

# CHAPTER 58 ■ Breast Cancer: Current Trends in Screening, Patient Evaluation, and Treatment

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## KEY POINTS

- In the United States, a woman born today has about a 1 in 8 chance of being diagnosed with breast cancer during her life.
- The American Cancer Society guidelines from 2015 recommend that women at the age of 55 years or older with average risk should have biennial screening mammography.
- Indications for postmastectomy radiation therapy include patients with large tumors (>5 cm), four or more involved lymph nodes, positive or close margins, and those with locally advanced breast cancer.
- The 2014 American Society of Clinical Oncology guidelines recommend axillary lymph node dissection for patients who have three or more metastatic sentinel lymph nodes on sentinel lymph node biopsy (SLNB) or who have one or two metastatic lymph nodes on SLNB but who do not desire whole-breast irradiation.
- Oncologic factors suggestive of suitable cases for nipple-sparing mastectomies include tumors >2 cm from the nipple and no clinical involvement of the skin or nipple.
- In breast cancer patients who have undergone mastectomy, there is no difference in survival in patients receiving chemotherapy within 4 to 8 weeks of surgery.

## INTRODUCTION

Breast cancer is the most common malignancy diagnosed worldwide; currently, it is the leading cause of cancer-related death in women.<sup>1</sup> It is estimated that in 2017 there were 252,710 Americans diagnosed with invasive breast cancer and 40,610 died of the disease. The lifetime risk of women developing breast cancer is approximately 12.4%, or 1 in 8 women. Over the last 10 years, the incidence of new female breast cancer cases has been relatively stable. Most women are diagnosed between 55 and 64 years old. The average 5-year survival rate is 89.7% and patients with higher disease stage have decreased 5-year survival. Death rates have been falling at an average rate of 1.8% per year.<sup>2</sup>

The Women's Health and Cancer Rights Act of 1998 increased access to reconstructive services for women with breast cancer. Since that time, an increased proportion of women have undergone reconstructive procedures by plastic surgeons. In the United States, there has been a nearly 20% increase in rates of reconstruction from 1998 to 2007. During the same time period, there was an increasing proportion of implant-based breast reconstruction compared with autologous-based breast reconstruction and higher rates of bilateral mastectomy.<sup>3,4</sup>

## RISK FACTORS

Although the etiology of most breast cancer is unknown, risk factors have been clearly defined. These include female gender, increasing patient age, family history of breast cancer at a young age, early menarche, late menopause, older age at first live childbirth, prolonged

hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, increased mammographic density, and genetic mutations. Aside from gender, increasing age and genetic mutations are the only substantial risk factors.

The National Cancer Institute (NCI) and National Surgical Adjuvant Breast and Bowel Project (NSABP) have developed the Breast Cancer Risk Assessment Tool that can help women to estimate their risk of developing invasive breast cancer (<https://www.cancer.gov/bcrisktool/>). This tool is also known as the Gail Model. The model uses a woman's history of prior breast malignancy, gene mutations, age, age to menarche, age at the time of her first live birth of child, family history, history of breast biopsy, and race/ethnicity to calculate 5 year and lifetime risk of developing breast cancer. The Gail Model has only been validated for women in the United States who are screened regularly for breast cancer.

Hereditary breast cancer accounts for up to 20% of breast cancer cases. More common syndromic breast cancer susceptibility genes include BRCA 1 and 2, TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), CDH1 (hereditary diffuse gastric cancer syndrome) STK11 (Peutz-Jeghers syndrome), mismatch repair genes (Lynch syndrome), and NF1 (Neurofibromatosis 1). More common nonsyndromic breast cancer susceptibility genes include PALB2, CHEK2, and ATM. Genetic testing should be performed if a patient has a known mutation in a breast cancer susceptibility gene, if there are two or more primary breast cancers on the same side of the family (in the same person or two separate individuals), if there is one or more ovarian cancers on the same side of the family, if there is a first- or second-degree relative who was diagnosed with breast cancer before the age of 45 years, or male breast cancer.<sup>5</sup> Patients with strong family history of breast cancer or known genetic predisposition should always be seen in coordination with a certified genetic counselor.

The BRCA1 and BRCA2 genes are autosomal dominant tumor suppressor genes that help to repair damaged DNA. BRCA 1 and 2 gene mutations account for 20% to 40% of the hereditary breast cancers. Women with the BRCA1 mutation have a 55% to 65% risk of developing breast cancer and a 39% chance of developing ovarian cancer by age 70 years. In contrast, women with the BRCA2 mutation have a slightly lower risk of 45% for developing breast cancer and 11% to 17% chance of developing ovarian cancer by age 70 years. In addition to breast and ovarian cancers, patients with the BRCA gene mutation are also at higher risk for fallopian tube, peritoneal, prostate, and pancreatic cancer. Although tests are helpful for identifying known genetic risk factors, those who have significant family history may have genetic mutations that have not yet been formally identified.<sup>6,7</sup>

## TYPES OF BREAST CANCER

The most common types of breast cancer include ductal carcinoma in situ (DCIS), invasive ductal carcinoma, and invasive lobular carcinoma. In situ, or noninvasive, cancers increase a patient's risk for developing invasive cancer. DCIS can transform into invasive cancer. Lobular carcinoma in situ (LCIS) does not transform into invasive disease but instead increases one's risk by 7 to 12 times for developing invasive cancer in either breast.<sup>8,9</sup> Other less common types of breast cancer include inflammatory breast cancer, Paget disease, Phyllodes tumor, and angiosarcoma.

## SCREENING

The updated American Cancer Society guidelines of 2015 recommend that women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. Women between the ages of 45 and 54 years are recommended to have annual screening mammography whereas women at the age of 55 years and older are recommended to have biennial screening mammography. Screening mammography is recommended to continue for as long as the patient has a life expectancy of 10 years or longer. In contrary to previous guidelines, no regular clinical breast examinations for breast cancer are recommended for average-risk women at any age.<sup>10</sup> Mammography is the standard imaging technique for breast cancer screening. Other screening modalities such as MRI are only indicated for patients with higher-than-average risk of developing breast cancer.

## STAGING

Tumor classification using the TNM staging system outlined by the American Joint Committee on Cancer (AJCC) is used to assist in prognosis and treatment of breast cancer. This system is built upon the extent of disease for the tumor (T), status of the regional lymph nodes (N), and presence of distant metastases (M). More recently, the AJCC has also added tumor grade, HER2, estrogen receptor (ER), progesterone receptor (PR), and genomic assays as part of the breast cancer staging system.<sup>11</sup> Early-stage breast cancer (stages I–II) is disease that is confined to the breast without extension to the chest wall or locoregional lymph nodes. Early-stage breast cancer is usually treated surgically and in selected patients with radiotherapy. Breast cancers that are stage III and above require locoregional control usually consisting of surgery and adjuvant systemic therapy.<sup>12</sup> Surveillance, Epidemiology, and End Results Program data from 2007 to 2013 showed that women with stage 0 or stage I breast cancer have a 5-year relative survival rate of nearly 100%. Women with stage II breast cancer have a 5-year relative survival rate of approximately 93%. Women with stage III and stage IV breast cancers have poorer prognoses with 5-year relative survival rates of 72% and 22%, respectively.<sup>13</sup>

## WORK-UP

An abnormal palpable breast mass or new mammographic finding is usually followed by an ultrasonic examination that can differentiate between solid and cystic breast masses. Ultrasound can also be used to detect lymph nodes that are suspicious for axillary metastases. The primary tumor is then evaluated by an image guided biopsy that, if found to be positive for malignancy, is treated with surgery. Although breast MRIs are generally more sensitive than mammography or ultrasonography, they have not been found to improve overall survival outcomes or improve locoregional recurrence rates.<sup>14–17</sup>

## SURGICAL TREATMENT

Improved local control is causally associated with improved breast cancer survival.<sup>18</sup> The surgical treatment of breast cancer has evolved. The first surgical treatment of breast cancer was the radical mastectomy that was popularized by William Halstead at the end of the nineteenth century. Since then, there has been a trend toward increasingly less invasive surgical management of breast cancer. Since the introduction of the radical mastectomy, other techniques, such as the modified radical mastectomy, partial mastectomy, skin-sparing mastectomy (SSM), and nipple-sparing mastectomy (NSM), have been developed. Although traditional surgical management has been used to treat the breast affected by cancer, there has also been an increasing trend toward risk reducing procedures such as contralateral prophylactic mastectomies.

## BREAST CONSERVATION THERAPY

Breast conservation therapy (BCT) couples surgical excision of the tumor with local radiotherapy. BCT is appropriate for early stage breast cancer and has been shown to provide equivalent overall survival rates compared to total mastectomy while still preserving the breast.<sup>18</sup> Despite similar survival rates, BCT has a reported positive margin incidence rate of 20% to 70%. Several techniques have been developed to decrease the positive margin rates including ultrasound needle localization, stereotactic needle localization, bracketing, or taking additional margins.<sup>19</sup>

## NEOADJUVANT SYSTEMIC THERAPY

Neoadjuvant systemic therapy is indicated for patients with inoperable tumors or if BCT is desired and the tumor size would have otherwise required a mastectomy. Cytotoxic, hormonal, and/or trastuzumab therapy can be used to reduce the amount of tumor burden in the breast and axilla without compromising survival. Although the entire initial tumor bed does not need to be removed, any residual palpable or radiographic lesions should be excised. For those who have complete clinical response, surgical excision is still indicated.<sup>18</sup> Decisions regarding radiation therapy should be based upon maximal stage from prechemotherapy tumor characteristics and/or pathologic stage regardless of the tumor's response to adjuvant systemic therapy.<sup>20</sup>

## MASTECTOMY

The goal of a mastectomy is to remove all breast tissue thus decreasing the risk for cancer recurrence. The anatomic borders of the breast are defined by the midline medially, the latissimus dorsi muscle laterally, the clavicle superiorly, and the insertion of the rectus abdominus muscle inferiorly. Contemporary techniques such as the SSM and the NSM can improve aesthetic outcome.<sup>21</sup>

The SSM was first described in June 1991 by Toth and Lappert. This technique is defined by removal of breast tissue with modified minimal incisions leaving as much skin as possible. Contraindications for SSM are inflammatory carcinomas, locally advanced carcinomas, and smoking (relative contraindication). Local recurrence rates after SSM are similar to other forms of mastectomy.<sup>22</sup>

The NSM was a natural evolution from the SSM. It is performed by removal of all breast tissue without excision of skin and the nipple-areolar complex. Oncologic contraindications for NSM include a tumor to nipple distance of <2 cm or clinical involvement of the skin and/or nipple. The NSM is generally performed with a frozen section from the posterior nipple margin to confirm no cancer invasion. If this frozen section is positive, the NSM is converted into a SSM. Partial or full nipple necrosis has been reported in 2% to 20% of NSMs. Overall survival, disease-free survival, or local recurrence has been shown to be similar between NSM, SSM, and modified radical mastectomy.<sup>21</sup>

## CONTRALATERAL MASTECTOMY

Rates of contralateral prophylactic mastectomy are increasing without evidence of substantial improvement of overall survival. The National Comprehensive Cancer Network currently recommends that women with breast cancer who are 35 years or younger, premenopausal, and carriers of a known BRCA gene mutation should only consider additional risk-reduction strategies with appropriate counseling. Except for the populations outlined earlier, risk-reduction prophylactic mastectomies of the breast contralateral to the known unilateral breast cancer are discouraged. It is important to discuss with those considering contralateral risk-reduction prophylactic mastectomy that these procedures are not without their own risk of minor and major complications, and that symmetry procedures match the native breast to the reconstructed side.<sup>20</sup>

## TIMING OF CANCER THERAPIES BEFORE AND AFTER SURGERY

Patients who do not receive neoadjuvant chemotherapy and who undergo surgery within 60 days of their diagnosis have improved overall survival.<sup>23</sup> For patients requiring neoadjuvant chemotherapy, overall survival, 5-year recurrence-free survival, and locoregional recurrence-free survival are equivalent when undergoing surgery within 8 weeks of completion of their neoadjuvant chemotherapy.<sup>24</sup> After a mastectomy for patients with estrogen receptor, progesterone receptor, or HER-2/neu-positive breast cancer, adjuvant systemic therapy has been shown to have similar outcomes on overall survival if initiated within 4 to 8 weeks of surgery. Patients with triple negative breast cancer (estrogen receptor, progesterone receptor, and HER-2/neu-negative breast cancers) have been shown to have an overall survival benefit if adjuvant chemotherapy is initiated within 30 days of their surgery.<sup>25</sup> Postmastectomy radiation therapy is associated with improved outcomes when performed within 6 to 8 weeks of surgery.<sup>26-29</sup>

## MANAGEMENT OF THE AXILLA

Removal of axillary lymph nodes both provides pathologic staging data and helps with local control. Unfortunately, removal of lymph nodes also results in significant morbidity. An axillary lymph node dissection (ALND) has a 16% risk of the development of lymphedema at 5 years. Although a sentinel lymph node biopsy (SLNB) is minimally invasive, it is still associated with a 5% rate of the development of lymphedema at 5 years. In addition to lymphedema, there can be arm stiffness, pain, and paresthesia. In the 1980s, two large studies (NSABP-B04 and the King's-Cambridge trials) compared ALND and radiation therapy with no treatment to the axilla in clinically node-negative patients. Each study demonstrated that treating the axilla significantly decreased the recurrence rate but did not improve survival rates in early stage breast cancer patients. With the development of lymphatic mapping techniques, SLNB became established as the new standard for staging the axilla. The SLNB was first described in 1994. The orderly manner with which lymph nodes drained allowed surgeons to use blue dye and/or radioactive technetium to biopsy the first 1 to 4 nodes that took up the technetium or blue dye to evaluate for metastases to the nodes.<sup>30</sup> SLNBs have been shown to have significantly less morbidity than an ALND. Patients who undergo SLNB have improved arm volume, sensibility, and ROM compared to those who undergo ALND.<sup>31</sup> In 2011, the American College of Surgeons Z0011 study was a prospective multicenter randomized trial that showed that for clinical T1-T2 invasive breast cancer patients with clinically negative lymph nodes that a SLNB with one to two positive SLNs was not inferior to a complete ALND for regional control of the axilla. Patients with clinically positive nodes at the time of diagnosis confirmed by fine needle aspiration (FNA) or core biopsy or patients who had no sentinel nodes identified (e.g., a failure of the sentinel lymph node mapping procedure) are recommended to have an ALND.<sup>21,32,30,33</sup>

## SYSTEMIC THERAPY

Systemic therapy has become increasingly precise. Chemotherapeutic regimens are becoming largely based on the pathologic analysis of one's tumor. In addition to a tumor's molecular profile, indications for chemotherapy include large tumor size (>2 cm), positive lymph nodes, ER-negative and PR-negative tumors, HER-2/neu-positive tumors, and inflammatory breast cancer. Anthracycline-based systemic therapies have been shown to improve survival compared to methotrexate-based regimens but they also have more substantial side effects. Anthracyclines can have associated cardiotoxicity and thus should be used carefully or avoided when treating elderly

patients and those with previous cardiac disease. Taxanes in combination with chemotherapy have also been shown to be more effective and thus have become used as standard treatment.<sup>5</sup>

## RADIATION THERAPY

Radiotherapy is an important component of local regional disease control. Whole-breast radiation therapy with or without boost to tumor bed is required as a part of BCT and occurs after lumpectomy. Current guidelines also recommend chest wall radiation after mastectomy if tumors are >5 cm, if pathology margins are positive, or if there are positive ALNs. Accelerated partial breast irradiation (APBI) is a technique that provides a more focused field of radiation after complete surgical excision of in-breast disease but is still considered investigational and should be used within the confines of clinical trials. The benefit of APBI is that it can be administered over a 1 to 2 week period as compared to the typical 6 to 7 week period for whole-breast radiation. APBI commonly combines brachytherapy with external-beam photon therapy to the tumor bed.<sup>20</sup>

## HORMONAL BLOCKADE AND BIOLOGIC THERAPIES

The relationship between breast cancer and hormone receptors has been well established since the 1950s. Since then, endocrine therapies such as tamoxifen have been used to treat breast cancer. Selective estrogen receptor modulators (SERMs), such as tamoxifen, block estrogen receptors in the breast, and effectively block estrogen activity in breast tissue. Tumors that are progesterone receptor positive often respond similarly to SERMs as ER-positive tumors. Hormonal blockade therapies are not without adverse events. Tamoxifen, while reasonably well tolerated, has been shown to be associated with hot flashes, headaches, menstrual abnormalities, a higher risk for endometrial cancer (cumulative risk 3.1% versus 1.6%), and a twofold increase in the incidence of pulmonary embolism. Current recommendations call for at least 5 years of treatment with a longer course of 10 years having been shown to further reduce recurrence and increase survival.

Aromatase inhibitors, such as anastrozole, have been demonstrated to increase disease-free survival, increase time to recurrence, and decrease rates of distant metastases and contralateral breast cancer with fewer adverse side effects compared to tamoxifen in ER-positive postmenopausal women.<sup>5,34-36</sup>

Targeted biologic therapies are used to treat patients with HER-2/neu receptor positivity. HER-2/neu receptor positive tumors are known to have a poorer prognosis with high rates of recurrence, relative resistance to hormonal therapy, and resistance to some chemotherapeutics. The monoclonal antibody against HER-2/neu, trastuzumab, has been shown to significantly improve outcomes in HER-2-positive cancers. Current guidelines recommend the use of trastuzumab in patients with HER-2/neu-positive tumors for 1 year.<sup>5</sup>

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*This is also known as the American College of Surgeons Z0011 study. The results of this paper set the standard for how surgeons decide on whether or not to perform an ALND.*



## QUESTIONS

1. A 62-year-old female presents with stage II invasive ductal carcinoma. The tumor measures 2.8 cm and is positioned 1.3 cm from her nipple. Clinically, she has no involvement of her axillary lymph nodes. She desires to undergo a NSM. What are her oncologic contraindications to undergoing a NSM?
  - a. Tumor is within 2 cm of her nipple
  - b. Tumor is >2.5 cm in size
  - c. Tumor is consistent with invasive ductal carcinoma
  - d. Patient is older than 60 years of age
  - e. Patient has stage II breast cancer
2. A 53-year-old female presents with stage III, ER/PR-positive, and Her-2/neu-positive right breast cancer. She undergoes a right SSM with placement of a prepectoral tissue expander. Her oncologist has recommended chemotherapy and would like to initiate it as soon as possible. How long after her mastectomy can you delay chemotherapy without impacting her overall survival?
  - a. 8 weeks
  - b. 9 weeks
  - c. 10 weeks
  - d. 12 weeks
  - e. 14 weeks
3. A 56-year-old female comes to your clinic to be evaluated for bilateral mastopexy. She appears to be a good candidate for a mastopexy. She has no personal or family history of breast cancer and denies any new masses in her breasts. Her last mammogram was performed 14 months ago, and there was no evidence of malignancy. How frequently should she have screening mammography?
  - a. Annually
  - b. Every 5 years
  - c. Biennially
  - d. No need for screening mammogram giving her low risk profile
  - e. Every 6 months
4. A 43-year-old female with an extensive family history of breast cancer was recently diagnosed with stage IIA left breast cancer. Her mother was diagnosed with breast cancer at age 46 and her sister was diagnosed at age 42. Genetic testing was performed, and she has no known genetic predisposing for breast cancer. She presents for a NSM with SLNB with a sub-muscular tissue expander placement. She had no clinically positive nodes preoperatively. Her SLNB demonstrated three positive lymph nodes, and she undergoes an ALND. What are her indications for the ALND?
  - a. Stage IIA breast cancer
  - b. Preoperative history of clinically negative nodes
  - c. Family history of breast cancer
  - d. Greater than 2 positive sentinel lymph nodes
  - e. NSM
5. Patients with the BRCA gene mutations are at increased risk of developing breast and ovarian cancer as well as which of the other cancers listed below?
  - a. Lung cancer
  - b. Pancreatic cancer
  - c. Basal cell carcinoma
  - d. Lymphoma
  - e. Glioblastoma

**1. Answer: a.** NSM is becoming more popular technique. The overall rate of occult nipple malignancy is 11.5%. Characteristics of the primary tumor that increase the risk for occult nipple malignancy include tumor-nipple distance <2 cm, tumor stage >2, lymph node metastasis, lymphovascular invasion, human epidermal growth receptor-2-positive, estrogen receptor/progesterone receptor-negative, tumor size >5 cm, retroareolar/central location, and multicentric tumors.

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**2. Answer: a.** There is no difference in overall survival when comparing initiation of adjuvant chemotherapy within 4 weeks or within 8 weeks after surgery for patients who have estrogen receptor, progesterone receptor, or HER-2/neu-positive breast cancers. In patients with triple negative breast cancers, initiation of adjuvant chemotherapy within 4 weeks of surgery has been shown to improve overall survival.

**Reference:**

Gagliato Dde M, Gonzalez-Angulo AM, Lei Xet al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *J Clin Oncol.* 2014;32(8):735-744.

**3. Answer: c.** The updated American Cancer Society guidelines of 2015 recommend that women with an average risk of breast cancer should undergo regular screening mammography starting at the age of 45 years. Women between the ages of 45 and 54 years are recommended to have annual screening mammography while women at the age of 55 years and older are recommended to have biennial screening mammography. Screening mammography is recommended to continue for as long as the patient has a life expectancy of 10 years or longer.

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Oeffinger KC, Fontham ET, Etzioni R, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA.* 2015;314(15):1599-1614.

**4. Answer: d.** In 2011, the American College of Surgeons Z0011 study was a prospective multicenter randomized trial that showed that for clinical T1-T2 invasive breast cancer patients with clinically negative lymph nodes that a SLNB with one to two positive SLNs was not inferior to a complete ALND for regional control of the axilla. Patients with clinically positive nodes at the time of diagnosis confirmed by FNA or core biopsy or patients who had no sentinel nodes identified (e.g., a failure of the sentinel lymph node mapping procedure) are recommended to have an ALND.

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Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305(6):569-575.

**5. Answer: b.** The BRCA1 and BRCA2 genes are autosomal dominant tumor suppressor genes that help to repair damaged DNA. BRCA 1 and 2 gene mutations account for 20% to 40% of the hereditary breast cancers. Women with the BRCA1 mutation have a 55% to 65% risk of developing breast cancer and a 39% chance of developing ovarian cancer by the age of 70 years. In contrast, women with the BRCA2 mutation have a slightly lower risk of 45% for developing breast cancer and 11% to 17% chance of developing ovarian cancer by the age of 70 years. In addition to breast and ovarian cancers, patients with the BRCA gene mutation are also at higher risk for fallopian tube, peritoneal, prostate, and pancreatic cancer.

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