactic mastectomy as a strategy for reducing the risk of contralateral breast cancer, but it also reduces quality of life. The American Society of Breast Surgeons does not recommend the routine use of contralateral mastectomy in the sporadic cancer patient, but as many women request such procedures, it favors a shared-decision model.[10]

Summary: Risk Assessment and Management

Understanding risk factors for the development of disease provides clues to pathogenesis and identifies patients likely to benefit from risk-reducing strategies. Although breast cancer can develop in both sexes, the risk of breast cancer development is much higher in women; breast cancer in men is uncommon. Age is a strong determinant of risk and is part of the NCI risk assessment tool. Family history is most significant when breast cancer affects first-degree relatives (mothers, sisters, and daughters) at a young age and when cases of ovarian cancer are found on the same side of the family. This type of family history may preclude the use of the NCI tool for accurate risk assessment. The most significant histologic risk factors for the development of breast cancer are LCIS, ADH, and ALH. A personal history of breast cancer predisposes to contralateral breast cancer, although adjuvant therapy (endocrine therapy and chemotherapy) reduces this risk.

BENIGN BREAST TUMORS AND RELATED DISEASES

Breast Cysts

Cysts within the breast parenchyma are fluid-filled, epithelial-lined cavities that vary in size from microscopic to large palpable

masses containing 20 to 30 mL of fluid. A palpable cyst develops in at least 1 in every 14 women, and 50% of cysts are multiple or recurrent. The pathogenesis of cyst formation is not well understood; however, cysts appear to arise from destruction and dilatation of lobules and terminal ductules. Microscopic studies showed that fibrosis at or near the lobule, combined with continued secretion, results in unfolding of the lobule and expansion of an epithelial-lined cavity containing fluid.

Cysts are influenced by ovarian hormones, a fact that explains their variation with the menstrual cycle. Most cysts occur in women older than 35 years; the incidence steadily increases until menopause and sharply declines thereafter. New cyst formation in older women is generally associated with exogenous HRT.

Intracystic carcinoma is exceedingly rare. Rosemond reported that only three cancers were identified in more than 3000 cyst aspirations (0.1%). Other investigators confirmed this low incidence. There is no evidence of increased risk for breast cancer associated with cyst formation.

A palpable mass can be confirmed to be a cyst by direct aspiration or ultrasonography. Cyst fluid can be straw-colored, opaque, or dark green and may contain debris. Given the low risk for malignancy within a cyst if it appears to be a simple cyst without internal perturbation and smooth borders an aspiration is not necessary. If the mass is complex, then aspiration may be necessary. If the cyst resolves after aspiration and the cyst contents are not grossly bloody, the fluid does not need to be sent for cytologic analysis. If the cyst recurs multiple times (more than twice is a reasonable rule), CNB should be performed to evaluate any solid elements. The entire cystic structure can be percutaneously removed with a vacuum-assisted core needle device.[11] Surgical removal of a cyst is usually not indicated but may be required if the cyst recurs multiple times or if needle biopsy reveals findings of atypia, incompletely removes the mass, or if the cyst is large and painful for the patient.

Fibroadenomas and Other Benign Tumors

Fibroadenomas are benign solid tumors composed of stromal and epithelial elements. Fibroadenoma is the second most common tumor in the breast (after carcinoma) and is the most common tumor in women younger than 30 years. In contrast to cysts, fibroadenomas most often arise during the late teens and early reproductive years. Fibroadenomas are rarely seen as new masses in women after age 40 or 45 years. Clinically, fibroadenomas manifest as firm masses that are easily movable and may increase in size over several months and wax and wane with the menstrual cycle. They slide easily under the examining fingers and may be lobulated or smooth. On excision, fibroadenomas are well-encapsulated masses that may detach easily from surrounding breast tissue. Mammography is of little help in discriminating between cysts and fibroadenomas; however, ultrasonography can readily distinguish between them because each has specific characteristics.

Fibroadenomas are benign tumors, although neoplasia may develop in the epithelial elements within them. Cancer in a newly discovered fibroadenoma is exceedingly rare (0.2%); 50% of findings in fibroadenomas are LCIS, which is no longer considered stage 0 breast cancer in the eighth edition of the American Joint Committee on Cancer (AJCC) staging system but signifies a high risk for developing breast cancer, 35% are invasive carcinomas, and 15% are intraductal carcinoma. When a tissue diagnosis confirms that the breast mass is a fibroadenoma, the patient can be reassured, and surgical excision is not needed. If the patient is bothered by the mass or it continues to grow, the mass can be removed with open excisional biopsy or via percutaneous approach.[11]

Two subtypes of fibroadenoma are recognized. *Giant fibroadenoma* is a descriptive term applied to a fibroadenoma that attains an unusually large size (typically >5 cm). The term *juvenile fibroadenoma* refers to a large fibroadenoma that occasionally occurs in adolescents and young adults and histologically is more cellular than the usual fibroadenoma. Although these lesions may display remarkably rapid growth, surgical removal is curative.

Hamartomas and Adenomas

Hamartomas and adenomas are benign proliferations of variable amounts of epithelium and stromal supporting tissue. A hamartoma is a discrete nodule that contains closely packed lobules and prominent, ectatic extralobular ducts. On physical examination, mammography, and gross inspection, a hamartoma is indistinguishable from a fibroadenoma. Page and Anderson described an adenoma or tubular adenoma as a benign cellular neoplasm of ductules packed closely together so that they form a sheet of tiny glands without supporting stroma. During pregnancy and lactation, adenomas may increase in size, and histologic examination shows secretory differentiation. Biopsy is required to establish the diagnosis.

Breast Infections and Abscess

There are two general categories of infections of the breast: lactational infections and chronic subareolar infections associated with duct ectasia. Lactational infections are thought to arise from entry of bacteria through the nipple into the duct system and are characterized by fever, leukocytosis, erythema, and tenderness. Infections of the breast are most often caused by *Staphylococcus aureus* and may manifest as cellulitis with breast parenchymal inflammation and swelling, termed *mastitis*, or as abscesses. Treatment requires antibiotics and frequent emptying of the breast. True abscesses require drainage. Initial attempts at drainage should include needle aspiration; surgical incision and drainage should be reserved for abscesses that do not resolve after aspiration and treatment with antibiotics. In such cases, abscesses are generally multiloculated. Ultrasound evaluation can assist in characterizing a breast abscess and help to guide needle aspiration.

In women who are not lactating, a chronic relapsing form of infection may develop in the subareolar ducts of the breast that is variously known as *periductal mastitis* or *duct ectasia*. This condition appears to be associated with smoking and diabetes. The infections are most often mixed infections that include aerobic and anaerobic skin flora. A series of infections with resulting inflammatory changes and scarring may lead to retraction or inversion of the nipple, masses in the subareolar area, and occasionally a chronic fistula from the subareolar ducts to the periareolar skin. Palpable masses and mammographic changes may result from the infection and scarring; these can make surveillance for breast cancer more challenging.

Subareolar infections may initially manifest as subareolar pain and mild erythema. Warm soaks and oral antibiotics may be effective treatment at this stage. Antibiotic treatment generally requires coverage for aerobic and anaerobic organisms. If an abscess has developed, needle aspiration is required in addition to antibiotics. Surgical incision and drainage are reserved for abscesses that do not resolve with these more conservative measures. Repeated infections are treated by excision of the entire subareolar duct complex after the acute infection has resolved completely, together

with intravenous antibiotic coverage. Rarely, patients have recurrent infections requiring excision of the nipple and areola.

A presumed infection of the breast generally clears promptly and completely with antibiotic therapy. If erythema or edema persists, a diagnosis of inflammatory carcinoma should be considered and biopsy of the skin as well as underlying breast tissue will be needed.

Papillomas and Papillomatosis

Solitary intraductal papillomas are true polyps of epithelial-lined breast ducts. Solitary papillomas are most often located close to the areola but may be present in peripheral locations. Most papillomas are smaller than 1 cm but can grow to 4 or 5 cm. Larger papillomas may appear to arise within a cystic structure, probably representing a greatly expanded duct. Papillomas are the benign tumor most associated with the development of DCIS.

Papillomas located close to the nipple are often accompanied by bloody nipple discharge. Less frequently, they are discovered as a palpable mass under the areola or as a density seen on a mammogram. Treatment is excision through a circumareolar incision. For peripheral papillomas, the differential diagnosis is between papilloma and invasive papillary carcinoma.

It is important to distinguish papillomatosis from solitary or multiple papillomas. Papillomatosis refers to epithelial hyperplasia, which commonly occurs in younger women or is associated with fibrocystic change. Papillomatosis is not composed of true papillomas but rather consists of hyperplastic epithelium that may fill individual ducts similar to a true polyp but has no stalk of fibrovascular tissue.

Sclerosing Adenosis

Adenosis refers to an increased number of small terminal ductules or acini. Adenosis is frequently associated with a proliferation of stromal tissue that produces a histologic lesion, sclerosing adenosis, which can be confused with carcinoma grossly and histologically. Sclerosing adenosis can be associated with deposition of calcium, which can be seen on a mammogram in a pattern indistinguishable from the microcalcifications of intraductal carcinoma. In many series, sclerosing adenosis is the most common pathologic diagnosis in patients undergoing needle-directed biopsy of microcalcifications. Sclerosing adenosis is frequently listed as one of the component lesions of fibrocystic disease; it is common and is not believed to have significant malignant potential.

Radial Scars

Radial scars belong to a group of abnormalities known as *complex sclerosing lesions*. Radial scars can appear similar to carcinomas mammographically because they create irregular spiculations in the surrounding stroma. Radial scars contain microcysts, epithelial hyperplasia, and adenosis and have a prominent display of central sclerosis. The gross abnormality is rarely more than 1 cm in diameter. Larger lesions may form palpable tumors and appear as spiculated masses with prominent architectural distortion on a mammogram. These tumors can cause skin dimpling by producing traction on surrounding tissues. Radial scars generally require excision to rule out an underlying carcinoma. Radial scars are associated with a modestly increased risk for breast cancer.

Fat Necrosis

Fat necrosis can mimic cancer on mammography by producing a palpable mass or density that may contain calcifications. Fat necrosis may follow an episode of trauma to the breast or be related to a prior surgical procedure or radiation therapy. Calcifications are characteristic of fat necrosis and can often be visualized on ultrasonography as well. Histologically, fat necrosis is composed of lipid-laden macrophages, scar tissue, and chronic inflammatory cells. This lesion has no malignant potential.

EPIDEMIOLOGY AND PATHOLOGY OF BREAST CANCER

Epidemiology

It has been estimated that 266,120 cases of invasive breast cancer and 63,960 cases of in situ breast cancer would be diagnosed in 2018 in the United States. Breast cancer is the second leading cause of cancer-related deaths, second to lung cancer, with approximately 40,920 deaths caused by breast cancer annually. Breast cancer is also a global health problem, with more than 2 million cases of breast cancer diagnosed worldwide each year. The overall incidence of breast cancer was increasing until approximately 1999 because of increases in the average life span, lifestyle changes that increase the risk for breast cancer, and improved survival rates for other diseases. Breast cancer incidence decreased from 1999 to 2006 by approximately 2% per year. This decrease may be attributed to a reduction in the use of HRT after the initial results of the Women's Health Initiative were published but may also be the result of a reduction in the use of screening mammography (70.1% of women ≥40 years old were screened in 2000 vs. 66.4% in 2005). During the years 2006 to 2010, breast cancer incidence rates were stable.

Survival rates in women with breast cancer have steadily improved over the last several decades, with 5-year survival rates of 63% in the early 1960s, 75% during the years 1975 to 1977, 79% during 1984 to 1986, and 90% during 1995 to 2005. The largest decreases in death rates from breast cancer have been in women younger than 50 years (decreases of 3.2% per year), although breast cancer death rates have also decreased in women older than 50 years (by 2% per year). The decreased mortality from breast cancer is thought to be the result of earlier detection via mammographic screening, a decreased incidence of breast cancer, and improvements in therapy. The survival rate for stage I breast cancer is 98.7%. The current treatment of breast cancer is guided by pathology, staging, and more recent insights into breast cancer biology. There is an increased emphasis on defining disease biology and status in individual patients, with the subsequent tailoring of therapies.

Pathology

Noninvasive Breast Cancer

Noninvasive neoplasms of the breast were previously broadly divided into two major types, LCIS and DCIS (Box 35.3). LCIS is no longer regarded as a neoplasm of the breast in the eighth edition of the AJCC staging system but is regarded as a risk factor for the development of breast cancer. LCIS is recognized by its conformity to the outline of the normal lobule, with expanded and filled acini (Fig. 35.8A). One variant of LCIS, pleomorphic LCIS, has been recognized more recently as a distinct, more aggressive histopathologic subtype. Pleomorphic LCIS shows marked nuclear pleomorphism compared with classic LCIS. One or more lobules are distended by discohesive cells with irregularly shaped, high-grade nuclei. Pleomorphic LCIS may or may not be associated with comedonecrosis and calcifications. If pleomorphic LCIS is associated with calcifications, it may be detected mammographically. The natural history of pleomorphic LCIS is unknown, and there is debate regarding treatment; many experts

BOX 35.3 Classification of primary breast cancer.

Noninvasive Epithelial Cancers

Lobular carcinoma in situ

Ductal carcinoma in situ or intraductal carcinoma

- Papillary, cribriform, solid, and comedo types

Invasive Epithelial Cancers (Percentage of Total)

Invasive lobular carcinoma (10%)

Invasive ductal carcinoma

- Invasive ductal carcinoma, not otherwise specified (50%–70%)
- Tubular carcinoma (2%–3%)
- Mucinous or colloid carcinoma (2%–3%)
- Medullary carcinoma (5%)
- Invasive cribriform carcinoma (1%–3%)
- Invasive papillary carcinoma (1%–2%)
- Adenoid cystic carcinoma (1%)
- Metaplastic carcinoma (1%)

Mixed Connective and Epithelial Tumors

Phyllodes tumors, benign and malignant

Carcinosarcoma

Angiosarcoma

Adenocarcinoma

suggest that pleomorphic LCIS be treated with surgical excision similar to DCIS.

DCIS is more morphologically heterogeneous than LCIS, and pathologists recognize four broad types of DCIS: papillary, cribriform, solid, and comedo. The latter three types are shown in Fig. 35.8. DCIS is recognized as discrete spaces filled with malignant cells, usually with a recognizable basal cell layer composed of presumably normal myoepithelial cells. The four morphologic types of DCIS are rarely seen as pure lesions; DCIS lesions are usually of mixed morphology. The papillary and cribriform types of DCIS are generally lower-grade lesions and may take longer to transform to invasive cancer. The solid and comedo types of DCIS are generally higher-grade lesions.

As the cells inside the ductal membrane grow, they have a tendency to undergo central necrosis. The necrotic debris in the center of the duct undergoes coagulation and finally calcifies, leading to the tiny, pleomorphic, and frequently linear forms of microcalcifications that can be seen on mammograms. In some patients, an entire ductal tree may be involved in the malignancy, and the mammogram shows typical calcifications that can span from the nipple extending posteriorly into the interior of the breast (termed *segmental calcifications*).If not treated, DCIS can transform into an invasive cancer, usually recapitulating the morphology of the cells inside the duct. In other words, low-grade cribriform DCIS tends to be associated with low-grade invasive lesions that retain some cribriform features. DCIS frequently coexists with invasive cancers, and when this is the case, the two phases of the malignancy are usually morphologically similar.

Invasive Breast Cancer

Invasive breast cancers are recognized by their lack of overall organized architecture with infiltration of cells haphazardly into a variable amount of stroma, or formation of sheets of continuous and monotonous cells without respect for form and function of a glandular organ. Pathologists broadly divide invasive breast cancer into ductal and lobular histologic types, which probably does not reflect histogenesis and imperfectly predicts clinical behavior. Invasive ductal cancer tends to grow as a cohesive mass; it appears as discrete abnormalities on mammograms and is often palpable as a discrete lump in the breast. Invasive lobular cancer tends to permeate the breast in a single-file nature, which explains why it remains clinically occult and often escapes detection on mammography or physical examination until the disease is extensive. The growth patterns of invasive ductal and lobular carcinomas are shown in Fig. 35.9.

Invasive ductal cancer, also known as *infiltrating ductal carcinoma*, is the most common form of breast cancer; it accounts for 50% to 70% of invasive breast cancers. Invasive lobular carcinoma accounts for 10% of breast cancers, and mixed ductal and lobular cancers have been increasingly recognized and described in pathology reports. When invasive ductal carcinomas take on differentiated features, they are named according to the features that they display. If the infiltrating cells form small glands lined by a single row of bland epithelium, they are called *infiltrating tubular carcinoma* (see Fig. 35.9C). The infiltrating cells may secrete copious amounts of mucin and appear to float in this material. These lesions are called *mucinous* or *colloid tumors* (see Fig. 35.9D). Tubular and mucinous tumors are usually low-grade (grade I) lesions; these tumors each account for approximately 2% to 3% of invasive breast carcinomas.

Medullary cancer is characterized by bizarre invasive cells with high-grade nuclear features, many mitoses, and lack of an in situ component (see Fig. 35.9E). The malignancy forms sheets of cells in an almost syncytial fashion, surrounded by an infiltrate of small mononuclear lymphocytes. The borders of the tumor push into the surrounding breast rather than infiltrate or permeate the stroma. In its pure form, medullary cancer accounts for only approximately 5% of breast cancers; however, some pathologists have described a so-called *medullary variant* that has some features of the pure form of the cancer. These tumors are uniformly high grade, ER and progesterone receptor (PR) negative, and negative for the human epidermal growth factor receptor 2 (HER-2/neu; HER-2) cell surface receptor.

Another rare subtype of breast cancer that is typically high grade and negative for ER, PR, and HER-2 is metaplastic carcinoma. Most metaplastic carcinomas are node negative, but they have high potential for metastatic spread, and 10% of patients present with de novo metastatic disease. Even patients presenting with localized metaplastic carcinoma have a poor prognosis: Approximately 50% experience local or distant relapse.

Tumors that lack expression of ER, PR, and HER-2 are often called *triple-negative breast cancers*. Gene expression profiling and microarray analysis of breast cancers have revealed that triple-negative breast cancers are distinctly different from other ductal breast cancers and may also express molecular markers found in basal or myoepithelial cells. There may be some overlap between triple-negative breast cancer and *basal-like breast cancer*, but these categories were developed using differing technologies, and the two categories do not exactly overlap. The term *basal-like breast cancer* describes a specific subtype of breast cancer defined by microarray analysis, whereas triple-negative breast cancer is defined by lack of immunohistochemical detection of ER, PR, and HER-2.

The different histologic subtypes of breast cancer have some relationship with prognosis, although this is influenced by tumor size, histologic grade, hormone receptor status, HER-2 status, lymph node status, and other prognostic variables. The prognosis

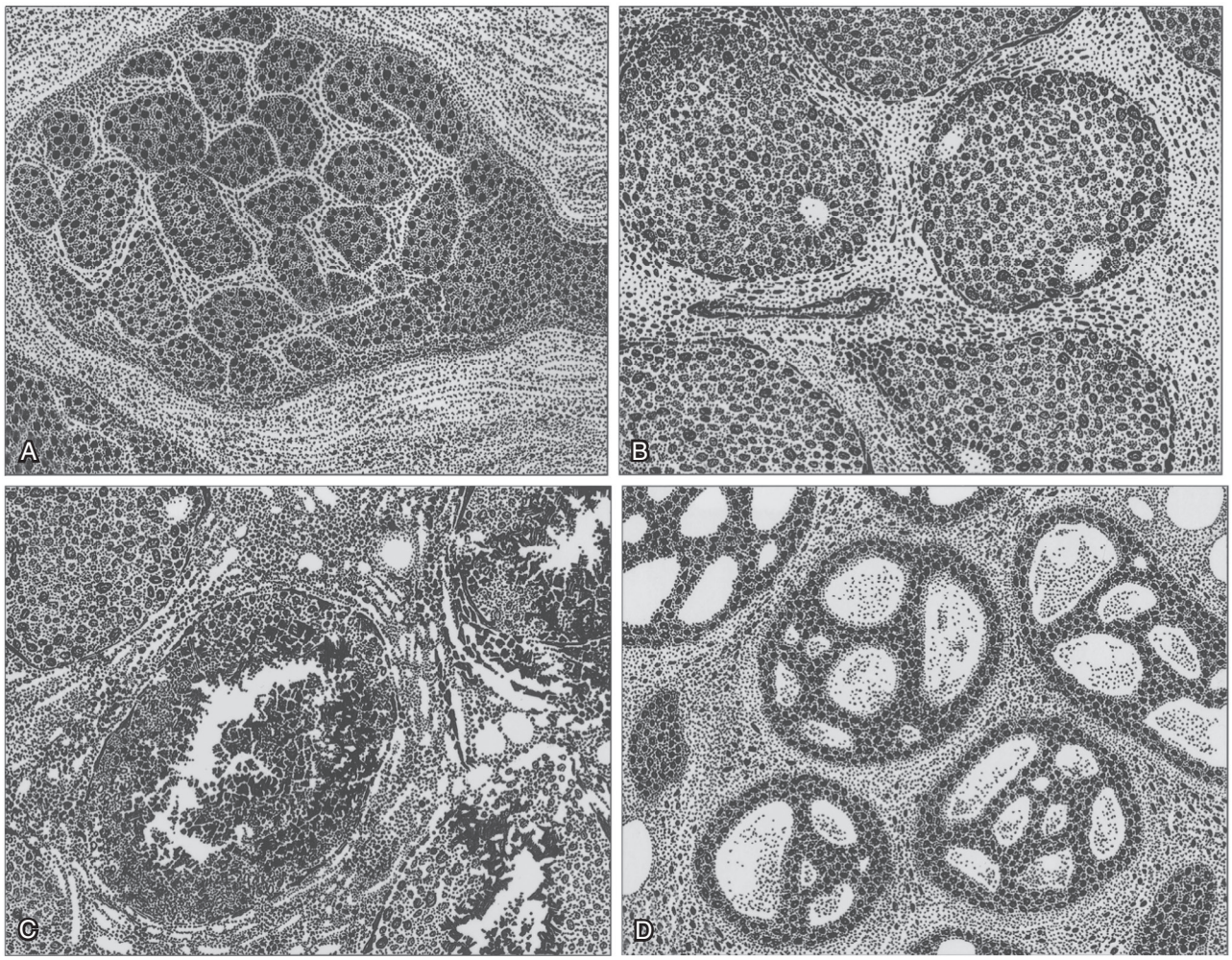

FIG. 35.8 Noninvasive breast cancer. (A) Lobular carcinoma in situ (LCIS). The neoplastic cells are small with compact, bland nuclei and are distending the acini but preserving the cross-sectional architecture of the lobular unit. (B) Ductal carcinoma in situ (DCIS), solid type. The cells are larger than in LCIS and are filling the ductal rather than the lobular spaces. However, the cells are contained within the basement membrane of the duct and do not invade the breast stroma. (C) DCIS, comedo type. In comedo DCIS, the malignant cells in the center undergo necrosis, coagulation, and calcification. (D) DCIS, cribriform type. In this type, bridges of tumor cells span the ductal space and leave round, punched-out spaces.

of invasive ductal carcinoma, not otherwise specified, is variable, modified by histologic grade and expression of molecular markers. Basal-like breast cancer is commonly aggressive, and because it is triple receptor negative, there are no targeted treatments for this form of cancer. Invasive lobular breast cancers carry an intermediate prognosis, and tubular and mucinous cancers have the best overall prognosis. These generalizations about the prognosis associated with different histologic subtypes are useful only in the context of tumor size, grade, and receptor status. Modern classification schemes based on determination of molecular markers and breast cancer subtype by microarray analysis are replacing these older morphologic descriptions.

Molecular Markers and Breast Cancer Subtypes

Numerous molecular markers have been reported to affect breast cancer outcomes, including molecules in the steroid hormone receptor pathway (ER and PR), molecules in the HER pathway (HER family), angiogenesis-related molecules, cell cycle–related molecules (e.g., cyclin-dependent kinases), apoptosis modulators, proteasomes, cyclooxygenase-2, peroxisome-proliferator-activated receptor γ, insulin-like growth factors (insulin-like growth factor family), transforming growth factor-γ, platelet-derived growth factor, and *p53*. Most of these markers are not routinely tested on breast cancer specimens at the time of diagnosis; such testing would not be feasible. Categorizing breast cancer according to the expression of molecular targets of treatments is practical, and the resulting classifications appear to agree with nonbiased classifications based on gene expression. Classification schemes reflect biology and predict treatment efficacy.

Incorporating predictive markers into the routine testing of breast cancers can help predict which patients would be most likely to benefit from therapies directed at those markers. The best example of this is testing for ER. Before the discovery of ER, all breast cancers were considered potentially sensitive to endocrine therapy. Pathologic assessment of ER is now performed on all primary tumors and predicts which patients may benefit from and should receive endocrine therapy. Patients whose tumors are ER negative can be spared endocrine therapy.

A second important predictive factor in breast cancer, discovered in 1985, is HER-2. This protein is the product of the *erb-B2* gene and is amplified in approximately 20% of human breast cancers. The extracellular domain of the receptor is present on the surface

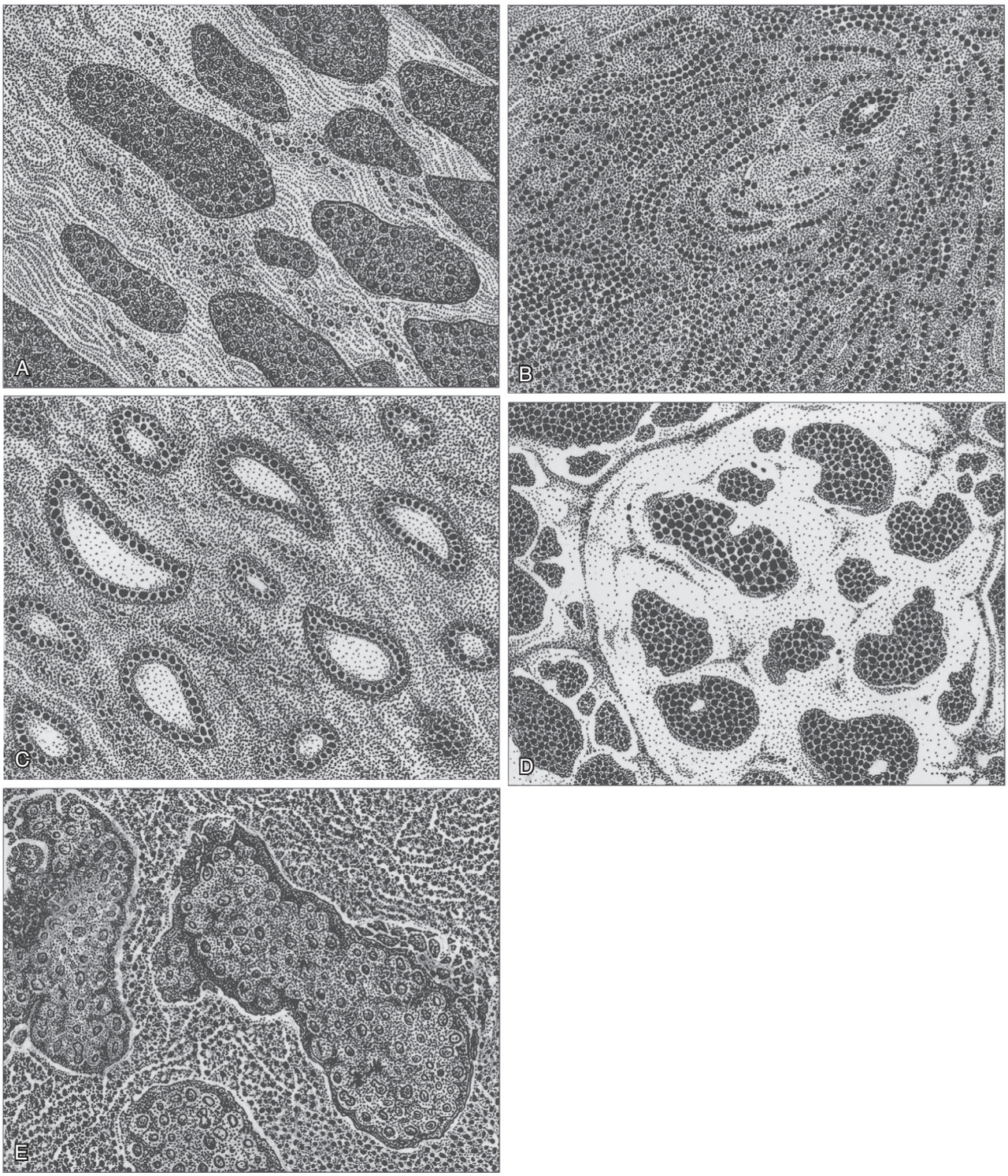

FIG. 35.9 Invasive breast cancer. (A) Invasive ductal carcinoma, not otherwise specified. The malignant cells invade in haphazard groups and singly into the stroma. (B) Invasive lobular carcinoma. The malignant cells invade the stroma in a characteristic single-file pattern and may form concentric circles of single-file cells around normal ducts (targetoid pattern). (C) Invasive tubular carcinoma. The cancer invades as small tubules, lined by a single layer of well-differentiated cells. (D) Mucinous or colloid carcinoma. The bland tumor cells float like islands in lakes of mucin. (E) Medullary carcinoma. The tumor cells are large and very undifferentiated with pleomorphic nuclei. The distinctive features of this tumor are the infiltrate of lymphocytes and the syncytium-appearing sheets of tumor cells.

of breast cancer cells, and an intracellular tyrosine kinase enzyme links the receptor to the internal machinery of the cell. HER-2 is a member of the epidermal growth factor receptor family of receptor tyrosine kinases. The tyrosine kinase of HER-2 is activated when the HER-2 receptor heterodimerizes with other members of the family that have been bound by growth factors or when the HER-2 receptor homodimerizes. There is no known ligand that binds to the HER-2 receptor. HER-2 protein overexpression is measured

clinically by immunohistochemistry and scored on a scale from 0 to 3+. Alternatively, fluorescence in situ hybridization, which directly detects the number of HER-2–gene copies, can be used to detect gene amplification. Inhibiting the function of the HER-2 receptor slows the growth of HER-2–positive tumors in laboratory models and in clinical trials. Trastuzumab and pertuzumab are antibodies directed against the extracellular domain of the HER-2 surface receptor and are effective treatment for HER-2–positive breast cancer (see "HER-2–Based Targeted Therapy" later on). HER-2 testing is now a standard part of pathologic reporting on the primary tumor and is a predictive marker for HER-2–directed therapies.

A logical classification scheme for invasive breast cancer is based on the expression of ER status and HER-2. This classification has the advantage of directing treatment choices. Patients with ER-positive tumors receive endocrine therapies, and patients with HER-2–positive tumors receive HER-2–targeted therapy generally with systemic chemotherapy. However, breast cancer is a heterogeneous disease, and different breast cancers behave in different ways. For example, some ER-positive tumors are indolent and not life-threatening, whereas other ER-positive tumors are very aggressive. In an attempt to subclassify the disease further, investigators are turning to global assessment of gene expression using microarrays; these are composed of oligonucleotide probes to almost every known expressed sequence of DNA in the human genome. Similar technologies based on single-nucleotide polymorphisms in the cancer DNA and profiles of expressed proteins are being developed to subclassify cancers and direct treatment.

A typical microarray experiment, commonly known as a *heat map*, is shown in Fig. 35.10; the colors indicate levels of gene expression. Such a portrayal of the disease shows how different ER-positive tumors are from ER-negative tumors and underscores the modern concept that subclassification is needed not only to define different groups of breast cancer but also to guide treatment. In Fig. 35.10, HER-2–positive tumors form two clusters (*in green at the top*), although these clusters are fused together in many depictions. HER-2–positive tumors cluster similarly and are responsive to inhibitors of the HER-2 receptor (e.g., trastuzumab and pertuzumab). An unexpected finding is the uniqueness of tumors that are both ER negative and HER-2 negative. These tumors, also negative for PR, are called *triple-negative cancers*. They express proteins in common with myoepithelial cells at the base of mammary ducts and are also called *basal-like cancers* (see earlier). Women who carry a deleterious mutation in *BRCA1* (but not *BRCA2*) are much more likely to contract a basal-like cancer (triple-negative) than other subtypes.

In addition to being used to classify breast cancer subtypes, molecular markers are used to select patients for systemic treatment (e.g., chemotherapy, endocrine therapy) and to predict the tumor response to these pharmacologic treatments. The simplest example is the use of ER or HER-2 status to predict the response to endocrine treatment or trastuzumab. Microarray experiments use thousands of gene transcripts (messenger RNAs) to provide a snapshot of the molecular phenotype of an individual cancer. To adapt this technology for clinical application, investigators selected critical assemblies of gene products that provide the same predictive ability as a nonbiased, genome-wide analysis. The most utilized in the United States is a 21-gene test that can be used on paraffin-embedded tumor material from breast surgical specimens (Oncotype DX assay, a 21-gene recurrence score assay). Originally designed to predict the recurrence of ER-positive, node-negative breast cancer treated with adjuvant endocrine therapy, the 21-gene recurrence score assay provides a recurrence score for ER-positive breast cancer that is used clinically to determine whether

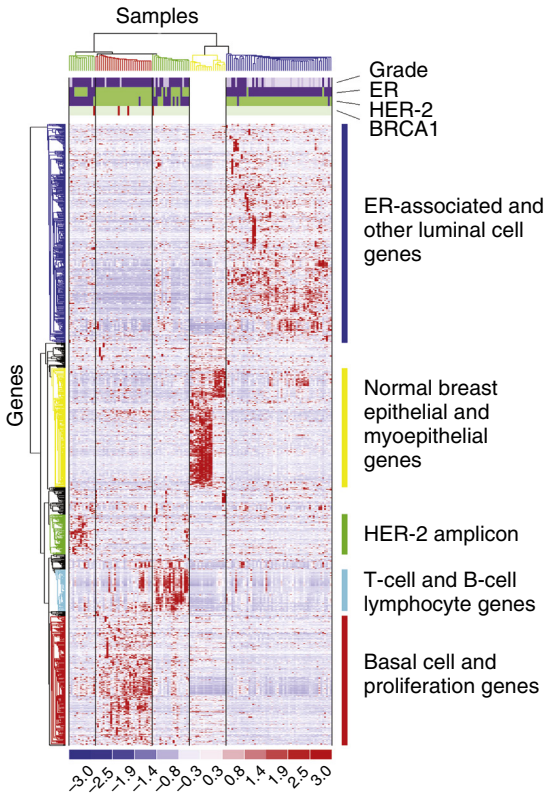

FIG. 35.10 Microarray representation of human breast cancer. This portrayal of global gene expression is called a *heat map*, with shades of red indicating high gene expression and shades of blue indicating low gene expression relative to a mean across tissue samples. Tissue samples are present across the top in columns, and individual genes are in rows down the side; the intersection is an individual gene in a particular sample. A computer-clustering algorithm aligns samples with similar gene expression and genes with similar expression patterns in the samples (two-way clustering). This illustration provides an unbiased look at breast cancer according to gene expression. The dendrogram at the top depicts the degree of similarity of the tissue samples: *yellow*, normal breast epithelium; *blue*, predominantly ER-positive cancers; *red*, basal-like or triple-negative cancers; and *green*, HER-2–positive cancers (in two clusters defined by the degree of lymphocytic infiltrate). The *stripes* at the top indicate grade (shades of darker purple are higher grades), ER expression (purple is positive; green is negative), and HER-2 (purple is positive; green is negative). *BRCA1* mutation was determined for other reasons in this experiment. (Courtesy Dr. Andrea Richardson, Department of Pathology, Brigham and Women's Hospital, Boston, MA.) *ER*, Estrogen receptor; *HER-2*, human epidermal growth factor receptor 2.

women with high-risk ER-positive breast cancer should receive adjuvant chemotherapy in addition to tamoxifen or other endocrine therapies (see "Endocrine Therapy" later on). Another multigene assay for determining prognosis is the MammaPrint assay. The MammaPrint assay analyzes data from 70 genes to develop a risk profile. The test provides a simple readout of low-risk or high-risk disease. This tool can be used for risk assessment in patients with ER-positive or ER-negative tumors. Tests based on critical combinations of genes will likely increasingly be used to guide clinical decision-making regarding breast cancer treatment.

Other Tumors of the Breast

Phyllodes tumors. Tumors of mixed connective tissue and epithelium constitute an important group of unusual primary breast tumors. On one end of the spectrum are benign fibroadenomas,

which are characterized by a proliferation of connective tissue and a variable component of ductal elements that may appear compressed by the swirls of fibroblastic growth. Clinically more challenging are phyllodes tumors, which contain a biphasic proliferation of stroma and mammary epithelium. First called *cystosarcoma phyllodes*, these tumors are now called *phyllodes tumors* in recognition of their usually benign course. However, with increasing cellularity, an invasive margin, and sarcomatous appearance, these tumors may be classified as malignant phyllodes tumors. Benign phyllodes tumors are firm lobulated masses that can range in size, with an average size of approximately 5 cm (larger than average fibroadenomas). Histologically, benign phyllodes tumors are similar to fibroadenomas, but the whorled stroma forms larger clefts lined by epithelium that resemble clusters of leaf-like structures. The stroma is more cellular than in a fibroadenoma, but the fibroblastic cells are bland, and mitoses are infrequent.

Phyllodes tumors are seen on mammography as round densities with smooth borders and are indistinguishable from fibroadenomas. Ultrasonography may reveal a discrete structure with cystic spaces. The diagnosis is suggested by the larger size, history of rapid growth, and occurrence in older patients. Cytologic analysis is unreliable in differentiating a low-grade phyllodes tumor from a fibroadenoma. CNB is preferred, although it is difficult to classify phyllodes tumors with benign or intermediate malignant potential on the basis of a limited sampling. The final diagnosis is best made by excisional biopsy followed by careful pathologic review.

Local excision of a benign phyllodes tumor, similar to local excision of a fibroadenoma, is curative. Intermediate tumors, also called *borderline phyllodes tumors*, are tumors to which it is difficult to assign a benign classification. These tumors are treated by excision with negative margins (often suggested to be at least 1 cm) to prevent local recurrence. Affected patients are at some risk for local recurrence, most often within the first 2 years after excision. Close follow-up with examination and imaging allows early detection of recurrence.

At the other end of the spectrum of tumors of mixed connective tissue and epithelium are frankly malignant stromal sarcomas. Malignant phyllodes tumors are characterized by features such as cellular atypia, high number of mitoses, and stromal overgrowth, the extent of which is the main predictor of survival. These tumors are treated similarly to soft tissue sarcomas that occur on the trunk or extremities. Complete surgical excision of the entire tumor with a margin of normal tissue is advised. When the tumor is large with respect to the size of the breast, total mastectomy may be required. If mastectomy is performed and the margins are negative, radiation therapy is not recommended. If the margins are concerning or close, if the tumor involves the fascia or chest wall, or if the tumor is very large (>5 cm), irradiation of the chest wall is considered. If only wide local excision is performed, adjuvant radiation therapy is recommended. As with other soft tissue sarcomas, regional lymph node dissection is not required for staging or locoregional control. Metastases from malignant phyllodes tumors occur via hematogenous spread; common sites of metastasis include lung, bone, abdominal viscera, and mediastinum. Systemic therapeutic agents used for sarcomas have resulted in minimal success.

Angiosarcoma. Angiosarcoma, a rare vascular tumor (1% of all breast tumors), may occur de novo in the breast parenchyma or within the dermis of the breast after irradiation for breast cancer. Angiosarcoma has also been seen to develop in the upper extremity of patients with lymphedema, historically 10 to 15 years after radical mastectomy and irradiation. Angiosarcomas arising in the absence of previous radiation therapy or surgery (primary angiosarcomas) generally form an ill-defined mass within the parenchyma of the breast. In contrast, angiosarcomas caused by prior radiation therapy (secondary angiosarcomas) arise in the irradiated skin as purplish vascular proliferations that may go unrecognized for a period of time. The development of angiosarcoma in the ipsilateral arm to surgery is called Stewart-Treves syndrome and is secondary to long-standing lymphedema. The differential diagnosis is frequently between malignant angiosarcoma and atypical vascular proliferations in irradiated skin. Histologically, angiosarcoma is composed of an anastomosing tangle of blood vessels in the dermis and superficial subcutaneous fat. The atypical and crowded vessels invade through the dermis and into subcutaneous fat. These tumors are graded by the appearance and behavior of the associated endothelial cells. Pleomorphic nuclei, frequent mitoses, and stacking of the endothelial cells lining neoplastic vessels are features seen in higher-grade lesions. Necrosis, rarely seen in hemangiomas, is common in high-grade angiosarcomas. Clinically, radiation-induced angiosarcoma is identified as a reddish brown to purple raised rash within the radiation portals and on the skin of the breast or chest wall. As the disease progresses, tumors protruding from the surface of the skin may predominate.

Mammography is unrevealing in most cases of angiosarcoma. In the absence of metastatic disease at initial evaluation, surgery is performed to secure negative skin margins and usually involves a total mastectomy. A split-thickness skin graft or myocutaneous flap may be needed to replace a large skin defect created by the resection. Metastasis to regional nodes is extraordinarily rare, and axillary dissection is not required.

Patients remain at high risk for local recurrence after resection of angiosarcoma. For patients who present with primary angiosarcoma of the breast, radiation therapy is beneficial in locoregional treatment. Metastatic spread occurs hematogenously, most commonly to the lungs and bone and less frequently to the abdominal viscera, brain, and contralateral breast. Adjuvant chemotherapy is generally recommended and may improve outcomes of patients with angiosarcoma. Angiosarcomas can be divided into low-, intermediate-, and high-grade lesions with the commensurate survival being 91%, 68%, and 14%, respectively

STAGING OF BREAST CANCER

Breast cancer stage is determined clinically by physical examination and imaging studies before treatment, and breast cancer stage is determined pathologically by pathologic examination of the primary tumor and regional lymph nodes after definitive surgical treatment. Staging is performed to group patients into risk categories that define prognosis and guide treatment recommendations for patients with a similar prognosis. Breast cancer is classified with the tumor-node-metastasis (TNM) classification system, which groups patients into four stage groupings based on the size of the primary tumor (T), status of the regional lymph nodes (N), and presence or absence of distant metastasis (M). The most widely used system is that of the AJCC. This system is updated every 6 to 8 years to reflect current understanding of tumor behavior. The TNM classification is shown in Table 35.4.[12] Staging with the eighth edition of the AJCC has become much more complex as it includes T, N, and M as well as biologic markers (ER, PR, and HER-2), histologic grade, and, where applicable, Oncotype Dx score. For example, a tumor with the same TNM staging and molecular markers but with different Oncotype Dx scores can have different stages. A staging website is best utilized to determine stage (https://cancerstaging.org/About/news/Pages/

TABLE 35.4 TNM classification for breast cancer (pathologic).

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma or carcinoma in situ (DCIS) in underlying breast parenchyma
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin
T4a	Extension to the chest wall, not including only pectoralis muscle adherence or invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema of the skin
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional Lymph Nodes (N)	
pNX	Regional lymph nodes cannot be assessed (e.g.,not removed for pathalogical study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (Level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

DCIS, Ductal carcinoma in situ; *IHC*, immunohistochemistry; *RT-PCR*, reverse transcriptase polymerase chain reaction pN stating that (SLN) or (f) can be added to denote staging only by SLN or fine needle or core biopsy only.
From Giuliano AE, Connolly JL, Edge SB et al. Breast Cancer – Major Changes in the American Joint Committee on Cancer Eighth Cancer Staging Manual *CA Cancer J Clin* 2017;67(4):290-303.

Updated-Breast-Chapter-for-8th-Edition.aspx). Metastasis to ipsilateral axillary nodes predicts outcome after surgical treatment more powerfully than tumor size. Before the incorporation of systemic therapies in the management of breast cancer, when treatment was with surgery alone, the survival rate decreased almost linearly with increasing nodal involvement.

Although staging is an important part of the initial assessment of breast cancer patients, it has traditionally been based

on anatomic variables without other important prognostic factors. The new staging form has a place to record other variables, including tumor grade, ER status, PR status, HER-2 status, circulating tumor cells, disseminated tumor cells (in bone marrow), multigene recurrence score, and response to chemotherapy.

Some prefixes and suffixes are used with the cTNM (clinical) and pTNM (pathologic) staging systems to designate special cases. These do not affect the stage group but indicate that they must be analyzed separately. These prefixes and suffixes include the "m" suffix, which signifies multiple primary tumors, pT(m)NM; the "y" prefix, which denotes patients who have received systemic therapy before surgery, ypTNM; and the "r" prefix, which indicates a recurrent tumor, rTNM. In clinical practice, physicians use the anatomic stage grouping in addition to important biologic factors to determine risk and guide treatment recommendations.

SURGICAL TREATMENT OF BREAST CANCER

Historical Perspective

Through the mid-twentieth century, breast cancer was thought to arise in the breast and progress to other sites largely via centrifugal spread. In this model, more extensive surgical procedures were expected to reduce mortality by resecting locoregional disease before it could spread to distant sites. This model was supported, in part, by the results of the Halsted radical mastectomy, which was the first procedure that demonstrated improvements in breast cancer survival relative to the local excision of tumors. Introduced in the 1890s, the radical mastectomy included removal of the breast, overlying skin, and underlying pectoralis muscles in continuity with the regional lymph nodes along the axillary vein up to the costoclavicular ligament. The procedure often required a skin graft to cover the large skin defect that was created. This approach was well suited to breast cancer biology of the time, when most tumors were locally advanced, frequently with chest wall or skin involvement and extensive axillary nodal disease. Radical mastectomy provided improved local control and led to an increasing population of long-term survivors. Radical mastectomy continued to be the mainstay of surgical therapy into the 1970s.

Numerous women continued to die of metastatic breast cancer after radical mastectomy and even after more extensive surgical procedures, including radical mastectomy with en bloc resection of the internal mammary and supraclavicular nodes. This situation eventually led to a shift in the theory of primary centrifugal spread to the more modern theory that breast cancer spreads centrifugally to adjacent structures and via lymphatics and blood vessels to distant sites.

In the modern era, breast cancer treatment includes local and regional approaches (surgery and radiation therapy) in addition to medical therapies designed to treat systemic disease. Multimodality treatment approaches were the first to show significant improvements in locoregional control and survival. As breast cancer was being recognized at earlier stages, radical mastectomy was abandoned in favor of more conservative surgical approaches in combination with radiation therapy. The result was dramatic reductions in the extent of surgery required for local control of breast cancer and decreases in treatment-related morbidity. Breast cancer is a heterogeneous disease, and current treatment is guided by molecular properties of the individual patient's tumor as well as the size and location of the tumor.

Surgical Trials of Local Therapy for Operable Breast Cancer

Radical Mastectomy Versus Total Mastectomy With or Without Radiation Therapy

In the NSABP B-04 trial, patients with clinically negative nodes were randomly assigned to radical mastectomy, total mastectomy with irradiation of the chest wall and regional nodes, or total mastectomy alone with delayed axillary dissection if nodes became clinically enlarged. Patients did not receive systemic therapy. Patients with clinically positive nodes were randomly assigned to radical mastectomy or total mastectomy with irradiation of the chest wall and regional lymphatics. At 25 years of follow-up, overall survival (OS) and disease-free survival (DFS) were equivalent in all treatment arms within the node-positive and node-negative groups. Of the patients with clinically node-negative disease who underwent radical mastectomy, 38% were found to have nodal metastases at surgery, yet only 18% of patients undergoing total mastectomy without axillary dissection or radiation therapy developed axillary recurrence requiring delayed dissection. Those individuals with axillary bed recurrences and delayed axillary node resection did very poorly. However, OS was equivalent in all three groups.

Mastectomy Versus Breast-Conserving Therapy

Six prospective clinical trials that included more than 4500 patients compared mastectomy versus breast-conserving therapy (Table 35.5). In all these trials, there was no survival advantage for the use of mastectomy over breast preservation. The largest of these trials, NSABP B-06, enrolled 1851 patients with tumors up to 4 cm in diameter and clinically negative lymph nodes. Patients were randomly assigned to undergo modified radical mastectomy, lumpectomy alone, or lumpectomy with postoperative irradiation of the breast without an extra boost to the lumpectomy site. All patients with histologically positive axillary nodes received chemotherapy. At 20 years of follow-up, OS and DFS were the same in all three treatment groups.

NSABP B-06 provided valuable information about rates of ipsilateral breast cancer recurrence after lumpectomy, with or without breast irradiation. At 20 years of follow-up, local recurrence rates were 14.3% in women treated with lumpectomy and radiation therapy and 39.2% in women treated with lumpectomy alone ($P < 0.001$). For patients with positive nodes who received chemotherapy, the local recurrence rate was 44.2% for lumpectomy alone and 8.8% for lumpectomy plus radiation therapy.

Another important trial that evaluated breast-conserving therapy was the Milan I trial. This trial enrolled patients with smaller tumors and used more extensive surgery and radiation therapy than the NSABP B-06 trial. There were 701 women with tumors up to 2 cm and clinically negative nodes randomly assigned to undergo radical mastectomy or quadrantectomy with axillary dissection and postoperative irradiation. Patients with pathologically positive nodes received chemotherapy. OS at 20 years did not differ between the two groups. Locoregional failure rates differed between the groups: Chest wall recurrence occurred in 2.3% of women who underwent radical mastectomy, and ipsilateral breast tumor recurrence occurred in 8.8% of women who underwent quadrantectomy and radiation therapy (20-year follow-up). After quadrantectomy, local failure rates were higher in younger women, with rates of 1% per year in women younger than 45 years and 0.5% per year in older women.

TABLE 35.5 Randomized trials comparing breast conservation versus mastectomy.

TRIAL	NO. PATIENTS	MAXIMUM TUMOR SIZE (CM)	SYSTEMIC THERAPY	FOLLOW-UP (YEARS)	% SURVIVAL LUMPECTOMY + XRT	% SURVIVAL MASTECTOMY	LOCAL RECURRENCE (BCT) (%)
NSABP B-06[a]	1851	4	Yes	20	47	46	14*
Milan Cancer Institute[b]	701	2	Yes	20	44	43	8.8*
Institute Gustave-Roussy[c]	179	2	No	14	73	65	13
National Cancer Institute[d]	237	5	Yes	10	77	75	16
EORTC[e]	868	5	Yes	10	65	66	17.6
Danish Breast Cancer Group[f]	905	None	Yes	6	79	82	3

BCT, Breast-conserving therapy; *EORTC*, European Organization for Research and Treatment of Cancer; *NSABP*, National Surgical Adjuvant Breast and Bowel Project; *XRT*, radiation therapy.

*Includes only women whose excision margins were negative.

[a]Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233.

[b]Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227.

[c]Arriagada R, Le M, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: Patterns of failure with 15 years of follow-up data. *J Clin Oncol*. 1996;14:1558.

[d]Jacobson J, Danforth D, Cowan K, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med*. 1995;332:907.

[e]van Dongen J, Voogd A, Fentiman I, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. *J Natl Cancer Inst*. 2000;92:1143.

[f]Blichert-Toft M, Rose C, Andersen J, et al: Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr*. 1992;11:19.

Three other randomized trials in patients with operable breast cancer found no survival benefit of mastectomy over breast-conserving therapy. In the European Organization for Research and Treatment of Cancer (EORTC) Trial 10801, in which 868 women were randomly assigned to modified radical mastectomy or lumpectomy and irradiation, there was no difference in survival at 10 years. This trial included patients with tumors up to 5 cm, and 80% of women enrolled had tumors larger than 2 cm. Positive margins were allowed, and the results showed lower rates of local recurrence with clear versus involved margins.

In the Institut Gustave-Roussy trial, 179 women with tumors smaller than 2 cm were randomly assigned to modified radical mastectomy or lumpectomy with a 2-cm margin of normal tissue around the cancer. No differences were observed between the two surgical groups in risk for death, metastases, contralateral breast cancer, or locoregional recurrence at 15 years of follow-up.

In the U.S. NCI trial, 237 women with tumors 5 cm or smaller were randomly assigned to lumpectomy with axillary dissection and radiation therapy or modified radical mastectomy. No differences were seen in OS or DFS rates at 10 years.

Planning Surgical Treatments

It is critical to establish the diagnosis of breast cancer firmly before initiation of definitive surgical treatment. CNB of a palpable or image-detected lesion is the preferred approach for diagnosis. Open surgical biopsy is reserved for lesions not amenable to CNB and cases in which CNB has proved nondiagnostic. Examination of biopsy material should provide information about tumor histologic type and grade, ER and PR status, and HER-2 status. Oncotype DX is indicated for patients with ER-positive, node-negative disease.

A history and physical examination, in addition to appropriate imaging studies, are important to establish the extent of disease and assign a clinical stage. The most common sites of distant metastases from breast cancer are the bone, liver, and lungs followed by brain. The National Comprehensive Cancer Network provides guidelines regarding the use of laboratory and radiologic testing in patients at initial diagnosis based on clinical stage. Computed tomography scans, bone scans, and other imaging studies are generally reserved for patients with clinically positive nodes, abnormalities on blood chemistry tests or chest radiographs, and for patients with locally advanced or inflammatory breast cancer. Thorough imaging of the ipsilateral and contralateral breast is performed to look for areas of concern other than the index lesion. Breast MRI may be used in selected cases to define the extent of tumor and look for additional breast lesions or to document response to neoadjuvant chemotherapy; however, there is no high-level evidence demonstrating that use of MRI to guide decisions regarding local therapy improves local recurrence rates or survival.

In the absence of metastatic disease, the first intervention for patients with early-stage breast cancer is surgery for excision of the tumor and surgical staging of the regional lymph nodes. Assessment of the primary tumor size and regional lymph nodes defines the pathologic stage and provides an estimate of the prognosis to inform decisions about systemic therapy. Patients with locally advanced and inflammatory breast cancers should receive systemic therapy before surgery (see "Neoadjuvant Systemic Therapy for Operable Breast Cancer" later on).

The selection of surgical procedures takes into account patient characteristics and other clinical and pathologic variables. Patient characteristics, including age, family history, menopausal status, and overall health, are assessed. Some patients may undergo

BOX 35.4 Contraindications to radiation.

Absolute
- Pregnancy

Relative
- Systemic scleroderma*
- Active systemic lupus erythematosus*
- Prior radiation to breast or chest wall
- Severe pulmonary disease
- Severe cardiac disease (if tumor is left sided)
- Inability to lie supine
- Inability to abduct arm on affected side
- *p53* mutation†

*Other collagen vascular diseases are not contraindications to radiation, although patients should not be taking immunosuppressants such as methotrexate because they are radiosensitizers.
†Patients with p53 mutations are highly susceptible to radiation-induced cancers.

genetic testing for *BRCA* or other gene mutations at the time of diagnosis. Patients with a known BRCA mutation are generally counseled toward bilateral mastectomy for treatment of the index breast and reduction of the risk of contralateral breast cancer. The location of the tumor within the breast and tumor size relative to breast size are evaluated. Patient preferences for breast preservation versus mastectomy are determined. For patients considering mastectomy, options for immediate reconstruction are discussed.

Selection of Surgical Therapy

Mastectomy and breast-conserving therapy have been shown to be equivalent in terms of patient survival, and the choice of surgical treatment is individualized. Patients who desire breast-conserving surgery must be willing to attend postoperative radiation therapy sessions and to undergo postoperative surveillance of the treated breast. Consultation with a radiation oncologist may be arranged before the planned surgery. Patients are advised about the risks and long-term sequelae of radiation therapy. A mastectomy is generally recommended for patients who have contraindications to radiation therapy (Box 35.4). Although pregnancy is an absolute contraindication to radiation therapy, many patients pregnant at diagnosis can complete their pregnancy and receive radiation therapy after delivery.

A significant factor in determining whether breast-conserving therapy is feasible is the relationship between tumor size and breast size. In general, the tumor must be small enough in relation to the breast size so that the tumor can be resected with adequate margins and acceptable cosmesis. In patients with large tumors for whom adjuvant (postoperative) systemic chemotherapy will likely be recommended, the use of preoperative chemotherapy may be considered. Chemotherapy administered before surgery may decrease the tumor size sufficiently to permit breast-conserving surgery in patients who would not otherwise appear to be good candidates. Another strategy is to consider oncoplastic breast surgery with local tissue rearrangement or pedicled myocutaneous flaps (latissimus dorsi) to fill the defect resulting from breast-conserving surgery.[13] Patients with multicentric tumors are usually served best by mastectomy because it is difficult to perform more than one breast-conserving surgery in the same breast with acceptable cosmesis, although clinical trials are ongoing to determine the feasibility of multiple resections followed by radiation therapy. Although high nuclear grade, presence of lymphovascular invasion, and negative steroid hormone receptor status all have been linked to increased local recurrence rates, none of these factors are considered contraindications to breast conservation.

Factors Influencing Eligibility for Breast Conservation

Randomized trials have demonstrated the efficacy of breast-conserving therapy for a wide variety of breast cancers and have defined eligibility criteria for breast conservation. With these criteria and current surgical and radiation therapy approaches, local recurrence rates after lumpectomy and radiation therapy are less than 5% at 10 years at many large centers.

Tumor Size

Tumors smaller than 5 cm tumors with clinically positive nodes, and tumors with lobular and ductal histology were included in the randomized trials of mastectomy versus breast-conserving therapy. In current practice, lumpectomy is considered when the tumor, regardless of size, can be excised with clear margins and an acceptable cosmetic result.

Margins

The appropriate margin width for lumpectomy specimens has been debated. Although the NSABP B-06 trial defined a negative margin as "no ink on tumor," other trials evaluating breast-conserving therapy did not specify a required margin width or did not evaluate microscopic margins. The optimal margin width has been open to interpretation, resulting in substantial variability in treatment and recommendations regarding the need for reexcision for wider margins. The Society of Surgical Oncology and American Society for Radiation Oncology convened a multidisciplinary panel to address the question of what margin width is required to minimize the risk of ipsilateral breast tumor recurrence.[14] The panel used a meta analysis of margin width and ipsilateral breast tumor recurrence from a systematic review of 33 studies including 28,162 patients. They found that positive margins, defined as ink on invasive carcinoma or DCIS, were associated with a twofold increase in ipsilateral breast tumor recurrence risk compared with negative margins. The risk was not affected by any specific clinicopathologic features, including favorable biology, use of endocrine therapy, or administration of a radiation boost. In addition, more widely clear margins than no ink on tumor did not significantly decrease the ipsilateral breast tumor recurrence risk, including in patients with unfavorable biology, lobular cancers, or cancers with an extensive intraductal component. The panel concluded that "no ink on tumor" should be used as the standard for an adequate margin in invasive breast cancer. European consensus groups vary on their recommendations for margin width ranging from 2 mm to 5 mm.

Histology

Invasive lobular cancers and cancers with an extensive intraductal component can be treated with lumpectomy if clear margins can be achieved. Atypical hyperplasia (ductal and lobular) and LCIS at resection margins do not increase local recurrence rates.

Patient Age

Local recurrence rates after breast-conserving surgery are higher for younger women than for older women. Local recurrence rates are reduced in patients of all ages with the use of radiation therapy. A radiation boost to the tumor bed has been shown to reduce local

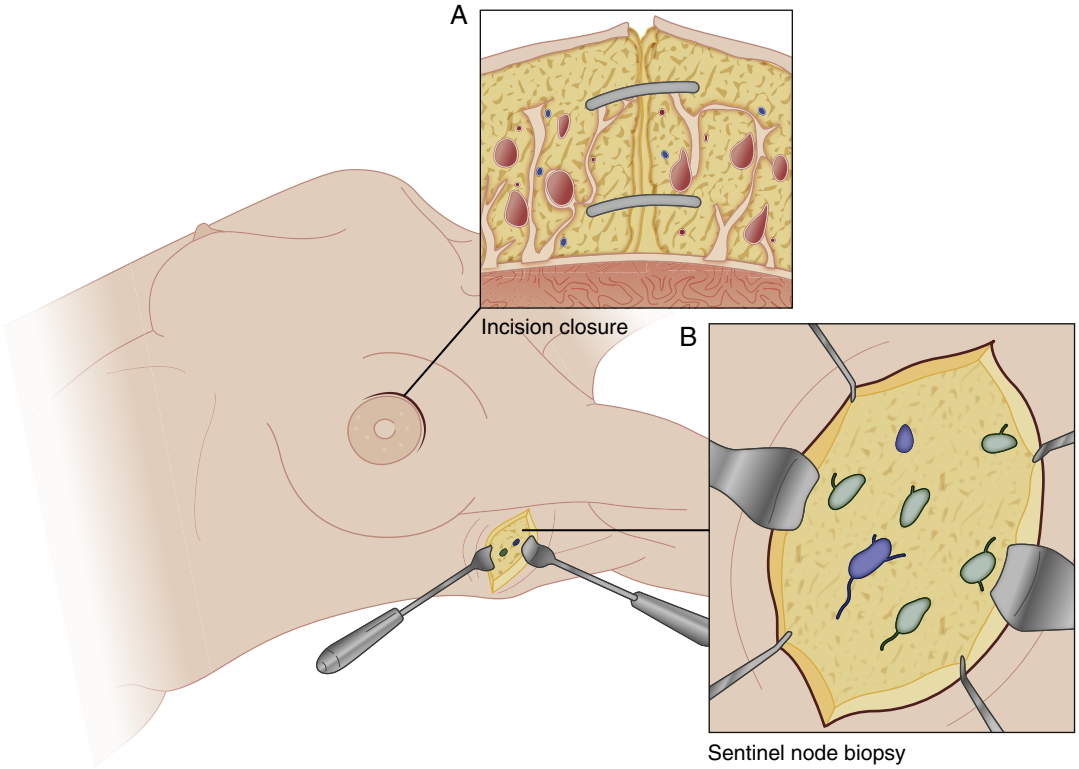

FIG. 35.11 Breast-conserving surgery. (A) Incisions to remove malignant tumors are placed directly over the tumor or around the areola. After the partial mastectomy has been completed, the parenchymal defect is closed *(inset)* to prevent a cosmetic deformity. (B) A transverse incision below the axillary hairline is used for sentinel node biopsy or axillary dissection. The boundaries of the axillary dissection are the axillary vein superiorly, the latissimus dorsi muscle laterally, and the chest wall medially. The inferior dissection enters the tail of Spence (the axillary tail of the breast). In sentinel node biopsy, a similar transverse incision is made, which may be located by percutaneous mapping with the gamma probe to detect a hot spot from the radiolabeled colloid. It is extended through the clavipectoral fascia, and the true axilla is entered. The sentinel node is located by staining with blue dye *(inset)*, radioactivity, or both and is dissected free as a single specimen.

failures after lumpectomy with negative margins, particularly in younger women.

Breast-Conserving Surgery

Technical Aspects

Excision of the primary tumor with preservation of the breast has been referred to by many terms, including *lumpectomy*, *partial mastectomy*, *segmental mastectomy*, *segmentectomy*, *tylectomy*, and *wide local excision*. Breast-conserving surgery removes the malignancy with a surrounding rim of grossly normal breast parenchyma. This procedure is depicted in Fig. 35.11, which shows the completed lumpectomy and skin incision for the axillary component of the procedure.

The breast specimen that is removed is oriented and its edges are inked before sectioning. Specimen radiography should be performed for all nonpalpable lesions or if there are microcalcifications associated with the palpable tumor. If a margin appears to be close or is positive histologically on intraoperative assessment, reexcision to remove more tissue frequently achieves a clear margin and allows conservation of the breast. Orientation of the surgical specimen allows focal reexcision of involved margins rather than global reexcision and improves the cosmetic result by reducing the amount of normal breast parenchyma that is excised.

There is level I evidence that shaved margins at the time of the lumpectomy reduces the need for reexcision.[15] The larger the volume of excision, the better the margin clearance, but the poorer the cosmetic result. The surgical defect created after lumpectomy is closed in cosmetic fashion. There is increasing interest in the use of advancement flap closure and other oncoplastic surgical techniques to maximize the cosmetic result.

Surgical staging of the axilla is performed through a separate incision in most patients undergoing breast conservation. SLND (see Fig. 35.11) has replaced anatomic axillary node dissection in patients with clinically negative axillary nodes. For patients who require axillary dissection, the extent of the dissection is identical to the axillary component of the modified radical mastectomy (see Fig. 35.11).

Cosmetic Challenges

The term *oncoplastic surgery* has been popularized to stress the importance of achieving the best possible esthetic result in the context of resecting the tumor with adequate oncologic margins. The goal is to retain as much of the natural breast size and contour as possible to provide optimal cosmesis and symmetry with the opposite breast. When the primary tumor is resected using an incision directly over the tumor and closure of the skin without reapproximation of any breast tissue, several deformities can occur, including volumetric deformity from a large parenchymal resection (retraction deformity when the seroma resorbs at the operative site); skin–pectoral muscle adherence deformity, in which

the skin adheres to the underlying pectoral muscle; and lower pole deformity with downward turning of the nipple (bird beak deformity) caused by excision of a tumor in the lower hemisphere of the breast. These deformities can make it difficult for patients to wear tight-fitting clothing because significant asymmetry may be evident. It is important to correct these deformities before radiation therapy because the irradiation may further accentuate any asymmetry and make it more challenging to correct the defect in the future. The surgeon should consider oncoplastic techniques in the following situations: (1) a significant area of skin is to be resected with the tumor, (2) a large-volume resection is expected, (3) the tumor is in an area associated with poor cosmetic outcomes (e.g., lower hemisphere below the nipple), or (4) resection may lead to nipple malposition.

Extent of breast resection. When oncoplastic surgery techniques are considered, it is not the absolute breast volume that will be resected but rather the ratio of the anticipated defect to the volume of the remaining breast parenchyma and the type of parenchyma present (fatty replaced vs. dense) that is important. In general, oncoplastic surgery should be considered when the size of the surgical defect is likely to be greater than 20% to 30% of the breast volume and for any tumor resection in the lower breast.

Breast size and body habitus. Patients with large breasts are often good candidates for tumor resection and bilateral reduction mammaplasty. Breast reduction can allow for improved esthetic outcomes after resection of large volumes of breast tissue at any location. Obese patients should be considered for this approach because they are often poor candidates for autologous tissue reconstruction after mastectomy, and implants are often not large enough to recreate a breast proportional in size to the contralateral breast. Breast reduction surgery is a good option because this can relieve the symptoms of macromastia and allow for improved outcomes after breast irradiation.

Tumor location. Tumors lying directly under the nipple-areolar complex and tumors located between the nipple-areolar complex and inframammary fold require special attention to avoid nipple-areolar complex distortion and contour deformity. In general, the skin and well-vascularized breast parenchyma must be adjusted to correct for the removal of breast tissue in these areas. As noted, deformities in the contour will be exacerbated by radiation and may be more challenging to correct at a later date. Fig. 35.12 shows the various incisions for tumors located in different parts of the breast. Upper pole lesions can be served by a variety of techniques (Fig. 35.12A), including round block (one or more lesion in any quadrant but especially nice for upper inner quadrant lesions), crescent mastopexy (for those who need a minor lift), and batwing or hemi-batwing (for those who need more of a lift).

Lower pole lesions (Fig. 35.12B) may use techniques that require a mastopexy based on a superior pedicle flap. Lower outer lesions may require a J or V plasty to retain the shape of the breast. A Benelli includes a deepithelization circumferentially around the areola and is especially useful for the lower inner quadrant of the breast as well as a minor reduction in breast volume.

These techniques can also be used to correct defects left from previous surgeries.

Short-term follow-up shows that oncoplastic techniques have greater patient satisfaction, less complications, and less local recurrence.[16]

Timing of Oncoplastic Surgery

Immediate repair of a partial mastectomy defect is almost always preferred to a delayed approach. Oncoplastic techniques such as tissue advancement and local tissue rearrangement at the time of the initial surgical procedure tend to provide the optimal solution. This approach has not been associated with delay in delivery of adjuvant systemic therapy or radiation. In general, local tissue transfer and breast reduction surgery cannot be performed on the irradiated breast; it is preferable to perform the procedure before radiation therapy. Tissue expanders and implants are not recommended to fill partial mastectomy defects because radiation may lead to capsular contracture, distortion, and infection.

If a cosmetic defect occurs after breast-conserving surgery and radiation therapy, reconstruction of the treated breast is generally not recommended for 1 to 2 years after radiation therapy has been completed. In fatty replaced and irradiated tissue, there is a higher rate of tissue necrosis, seroma formation, and infection. The use of vascularized tissue from outside the radiation field is the favored approach. If the main deformity is caused by asymmetry with the contralateral breast, a mastopexy of the contralateral breast can be considered. In general, surgical procedures on the irradiated breast should be minimized because healing and recovery are impaired even when the skin appears healthy.

Mastectomy

Indications

Certain tumors still require mastectomy, including tumors that are large relative to breast size, tumors with extensive calcifications on mammography, tumors for which clear margins cannot be obtained on wide local excision, and tumors in patients with contraindications to breast irradiation (see Box 35.4). Patient preference for mastectomy or a desire to avoid radiation is also a valid indication for mastectomy.

Postmastectomy Breast Reconstruction

Breast reconstruction may be performed immediately—that is, the same day as mastectomy—or as delayed reconstruction, months or years later. Immediate reconstruction has the advantages of preserving the maximum amount of breast skin for use in reconstruction, combining the recovery period for both procedures, and avoiding a period of time without a breast mound. Immediate reconstruction does not have a detrimental effect on long-term survival, local recurrence rates, or detection of local recurrence. Reconstruction may or may not be delayed in patients who might require postmastectomy radiation therapy. Reconstruction options include tissue expander/implant and autologous tissue reconstructions, most often with transverse rectus abdominis muscle flaps, latissimus dorsi flaps, or muscle-preserving perforator abdominal flaps.

Technical Details

Simple or total mastectomy refers to complete removal of the mammary gland, including the nipple and areola. Modified radical mastectomy refers to removal of the mammary gland, nipple, and areola, with the addition of a complete axillary lymph node dissection (ALND) (Fig. 35.13). For either a total mastectomy or a modified radical mastectomy, an elliptical skin incision is planned to include the nipple and areola and usually any previous excisional biopsy scars (see Fig. 35.13). Skin flaps are raised to separate the underlying gland from the overlying skin along the subdermal plexus (see Fig. 35.13). If immediate reconstruction is not planned, sufficient skin is taken to allow smooth closure of skin flaps without redundant skin folds; this facilitates comfortable use of a breast prosthesis.

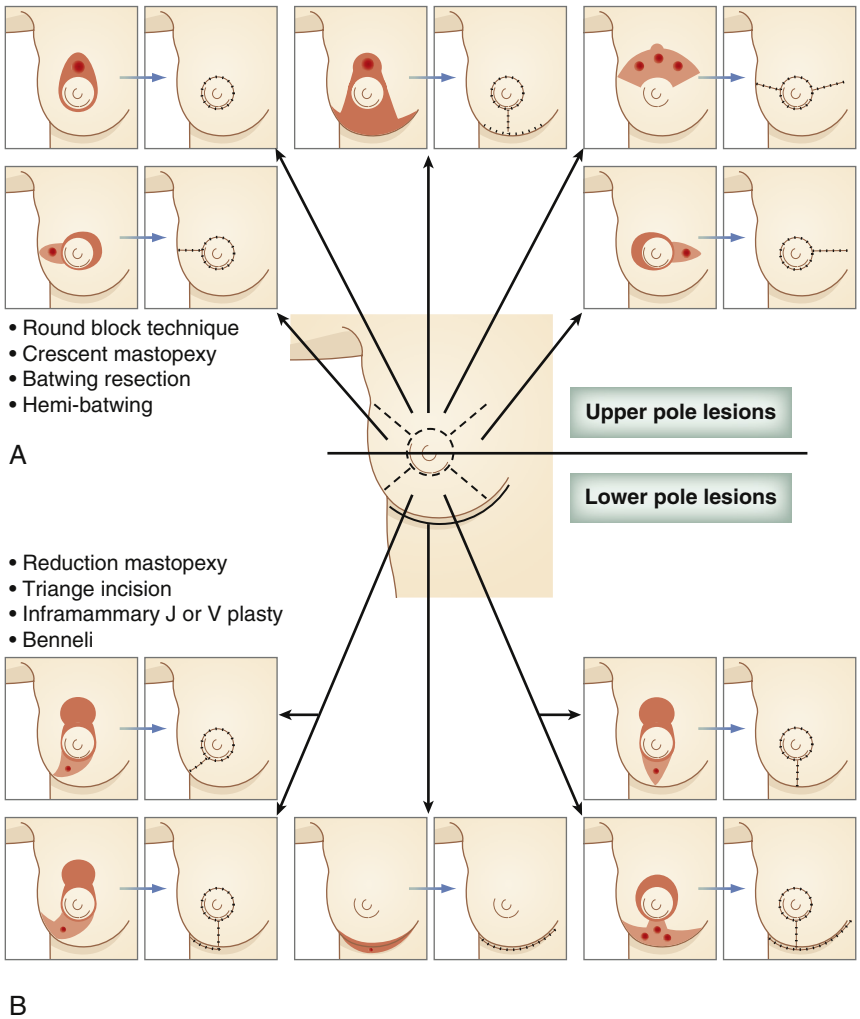

FIG. 35.12 The various incisions for tumors located in different parts of the breast. (A) Upper pole lesions can be served by a variety of techniques, including round block, crescent mastopexy, and batwing or hemi-batwing. (B) Lower pole lesions may use techniques that require a mastopexy based on a superior pedicle flap. Including reduction mastopexy, triangle insision, J or V plasty, and Benneli. (Adapted from Fitoussi A, Berry MG, Couturaud B, et al. *Oncoplastic and reconstructive surgery for breast cancer: The Institut Curie Experience*. Paris: Springer; 2008.)

If immediate reconstruction is planned, a skin-sparing mastectomy may be performed in which only the nipple-areola complex is removed and the maximum amount of skin is left for use in the reconstruction. Nipple-areola–sparing mastectomy has been used with increasing frequency for selected patients with breast cancer. Multiple studies have shown the safety and feasibility of this approach, with many series showing comparably low recurrence rates in patients undergoing nipple-areola–sparing mastectomy (Table 35.6). Nipple-areola–sparing mastectomy has also been demonstrated to be safe in patients undergoing prophylactic mastectomy for risk reduction, including *BRCA1* and *BRCA2* gene mutation carriers.[17]

Breast tissue is separated from the underlying pectoralis muscle, and the pectoral fascia is generally taken with the breast specimen. In a total mastectomy (see Fig. 35.13), breast tissue is separated from the axillary contents, and all breast tissue superficial to the fascia of the axilla is removed. In a modified radical mastectomy, the level I and II axillary lymph nodes are taken with the axillary breast tissue (see Fig. 35.13). Level I nodes are nodes inferior to the axillary vein and lateral to the pectoralis minor muscle, and level II nodes are nodes anterior or posterior to the pectoralis minor.

Lymph Node Staging

The pathologic status of the axillary lymph nodes is one of the most important prognostic factors in patients with breast cancer. Identification of metastatic tumor deposits in the axillary nodes indicates a poorer prognosis and often prompts a recommendation for more aggressive systemic and locoregional therapies.

Historical Perspective

Historically, ALND was a routine component of the surgical management of breast cancer. It provides prognostic information about axillary nodal status and plays a therapeutic role in

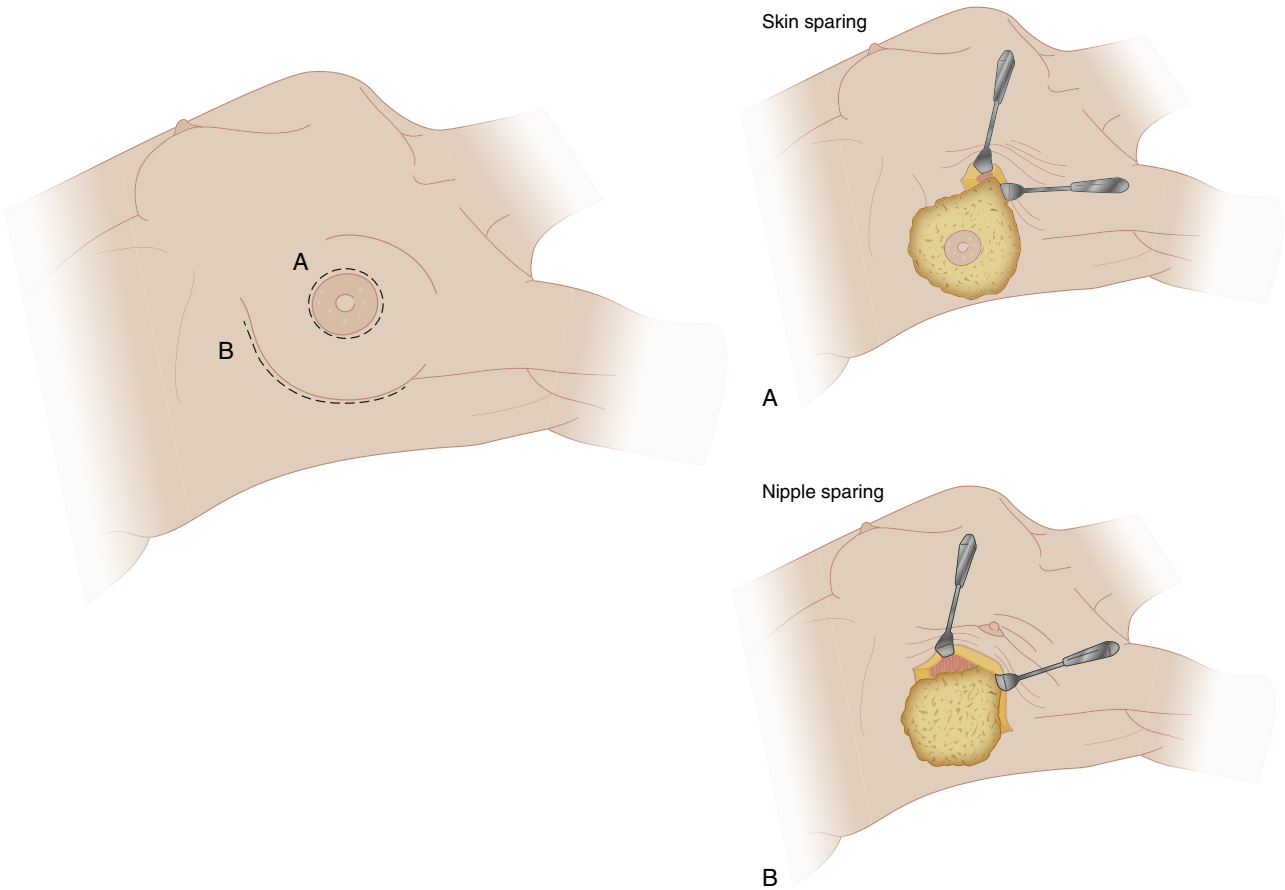

FIG. 35.13 Total mastectomy with and without axillary dissection. For patients undergoing mastectomy without reconstruction, skin incisions are generally transverse and surround the central breast and nipple-areolar complex. (A) Circumareolar incisions are most common for patients undergoing skin-sparing mastectomy with immediate reconstruction. Skin flaps are raised to separate the gland from the overlying skin and then the gland from the underlying muscle. Simple mastectomy divides the breast from the axillary contents and stops at the clavipectoral fascia. If axillary staging is planned, this is generally performed through a separate transverse axillary incision. (B) An inframammary incision is shown for nipple-areolar–sparing mastectomy.

removing axillary disease in patients with positive nodes. The surgical procedure includes clearance of node-bearing tissue between the pectoralis major and latissimus dorsi muscles from the edge of the breast tissue in the low axillary region to the axillary vein and removal of the nodes posterior to the pectoralis minor muscle. Axillary dissection is the main source of morbidity in patients with early-stage breast cancer. The immediate problems include acute pain and paresthesias, need for hospitalization, reduced range of motion at the shoulder joint, and need for a drain in the surgical bed for 7 to 10 days. Long-term problems resulting from axillary dissection include lymphedema of the ipsilateral arm, numbness, chronic pain, and reduced range of motion at the shoulder joint.

Sentinel Lymph Node Dissection

Identification of the first, or sentinel, node draining the area of the primary tumor in the breast allows for a more selective approach to the axilla. The sentinel node is the most likely node to contain metastatic disease, if present, and the pathologist can focus the examination on the sentinel node(s) without the added cost and time required to examine the full axillary contents. The technique of SLND was developed to reduce the morbidity associated with axillary surgery, while still providing accurate staging information. Many patients now present with clinically node-negative disease, and SLND can identify those patients with node-positive disease who may benefit from completion of ALND. Patients with negative sentinel lymph nodes can avoid the morbidity of axillary dissection. In sentinel node surgery, radiolabeled colloid, blue dye, or both are injected into breast tissue at the site of the primary tumor; the material passes through the lymphatics to the first draining node(s), where it accumulates. The procedure can also be performed with injection of the mapping agents that can be injected subareolar position or in a subdermal location overlying the site of the primary tumor. The sentinel node is identified as a blue, radioactive, fluorescent, or magnetic node or a combination of these. If the pathologic analysis of the sentinel node is negative for evidence of metastasis, the likelihood that other nodes are involved is sufficiently low that ALND is not required.

The NSABP B-32 trial was a critical study evaluating SLND.[18] In that study, 5611 patients with clinically node-negative breast cancer were randomly assigned to undergo SLND plus ALND or SLND with ALND only if the sentinel node was positive. The sentinel node was positive in 26% of patients in both groups. For patients with a pathologically negative sentinel node (n = 3986), in whom the primary analysis was performed, there was no difference in OS, DFS, or regional control rates, demonstrating that when the sentinel node is negative, SLND alone without further ALND is appropriate for patients with clinically negative lymph nodes. A randomized trial conducted at the European Institute of Oncology

TABLE 35.6 Studies on nipple and local recurrence rates in patients undergoing nipple-areola–sparing mastectomy.

AUTHOR	YEAR	PROCEDURES N	FOLLOW-UP (MONTHS)	NAC RECURRENCE (%)	LOCAL RECURRENCE (%)
Crowe[a]	2004	54	NA	10*	NA
Margulies[b]	2005	50	7.9	0	0
Boneti[c]	2011	281	25.3	0	7
Filho[d]	2011	157	10	0	0
Jenson[e]	2011	127	60	0	0
Peled[f]	2012	412	28	0	2
Loshiriwat[g]	2012	934	64	0	0
Coopey[h]	2013	156	22	0	2.6
Krajewski[i]	2015	226	24	0	1.7
Orzalesi[j]	2016	755	36	0.6	2.9
Smith[k]	2017	2182	51	0	3.7
Radovanovic[l]	2018	441	108	5.4*	7.3
Galimberti[m]	2018	1989	94	1.8	5.3

*Nipple-areolar complex involved at the time of surgery and excised.

[a]Crowe JP Jr, Kim JA, Yetman R, et al. Nipple-sparing mastectomy: technique and results of 54 procedures. *Arch Surg*. 2004;139:148–150.

[b]Margulies AG, Hochberg J, Kepple J, et al. Total skin-sparing mastectomy without preservation of the nipple-areola complex. *Am J Surg*. 2005;190:907–912.

[c]Boneti C, Yuen J, Santiago C, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. *J Am Coll Surg*. 2011;212:686–693; discussion 693–685.

[d]de Alcantara Filho P, Capko D, Barry JM, et al. Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience. *Ann Surg Oncol*. 2011;18:3117–3122.

[e]Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. *Ann Surg Oncol*. 2011;18:1665–1670.

[f]Warren Peled A, Foster RD, Stover AC, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann Surg Oncol*. 2012;19:3402–3409.

[g]Lohsiriwat V, Martella S, Rietjens M, et al. Paget's disease as a local recurrence after nipple-sparing mastectomy: clinical presentation, treatment, outcome, and risk factor analysis. *Ann Surg Oncol*. 2012;19:1850–1855.

[h]Coopey SB, Tang R, Lei L, et al. Increasing eligibility for nipple-sparing mastectomy. *Ann Surg Oncol*. 2013;20:3218–3222.

[i]Krajewski AC, Boughey JC, Degnim AC, et al. Expanded indications and improved outcomes for nipple-sparing mastectomy over time. *Ann Surg Oncol*. 2015;22:3317–3323.

[j]Orzalesi L, Casella D, Santi C, et al. Nipple sparing mastectomy: surgical and oncological outcomes from a national multicentric registry with 913 patients (1006 cases) over a six year period. *The Breast*. 2016;25:75–81.

[k]Smith BL, Tang R, Rai U, et al. Oncologic safety of nipple-sparing mastectomy in women with breast cancer. *J Am Coll Surg*. 2017;225:361–365.

[l]Radovanovic Z, Ranisavljevic M, Radovanovic D, et al. Nipple-sparing mastectomy with primary implant reconstruction: surgical and oncological outcome of 435 breast cancer patients. *Breast Care (Basel)*. 2018;13:373–378.

[m]Galimberti V, Morigi C, Bagnardi V, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. *Ann Surg Oncol*. 2018;25:3849–3857.

and numerous single-institution reports confirmed the findings from the NSABP B-32 trial showing that the technique is accurate. Identification of the sentinel node allows for a more detailed analysis of the lymph node most likely to have a positive yield.

In general, pathologists section the sentinel node along its short axis and submit all the sections for paraffin embedding of the tissues. The paraffin blocks can be sectioned and examined with hematoxylin-eosin staining of sections from each block. Some pathologists perform more detailed analysis of the sentinel nodes with step-sectioning of the paraffin blocks and immunohistochemical staining for cytokeratin, which enhances sensitivity by allowing detection of micrometastases. However, the clinical relevance of these micrometastases and small tumor deposits detected by immunohistochemical techniques has been questioned. The NSABP B-32 trial provided an opportunity to investigate the clinical significance of occult metastatic disease. For patients with negative sentinel nodes by hematoxylin-eosin staining, additional sections were evaluated by immunohistochemistry to identify occult metastases. The 5-year DFS rate was 86.4% for patients with occult metastases compared with 89.2% for patients without occult metastases (absolute difference = 2.8%), and the 5-year OS rate was 94.6% for patients with occult metastases compared with 95.8% for patients without occult metastases (absolute difference = 1.2%). These differences were statistically significant given the large number of patients enrolled in the study; however, because the absolute differences were small, the NSABP investigators concluded that the presence of occult metastases was not clinically significant. This conclusion was confirmed by the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial, which was designed to evaluate the significance of sentinel node and bone marrow micrometastases in patients with early-stage breast cancer undergoing breast-conserving therapy.[19] In that study, the 5-year DFS rates for patients with immunohistochemistry-positive and immunohistochemistry-negative sentinel nodes were 90% and 92%, respectively ($P = 0.82$), whereas the 5-year OS rates were 95% and 96%, respectively ($P = 0.64$).

Lymphatic Mapping Technique and Selection of Patients for Sentinel Lymph Node Dissection

Lymphatic mapping can be performed with a combination of ^{99m}Tc-labeled sulfur colloid and a vital blue dye, isosulfan

blue (Lymphazurin), fluorescence, magnetic particles, or with a single agent for localization of the sentinel node(s). Studies indicate that using the combination technique may result in the lowest possible false-negative rate. Preoperative lymphoscintigraphy can provide information on the specific nodal basins draining the primary tumor. Using a peritumoral injection technique, approximately 70% of patients have drainage to the axilla, 20% have drainage to the axilla and the internal mammary nodal basin, 2% to 3% have drainage to the internal mammary nodal basin alone, and 8% do not show any drainage to the regional nodal basins. If a subareolar or subdermal injection technique is used, drainage is seen almost exclusively in the axillary nodal basins. A dose of 2.5 mCi of ^{99m}Tc-labeled sulfur colloid can be injected on the day before surgery for preoperative lymphoscintigraphy; this allows for adequate activity to remain in the sentinel nodes for the intraoperative lymphatic mapping procedure the following day without the need for reinjection. Alternatively, for surgeons not using preoperative lymphoscintigraphy, 0.5 to 1.0 mCi of ^{99m}Tc-labeled sulfur colloid can be injected in the operating suite and avoids the preoperative pain and vasovagal events.

In the operating suite, 3 to 5 mL of blue dye can be injected peritumorally, and the injection site is massaged to facilitate passage of the dye through the lymphatics. A handheld gamma probe is used to localize transcutaneously the area of increased radioactivity; this helps to guide placement of the incision for the sentinel node procedure. After the incision is made, an area of increased radioactivity is localized with the handheld gamma probe, and the surgeon visualizes blue lymphatic channels leading to the sentinel node. Dissection is performed to avoid prematurely disrupting the afferent lymphatics. If a blue-stained lymphatic channel or a specific area of radioactivity ("hot spot") cannot be identified, the primary tumor can be resected to remove the site of injection, decreasing the background shine-through radioactivity. The sentinel node may be identified and removed, after which the nodal basin is checked again to confirm that the level of radioactivity has decreased. If the level of radioactivity remains high, additional sentinel nodes may remain in the nodal basin, and additional dissection should be completed to remove all sentinel nodes. Published studies have demonstrated an average of two or three sentinel nodes per patient.

Surgeons experienced in SLND can identify a sentinel node in more than 95% of patients. The false-negative rate for sentinel node surgery ranges from 0% to 11%, as reported in the NSABP B-32 trial.[18] Surgeons should be trained in SLND before using this procedure as a staging tool. Patients who present with clinically palpable lymph nodes should be evaluated with axillary ultrasonography and fine-needle aspiration biopsy (FNAB) of the nodes. If axillary metastasis is confirmed, patients can proceed directly to standard axillary node dissection or be considered for preoperative chemotherapy. If axillary metastasis is not confirmed by FNAB, patients can proceed to sentinel node surgery for staging.

Some studies have shown that patients who have undergone previous excisional biopsy of the primary tumor are more likely to have a false-negative sentinel node.[18] The lymphatics may be disrupted by the biopsy, which can affect drainage patterns of the area surrounding the excisional biopsy site. To avoid this scenario, CNB is the preferred diagnostic approach in patients suspected to have breast cancer.

In older studies, SLND was reported to be less accurate in patients treated with preoperative chemotherapy. A meta analysis of the published studies on sentinel node surgery after chemotherapy suggested that this technique is accurate; a more recent comparison showed that false-negative rates after chemotherapy compared favorably with false-negative rates observed in patients who undergo surgery first.[20]

Outcomes of Sentinel Lymph Node Dissection

Morbidity rates are substantially lower with SLND than with ALND. Another advantage is that SLND can be performed as an outpatient procedure and does not require a drain. Patients have more rapid return to full mobility and are able to return to work and other activities weeks sooner than after axillary dissection. Long-term morbidity, including lymphedema, numbness, and chronic pain, is greatly reduced.

SLND has been shown to provide reliable pathologic staging of the axilla, with false-negative rates generally less than 5% in experienced hands. Axillary recurrence rates have been shown to be extremely low after a negative sentinel node biopsy without axillary dissection. A negative sentinel node is now widely accepted as sufficient to establish node-negative disease in a patient, with no further axillary treatment required.[18]

When the sentinel node contains metastatic disease, the likelihood of additional involved nodes is directly proportional to the size of the primary breast tumor, presence of lymphatic vascular invasion, and size of the lymph node metastasis. Although ALND has been standard practice for patients with positive sentinel nodes, the need for ALND in all patients with a positive sentinel node has been called into question because many patients have small-volume metastases, and the sentinel node is often the only positive node. A meta analysis of studies evaluating patients with positive sentinel nodes showed that 53% of patients have additional positive nodes at ALND. In the case of micrometastatic disease in the sentinel nodes, the rate of nonsentinel node involvement is 20%, and for patients with isolated tumor cells, it is less than 12%. These findings led to a trend of omitting ALND in selected patients with positive sentinel nodes. An analysis of SEER data from the years 1998 to 2004 revealed that 16% of patients with sentinel node–positive disease did not undergo ALND. These patients were more commonly older patients with low-grade, ER-positive tumors. During this time period, the proportion of patients with micrometastasis in the sentinel node who did not undergo ALND increased from 21% to 38%. A review of the National Cancer Data Base data from the years 1998 to 2005 revealed similar findings, with 20.8% of patients with sentinel node–positive disease avoiding ALND. There were no differences in axillary recurrence rates or survival between patients who had sentinel node surgery only and patients who underwent ALND.

The ACOSOG initiated a prospective randomized trial in 1999 designed specifically to evaluate the impact of ALND on locoregional recurrence and survival in patients with early-stage breast cancer.[21,22] The trial now with 10-year follow-up, ACOSOG Z0011, enrolled patients with clinical T1 or T2 breast cancer with one or two positive sentinel nodes who were planning to undergo breast-conserving surgery and whole breast irradiation (WBI). Patients were randomly assigned to undergo completion ALND or no further surgery (sentinel node surgery alone). The primary end point of the Z0011 study was OS; secondary end points were locoregional recurrence and lymphedema. Patients enrolled in the Z0011 study had relatively favorable disease characteristics: The median age was 55 years, 70% of patients had T1 tumors, 82% had ER-positive tumors, 71% had only one positive sentinel node, and 44% had micrometastases. At a median follow-up of 9.3 years, the 10-year OS was 86.3% in the SLND-alone group

and 83.6% in the ALND group ($P = 0.02$). The 10-year DFS was 80.2% in the SLND-alone group and 78.2% in the ALND group ($P = 0.32$). Ten-year regional recurrence did not differ significantly between the two groups. The Z0011 study investigators concluded that ALND may be safely omitted in patients with early-stage breast cancer with a positive sentinel node who are undergoing breast-conservation surgery (BCS), have one to two positive nodes, and receive whole breast radiation and systemic therapy. This study did not include mastectomy patients. Trials are ongoing to determine the feasibility of omitting ALND in mastectomy patients. It should be noted, however, that there was no significant difference in lymphedema seen between the groups. This may be because this trial included WBI, which in most patients included the Level I axilla or higher.

Conventional wisdom teaches that the lymphatics reside juxtaposed to the vein, and if the surgeon can avoid skeletonizing the vein, then the risk of lymphedema could be minimized or avoided (Fig. 35.2). If this were the case, then SLND should have cured the problem of surgical lymphedema. In fact, lymphatics are seen from the SLN incision nearly one-third of the time. In the more than 10 randomized studies of SLND versus ALND for breast cancer, the lymphedema rate varies between 0% and 13% for SLND and 7% and 77% for ALND. From these varying rates, it is obvious that not everyone is performing the same procedure. Klimberg and colleagues developed the axillary reverse mapping (ARM) procedure to intraoperatively recognize the lymphatic drainage of the upper extremity and preserve it. The procedure consists of radioactivity in the breast and blue dye in the arm (split mapping) in order to identify and protect the lymphatics draining the upper extremity. In a 26-month median follow-up of a phase II trial of 654 patients receiving SLND or ALND with ARM, the rate of lymphedema was less than 1% and 6%, respectively.[23] When any cut lymphatics were reapproximated, the rate of lymphedema was nil for either group. Alliance 221702 is a randomized trial that will further determine the efficacy of ARM.

ALND remains the standard of care for patients with locally advanced breast cancer or inflammatory breast cancer, patients with a positive sentinel node who are scheduled for mastectomy, patients with a positive sentinel node who are scheduled for accelerated partial breast irradiation (PBI), and patients with clinically positive nodes as well as a positive sentinel node after neoadjuvant chemotherapy.

TREATMENT OF DUCTAL CARCINOMA IN SITU

DCIS, or intraductal cancer, accounts for approximately 25% of all newly diagnosed breast cancers. It was anticipated that more than 63,960 new cases of DCIS would be diagnosed in 2016. Most cases of DCIS are detected as an area of clustered calcifications on a screening mammogram without an associated palpable abnormality. Rarely, DCIS manifests as a palpable mass or as unilateral, single-duct nipple discharge.

Findings on mammography in patients with DCIS include clustered calcifications without an associated density in 75% of patients, calcifications coexisting with an associated density in 15%, and a density alone in 10%. The calcifications seen on a mammogram generally correspond to areas within the central involved duct in which there is often necrosis and debris. DCIS calcifications tend to cluster closely together, are pleomorphic, and may be linear or branching, suggesting their ductal origin.

DCIS is viewed as a precursor to invasive ductal cancer, and treatment aims to remove the DCIS to prevent progression to invasive disease. Because the prevalence of metastatic disease in patients with DCIS without demonstrable invasion is low (<1%), systemic chemotherapy is not required. Hormonal therapy may be used for prevention of new primary tumors and to improve local control after breast-conserving therapy but is generally recommended only when the DCIS is positive for ER on immunohistochemistry.

Treatment recommendations for a patient with DCIS are based on the extent of disease within the breast, histologic grade, ER status, and presence of microinvasion as well as patient age and preference. Treatment options for DCIS include mastectomy, breast-conserving surgery with irradiation, and breast-conserving surgery alone. When the patient is treated with breast conservation or unilateral mastectomy, there is also the option of adjuvant hormonal therapy with tamoxifen to reduce the risk of local recurrence or contralateral breast cancer.

Mastectomy

Local recurrence of DCIS is ~1% to 2% per year when treated with BCS versus 1% to 2% lifetime when treated with mastectomy. The survival rates with either treatment are the same, 98% to 99%.

Reasons to select total mastectomy for treatment of DCIS include the following:

1. Diffuse suspicious mammographic calcifications suggestive of extensive disease
2. Inability to obtain clear margins with breast-conserving surgery
3. Likelihood of a poor cosmetic result after breast-conserving surgery
4. Patient not motivated to comply with follow-up surveillance imaging
5. Patient choice
6. Contraindications to radiation therapy (see Box 35.4)

Breast-Conserving Therapy

As for invasive breast cancer, breast-conserving therapy for DCIS requires resection to microscopically clear margins. The Consensus Conference on DCIS[24] that more widely clear margins do not significantly decrease ipsilateral breast tumor recurrence compared with 2-mm margins was based on a meta analysis of 20 studies.[25] The use of adjuvant whole breast radiation therapy has been demonstrated in prospective randomized trials to decrease the risk for local recurrence. The use of hormonal therapy in patients with ER-positive DCIS can decrease further the risk for local recurrence and reduces the risk for development of new contralateral and ipsilateral breast cancers.

The use of radiation therapy after lumpectomy was investigated in four prospective randomized trials (Table 35.7), the results of which are remarkably consistent. In the NSABP B-17 trial, 818 women with DCIS were randomly assigned to lumpectomy alone versus lumpectomy plus 50 Gy of postoperative WBI. The addition of radiation to surgery decreased the ipsilateral recurrence rate from 30.8% to 14.9% ($P < 0.000005$), as shown by 12-year actuarial recurrence data. The addition of radiation also decreased the incidence of invasive breast cancer, from 16.4% to 7.1% ($P < 0.00001$), and produced a smaller decrease in the incidence of in situ recurrence, from 14.1% to 7.8% ($P < 0.001$) (see Table 35.7). In the EORTC 10853 trial, 1010 women with DCIS were randomly assigned to lumpectomy alone versus lumpectomy plus 50 Gy of radiation therapy. Radiation reduced the 10-year breast recurrence rate from 26% to 15% ($P < 0.0001$) and reduced the rate of invasive recurrences from 13% to 8% ($P = 0.0011$). The UK ANZ (United Kingdom, Australia, and New Zealand) trial, which included 1701 patients, was a large randomized trial

TABLE 35.7 Randomized trials of lumpectomy for ductal carcinoma in situ: impact of radiation therapy and tamoxifen.

TRIAL	NO. PATIENTS	FOLLOW-UP (YEAR)	LOCAL RECURRENCE RATES (%)			*P* VALUE
			LUMPECTOMY	LUMPECTOMY + XRT	LUMPECTOMY + XRT + TAMOXIFEN	
NSABP B-17[a]	818	12	30.8	14.9		<.000005
EORTC 10853[b]	1010	4.25	16	9		<.005
UK ANZ	1701	5	20	8	6	<.0001
SweDCIS	1067	5	7	22		<.0001
NSABP B-24[c]	1804	7		9	6	.04

EORTC, European Organization for Research and Treatment of Cancer; *NSABP,* National Surgical Adjuvant Breast and Bowel Project; *SweDCIS,* Swedish Ductal Carcinoma In Situ trial; *UK ANZ,* United Kingdom, Australia, and New Zealand; *XRT,* radiation therapy.

[a]Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16:441.

[b]Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet.* 2000;355:528.

[c]Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol.* 2001;28:400.

that simultaneously evaluated the benefits of radiation therapy and tamoxifen after breast-conserving surgery for patients with DCIS. This trial also demonstrated that radiation therapy reduced the risk of breast cancer recurrence (hazard ratio [HR], 0.38; $P < 0.0001$) and invasive breast cancer recurrence (HR, 0.45; $P = 0.01$). Finally, the SweDCIS trial included 1067 patients with DCIS. After a median follow-up of 5 years, the cumulative incidence of breast recurrence was 22% in the group that underwent surgery only versus 7% in the group that underwent surgery plus radiation therapy ($P < 0.0001$).

Attempts have been made to identify subsets of DCIS for which wide excision without irradiation would provide sufficient local control. Silverstein[26] derived the Van Nuys criteria for classifying DCIS from a series of patients with DCIS treated by wide excision with and without radiation therapy. A system was proposed to identify patients who do not need radiation therapy because they have a low DCIS nuclear grade, a small lesion (<1.4 cm), older age (>60), and wide surgical margins (>1 cm). Silverstein reported low breast recurrence rates with surgery alone for patients with favorable Van Nuys scores. However, in a prospective trial testing this approach, investigators from Harvard enrolled 158 patients from the most favorable Van Nuys subset (low-grade or intermediate-grade DCIS <2.5 cm, with a minimum 1-cm margin on excision) and were unable to reproduce the results; the Harvard investigators stopped the trial early because the rates of recurrence exceeded the predefined stopping rules. More recently, Eastern Cooperative Oncology Group investigators reported the first result of a relatively large prospective single-arm study of surgery with negative margins of at least 3 mm without radiation therapy for patients with favorable subsets of DCIS.[27] Patients with low-grade or intermediate-grade DCIS measuring 2.5 cm or smaller had a 5-year rate of ipsilateral breast recurrence of only 6.1%. In contrast, patients with high-grade disease had a much higher 5-year ipsilateral breast recurrence rate of 15.3%.

Taken together, the data from these trials of treatment for DCIS suggest that WBI after lumpectomy should be recommended for most patients with DCIS. The one subgroup that appears to have favorable outcomes without radiation are patients with small-grade, low-grade or intermediate-grade lesions.

Role of Tamoxifen and Aromatase Inhibitors

The use of tamoxifen has been shown to reduce the risk for development of new breast cancers in high-risk women, including women with a previous breast cancer (see "Chemoprevention for Breast Cancer" earlier). The NSABP B-24 protocol evaluated the benefit of tamoxifen for patients with DCIS. In this trial, 1804 women who had undergone lumpectomy and radiation therapy for DCIS were randomly assigned to 5 years of tamoxifen or placebo. Study criteria allowed enrollment of patients with positive margins, and ER was not measured. At 7 years of follow-up, the addition of tamoxifen to lumpectomy and radiation therapy decreased the incidence of recurrent ipsilateral breast cancers from 9% to 6% and reduced the risk for a new contralateral breast cancer by 47% (an absolute reduction of 2%) (see Table 35.7).

For the NSABP B-17 and NSABP B-24 trials combined, at 7 years of follow-up, the total (ipsilateral plus contralateral) breast cancer recurrence rate was 30% for excision alone; 17% for excision with radiation therapy; and 10% for excision, irradiation, and tamoxifen. Subsequent analyses demonstrated that the benefit from tamoxifen is seen only in women with ER-positive DCIS. Patients at highest risk for local recurrence—and most likely to benefit from tamoxifen—were patients with positive margins, comedonecrosis, a mass on physical examination, and age younger than 50 years. For individual patients, the benefits of tamoxifen are weighed against its side effects, including risk for endometrial carcinoma, thromboembolic events, hot flashes, and cataracts.

IBIS-II enrolled 2980 postmenopausal women in a randomized trial comparing tamoxifen versus arimidex. There were no differences between the groups in recurrence rates or side effects.[28]

Sentinel Node Surgery

DCIS, by definition, represents breast cancer contained within an intact basement membrane and without access to lymphatic or vascular channels. However, when ALND was performed during mastectomy for DCIS, positive nodes were found in 3.6% of cases, as indicated by a review of more than 10,000 patients in the National Cancer Data Base. These positive nodes probably result from microinvasive disease in the primary tumor that was not detected on routine pathologic analysis.

Sentinel node surgery is currently recommended in patients undergoing mastectomy for DCIS because 20% to 30% of patients with DCIS on a diagnostic CNB are found to have invasive cancer on detailed evaluation of the mastectomy specimen. The addition of sentinel node surgery to mastectomy adds minimal

morbidity and avoids the need for ALND if invasive cancer is identified (sentinel node mapping is not possible after mastectomy). For patients undergoing breast-conserving surgery for DCIS, sentinel node surgery may be considered for patients with larger areas of DCIS, particularly patients with high-grade histology or with high suspicion of microinvasion.

RADIATION THERAPY FOR BREAST CANCER

Radiation Therapy after Breast-Conserving Surgery

For patients with invasive breast cancer treated with breast-conserving surgery, adjuvant irradiation of the breast has been conclusively demonstrated to reduce the probability of a breast recurrence and improve outcome. The EBCTCG published a meta analysis of the data from 7300 women who participated in randomized trials of breast-conserving surgery with or without WBI therapy. In this analysis, radiation was found to reduce the 10-year rate of in-breast recurrence from 29% to 10% for patients with negative lymph nodes and from 47% to 13% for patients with positive lymph nodes. This improvement in local control led to a reduction in the 15-year breast cancer mortality rate and overall death rate. On the basis of these data, radiation therapy after breast-conserving surgery should be considered as a standard. Most trials attempting to define subgroups of patients who could potentially avoid radiation after lumpectomy have been unsuccessful. The only group identified that might have been able to avoid irradiation safely is patients older than 70 years who undergo lumpectomy and adjuvant hormonal therapy for a stage I ER-positive breast cancer. However, at 10 years, 98% of patients receiving tamoxifen and radiation compared with 90% of those receiving tamoxifen alone were free from local and regional recurrences.[29]

Historically, radiation therapy after lumpectomy has consisted of a 6- to 8-week treatment course, which can be a hardship for patients. An important Canadian trial successfully compared this historical schedule with a more abbreviated WBI schedule. On the basis of long-term outcome results from this study, it is reasonable to treat a postmenopausal patient with a non–high-grade, ER-positive, stage I breast cancer with a 16-fraction course of treatment, which shortens the overall treatment time to approximately 3 weeks.

There has also been significant interest in shortening the treatment course to 1 week or less through an approach that focuses the radiation exclusively on the area around the tumor bed. This approach, called *partial breast irradiation*, may be performed with brachytherapy catheters, balloon catheters, or external-beam radiation.

The NRG (NSABP B-39/RTOG 0413) trial randomly assigned 4216 women who had recently undergone lumpectomy to receive either WBI or accelerated PBI. Women enrolled in the study had zero to three positive axillary nodes on study entry. Twenty-five percent of the group had DCIS, 65% had stage I breast cancer, and 10% had stage II disease. The majority of women also had hormone receptor–positive tumors. Women who were assigned to the WBI arm following adjuvant chemotherapy received daily treatment with 2.0 Gy/fraction of radiation totaling 50 Gy with a sequential boost to the surgical site.

Those assigned to accelerated PBI prior to adjuvant chemotherapy received a total of 10 treatments given twice-daily treatment with 3.4 to 3.85 Gy given as either brachytherapy or 3D external-beam radiation. The 10-year cumulative incidence of ipsilateral breast tumor recurrence was very low in both groups, at 4.6% for patients in the accelerated PBI arm versus 3.9% for those in the WBI arm but did not meet equivalence. There were no differences in distant disease-free interval, OS, or DFS.

The American Society for Radiation Oncology published a consensus statement highlighting appropriate selection criteria that should be considered if patients are to be treated with PBI outside the context of a clinical trial (Table 35.8).[30]

Postmastectomy Radiation Therapy

For patients with T1N0 or T2N0 breast cancer, mastectomy and SLND provide effective local control, and radiation therapy is not required. In contrast, patients with stage III breast cancer have high rates of locoregional recurrence after treatment with a modified radical mastectomy and adjuvant or neoadjuvant chemotherapy. Clinical trial data indicate that postmastectomy radiation therapy can significantly improve the outcome of patients who would be expected to have a 20% to 40% risk of locoregional recurrence without radiation therapy.

Three prospective randomized trials addressed the role of postmastectomy irradiation. In the Danish Trials, premenopausal women with stage II or III breast cancer were randomly assigned to chemotherapy alone or chemotherapy plus chest wall and nodal irradiation (protocol 82b); postmenopausal women were randomly assigned to tamoxifen alone or tamoxifen plus radiation therapy (protocol 82c). In the British Columbia study, premenopausal women with node-positive breast cancer were randomly assigned to chemotherapy alone or chemotherapy plus chest wall and nodal irradiation.[31] In addition to reducing locoregional recurrences, as expected, postmastectomy irradiation significantly improved OS in all three trials (Table 35.9).

In 2005, the EBCTCG published the results of a meta analysis of trials of postmastectomy radiation therapy, which included data from 9933 patients treated with mastectomy or axillary clearance with or without postmastectomy radiation. Postmastectomy radiation therapy decreased the 15-year isolated locoregional recurrence rate for patients with lymph node–positive disease from 29% to 8% and reduced the 15-year breast cancer mortality rate from 60% to 55%. The most recent analysis from this group suggested that benefits of postmastectomy radiation therapy are similar for patients with one to three positive lymph nodes and patients with four or more positive lymph nodes.[32]

There is consensus that patients with four or more positive lymph nodes or other features characteristic of stage III disease should be counseled to undergo radiation therapy. However, the use of postmastectomy radiation therapy for patients with stage II disease is controversial because many U.S. series indicated that locoregional recurrence rates after a standard modified radical mastectomy and adjuvant chemotherapy are only 12% to 15%, much lower than rates reported in the clinical trials of postmastectomy irradiation and the EBCTCG meta analysis. On the basis of this disparity, it is reasonable to consider postmastectomy radiation therapy only for selected patients with stage II disease, such as patients with extracapsular extension, lymphovascular invasion, age 40 years or younger, close/positive surgical margins, or a nodal positivity ratio (ratio of positive nodes to total nodes examined) of 20% or greater and patients who have undergone less than a standard level I or II axillary dissection.

SYSTEMIC THERAPY FOR BREAST CANCER

Despite advances in locoregional therapy, a significant proportion of women with breast cancer develop metastatic disease within 5 to 10 years after diagnosis. Most patients who develop metastatic

TABLE 35.8 American Society for Radiation Oncology guidelines for accelerated partial breast irradiation.

FACTOR	"SUITABLE" GROUP	"CAUTIONARY" GROUP	"UNSUITABLE" GROUP
Patient Factors			
Age (years)	≥60	50–59	<50
Tumor Factors			
Tumor size (cm)	≤2	2.1–3.0	>3
T stage	T1	T0 or T2	T3 or T4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Histology	Invasive ductal carcinoma or other favorable subtypes	Invasive lobular carcinoma	NA
Pure DCIS	Not allowed	≤3 cm	>3 cm
Grade	Any	NA	NA
LVI	None	Limited/focal	Extensive
ER status	Positive	Negative	NA
Multicentricity	Unicentric	NA	If present
Multifocality	Clinically unifocal with total size ≤2 cm	Clinically unifocal with total size 2.1–3 cm	Clinically multifocal or microscopically multifocal >3 cm
Nodal factors			
N stage	pN0	NA	pN1-3
Treatment factors			
Neoadjuvant chemotherapy	Not allowed	NA	If used

Adapted from Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J Am Coll Surg*. 2009;209:269.
DCIS, Ductal carcinoma in situ; *ER*, estrogen receptor; *LVI*, lymphovascular invasion; *NA*, not available.

TABLE 35.9 Trials of systemic therapy with or without irradiation after mastectomy.

	NO. PATIENTS			LOCAL RECURRENCE RATE (%)			OS (%)		
TRIAL	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	TOTAL	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	*P* VALUE	SYSTEMIC THERAPY + XRT	SYSTEMIC THERAPY ALONE	*P* VALUE
DBCG 82b (10 years; chemo)[a]	852	856	1708	9	32	<0.001	54	45	<0.001
DBCG 82c (10 years; tamoxifen)[b]	686	689	1375	8	35	<0.001	45	38	0.03
DBCG 82c (combined 18 years)[b]	1538	1545	3083	14	49	<0.001	37	27	
British Columbia Trial (20 years)[c]	164	154	318	13	25	0.003*	64	54	0.003*

chemo, Chemotherapy; *DBCG*, Danish Breast Cancer Group; *OS*, overall survival; *XRT*, radiation therapy.
*Aggregate *P* value for comparisons at various follow-up intervals; this is the 10-year result.
[a]Overgaard M, Hansen Per S, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med*. 1997;337:949.
[b]Overgaard M, Jensen M-B, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. *Lancet*. 1999;353:1641.
[c]Ragaz J, Jackson S, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med*. 1997;337:956.

breast cancer die of their disease. Metastatic disease is the principal cause of death from breast cancer.

Systemic therapy is used to treat and prevent recurrence of microscopic metastatic breast cancer. For women with stage IV breast cancer, systemic therapy is given to palliate symptoms from cancer and potentially prolong survival. Current thinking is that metastasis occurs early in the progression of breast cancer, probably before initial clinical evaluation in most patients. This concept argues for

administration of systemic therapy for breast cancer in concert with local treatment. What is missing at the present time is the ability to detect occult metastatic disease accurately and select appropriate patients to receive systemic treatment.

The first prospective trials of systemic therapy for breast cancer combined oophorectomy, to deprive patients of estrogens, with radical mastectomy. Since these early trials, hundreds of prospective studies of systemic therapy have been conducted involving thousands of women. Medications used to treat early breast cancer have their foundation as treatment for advanced disease. In general, treatments that are used effectively to improve outcome for patients with incurable breast cancer are estimated to have an increased impact on outcomes for patients with earlier stages of breast cancer, who have smaller volumes of disease and potentially less resistance to therapy. When medications are identified that improve outcomes for patients with incurable stage IV breast cancer, they are often brought forward into clinical studies for earlier stages of disease.

Goals of Therapy and Assessment of Potential Benefits and Risks from Therapy

For patients with stage I to III invasive breast cancer, the goal of treatment is cure. In selecting treatment, the potential benefits of therapy (reduction in the risk of recurrence) are considered together with the potential harms of treatment. Patient preferences, particularly preferences regarding adjuvant therapy, are carefully considered. Some patients believe that the reduction in risk of recurrence with adjuvant therapy is not worth the adverse effects of the therapy, particularly in the case of chemotherapy. Often, several long discussions with the patient are essential to determine the treatment that best suits that patient.

The risk of systemic recurrence increases with increasing stage of disease. The biologic characteristics of an individual tumor also influence the risk of systemic recurrence. The most commonly used breast cancer biomarkers—ER, PR, and HER-2—not only affect prognosis but also predict response to different systemic therapies. In general terms, tumors that have no ER or PR expression and tumors with high levels of HER-2 are associated with worse cancer outcomes than tumors that are strongly positive for ER and PR and have negative or normal levels of HER-2. For most patients, risk of recurrence is estimated on the basis of population-based statistics. Current federal and international guidelines use stage and biologic characteristics in the development of treatment recommendations to guide decisions regarding systemic therapy for breast cancer (Table 35.10).

Multigene assays, such as the 21-gene recurrence score assay (Oncotype DX Breast Cancer Assay, Genomic Health, Inc., Redwood City, CA), have been developed in an attempt to identify a specific molecular phenotype of a tumor in an individual patient and use the phenotype to predict the response to therapy or provide information regarding prognosis. The Oncotype DX assay was developed from a candidate pool of 250 genes and narrowed to a specific 21-gene panel on the basis of three independent studies of the candidate genes. This assay was validated first in patients with ER-positive, lymph node–negative breast cancer (NSABP B-14). The Oncotype DX assay was found to be prognostic for OS and predictive of the benefits of different systemic therapies, with higher recurrence scores predicting increased benefit from chemotherapy and lower scores predicting lesser benefit from chemotherapy and increased benefit from endocrine therapy. This assay was validated in subsequent studies. The Oncotype DX assay can help clinicians estimate the benefits of therapy for patients with lymph node–negative, ER-positive breast cancer. For patients with low recurrence scores, chemotherapy appears to have marginal benefit in terms of reducing the risk of distant recurrence, but for patients with high recurrence scores, chemotherapy offers marked benefit. A cooperative group trial, TAILORx, was conducted to determine the benefit from chemotherapy in patients with intermediate recurrence scores. This trial was recently reported involving 9719 women with hormone receptor–positive, HER-2–negative, axillary node–negative breast cancer.[33] Patients with a recurrence scores less than 11 received endocrine therapy. Patients with a recurrence scores greater than 25 received chemotherapy. There were 6711 patients who had midrange recurrence scores of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive DFS, invasive disease recurrence, second primary cancer, and OS at 9-year follow-up. Some benefit of chemotherapy was found in women 50 years of age or younger with a recurrence score of 16 to 25. Therefore, chemotherapy is not recommended for patients with hormonal receptor–positive, HER-2–negative and node-negative disease and recurrence scores of less than 25 for women over 50 years of age or recurrence scores of less than 16. This represents a majority of the patients presenting for breast cancer treatment today.

Chemotherapy

The main classes of chemotherapeutics used to treat early-stage breast cancer include anthracyclines (e.g., doxorubicin, epirubicin) and taxanes (e.g., paclitaxel, docetaxel). The anthracyclines, which act as topoisomerase II inhibitors and antimetabolites, have high levels of activity in the treatment of breast cancer. When anthracyclines are delivered as single agents for the treatment of metastatic breast cancer, responses to therapy are generally seen in 45% to 80% of patients. The 2005 EBCTCG analysis[32] noted that compared with nonanthracycline, CMF (cyclophosphamide, methotrexate, 5-fluorouracil)-type therapies, anthracyclines are associated with a 16% reduction in the risk of death and an 11% reduction in the risk of recurrence. Anthracyclines are associated with the potential long-term toxic effect of cardiomyopathy, which may lead to congestive heart failure, often many years after treatment. The risk of cardiac dysfunction resulting from anthracyclines is dose dependent, and current anthracycline-containing chemotherapy regimens are associated with a risk of cardiac dysfunction of 1.5% to 3%. An additional dangerous risk of anthracycline-based chemotherapy is the risk of development of leukemia (<1%).

Taxanes (microtubule inhibitors) have significant activity in the treatment of metastatic breast cancer and are active not only in tumors previously unexposed to chemotherapy but also in anthracycline-resistant tumors. Numerous clinical trials have evaluated the use of taxanes for treatment of early-stage breast cancer. A meta analysis of the use of taxanes in 13 different studies from the Intergroup Trial C9741/Cancer and Leukemia Group B (CALGB) trial 9741 found improvement in DFS (HR, 0.83; 95% CI, 0.79–0.87; $P < 0.0001$) and OS (HR, 0.85; 95% CI, 0.79–0.91; $P < 0.0001$). The antitumor activity of paclitaxel depends on the timing of treatment: More frequent administration of paclitaxel improves outcomes. The activity of docetaxel depends less on the timing of treatment, and docetaxel is generally administered on an every-3-week schedule. The two taxanes, when given at their optimal dose and schedule, produce equivalent outcomes. The taxanes are associated with the potential permanent toxic effect of peripheral neuropathy but do not cause long-term increased risk of cardiac dysfunction or second cancers.

TABLE 35.10 Decision-making for systemic therapy.

STAGE	SYSTEMIC THERAPY	COMMENTS
I (<1 cm)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Consider chemotherapy	
HER-2–positive	Strongly consider trastuzumab and chemotherapy	
I (>1 cm)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Chemotherapy	
HER-2–positive	Trastuzumab and chemotherapy	
II (Lymph Node–Negative)		
Hormone receptor–positive	Endocrine therapy ± chemotherapy	Consider genomic testing
Hormone receptor–negative	Chemotherapy	
HER-2–positive	Trastuzumab and chemotherapy	
II (Lymph Node–Positive), III		
Hormone receptor–positive	Chemotherapy + endocrine therapy	Endocrine therapy should be recommended for all patients
Hormone receptor–negative	Chemotherapy	Decision-making for chemotherapy may be influenced by results from ongoing clinical trials
HER-2–positive	Trastuzumab and chemotherapy	Consider neoadjuvant chemotherapy with dual HER-2–targeted therapy

HER-2, Human epidermal growth factor receptor 2.

Chemotherapy is generally administered with combinations of medications in an effort to take advantage of nonoverlapping toxic effects and to maximize different mechanisms of action in targeting tumor cells. The largest comprehensive analysis to date of the benefits of polychemotherapy for breast cancer is the EBCTCG analysis published in 2012. This analysis summarized data from randomized trials that were initiated between 1973 and 2003. The authors presented individual patient data from trials comparing a taxane-plus-anthracycline–based regimen versus a nontaxane-containing regimen with the same or higher cumulative doses of each nontaxane component (n = 44,000), trials comparing one anthracycline-based regimen versus another (n = 7000) or versus CMF (n = 18,000), and trials comparing polychemotherapy versus no chemotherapy (n = 32,000). On the basis of the drug dosages and the anthracycline used (either doxorubicin [Adriamycin; A] or epirubicin [E]), regimens were defined as including standard CMF, standard Adriamycin/Cytoxin (AC), Cytoxin/Adriamycin/fluorouracil (CAF), or Cytoxin/epirubicin/fluorouracil (CEF). A meta analysis showed that compared with no chemotherapy, use of CMF or standard AC reduced the recurrence rate by one-third at 8 years and produced a 20% to 25% reduction in breast cancer mortality. The addition of more chemotherapy (i.e., CAF or CEF compared with CMF or AC) resulted in an additional proportional reduction of 15% to 20% in breast cancer mortality. On average, the taxane-plus-anthracycline–based control regimens were superior to standard AC but were not superior to anthracycline regimens with extra cycles (i.e., CAF or CEF). In analyses comparing taxane-based and anthracycline-based regimens, the proportional risk reductions were not significantly affected by age, tumor size, nodal status, tumor grade, or ER status. Taken together, these data suggest that independent of age or tumor characteristics, a chemotherapy regimen that include a taxane or anthracycline regimens with higher cumulative dosages reduced breast cancer mortality by approximately one third.

HER-2–Based Targeted Therapy

HER-2 gene amplification or protein overexpression occurs in approximately 20% to 25% of breast cancers. Amplification leads to protein overexpression, measured clinically by immunohistochemistry and scored on a scale from 0 to 3+. Alternatively, fluorescence in situ hybridization directly detects the quantity of HER-2 gene copies; the normal copy number is two (see "Molecular Markers and Breast Cancer Subtypes" earlier).

Trastuzumab is a humanized monoclonal antibody developed to target the extracellular domain of the HER-2 receptor. When trastuzumab is used as a single agent for treatment of metastatic breast cancer, response is seen in approximately 30% of patients. Trastuzumab combined with chemotherapy is even more effective, with synergy seen with multiple agents. Trastuzumab-based chemotherapy regimens improve DFS and OS for patients with metastatic disease. Given the promising activity of trastuzumab against metastatic disease, numerous trials of trastuzumab for adjuvant and neoadjuvant therapy have been conducted; these trials demonstrated improved outcomes for patients with stage I to III breast cancer. The HERA (HERceptin Adjuvant) trial (N = 5090) enrolled patients with HER-2–positive breast cancer and randomly assigned them to trastuzumab treatment (for 1 or 2 years) versus observation after completion of chemotherapy. In a comparison of 1-year of trastuzumab treatment versus observation, trastuzumab reduced the risk of a breast cancer–related event by 46% (HR, 0.54; 95% CI, 0.43–0.67; $P < 0.001$) and improved OS by 34% (HR, 0.66; 95% CI, 0.47–0.91; $P < 0.0115$). Treatment with trastuzumab for 2 years was not more effective than 1 year of treatment and 6 months was inferior, which established 1 year of treatment as standard of care.

Long-term follow-up of the NSABP B-31 and NCCTG-N9831 adjuvant trials, which were similar in study design, demonstrate that the initial benefit seen with adjuvant trastuzumab

persist with an improvement in 10-year OS from 75.2% to 84%.[34] Patients receiving trastuzumab-based therapy in NSABP B-31 (AC followed by paclitaxel-trastuzumab) had an increased risk of cardiac dysfunction, with a 3-year event rate of 4.1% versus 0.8% in the control arm.[34] Patients with lower ejection fraction at the initiation of therapy, older age, or hypertension were at highest risk of cardiac dysfunction.

The BCIRG 006 trial used a nonanthracycline-containing regimen as one of its treatment groups and showed equivalence in outcome between AC followed by docetaxel-trastuzumab (AC-TH) and docetaxel combined with carboplatin and trastuzumab (TCH).[35] Both trastuzumab-containing treatments were superior in terms of DFS to the control treatment of AC followed by docetaxel, with HR of 0.61 (95% CI, 0.48–0.76; $P < 0.001$) for the AC-TH group and HR of 0.67 for the TCH group (95% CI, 0.54–0.83). Rates of cardiac toxic effects were markedly lower in the TCH group (0.37%) than in the AC-TH group (1.87%).

Additional drugs targeting HER-2 in combination with trastuzumab are being evaluated, including the tyrosine kinase inhibitor lapatinib; the trastuzumab drug conjugate trastuzumab emtansine; neratinib and pertuzumab, a monoclonal antibody that inhibits dimerization of HER-2 with other HER-2 receptors. The combination of trastuzumab and pertuzumab is approved in all disease settings, while trastuzumab/neratinib is approved in the adjuvant setting and trastuzumab/lapatinib in metastatic disease. Trials are ongoing with further combinations with PI3/AKT/mTOR inhibitors, CDK4/6 inhibitors, anti-PD(L)1 antibodies, endocrine therapy, and new anti-HER-2 agents.[36]

Endocrine Therapy

One of the original targeted therapy approaches was the use of oophorectomy to reduce systemic estrogen production as a treatment for breast cancer. Most breast cancers (>60%) express ER or PR or both; interruption of the production of estrogen or the ability of estrogen to interact with the ER has been associated with improved DFS and OS for women with metastatic breast cancer. This therapeutic approach is associated with a generally favorable adverse effect profile compared with the adverse effects of chemotherapy.

Tamoxifen

Tamoxifen is a selective ER modulator that has antagonistic and weak agonistic effects. It is generally well tolerated; the most common side effect is hot flashes or vasomotor symptoms, which occur in less than 50% of patients. Potentially serious but rare effects include increased risk of thromboembolic disease and uterine cancer.

Clinical trials of tamoxifen as treatment for early-stage breast cancer began in the 1970s. In 2005, the EBCTCG meta analysis reported data of more than 80,000 women treated in clinical studies.[32] Tamoxifen administered for 5 years was found to reduce the risk of recurrence of breast cancer for patients with hormone receptor–positive disease by 41% (recurrence rate ratio, 0.59; SE, 0.03). The risk of death from breast cancer was reduced by approximately one third (death rate ratio, 0.66; SE, 0.04). Tamoxifen was shown to be beneficial for premenopausal and postmenopausal women and had a similar magnitude of benefit for patients with lymph node–positive and lymph node–negative disease. The duration of therapy with tamoxifen was also evaluated; 5 years of therapy was found to be superior to only 1 to 2 years of therapy in terms of breast cancer recurrence (15.2% proportionate reduction; $P < 0.001$) and death from breast cancer (7.9% proportionate reduction; $P = 0.01$).

Tamoxifen therapy for more than 5 years has been investigated, and results from the two largest studies with the longest follow-up were recently reported. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial showed an approximately 25% reduction in the rate of recurrence and approximately 3% reduction in mortality risk in women taking 10 years of tamoxifen versus 5 years, with the benefit being most pronounced after year 10.[37] These findings were confirmed in the Adjuvant Tamoxifen–to Offer MDore? (aTTom) trial, in which patients were also randomly assigned to 5 years versus 10 years of tamoxifen. There was a decrease in breast cancer recurrence rates and breast cancer mortality rates in patients treated for a longer duration. In light of these findings, the American Society of Clinical Oncology (ASCO) updated their guidelines regarding adjuvant endocrine therapy. For premenopausal or perimenopausal women, tamoxifen for 5 years is recommended. After 5 years, if the patient is still premenopausal, she should be offered an additional 5 years of tamoxifen therapy.[38]

Aromatase Inhibitors

AIs block the conversion of the hormone androstenedione into estrone by inhibition of the aromatase enzyme. This enzyme is present in adipose tissue, breast tissue, breast tumor cells, and other sites. Multiple generations of medications that block the aromatase enzyme have been evaluated, less specific agents such as aminoglutethimide also suppress production of other hormones, and this is associated with unacceptable side effects. Selective or third-generation AIs purely block the final step of conversion of hormones into estrogen and are not associated with the broad hormone suppression seen with earlier AIs. Selective AIs, which include anastrozole, exemestane, and letrozole, are unable to suppress ovarian function completely in a premenopausal or perimenopausal woman and are restricted for use in postmenopausal women. Selective AIs as a group have similar adverse effects, including hot flashes, vasomotor symptoms, joint symptoms, myalgias, bone loss, and vaginal dryness.

Several different trial designs have been used to evaluate AIs as adjuvant therapy. Direct comparisons of 5 years of a selective AI versus 5 years of tamoxifen demonstrated improvement in cancer outcomes for anastrozole and letrozole.[39] The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial demonstrated that 5 years of anastrozole significantly improved DFS by 17% compared with 5 years of tamoxifen (HR, 0.83; 95% CI, 0.73–94; $P = 0.05$). In addition to reducing the risk of distant recurrence (distant DFS HR, 0.86; 95% CI, 0.74–0.99; $P = 0.04$), anastrozole reduced the risk of development of contralateral breast cancers by 42%.[39]

Administration of selective AIs for 2 to 3 years after tamoxifen for 2 to 3 years has been compared with 5 years of tamoxifen treatment.[40] The use of all three modern AIs after 2 to 3 years of tamoxifen was associated with better cancer outcomes than the use of tamoxifen alone. In addition, extended adjuvant therapy with 5 years of the AI letrozole after 5 years of tamoxifen was shown to improve outcome compared with placebo after 5 years of tamoxifen. The use of letrozole versus placebo reduced the risk of breast cancer events by 43% ($P < 0.008$). In the most recent ASCO guidelines, if women are pre- or perimenopausal and have received 5 years of adjuvant tamoxifen, they should be offered 10-years total duration of tamoxifen. If women are postmenopausal and have received 5 years of adjuvant tamoxifen, they should be offered the choice of continuing tamoxifen or switching to an AI for 10-years total adjuvant endocrine therapy.[41]

Ovarian Ablation

The EBCTCG meta analysis evaluated premenopausal women who were treated with ovarian ablation or suppression and found that this treatment reduced the risk of relapse and death from breast cancer.[32] Compared with the use of CMF chemotherapy, the use of ovarian ablation with goserelin as treatment for lymph node–positive, stage II breast cancer in premenopausal women resulted in equivalent outcomes in terms of DFS (HR, 1.01; P = 0.94) and OS (HR, 0.99; P = 0.94). Even with this high level of activity, the optimal role for addition of ovarian ablation is unknown.

Results were reported from two phase III trials that evaluated use of an AI with ovarian suppression in premenopausal patients with hormone receptor–positive early breast cancer. These trials were Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT).[42] TEXT was designed to evaluate 5 years of the AI exemestane plus ovarian suppression with a gonadotropin-releasing hormone agonist versus tamoxifen plus the gonadotropin-releasing hormone agonist. SOFT was designed to evaluate 5 years of the AI exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression versus tamoxifen alone. The initial combined analysis looked at AI plus ovarian suppression versus tamoxifen plus ovarian suppression; the tamoxifen-alone arm from SOFT was not included. After a median follow-up of 68 months, the addition of ovarian suppression to hormone suppression did not show an overall clinical benefit but did show a benefit in those with the highest risk disease. Therefore, the consensus guidelines state that if the patient has high-risk disease, then ovarian suppression should be considered in addition to hormonal suppression.[43]

Neoadjuvant Systemic Therapy for Operable Breast Cancer

Chemotherapy is most commonly administered as adjuvant therapy after completion of surgery. Neoadjuvant therapy, the administration of systemic chemotherapy or endocrine therapy before surgery, can result in a significant reduction in tumor size and convert inoperable tumors to operable ones, make tumors that would require mastectomy amenable to lumpectomy, and shrink larger tumors to allow an improved cosmetic outcome with breast-conserving surgery.

Several prospective randomized trials evaluated the efficacy of chemotherapy and endocrine therapy administered as neoadjuvant (before surgery) versus adjuvant (after surgery) therapy. These studies all demonstrated increased rates of breast conservation with the use of neoadjuvant systemic therapy. The NSABP B-18 trial included 1523 patients and found no survival advantage (or detriment) in patients who received preoperative doxorubicin and cyclophosphamide chemotherapy versus the same regimen delivered postoperatively. The breast conservation rate was higher in women completing neoadjuvant chemotherapy, and the rate of in-breast recurrence in women who underwent neoadjuvant therapy followed by lumpectomy was not significantly different from the rate of in-breast recurrence in women who underwent lumpectomy before adjuvant chemotherapy.

Delivering chemotherapy before surgery has other theoretical advantages, including the potential to lower the volume of microscopic metastatic disease, decrease drug resistance by treating tumors before resistance has developed, increase the efficacy of treatment because the vascular system has not been disrupted by surgery, and permit evaluation of the response to treatment in vivo. In theory, the ability to evaluate response to therapy in vivo may help avoid administration of ineffective therapy and allow the clinician to tailor therapy to the individual patient. In addition, it has been shown that response to neoadjuvant chemotherapy correlates with survival outcomes. In the NSABP B-18 trial, after 9 years of follow-up, the DFS rate in patients achieving a complete pathologic response in the neoadjuvant therapy arm (no evidence of tumor at surgery) was 75% compared with 58% in patients who had any residual invasive disease after chemotherapy. A meta-analysis of 12 randomized trials evaluating neoadjuvant chemotherapy found that 18% of patients had a pathologic complete response, defined as no residual invasive disease in the breast or axilla, and 13% had a pathologic complete response defined as no residual invasive or in situ disease. A pathologic complete response by either definition was associated with improved event-free survival and OS.[44] The association between pathologic complete response and long-term outcomes was strongest in patients with aggressive tumor subtypes, including patients with triple-negative breast cancer and patients with HER-2–positive, hormone receptor–negative breast cancer who received trastuzumab as part of their neoadjuvant regimen.

There are several surgical considerations for patients receiving neoadjuvant chemotherapy. By the end of systemic therapy, a percentage of patients has complete resolution of their tumors by clinical examination and imaging but might have microscopic residual disease. This percentage ranges from 10% to 15% in patients with hormone receptor–positive tumors to approximately 50% in patients with HER-2–positive tumors receiving trastuzumab in combination with chemotherapy as neoadjuvant therapy. Consequently, a metallic clip is placed at the primary tumor site under image guidance before neoadjuvant chemotherapy is initiated to allow identification of the original tumor site for excision after therapy.

Management of the axilla in patients undergoing neoadjuvant therapy has evolved. The timing of SLND has been debated, with some centers performing SLND before neoadjuvant therapy in patients with clinically negative nodes to inform decisions about systemic and radiation therapy. Advocates of SLND before neoadjuvant chemotherapy cite concerns about lower successful mapping rates and higher false-negative rates after neoadjuvant therapy. Other centers favor SLND after neoadjuvant therapy for any patient whose axilla is clinically negative after therapy to obtain more information about the status of the nodes after neoadjuvant therapy. Two meta analyses of single-institution and multicenter studies were conducted and concluded that SLND is feasible and accurate after neoadjuvant chemotherapy, resulting in sentinel node identification rates of approximately 91%.[45] Both of these meta analyses included patients with clinically node-negative and node-positive disease. In one, the authors evaluated studies that included only patients with clinically node-negative disease and found a pooled sentinel node identification rate of 93%. These two meta analyses also examined the accuracy of SLND in patients receiving neoadjuvant chemotherapy and reported false-negative rates of 10.5% to 12%.

In addition, neoadjuvant chemotherapy eradicates microscopic disease in the regional nodes in 40% of patients, reducing the need for complete ALND at the time of surgical intervention. Complete ALND remains the standard for all patients receiving neoadjuvant therapy who have biopsy-proven, node-positive disease at initial presentation; however, there is significant interest in identifying patients in whom SLND might be appropriate after neoadjuvant chemotherapy. The ACOSOG reported the results of the Z1071 trial, a phase II study in which patients with clinically

node-positive disease (clinical N1 disease) receiving neoadjuvant chemotherapy underwent SLND followed by planned completion ALND. This study allowed for determination of the false-negative rate for SLND, which was 12.6%—higher than the prespecified end point of 10%.[46] The false-negative rate was lower when dual tracers were used for mapping (false-negative rate, 10.8%) and when three or more sentinel nodes were identified (false-negative rate, 9.1%). These data are consistent with two other trials that evaluated SLND in patients with clinically node-positive disease, the Sentinel Neoadjuvant (SENTINA) trial and the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) trial (in biopsy-proven, node-positive breast cancer). The results of these studies suggest that surgical technique is critical in reducing the false-negative rate for SLND in patients with clinically node-positive disease receiving neoadjuvant chemotherapy. If a clip is left in the positive axillary node prior to chemotherapy and that clip and the SLN are retrieved at the time of axillary surgery (targeted axillary dissection), then the false-negative rate was lowered in a single institution trial to 1.4%.[47] Trials are ongoing to determine if, in the neoadjuvant setting, it is safe to omit ALND if the sentinel lymph node is negative.

Some key concepts have been gleaned from the results of neoadjuvant therapy trials. The use of neoadjuvant chemotherapy as a research platform has led to the identification of patient and tumor characteristics that can predict response to therapy. This information allows clinicians to define better the population of patients who are most likely to benefit from neoadjuvant chemotherapy. Targeted therapies, such as trastuzumab, can be safely administered in combination with chemotherapy for neoadjuvant treatment in patients with HER-2–positive breast cancer, resulting in markedly increased rates of pathologic complete response. More recently, studies showed the benefit of dual HER-2 targeting. In the NeoSphere trial, patients with operable, HER-2–positive breast cancer were randomly assigned to one of four neoadjuvant regimens: (1) trastuzumab plus docetaxel, (2) pertuzumab and trastuzumab plus docetaxel, (3) pertuzumab and trastuzumab, or (4) pertuzumab plus docetaxel.[48] The study included 417 patients, and the primary end point was pathologic complete response, which was seen in 46% of patients in the pertuzumab and trastuzumab plus docetaxel arm versus 29% of patients in the trastuzumab plus docetaxel arm. On the basis of these results, the Food and Drug Administration granted pertuzumab accelerated approval as the first drug approved for the neoadjuvant treatment of breast cancer. A pathologic complete response was shown in 17% of patients in the trastuzumab plus pertuzumab arm, suggesting that some patients with HER-2–positive breast cancer could be treated with targeted therapy alone without chemotherapy.

In the context of targeted therapy, patients with ER-positive disease can be treated with endocrine therapy as neoadjuvant therapy, and this approach produces significant response rates and increased rates of breast-conserving surgery. This approach is optimal in postmenopausal women with ER-positive tumors for whom endocrine therapy provides more protection than standard chemotherapy against risk of recurrence and death caused by breast cancer. Finally, because new and more targeted regimens have led to an increasing population of patients with a clinical complete response to neoadjuvant therapy, accurately assessing the residual tumor burden in the breast and regional nodes will become increasingly important in terms of defining prognosis and determining what further therapy is needed. Neoadjuvant chemotherapy has potential disadvantages in terms of loss of prechemotherapy prognostic information (e.g., axillary lymph node status, actual invasive tumor size), which may have an impact on decision-making with respect to postmastectomy radiation therapy.

TREATMENT OF LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER

Patients with locally advanced breast cancer include patients with large primary tumors (>5 cm), tumors involving the chest wall, skin involvement, ulceration or satellite skin nodules, inflammatory carcinoma, bulky or fixed axillary nodes, and clinically apparent internal mammary or supraclavicular nodal involvement (stages IIB, IIIA, and IIIB disease). Central to treatment is the concept that the disease is advanced on the chest wall, in regional lymph nodes, or both with no evidence of metastasis to distant sites. These patients are recognized to be at significant risk for the development of subsequent metastases, and treatment must address the risk for local and systemic relapse. Experience before the 1970s demonstrated that surgery alone provided poor local control, with local relapse rates of 30% to 50% and mortality rates of 70%. Similar results were reported when radiation therapy was the sole modality of treatment. Current management includes surgery, radiation therapy, and systemic therapy, with the sequence and extent of treatment determined by specifics of the patient's circumstance.

Although inflammatory breast cancer is rare, accounting for approximately 1% to 5% of all breast tumors, it is the most aggressive subtype of breast cancer. The hallmark of inflammatory breast cancer is diffuse tumor involvement of the dermal lymphatic channels within the breast and overlying skin, often without a discrete underlying tumor mass. Inflammatory breast cancer manifests clinically as erythema, edema, and warmth of the breast as a result of lymphatic obstruction. There may be no abnormality on mammography beyond skin thickening, and a palpable mass is not required for the diagnosis. The term *peau d'orange* is used to describe the orange-peel appearance of the skin resulting from edema and dimpling at sites of hair follicles (see Fig. 35.6D). The history should reveal a rapid onset of the disease, with progression over weeks to 3 months. Neglected primary breast tumors that lead to secondary inflammatory changes within the breast should not be categorized as inflammatory breast cancer. Inflammatory cancer is a clinical diagnosis and can occur with tumors of ductal or lobular histology. The pathologic hallmark of inflammatory cancer is the presence of tumor cells within dermal lymphatics, but this is often missed because of sampling error and is not a prerequisite for diagnosis. Axillary nodal metastases are common, and there is a significant risk for distant metastases. Sentinel lymph node biopsy is not performed for inflammatory breast cancer as ALND should always be performed.

Current treatment approaches emphasize aggressive use of combined-modality treatment, including neoadjuvant chemotherapy, mastectomy, and radiation therapy, with endocrine therapy for ER-positive tumors and trastuzumab for HER-2–positive tumors. With multimodality treatment, relapse-free survival rates are 50% or higher at 5 years; in contrast, a single-institution historical series showed a 5-year survival rate of 7% in patients receiving less aggressive treatment.[49]

TREATMENT OF SPECIAL CONDITIONS

Breast Cancer in Older Adults

Several studies have explored options that reduce the extent of surgery and radiation therapy for older women with breast

cancer. In two trials, older women were randomly assigned to lumpectomy with or without irradiation. In the CALGB 9343 trial, 636 women 70 years or older with ER-positive tumors 2 cm or smaller and clinically negative nodes received lumpectomy and tamoxifen and were randomly assigned to irradiation or no irradiation.[29] At 10 years, the in-breast recurrence rate was 9% in the no-radiation arm versus 2% in the radiation arm. This difference in in-breast recurrence did not translate into a survival benefit: The 10-year breast cancer–specific survival estimates were 98% in the no-radiation arm and 97% in the radiation arm.

Fyles and colleagues reported the results of a Canadian trial with more inclusive eligibility criteria in which 769 women 50 years or older with tumors up to 5 cm and positive or negative ER status were enrolled. All patients underwent wide excision and received tamoxifen and were randomly assigned to irradiation or no irradiation. Recurrence rates were significantly higher overall in patients who did not receive radiation therapy. However, in an unplanned analysis of a subset of 193 women older than 60 years, the local recurrence rate was only 1.2% without radiation therapy, and there were no recurrences with radiation therapy. These low rates of local recurrence and the significant rates of death from other comorbid conditions led to the acceptance of wide excision and endocrine therapy without irradiation for selected older patients with small ER-positive tumors and clinically negative axillary nodes. Axillary surgery was omitted in such patients in the past; however, SLND can easily be incorporated, with minimal morbidity.

Paget Disease

Paget disease accounts for 1% or less of breast malignancies. It is characterized clinically by nipple erythema and irritation with associated pruritus and may progress to crusting and ulceration. The condition may spread outward from the nipple and onto the areola and surrounding skin of the breast (see Fig. 35.6). The differential diagnosis of scaling skin and erythema of the nipple-areola complex includes eczema, contact dermatitis, postradiation dermatitis, and Paget disease. A biopsy of the skin of the nipple should be performed; a specimen containing Paget cells confirms the diagnosis.

Pathologically, a Paget cell is a large, pale-staining cell with round or oval nuclei and large nucleoli located between the normal keratinocytes of the nipple epidermis. Paget cells spread into the lactiferous sinuses under the nipple and upward to invade the overlying epidermis of the nipple. Paget cells do not invade through the dermal basement membrane and are categorized as carcinoma in situ. More than 95% of patients with Paget disease have an underlying breast carcinoma. Paget disease may be accompanied by a palpable mass in slightly more than 50% of patients. Invasive breast cancer is identified in more than 90% of patients with a palpable mass and Paget disease.

Treatment of Paget disease includes mastectomy with axillary staging or wide local excision of the nipple and areola to achieve clear margins, axillary staging, and radiation therapy. For many patients, lumpectomy and irradiation provide an acceptable cosmetic appearance and obviate the need for mastectomy and breast reconstruction. Nipple-areolar reconstruction can be performed 4 to 6 months after radiation therapy or via 3D tattoo (Fig. 35.14). For patients considering lumpectomy, thorough preoperative evaluation is required to rule out occult multicentric disease.

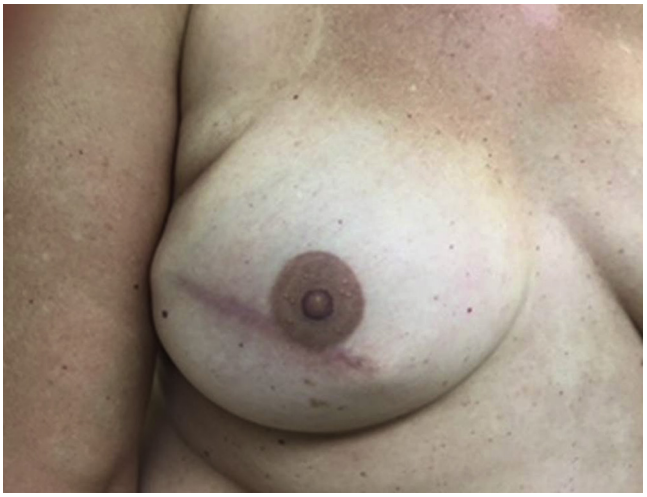

FIG. 35.14 Three-dimensional tattoo of the nipple-areolar complex.

Breast Cancer in Men

Breast cancer occurring in the mammary gland of men is infrequent; it accounts for 0.8% of all breast cancers, less than 1% of all newly diagnosed cancers in men, and 0.2% of cancer deaths in men. In the United States, 1500 new cases of breast cancer in men and 400 deaths from this disease are reported annually. The median age at diagnosis is 68 years, 5 years older than in women. Risk factors include increasing age; radiation exposure; and factors related to abnormalities in estrogen and androgen balance, including testicular disease, infertility, obesity, and cirrhosis. Risk factors related to a genetic predisposition include Klinefelter syndrome (47,XXY karyotype); family history; and *BRCA* gene mutations, particularly *BRCA2* mutations. Gynecomastia is not a risk factor.

Histologically, 90% of breast cancers in men are invasive ductal carcinomas. Approximately 80% are ER positive, 75% are PR positive, and 35% overexpress HER-2. The remaining 10% are DCIS. Given the absence of terminal lobules in the normal breast in men, invasive and in situ lobular carcinoma is rarely seen.

Most men with breast cancer have a breast mass. The differential diagnosis includes gynecomastia, primary breast carcinoma, metastasis to the breast from carcinoma at another site, sarcoma, and breast abscess. In addition to local pain and axillary adenopathy, initial symptoms may include nipple retraction, ulceration, bleeding, and discharge. Evaluation includes breast imaging studies and diagnostic CNB. Prognostic factors for breast cancer in men are the same as prognostic factors for breast cancer in women and include nodal involvement, tumor size, histologic grade, and receptor status. Survival in men with breast cancer is similar to survival in women with breast cancer matched for age and stage.

Treatment of breast carcinoma in men depends on the stage and local extent of the tumor, with treatment options similar to the options for women. Small tumors may be treated by local excision and irradiation or by mastectomy. Sentinel node biopsy has been shown to be effective for staging breast cancer in men. Breast tumors in men more commonly involve the pectoralis major muscle, probably because breast tissue in men is scant. If the underlying pectoral muscle is involved, modified radical mastectomy with excision of the involved portion of muscle is adequate treatment, but it may be combined with postoperative radiation therapy. Adjuvant systemic therapy for breast cancer in men is the same as adjuvant therapy for breast cancer in women. Most breast

cancers in men are hormone receptor positive. Adjuvant endocrine therapy with tamoxifen or AIs is indicated for patients with node-positive disease and high-risk patients with node-negative disease. Adjuvant chemotherapy is used in men at substantial risk for metastatic disease.

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