Concepts in Breast Surgery

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Sonia L. Sugg, Sophia L. Fu, and Carol E. H. Scott-Conner

Introduction

The multidisciplinary management of breast cancer is best led by a surgeon. In order to fulfill this role, the surgeon must keep current with the literature and new consensus statements. Most surgeons who treat patients with breast cancer also take care of women with benign breast problems. This chapter provides a brief overview of both.

Breast Cancer

Epidemiology

Breast cancer is the most common type of cancer in women, with an estimated 266,120 new cases in 2018 (National Cancer Institute SEER Program 2019). It represents 15.0% of all cancer cases in women and is the fourth leading cause of cancer death in the United States, with 126 new cancers and 20.9 deaths per 100,000 women per year, based on 2011–2015 SEER data (National Cancer Institute SEER Program 2019). The survival rate has been improving by 1.8% each year. Because the rates of new female breast cancer cases are now stable, we are making progress in this once deadly disease. Breast cancer can also occur in men but is much less common (see section "Breast Problems in Men," which concludes this chapter).

S. L. Sugg · C. E. H. Scott-Conner (✉)
Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: carol-scott-conner@uiowa.edu

S. L. Fu
Department of Oncology, Good Samaritan Hospital Medical Center, West Islip, NY, USA

Breast Cancer Risk

Breast cancer risk assessment should be part of the initial history and physical of any woman with a breast problem. Hormonal exposure, a known risk factor for breast cancer, should be assessed by querying for age at menarche, first parity, menopause, and use of hormonal contraceptives or replacement. Alcohol intake is associated with breast cancer risk in a dose-dependent fashion and needs to be documented. A detailed family history of breast, ovarian, and other cancers should be obtained. Known genetic mutations (BRCA, Li-Fraumeni, Cowden syndrome, NF1, and others), history of chest radiation, or previous biopsies showing atypical hyperplasia or lobular carcinoma in situ should be noted. Risk assessment models such as the Gail or the Tyrer-Cuszk models can be used to calculate breast cancer risk. This patient-specific risk information assists in tailoring screening regimens, threshold for biopsy, and prophylactic surgery.

Breast Cancer Screening

Breast cancer screening consists primarily of screening mammography. Self-breast exam and clinical breast exam are no longer recommended for screening modalities in breast cancer screening due to lack of survival benefit (Oeffinger et al. 2015). Screening mammography has been shown to decrease mortality from breast cancer. Despite this, there is controversy as to the recommended age to begin screening mammography. Younger women have higher breast density, reducing the sensitivity of screening mammography (Melnikow et al. 2016). Their prevalence of breast cancer is also lower, which increases the chance of false-positive results. The risks of screening such as false positives requiring additional testing, anxiety, and overdiagnosis are being weighed against the benefits of screening in the development of these guidelines. The American Cancer Society now recommends that women at average risk have their first

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screening mammogram at age 45. Radiology and breast surgery guidelines recommend starting at age 40, while the U.S. Preventative Task Force and many European countries recommend starting at age 50. Patients at increased risk based on genetics, family and medical history, or breast biopsy results should begin screening earlier. There is also controversy as to how frequently women should have screening mammograms. The American Cancer Society recommends that women 55 years or older may have mammograms every 1 or 2 years, and that screening should continue as long as there is a 10-year life expectancy (American Cancer Society 2019a). Most guidelines recommend risk assessment and shared decision-making to help guide screening regimens. Risk-stratified screening protocols are currently undergoing clinical trials.

Imaging Modalities

Mammography: Screening mammography is used for detection of breast cancer, and diagnostic mammography is used to further characterize abnormal findings. Screening mammography fails to detect breast cancers in 20–30% of cases (Hoff et al. 2012). Digital breast tomosynthesis (DBT) or 3D mammography has significantly better sensitivity and specificity, especially in women with dense breast tissue. There is a slightly higher radiation dose with current techniques (Gilbert et al. 2016).

Ultrasound: Ultrasound (US) is useful for characterizing mass lesions, and is particularly helpful in guiding procedures such as needle biopsies and lumpectomies. All breast surgeons should be facile in this modality. It can also be used in screening, particularly with the whole breast ultrasound machines, which renders the procedure less operator dependent. The role of whole breast ultrasound as a supplemental screening test remains to be defined.

MRI: Magnetic resonance imaging (MRI) may be used for screening in some cases, such as those with a lifetime risk of cancer >20–25% (Saslow 2007). The false-positive rate of MRI is high and, therefore, its use is restricted to high-risk patient populations for screening purposes. In selected patients with DCIS or breast cancer, It is used to define the extent of disease, and it can be used to evaluate the results of neoadjuvant chemotherapy. Use of MRI is associated with an increased rate of mastectomy and, therefore, must be used judiciously (Houssami et al. 2017).

Breast Biopsy: Obtaining a Tissue Diagnosis

Any lesion that is deemed suspicious should be biopsied by needle rather than surgically excised. Although a fine-needle aspiration (FNA) may be performed, it cannot distinguish in situ disease versus invasive disease, and biomarker assessment is difficult. A core needle biopsy (CNB) provides information on the histologic subtype, grade, and accurate tumor biomarker status for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu (HER2).

If the lesion is not palpable, the needle biopsy can be performed percutaneously guided by the imaging modality which detected the lesion. Commonly, the biopsy is performed via ultrasound guidance or stereotactically via mammography. Occasionally, if the lesion is only seen on MRI, then an MRI-guided biopsy can, and generally should, be performed.

Core needle biopsy is performed with spring-loaded (12-14G) or vacuum-assisted (7-10G) devices. Multiple samples are taken to ensure adequate biopsy of the target lesion. A clip is then placed at the biopsy site to allow subsequent excision or follow-up. Markers that incorporate hydrophilic markers are particularly useful if ultrasound-guided lumpectomy is planned.

If a lesion is palpable, then a CNB can be performed without imaging, although it may be prudent to use ultrasound assistance. Ultrasound allows the targeting of the most high-yield part of a tumor, which may be heterogeneous. A clip should be placed in case subsequent neoadjuvant therapy is used; such treatment may shrink the tumor so well that it is no longer palpable or even detectable by imaging modalities.

The pathology report must be examined for concordance. Was a lesion such as a fibroadenoma identified (may be concordant with imaging findings) or was it "normal breast" (which suggests that the target was missed)? If a percutaneous biopsy result is not concordant with radiologic imaging, then the next step is generally an open excisional biopsy in the operating room. A weekly mammography/biopsy conference, in which all biopsies are reviewed by a multidisciplinary team including the radiologist, helps ensure that all biopsy findings are either concordant or, if discordant, managed appropriately.

Management of Common Benign Breast Lesions

Nipple Discharge

Nipple discharge is common and occurs in 2–5% of women (Ashfaq et al. 2014). Physiologic nipple discharge related to lactation, medications, or conditions such as prolactinoma is not treated with surgery. Pathologic nipple discharge is defined as being unilateral, spontaneous, and arising from a single duct. It does not have to be bloody. It is most often caused by a papilloma or benign duct ectasia, but can also be caused by DCIS or invasive ductal carcinoma in 5–10% of cases (Ashfaq et al. 2014; Morrogh et al. 2007). The workup

includes mammography and ultrasound, which may identify associated malignancy. US is highly sensitive and predictive of lesions in the setting of pathologic discharge (Ballesio et al. 2007). If negative, galactography may identify lesions within the ductal system; however, it is not a widely available test. Contrast-enhanced breast MRI is less operator dependent, highly sensitive, and specific for detecting lesions and may be preferred over galactography (Berger et al. 2017). A duct exploration and excision should be undertaken in persistent pathologic nipple discharge, even if a lesion is not identified on imaging. This resolves the nipple discharge and will often excise the papilloma or less commonly the DCIS or invasive cancer causing the discharge. If a lesion is seen on imaging, it should undergo image-directed core needle biopsy prior to surgical excision.

Breast Abscess

Breast abscesses can be divided into two categories: lactational (puerperal) or nonlactational (nonpuerperal). The most common organism in lactational abscesses is *Staphylococcus aureus* (including MRSA), followed by streptococci and *Staphylococcus epidermidis*. The treatment plan for these abscess include: (1) appropriate antibiotic coverage early on, (2) promoting milk drainage, and (3) ultrasound-guided aspiration with a large-bore needle. Patients may need serial aspirations every 2–3 days. If the overlying skin is thinned out or necrotic or the abscess appears too complex with multiple loculations, then an incision and drainage may need to be performed (Dixon & Khan 2011). Nonlactational abscesses are typically located in the central subareolar or peripheral regions. Central subareolar abscesses develop because of periductal mastitis. They are usually attributed to anaerobic bacteria in the context of damaged subareolar ducts. A very typical location would be centered under the areolar margin. Subareolar abscesses appear to be more common in smokers and are associated with nipple piercing (Gollapalli et al. 2010). Nonlactational peripheral abscesses may be associated with diabetes, rheumatoid arthritis, or granulomatous lobular mastitis. These are treated with serial aspirations with antibiotic coverage, reserving incision, and drainage for refractory cases. Granulomatous mastitis may require medical comanagement with rheumatology and infectious disease specialists, and surgery should be used sparingly. When the infection has resolved, breast imaging should be performed to rule out a malignancy that may rarely present with infection or abscess.

Benign Breast Mass or Cyst

Ultrasound can be used to distinguish between a solid mass and cyst. A *benign cyst* is typically simple in nature as seen on ultrasound. It can be aspirated if symptomatic. A *complex cyst* may have septations or solid components and may require aspiration for cytology and/or biopsy of solid components to rule out malignancy. Fibroadenomas and phyllodes tumors are classified as fibroepithelial lesions and are stromal tumors of the breast. A *fibroadenoma* is a solid benign tumor that does not need excision unless symptomatic. *Pseudoangiomatous stromal hyperplasia (PASH)* is a benign proliferative lesion affecting women in the reproductive years. It does not require excision if diagnosed on image-guided core needle biopsy of a nonpalpable mass (Protos et al. 2016). Large palpable masses may require excision on a case-by-case basis.

Phyllodes tumors can mimic fibroadenomas on imaging and histopathology, but will often grow more rapidly. They are graded as benign, borderline, and malignant based on WHO-defined histologic features (Krings et al. 2017). Local recurrence varies with grade. Malignant phyllodes tumors will rarely metastasize. Uniformly poor pathologic features of marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 or more mitoses per 10 high-power fields are associated with distant metastases (Spanheimer et al. 2019). When the pathologist is unable to distinguish a fibroadenoma from a phyllodes tumor on core biopsy, excision is then indicated (see below). A recent metaanalysis found an overall 11% recurrence rate after excision of benign phyllodes tumors, with no difference in recurrence between 1 mm and 10 mm margins. Positive margins had a recurrence rate of 12% (Shaaban & Barthelmes 2017). Therefore, benign phyllodes tumors that have been enucleated with no margins may be observed. With borderline and malignant phyllodes tumors, a positive margin should be reexcised as the local recurrence rates are higher at around 30%. An ideal margin width has not been established (Tan et al. 2016). Larger tumors may require a mastectomy.

Breast Lesions on CNB That May Require Excision

Although many lesions found on CNB are benign and require no further surgery, there are certain "benign" findings that do require a surgical excision either to treat the condition or to exclude associated malignancy. The "upgrade rate" is the rate of discovering associated malignancy (DCIS and invasive ductal and lobular cancer) upon surgical excision. This used to determine whether or not a "high risk lesion" seen on core needle biopsy needs surgical excision. Some of these lesions are also associated with an increased risk of developing breast cancer, making the nomenclature somewhat confusing. As core needle biopsy specimens have become larger, the ability to adequately sample the lesion has improved and more specific criteria are being developed to decrease the number of surgical excisions without missing malignancy. A general observation is that atypia seen in the core biopsy is associated with a higher upgrade rate and also increases the

risk for developing breast cancer. The need for a surgical excision for various lesions continues to evolve and is an area of controversy. Not surgically excising a lesion requires meticulous follow-up.

As noted above, *benign phyllodes tumors* generally deserve excision; and often the pathologist is unable to distinguish a fibroadenoma from a benign phyllodes tumor and may give the diagnosis of fibroepithelial lesion on CNB. In this case, excision is warranted after clarification with the pathologist.

A *radial scar* has a stellate appearance very similar to carcinoma on imaging. Lesions smaller than 1 cm may be called complex sclerosing lesions. They are proliferative lesions but are not thought to be premalignant, or increase breast cancer risk. The upgrade rates vary from 0% to 28% and depend upon whether atypia is present and whether the lesion was sampled extensively or not. Contemporary series have 0–2% rates in lesions without atypia. Small, adequately sampled lesions, with radiologic and pathologic concordance, may not need to be excised (Cohen & Newell 2017).

Intraductal papillomas may present in association with nipple discharge, as a palpation or image detected mass, or as an incidental finding on core biopsy. They can be solitary or multiple, and are more commonly located near the nipple rather than at the periphery of the breast. Intraductal papillomas are not thought to be premalignant, but may increase the risk of developing breast cancer very slightly, especially if multiple. In the past, *intraductal papillomas* were excised surgically as a standard (Wen & Cheng 2013) because of the high upgrade rates. Studies show that papillomas with atypia need surgical excision due to an upgrade rate of up to 25% (Arora et al. 2007), but solitary papillomas without atypia diagnosed on image-guided core biopsy have an upgrade rate of 5% or less, and may be observed (Lewis et al. 2006; Ahmadiyeh et al. 2009). Surgical excision should be considered for larger (>1 cm) size, age greater than 50, a location more than 3 cm from the nipple, and the presence of microcalcifications, as these are features associated with higher upgrade rates (Agoumi et al. 2016).

Atypical ductal hyperplasia (ADH) found on CNB is associated with a 20–50% upgrade rate to ductal carcinoma in situ (DCIS) or to invasive breast cancer (Sutton et al. 2019; Salagean et al. 2019). Therefore, a surgical excision of the area is recommended. The risk for upgrade is related to the sampling and severity of ADH, the lesion size on imaging, and patient age that can be calculated using a risk prediction model (Salagean et al. 2019). In select patients with no mass and small-volume low-grade ADH that was completely excised on CNB (especially if a vacuum-assisted device was used to remove >90% of the target calcifications), follow-up with serial mammograms and risk assessment and management (without surgical excision) may be safe (Racz & Degnim 2018).

Atypical lobular hyperplasia (ALH) or *lobular carcinoma in situ (LCIS)* is commonly identified on CNB and has been increasingly found to have lower upgrade rates in the setting of imaging-pathologic concordance (Muller et al. 2018). If there are no other pathologic findings, such as ADH, papilloma, or radial scar, upgrade rates are less than 5% (Morrow et al. 2015; Middleton et al. 2014). In this setting, the American Society of Breast Surgeons no longer recommends routine excision of ALH or LCIS (Pesce et al. 2014). *However, excision is warranted if there is pleomorphic LCIS, LCIS with necrosis, other nonclassical variants, discordant findings, or other high-risk lesions* (Nakhlis et al. 2019).

Flat epithelial atypia (FEA) may be found incidentally on biopsies performed for calcifications seen on screening mammogram. There is a low upgrade rate (1–7.5%) mostly to DCIS, but FEA can be associated with ADH (18%) and lobular neoplasia in a significant proportion of subsequent excisions (Hugar et al. 2019), especially if there is a genetic mutation or personal history of breast cancer (Lamb et al. 2017). These findings could alter patient management and underlies the rationale to surgically excise FEA despite its low upgrade rate to malignancy (Rudin et al. 2017). Recommendation to excise FEA is, therefore, dependent on patient factors, how diagnosing a high-risk lesion may affect management, and shared decision-making.

Breast Malignant Diseases

Ductal Carcinoma In Situ (DCIS)

DCIS is considered to be a potential precursor of invasive ductal carcinoma in which the malignant cells, though sharing molecular changes with invasive cancer cells, are still contained within the basement membrane. Thus, DCIS is generally not thought to have metastatic potential. As a precursor lesion, it will progress to invasive cancer some of the time. It most often presents with microcalcifications on screening mammography, but may also present with nipple discharge or a mass. The incidence of DCIS increased greatly after screening mammography, and currently it is postulated that many cases of DCIS represent overdiagnosis. *Overdiagnosis* is the discovery of DCIS or breast cancer through screening that would never have become clinically apparent during the patient's lifetime. Estimates of breast cancer overdiagnosis vary with statistical modeling methodology, ranging from 5% to 30%, and are highly controversial (Etzioni et al. 2013). DCIS is treated much like cancer, yet the treatment has virtually no impact on mortality. Because of the likely overdiagnosis and subsequent overtreatment of DCIS, there are currently several randomized clinical trials (COMET in the United States and LORIS in the United Kingdom) investigating if low-risk DCIS may safely be

observed under active surveillance protocols instead of standard treatment (see below). AJCC staging of DCIS is Tis and stage 0.

Surgical treatment of DCIS The goal of surgery in DCIS is to remove the lesion(s) from the breast, and this can be done with either removing part of the breast (lumpectomy, partial mastectomy) or the entire breast (mastectomy). In a recent review of patients with DCIS in the Surveillance, Epidemiology, and End Results (SEER) database, 10-year disease-specific survival showed no clinically meaningful difference between those treated with lumpectomy with radiation (98.9%), mastectomy (98.5%), or lumpectomy alone (98.4%) (Worni et al. 2015). In general, lymph node staging is not required in DCIS because it does not metastasize. However, invasive cancer will be found on the final surgical specimen of 10–20% of DCIS diagnosed on CNB. The presence of a palpable mass, younger age, large size on imaging, and high-grade DCIS increases the risk of invasive cancer (Yen et al. 2005). With a lumpectomy, SLN biopsy may be performed at a second operation, and therefore, SLN biopsy is only done concurrently with the lumpectomy when there is a high risk of invasive cancer based on clinical features (mass, pathology suspicious for microinvasion, and large area). After a mastectomy, the feasibility and accuracy of SLN biopsy are not known, therefore, a SLN biopsy is recommended in patients with DCIS diagnosed on CNB undergoing mastectomy (Chin-Lenn et al. 2014).

Radiation therapy in DCIS The role of radiation in DCIS has been controversial. Adjuvant radiation therapy decreases the local recurrence rate by 50% when used with lumpectomy (Wapnir et al. 2011) but there is no improvement in overall survival (Krings et al. 2017). Fifty percent of recurrences in DCIS will be invasive cancer, and this is associated with a slight increase in breast cancer-specific mortality (Wapnir et al. 2011). Lumpectomy without radiation therapy may be appropriate for some patients, including those with advanced age, extensive comorbidities, or small foci of low-grade disease with negative margins. The oncotype Dx DCIS recurrence score calculated from a multigene assay was developed to identify a low-risk subgroup in whom RT may be omitted (Solin et al. 2013). The test has not yet been widely adopted and its clinical utility is still under investigation (Lin et al. 2018; Manders et al. 2017).

Adjuvant therapy in DCIS For hormone receptor-positive DCIS, adjuvant endocrine therapy in the form of tamoxifen was shown to decrease local recurrence but not survival in women with breast-conserving therapy (Staley et al. 2012). Contralateral new breast cancers were also reduced, with tamoxifen acting as a prevention drug. Currently, tamoxifen is recommended for 5 years (Early Breast Cancer Trialists' Collaborative, G 2011a). The NRG Oncology/NSABP B-35 trial showed that the aromatase inhibitor anastrozole was superior to tamoxifen in preventing recurrence, mainly in women younger than 60, with fewer episodes of thrombosis (Margolese et al. 2016).

Paget's Disease of the Breast

Paget's disease of the breast is rare (3% of all breast cancers) (Ashikari et al. 1970) and presents with a refractory pruritic, eczematous rash involving the nipple-areolar complex (NAC). Recognition of the disease may be delayed, and the diagnosis can be made with a simple core needle biopsy (2 mm) of the affected nipple, which will demonstrate epidermal invasion by malignant cells. Most (90%) patients have an associated breast neoplasm, and up to 50% present with an associated breast mass (Ashikari et al. 1970). Multifocal disease is common. However, mammogram and US may not identify the associated neoplasm in some cases, but MRI is highly sensitive and should be routinely used to determine the extent of disease (Morrogh et al. 2008). Although mastectomy was the recommended therapy in the past, breast-conserving therapy with a central lumpectomy and radiation appears to be safe in patients with limited disease (Trebska-McGowan et al. 2013). SLN biopsy is driven by the underlying disease of DCIS or invasive cancer, and the role of SLN biopsy for isolated noninvasive Paget's disease is unclear.

Invasive Breast Cancer

Invasive cancer has acquired the ability to spread beyond the breast to the lymph nodes and distant organs. Invasive ductal carcinoma is the most common type (70–80%), followed by invasive lobular carcinoma (7%). Other types include tubular, mucinous, papillary, and metaplastic, which altogether account for less than 5% of invasive cancers. These histologic subtypes have well-characterized clinical features, which include prognosis; however, significant advances have been made in characterizing tumors and individualizing treatment based on receptor expression and mRNA expression in breast cancer. Breast cancer was initially characterized by the presence of estrogen (ER) and progesterone (PR) receptors, which was associated with response to hormonal treatment. HER2/neu receptor amplification was identified as a predictor of breast cancer relapse (Slamon et al. 1987), and the anti-HER2 monoclonal antibody showed efficacy (Pegram et al. 1998), ushering the era of molecular targeting in cancer treatment. These three receptors, ER, PR, and HER2, are the only receptors routinely analyzed on invasive breast cancer pathology because they are useful in treatment

planning with antiestrogen therapy and anti-HER2 therapy and prognosis (Waks & Winer 2019). All three are analyzed by immunohistochemistry, and fluorescent in situ hybridization (FISH) is used in cases where HER2 staining is equivocal. The classification of breast tumors via transcriptome analysis (Sorlie et al. 2001) has led to identification of molecular subtypes that correlate clinical behavior, response to treatment, and prognosis. *Luminal A* and *Luminal B* subtypes are ER-positive, HER2-enriched subtype has high expression of HER2, and *basal* subtypes which are ER, PR, and HER2 negative, or triple negative. Genomic assays such as Oncotype DX and MammaPrint are used to characterize the primary tumor according to risk of recurrence, and this information is used to guide recommendations for chemotherapy (Varga et al. 2019). The assays vary in terms of the tumor type and patient population studied and, therefore, multidisciplinary input may be required to use the assays appropriately.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a distinct clinical entity, presenting with a rapid (≤3 months) onset of skin changes with erythema and edema (peau d'orange), encompassing more than a third of the breast, with or without an underlying mass. Its pathologic hallmark is dermal lymphatic invasion, but a biopsy is not required to make this clinical diagnosis. A delay in diagnosis is common, the disease may be mistaken for mastitis and treated with antibiotics. It is staged as T4d. It is the most lethal of breast cancer types, associated with a 5-year survival of 30% (Yamauchi et al. 2012). At presentation, 85% of patients have regional lymph node involvement, and 30% have distant metastases (Masuda et al. 2014). At diagnosis, IBC is considered surgically unresectable and the initial treatment is neoadjuvant chemotherapy, followed by modified radical mastectomy and radiation therapy.

Surgical Treatment of Breast Cancer

The radical mastectomy as described by Halstead in 1894 (Halsted 1894–1895) and others (Sakorafas 2008) was the preferred operation for breast cancer until the 1970s. Landmark clinical trials by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and others (Julian et al. 2015) paved the way to modern treatment plans, reducing surgery in the breast and axillary lymph nodes, and incorporating the adjuvant therapies of radiation, combination chemotherapy, anti-HER2 therapy, and antiestrogens. Breast conservation surgery with radiation was found to be comparable to mastectomy with slightly higher local recurrence rates but with no difference in survival. Sentinel lymph node biopsy is now performed for staging to direct the adjuvant radiation and systemic therapy, reserving axillary lymph node dissection as therapy for node-positive patients. The continued improvement in breast cancer survival results from this evidence-based, multidisciplinary approach to treatment. Breast Tumor Board facilitates collaboration among specialists, the optimal sequencing of treatment, enrollment in clinical trials, and is a feature of breast cancer specialty care. With increasing numbers of breast cancer patients living many years after treatment, survivorship issues such as surveillance, physical and psychological health, and quality of life are under scrutiny for improvements.

Considerations Prior to Surgery

Is the Patient a Surgical Candidate?

It is rare that a patient is unable to undergo surgery due to comorbid conditions. A lumpectomy under local anesthesia can be performed safely in most cases where the risk of general anesthesia is prohibitive. In women who have metastatic disease at time of diagnosis, surgery does not play a major role and is reserved for palliation, although recent studies suggest that there may be a benefit in selected patients (Xiao et al. 2018).

Is the Patient a Candidate for Breast Conservation?

The aim of breast conservation is to remove the area of DCIS or invasive cancer with negative margins and a cosmetically acceptable result. Therefore, the primary consideration for breast conservation suitability is the extent of disease in the breast compared with the breast size and ability to undergo radiation therapy (see below for details).

Surgery First or Neoadjuvant Treatment Followed by Surgery?

In early stages, surgery (BCT or mastectomy) is the primary treatment, followed, if appropriate, by adjuvant systemic therapy. There is a general tendency to offer some kind of adjuvant systemic therapy (whether chemotherapy, HER2/neu-directed therapy, or hormonal therapy) to all patients with invasive breast cancer who are physically able to take it.

In more advanced stages, neoadjuvant chemo- or hormonal therapies are used prior to surgery to decrease the extent of surgery in both the breast and axilla. Neoadjuvant chemotherapy is the initial treatment for inflammatory breast cancer, as previously discussed. In the breast, neoadjuvant therapy can convert women needing mastectomy to candidates for BCT (Mieog et al. 2007; Spanheimer et al. 2013).

In addition, resection of less breast tissue or skin may result in improved cosmetic outcomes in both BCT and mastectomies with reconstruction. In the axilla, pCR in node-positive patients could convert an ALND into SLN biopsy (Caudle et al. 2017) with a decrease in lymphedema risk. If clinically evident lymph node metastases are present at initial diagnosis, neoadjuvant chemotherapy is often recommended to facilitate subsequent ALND, even if a pCR is not anticipated. The rate of complete pathologic response (pCR) is dependent on the receptor subtype (Table 115.1). Neoadjuvant therapy also provides important prognostic information by allowing the team to determine response to therapy: pCR is generally associated with better survival (Boughey et al. 2017). Conversely, patients with residual disease could benefit from additional therapy such as capecitabine in TN tumors (Masuda et al. 2017), or ado-trastuzumab emtansine (TDM1) in HER2+ disease (von Minckwitz et al. 2019), or enroll in clinical trials evaluating novel agents.

Prior to commencing neoadjuvant treatment, it is imperative that the extent of disease in the breast and axilla is fully evaluated with imaging and marked (usually with clips) so that pCR can be confirmed if no disease is found on surgical pathology. MRI is most commonly used, but US is less expensive and useful in well-circumscribed tumors. The extent of disease in the breast should be reevaluated by imaging at the conclusion of neoadjuvant treatment.

Is the Patient a Candidate for Omitting SLN Biopsy?

In patients where axillary staging would not impact adjuvant treatment decisions, SLNB may be omitted. This could be considered in older women (over age 70) with early-stage cancers that are clinically node negative and estrogen receptor positive and HER2 negative as per the Society for Surgical Oncology (SSO) Choosing Wisely guidelines. This guideline was based on the CALGB 9343 results, where patients meeting those criteria were treated with lumpectomy plus tamoxifen with or without breast irradiation and had no difference in overall survival or distant disease-free survival (Hughes et al. 2013). The decision to deescalate surgical therapy should be made in conjunction with radiation and medical oncologists in a multidisciplinary setting. Some healthy elderly patients who have a longer life expectancy may want to have the same treatment as younger patients.

Table 115.1 Response to neoadjuvant chemotherapy

Breast cancer type	Pathologic complete response (pCR) rate
Triple negative	Up to 60%
HER2+ (ER−)	Up to 80%
HER2+ (ER+)	Up to 45%

From Pusztai et al. 2019, with permission

Will the Patient Require Postmastectomy Radiation?

Knowing if a patient will require postmastectomy radiation is important in preoperative planning, even after neoadjuvant treatment and/or a mastectomy (see below for details). With radiation, reconstruction options are more limited and favor delayed autologous over implant reconstruction. Therefore, if BCT is possible, it should be strongly recommended.

Are There Indications for Genetic Counseling?

Genetic testing should be offered to patients with a personal or family history suggestive of/or known to have a hereditary cancer syndrome involving breast cancer. Genetic counseling, if available, is an essential part of this evaluation. Identification of a high-risk mutation is important information that should be available to a woman if it will change her choice of surgery (BCT vs. bilateral mastectomy), especially for early-stage disease. If BRCA 1 or 2 is confirmed, ovarian cancer screening or risk-reducing oophorectomy is performed. The additional information obtained by testing may be of value not only to the woman but to her children or siblings.

The Role of Shared Decision-Making

It is the responsibility of the surgeon to educate the patient, help identify goals of treatment, and thoroughly discuss the risks and benefits of the treatment options. Colleagues in genetic counseling, radiation and medical oncology, and plastic surgery should be appropriately consulted to ensure the patient has adequate information to make an informed decision prior to surgery. The surgeon should not hesitate to offer an opinion including recommending against options that have significant potential for harm, but must also respect the patient's autonomy and values.

Surgical Treatment of the Breast

The surgical choices for management of the breast are the same for invasive cancer as for DCIS: BCT versus mastectomy. Since there is a risk of distant spread, the axilla is usually staged with a sentinel lymph node biopsy, followed by a complete axillary lymph node dissection (ALND) if necessary (see Lymph Node Staging, below).

Breast Conservation Therapy (BCT)

BCT is removal of part of the breast and generally includes radiation therapy. Resection of part of the breast is most commonly known as lumpectomy, but can also be referred to

as partial or segmental mastectomy or quadrantectomy. Survival rates for BCT were equivalent to mastectomy in multiple randomized controlled trials (Julian et al. 2015). Contraindications to BCT include factors related to extent of disease such as multicentric disease (synchronous foci of cancer more than 5 cm apart), inflammatory breast cancer, large tumor-to-breast ratio, diffuse malignant-appearing calcifications seen on imaging, persistently positive margins despite reexcision, and factors related to radiation delivery such as early pregnancy, or prior chest wall radiation (Morrow et al. 2002). Technical factors such as inability to deliver radiation due to patient positioning, weight limits, pacemaker, or other large implanted metal devices on the side of the radiation could also preclude it. Patients with collagen vascular disease, especially scleroderma and systemic lupus erythematous, are at higher risk for developing late toxicity (Lin et al. 2008).

The goal of the breast resection is to remove the tumor with negative margins with an acceptable cosmetic result and, therefore, a certain degree of precision is required. The extent of disease, including suspicious microcalcification, needs to be determined prior to surgery. This may require additional breast imaging and biopsies. Well-circumscribed, palpable lesions can be excised without imaging; however, we have found intraoperative US to be useful even in these lesions. Nonpalpable lesions require a localization method. These methods include wire localization, hematoma ultrasound-guided (HUG) lumpectomy (Larrieux et al. 2012), or the use of implanted, detectable tags such as radioactive or magnetic seeds, radiofrequency emitters, etc., which are also gaining popularity. Large areas of resection may require several wires or "tags" to delineate the area of removal. Specimen radiographs are performed to ensure removal of the clip or "tag" and associated mass and/or microcalcifications. The specimen must be oriented so that a positive margin can be identified for reexcision. An adequate margin for DCIS is ≥2 mm (Morrow et al. 2016), whereas for invasive carcinoma it is "no tumor on ink" (Moran et al. 2014). In patients with DCIS and invasive cancer, "no tumor on ink" applies to both the DCIS and the invasive component (Morrow et al. 2002).

With recent increasing interest in oncoplastic techniques, larger lumpectomies may be performed with good cosmetic and oncologic outcomes (De La Cruz et al. 2016), particularly in large-breasted women. These techniques involve tissue rearrangement and sometimes contralateral mastopexies for symmetry. Oncoplastic techniques may be performed by the trained breast surgeon and/or with a plastic surgeon, especially when a contralateral symmetry procedure is needed.

Radiation with breast conservation Local recurrence (10-year risk by 50%) and mortality (15-year risk by 4%) after breast conservation are reduced significantly with radiation therapy (Early Breast Cancer Trialists' Collaborative, G 2011b). For patients with a low risk of recurrence, or with sufficient competing causes for mortality, radiation may not be beneficial. For example, in women over age 65 with hormone-positive tumors and taking antiestrogen therapy, radiation therapy reduced a 5-year recurrence rate from 6.5% to 2.2%, with no change in survival (van de Water et al. 2014). Conventional whole breast radiation (WBRT) delivers 1.8–1 Gy daily fractions over a 4.5- to 5-week period to a total dose of 45–50 Gy. A boost dose of 10–14 Gy in 2–2.5 Gy fractions to the tumor bed is given in most cases. It is generally well tolerated, with the most common acute toxicities being fatigue and skin burn, although long-term complications such as cardiotoxicity, lung injury, and secondary malignancies can occur (Taylor et al. 2017). Access for rural and elderly patients may preclude the use of radiotherapy. Additional breast radiation options include (1) hypofractionated whole breast radiation (delivering 40–42.5 Gy over a shorter time (3–5 weeks)), and (2) partial breast radiation (delivering radiation to the tumor bed via a catheter, external beam, or intraoperative radiation therapy). These alternate methods require careful patient selection and have shorter follow-up time compared to conventional whole breast radiation therapy.

Mastectomy

Mastectomy is removal of the entire breast. The nomenclature of mastectomy has evolved with changes in surgical treatment. A *simple* mastectomy is defined as removal of the breast and nipple, whereas a *total* mastectomy does not include removal of the nipple (American Medical Association 2019); therefore, a nipple-sparing mastectomy (NSM) would be classified as a *total* mastectomy for billing purposes. A *modified radical* mastectomy is a mastectomy with an axillary lymph node dissection (ALND), whereas a *radical* mastectomy is a mastectomy, ALND, and removal of the pectoralis major and minor muscles. As noted above, a mastectomy is equivalent to BCT in terms of survival. The local recurrence after a mastectomy is dependent on tumor biology and is around 4% overall (Glorioso et al. 2017). After a long period of decline, mastectomy rates have increased, and in particular, contralateral prophylactic mastectomies (CPM) (Marmor et al. 2019). The ASBrS has issued a consensus statement discouraging the use of CPM for women of average risk due to increased complications with no survival benefit (Boughey et al. 2016).

If a mastectomy is required or chosen as a treatment option, the skin-sparing and nipple-sparing techniques can be used with immediate reconstruction with excellent cosmetic outcomes. Reconstruction may be performed by autol-

ogous or implant-based techniques by a plastic surgeon. It is important to preoperatively discuss with the patient that the reconstructed breast will not have normal sensation. Sexual and arm function may be impaired (Anderson et al. 2017; Chrischilles et al. 2019), and additional surgeries are often required. Delayed reconstruction is usually recommended if radiation is indicated, although many plastic surgeons will insert a tissue expander to preserve skin and maintain a space for the future reconstructed breast.

Postmastectomy radiation (PMRT) Most patients undergoing mastectomy will not require radiation. However, chest wall and nodal radiation after mastectomy is usually recommended in those with locally advanced disease (T3-4, N2-3): tumors ≥5 cm, positive margins, and extranodal extension, in addition to those with residual nodal disease after neoadjuvant chemotherapy (Liu et al. 2016). Patients with 1–3 positive lymph nodes may have not only a survival benefit with PMRT but also a slightly higher rate of complications (Ragaz et al. 2005). Therefore, PMRT in this group of patients require careful weighing of risks and benefits and consideration of the patient's treatment goals.

Lymph Node Surgery

Lymph node surgery in breast cancer is performed for either staging or therapeutic purposes. The majority of lymph node metastases occur in the axillary lymph nodes, though internal mammary, supraclavicular, and cervical lymph nodes can be involved, especially with advanced disease. In early-stage disease, sentinel lymph node biopsy has replaced routine axillary lymph node dissection for staging, leading to a reduction in lymphedema and arm dysfunction.

Sentinel lymph node biopsy was initially only done in women with early-stage disease and a clinically negative axilla. The procedure identifies the lymph node(s) that drain the breast by injecting a tracer, most commonly blue dye and/or radioactive technetium sulfur colloid, and identifying and removing the axillary lymph nodes that have taken up the substance. It is highly accurate in predicting the status of the axillary lymph nodes, with a false-negative rate of 7.3% (Kim et al. 2006). If it is negative, no further axillary surgery is done. SLN has lower lymphedema rates, and improved quality-of-life measures than ALND (Fleissig et al. 2006). In the case of a positive sentinel lymph node, the ACOSOG Z-11 randomized clinical trial in clinically node-negative women undergoing BCT for early-stage tumors indicated that it was safe to omit ALND if there were fewer than three positive lymph nodes, no extranodal extension, or lymphovascular invasion. Although 30% of patients had additional positive lymph nodes, there was no difference in survival and excellent regional control (Giuliano et al. 2010), and the result of excellent systemic and radiation therapy. Similar results were seen in the IBCSG 23-01 trial (Galimberti et al. 2013). In women with positive sentinel lymph nodes who do not fit the Z-11 criteria, such as those having mastectomy, data are insufficient to advocate omitting ALND.

Sentinel lymph node biopsy after neoadjuvant chemotherapy was investigated in the ACOSOG Z-1071 trial. This trial showed that the ability of the SLN to predict the status of the axillary lymph nodes approaches that of conventional SLN biopsy. Retrieval of three or more nodes, using dual dye for SLN identification, and retrieving the clipped node (if previous biopsy had demonstrated nodal disease), all contributed to lowering the false-negative rate (Boughey et al. 2013). Subsequent work by Caudle et al. showed that targeted axillary dissection (TAD), in which the clipped node is removed along with any sentinel node(s) decreased the FNR to 1.4% (Caudle et al. 2016).

Because of the significant harm of *ALND*, with a 20% rate of lymphedema and associated arm dysfunction, it was rapidly replaced by SLN biopsy in the 1990s for axillary staging. However, there continues to be a role for ALND in the removal of axillary disease in (1) patients with positive lymph nodes who do not meet Z-11 criteria, including patients with positive lymph nodes undergoing a mastectomy, (2) those with residual lymph node disease after neoadjuvant therapy, and (3) those with inflammatory breast cancer regardless of response. Left untreated, axillary lymph node disease can sometimes progress to encase the axillary vessels and brachial plexus, producing a painful situation that is very difficult to palliate.

Axillary reverse mapping (ARM) is a procedure described by Klimberg (Klimberg 2008), which identifies the arm lymphatics within the axilla. Blue dye or indocyanine green is injected in the ipsilateral upper arm to identify the arm lymphatics, which are then avoided where possible. In a prospective study of 654 patients, who underwent ARM procedures with SLNB versus ALND, lymphedema rates were 0.8% and 6.5% and recurrence rates were 0.2% and 1.4%, demonstrating significantly reduced rates compared with published results (Tummel et al. 2017). A multi institutional prospective clinical trial is now underway to confirm the findings.

Lymph node radiation considerations WBRT radiation fields cover a portion of the axilla in most patients. Therefore, WBRT may have contributed to the low axillary recurrence rates in the IBCSG 23-01 (Galimberti et al. 2013) and ACOSOG Z11 (Giuliano et al. 2010) trials, which enrolled women with micrometastatic or up to two positive lymph nodes. In the AMAROS trial, axillary recurrence was shown to be equivalent for axillary radiation and ALND in patients with a positive sentinel lymph node, but with fewer complications (Donker et al. 2014). In patients with high-risk disease (greater than 3 positive lymph nodes, T3/T4 primary,

etc.), regional nodal radiation is recommended. Regional nodal radiation includes the infra-, supraclavicular, and internal mammary nodes. It reduces the risk of locoregional recurrence but has added toxicity. Axillary nodes may be included if there was no ALND and/or if high-risk disease in the axilla was present. The combination of ALND + axillary radiation has a higher lymphedema rate than either treatment alone.

Adjuvant Systemic Therapy

The goal of adjuvant systemic therapy is to reduce the risk of distant metastatic disease; however, local recurrence is also significantly reduced. The risks and benefits of systemic therapy are tailored to the recurrence risk and to the patient characteristics, including comorbid conditions and life expectancy. Systemic therapy includes antiestrogen therapy for hormone-positive tumors, combination chemotherapy for triple-negative and high-risk hormone-positive breast cancer, and anti-HER2 therapy in combination with chemotherapy for HER2-positive tumors. Significant progress is being made in deescalation of chemotherapy when there is no benefit, especially with molecular testing.

Antiestrogen therapy alone reduces the risk of systemic recurrence of hormone-positive (ER and/or PR positive) tumors and mortality (Early Breast Cancer Trialists' Collaborative, G 2011a). Aromatase inhibitors are more effective than the selective estrogen receptor modulator (SERM) tamoxifen (Early Breast Cancer Trialists' Collaborative, G 2015), and is preferred in postmenopausal women. Premenopausal women can only take tamoxifen, unless ovarian function is suppressed. Antiestrogen therapy is given for 5 years. An extended course of up to 10 years may decrease recurrence and contralateral breast cancer but does not improve survival (Burstein et al. 2019). Antiestrogen therapy is generally well tolerated.

Adjuvant multiagent chemotherapy was shown to improve survival in multiple clinical trials (Early Breast Cancer Trialists' Collaborative, G 2012). Iterations that incrementally improved survival include the addition of anthracyclines, taxanes in node-positive patients, and administration of chemotherapy in a dose-dense fashion. The side effects of chemotherapy include acute toxicities of nausea, vomiting, hair loss, myelosuppression, and neuropathy, and there can be long-term cardiotoxicity, leukemia, permanent neuropathy, and cognitive impairment. Patients with triple negative breast cancer (TNBC) benefit from chemotherapy unless their Stage is T1aN0, as they have no other systemic therapy option. Patients with hormone-positive disease derive a significant survival benefit from hormone therapy alone, and the addition of chemotherapy may not have a clinically significant benefit. Therefore, assays based on tumor gene expression (Table 115.2) were developed to categorize patients into risk categories for recurrence, allowing patients at low risk to avoid chemotherapy. Clinical trials evaluating these molecular tests have recently come to fruition, allowing many patients to forego chemotherapy.

Adjuvant anti-HER2 therapy, one of the first biologic therapies for cancer, was a major advance in the treatment of breast cancer. Patients whose tumors express HER2 have poor prognosis, and the addition of anti-HER2 therapy showed a 30% improvement in survival (Moja et al. 2012). Anti-HER therapy is given together with chemotherapy and is continued for a total of 1 year after the chemotherapy is completed. Toxicity is primarily cardiac. Additional targeted therapies such as CDK 4/6 inhibitors and PARP inhibitors are used primarily in the metastatic setting or in clinical trials.

Treatment of Local Recurrence

In-breast recurrences after BCT are typically treated by completion mastectomy. SLN may be repeated in selected patients, even if the technical success rate is lower than de novo SLN biopsy. Systemic therapy is added as indicated. The rare patient who has not undergone radiation therapy

Table 115.2 Genomic assays for invasive breast cancer patient risk classification

Multigene test	No. of genes	Testing indication	Categories	Prognostic validation (year[a])	Prediction validation
MammaPrint	70	pT1-2, pN0-1, age < 55	High/Low	2002	Mindact 2016
Oncotype Dx	21	pT1-2, ER+/HER2-, pN0-1		2004	NSABP B20, SWOG8814, TailorX 2018
Breast Cancer Index	7	pT1-3, ER+/HER2-, pN0, adjuvant ET	High/Low	2009	NA
Prosigna	58	pT1-2/pN0 or pT2pN1, ER+, adjuvant ET, PM	High/Int/ Low	2009	NA
Endopredict	12	pT1-2, ER+/HER2, pN0/pN1, PM	High/Low	2011	NA

From Varga et al. (2019), with permission
ET endocrine therapy, *PM* post menopausal
[a]Year of first validation study

may be treated by re-resection and radiation. Occasionally, a second course of radiation can be done, but the toxicity is significant. Recurrences after mastectomy are treated by local excision (if possible) and chest wall radiation including extended nodal basins. Not all local recurrences are amenable to local excision, even with removal of part of the chest wall. Staging and systemic therapy are usually added. In rare instances of isolated axillary recurrences, axillary lymph node dissection and radiation are indicated. With any recurrence, there is the chance of metastases, and metastatic workup should be performed prior to any locoregional therapy such as surgery or radiation.

Metastatic Disease

The main treatment for patients presenting with metastatic disease is systemic therapy. Recent data suggest that patients may do better with surgical intervention (Xiao et al. 2018), but for the most part, surgery is performed for palliation (i.e., bleeding, infection, or wound management). Radiation may be used for palliation of bone metastases. Oligometastases in liver, lung, or brain may selectively be resected. Extended survival is possible, especially for those with a response to systemic therapy and a long interval from treatment of their primary tumor.

Breast Problems in Men

Men can develop breast cancer and other benign conditions of the breast. The incidence of breast cancer in men is much lower, with a lifetime risk of 1 in 833 (American Cancer Society 2019b). It is associated with BRCA germline mutations, and is mostly hormone receptor positive (Gucalp et al. 2019). The workup is no different from that of women and should include mammography and ultrasound as indicated. The treatment recommendations and stage-specific survival are similar to that of women, but inclusion of men into clinical trials will be important in optimizing treatment options and survival.

Gynecomastia is the most common benign breast disease in men. It consists of persistent benign mammary gland enlargement, and can be unilateral or bilateral (Baumann 2018). The most common cause is medication, diseases such as chronic liver disease or hyperthyroidism, and drug abuse with marijuana or anabolic steroids. Surgical excision may be considered if the disease is symptomatic and persistent. Operations requiring removal of skin in addition to breast tissue, or where difficulty attaining a smooth normal contour after surgery, may require plastic surgery input for optimal cosmetic results. Nipple discharge is rare and frequently associated with malignancy (Morrogh & King 2009). Other benign breast conditions such as fibroadenomas and cysts are rare in men (Fentiman 2018).

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