# Cancer of the Breast

N. Lynn Henry, Payal D. Shah, Irfanullah Haider, Phoebe E. Freer, Reshma Jaggi, and Michael S. Sabel

## Summary of Key Points

### Incidence and Epidemiology
- Breast cancer is the most frequently diagnosed cancer in women in the United States, accounting for an estimated 268,670 new cases of invasive breast carcinoma, 63,960 new cases of in situ carcinoma, and 41,400 deaths in 2018.
- In the United States, the age-specific incidence of breast cancer increases with age, to a lifetime risk of breast cancer of 1 in 8; by age 40 years, approximately 1 in 203 women will have been diagnosed with breast cancer; at 60 years of age, the figure is 1 in 28 women.
- Incidence rates have been rising about 1% per year; mortality rates stayed relatively constant until recently, when annual decreases were seen.
- A sharp decline in the incidence of breast cancer in the early 2000s followed a decrease in the use of postmenopausal hormone replacement therapy; the incidence rate has since remained stable.
- Age, family history, and both endogenous and exogenous ovarian hormone exposure have an important effect on risk and have been incorporated into models that predict individual risk of breast cancer; diet, alcohol use, and other factors play a smaller role.
- African Americans with breast cancer are diagnosed at more advanced stages and have worse outcomes, including survival.
- Inherited mutations in *BRCA1*, *BRCA2*, *PTEN*, *TP53*, *STK11*, *ATM*, *CHEK2*, *PALB2*, and other genes can increase the risk of breast cancer; individuals with a personal or family history of hereditary breast cancer should be referred for genetic evaluation.

### Biology and Estimation of Risk
- The expression of nuclear estrogen and progesterone receptors plays an important role in the differentiation and growth of normal breast epithelium and the response of breast cancer cells to hormonal therapeutics.
- ERBB2 (human epidermal growth factor receptor 2 [HER2]) is a growth-signaling molecule on the surface of normal breast cells that is overexpressed in approximately 20% of breast cancer tumors, contributing to growth autonomy and genomic instability.
- Molecular analyses have defined at least four biologic subtypes of breast cancer, including basal type, two luminal types (luminal A and luminal B), and the HER2-enriched type.
- *BRCA1* and *BRCA2* are tumor suppressor genes that play a critical role in homologous recombination repair (HRR) of DNA damage; inherited mutations in these and other HRR genes are associated with an increased risk of breast cancer.
- Regardless of the criteria used by an individual physician and patient to define high risk, four possible actions may be taken, some of which can be used simultaneously: (1) enhanced surveillance, (2) behavioral modification, (3) chemopreventive strategies, and (4) prophylactic mastectomy or oophorectomy.

### Screening and Diagnosis
- Although exact guideline recommendations for mammography screening remain controversial and are debated, all guidelines agree that most lives are saved with screening starting at age 40. The 2015 American Cancer Society (ACS) guidelines recommend a yearly mammogram starting at age 45, with the option to transition to biennial screening at age 55, and the option to begin screening between ages 40 and 44. Similarly, the American College of Radiology recommends yearly mammography starting at age 40. The 2016 US Preventive Services Task Force (USPSTF) breast cancer screening guideline recommends biennial screening mammography for women ages 50 to 74 years and an individualized approach for women ages 40 to 49 years. The ACS also recommends that breast magnetic resonance imaging (MRI) be used in addition to mammographic screening in women with a lifetime risk of breast cancer greater than 20%.
- Microcalcification and soft tissue density are the major indications for biopsy after mammographic screening; the mammographic abnormality with the highest rate of malignancy is a mass with associated calcification.
- For patients with breast symptoms or palpable abnormalities, mammography, in conjunction with other imaging modalities such as ultrasonography and breast MRI as indicated, is used to characterize the suspicious area, evaluate the remainder of the breast for occult lesions, and assess the contralateral breast.
- Malignant breast masses classically are nontender and firm, with irregular borders.
- Diagnostic methods include needle-core biopsy with ultrasound or stereotactic guidance, fine-needle aspiration cytology, and excisional...
biopsy, with or without wire localization.

Management of Noninvasive Disease
- Lobular carcinoma in situ (LCIS) is a nonpalpable lesion that usually is discovered with another indicator for biopsy; it is an indicator of risk of subsequent invasive breast cancer. The rare pleomorphic variant of LCIS seems to have a more aggressive behavior and is considered more as a precursor of invasive lobular cancer rather than a marker of breast cancer risk.
- Management of LCIS has shifted toward observation after biopsy rather than mastectomy; increasing evidence shows that tamoxifen should be considered as a preventive approach.
- Unlike LCIS, ductal carcinoma in situ (DCIS) is almost always first identified with mammography; it accounts for most of the increasing number of carcinoma in situ lesions diagnosed.
- DCIS is more likely to be localized to one area of the breast; therefore most patients are candidates for breast conservation. Tamoxifen or, in postmenopausal women, aromatase inhibitors should also be considered after lumpectomy and radiation therapy to reduce the risk of another ipsilateral or a new contralateral breast cancer event, which can be invasive or noninvasive.

Management of Early-Stage Breast Cancer
- Patients should undergo a complete history and physical examination.
- Bilateral mammography is indicated for all patients, and other breast imaging (ultrasound and MRI) should be used as needed for each individual patient; advanced imaging studies are recommended only to evaluate specific signs or symptoms or in patients with locally advanced disease.
- Prognostic factors include pathologic tumor size, hormone receptor expression, HER2 status, axillary nodal status, histologic subtype, and tumor grade.
- Multiple gene expression profiling assays have been developed as prognostic tests.
- The 21-gene recurrence score assay predicts benefit from systemic chemotherapy in addition to endocrine therapy in node-negative, hormone receptor-positive breast cancer, and is undergoing evaluation for use in node-positive disease.
- The seventh edition of the American Joint Committee on Cancer TNM staging system takes into account the increasing use of advanced imaging and pathology techniques, such as sentinel node biopsy and immunohistochemistry; it also considers the number of involved nodes as a strong prognostic factor.
- Sentinel lymph node mapping is now the standard of care for many women with early breast cancer because it is more accurate and less morbid than axillary dissection.
- For patients with stages I and II disease, breast conservation (lumpectomy followed by radiation therapy) and simple mastectomy are the major therapeutic options; for most patients, breast conservation is the preferred approach.
- Adjuvant therapy with cytotoxic drugs, endocrine therapy, and/or anti-HER2 therapy is recommended depending on stage of disease and pathologic characteristics.
- For patients with locally advanced disease, multimodality therapy is recommended; the sequence of systemic therapy, surgery, and radiation therapy depends largely on the operability of the primary disease.
- For women with inoperable or inflammatory breast cancer, preoperative chemotherapy is recommended, followed by surgery, radiation therapy, and endocrine therapy, if appropriate. Patients with HER2-positive disease should also receive anti-HER2-targeted therapy. Preoperative endocrine therapy for patients with hormone receptor-positive disease may also be a reasonable option.
- HER2 is a strong predictive marker, and accurate determination of HER2 status identifies patients with T1bN0 tumors and above who should be considered candidates for adjuvant therapy with a trastuzumab-based regimen.
- Expression of estrogen receptor and/or progesterone receptor is a predictive marker for response to endocrine therapy.
- The results of the serial meta-analyses performed by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) show that the survival benefits of adjuvant chemotherapy and endocrine therapy persist after 15 years of follow-up.
- Challenges that require resolution include identification of biologic parameters that more precisely predict the natural history of disease and the response to systemic therapy; more effective treatments are needed.

Management of Locally Recurrent Disease
- Local recurrence is an indicator of systemic relapse in most cases; an exception may be local relapse in a breast that has undergone conservation therapy.
- Surgical removal alone may be sufficient in some cases, but it often is combined with locoregional radiotherapy and/or systemic therapy.

Management of Metastatic Disease
- Although a small percentage of patients with metastatic breast cancer achieve long-term disease-free survival, this stage of disease is generally not curable, and therapy is largely palliative.
- A wide range of systemic, local, and supportive therapies are available for the palliation of metastatic breast cancer. Primary breast surgery may be indicated in selected patients with stage IV disease.
- The selection of endocrine, cytotoxic, or biologic therapy usually is based on disease-free interval, receptor status, HER2 status, presence or absence of visceral involvement, performance status, age, and previous exposure to systemic therapy.
- The treatment approach for metastatic breast cancer generally involves sequential therapies, each continued until disease progression or unacceptable toxicity.
- Patients with hormone receptor-positive, HER2-nonamplified metastatic breast cancer should be considered initially for endocrine-based therapy, with systemic chemotherapy reserved for patients who are significantly
symptomatic or have compromised organ function.
- Anti-HER2 agents, such as trastuzumab, lapatinib, pertuzumab, and ado-trastuzumab emtansine have changed the natural history of patients with HER2-positive metastatic breast cancer.
- Treatment with bisphosphonates or denosumab is indicated to minimize bone complications in patients with bone metastases.

EPIDEMIOLOGY

Incidence

Worldwide, breast cancer is the most common type of cancer among women. In the United States, approximately 268,670 new cases of invasive breast carcinoma, 63,960 new cases of in situ carcinoma, and 41,400 deaths were expected in 2018. In women, breast cancer accounts for 29% of new cases of cancer and 14% of cancer deaths, second only to lung cancer as a cause of cancer-specific death. Approximately 1% of breast cancers occur in males, and 90% of these are estrogen receptor (ER) positive. Incidence rates of breast cancer decreased by 2% per year from 1999 to 2005, and have remained relatively stable since then. The decline appears to be partly the result of a decrease in the use of postmenopausal hormone replacement therapy (HRT). Although incidence rates (all races combined) are substantially higher for women older than age 50 years, approximately 23% of breast cancers are diagnosed in women younger than age 45 years (Table 88.1).

Between 2008 and 2012, breast cancer was the most common cancer diagnosed in women in the United States (overall incidence 123.1 per 100,000 women), followed by lung cancer (overall incidence 54.1 per 100,000 women). However, the leading cause of cancer death was lung cancer (37.8 per 100,000 women), followed by breast cancer (21.9 per 100,000 women). Mortality rates from breast cancer have been decreasing over time in the United States (see Fig. 88.1). Around the world, there are large variations in incidence, mortality, and survival, which may be a result of several underlying complex factors, including age, ethnicity, diet, and lifestyles, including reproductive issues. Breast cancer is increasing in less-developed countries, likely related to changes in lifestyle factors. Most of our knowledge regarding specific risk factors has been derived from large observational studies in developed countries, such as the Nurses’ Health Study (NHS) and NHS II in the United States, and the Million Women Study in the United Kingdom. Some of these risk factors are briefly summarized in the following sections.

Diet

The best-established dietary factor associated with increased risk for breast cancer is higher consumption of alcohol. Initial studies correlated higher fat intake and decreased intake of fruit and vegetables with an increased risk for breast cancer, but more recent prospective studies have failed to confirm those observations. One randomized study (Women’s Healthy Eating and Living [WHEL] Study) in breast cancer patients who consumed a low-fat and high–fruit-and-vegetable diet did not demonstrate a decreased risk of breast cancer recurrence. However, a second randomized study (Women’s Intervention Nutrition Study [WINS]) demonstrated a lower risk of recurrence with a decreased intake of dietary fat associated with modest weight loss in breast cancer survivors.

Dietary phytoestrogens, such as those found in soybeans, have a chemical structure that is similar to that of 17β-estradiol and can bind to the ER to compete with estrogens. Their consumption may have a weak protective effect against breast cancer. More recent studies have suggested an inverse association of soy intake and breast cancer in Asian but not non-Asian populations. Although there is significant interest in the association of vitamin D intake and breast cancer risk, there are insufficient data to draw conclusions regarding potential benefit at this time; some data suggest that there may be an association in postmenopausal women.

### Table 88.1 Risk of Breast Cancer in US Women

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>Breast Cancer Risk</th>
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<tbody>
<tr>
<td>30–40</td>
<td>1.227</td>
</tr>
<tr>
<td>40–50</td>
<td>1.68</td>
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<tr>
<td>50–60</td>
<td>1.44</td>
</tr>
<tr>
<td>60–70</td>
<td>1.29</td>
</tr>
<tr>
<td>Lifetime (to age 110 years)</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Ionizing Radiation

The accumulated knowledge about radiation-related breast cancer risk in women derives mainly from epidemiologic studies of patients exposed to diagnostic or therapeutic radiation and of Japanese atomic bomb survivors. Therapeutic radiation, particularly extended-field radiation therapy for Hodgkin lymphoma, has been associated with an increased risk of breast cancer. The age of exposure is important, with the highest breast cancer risk seen in women undergoing mantle irradiation around puberty, and is minimal for women exposed after menopause.16-17

Exogenous Hormones

The NHS originally was designed to determine whether oral contraceptive use was associated with an increase in breast cancer. Analysis of data from that study and many additional studies has confirmed that current users of exogenous hormones have a slightly increased risk of developing breast cancer, although this risk resolves within 5 years of discontinuation of therapy.18 In addition, use of exogenous hormones is associated with a decreased risk of colon and ovarian cancer; there is no increase in overall cancer mortality associated with their use.19 The Women’s Health Initiative (WHI) randomized study of HRT in postmenopausal women demonstrated an increased risk of invasive breast cancer with the combination of estrogen plus progesterone therapy,20 but not with estrogen alone.21 Other studies have also demonstrated that breast cancer risk is affected by type of HRT and time of initiation of HRT, with an increased risk seen with therapy started soon after menopause.22 After initial publication of the WHI results23 and widespread discontinuation of HRT, age-adjusted incidences of invasive breast cancer decreased in the United States between 2002 and 2003 by 7%, primarily in ER-positive tumors in women 50 years of age or older.

Reproductive Factors and Endogenous Hormones

Breast cancer risk consistently has been correlated with an earlier age of menarche, later age of menopause, nulliparity, and late age of first birth, all of which determine the cumulative number of ovarian cycles. This finding is consistent with the correlation between estrogen levels and breast cancer risk. In postmenopausal women, an increased risk of breast cancer has been demonstrated in those with estradiol levels in the highest quartile.24

Obesity and Body Habitus

There is a clear association between obesity and breast cancer risk. Women with a body mass index (BMI) in the overweight (25–30) or obese (>30) range have been shown to have an elevated risk of breast cancer. In addition, increased BMI is associated with an increased risk of breast cancer death.25-27 The increased risk of breast cancer with obesity in postmenopausal women appears to be mediated, at least in part, by elevated endogenous estrogen and, possibly, insulin levels.28 An increased risk of breast cancer has also been associated with increasing height, with a relative risk (RR) of 1.17 (95% confidence interval [CI], 1.15–1.19) for every 10 cm of additional height.29

Prior Breast Biopsy

Finding a nonproliferative lesion such as a cyst or mild hyperplasia of the usual type with a breast biopsy is generally not associated with an increased risk of breast cancer (Table 88.2). Proliferative lesions without evidence of atypia, such as usual ductal hyperplasia, sclerosing adenosis, and intraductal papillomas, are associated with a 1.5- to 2-fold increased risk of developing breast cancer. In contrast, the risk of developing breast cancer is substantially increased in patients with a prior breast biopsy with evidence of atypical hyperplasia, with an RR of breast cancer of 3.7 to 5.3.30-32 In contrast, the risk of developing breast cancer after a finding of flat epithelial atypia (FEA) was only marginally increased compared with the risk from a nonproliferative lesion.

Familial History and Predictive Models of Breast Cancer Risk

Breast cancer is approximately twice as common among first-degree relatives of breast cancer patients as in those women with no family history of the disease. The two most prevalent breast cancer susceptibility genes, BRCA1 and BRCA2, were identified by linkage analyses in the mid-1990s but account for less than 20% of familial clustering of breast cancer.30 Since then, rare germline mutations in several other high-penetration hereditary breast and ovarian cancer genes, such as TP53, PTEN, CDH1, and SKT11, have been shown to confer a substantially increased risk of breast cancer. Additional details about BRCA1- and TP53-mutated cancers are provided later.

Given that linkage analyses have failed to yield additional susceptibility loci, it is likely that most of the remaining genetic susceptibility is a result of a number of moderate- and low-penetrance alleles that coexist in highly penetrant combinations in a polygenic model, although some familial risk may still be a result of rare, undiscovered, high-penetrance gene mutations.31 Multiple moderate-penetrance hereditary breast cancer genes including ATM, CHEK2, PALB2, and NBN have been identified.32 Pathogenic mutations in these genes are associated with an RR of breast cancer of 2 to 5, and risk management strategies have been delineated.32,33

Apart from specific cancer susceptibility genes, an increasing understanding of relevant predisposing factors has led to integrated efforts at evaluating a women’s individual risk.34 Several individualized risk assessment tools are available, including the Gail, Claus, BRCAPRO, Tyrer Cuzick, and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) models.35 Many of these tools are now available on the Internet—for example, http://www.cancer.gov/bcrisktool/ can be accessed on the National Cancer Institute (NCI) website. These tools are being used for clinical counseling for healthy women perceived to be at risk and to determine candidates for enhanced surveillance or chemoprevention.36-37 Given that for women living in the Western hemisphere the lifetime risk of breast cancer is approximately 11%, even a small RR reduction could translate into many thousands of lives saved.

Table 88.2 American Board of Pathology Histologic Classification of Benign Disease

<table>
<thead>
<tr>
<th>Histopathologic Findings</th>
<th>Approximate Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>Nonproliferative</td>
<td>No added risk</td>
</tr>
<tr>
<td>Cysts</td>
<td>Slight added risk</td>
</tr>
<tr>
<td>Duct ectasia</td>
<td>?</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.5:1–2:1</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>4:1</td>
</tr>
<tr>
<td>Milk ductal epithelial hyperplasia</td>
<td>7:1</td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>10:1</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>10:1</td>
</tr>
<tr>
<td>Radial scars</td>
<td>10:1</td>
</tr>
<tr>
<td>Complex sclerosing lesions</td>
<td>10:1</td>
</tr>
<tr>
<td>Moderate florid hyperplasia</td>
<td>10:1</td>
</tr>
<tr>
<td>Atypical hyperplasia (ductal and lobular)</td>
<td>10:1</td>
</tr>
<tr>
<td>Extensive ductal involvement of atypical hyperplasia</td>
<td>10:1</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>10:1</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>10:1</td>
</tr>
</tbody>
</table>
**BRCA1, BRCA2, TP53, and Hereditary Susceptibility to Breast Cancer**

Germline mutations in BRCA1 and BRCA2 represent the most common identifiable cause of hereditary breast cancer. BRCA1 (chromosome 17q) and BRCA2 (chromosome 13q) are tumor suppressor genes; inherited mutations in BRCA1/2 confer impaired homologous recombination repair of DNA and are highly penetrant for hereditary breast and ovarian cancer syndrome. Mutations are particularly prevalent in the Ashkenazi Jewish population. Depending on multiple factors including the specific gene mutation, modifiers, and the population studied, the cumulative cancer risks by age 70 are estimated for a female BRCA1 mutation carrier at approximately 60% to 70% for breast cancer and 20% to 50% for ovarian cancer, and for a female BRCA2 mutation carrier, 50% to 70% for breast cancer and 10% to 30% for ovarian cancer, with higher estimates in earlier studies due to ascertainment bias and the early examination of families with multiple breast and ovarian cancer cases. Individuals with pathogenic BRCA mutations may also be at increased risk for male breast cancer, prostate cancer, pancreatic cancer, and melanoma. Multiple other genes interact with BRCA1 and/or BRCA2 and play a role in homologous recombination repair, such as PALB2, ATM, and CHEK2; mutations in several of these genes also confer risks of breast and other cancers, although the magnitude of these risks are lower than the those conferred by BRCA. Why these genes predispose primarily to breast and ovarian cancers remains unclear. Important to note, prognosis of BRCA mutation carriers with breast cancer appears similar to prognosis for sporadic breast cancer patients.

Inheritance of a germline pathogenic p53 mutant allele causes the rare high-penetrance familial Li-Fraumeni syndrome, characterized by multiple early-onset cancers, including sarcoma, leukemia, adenocortical tumors, and breast cancer in women who survive childhood cancers. Thirty percent to 50% of sporadic cases of breast cancers harbor somatic mutations in p53, based primarily on sequencing of exons 5 through 8 (the DNA-binding core), where approximately 90% of mutations are found. Currently, p53 mutations that have been observed in breast cancers are listed in the p53 database maintained by the International Agency for Research on Cancer.

Myriad personal and family history factors should prompt a clinician to refer a breast cancer patient for genetic evaluation, including diagnosis before the age of 45, Ashkenazi Jewish ancestry, or diagnosis of triple-negative disease before age 60. Genetic evaluation begins with a comprehensive assessment of risk factors. Genetic testing, if indicated, should be preceded by a thorough informed consent that includes potential issues of uninformative results or variants of uncertain significance, and general implications of a positive result.

Genetic testing for hereditary breast and ovarian cancer syndrome mutations can occur in a targeted fashion or with full gene sequencing and evaluation of large genomic rearrangements. In addition, testing can be conducted with multigene panels using massively parallel sequencing that evaluates BRCA1/2 and multiple other genes simultaneously. The clinical usefulness of testing for mutations in moderate- and low-penetrance genes, particularly in the setting of phenotypic discordance, is often unclear. When testing with a multiplex panel, pretest counseling should also include discussion of the possibilities of unanticipated or phenotypically discordant findings in high-penetrance genes and low- or moderate-penetrance mutations that may have undefined clinical validity.

The most recent Genetic/Familial High-Risk Assessment: Breast and Ovarian National Comprehensive Cancer Network (NCCN) Guidelines (Version 2.2017) provides recommendations for management of breast cancer risk in the context of pathogenic mutations in multiple genes, including ATM, BRCA1/2, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, and TP53. Testing should be followed by posttest counseling including a discussion of the known and unknown data regarding cancer risks and management strategies.

**BIOLOGIC CHARACTERISTICS AND PATHOLOGY**

For years, the traditional breast cancer biomarkers (ER; progesterone receptor [PR]; and Her2/neu [HER2]) have been a principal determinant of adjuvant and metastatic breast cancer therapy. Although it was originally recognized in the late 1800s that antiestrogen treatments could be effective for breast cancer when Sir George Beatson first reported the benefits of oophorectomy as palliative therapy for several young women with metastatic breast cancer, traditional cytotoxic chemotherapy was the mainstay of treatment for decades although it rarely led to the cure of metastatic breast cancer. More recently, the discovery of cancer-specific therapeutic targets such as ER and HER2 has led to the successful development of therapies that are effective only in the subset of patients whose tumors harbor these targets. Antiestrogen therapy in tumors that are ER and/or PR positive and anti-HER2 therapy in tumors that demonstrate amplification of HER2 are strategies that have demonstrated a survival benefit beyond that provided by cytotoxic therapy alone.

The modern diagnosis and therapy of breast cancer have evolved from focusing almost entirely on these immunophenotypic features to considering other biologic targets and pathways that might promote tumor development and growth. Standard biologic therapies beyond those targeting hormone receptors and HER2 include the mammalian target of rapamycin (mTOR) inhibitor everolimus and the cell cycle inhibitor palbociclib.

Perhaps the most significant paradigm shift has been in the setting of metastatic disease, with widespread active efforts to therapeutically exploit the genomic profile of a tumor. This concept, which has been successful in other cancers in which the underlying genetic aberration can be targeted, such as imatinib mesylate in chronic myelogenous leukemia and gastrointestinal stromal tumor, has provided the impetus for large-scale sequencing efforts of cancer genomes to identify additional targets. With the incorporation into the clinic of both germline genetic and somatic molecular testing, clinicians are increasingly aware of factors such as deficient DNA repair and activation of molecular signaling pathways that affect both standard and investigational breast cancer treatment options.

In addition, microarray technologies that enable the simultaneous quantitation of all RNA species and genome-wide DNA copy number changes have begun to provide diagnostic classifications that may be superior to traditional histologic criteria for determining prognosis and therapy. Finally, the identification of both normal mammary gland and breast cancer stem cells has led to novel therapeutic approaches that are being tested in clinical trials. These advances and their implications for therapy are summarized in the following sections.

**Histology**

**Invasive Breast Carcinoma**

The majority of invasive breast cancers are epithelial in origin and are histologically heterogeneous. Most are adenocarcinomas arising from the terminal ducts. Invasive ductal carcinoma accounts for approximately 85% of breast cancers and can form ductal structures (Fig. 88.2). In contrast, invasive lobular carcinoma, which is characterized by small, regular epithelial cells that tend to align in single file and grow around ducts and lobules, accounts for 5% to 15% of breast cancers (Fig. 88.3). The overall prognosis of classic invasive lobular cancer is thought to be similar to that of the invasive ductal subtype, although there may be some differences in likelihood of response to chemotherapy and endocrine therapy compared with ER-positive, HER2-negative invasive ductal carcinomas.

There are a number of less common types of breast carcinoma, including mucinous, tubular, and papillary, which are generally hormone receptor positive. Tubular cancers often resemble normal mammary ducts (Fig. 88.4), whereas mucinous (colloid) carcinoma is characterized microscopically by abundant accumulation of extracellular mucin...
around tumor cells (Fig. 88.5). In contrast, a frond-forming growth pattern characterizes papillary carcinoma (Fig. 88.6). All three subtypes usually have a more favorable prognosis compared with hormone receptor–positive invasive ductal carcinomas of similar size and nodal status. In fact, according to the NCCN guidelines, adjuvant endocrine therapy is not strongly recommended for node-negative favorable-histology tumors measuring up to 3 centimeters in size, whereas treatment is recommended for invasive ductal or lobular carcinomas that are larger than 1 cm.

Although medullary carcinoma is typically ER, PR, and HER2 negative, which generally portends a poor prognosis, when it meets all the histologic criteria defined hereafter it too has a more favorable prognosis. The required histopathologic features include a well-circumscribed border, intense reaction with lymphocytes and plasma cells, poorly differentiated nuclei, a syncytial growth pattern, and little or no intraductal carcinoma (Fig. 88.7). On the other hand, atypical medullary tumors, which do not meet all of these criteria, do not have the same excellent outcome, and care must be taken to avoid an incorrect diagnosis.

Adenoid cystic carcinoma and apocrine carcinoma are other rare subtypes that are typically ER, PR, and HER2 negative. In addition, apocrine carcinomas often express androgen receptor. Despite these characteristics, these tumors also typically have more indolent behavior. In contrast, some uncommon histologic types are associated with a poor prognosis and poor response to standard treatment. For example, metaplastic carcinomas generally have differentiation of neoplastic epithelial cells into other phenotypes, including squamous, spindle cell, or mesenchymal. Although they are less likely to have nodal involvement at the time of diagnosis, relapse rates are high.

BRCA-Associated Breast Cancers

BRCA1- and BRCA2-associated tumors have typical pathologic features. BRCA1-associated breast cancers are usually of the basal-like subtype and are more likely to be negative for hormone receptors and HER2 overexpression. Conversely, BRCA2-associated breast cancers have more variable pathologic features and are often phenotypically similar to sporadic cancers, with a predominance of hormone receptor–positive tumors.53,54 Once cancer has been diagnosed, standard therapy is dictated by similar prognostic and predictive features to sporadic breast cancer, and no specific regimens are indicated on the basis of genetic predisposition at this time. The involvement of BRCA proteins in DNA repair by homologous recombination suggests that these tumors would be particularly sensitive to chemotherapies that induce DNA interstrand cross-links such as platinum salts, and there are clinical data supportive of this hypothesis.55–58 Furthermore, data suggest that
Part III: Specific Malignancies

**Figure 88.6** • (A) Invasive carcinoma arising in papillary ductal carcinoma in situ (invasive papillary carcinoma). The in situ component shown on the right has a frondlike appearance, and the invasive carcinoma component on the left consists of irregularly shaped small glands. (B) Invasive micropapillary carcinoma of the breast. The tumor resembles ovarian serous carcinoma, and small clusters of invasive tumor cells are separated from the stroma by spaces. A psammoma body is visible.

**Figure 88.7** • Medullary carcinoma characterized by a well-defined border, an intense lymphoplasmacytic reaction, and pleomorphic tumor cells with vesicular chromatin.

BRCA-associated breast cancers may have higher 21-gene recurrence scores (RSs), potentially consistent with chemosensitivity of these tumors. Finally, poly (ADP-ribose) polymerase 1 (PARP1) is involved in the base excision repair pathway; when this repair pathway is pharmacologically inhibited in the setting of BRCA deficiency, synthetic lethality may result in cytotoxicity. The sensitivity of BRCA-associated ovarian cancer to the PARP inhibitor olaparib is demonstrative of this principle; studies in BRCA-associated breast cancer have not yet demonstrated the same magnitude or consistency of response to date.

**Noninvasive Breast Carcinomas**

Much evidence supports the view that the development of malignancy is a multistep process and that invasive breast cancer has a preinvasive phase. During the carcinoma in situ (CIS) phase, normal epithelial cells undergo enough genetic alterations to result in malignant transformation. Transformed epithelial cells proliferate and pile up within lobules or ducts but lack the additional required genetic alteration that enables cells to penetrate the investing basement membrane. Two types of noninvasive breast cancers have been described: lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS).

The original description of LCIS characterized the lesion as a lobular unit with a cluster of ductules or acini filled, distorted, and distended by proliferating epithelial cells (Fig. 88.8). LCIS cells have a fairly uniform pattern of clear cytoplasm containing rounded, bland nuclei. Intercellular spaces are preserved, and clear vacuoles within the cytoplasm may displace the nucleus. This often is referred to as classic LCIS. In contrast, pleomorphic LCIS is a morphologic variant that is more aggressive. Pleomorphic LCIS elicits a similar pattern of infiltrative growth as invasive lobular carcinoma, yet neoplastic cells have marked nuclear atypia and pleomorphism.

The terminal ductal lobular unit has been proposed as the site of origin of most breast cancer, including DCIS (Fig. 88.9). In contrast to LCIS, which tends to be multicentric, DCIS is generally confined to one branching ductal system in the breast. DCIS, by definition, has intact basement membrane on light microscopy. Unlike pure DCIS, when microinvasion is present, type IV collagen and lamina are lost from the basement membrane in association with loss of membrane continuity. Such observations lend weight to the argument that DCIS is a precursor of invasive ductal cancer. Not all cases of DCIS progress to invasive cancer. Identifying the predictors of this process is a major challenge in understanding the biology of this disease.

The pathologic classification of DCIS previously was based primarily on the architectural patterns of DCIS as seen microscopically, including solid, cribriform (Fig. 88.10), comedo, micropapillary, and papillary variants. The features of DCIS that are currently routinely used to classify lesions as low or high risk for clinical care include nuclear grade, size, presence of comedo or necrosis, and, to a lesser extent, the architectural patterns.

**Estrogen and Progesterone Receptors**

Estrogen plays a key role in the development of both normal breast epithelium and breast cancer, and the modulation of estrogen concentrations and ER signaling are key therapeutic modalities for the majority of breast cancers. Estrogens interact with mammary epithelial cells via specific ERs that function as nuclear transcription factors. The two known receptors, ERα and ERβ, are encoded by different genes and share an overall sequence homology of approximately 30%, although the homology is higher in the DNA- and hormone-binding regions. ERα is the receptor most closely associated with breast cancer; it is expressed mainly in the breast, uterus, and ovary. ERβ is more widely expressed, and its relationship to breast cancer is less clear.

Binding of estrogen to the receptor results in a conformational change, displacement of heat shock proteins, and homodimerization. This homodimer then binds to the estrogen-responsive elements of the target genes and recruits coactivators or corepressors that further influence transcription. This participation in a multimeric signaling
between ER activity and receptor tyrosine kinase (RTK) signal transduction pathways. Approximately 70% of breast cancers express ERα (i.e., they are ER positive); these tumors tend to grow more slowly and appear better differentiated than ER-negative tumors. Moreover, antiestrogen therapy is effective in preventing development of breast cancer.

Figure 88.8 • (A) Lobular carcinoma in situ. The lobular unit (see Fig. 88.9) is distended and distorted by proliferating cells. The cells are uniform and round, with bland nuclei. (B) The same specimen at a higher magnification.

Figure 88.9 • Anatomy of the breast, showing the organization of the elements of the terminal duct lobular unit and their relationship to specific pathologic abnormalities. (From Hayes D. Breast cancer. In: Skarin AT, ed. Atlas of Diagnostic Oncology. Philadelphia: JB Lippincott; 1991; l64.)
cancer, reducing the likelihood of recurrence in the adjuvant setting, and prolonging survival once metastases have developed.

PR, itself encoded by an estrogen-regulated gene, gives rise to two distinct isoforms, PRA and PRB, by alternative splicing. PRB appears to be more specific to breast cancer. Interesting to note, a polymorphism in the PR promoter (+331 G/A) that increases transcription of PRB is associated with an elevated risk of endometrial and breast cancer. PR is variably expressed in ER-positive tumors, and this variability has prognostic relevance. ER-positive/PR-negative tumors occur more commonly in women older than 50 years, tend to be more aneuploid, and present as larger tumors with more frequent nodal involvement than ER- and PR-positive tumors. Furthermore, ER- and PR-positive tumors may be more likely to respond to antiestrogen therapy than ER-positive/PR-negative tumors, although more recent data suggest this likely reflects the better prognosis of the dual positive tumors as opposed to increased responsiveness to tamoxifen.

ERBB2 (HER2)

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of breast cancers as a result of amplification of the HER2/new gene on chromosome 17q. HER2 functions as a transmembrane RTK, activated on dimerization with another member of the epidermal growth factor family of receptors, including EGFR (ERBB1), ERBB3 (HER3), and ERBB4 (HER4). The dimerization domain of a partner receptor, such as EGFR or HER3, is exposed on binding of a ligand such as heregulin or, alternatively, through ligand-independent mechanisms. Of note, HER2 itself does not have ligand-binding capacity. The HER2-HER3 heterodimer is the most potent of these dimer pairs, based on strength of interaction and downstream signaling. The oncogenic effects of this dimer pair are predominantly exerted through activation of intracellular signaling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR pathway, which in turn promotes proliferation and cell survival. In contrast to EGFR, in which amplifications in lung cancers frequently harbor activating mutations in the kinase domain, such activating mutations have not been found frequently in HER2 in breast cancer according to the Sanger Centre's COSMIC database, and HER2 oncogenic activity is exerted primarily through amplification.

Clinically, breast cancers marked by HER2 amplification have a more aggressive clinical course and decreased survival as compared with HER2-nonamplified tumors. HER2-amplified tumors can be associated with intracranial metastases. The identification of HER2 as an oncogene in breast cancer facilitated the development of therapies directed against it. The development and incorporation of HER2-targeted therapies into the adjuvant and metastatic settings have altered the natural history of HER2-amplified breast cancer dramatically. Trastuzumab is a HER2-targeted humanized monoclonal antibody that forms the cornerstone of HER2 targeted treatment, with proposed mechanisms of action including downregulation of HER2 dimerization and growth factor signaling cascades and induction of antibody-dependent cytotoxicity. Trastuzumab and other anti-HER2–directed therapies for treatment of both early-stage and metastatic breast cancer are described in more detail later.

Although the advent of HER2-targeted therapy has dramatically improved survival for patients with HER2-amplified breast cancer, de novo and acquired resistance to these treatments contributes to mortality. Studies aimed at elucidating mechanisms of resistance are providing further insight into the pathophysiology of HER2-positive breast cancer; two proteins, HER3 and PI3K, have emerged as key mediators of this resistance, including mutational activation of the latter. HER3 can promote oncogenic PI3K signaling, even in the presence of HER2 inhibition with trastuzumab. Furthermore, the CLEOPATRA phase III trial demonstrated that patients whose tumors harbored somatic activating mutations in the PIK3CA gene had shorter survival than those with wild-type disease. Data in the preoperative systemic therapy setting similarly identified an association between PIK3CA mutations and decreased pathologic complete response (pCR). However, these findings, while intriguing, do not yet have sufficient clinical usefulness to affect selection of therapy for individual patients. Increased levels of insulin-like growth factor–1 receptor (IGF1R) may bypass HER2 blockade by trastuzumab and allow growth factor activation of AKT, and a similar outcome may result from PTEN loss.

In addition to alterations that may circumvent HER2 signaling, changes in HER2 itself or effects of genes located nearby on chromosome 17 may also influence response to therapy. A truncated form of the HER2 protein itself that lacks the extracellular domain but retains the kinase activity has been described to correlate with trastuzumab resistance. Activating mutations in the HER2 gene in non-HER2-amplified breast cancer have been identified that may confer sensitivity to anti-HER2 directed therapy. Finally, the amplicon containing HER2 frequently contains additional genes that influence therapeutic efficacy. Although initially it was thought that HER2-positive disease is more sensitive to anthracyclines, recent data suggest that this sensitivity is conferred by the topoisomerase II gene (TOP2A) when it is present in the amplicon. Other cellular mechanisms of anti-HER2 therapy resistance are under investigation.

PI3K and PTEN

The PI3K pathway includes the PI3K holoenzyme and the downstream effectors kinases AKT and mTOR; this pathway is critical for cancer cell growth, proliferation, and survival. This pathway is aberrantly activated through various mechanisms including activation of upstream RTKs including HER2, as described earlier, and activating mutations in pathway components such as PIK3CA kinase domain mutations and loss of functional regulatory components such as PTEN. Activating mutations in the PI3K catalytic subunit are common in breast cancer, particularly in ER-positive, HER2-nonamplified tumors, with an incidence in these tumors of approximately 30% to 40%.

PI3K pathway signaling is initiated by membrane-bound RTKs that undergo activation, for example, by dimerization. These activated RTKs bind to the regulatory subunit of PI3K, p85. This binding relieves inhibitory interactions and allows activation of the kinase subunit of PI3K, called p110, which is encoded for by the PIK3CA gene. Activated PI3K phosphorylates PIP2 to the second messenger PI(3,4,5)P3, which is recognized by AKT, activating it and allowing for induction of downstream signaling pathways involved in cell growth, proliferation, and survival.

Figure 88.10 • Cribriform ductal carcinoma in situ, which accounts for most of the ductal carcinoma in situ detected. It is characterized by interconnecting strands of hyperchromatic cells. Few necrotic cells are seen, and arches of connecting strands appear rigid.
PIPK3, which then ultimately results in activation of AKT and mTOR. Ultimately, cell survival and proliferation result. The tumor suppressor phosphatase and tensin homolog (PTEN) counteracts PIP3K activity by dephosphorylating PIP3 to PIP2.

Germline PTEN mutations cause a hereditary cancer predisposition syndrome known as Cowden syndrome, characterized by a high incidence of breast, uterine, thyroid, and skin neoplasms. PTEN is inactivated in a wide variety of human tumors as a result of either mutation or, more commonly, epigenetic silencing through methylation, including in breast cancer. PTEN loss is associated with genetic instability, and primary breast tumors that lack PTEN have increased aneuploidy. In addition, PTEN loss has been associated with a decreased likelihood of response to anti-HER2 therapy with trastuzumab. Data elucidating the relationship between presence of PI3KCA mutations and PTEN status show that they are inversely correlated.

The observed frequency of PI3K activation in breast cancer has led to clinical investigation of inhibitors of PI3K in the context of hormone receptor–positive and HER2-amplified disease (NCT02167854). These agents have demonstrated some efficacy but are also associated with substantial toxicity including rash, diarrhea, hyperglycemia, and depression. Their role in breast cancer remains to be elucidated.

TP53

The tumor suppressor TP53 (p53), also termed the “guardian of the genome,” is the most frequently mutated gene in human cancer. It plays a central role in sensing genotoxic and nongenotoxic stresses and transducing an antiproliferative effect (cell cycle arrest or apoptosis) in response. It is activated and regulated by posttranslational modifications to the N-terminal region, including phosphorylation and ubiquitination. In addition, by binding as a tetramer to specific DNA sequences via a central DNA-binding core region, it exerts its primary biologic function by modulating the transcription of dozens of genes.

In transgenic mice, loss of p53 is associated with multiple spontaneous tumors, although not of the mammary glands. However, p53 loss accelerates the appearance of mammary tumors in murine mammary tissue that also overexpresses MYC, HER2, IGF1, and/or WNT1. These genetic studies are consistent with a role for p53 loss late in tumor development. Indeed, the transgenic restoration of p53 function leads to tumor regressions.

Mutant p53 accumulates in the nucleus of neoplastic cells. Thus initial studies that described only a weak association between aberrant p53 and adverse prognosis in breast cancer relied on immunohistochemistry (IHC) detection; more recent analyses based on mutation detection have confirmed a strong association. Mutations in exons 5 through 8 are more common in ductal and medullary tumors, tumors with an aggressive phenotype (high grade, large size, nodal-positive cases, and low hormone receptor content), and in women younger than 60 years. Furthermore, the presence of a mutation conferred an overall 2.27-fold increased RR of breast cancer–specific mortality, independent of other known prognostic markers (e.g., tumor size, node status, and estrogen receptor and PR expression). Finally, although not all mutations confer the same biologic properties (e.g., missense versus nonsense), all have similar prognostic usefulness.

Breast cancers in individuals with germline p53 mutations are frequently ER and HER2 positive. Adjuvant radiation therapy is generally avoided in breast cancer patients with Li-Fraumeni syndrome owing to the risk of radiation-induced sarcomas; mastectomy, often bilateral mastectomy, is more common. As noted earlier, many tumors harbor sporadic p53 mutations; p53 is an obvious target for cancer therapy, despite the apparent intractability of a loss-of-function genotype. Multiple approaches are being studied to overcome this limitation, including small molecules to restore p53 function or inhibit its interaction with MDM2 and adenoviral-mediated gene delivery.

There are now multiple compounds in clinical trials, although no results are yet available in breast cancer.

Breast Cancer Genome

The elucidation of genetic aberrations in cancer genomes, including mutations, deletions, and amplifications, has led to a better understanding of cancer pathophysiology. In addition, this knowledge is assisting with rational drug development by identifying potential targets. With the determination of the DNA sequence of the normal human genome, efforts have shifted toward a more comprehensive analysis of cancer genomes. The first report of a comprehensive sequence analysis of 21,000 of the best studied and annotated human genes was published that included data from 11 breast cancer samples. This screen discovered cancer genes known to be associated with breast cancer (e.g., p53 and BRCA1) in addition to genes not previously characterized as associated with cancer. An individual breast cancer was shown to harbor an average of about 90 mutant genes, although only a minority are likely to be driver mutations. In addition, although the functionally important mutations often differed among tumors, when the genes were analyzed in functional groups, mutations in signal transduction pathway and transcription factor genes were found in nearly all breast tumor samples. As detailed subsequently, rapid advancements in sequencing technology and bioinformatics have significantly expanded the information available.

Molecular Profiling in Breast Cancer

Genome-wide RNA transcriptional profiling in combination with novel bioinformatic approaches has led to the development of molecular classifications based on gene signatures comprising the quantitative expression of thousands of genes. Tumors can be classified either according to transcripts that tend to segregate together according to underlying biologic differences (unsupervised clustering) or sorted according to a given end point such as prognosis or response to therapy (supervised clustering).

Initial studies with array-based expression profiling showed the ability of the technology to classify breast cancer according to five gene clusters: luminal subtype A, luminal subtype B, HER2-positive, basal, and normal breast–like subtypes (Fig. 88.11). The ER-positive group was characterized by high expression of many genes expressed by breast luminal cells, and the ER-negative group showed gene expression characteristic of basal epithelial cells. However, a third group showed genes related to HER2 overexpression, suggesting that this molecular characteristic may have equal or greater weight than ER expression in subclassifying breast cancers. Finally, the normal breast-like group of breast cancers clustered with normal breast epithelium. These distinct subtypes of breast tumors show distinctive molecular signatures and appear to represent diverse biologic entities associated with distinct clinical outcomes, and the comparison of several independently developed gene signatures appears to show similar prognostic information, suggesting the existence of a common set of biologic phenotypes.

Luminal A–type cancers have the most favorable long-term survival, whereas HER2-positive and basal-like cancers may be more sensitive to chemotherapy but have the worst overall prognosis. These patterns of gene expression appear to provide more specific information than identification of a single gene with a specific effect. Thus breast cancer is not a single disease with heterogeneous ER and HER2 expression but appears to comprise three to five molecularly and clinically distinct subtypes.

A similar approach can be taken by examining DNA copy number abnormalities, including amplifications and deletions, across the genome. Mapping these abnormalities against both the biologic subtypes described earlier and clinical outcome data demonstrates the potential to identify high-level DNA amplification that, similar to HER2, may be useful in identifying therapeutic targets. Emerging knowledge now aims to integrate patterns of gene expression, methylation, copy number variation, and mutation. This approach, using The Cancer Genome Atlas (TCGA) Network, holds significant potential but will require independent validation using data sets that include treatment and outcome.
Part III: Specific Malignancies

Non–protein-coding DNA of transcription factor association, transcription, chromatin structure, and histone modification with the goal of determining biochemical functions for many areas of the genome, including those mutated in cancer. As technology advances and becomes more inexpensive, even more comprehensive analysis of breast cancer genomes will likely continue to increase our understanding of both breast cancer and how to use the information for both treatment and prevention.

Breast Cancer Stem Cells

Cancer cells have two somewhat contradictory traits. Although they originate from a single clone, they often display marked genetic, biologic, and morphologic heterogeneity. Historically, the prevailing hypothesis was that genomic instability contributed to continuing tumor evolution and emergence of different and ultimately more virulent subclones, leading to disease progression and resistance to therapy. More recently, an alternative explanation was provided by groundbreaking work elucidating the “cancer stem cell” model.
division (such as Wnt and Notch pathways) might provide novel targets for therapy. A phase I trial of a Notch-targeting γ-secretase inhibitor in combination with cytotoxic chemotherapy in breast cancer identified preliminary evidence of efficacy. Additional trials of drugs targeting the Notch pathway and others involved in cancer stem cells are underway.

**Breast Cancer Detection in the Circulation**

**Disseminated Tumor Cells**

More than 90% of patients diagnosed with breast cancer have no evidence of disease outside of the breast and ipsilateral axillary lymph nodes. However, approximately 30% of patients with primary operable breast cancer have disseminated tumor cells (DTCs) that can be detected in bone marrow, at the time of diagnosis. In a follow-up study, 15.5% of patients had detectable DTCs 3 years after diagnosis, a finding that was associated with increased risk of relapse and death. Despite these data, however, assessment of DTCs has not been incorporated into routine practice, in part because of the need for a relatively invasive procedure.

**Liquid Biopsies**

Tumor markers are proteins, such as those derived from MUC1 (e.g., CA15-3, CA27.29) and carcinoembryonic antigen, that are shed from tumors and identified in the circulation. However, their usefulness is limited to monitoring of response to therapy or progression of disease. More recently there have been considerable methodologic advances in the assessment of circulating cancer biomarkers, including circulating tumor cells (CTC) and circulating nucleic acids, which may play a role in diagnosis, monitoring, and treatment of disease.

It is possible to measure CTCs using an automated immunochemistry approach, presence of five or more CTCs per 7.5 mL of blood is prognostic, with significantly worse overall survival (OS; 8.2 months versus 18 months) compared with those patients with fewer CTCs. The clinical usefulness of CTCs for treatment decision making in metastatic breast cancer was prospectively tested in a randomized phase III trial; however, use of the assay was not shown to result in improved disease outcomes and therefore it is unclear how best to incorporate it into routine clinical care. The immunochemistry method lacks sensitivity owing to the use of epithelial cell adhesion molecule (EpCAM)–based detection, because less differentiated cells often lack EpCAM expression and will avoid detection, so newer methodologies including isolation of CTCs based on size or other properties are being developed. Furthermore, the ability to isolate CTCs permits single-cell analysis, including assessment of molecular markers such as ER expression and HER2 amplification in real time.

Technologic advances have also resulted in the ability to detect nucleic acids, including circulating tumor DNA (ctDNA) and microRNA (miRNA), that are shed from dying tumor cells into the blood and may be more sensitive and specific than standard biomarkers. Because analysis of circulating nucleic acids has the potential to identify emerging mutations that could lead to altered treatment options, their use has potential to improve disease outcomes. ctDNA can be specifically identified by the presence of tumor-specific mutations, including in more than 90% of patients with metastatic breast cancer. Serial assessment of ctDNA via detection of these mutations may be useful for monitoring of patients for disease recurrence or progression; relative levels have been shown to correlate with tumor burden. Similar findings have been demonstrated with miRNAs.

More recently, it has become apparent that in addition to detection of cancer, assessment of circulating biomarkers may be useful for monitoring changes in tumors that could affect treatment. For example, multiple groups have identified activating mutations in the ligand-binding domain of ESR1, the gene that encodes ERα, which are present in up to 30% of endocrine therapy–resistant patients.
but which are only rarely detected in primary tumor specimens. Studies have also demonstrated the use of massively parallel sequencing of ctDNA for examining intratumor heterogeneity, which could also potentially be used to identify targetable mutations. Companies are now capitalizing on the new technology and providing assays for monitoring patients, although the clinical usefulness of these commercial assays is currently still in question. As the sensitivity of detection of these circulating biomarkers improves with advances in technology, it is likely that liquid biopsies will become routinely used for monitoring patients with metastatic breast cancer. However, use of this technology for diagnosis or detection of disease recurrence remains questionable.

### PREVENTION AND EARLY DETECTION

An individual can be deemed at high risk for breast cancer based on a calculation from a breast cancer risk assessment model, a genetic test result, or other family or personal history considerations that result in an estimation of an individual’s lifetime risk of breast cancer that is above population risk. There is no universally accepted definition of “high risk.” Whatever criteria an individual physician and patient use to define high risk, four possible actions may be taken, some of which can be used simultaneously: (1) enhanced surveillance; (2) behavioral modification; (3) chemopreventive strategies; and (4) prophylactic mastectomy and/or oophorectomy.

#### Increased Surveillance

As discussed in the section on mammographic screening, there is significant debate about the age at which to begin mammographic screening in average-risk women. Nonetheless, ample evidence supports increased surveillance in women at high risk for breast cancer, and strategies are being developed. Carriers of germline BRCA mutations, for example, may begin mammographic surveillance at age 30. The American Cancer Society (ACS) and the American College of Radiology (ACR) appropriateness criteria recommend consideration of annual breast magnetic resonance imaging (MRI) in addition to mammography for individuals who have a 20% or greater lifetime risk of breast cancer, including those with germline BRCA mutations, those who have a family history suggestive of a familial risk of breast cancer but in whom genetic testing has not been performed, those with a history of atypia, and those with a personal history of breast cancer or chest irradiation between ages 10 and 30. The timing of such imaging is not evidence based. Some providers recommend alternating mammography and MRI every 6 months, whereas others recommend annual simultaneous imaging for convenience. Recommendations regarding age at which breast surveillance should be initiated may be individualized based on earliest age of onset of breast cancer in the family. In addition, other genetic mutations and syndromes also increase the risk for breast cancer and require initiation of screening at an earlier age according to both the ACS and NCCN guidelines, although the recommended age of initiation of screening MRI varies by gene.

Finally, although controversy remains about the role of breast self-examination in the general population, experts in the surveillance of high-risk women still recommend breast awareness for women with BRCA mutations in addition to clinical breast examinations. For males with pathogenic germline mutations, it is important to recognize that the absolute risk of breast cancer remains relatively low (≤10%) and that evidence for screening with use of any modality is limited.

#### Behavior Modification

Multidisciplinary centers that provide counseling for women who are at substantial risk for breast cancer are well established throughout the United States. These multidisciplinary consultations provide recommendations for a range of surveillance and interventional approaches. In addition to the available surgical and medical preventive strategies, modification of lifestyle factors, such as diet, alcohol consumption, and exercise, may be discussed. At this time, behavioral modifications do not have demonstrated efficacy as primary prevention for breast cancer in high-risk individuals.

#### Chemoprevention

A significant 49% reduction in risk of invasive breast cancer with tamoxifen compared with placebo was seen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study; similar findings were noted in the International Breast Cancer Intervention Study (IBIS-I). Subsequently, two SERMs, tamoxifen and raloxifene, were directly compared in the NSABP STAR trial; long-term follow-up demonstrated that although raloxifene was less toxic than tamoxifen, it was slightly less effective in decreasing invasive breast cancer. Based on these findings, multiple groups have recommended that SERMs be considered to reduce the risk of breast cancer in women with a 5-year projected risk of developing breast cancer of 1.66% or greater. More recently, the aromatase inhibitors (AIs) exemestane and anastrozole have been shown to decrease the risk of invasive breast cancer in the randomized placebo-controlled, double-blind MAP.3 and IBIS-II clinical trials, respectively. Longer follow-up is required to confirm these data, including possible long-term side effects of the medications.

Tamoxifen has been shown to reduce the risk of contralateral breast cancer by 50% to 60% in BRCA1 and BRCA2 carriers, respectively, even though BRCA1-associated cancers are generally ER negative. However, two European chemoprevention studies performed at the Royal Marsden Hospital and by the Italian Tamoxifen Prevention Study Group, respectively, did not show a decrease in the incidence of breast cancer in women from high-risk families when tamoxifen was used.

For all of these agents, it is not known whether they reduce the incidence of breast cancer by preventing the formation of cancer or by treating small, clinically occult cancers. In practice, the potential chemopreventive benefits of these agents, along with consideration of an individual’s baseline risk, must be balanced in the context of their known toxicity profiles. Indeed, patients and providers alike are often cautious about chemoprevention in light of potential adverse events.

#### Prophylactic Mastectomy and/or Oophorectomy

Prophylactic mastectomy is associated with a reduction in breast cancer risk of approximately 90%, which is a substantial absolute reduction in patients with either a strong family history of breast and/or ovarian cancer or a genetic predisposition to breast cancer. Additional data show that contralateral prophylactic mastectomy (CPM) can reduce the risk of breast cancer in patients with a previous diagnosis of unilateral disease. A high prevalence of premalignant lesions, including atypical hyperplasia, is seen in prophylactically removed breasts from women who are at hereditary risk for breast cancer. Statistical analysis has shown that, depending on the assumed penetrance of the BRCA mutation, compared with surveillance alone, 30-year-old patients with early-stage breast cancer who have BRCA mutations may gain 2.9 to 5.3 years from prophylactic bilateral mastectomy and 0.6 to 2.1 years from CPM. A survival analysis suggested that prophylactic mastectomy at age 25 years and oophorectomy at age 40 years maximized survival at 70 years of age; it is important to note, however, that substituting enhanced breast cancer screening (with MRI and mammography) for mastectomy resulted in similar survival. The gain in quality of life in these high-risk women who chose to undergo prophylactic mastectomy is controversial. Given the impact on quality of life, the potential medical repercussions of an operation, including the reconstruction that sometimes follows, and the presence of an effective, alternate breast cancer risk mitigation strategy (enhanced surveillance), the choice of...
prophylactic mastectomy is personal and certainly not mandated by providers counseling high-risk women. However, if a patient opts for enhanced surveillance, the possibility of diagnosis of an early-stage breast cancer that may require systemic chemotherapy must be clearly discussed.

Although physicians caring for women at increased risk of breast cancer generally do not mandate prophylactic mastectomy, women at increased risk for ovarian cancer, for example because of germline mutations in BRCA1/2, are strongly encouraged to undergo risk-reducing salpingo-oophorectomy. Unlike breast MRI and mammo- 
graphy, ovarian cancer screening with transvaginal ultrasound and CA125 measurement is not effective at diagnosing ovarian cancer early, and ovarian cancer is generally diagnosed at a stage when curative treatment options are limited. Furthermore, the benefits of risk-reducing oophorectomy in BRCA carriers are significant and include a reduction in breast and ovarian cancer risk, and reduced breast and ovarian cancer–specific mortality and all-cause mortal- ity.154 Despite the limitations of ovarian cancer screening, for some women with BRCA mutations whose ovaries and fallopian tubes are intact, transvaginal ultrasonography and CA125 screening are recommended.

The age at which risk-reducing bilateral salpingo-oophorectomy is performed is not trivial, because the induction of early surgical menopause may have long-term systemic effects including those on bone health and cardiac function, in addition to significant effects on quality of life. The age at which surgery is recommended is based on the age-adjusted risks of ovarian cancer and is generally slightly earlier for BRCA1 carriers than BRCA2 carriers.155 A limited duration of HRT is safe in terms of breast cancer risk for premenopausal women with no personal history of breast cancer and with intact breasts, and may provide substantial benefits in terms of quality of life and overall health. It is generally recommended that these women stop HRT around the age of natural menopause. Important to note, BRCA carriers who undergo risk-reducing salpingo-oophorectomy remain at risk for developing primary peritoneal cancer, for which no screening or risk reduction strategies are delineated.

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

Detection of Breast Cancer

Despite a lifetime probability of developing breast cancer that is currently estimated at 1 in 8, only 30% of all women have one or more identifiable risk factors. At present, there is no preventive treatment for breast cancer that is widely available to the average population. The goal of breast cancer screening is early detection that will lead to a reduction in mortality and morbidity, with a minimum of false-positive findings and minimal risks. In addition, the screening program should be feasible to provide to the public, acceptable to both patients and physicians, and cost-effective. Because 70% to 75% of women diagnosed with breast cancer have no identifiable risk factors other than being female, current screening and education programs include all women aged 40 and older regardless of risk, although there is some variability in the recommendations from different medical societies. In addition, as noted earlier, there is supplemental screening available for women who are at high risk of developing breast cancer.

Multiple international randomized controlled trials have repeatedly demonstrated that mammography decreases the mortality from breast cancer by 15% to 30% in women invited to be screened.162 A number of case-control and cohort observational trials have shown that the mortality reduction is even higher, up to 48% in women who actually undergo mammographic screening relative to women who do not.162,165 Furthermore, a failure analysis study looking at women diagnosed with breast cancer in Massachusetts in the 1990s found that 71% of breast cancer deaths were in women who did not undergo screening mammography, whereas only 29% of the deaths were in women who did undergo mammography.164 There continues to be active and lively debate about the usefulness of breast cancer screening, which is beyond the scope of this chapter.

Mammography has evolved from film screen mammography to digital mammography, which is now used in more than 97% of all mammography units because it allows for a lower average dose of radiation, improvement in storage and retrieval, easier image sharing across institutions, and computer-assisted diagnosis.167 Digital breast tomosynthesis (DBT), described in detail later, is a new method of acquiring multiple mammographic projections that mitigates some of the limitations of standard plane mammography. Important to note, mammography and DBT are anatomic approaches to screening based on calcifications, architectural distortion, and radiographically apparent masses, in contrast to functional assessment methodologies such as breast MRI.

Screening and Early Detection

The efficacy of screening for occult cancer depends heavily on the following factors: (1) tumor growth rate, (2) the sensitivity of the test related to tumor volume, and (3) the interval between screens. Growth rates of breast cancer vary. In determining the efficacy of screening, four biases must be considered: lead-time, length, selection, and overdiagnosis bias. Lead-time bias is the interval that the diagnosis has been advanced by screening. Length bias concerns the timing of detection. When screening is infrequent, fast-growing tumors are not detected as early in their natural history as more slowly growing tumors. Thus the outcome of cancers detected by screening is better than that for interval cancers. Women who participate in breast cancer screening have been shown to be more health conscious; they also are more likely to obtain Pap smears, use seat belts, and not smoke.163 Thus it is likely that their outcomes would be better even in the absence of screening, contributing to selection bias. Overdiagnosis is the detection of cancers that would not be fatal for the patient in her lifetime and that would not be diagnosed without screening. The contributions of all of these biases make assessment of benefits of breast cancer screening programs more complicated.

Screening guidelines

Table 88.3 lists the current screening guidelines for mammography for the ACS, ACR, NCCN, and the US Preventive Services Task Force (USPSTF).161,166,167 All of the major screening guidelines agree that the most lives are saved from breast cancer when screening begins at 40 and continues annually. However, some of the guidelines suggest routine screening starting at a later age (45 or 50) or biennially, based on different perceptions of the trade-offs between the benefit (mortality reduction) and the risks of screening (false-positive recalls with psychologic anxiety and overdiagnosis are the main cited risks in the current guidelines).

Risks of screening

There are several risks of screening noted in the breast cancer screening guidelines issued by the ACS166 and USPSTF.161,168 One major concern about breast cancer screening is the risk of overdiagnosis, which reflects breast cancers that would not have led to symptomatic disease during a patient’s lifetime. False-positive findings are an inherent risk of a screening program. They have been shown to result in increased short-term anxiety, although this has not been shown to translate to long-term anxiety or decrement in health utility.167 Furthermore, a cross-sectional study in the United States demonstrated that women are aware of the possibility of a false-positive result and view it as an acceptable consequence, rather than a harm.168 Radiation exposure associated with breast cancer screening is a concern that some patients express. All of the major societies that issue breast screening guidelines acknowledge that the current doses of radiation used in screening mammograms are of negligible risk to the screening age patient.161,168,167 The average effective radiation dose
Several states in the United States have enacted breast density notification laws that require patient notification acknowledging and offering options for supplemental screening for those with dense breasts. Mammographic technologies have evolved to address the decreased limitations of screen-film mammography. A large multicenter trial comparing conventional and digital mammography showed an improvement over conventional film mammography in the detection of breast cancer in young, premenopausal, and perimenopausal women, and in women with dense breasts.22 However, there was no significant difference in diagnostic accuracy between digital and film mammography in the population as a whole or in the other predefined subgroups. For women with an average risk of developing breast cancer, supplemental screening with other modalities such as ultrasonography and breast MRI has not been shown to be cost-effective and has a high rate of false positives, and accordingly may not be offered by many practices because it is not currently endorsed by any major societal recommendation for routine use.164,173,174

Digital breast tomosynthesis
To mitigate some of the limitations of mammography, DBT screening is a new method of anatomic imaging that has been introduced. DBT acquires several angular projections that may be evaluated spatially across the acquired slices. DBT provides improved discrimination of masses and architectural distortion, which may be otherwise obscured by overlapping breast tissue within the acquired images. Conversely, an apparent mass on a single-projection two-dimensional (2D) image may simply represent a summation artifact of breast tissue, and use of DBT helps avoid this false-positive finding. Overall, DBT results in lower false-positive recall of patients from screening and maintains or increases the cancer detection rate.175 In particular, DBT further increases the sensitivity and decreases the false-positive results from dense breasts relative to digital mammography, especially in women with heterogeneously dense breasts.176

Standard DBT is nearly equivalent in radiation dose to digital mammography. However, most practices that have adopted DBT for screening currently acquire both 2D mammograms and DBT scans, which results in increased radiation exposure. It is possible that the increased radiation dose from the additional projections may be offset by use of the newer technology of synthesized mammography, which is created from the DBT acquired images, thereby eliminating the need to acquire a traditional 2D mammogram in addition.

Other methods of screening
As noted earlier, mammography and DBT provide an anatomic approach to screening. To overcome some of the variables that affect the predictive value of mammography, a number of new technologies have been developed. Extending beyond just anatomic abnormalities, techniques such as MRI, scintimammography and contrast-enhanced spectral mammography provide a functional approach to screening based on injected contrast material or radiotracer that is taken up by biologically active breast cancer. The aforementioned additional functional techniques, in addition to ultrasonography, are available for select women who have abnormalities on screening mammograms or who are at higher risk of developing breast cancer.177

Breast magnetic resonance imaging. The combination of angiogenesis and associated increased vascular permeability creates leaky vessels, which, when combined with proteolysis, results in increased intravascular contrast uptake in areas of biologically active malignancy that can be detected with breast MRI. Breast MRI provides excellent sensitivity (ranging from 75% to 97% for breast MRI alone),178,179 although its ability to detect microcalifications is limited. There is mildly decreased specificity with breast MRI, resulting in false-positive findings at biopsy. Breast tissue can normally enhance, which is termed background parenchymal enhancement (BPE). BPE is highest during the luteal phase of the menstrual cycle, and thus patients are typically scheduled for imaging outside of that phase. Infrequently, BPE can be focal or asymmetric rather than diffuse, which can limit evaluation.
or lead to false-positive biopsy results. Unlike with conventional mammography, dense breasts do not limit the sensitivity. In addition, there is no radiation involved with MRI. Breast MRI is not recommended for routine screening of women at average risk of breast cancer who are asymptomatic. Recommendations for screening patients at high risk of breast cancer with breast MRI are described earlier in this chapter.

**Ultrasonography.** Although commonly used in the diagnostic workflow, whole-breast screening ultrasound examination is not widely endorsed by guidelines and may not be cost-effective, in part because of an increased false-positive rate. For asymptomatic women with dense breasts and a negative screening mammogram, some sites supplement with whole-breast screening ultrasonography because it results in a slightly increased incremental cancer detection rate. The addition of ultrasound to mammography enables detection of a median of 3.2 additional cancers (range, 0.4–14.2) per 1000 patients screened, with a biopsy positive predictive value median of 6.8 per 1000 patients (range, 3.2–18.4).150

On the other hand, ultrasonography is a very effective imaging tool in the diagnostic setting and is indicated for evaluation of women with either palpable or mammographically detected lesions (Fig. 88.13). Ultrasonography is very accurate (>95%) for diagnosing breast cysts, which have well-demarcated, smooth margins with an echo-free center (Fig. 88.14) and are usually rounded and thin-walled and produce distal shadowing. Simple cysts require no further evaluation. Complicated cysts contain echogenic debris and are benign, often undergoing inflammatory change. A cystic mass containing a solid component requires biopsy, because the histologic findings can be papilloma, papillary carcinoma, or invasive ductal carcinoma.

The intrinsic architecture of axillary lymph node anatomy may also be evaluated with ultrasound in the setting of breast cancer staging. Identification of cortical thickening, defined as greater than 3 mm, at ultrasound examination is suggestive of lymph node involvement in a woman with a known or suspected underlying breast malignancy. However, the sensitivity of axillary lymph node sonography for evaluation of nodal metastasis remains limited. Therefore sentinel node biopsy remains the gold standard because lymph nodes may appear normal on sonographic examination and still contain metastasis.

Sonographic evaluation can also be used to image the subareolar area to evaluate for an intraductal mass, especially in the setting of nipple discharge. Calcifications are poorly characterized by ultrasound, although they can appear as an echogenic area with acoustic shadowing posteriorly, particularly when large in size. As ultrasound contrast examination is not indicated for use in the United States; there is limited indication for ultrasound for functional evaluation of masses. Doppler flow analysis provides limited information on blood flow within a mass. However, because malignant masses may demonstrate absence of detectable color Doppler flow, this is not used as a differentiating factor.

**Screening the elderly patient**

The life expectancy for women in the United States increased from 77.4 years in 1980 to 80.4 years in 2002, although it decreased to 78.8 in 2014.181 Biologic parameters suggest a higher prevalence of higher-risk tumors in younger women, with better differentiated and hormone receptor–rich, lower-risk tumors generally occurring in older women. In addition, for a given tumor size, the likelihood of nodal involvement is lower in older than in younger women.182 These data in aggregate have led some, including the USPSTF, to suggest that it may be appropriate to increase the screening interval to 2 years in older women and to stop screening mammography at age 75 years, although there are insufficient data to suggest an age at which routine screening can be abandoned. At 75 years of age, the average additional life expectancy for a woman in the United States is 12 years or more. Multiple studies have demonstrated the benefits of screening detection of breast cancer in elderly women, because persistence with screening is associated with diagnosis of earlier-stage disease and lower breast cancer–related mortality.183-186 Although the benefits of screening appear to be seen in all age groups, the magnitude of the benefit appears to diminish with age and with the severity of comorbid illnesses. Indeed, it seems reasonable to forego screening mammography for women whose life expectancy is less than 5 to 10 years.187

![Figure 88.13](image1) - Ultrasound image confirms the presence of a solid mass.

![Figure 88.14](image2) - Ultrasound image of the breast showing the palpable lump to be cystic. Cystic lesions have a characteristic hypoechoic pattern, with prominent acoustic shadowing.
Table 88.4  Breast Imaging Reporting and Data System (BI-RADS) Assessment Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Assessment</th>
<th>Likelihood of Malignancy</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Incomplete</td>
<td>N/A</td>
<td>Recall for additional imaging</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
<td>Essentially 0%</td>
<td>Routine screening</td>
</tr>
<tr>
<td>2</td>
<td>Benign</td>
<td>Essentially 0%</td>
<td>Routine screening</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign</td>
<td>( \leq 2% )</td>
<td>Short-term follow-up</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious</td>
<td>( &gt;2% \text{ to } \leq 10% )</td>
<td>Biopsy</td>
</tr>
<tr>
<td>4A</td>
<td>Low suspicion</td>
<td>( &gt;2% \text{ to } \leq 10% )</td>
<td></td>
</tr>
<tr>
<td>4B</td>
<td>Moderate suspicion</td>
<td>( &gt;10% \text{ to } \leq 50% )</td>
<td></td>
</tr>
<tr>
<td>4C</td>
<td>High suspicion</td>
<td>( &gt;50% \text{ to } &lt;95% )</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Highly suggestive of malignancy</td>
<td>( \geq 95% )</td>
<td>Biopsy</td>
</tr>
<tr>
<td>6</td>
<td>Known biopsy-proven malignancy</td>
<td>N/A</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

N/A, Not applicable.


Mammographic Abnormalities

The ACR Breast Imaging Reporting and Data System (BI-RADS) standardizes reporting nomenclature and defines specific terms to describe breast imaging findings. Based on the imaging findings, BI-RADS provides an assessment category (0 through 6) as shown in Table 88.4. Features with the highest positive predictive value for carcinoma are spiculated margins, irregular shape, linear calcification, and segmented or linear calcification distribution. In general, the positive predictive value of a BI-RADS category 5 lesion is greater than 80%, whereas that of a category 4 lesion approaches 30% to 40%.

Masses

BI-RADS defines a mass as three dimensional, convex, space occupying, and seen in two projections. If a probable mass is seen in only one view, it is called an asymmetry. If seen on both views but lacks convex borders, it is called a focal asymmetry. Benign masses typically are well defined, with sharp margins, and have little effect on the surrounding breast architecture. Fibroadenomas, papillomas, intramammary lymph nodes, and cysts are the most common causes of benign masses (Fig. 88.15). Malignant masses classically have irregular borders that blend into the surrounding tissue and often appear to infiltrate the breast background tissue with a stellate appearance. Usually there is some distortion of adjacent breast stroma. The mammographic abnormality that has the highest rate of malignancy is a mass with associated calcification (Figs. 88.16 and 88.17).

Calcifications

Calcifications are highly radiodense and therefore best visualized with mammography compared with other modalities such as MRI and...
ultrasound. The type of calcification and the distribution of calcification provide risk stratification. Benign calcifications usually are larger and coarser, and are often round with smooth margins. Benign causes of microcalcification include involuting fibroadenoma, arteriosclerosis, sclerosing adenosis, fat necrosis, and previous mastitis with ductal calcium deposits. A diffuse distribution pattern of calcifications and skin calcifications are typically benign. Malignant calcifications typically are linear, or small (<1 mm) in diameter and nonuniform in size. Segmental or linearly distributed calcifications have the highest association with malignancy (60%–62% positive for cancer on biopsy), with grouped distribution comprising a smaller proportion (20%–25%).

Architectural Distortion
Distortion of the breast parenchyma is called architectural distortion and may occur by itself or may be a feature associated with a mass, calcifications, or asymmetry. The presence of architectural distortion should prompt the search for an underlying abnormality and should be attributed either to a benign cause such as prior surgery, radial scar, complex sclerosing lesion, or fat necrosis, or to a malignant condition such as invasive lobular or ductal carcinoma.

Approach to the Patient
Management of the Palpable Mass
At presentation, many patients will have a mass in the breast detected during self-examination or incidentally. Determination of whether a palpable abnormality is malignant can be challenging. The first step should be a detailed history and physical examination. Patients with a palpable mass should undergo diagnostic bilateral mammography, and often will undergo breast ultrasonography (Fig. 88.18). As opposed to a screening mammogram, a diagnostic mammogram is typically reviewed immediately and additional images, including spot views, are obtained to characterize the specific area of concern. Bilateral mammography is important to evaluate the rest of the breast for additional occult lesions, in addition to the contralateral breast.

For patients younger than 30 years, it may be reasonable to perform an ultrasound scan only. This will be partly based on the characteristics of the palpable abnormality. In this age group, masses that are round, smooth, and mobile are more likely to represent fibroadenomas or cysts. Ultrasonography is simple to perform and may distinguish solid from cystic masses. Cystic lesions can be aspirated. Cytologic examination of the aspirated fluid is not indicated. Chronically recurrent cysts, or bloody fluid on aspiration should prompt excision. In addition, complex breast cysts, defined as cysts with thick walls, thick septa, intracystic masses, or other discrete solid components, may require either ultrasound-guided core biopsy of the solid components or surgical excision. For select younger patients with solid masses that have the classic clinical and radiologic features of a fibroadenoma, observation with short-term clinical follow-up and repeat ultrasound examination to ensure stability may be reasonable.

For all other patients with solid masses on breast imaging, a biopsy is strongly recommended. Fine-needle aspiration (FNA) biopsy is easy to perform in the office with minimal complications, although this does require an experienced cytopathologist for accurate interpretation. However, core biopsy has several advantages with respect to FNA in evaluating a solid breast mass, and is generally preferred. As opposed to the cytologic assessment enabled by an FNA, core biopsy provides adequate tissue to differentiate between fibroadenoma and phyllodes tumors, or in situ and invasive cancer. In the case of malignancy, it allows for immunohistochemical staining for ER, PR, and Her-2/neu expression, enabling definitive surgical or neoadjuvant planning. FNA biopsy has a small risk of false-positive findings, so a positive FNA biopsy result may still necessitate a core biopsy before one proceeds with surgery. It is important to remember that both FNA biopsy and core needle biopsy can have false-negative findings, so there must be concordance between the biopsy results and the imaging or physical examination findings. In cases in which a biopsy of a suspicious lesion results in a discordant benign finding, excisional or incisional biopsy should be performed.

**Figure 88.18** • Algorithm for breast lump management. *ADH*, atypical ductal hyperplasia; *ALH*, atypical lobular hyperplasia; *DCIS*, ductal carcinoma in situ; *FNA*, fine-needle aspiration.
Management of the Nonpalpable Mammographic Abnormality

As screening mammography is increasingly used, many patients will have screening-detected mammographic abnormalities in the face of normal breast examination findings. If any abnormality is seen on screening mammograms, diagnostic mammograms including magnification views will be required. These lesions are often then categorized according to BI-RADS as shown in Table 88.4. Short-term follow-up is typically recommended for BI-RADS category 3, and biopsy is recommended for BI-RADS categories 4 and 5. Indications for biopsy include new or changing densities, densities with spiculations, ill-defined borders or stellate distortion of the stroma, or suspicious microcalcifications, with or without an associated mass (Table 88.5). When a biopsy is recommended, an image-guided core needle biopsy is preferred. This can be performed using ultrasound guidance (if the lesion is clearly visualized with ultrasound), or a stereotactic core biopsy may be preferred. Some patients may not be candidates for stereotactic core biopsy. These include patients with lesions close to the skin or chest wall, those with small or thin breasts, or those unable to lie prone and immobile for 30 to 45 minutes. In these cases, localization and guided excisional biopsy with specimen radiography is recommended; localization has traditionally been performed with a wire placement. There are newer techniques, including localization using radioactive seeds or nonradioactive reflector chips, that may hold several

<table>
<thead>
<tr>
<th>Type of Calcification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPICAL BENIGN</strong></td>
<td></td>
</tr>
<tr>
<td>Skin (dermal)</td>
<td>Typical lucent-centered deposits that are pathognomonic. Atypical forms may be confirmed by tangential views to be in the skin.</td>
</tr>
<tr>
<td>Vascular</td>
<td>Parallel track or linear tubular calcifications that are clearly associated with blood vessels.</td>
</tr>
<tr>
<td>Coarse or popcornlike</td>
<td>The classic calcifications produced by an involuting fibroadenoma.</td>
</tr>
<tr>
<td>Large rodlike</td>
<td>Benign calcifications forming continuous rods that occasionally may be branching. They usually are &gt;1 mm in diameter, and may have lucent centers, if calcium surrounds rather than fills an ectatic duct. These are the kinds of calcifications found in secretory disease, “plasma cell mastitis,” and duct ectasia.</td>
</tr>
<tr>
<td>Round</td>
<td>When multiple, they may vary in size. They usually are considered benign, and when small (&lt;1 mm), they often are formed in the acini of lobules. When &lt;0.5 mm, the term “punctate” can be used.</td>
</tr>
<tr>
<td>Rim</td>
<td>Very thin, benign calcifications that appear as calcium deposited on the surface of a sphere. These deposits usually are &lt;1 mm thick when viewed on edge. Although fat necrosis can produce these thin deposits, calcifications in the walls of cysts are the most common “rim” calcifications.</td>
</tr>
<tr>
<td>Milk of calcium</td>
<td>Consistent with sedimented calcifications in cysts. On the craniocaudal image, they often are less evident and appear as fuzzy, round, amorphous deposits; on the 90-degree lateral view, they are sharply defined, semilunar, crescent-shaped, curvilinear, or linear, defining the dependent portions of cysts.</td>
</tr>
<tr>
<td>Suture</td>
<td>Calcium deposited on suture material. They are relatively common in the postirradiation breast. They typically are linear or tubular in appearance, and knots often are visible.</td>
</tr>
<tr>
<td>Dystrophic</td>
<td>Calcifications that usually form in the irradiated breast or in the breast after trauma. Although irregular in shape, they usually are &gt;0.5 mm in size. They often have lucent centers.</td>
</tr>
<tr>
<td><strong>INTERMEDIATE CONCERN</strong></td>
<td></td>
</tr>
<tr>
<td>Amorphous</td>
<td>Often round or flake-shaped calcifications that are so small or hazy that a more specific morphologic classification cannot be determined.</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>Smaller than dystrophic calcification, these irregular calcifications are typically between 0.5 mm and 1 mm.</td>
</tr>
<tr>
<td><strong>HIGHER PROBABILITY OF MALIGNANCY</strong></td>
<td></td>
</tr>
<tr>
<td>Fine pleomorphic</td>
<td>These have discrete sharply defined varying shapes and sizes, although they are usually &lt;0.5 mm in diameter.</td>
</tr>
<tr>
<td>Fine linear, or fine linear branching (casting)</td>
<td>Thin, irregular calcifications that appear linear, but are discontinuous and &lt;0.5 mm wide. Their appearance suggests filling of the lumen of a duct involved irregularly by breast cancer.</td>
</tr>
<tr>
<td><strong>DISTRIBUTION MODIFIERS</strong></td>
<td></td>
</tr>
</tbody>
</table>

Used as modifiers of the basic morphologic description. These terms describe the arrangement of the calcification. Multiple similar groups may be indicated when there is more than one group of calcifications that are similar in morphology and distribution.

<table>
<thead>
<tr>
<th>Type of Calcification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouped</td>
<td>Although historically the term “clustered” has connoted suspicion, the term is now used as a neutral distribution modifier and may reflect benign or malignant processes. It is used when multiple calcifications occupy a small volume (&lt;2 mL) of tissue.</td>
</tr>
<tr>
<td>Linear</td>
<td>Calcifications are arrayed in a line that may have branch points.</td>
</tr>
<tr>
<td>Segmental</td>
<td>Worrisome in that their distribution suggests deposits in a duct and its branches, raising the possibility of multifocal breast cancer in a lobe or segment of the breast. Although benign causes of segmental calcifications exist (e.g., secretory disease), this distribution is of greater concern when the morphology of the calcifications is not specifically benign.</td>
</tr>
<tr>
<td>Regional</td>
<td>Calcifications scattered in a large volume of breast tissue and not necessarily conforming to a duct distribution. They are likely benign, but are not everywhere in the breast, and do not fit the other, more suspicious categories.</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Calcifications that are distributed randomly throughout the breast.</td>
</tr>
</tbody>
</table>

Modified from Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 1998; 27.
advantages over wire localization. After excision, the specimen is sent to the radiology department to ensure that the suspicious lesion or microcalcifications, and the wire or localization seed or chip, have been removed.

Wire localization biopsy is recommended when the core biopsy results are either nondiagnostic or equivocal, or when certain benign diagnoses are encountered. If atypia, including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), FEA, or LCIS, is seen at core biopsy, it is generally recommended that excisional biopsy be performed to rule out concomitant DCIS or invasive cancer, which may be present in 10% to 15% of patients, although there may be some bias in patient selection. Surgical biopsy is also recommended when the core biopsy reveals a papillary lesion or a radial scar, as these may also be upstaged after excision.

With the increasing use of MRI screening in women at high risk for breast cancer, radiologists and breast surgeons are often faced with the need to perform biopsy on a lesion not visible with mammography or ultrasonography. When an abnormality requiring biopsy is detected with MRI but is not visible on mammograms, a focused ultrasound examination should be performed. If the lesion is visible, ultrasound-guided core biopsy may be performed. MRI may be necessary after biopsy to ensure that the ultrasound-detected lesion and the MRI-detected lesion are one and the same. If no lesion can be detected with ultrasound examination, MRI-guided biopsy should be performed. Open surgical biopsy with MRI needle localization is rarely needed, but if it is, it is important to note that the nonmagnetic wire used for MRI localization is thinner and more easily transected during surgery. In addition, specimen mammography may not be useful, so postexcisional MRI may be necessary to confirm removal of the lesion.

STAGING

Once a tissue diagnosis of breast cancer has been made, additional evaluation will determine if the patient has operable disease that is potentially curable with multimodality therapy. Treatment options include one or more of the following: surgery to the breast and axilla, radiation therapy, and systemic therapy. Selection of treatment is dependent on both stage of disease and predictive and prognostic factors, in addition to individual patient characteristics.

Seventh Edition of the TNM Staging System

The American Joint Committee on Cancer (AJCC) staging system is used to stage breast cancer according to the TNM. Changes have been made over time to reflect advances in surgical treatment and imaging and pathologic assessment of breast cancer. For example, in the current version of the AJCC staging system for breast cancer, the seventh edition, stage IB was added to reflect the diagnosis of tumors 2.0 cm or smaller (T1) with associated micrometastatic (N1mi) nodal disease. Another update was the use of clinical measurement to determine the tumor size before neoadjuvant therapy and the use of gross and microscopic histologic features to describe the size of the residual disease after neoadjuvant chemotherapy.

Prognostic and Predictive Factors for Invasive Carcinoma

Pure prognostic markers predict the likelihood of patient outcome in the absence of therapy, whereas pure predictive markers predict response to a specific therapy. Many markers serve dual roles. For example, ER is predictive for response to treatment with adjuvant endocrine therapy, and it is also a moderate positive prognostic factor because patients with tumors with high levels of ER expression generally have a lower likelihood of disease recurrence even without treatment. Similarly, HER2 is predictive of response to anti-HER2 therapy, but it is a moderate negative prognostic factor because patients with high levels of HER2 have a higher likelihood of disease recurrence if untreated. In breast cancer, the standard biomarkers are ER, PR, and HER2, which are all critical for both patient assessment and treatment decision making. However, reliability of marker assessment was lacking. Guidelines have now been developed by the College of American Pathologists and the American Society of Clinical Oncology (ASCO) in order to optimize standardization and reliability of the assays.

Multiple additional prognostic markers have been identified to predict the likelihood of recurrence of invasive carcinoma, including number of involved axillary lymph nodes, tumor size, and tumor grade. Additional pathologic characteristics of the primary tumor, including histologic subtype, Ki67, and lymphovascular invasion, have also been evaluated as additional prognostic factors. Ki67 in particular has been studied extensively, and although it appears to be useful for estimating tumor proliferation, the assay lacks standardization across laboratories and therefore is of questionable clinical usefulness at this time and is not recommended for routine clinical use by the ASCO guidelines. Newer prognostic and predictive biomarkers, such as gene expression profiles and assessment of tumor-infiltrating lymphocytes, have also been developed or are currently in development to complement traditional pathologic markers, as described elsewhere in this chapter.

PRIMARY THERAPY

Management of Noninvasive Breast Cancer

Because of the increasing acceptance of breast cancer screening in the United States, CIS accounts for an increasing proportion of all new breast cancers. Between 1975 and 1978, surveys suggested an incidence of pure in situ lesions of 1.4% to 5.1%. By 2001, nearly 20% of all new breast cancers in the United States were DCIS, and this denominator did not include cases of LCIS. Important research questions attempt to address which CIS is preinvasive cancer, which indicates an unstable epithelium that represents an increased risk of subsequent invasive cancer, and how to intervene optimally (with surgery or other preventive measures). Until better predictive markers are identified, traditional methods of estimating risk are still in use.

Lobular Carcinoma in Situ

LCIS is a microscopic diagnosis and is usually not associated with a mammographic abnormality. When LCIS is found after needle-localization biopsy of suspicious microcalcifications, the calcifications usually are outside the LCIS and the LCIS itself is usually an incidental finding. LCIS often is multicentric and is associated with an increased risk of subsequent invasive cancer in both breasts. The risk appears to be higher in the ipsilateral breast, suggesting that it may be a precursor lesion.

Classic LCIS itself does not require treatment. Evaluation for risk-reducing surgery in LCIS must take into account other risk factors, including family history and inherited genetic predisposition. Chemoprevention can also be considered to reduce the risk of subsequent breast cancer diagnosis, as discussed earlier. Pleomorphic LCIS is a morphologic variant with an aggressive behavior. Accumulating clinical data demonstrate that it may therefore require more aggressive treatment, including free margins at the excision, similar to treatment for DCIS.

Ductal Carcinoma in Situ

Before the widespread use of mammography, DCIS was not commonly diagnosed and usually manifested as a palpable mass or bloody nipple discharge. The increasing use of screening mammography has resulted in a significant increase in the number of patients diagnosed with DCIS. Most of these cases are clinically occult. Even when palpable DCIS is present, the mammographic findings are quite characteristic, with a diffuse, often linear, and extensive pattern of pleomorphic calcifications. However, the screening mammogram usually is the first
indicating DCIS. Less common mammographic findings include architectural distortion or a mass. Table 88.6 summarizes the evaluation and treatment of DCIS identified with imaging.

**Treatment of ductal carcinoma in situ**
The overwhelming majority of cases of DCIS are diagnosed with mammography; almost three-quarters of those are diagnosed based on the presence of microcalcifications without a concomitant mass. When offering the patient a breast-conserving approach, the surgeon must be confident that the remaining breast is free of suspicious mammographic abnormalities. Other clusters of microcalcifications within the breast take on greater significance after a diagnosis of DCIS is established, and biopsy is often necessary to exclude multicentricity. In cases where multicentricity is documented, or the extent of calcifications requiring excision makes lumpectomy impossible because of the proportions of DCIS is subject to sampling errors, and the cancer is often upstaged of DCIS is subject to sampling errors, and the cancer is often upstaged in invasive local recurrence. Although the effect of radiation therapy was homogeneous across risk factors, it is noteworthy that a number of identifiable clinicopathologic features were independently associated with local recurrence risk in this study (Table 88.7). Similarly, the European Organisation for the Research and Treatment of Cancer randomized phase III trial 10853 trial, in which 1010 women were randomized, revealed a 48% reduction in the risk of DCIS recurrence and 42% reduction in invasive local recurrence. Although the effect of radiation therapy was homogeneous across risk factors, it is noteworthy that a number of identifiable clinicopathologic features were independently associated with local recurrence risk in this study (Table 88.7). The patients from these two trials were combined with those enrolled in trials conducted in Sweden and in the United Kingdom, Australia, and New Zealand in a meta-analysis of individual patient data from 3925 women by Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24:3381–3387.

### Table 88.6 Guidelines for Evaluation and Treatment of Nonpalpable Ductal Carcinoma in Situ

| 1. Careful multiview mammography with or without ultrasound and including magnification views |
| - Document extent of disease |
| - Identify other areas of microcalcification |
| 2. Suspicious microcalcifications and densities cleared with needle localization biopsy |
| 3. Specimen radiography with magnification techniques |
| 4. Radiograph-directed histopathologic evaluation with orientation of specimen by surgeon using multicolored inked margins |
| 5. Complete pathologic description to include: |
| - Type of DCIS and size of tumor |
| - Relation to microcalcifications |
| - Distance of lesion from inked margins |
| - Presence of multifocality |
| - Presence or risk of microinvasion |
| 6. Repeat mammography with magnification to confirm successful clearing of suspicious areas |
| 7. Repeat breast excision if: |
| - Residual microcalcifications are found |
| - Margins are unacceptable |

**DCIS**, Ductal carcinoma in situ.

### Table 88.7 Multivariate Analysis of Risk Factors Related to Local Recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (YEARS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>1.89</td>
<td>1.12–3.19</td>
<td>.026</td>
</tr>
<tr>
<td><strong>METHOD OF DETECTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic finding only</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>1.55</td>
<td>1.11–2.16</td>
<td>.012</td>
</tr>
<tr>
<td><strong>HISTOLOGIC TYPE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediately differentiated</td>
<td>1.85</td>
<td>1.18–2.90</td>
<td>.04</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1.61</td>
<td>0.93–2.79</td>
<td></td>
</tr>
<tr>
<td><strong>ARCHITECTURE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinging or micropapillary</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cribriform</td>
<td>2.39</td>
<td>1.41–4.03</td>
<td>.002</td>
</tr>
<tr>
<td>Solid or comedo</td>
<td>2.25</td>
<td>1.21–4.18</td>
<td></td>
</tr>
<tr>
<td><strong>MARGINS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not free</td>
<td>1.84</td>
<td>1.32–2.56</td>
<td>.0005</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE + RT</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE</td>
<td>1.82</td>
<td>1.33–2.49</td>
<td>.0002</td>
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LE, Local excision; RT, radiation therapy.

appear to predict risk of local recurrence, and retrospective studies have suggested that tumor size, grade, age, and margin status can help to identify patients with DCIS who are at low risk of local recurrence after lumpectomy alone.227 Prospective studies enrolling such patients have not yet clearly identified patients in whom the long-term risk of local recurrence is extremely low after excision alone. In a single-arm trial of wide local excision alone at Harvard, even patients with limited amounts of DCIS excised with widely negative margins had a 5-year risk of local recurrence of 12%, leading the authors to conclude that even patients with favorable clinicopathologic features have a sufficient risk of local failure to justify adjuvant radiotherapy.218 Similarly, in the ECOG 5194 single-arm trial, the 561 patients with low- or intermediate-grade DCIS smaller than 2.5 cm in extent, treated with excision with at least 3-mm negative margins, had a 12-year risk of local failure of 14%, and the risk was 25% among 104 patients with high-grade disease 1 cm or smaller.219 A genomic assay has been developed using these data to help provide more refined predictions of the risk of local recurrence in such patients, but given that the low-risk group identifiable with that assay still appears to have a 10-year risk exceeding 10%, many patients and physicians continue to pursue adjuvant radiotherapy in this setting.220 Concerns about possible late recurrences have also limited the impact of the early results of the randomized Radiation Therapy Oncology Group (RTOG) 9804 trial, which showed a promisingly low risk of local recurrence (6.7% at 7 years) in patients who did not receive radiotherapy, and which was reduced to 0.9% with the addition of radiation therapy.221 Of note, 62% of the patients in the RTOG trial received tamoxifen, which has been established in randomized trials from the United Kingdom, Australia, and New Zealand and in NSABP B-24 to reduce the risk of both ipsilateral breast tumor recurrence and contralateral breast cancer in patients with DCIS, as described in detail subsequently.222 Approximately 50% to 75% of DCIS lesions express ER and/or PR. Tamoxifen has been shown to reduce the risk of local recurrence in DCIS. In the NSABP B-24 study, 1804 women were randomized to tamoxifen or placebo after lumpectomy and radiation therapy.214 With a median follow-up of 163 months, the risk of ipsilateral invasive recurrence was reduced by approximately 32%, although the absolute risk reduction was only 3%. In the United Kingdom, Australia, and New Zealand DCIS trial, patients who underwent lumpectomy for DCIS were randomized to radiation therapy, tamoxifen, both, or neither.224 In those patients who underwent lumpectomy, after a median follow-up of 12.7 years tamoxifen reduced recurrence of DCIS with a hazard ratio (HR) of 0.70 (95% CI, 0.51–0.86), but not invasive disease. In the same trial, radiation therapy reduced the incidence of both ipsilateral invasive disease (HR, 0.32 [0.19–0.56]) and ipsilateral DCIS (HR, 0.38 [95% CI, 0.22–0.63]). Meta-analysis of the results of these two randomized trials showed that the addition of tamoxifen to breast-conserving therapy for DCIS reduced the risk of both ipsilateral and contralateral DCIS, and revealed a trend toward a reduced risk of ipsilateral and contralateral invasive carcinoma, although there was no survival benefit.215 For postmenopausal women, the AI anastrozole is a reasonable alternative based on findings from the NRG Oncology/NSABP B-35 trial, in which anastrozole was associated with a longer breast cancer–free interval compared with tamoxifen.224

**Management of Early-Stage Invasive Breast Cancer**

The management of stages I to III breast cancer is multidisciplinary and involves specialists in breast imaging, pathology, surgical oncology, radiation oncology, medical oncology, and reconstructive surgery. Depending on the extent of disease at diagnosis and other factors such as family history, patients may be candidates either for breast-conserving therapy with lumpectomy plus radiation therapy or for mastectomy. Preoperative systemic therapy may also be a consideration, with the goal of treating subclinical micrometastatic disease, reducing local and regional tumor bulk, and increasing the likelihood of successful surgical resection.

Adjuvant radiation therapy decisions are made based on the final surgery performed, pathologic characteristics of the tumor, and clinical factors such as age and comorbidities. Decisions about adjuvant systemic therapy are made using a combination of predictive and prognostic factors. Additional details about each of these treatment modalities are provided in the following sections.

**Surgery for Early-Stage Breast Cancer**

Mastectomy was the initial surgical approach to treating breast cancer. Pioneering investigations in the 1920s and 1930s began to treat groups of women with breast-conserving partial mastectomy, followed by irradiation to the intact breast, challenging the need for total mastectomy. Results from those early studies were promising. Beginning in Europe and Canada, and later in the United States, several institutions initiated programs, including excision plus radiation therapy for select breast cancer patients. In the early 1970s, several European reports created worldwide interest in nonmastectomy treatments based on individual series that suggested local recurrence rates of 5% to 10%, and similar survival.

These studies caused considerable controversy between breast surgeons who embraced breast conservation and those who believed mastectomy should remain standard of care. This led to six randomized prospective trials across Europe and the United States comparing breast conservation and mastectomy, which demonstrated survival equivalency between the two approaches. Investigators of both the NSABP B-06 trial and the Milan Cancer Institute Trial reported 20-year results showing equivalent outcomes.225,226 The breast-conserving therapy data were so convincing that in 1990, the NCI held a consensus development conference on the treatment of early breast cancer and declared that breast-sparing therapy not only was equivalent to mastectomy, but was actually the “preferable” treatment.227 In the NSABP B-06 trial, women were randomly assigned to three treatment arms: mastectomy, breast conservation with radiation therapy, and breast conservation without radiation therapy. Although all three arms had a similar survival, the breast conservation-alone arm experienced a nearly 40% in-breast local failure rate. The absence of a relationship between local failure and distant metastases suggested that this was an acceptable approach. However, the EBCTCG performed a meta-analysis that included 78 randomized studies involving over 42,000 patients. These researchers found that avoidance of a local recurrence affected 15-year breast cancer mortality. Improved local control translates to avoiding one breast cancer death for every four local recurrences avoided. Therefore lumpectomy alone is generally discouraged, although there are some groups in which this may be acceptable, as discussed further later.228

**Resection of the Primary Tumor**

Initially there was considerable variability in the techniques used for resecting the primary tumor. In Europe, this often meant a segmentectomy or quadrantectomy, procedures that were characterized by a significantly larger resection volume compared with the lumpectomies or wide excisions performed in the United States.229 The concept of large excisions has been progressively replaced by the concept of free margins. There has been considerable debate as to the definition of the free margin distance, with multiple retrospective studies examining the relationship between local recurrence and the microscopic margin distance. The Society of Surgical Oncology and the American Society for Radiation Oncology convened a multidisciplinary panel and performed a meta-analysis of 33 studies including over 28,000 patients.230,231 They concluded that although a positive margin was associated with a greater than twofold increase in local recurrence (odds ratio [OR], 2.44 [95% CI, 1.97–3.03]), margins wider than “no ink on tumor” were not associated with a lower incidence of local recurrence. However, the meta-analysis was based on retrospective studies with significant selection bias, so there should be some flexibility in application, with re-excision recommended for select patients.
Orientation of the specimen is mandatory to allow accurate pathologic assessment of the margins and guide re-excision. Pathologists ink the surface of the specimen by using six different colored inks. The specimen is then cut and histologic sections are prepared. Extra attention is paid to areas near the surgical margin whenever tumor is seen to encroach grossly.

Several intraoperative techniques have been described to reduce the re-excision rate, which in some studies can be as high as 40% to 50%. Obtaining routine cavity shave margins in all anatomic directions at the time of the lumpectomy can reduce the rate of re-excision.\textsuperscript{132} Intraoperative margin analysis has been shown to significantly decrease re-excision rates, but implementation can be challenging.\textsuperscript{219,220} Cytologic touch preparation analysis and intraoperative margin assessment devices can also be used. There is no prevailing standard of care, and practices vary widely.\textsuperscript{216} At the completion of the lumpectomy, small titanium clips should be placed at the margins to guide the radiation oncologist for precise placement of a boost, or for partial breast irradiation. After lumpectomy, the skin should be closed, but reapproximation of the breast tissue should be avoided because this leads to distortion of the breast shape.\textsuperscript{237} For patients with a significant defect, oncoplastic techniques can be used to rearrange the breast parenchyma to avoid excess concavity.\textsuperscript{238} These are best planned preoperatively. Although most women today are candidates for breast conservation, there are several contraindications:

- Scleroderma, cutaneous lupus erythematosus, and other collagen vascular diseases are considered relative contraindications to breast conservation, particularly if active, because evidence suggests an increased severity and frequency of radiation-related complications in such patients.
- Diffuse microcalcifications throughout the breast.
- Multicentric invasive cancer or DCIS.
- Inability to achieve negative margins despite repeated attempts at re-excision.
- Patients with previous chest wall irradiation require evaluation by a radiation oncologist to determine the feasibility of breast conservation; innovative approaches such as partial breast reirradiation are under investigation,\textsuperscript{239} but a history of prior therapeutic doses of radiotherapy to the whole breast is still generally considered a contraindication to breast conservation.

**Mastectomy**

For patients who have a contraindication to breast conservation, mastectomy is indicated. When patients are unable to achieve complete removal of the cancer and an acceptable cosmetic result, mastectomy and reconstruction may be a better option. Some patients may strongly desire conservation despite less than satisfactory cosmetic outcome, and several techniques exist for addressing defects in the breast including local tissue flaps or fat grafting.

For many decades, the Halsted radical mastectomy was the treatment of choice for all stages of breast cancer. This involved the resection of the breast parenchyma, a large portion of the skin overlying the breast, and the major and minor pectoral muscles en bloc with levels I to III of the axillary nodes. This eventually gave way to a less-aggressive operation—the modified radical mastectomy—without compromising survival. The modified radical mastectomy consists of resecting the breast parenchyma en bloc with levels I and II axillary lymph nodes, but preserving adequate skin and the pectoralis muscles.

With the evolution of SLN biopsy for axillary staging, the efficacy of systemic therapies, and the use of postmastectomy radiation therapy, the modified radical mastectomy has become less common. Total or simple mastectomy, with removal of enough skin to allow closure and the nipple-areolar complex and all the breast tissue without the axillary lymph nodes, has supplanted modified radical mastectomy for most patients. When elliptical or transverse incisions are used, it is ideal to excise any previous biopsy scar along with the nipple-areolar complex.

Skin flaps are carefully developed—thin enough to remove all apparent breast tissue, but without removing the subcutaneous tissue of the flaps that carry the blood vessels of the skin. The inferior flap extends inferiorly to the inframammary crease. The superior flap is extended just beneath the clavicle. The medial extension of the flaps reaches the lateral edge of the sternum; the lateral extension should include the axillary tail of Spence but, unless a modified radical mastectomy is being performed, should not include the axillary contents. During dissection, it is important to spare the medial pectoral nerves, which wrap around the lateral border of the pectoralis minor muscle and insert into the posterior aspect of the pectoralis major. Injury to these nerves leads to atrophy of the central portion of the pectoralis major muscle. When bilateral mastectomies are being performed, it is critical not to cross the sternum, creating a tunnel between the two medial flaps. Once the flaps are developed, the breast is dissected from the chest wall by dissecting the pectoralis major fascia off of the muscle.

Reconstruction of the breast is a valid option that can be done immediately or after the procedure (i.e., “delayed”). With attempts to improve overall cosmesis after mastectomy and breast reconstruction, more ‘conservative’ mastectomy procedures have evolved. Skin-sparing mastectomy, in which removal of the skin is limited to the nipple-areolar complex (sometimes with a small portion of skin), is an oncologically safe approach that minimizes deformity and improves cosmesis. Retrospective series of skin-sparing mastectomy and breast reconstruction show similar rates of local control with those of conventional mastectomy. The nipple-sparing mastectomy, in which only the breast parenchyma is removed, has also emerged as an acceptable choice for select early-stage breast cancers and high-risk women pursuing mastectomy, although the ductal tissue below the nipple may be an oncologic concern when this is being performed for cancer. Nipple-sparing mastectomy should be considered for cancer patients only when the tumor is at least 2 cm from the nipple-areolar complex and in the absence of skin or nipple involvement, widespread microcalcifications, or microcalcifications extending to the nipple. Complete removal of this tissue may compromise the vascularity of the nipple and lead to necrosis. Intraoperative analysis of the subareolar tissue is often performed, and the nipple-areolar complex is sacrificed if findings in frozen sections are positive.

**Contralateral Prophylactic Mastectomy**

There has been a recent trend toward women with unilateral breast cancer opting for removal of both breasts—the affected ipsilateral breast along with a CPM. Even while the indications for mastectomy have decreased, more women deemed eligible for breast-conserving therapy have opted for bilateral mastectomies.\textsuperscript{240} This started with the availability of BRCA testing in the preoperative period in 2002, but the rates of bilateral mastectomies have markedly increased since that time.\textsuperscript{241,242} Today, most patients who undergo CPM do not have strong genetic or familial risk factors for developing contralateral breast cancer.\textsuperscript{243} This trend is primarily being driven by an overestimation of the risk of contralateral breast cancer and potentially unrealistic outcomes from CPM.\textsuperscript{244,245} Although women who have had one breast cancer do have an increased risk of a second cancer, this risk is not as high as expected, estimated to be approximately 0.4% per year among BRCA1/2-negative patients with hormone receptor–positive tumors taking antiestrogen therapy, and 0.5% per year among hormone receptor–negative patients.\textsuperscript{246} CPM does nothing to decrease the risk of distant recurrence, which is significantly higher than the risk of a second primary cancer, and thus CPM has no impact on survival. The misconceptions regarding the benefits of CPM come from multiple sources, including physicians and the media.\textsuperscript{247–249} For these reasons, groups such as the Society of Surgical Oncology and the American Society of Breast Surgeons have advocated for having detailed conversations with patients regarding their expectations, educating them on the true benefits and risks of CPM, and discouraging CPM among women without a high risk of future breast cancer.\textsuperscript{250}
Management of the Axilla

In addition to resection of the primary lesion, the surgical treatment of invasive breast cancer involves management of the axilla. This is not only important in maximizing locoregional control, but significant prognostic information is gained by determining the pathologic nodal status, which helps guide adjuvant systemic therapy decisions and radiation planning.

For patients with no evidence of regional metastases at either physical examination or imaging (clinically node-negative patients), SLN biopsy is the standard surgical approach to staging the axilla. More than 60 observational studies (in more than 6000 patients) in which SLN biopsy was followed by ALND have established a greater than 95% success rate for SLN identification and a false-negative rate below 10%. This false-negative rate, although potentially affecting adjuvant therapy decisions, does not pose an increased risk for the development of axillary recurrence among patients staged with SLN biopsy alone. Data from several observational studies and one randomized trial demonstrate that axillary recurrence after a negative SLN biopsy result is a rare event, occurring in 0.2% of cases. Possible explanations may include the local effect of systemic therapy and the use of breast radiotherapy, which inevitably treats a portion of the axillary lymph nodes.

NSABP B-32 was a prospective randomized phase III clinical trial designed to compare SLN biopsy with conventional axillary dissection in clinically node-negative patients. A total of 5611 patients with clinically negative axilae were randomly assigned to SLN biopsy and ALND versus SLN biopsy and ALND only if the SLN was positive. There was significantly less morbidity with SLN biopsy, but no difference in disease-free survival (DFS) or OS between the two groups. As expected, patients with hematoxylin-eosin (H&E)–positive nodes had worse OS with respect to node-negative patients. After pathologic examination at the treating institution, paraffin blocks of all SLN-negative specimens from B-32 were sent to a central laboratory for a clinically blinded search for occult metastases. Additional sections were evaluated with H&E and cytokeratin-IHC stains, with additional micrometastases and IHC-positive cells detected. Although these were associated with a worse prognosis than truly negative SLN patients, the difference was minimal (1.2% decrease in OS). For this reason, the presence of isolated tumor cells (ITCs) is considered node-negative disease in the AJCC staging system, with an “i+” designation (N0i+).

The management of the positive SLN has changed dramatically. Initially, all patients with a positive SLN were recommended to undergo completion ALND. However, over half of patients had no additional disease identified, and SLN-positive patients go on to receive systemic therapy and adjuvant radiation therapy, which may help control any residual micrometastatic disease in the axilla, calling into question the benefit of the completion dissection. The American College of Surgeons Oncology Group (ACOSOG) Z0011 study was designed to address this question among patients with a positive SLN undergoing breast-conserving surgery followed by radiotherapy. Patients with T1 or T2 tumors and fewer than three positive SLNs were randomized to completion ALND or observation. There were similar 5-year OS rates (92.5% versus 91.9%) and DFS rates (83.9% versus 82.2%). The trial was underpowered and was heavily biased toward micrometastatic disease in the SLNs. Nevertheless, the very low ipsilateral regional recurrence rate (0.5% in the ALND arm and 1.5% in the SLN-alone arm) was convincing that for patients similar to those enrolled in Z0011, ALND is not necessary for a positive SLN, particularly in patients with micrometastatic disease. This was confirmed by the International Breast Cancer Study Group (IBCSG) 23-01 trial, in which patients with tumors smaller than 5 cm and nodal metastases in the SLN smaller than 2 mm were randomized to completion ALND or no further surgery.

Although this study also had low accrual, it found no statistically significant differences in DFS (84% versus 88%) or OS (98% versus 97.6%).

Ninety percent of the patients in the IBCSG 23-01 trial and a similarly high proportion of the women in the Z0011 trial received whole-breast irradiation, which covers much of the axilla. In the Z0011 trial, although the protocol called for no radiation therapy to the axilla, several patients had either adjusted tangents or direct axillary radiation therapy. In addition, the EORTC conducted the AMAROS trial, in which 4806 patients with T1 or T2 tumors with positive SLNs were randomized to either ALND or axillary radiotherapy. There were no significant differences in the axillary recurrence rate (0.43% versus 1.19%), DFS, or OS. Lymphedema was significantly more common after ALND than after radiation therapy. Looking at all three trials, it seems reasonable that patients with a positive SLN may avoid completion ALND if irradiation is planned (either for breast-conserving therapy or postmastectomy radiation therapy). Whether to adjust the tangents or perform direct axillary irradiation should be based on individual clinicopathologic features, including tumor burden within the SLNs. ALND should be performed for a positive SLN when no radiation therapy or partial breast irradiation is planned. ALND should also still be performed in SLN-positive patients with three or more positive nodes, when extranodal extension is present, or when the SLN is positive after neoadjuvant chemotherapy.

Clinically node-positive patients—those who have adenopathy at physical examination or suspicious nodes at imaging—require a different approach. Any suspicious nodes at examination or imaging should be biopsy proven, because these may often be reactive. For biopsy-proven regional metastases, ALND is recommended. Axillary clearance for breast cancer typically involves levels I and II, those lymph nodes lateral and inferior to the pectoralis minor muscle. If there is significant axillary disease, the level III nodes should also be included. The level III nodes lie medial to the pectoralis minor and are bordered medially by the Halsted ligament. If possible, the pectoralis minor muscle is preserved.

If the axilla is to be dissected, either in continuity with the breast in a modified radical mastectomy or as a separate axillary dissection, the clavipectoral fascia is divided. Fat from the axilla then pops through this division, and differs in appearance from the subcutaneous fat. The inferior border of the axillary vein is roughly two fingerbreadths below the highest extent of the pectoralis major fascia. Staying below the axillary vein is critical in order to avoid brachial plexus injury and spare the brachial lymphatics, minimizing the risk of lymphedema. The thoracodorsal vein is identified inferiorly and posteriorly to the axillary vein. The thoracodorsal nerve is seen to emerge from behind the axillary vein, just medial to the thoracodorsal vessels. It joins these vessels, continuing onto the anterior surface of the thoracodorsal vein. Between 1 and 2 cm below the axillary vein, the highest branch of the intercostobrachial nerve is seen coming from the chest wall and going to the arm. If there is no concern regarding its proximity to cancer, it is possible to spare this nerve branch to avoid the dysesthesias and numbness of the inner posterior arm. When the thoracodorsal bundle has been identified along its length (to its insertion into the latissimus dorsi), elevating the pectoralis minor muscle and sweeping the axillary fat downward off the chest wall moves the level II axillary nodes out from behind the pectoralis minor muscle. The long thoracic nerve is found in the same anteroposterior plane as the thoracodorsal nerve. At this point, the three major midaxillary nerves have been identified. The axillary contents can now be cleared inferiorly, with all of the important nerves and vessels in view.

When suspicious palpable lymph nodes are present high within level II or level III, removal of the level III nodes is advised. If possible, the pectoralis minor muscle is preserved. The lateral borders of the pectoralis major and minor muscles are dissected, thereby preserving the medial pectoral nerve. In this way it is possible to dissect the apex without division or removal of the pectoralis minor. Both pectoral muscles are retracted medially to maintain the exposure of the level III region. This may require the use of a Thompson retractor and bringing the arm across the chest to relax the muscles. This is why...
Irradiation of the Intact Breast

The numerous randomized trials comparing outcomes after lumpectomy with or without adjuvant radiotherapy have been combined by the EBCTCG (Fig. 88.19). Because adjuvant whole-breast radiotherapy halves the risk of any breast cancer recurrence and yields a modest survival benefit, it is widely considered to be the standard of care after lumpectomy for invasive breast cancer. Still, the absolute benefits of treatment vary considerably across subgroups. Therefore just as in the case of DCIS, research has focused on trying to identify women with sufficiently low risk of recurrence in the absence of radiotherapy to justify its omission, particularly among patients with endocrine-sensitive disease who receive effective systemic therapies.

Figure 88.19 • Effect of radiation therapy after breast-conserving surgery on risk of first recurrence (locoregional or distant) and on breast cancer mortality. Data from 17 trials. Vertical lines indicate 1 standard error (SE) above or below the 5-, 10-, and 15-year percentages. CI, Confidence interval; RR, relative risk. (From Early Breast Cancer Trialists' Collaborative Group et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378[9804]:1707–1716.)
In the Cancer and Leukemia Group B (CALGB) 9343 trial, patients aged 70 and older with clinical stage I, ER-positive invasive breast cancer treated with lumpectomy and tamoxifen were randomized to adjuvant whole-breast radiotherapy or not. Even in this highly select group, adjuvant radiotherapy significantly reduced the risk of local recurrence (from 10% to 2% at 10 years). Still, because this reduction in local recurrence was not associated with an improvement in survival, freedom from mastectomy, or other end points, this trial has been interpreted as establishing radiotherapy omission as a reasonable option for consideration in this small subgroup of patients. In all other patients who undergo lumpectomy outside of the context of a clinical investigation, radiation therapy remains the standard of care. Ongoing studies may identify additional populations at sufficiently low risk of local recurrence after lumpectomy alone to warrant avoidance of radiation therapy.

Attempts to reduce the burden of adjuvant radiation therapy in this setting have included investigation of whole-breast hypofractionation, in which the whole breast is treated in fewer fractions (e.g., 40 Gy in 15 fractions or 42.5 Gy in 16 fractions) rather than the conventional fractionation schedule of 50 Gy in 25 fractions. Strong evidence from randomized trials in the United Kingdom and Canada have established this to be equivalent in terms of both efficacy and safety for women with early-stage invasive cancer, and observational data suggest good outcomes also in patients with DCIS.

Whole-breast irradiation is typically delivered with tangentially oriented beams that treat the entire breast while minimizing dose to the underlying heart and lungs. Particularly given recent studies emphasizing the dose-response relationship for cardiac toxicity of radiotherapy, care is taken to shield the heart or to alter the anatomic relationships between the breast tissue and the heart with use of techniques such as breath holding or prone positioning (Fig. 88.20). This is often followed by boost treatment of an additional 10 to 16 Gy to the tumor bed. A randomized trial from the EORTC established the benefit of this boost treatment in improving local control in all patients, but with considerably lower absolute benefits in older patients. Judicious selection of patients expected to benefit meaningfully from boost treatment includes consideration of factors known to correlate with the risk of local recurrence, such as age, grade, margin status, and systemic therapy.

Given the observation that most local failures occur in the vicinity of the original lesion, partial breast irradiation, which can be accomplished with a variety of approaches ranging from external beam delivery to brachytherapy implants or intraoperative treatment, has also been the subject of active investigation. Although concerns have been raised by the observation of a small increase in the rate of mastectomy in a claims-based study of patients who received balloon implants in the early days of development of that technique (a finding that might reflect toxicity before experience established parameters for safe spacing of the balloon with respect to skin surface, for example, or perhaps an indication that early patient selection was suboptimal) and the observation of impaired cosmetic outcomes among patients treated with external beam approaches in a large Canadian trial, promising early results from other studies motivate eager anticipation of mature results from the large RTOG 0413/NSABP B-39 trial. In the meantime, consensus guidelines exist to select patients appropriate for treatment with partial breast approaches outside of the context of an ongoing trial.

For patients who have no positive axillary nodes after ALND or have negative SLN biopsy findings, the axilla and other regional nodal basins (supraclavicular and internal mammary) are not targets of treatment. For those in whom at least one axillary node is positive, consideration is given to irradiating these regions in conjunction with treatment to the whole breast. Treatment of the supraclavicular, infraclavicular, and internal mammary nodal regions is well accepted for patients with four or more lymph nodes involved, for the same reasons that postmastectomy radiotherapy is widely accepted in these patients, as discussed later. For patients with fewer than four lymph nodes involved, there is greater controversy, given that some of these patients were eligible for trials that have demonstrated benefits from regional nodal radiotherapy after lumpectomy and ALND (NCIC MA.20 and EORTC 22922) and for the ACOSOG Z0011 trial, which, as more fully described earlier, demonstrated excellent outcomes in patients who underwent lumpectomy with SLN biopsy alone.

The low (levels I and II) axilla itself may be treated with minor modifications of the standard tangential beams used to treat the breast, an approach often called “high tangent” radiation therapy. This is often an approach favored in patients whose node-positive disease was identified at SLN biopsy and who did not undergo ALND; for patients with favorable features similar to those in the ACOSOG Z0011 and IBSCG 23-01 trials, many radiation oncologists will use this minor modification of treatment fields, which is not believed to cause meaningful changes in toxicity. Alternatively, in patients who have more concerning features, such as numerous lymph nodes involved or ER-negative disease, the additional lymph nodes in the infraclavicular (level III axilla) and supraclavicular regions may then also be targets of treatment; a third anterior field may be added to include just those regions or also to include the axilla if undissected or heavily involved. The internal mammary nodes may also be targeted in high-risk patients.

### Complications of Treatment

Advanced treatment planning and delivery approaches allow for improved dose homogeneity and visualization and exclusion of critical normal tissues, reducing the risks of radiation-related toxicity. Even with treatment to the whole breast and regional nodes after lumpectomy and ALND, the MA20 trial showed only a 1.2% incidence of radiation pneumonitis (and that rate was only 0.2% with breast irradiation alone, without regional nodal irradiation) and an 8.4% risk of lymphedema (a risk that was 4.5% with breast irradiation alone). Pneumonitis typically resolves spontaneously or after a short course of corticosteroids and is not expected to result in clinically significant long-term changes in lung function; lymphedema can be more...
problematic but is reduced in the modern era with less extensive surgery. Rib fractures occur infrequently and heal spontaneously, but the possibility merits care to ensure that when such a finding is discovered, appropriate consideration is given to treatment-related toxicity rather than disease recurrence if the fracture is within the radiation treatment field. Dose-dependent cardiac toxicity has been shown in historical trials in which mean heart doses were substantially higher than those delivered in modern US practice; observational studies suggest very low risk of cardiac sequelae from regimens administered in contemporary practice with appropriate care to reduce cardiac exposure. Brachial plexus injury has been reported from treatment to the supraclavicular region, and because this risk appears related to daily fraction size, US practitioners frequently use conventional fractionation rather than hypofractionation in patients in whom regional irradiation is intended. Perhaps the most dreaded consequence of therapeutic radiotherapy is secondary malignancy; the risk of soft tissue sarcoma is approximately 0.2% at 15 years, and the risk of lung cancer is also increased by radiotherapy, with epidemiologic analyses suggesting that patients who smoke are at highest risk.

Adjuvant Postmastectomy Irradiation

Even after mastectomy, some patients have sufficient risk of harboring residual disease in the chest wall or regional nodes that adjuvant radiotherapy may be beneficial. Historical trials initially indicated a detriment from the addition of radiotherapy in this setting because the benefits in local control were offset by increases in treatment-related toxicity, particularly cardiac mortality. However, landmark trials from Denmark275,276 and British Columbia,277 conducted in samples that primarily included node-positive patients, revealed that postmastectomy radiotherapy reduced local recurrence by two-thirds and improved survival. The generalizability of these trials, particularly with respect to the findings in patients with only one to three lymph nodes involved, was questioned in light of the limited extent of ALND in the Danish trials. Therefore prior consensus guidelines recommended postmastectomy radiotherapy in patients with four or more lymph nodes involved, but failed to recommend for or against treatment in patients with one to three positive nodes and tumors 5 cm or smaller in size. However, a recent EBCTCG meta-analysis that focused on 3786 patients who were randomized to radiotherapy or not but who had all received complete ALND also revealed substantial benefits, including improved breast cancer mortality, from postmastectomy radiation therapy in node-positive patients (Fig. 88.21).278 Even in the 1314 patients with axillary dissection and only one to three nodes involved, the improvement in breast cancer mortality was substantial (RR, 0.80; \( P = .01 \)). Therefore the most recent consensus guidelines note that postmastectomy radiotherapy reduces the risks of locoregional failure, any recurrence, and breast cancer mortality for patients with T1 or T2 breast cancer with one to three positive axillary notes, but because some subsets are likely to have such a low risk of locoregional failure that the absolute benefit of radiation therapy is outweighed by risks, they call for individualized decision making in this context.279 Physicians are encouraged to consider in their recommendations a constellation of factors that may affect the risk of locoregional failure, attenuate the benefit of reduced breast cancer–specific mortality, and/or increase complication risks. These factors include patient characteristics such as age, life expectancy, coexisting conditions that might increase risk of complications; pathologic features such as tumor size, lymphovascular invasion, number and size of nodal metastases, response to neoadjuvant systemic therapy if any administered; and biologic characteristics such as grade, hormonal sensitivity, and subtype. The panel further encourages multidisciplinary decision making in this complex context, shared with patients to incorporate values regarding the weighting of benefits and risks in the light of the best estimates that physicians can provide.

Although the most recent consensus guidelines primarily focus on the groups for whom there has been greatest controversy over the past decade, it is important to stress that there is strong consensus to support the use of postmastectomy radiotherapy for patients with more extensive disease, including T3 or T4 primary tumors, four or more lymph nodes involved, or residual axillary involvement after preoperative systemic therapy.

Adjuvant Systemic Therapy

Along with mammography, adjuvant systemic therapy changed the course of early-stage breast cancer.280 Since the 1970s, randomized trials have shown a survival benefit from adjuvant chemotherapy in operable, node-positive disease. Starting in 1985, the systematic reviews and meta-analyses by the EBCTCG led to the rapid adoption of adjuvant systemic therapy, with updates published on chemotherapy and endocrine therapy.281-283 Although adjuvant chemotherapy was initially used primarily to treat patients with node-positive disease, by the mid-1990s it was routinely used to treat node-negative disease as well, regardless of hormone receptor status. In the same time period, tamoxifen started being used for treatment of those with ER-positive disease.

Soon, data began to suggest that not all patients with ER-positive disease obtained benefit from treatment with adjuvant chemotherapy. For the average patient, decision algorithms based on routine clinicopathologic factors (e.g., tumor size, nodal status, grade, ER, and HER2) had proved quite useful for decision making. However, by the mid-2000s new genomic tools for prognosis and prediction became available to better estimate recurrence risk and likelihood of benefit from chemotherapy, respectively, to further individualize clinical decisions. Data from prospective and retrospective studies demonstrated that gene expression profiles such as Oncotype DX, described later, and routine standard clinicopathologic parameters offered independent prognostic usefulness in ER-positive disease.284-286 Therefore it was important to develop optimal ways to integrate the complementary data provided by standard clinicopathologic tumor assessment and molecular markers.

Although screening mammography and consequent earlier diagnosis of breast cancer was responsible for at least half of the breast mortality reduction observed between 1990 and 2003, the introduction of adjuvant systemic therapy, including both cytotoxic chemotherapy and endocrine therapy, also significantly reduced the odds of disease recurrence and death.280 Analysis of large databases also indicates that the 5-year survival rate in women with small hormone-receptor positive tumors is not likely to be affected by their disease, and that chemotherapy offers minimal potential benefit.287 However, data from the NSABP suggest improvements in both recurrence-free survival and OS in women with ER-positive and ER-negative tumors no more than 1 cm in size who are treated with adjuvant chemotherapy.288 These discrepancies likely result from the modest treatment benefits obtained with available systemic therapies at a population level, combined with the considerable heterogeneity observed in breast cancer even when considering tumors with a similar profile based on standard pathologic characteristics (e.g., tumor size, nodal status, ER and PR expression). Although systematic reviews and computerized nomograms have been quite useful to demonstrate the average benefit for specific patient subgroups, especially when the absolute benefit is otherwise small, these efforts fail to recognize the variability among individuals.

It is now understood that the small to modest therapeutic effects noted in individual clinical studies are of great value if applied to the large population of women with breast cancer. The 2005 EBCTCG meta-analysis demonstrated a significant survival advantage after polychemotherapy for all adequately studied age categories, although the number of patients older than 70 who were included was limited.281-283 There is now Level I evidence that chemotherapy is of benefit for older women with ER-negative disease.289 Likewise, chemotherapy has been shown to be effective in patients with either node-negative or node-positive disease.290 Polychemotherapy was demonstrated to be superior to monochemotherapy, and more prolonged administration of chemotherapy (for 12 months or longer) has not
been associated with greater benefit compared with shorter duration of treatment (e.g., 6 months).

For patients with hormone receptor–positive disease, the EBCTCG also showed that adjuvant tamoxifen improves survival, irrespective of age or menopausal status. In contrast to chemotherapy, longer duration of treatment with tamoxifen (i.e., 5 years) provides greater benefit than a single year of administration. Although initial studies revealed no additional benefit when tamoxifen was continued beyond 5 years, more recent large randomized clinical trials including Adjuvant Tamoxifen Long Versus Short (ATLAS) and Adjuvant Tamoxifen Treatment, Offer More? (aTTom) demonstrated superiority of 10 years over 5 years. Ovarian function suppression (OFS) reduces the mortality rate in women younger than 50 years when compared with no therapy and is similar to the benefit offered by first-generation chemotherapy. In addition, recent data demonstrated improvement in DFS when added to adjuvant endocrine therapy, especially in specific patient subsets.

However, it is now generally acknowledged that breast cancer is a heterogeneous disease. Decisions about whether to consider adjuvant systemic therapy must take into account a combination of prognostic markers of risk (e.g., nodal status, tumor grade, and tumor size), predictive markers of response (e.g., ER, PR, and HER2), and patient factors such as comorbidities. By including all three categories of data, one can accurately estimate both the potential benefits and risks of treatment for an individual patient. Breast cancer patients traditionally have overestimated the absolute value of systemic therapy, and a common misinterpretation is that the treatment benefit is similar across all patients, with most having some benefit. It is important to consider the estimated individual risk of recurrence, comorbidity, and personal patient preferences when discussing the potential benefits of adjuvant systemic therapy.

**Adjuvant Chemotherapy**

**Who Should Receive Chemotherapy?**

What tools are available to guide chemotherapy decision making? Using standard pathologic data, multiple tools are available to clinicians. Clinical practice guidelines often are used, such as those from NCCN or ASCO in the United States or the St. Gallen International Expert Consensus Panel Meeting in Europe. Quantitative tools such as Adjuvant! Online were developed to help patients and health care providers estimate the potential actual benefit...
from adjuvant systemic therapy. However, estimates of benefit from adjuvant trastuzumab for patients with HER2-positive disease have not yet been incorporated into this model. More recently, the PREDICT (http://www.predict.nhs.uk/) tool was developed; it also includes HER2 status and Ki67 expression levels, although most studies about the tool published to date have focused on its prognostic use rather than its role in prediction of response to therapy.

Multiple gene expression profiles were included in the 2016 ASCO guidelines for use for guiding decisions on chemotherapy in select populations. These include the 21-gene RS Oncotype DX assay, the 12-gene EndoPredict assay, the PAM50 risk of recurrence Prosiga assay, the Breast Cancer Index, and the combination of urokinase plasminogen activator and plasminogen activator inhibitor type 1 (uPA/PAI-1). The strength of each recommendation varies by assay; additional details about a subset of these assays are provided subsequently.

For patients with hormone receptor–positive, HER2-negative, node-negative breast cancer, gene expression profiling with Oncotype DX was validated with a prospective and retrospective approach as a tool to identify the predictive benefit from adding adjuvant chemotherapy to endocrine therapy. Patients with a low recurrence score (0–17) have a less than 10% risk of distant recurrence over 10 years, assuming treatment with 5 years of tamoxifen, and minimal or no benefit from chemotherapy. On the other hand, patients with a high RS (31–100) have a greater than 20% risk of distant recurrence over 10 years despite 5 years of tamoxifen therapy, and obtain substantial benefit from the addition of chemotherapy. The most beneficial treatment approach for patients with intermediate RS (18–30) has not yet been defined. More recently, prospective and retrospective data from patients with lymph node involvement demonstrated similar trends, although the magnitude of risk of recurrence was greater than for patients with node-negative disease.

The main use of predictive assays such as the Oncotype DX appears to be in clinical situations in which chemotherapy is being considered, as opposed to situations in which it is clear that chemotherapy is or is not indicated. There are no data to support use of the assay results for selection of individual chemotherapy regimens. Many questions remain to be addressed, including how best to treat patients with node-negative disease and intermediate RS, and how best to use results for patients with node-positive disease. To address these questions, the TAILORx (NCT00310180) and RxPONDER (NCT01272037) randomized clinical trials are prospectively testing use of the Oncotype DX assay to guide decision making regarding the addition of chemotherapy to endocrine therapy. Prospective observational data from patients with node-negative disease enrolled on TAILORx who had RS 0 to 10 demonstrated very low rates of invasive DFS (93.8%) and freedom from recurrence of breast cancer at a distant or locoregional site (98.7%) at 5 years.

MammaPrint (Agenda), a gene expression assay with prognostic usefulness based on a 70-gene prognostic signature, became the first US Food and Drug Administration (FDA)–cleared in vitro diagnostic multivariate assay based on prospective and retrospective analyses. It was not recommended in the aforementioned ASCO guidelines that were published in early 2016, although prospective data were subsequently published from the MINDACT trial examining its role in chemotherapy decision making. Patient tumors were characterized with both MammaPrint, which dichotomizes tumors into low and high risk based on the genomic signature, and Adjuvant! Online, which uses standard clinicopathologic characteristics. Patients whose tumor classification was discordant between the two approaches were randomized to receive chemotherapy or not. In the 23% of enrolled patients who were at high clinical risk but low genomic risk and who did not receive chemotherapy, the 5-year rate of survival without distant metastases was 94.7% (95% CI, 92.5–96.2), which met the criteria for success in the trial. These findings suggested that a subset of patients at high risk of recurrence based on clinical characteristics may not obtain substantial benefit from treatment with chemotherapy.

Studies have explored the combined value of routine markers such as ER, PR, Ki67, and HER2 as a prognostic score (so-called IHC4) when compared with gene expression profiling. But this approach requires optimal standardization of all these individual parameters. Until then, use of commercially available assays will continue to provide additional information about prediction and prognosis to complement standard clinicopathologic assessment. In addition, access to accurate and reliable routine clinicopathologic markers for all patients worldwide remains critical to ensure the best outcome for all patients.

At present, no molecular tools have been developed to guide treatment selection for patients with either triple-negative disease or HER2-positive disease, which tend to be more aggressive tumors with higher risk of recurrence. Consequently, decision algorithms for these breast cancer subtypes are exclusively based on clinicopathologic factors such as tumor size, nodal involvement, and tumor grade. Studies are
ongoing to test new molecular assays based on DNA methylation, immune markers, and other gene expression signatures. At present, adjuvant chemotherapy is routinely offered to all triple-negative node-negative breast cancer patients with at least T1b tumors, despite the fact that most patients with triple-negative, node-negative disease remain disease free in the long term when treated with locoregional therapy alone.314 Similarly, chemotherapy plus trastuzumab is offered to most patients with at least T1c node negative tumors, and to many with T1b tumors, because of the inability to accurately assess the likelihood of disease recurrence without treatment for individual patients.315,316

Chemotherapy Regimens

For patients who are candidates for adjuvant chemotherapy, treatment regimens for early-stage breast cancer have evolved over time because of the conduct of multiple large randomized controlled trials. Polychemotherapy regimens are now considered standard practice over monotherapy regimens, and the EBCTCG has confirmed the improved recurrence and survival outcome observed with anthracycline-based regimens (Table 88.8).241,242,246 However, the magnitude of this survival benefit is modest, especially for patients with lower-risk disease. For an individual patient, it remains challenging to determine the benefit from treatment with different chemotherapeutic regimens.

In view of the potential toxicities and costs, the actual absolute benefit offered by individual therapies must be considered. Predictive factors of benefit (e.g., hormone receptor and HER2 status) and prognostic factors of risk (e.g., size, nodal status, and tumor grade) must be discussed with each patient, along with potential short- and long-term toxicities, preferences, and comorbidities, as part of a shared decision model. More intensive combination regimens, usually with an anthracycline and often a taxane, are expected to offer higher benefit in patients with more chemoresponsive disease (e.g., hormone receptor negative) but also are associated with greater toxicity.317-319 It is worth noting that the administration of taxane-containing regimens in lymph node–positive, early-stage breast cancer appears to be particularly useful in those with hormone receptor–negative320 and HER2-positive321 disease. However, it is important to note that these analyses were retrospective in nature.

Patients with lower-risk disease often are offered potentially more tolerable first- or second-generation regimens such as TC (docetaxel plus cyclophosphamide),322 classic CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), AC (doxorubicin plus cyclophosphamide), or sometimes just endocrine therapy if they have no nodal involvement and their tumors are strongly ER positive.

There is debate about which patients obtain benefit from anthracycline-based chemotherapy. The ABC trials compared anthracycline-based doxorubicin, cyclophosphamide and taxane-containing regimens with the non–anthracycline-containing docetaxel-cyclophosphamide regimen.323 These investigators were unable to demonstrate noninferiority of the nonanthracycline regimen, so the trial was reported early for futility; longer-term follow-up is planned. In summary, the reason why some individual patients may derive more benefit from anthracycline-containing regimens remains uncertain, and no clear predictors of benefit from anthracyclines have yet been identified to guide treatment selection.296 Table 88.9 lists examples of commonly used adjuvant chemotherapy regimens.

Adjuvant Therapy for Triple-Negative Breast Cancer

In triple-negative breast cancer (TNBC), neither antiendocrine therapy nor anti-HER2 therapy is effective. Therefore at present, cytotoxic therapies, with or without taxanes, are the only options for adjuvant treatment.313,314324,325 In general, the risk of recurrence of patients with triple-negative breast cancer is higher than for patients with hormone receptor–positive disease. However, the increased risk of recurrence in those with hormone receptor–negative disease is relatively small compared with the risk in patients with HER2-positive disease. Therefore, and because of the potential for higher toxicity and lower efficacy, the benefit of adjuvant chemotherapy for patients with hormone receptor–negative disease is not as clear as for patients with HER2-positive disease.314,315 However, it remains challenging to determine the benefit from treatment with different chemotherapeutic regimens.

Table 88.8 Overall Survival Improvements With Adjuvant Systemic Therapy

<table>
<thead>
<tr>
<th>Systemic Adjuvant Treatment and Age at Diagnosis (Years)</th>
<th>Chemotherapy Only in ER-Poor or ER-Positive Disease*</th>
<th>15-Year Breast Cancer Mortality With Treatment (Risk [%] and Absolute Gain) Versus Corresponding Risk Without Treatment (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PROPORTIONAL EFFECT ON ANNUAL BREAST CANCER MORTALITY RATE</td>
<td>M = 12.5 (E.G., LOW RISK, NODE NEGATIVE)</td>
</tr>
<tr>
<td></td>
<td>(TREATMENT VS CONTROL)</td>
<td>M = 25 (E.G., NODE NEGATIVE)</td>
</tr>
<tr>
<td></td>
<td>M = 50 (E.G., NODE POSITIVE)</td>
<td></td>
</tr>
<tr>
<td>Ratio of Rates (R)</td>
<td>Proportional Reduction</td>
<td>Risk</td>
</tr>
<tr>
<td>None (any age)</td>
<td>1.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Anthracycline (age &lt;50)</td>
<td>0.62 38%</td>
<td>7.9</td>
</tr>
<tr>
<td>Anthracycline (50–69)</td>
<td>0.80 20%</td>
<td>10.1</td>
</tr>
<tr>
<td>*<em>Endocrine, or Chemoenocrine, Therapy in ER-Positive Disease</em></td>
<td></td>
<td>Risk</td>
</tr>
<tr>
<td>None (any age)</td>
<td>1.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Tamoxifen (any age)</td>
<td>0.69 31%</td>
<td>8.8</td>
</tr>
<tr>
<td>Anthracycline + tamoxifen (age &lt;50)</td>
<td>0.62 × 0.69 57%</td>
<td>5.6</td>
</tr>
<tr>
<td>Anthracycline + tamoxifen (50–69)</td>
<td>0.80 × 0.69 45%</td>
<td>7.1</td>
</tr>
<tr>
<td>Anthracycline + tamoxifen (≥70)</td>
<td>? × 0.69</td>
<td>?</td>
</tr>
</tbody>
</table>

*For women of given nodal status the 5-year mortality is greater for ER-poor than for ER-positive disease, but the 15-year risks may be similar, as may the 15-year benefits of anthracycline-based chemotherapy (because the age-specific breast cancer mortality ratios for anthracycline-based versus no chemotherapy do not depend significantly on ER status). Combination of the direct and indirect randomized evidence yields breast cancer death rate ratios (treatment versus control) of 0.62 (standard error [SE] 0.05) at younger than age 50 years and 0.80 (SE 0.04) at age 50–69 years for allocation to anthracycline and 0.69 (SE 0.03) for allocation to tamoxifen. (Allowance for any inappropriate noncompliance with the treatment allocations in these trials would, in expectation, further reduce breast cancer mortality.)

ER, Estrogen receptor; FAC, fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide.

Part II: Specific Malignancies

Table 88.9: Examples of Commonly Used Adjuvant Chemotherapy Regimens for Early-Stage Breast Cancer

**NON–TRASTUZUMAB-BASED REGIMENS**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC × 4 (doxorubicin + cyclophosphamide) every 2 weeks followed by paclitaxel every 2 weeks or weekly</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>AC × 4 (doxorubicin + cyclophosphamide) every 2 weeks or 3 weeks followed by docetaxel every 3 weeks</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>TAC × 6 (docetaxel + doxorubicin + cyclophosphamide)</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>TC × 4 (docetaxel + cyclophosphamide) × 4</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>FAC/CAF (fluorouracil + doxorubicin + cyclophosphamide)</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>FEC/CEF (cyclophosphamide + epirubicin + fluorouracil)</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>FEC (or FAC) × 4 followed by paclitaxel weekly × 12</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>CMF (cyclophosphamide + methotrexate + fluorouracil)</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
</tbody>
</table>

**TRASTUZUMAB-BASED REGIMENS**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC × 4 followed by weekly paclitaxel plus concurrent trastuzumab</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>TCH (docetaxel + carboplatin + trastuzumab) × 6</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
<tr>
<td>TH (paclitaxel + trastuzumab) weekly × 12</td>
<td>Complete 1 year of anti-HER2 therapy</td>
</tr>
</tbody>
</table>

Adjuvant Anti-HER2 Therapy

HER2 is amplified or overexpressed in approximately 18% to 20% of breast cancers. HER2 overexpression is a negative prognostic factor, but is also predictive of response to anti-HER2 therapies. Even for T1 tumors, rates of recurrence are substantially greater for HER2-positive tumors compared with HER2-negative tumors of the same size and nodal status.

Multiple HER2-targeted therapies have been developed or are in development. The first therapeutic agent was trastuzumab, a humanized monoclonal antibody directed toward the extracellular domain of HER2 that acts to block HER2 activity through several mechanisms. A few decades later a second monoclonal antibody, pertuzumab, was developed; it also binds the extracellular domain of HER2, but at a separate site. Pertuzumab prevents homodimerization and heterodimerization of HER2 with other members of the EGFR family and inhibits signaling downstream of HER2. In addition to these antibody-based therapeutics, the small-molecule tyrosine kinase inhibitors lapatinib and neratinib have been developed; they target HER2 and other members of the HER family.

Several studies now show that anti-HER2 therapy is effective in the adjuvant setting for patients with HER2-positive disease, defined as 3+ based on immunohistochemical staining or fluorescence in situ hybridization (FISH) ratio of 2.0 or greater. Five international, prospective randomized clinical trials have demonstrated that treatment with adjuvant trastuzumab for 1 year reduces the risk of recurrence and mortality by one-half and one-third, respectively, in patients with early-stage breast cancer compared with the same chemotherapy regimen without anti-HER2 therapy. Additional studies investigating the optimal duration of trastuzumab therapy demonstrated that 6 months of therapy was inferior to 1 year, and that 2 years of therapy was not more effective than 1 year. Therefore the standard-of-care treatment in the adjuvant setting is chemotherapy in combination with 1 year of trastuzumab therapy. No data currently exist to support giving trastuzumab without chemotherapy for treatment of lower risk disease. Because of concerns about overtreatment of patients, a single-arm trial of paclitaxel and trastuzumab weekly for 12 weeks followed by 9 months of trastuzumab monotherapy was conducted in patients with tumor size of 3.0 cm or smaller and node-negative, HER2-positive disease. With 4 years of follow-up, 3-year rate of survival free from invasive disease was demonstrated to be 98.7% (95% CI, 97.6–99.8), which is substantially better than the rate of recurrence in historical controls.

Based on its approval in the metastatic setting, lapatinib was tested with trastuzumab in the adjuvant setting in patients with HER2-positive, lymph node–positive disease. Initial results in the preoperative systemic therapy setting were promising, with increased rates of pCR with dual targeting of HER2. However, results of the combination in the adjuvant ALTTO trial demonstrated no improvement in DFS or OS for dual targeting of HER2 plus chemotherapy compared with trastuzumab plus chemotherapy without lapatinib. Therefore lapatinib is not indicated for treatment of early-stage breast cancer. More recently, 12 months of adjuvant neratinib after completion of adjuvant trastuzumab was shown to increase 2-year invasive DFS from 91.6% for placebo to 93.9% for neratinib (stratified HR, 0.67 [95% CI, 0.50–0.91]; P = .0091), and is FDA approved in this setting.

More recently, pertuzumab was studied in combination with trastuzumab in the neoadjuvant setting. In the Neosphere study, the addition of pertuzumab to trastuzumab plus docetaxel led to an increase in pCR rate compared with trastuzumab plus docetaxel, from 29.0% to 45.8%. These promising results led to provisional FDA approval of pertuzumab in the neoadjuvant setting. The confirmatory adjuvant trial (APHINITY, NCT01358877) is currently underway, although results are not yet available. Interesting to note, the pCR rate for trastuzumab and pertuzumab alone without chemotherapy was 16.8%.

Trastuzumab therapy is associated with a risk of cardiac toxicity, especially among older patients and those previously exposed to an anthracycline.
been raised about the likelihood of full recovery based on long-term data from BCIRG-006. Late onset of cardiac dysfunction from trastuzumab after discontinuation of treatment appears uncommon, however.

These results confirm that HER2 is a useful marker for decision making for patients with breast cancer. Treatment with an anti-HER2 agent is recommended for all patients with HER2-positive breast cancer that is node positive or has a tumor size at least 1.0 cm, and should be considered for treatment of tumors smaller than 1 cm. These findings also emphasize the importance of having an accurate and reliable HER2 assay, and confirm the critical need to assess HER2 tumor expression in all patients with a new diagnosis of invasive breast cancer. A false-positive finding could result in exposure of patients to the toxicity of anti-HER2 therapy without the potential for benefit, whereas a false-negative result would deny a patient treatment with a potentially useful drug. Because of prior excessive testing inaccuracy, joint ASCO and College of American Pathologists guidelines were developed to guide appropriate testing and interpretation of the results of HER2 assays.

Interesting to note, retrospective data from some of the original adjuvant trastuzumab trials suggest that a DFS and OS benefit from trastuzumab is also observed in patients tested locally as having HER2-positive disease but centrally as having HER2-negative disease. This raises questions about heterogeneity of HER2 expression within tumors. Of note, measures of ER and HER2 expression were only minimally discordant when test results between core biopsy and definitive surgical specimens in otherwise unselected patients were compared. The potential benefit of anti-HER2 therapy for patients with tumors defined as being HER2 IHC 1+ or IHC 2+/FISH-negative is now being prospectively tested in the NSABP B-47 randomized trial (NCT01275677). At this time, currently available Level I evidence from metastatic trials does not support a role for anti-HER2 therapy in HER2-negative breast cancer.

Preoperative Systemic Therapy

Although chemotherapy was traditionally administered after surgery, preoperative systemic therapy, also referred to as neoadjuvant therapy, with either chemotherapy or endocrine therapy is increasingly also an option. Preoperative systemic therapy was traditionally reserved for women with locally advanced breast cancer (LABC) to enhance the likelihood of negative surgical margins. It is also used for downstaging, to increase the likelihood of breast conservation in select women who are not initially lumpectomy candidates. However, the absolute increase in the number of women ultimately treated with breast conservation after preoperative systemic therapy is small. In a large clinical trial, preoperative chemotherapy therapy increased the proportion of patients eligible for breast-conserving therapy from 41% to 64%, although only 77% of eligible patients chose to undergo lumpectomy.

There is growing interest in preoperative systemic therapy to reduce the extent of needed locoregional treatments, not only by allowing for certain patients who would have required mastectomy to conserve their breasts but also by potentially downstaging axillary disease to allow for omission of ALND or postmastectomy radiotherapy. The optimal radiotherapeutic management of patients who have pCR to preoperative systemic therapy in the axilla is an area of ongoing investigation; for patients with residual disease, studies are exploring whether radiation therapy to the axilla can obviate the need for complete ALND. However, it is important to note that the standard of care remains postmastectomy radiation therapy for patients with residual axillary involvement after neoadjuvant therapy.

Initially there were concerns about the use of preoperative systemic therapy. On one hand, preclinical data suggested that the administration of systemic therapy before surgery may be associated with early eradication of micrometastases and improved long-term outcomes by decreasing the risk of drug resistance and leading to more favorable growth kinetics. Conversely, there was concern that delaying removal of the bulk of the tumor could lead to increased risk of recurrence. However, initial data did not show a survival advantage for either approach.

More recent data have demonstrated that pathologic response (especially if complete) after preoperative chemotherapy correlates with improved DFS or OS, especially for triple-negative and HER2-positive breast cancer. Therefore the initial response to preoperative systemic therapy offers the potential of in vivo assessment of sensitivity or resistance to treatment. Of great interest, the identification of intermediate (surrogate) markers, including imaging-, tissue-, and blood-based markers, that correlate with disease outcome, such as pathologic response or survival, in carefully selected patient groups may have clinical usefulness, especially those that can identify early response or resistance to therapy.

Also as a result of these findings, there has been increasing interest in leveraging the preoperative setting to conduct clinical trials of new therapies with surrogate end points that are faster to complete and require smaller sample sizes compared with adjuvant trials. Administration of systemic therapy after surgery has been the gold standard for examining the effect of new treatment strategies on disease end points in the adjuvant setting. Traditionally, trials have required large sample sizes and long-term follow-up to achieve the number of events required to assess adjuvant end points such as DFS and OS. This problem is compounded by the increasing number of patients diagnosed with earlier stages of disease.

There are potential downsides to preoperative therapy, however, because it could lead to the loss of baseline parameters (e.g., tumor size and lymph node involvement) that generally are used to guide recommendations for adjuvant therapy. Results from NSABP B-27 confirm the feasibility of performing SLN biopsy after preoperative chemotherapy. In contrast, in the ACOSOG Z1071 clinical study of patients with clinically positive nodes before preoperative chemotherapy, the false-negative rate of SLN biopsy after chemotherapy was unacceptably high (12.5%). Similarly, in the SENTINA trial the false-negative rate was 14.2% in all patients, although for those with three or more lymph nodes removed it was 7.3% or lower. Therefore this issue remains controversial. In addition, many radiation oncologists have wanted to know the axillary status at presentation to guide use of postmastectomy radiation therapy and/or regional nodal irradiation, although as described earlier, there is increasing interest in potentially using preoperative systemic therapy to reduce the extent of necessary locoregional therapy and tailor adjuvant radiotherapy decisions.

In terms of systemic therapies, patients with hormone receptor–positive disease will all receive 5 to 10 years of endocrine therapy after completion of local therapy, regardless of pathologic findings. Similarly, those with HER2-positive disease will receive a total of 1 year of anti-HER2 therapy. However, there is uncertainty about what to do for patients with ER-negative, HER2-negative disease with residual disease at surgery; as described later, ongoing clinical trials are investigating the use of additional systemic therapy after surgery in this setting.

Interesting to note, there is now the potential for different treatment regimens to be administered in the preoperative versus the postoperative setting, at least for short periods of time. One example is for treatment of HER2-positive breast cancer, wherein the FDA provided conditional approval for pertuzumab specifically in the preoperative setting based on data from multiple primary systemic therapy trials. Final approval of the drug will be based on the results of an adjuvant trial that is still underway. Although initially after the FDA’s action pertuzumab could be given only in the preoperative setting, the NCCN subsequently added a footnote to its guidelines recommending consideration of the addition of pertuzumab to adjuvant chemotherapy in the setting in which a patient would have met criteria for treatment in the preoperative setting.

Preoperative systemic therapy might allow trials with smaller sample sizes and adaptive designs to test new strategies that can then quickly evolve into larger trials with survival as the primary end point. One
example is the Investigation of Serial Studies to Predict Your Therapeutic Response Through Imaging and Molecular Analysis 2 (I-SPY 2) platform trial, which uses adaptive randomization to examine the efficacy, based on pCR, of multiple drugs compared with a single control backbone regimen in patients with high-risk breast cancer. Each patient is assigned to one of multiple competing regimens based on her tumor’s biomarker subtype.

The findings for two drugs in I-SPY 2 have been reported to date. In patients with TNBC, the pCR rate for the PARP inhibitor veliparib plus carboplatin and paclitaxel in patients with TNBC was greater than for paclitaxel alone for 12 weeks. Similarly, in patients with HER2-positive disease, the pCR rate for paclitaxel plus neratinib was greater than for paclitaxel plus trastuzumab for 12 weeks; all patients had also received doxorubicin plus cyclophosphamide for four cycles prior to surgery. Both drugs are considered to have “graduated” to phase III testing in those particular subsets of patients with breast cancer.

As mentioned earlier, in the NeoALTTO trial preoperative trastuzumab combined with laptuzib was shown to result in a higher rate of pCR compared with trastuzumab alone. However, although pCR has been shown to correlate with improved disease outcomes in patients with HER2-positive breast cancer, improvement in this intermediate end point in the NeoALTTO trial failed to translate to a DFS or OS benefit in the definitive large ALTTO clinical trial. Therefore the usefulness of neoadjuvant trials is now in question.

Optimal patient selection for preoperative chemotherapy is key, especially if the goal is tumor shrinkage (to allow breast conservation) and pCR (for prognostic purposes). Hormone receptor status and tumor histology should be considered carefully, because patients with ER-positive disease and lobular histologic type are less likely to respond to preoperative chemotherapy, even though their long-term outcome (especially among the small minority of patients who achieve a pCR) is improved overall.

Adjuvant Endocrine Therapy

Adjuvant endocrine therapy arguably is the most effective targeted therapy in women with early-stage, ER-positive breast cancer, regardless of age or nodal status. Surgical hormonal manipulation (e.g., oophorectomy, adenecotomy, and hypophysectomy) in metastatic disease was considered the first example of targeted antitumor therapy, and has largely been supplanted by pharmacologic approaches with SERMs such as tamoxifen and raloxifene, AIs, the selective estrogen receptor degrader (SERD) fulvestrant, and ovary-suppressing luteinizing hormone–releasing hormone (LHRH) agonists, alone or in combination. For postmenopausal women, both tamoxifen and the AIs have been shown to be active agents in the adjuvant setting.

Although breast cancer is primarily a disease of older women, up to 25% of all patients newly diagnosed with invasive disease are younger than age 50 years, half of whom have hormone receptor–positive disease. Either tamoxifen alone or ovarian suppression/ablation plus endocrine therapy is standard of care for premenopausal women in the adjuvant setting. For those who decline or cannot tolerate endocrine therapy, OFS is a reasonable alternative.

The survival benefit of tamoxifen in premenopausal women with hormone receptor–positive breast cancer was not fully recognized until the mid-1990s. Factors that confounded therapeutic decisions for younger women included age-related chemotherapy effects on ovarian function and its indirect endocrine effect and the belief that chemotherapy was more active than endocrine therapy in this population. Retrospective data show that very young premenopausal women (age <35 years) have a higher likelihood of worse disease outcomes when treated with chemotherapy alone, especially those with hormone-sensitive cancer, a finding that may be due to a higher likelihood of retaining ovarian function after chemotherapy. Additional data from prospective randomized trials are now available to guide treatment decision making for premenopausal women, as outlined subsequently.

Tamoxifen

SERMs, such as tamoxifen and raloxifene, may function as ER agonists, antagonists, or mixed agonist-antagonists, depending on the target tissue. Tamoxifen has been in use for decades and is approved in the United States for risk reduction in high-risk women, for reduction in the risk of invasive breast cancer after breast conservation in women with DCIS, in the adjuvant treatment of hormone receptor–positive disease, and in the management of advanced disease. Important to note, tamoxifen can be used to treat both premenopausal and postmenopausal women.

Data from the 2005 EBCTCG meta-analysis showed that 5 years of adjuvant tamoxifen for ER-positive disease reduced the annual breast cancer mortality rate by 31% regardless of age or chemotherapy use. Duration of tamoxifen therapy is important. Assuming treatment for a total of 5 years, the annual breast cancer mortality rates are similar during years 0 to 4 and 5 to 14, with a cumulative reduction in mortality twice as large at 15 years as after 5 years since diagnosis, demonstrating a carryover effect following completion of therapy.

Two recent trials have demonstrated the benefit of extended adjuvant tamoxifen. However, two large international trials, ATLAS and ATOM, demonstrated superiority of 10 years of tamoxifen compared with 5. In the multinational ATLAS trial, women with early-stage hormone receptor–positive breast cancer who had been treated with 5 years of adjuvant tamoxifen were randomized to take either tamoxifen or placebo for an additional 5 years. Compared with placebo, extended tamoxifen reduced the risk of recurrence (18% versus 21%; P = .002), breast cancer mortality (9.7% versus 11.6%; P = .01), and overall mortality (19% versus 21%; P = .01), although the risk of toxicity, including venous thromboembolic disease and uterine cancer, persisted during the subsequent 5 years. Most of the improvement in disease outcomes from extended tamoxifen was noted once 10 years of treatment was complete. No differences in benefit were noted based on stage, age at diagnosis, or menopausal status. Overall, these data support the use of extended adjuvant tamoxifen.

Ovarian function suppression

The ovary is the primary site of estrogen production in premenopausal women. OFS is effective when compared with no therapy in women younger than age 50 years. Similar outcomes are seen with OFS versus CMF chemotherapy and with OFS plus tamoxifen versus chemotherapy. At this time, though, data comparing OFS with contemporary chemotherapy regimens containing anthracyclines and taxanes are lacking. Clinical benefit was seen in young premenopausal women who received OFS following chemotherapy, but it was unclear if it was of added benefit in this group of women when they were also treated with endocrine therapy. Indirect evidence from IBCSG trial 13-93 suggested that some degree of benefit from chemotherapy-induced amenorrhea might exist even when tamoxifen was also given. A 2007 meta-analysis of OFS with LHRH agonists in premenopausal women with ER-positive disease showed that chemically induced ovarian suppression offered a significant reduction in the relative risk for recurrence and death when added to tamoxifen, chemotherapy, or both.

The question of combined endocrine therapy for premenopausal women with OFS plus tamoxifen or OFS plus an AI was further investigated in a number of clinical trials. Initially, the Austrian Breast and Colorectal Cancer Study Group [ABCSG]-12 trial, which used a 2 × 2 factorial design comparing 5 years of treatment with the AI anastrozole versus tamoxifen and treatment with zoledronic acid versus placebo, was conducted in 1803 premenopausal women who received concomitant OFS. Important to note, the majority of patients were
not treated with chemotherapy. After a median follow-up of 62 months, there was no difference in DFS between those treated with tamoxifen alone versus anastrozole alone (HR, 1.08 [95% CI, 0.81–1.44]; P = .59), although OS was worse in the anastrozole-treated patients (HR, 1.75 [95% CI, 1.08–2.83]; P = .02).

More recently, results from two large trials, the Suppression of Ovarian Function Trial (SOFT; IBCSG 24-02) and the Tamoxifen and Exemestane Trial (TEXT), were published.292,293 In SOFT, 3066 premenopausal women who had regained biochemically confirmed ovarian function after chemotherapy or who did not receive chemotherapy were randomized to tamoxifen alone, tamoxifen plus OFS, or exemestane plus OFS. In the TEXT trial, 2672 premenopausal women were treated with OFS and randomized to tamoxifen or to exemestane at the time of initiation of adjuvant therapy.

In the initial analysis of the SOFT trial, the difference in 5-year DFS between those patients treated with tamoxifen versus those treated with tamoxifen plus OFS was not statistically significant (84.7% versus 86.6%; HR, 0.83 [95% CI, 0.66–1.04]; P = .10), although there was a greater benefit in 5-year freedom from breast cancer in those who received chemotherapy (78% versus 82.5%; HR, 0.78 [95% CI, 0.60–1.02]).293 However, in the joint analysis of the two trials, after 68 months of follow-up, patients treated with exemestane plus OFS had superior DFS (91.1%) compared with those treated with tamoxifen plus OFS (87.3%; HR, 0.72 [95% CI, 0.60–0.85]; P < .001).292 Important to note, most of the benefit was identified in very young women (<35 years of age) and those with higher-risk disease who had received chemotherapy.

**Aromatase inhibitors**

In postmenopausal women, estrogens are primarily generated through the conversion of androgens in peripheral tissues. AIs can block the action of the aromatase enzyme and reduce circulating estrogen concentrations up to 10-fold.389 First-generation inhibitors (e.g., aminoglutethimide) were associated with significant toxicity in the adjuvant setting because of nonspecific effects. Currently used third-generation drugs include steroidal nonreversible inhibitors (e.g., exemestane) and nonsteroidal reversible inhibitors (e.g., letrozole and anastrozole). The more specific, and less toxic, third-generation AIs are good candidates for late administration of adjuvant therapy for those patients who switched therapy (RR, 0.56 [95% CI, 0.46–0.67]). In contrast, less difference in recurrence rates was noted for those treated with 5 years of tamoxifen versus 2 to 3 years of tamoxifen followed by AI therapy for 2 to 3 years, recurrence rates were statistically significantly lower for those patients who switched therapy (RR, 0.56 [95% CI, 0.46–0.67]).

Risks are higher in patients with higher-stage disease at diagnosis. Potential strategies for which there are data include the use of different sequences of tamoxifen and AIs, and the use of longer durations of therapy, as described earlier.

In a large meta-analysis from the EBCTCG that included patients treated with up to 5 years of adjuvant endocrine therapy, AIs were demonstrated to reduce risk of recurrence of breast cancer by about 30% compared with tamoxifen, and to reduce risk of breast cancer mortality by about 15%.393 When comparing patients receiving 5 years of tamoxifen versus 2 to 3 years of tamoxifen followed by AI therapy for 2 to 3 years, recurrence rates were statistically significantly lower for those patients who switched therapy (RR, 0.56 [95% CI, 0.46–0.67]).

**Schedule and duration of adjuvant endocrine therapy**

The optimal schedule and duration of endocrine therapy remain undefined. ER-positive breast cancer has a long natural history, and half of the residual risk of recurrence occurs after the first 5 years.290,402 More recently, data for treatment with an AI for 10 years versus tamoxifen are good candidates for late administration of adjuvant therapy.

In summary, evidence-based guidelines from ASCO support the administration of an AI at some point during the adjuvant treatment of postmenopausal women with early-stage hormone-responsive breast cancer.393 For patients with higher-risk disease, including premenopausal women receiving concomitant OFS, the absolute difference in benefit from treatment with an AI versus tamoxifen is substantial. There are no clinically important differences among the three commercially available AIs, and no predictors of benefit or toxicity have been identified that can be used to select one AI over another for an individual patient. Safety data support the use of an AI for up to 10 years as monotherapy or used sequentially after tamoxifen.

In addition, research is underway to identify molecular predictors of delayed recurrence of breast cancer. Evidence is available for a number of markers that may be both prognostic for late recurrence and predictive of benefit from extended adjuvant therapy, including the Breast Cancer Index, although use of these markers for clinical care is not currently recommended.199,309 For now, the decision regarding which treatments to use, in which order, and for which duration, should be made by the physician and patient after careful consideration of benefits and risks.

**Combined chemoendocrine therapy**

Adjuvant endocrine therapy has a more favorable therapeutic index than chemotherapy in patients with endocrine-responsive breast cancer, and endocrine therapy is considered the primary component of any adjuvant systemic regimen in patients with hormone receptor–positive disease, regardless of age. However, as described earlier, patients who also have prognostic factors associated with an increased risk of recurrence and death may benefit from the addition of chemotherapy to
endocrine therapy as part of the adjuvant regimen. For most treatment regimens that include treatment with both chemotherapy and endocrine therapy, it is recommended that chemotherapy be completed before initiation of endocrine therapy. This recommendation is primarily based on the results of SWOG 8814 (Intergroup 0100), which demonstrated a survival advantage associated with sequential versus concurrent administration of chemotherapy and tamoxifen.403 A second trial (GEICAM 9401) compared epirubicin and cyclophosphamide with sequential versus concurrent tamoxifen, and showed a trend favoring a sequential approach.404 Based on these results, chemotherapy and endocrine therapy are generally not given simultaneously for treatment of endocrine-sensitive breast cancer.

Preoperative endocrine therapy
Some patients may be appropriate candidates for preoperative therapy yet are unlikely to respond well to cytotoxic chemotherapy. In this setting, preoperative endocrine therapy is an attractive alternative to chemotherapy, especially in older patients with strong ER-positive tumors who may not be good candidates for chemotherapy or patients with strongly hormone receptor–positive, low-grade tumors. However, clinical responses are slower to occur and are rarely complete. Optimal markers to predict long-term outcome after preoperative endocrine therapy are lacking, but expression of tumor Ki67 after short-term endocrine treatment may help predict response to therapy by combining the prognostic value of Ki67 level at baseline with observed changes in levels at 2 weeks.405–407

Secondary Effects of Adjuvant Systemic Therapy
Secondary effects of chemotherapy
As more patients with earlier stages of disease are offered adjuvant systemic therapy, its benefits must be carefully examined, taking into consideration the potential short- and long-term toxicity. The chemotherapy regimens commonly administered to patients with breast cancer are generally well tolerated. Acute life-threatening toxicity in patients receiving therapy is quite rare. Common short-term effects include alopecia, gastrointestinal symptoms, myelosuppression, and febrile neutropenia or neutropenic infection. Chemotherapy-induced peripheral neuropathy (CIPN), arthralgia, myalgia, capillary leak syndrome, and skin and nail changes also are seen with taxanes. Use of growth factors to stimulate white blood cell production has reduced the risk of febrile neutropenia and neutropenic infection.408 However, because of concerns about a potential worse survival outcome with the use of erythropoietin-stimulating agents, these agents are generally no longer used in the adjuvant setting, where the intent is cure.409

Although many women accept these short-term toxicities, greater attention is being paid to long-term and late effects from systemic therapy because the number of patients who will become long-term survivors is increasing. Long-term effects are those that occur during treatment and do not resolve, whereas late effects are those that develop many years after completion of therapy. For some, the actual absolute reduction in risk of recurrence and death from treatment is relatively small compared with the potential risk of late toxicity. A few rare long-term or late effects of therapy are serious or life-threatening. One example is anthracycline-related cardiac toxicity. Approximately 8% of women may have asymptomatic systolic dysfunction 10 years after receiving doses of doxorubicin around 300 mg/m2, and cardioprotective drugs such as dexrazoxane are not approved for use in the adjuvant setting.410 Although the risk of clinical congestive heart failure associated with conventional doses of anthracyclines is small (≤1%),411 this risk is increased in patients subsequently treated with adjuvant trastuzumab.412,413 Older age, lower left ventricular ejection fraction at baseline, and presence of multiple cardiac comorbidities appear to increase this risk, but good predictive models and biomarkers are not yet sufficiently refined for use in clinical practice.414 In addition, other than a single nucleotide polymorphism in an intergenic region that was recently identified in a genome-wide association study,415 genetic predictors of increased risk have not yet been validated.416

Secondary acute myeloid leukemia and myelodysplastic syndrome have been linked to exposure to alkylating agents, topoisomerase II inhibitors, and antimetabolites.417,418 The risk of acute myeloid leukemia or myelodysplastic syndrome after four cycles with conventional doses of doxorubicin and cyclophosphamide (60 and 600 mg/m2, respectively) at 5 years is at least 0.21%, and cumulative incidence is 0.48% by 10 years. Age has been associated with increased risk of developing myeloproliferative neoplasms.

Other potential toxicities are not life-threatening but can negatively affect health-related quality of life. CIPN is a long-term toxicity caused by taxane and platinum therapy that can persist in a subset of patients and affect function. Despite considerable research, no agents to prevent CIPN or to allow patients to regain sensation have yet been identified.419 However, data from randomized phase III trials are now available to support the use of medications, including duloxetine, for treatment of painful neuropathy.420

Symptoms of fatigue, insomnia, weight gain, and cognitive dysfunction have been reported with some frequency after the completion of chemotherapy.420,421 Both short- and long-term cognitive dysfunction has been reported, including poor memory, impaired concentration, and language deficits.422 Confirmation of an association with chemotherapy has been challenging, because of both limitations with objective assessment of the symptom and confounding by factors such as onset of menopause and use of adjuvant endocrine therapy. Fatigue may also affect cognitive function. Although data to support the use of pharmacologic interventions for fatigue and insomnia are lacking, nonpharmacologic approaches such as exercise and cognitive behavioral therapy have been shown to be beneficial.423 Long-term survivors report more frequent physical and menopausal symptoms than do healthy women, but their health-related quality of life and sexual functioning are comparable to those reported by healthy, age-matched control subjects.424 Still, the various long-term needs of breast cancer survivors and the crucial role to be played by both oncologists in the short run and gynecologists and internists in the long run cannot be overemphasized.424,425

Young women are at risk for premature menopause after adjuvant chemotherapy, and the risk correlates with both age and adjuvant chemotherapy regimen (classic CMF for six cycles > AC followed by paclitaxel = TAC with docetaxel > AC for four cycles).426,427 Temporary cessation of menses during adjuvant therapy also correlates with earlier occurrence of menopause.428 Although ovarian suppression as a result of chemotherapy may further decrease the odds of recurrence and death in premenopausal women with endocrine-responsive disease, premature menopause can have a significant effect on quality of life because of severe hot flashes and vaginal dryness. Hot flashes resulting from discontinuation of menopausal hormonal therapy or loss of ovarian function are a common symptom after chemotherapy, although nonhormonal options are now available, as described later.429 For women who retain fertility, pregnancy does not appear to increase the risk of another breast cancer event.429 Data support the use of LHRH agonists during chemotherapy to preserve fertility in women with hormone receptor–negative breast cancer.430

Side effects from LHRH agonists occur earlier but are short-lasting when compared with chemotherapy, and may include hot flashes, decreased libido, mood lability, and potential cardiovascular and skeletal-related sequelae such as bone loss. In the SOFT trial, the addition of OFS to endocrine therapy increased the rate of side effects compared with tamoxifen alone.431 However, in the groups treated with OFS plus either tamoxifen or AI therapy, although the side effect profiles were different and reflected the specific adjuvant endocrine therapy, overall patient-reported health-related quality of life was similar.432

One potentially long-lasting effect of chemotherapy-induced ovarian failure or OFS is the negative impact on bone mineral density (BMD), which can increase the risk of osteoporosis and fracture.433 NCCN guidelines derived from the Bone Health Task Force recommend baseline and on-treatment monitoring of BMD, with advice on lifestyle interventions, calcium and vitamin D supplementation, and
antiestrocalcit therapy initiation depending on the dual-energy x-ray absorptiometry (DXA)–derived T-score or Fracture Risk Assessment Tool (FRAX) 10-year risk of fracture. 435

**Secondary effects of endocrine therapy**

Tamoxifen is associated with an increase in BMD in the axial skeleton and with stabilization in the appendicular skeleton in postmenopausal women. 434 Although tamoxifen in premenopausal women leads to bone mineral loss in the lumbar spine and hip, the NSABP P-1 study showed a 19% reduction in fractures of the hip, radius, and spine in all age groups with tamoxifen compared with placebo, especially among those aged 50 years and older. 435 Tamoxifen is also associated with a reduction in low-density-lipoprotein cholesterol, and individual studies have suggested that tamoxifen might reduce the risk of coronary heart disease. However, the EBCTCG meta-analysis did not show any statistically significant effect of cardiovascular events from tamoxifen on OS. 67

Similar to its antiestrogen effects in breast tissue, the toxicity profile of tamoxifen is also related to its tissue-specific effects on ER. There are a few key serious but rare tamoxifen–related toxicities: uterine malignancies, venous thromboembolic disease, and ocular toxicity. Both the NSABP P-1 prevention trial and the 1995 EBCTCG meta-analysis showed a higher incidence of uterine malignancies with tamoxifen treatment. 455,290 Although uterine cancer is likely to be diagnosed at an early stage and cured with surgery alone, longer duration of tamoxifen therapy is associated with worse histology and higher grade, 432 and 2% to 5% of all cases represent uterine sarcoma. 456 Important to note, tamoxifen is expected to cause endometrial thickness, although neither transvaginal ultrasound nor endometrial biopsy is a useful screening tool in an asymptomatic patient. 437,438 Instead, women who are taking tamoxifen should undergo routine gynecologic evaluation and notify their physicians of abnormal vaginal spotting or bleeding or pelvic pain. Thromboembolic complications caused by tamoxifen, including pulmonary embolus and deep vein thrombosis, occur in fewer than 1% of patients. Risk factors are poorly defined but include obesity, smoking, and possibly factor V Leiden mutation, although results have been mixed. 439,440 Ocular toxicity, including retinopathy and cataract formation, is also uncommon.

Tamoxifen is more commonly associated with bothersome side effects, including hot flashes, night sweats, leg cramps, decreased libido, and vaginal discharge; a statistically significant negative impact on quality of life has not been noted. 441 The NSABP prevention P-1 trial showed no detrimental effects on quality of life, mood, or sexual function and no increase in weight gain in the tamoxifen-treated group. 442 Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors such as citalopram and venlafaxine, and antiepileptics such as gabapentin and pregabalin, have been shown to be effective for managing hot flashes. 443 Data to support the use of clonidine are mixed, however, and popular herbal supplements such as black cohosh and evening primrose oil are ineffective. 444 In contrast, AIs act by lowering circulating estrogen concentrations, which is a different mechanism compared with tamoxifen, and therefore have a different toxicity profile. The primary serious toxicity is loss of bone density and concomitant increased risk of fracture. Women considered for AI therapy should have a baseline bone density and vitamin D assessment, and ensure adequate daily intake of calcium and vitamin D. Concurrent therapy with an antiestrocalcit inhibitor can ameliorate this bone loss. 445, 446 Raloxifene should not be used in AI-treated women to increase bone density based on the data from the ATAC trial, which noted an increased risk of recurrence when anastrozole and tamoxifen were given concurrently compared with anastrozole alone. 447

Multiple bothersome toxicities have been reported. The most common toxicities are aromatase inhibitor–associated musculoskeletal symptoms (AIMSS), including arthralgias, myalgias, joint stiffness, carpal tunnel syndrome, and tendinopathies. 448 Other menopausal symptoms, including hot flashes and vaginal dryness, are also commonly reported side effects. However, vaginal dryness is challenging to manage because of the concern about potential systemic absorption of intra-vaginal estrogen, which could negate the benefits from AI therapy. 449 In AI-treated women, recently presented data suggest that intravaginal dehydroepiandrosterone (DHEA) may be effective for sexual function, 450 and topical lidocaine may improve penetrative dyspareunia. 451 Unfavorable changes in lipid profile including decreases in high-density lipoprotein also have been noted, 451, 452 although a large meta-analysis did not demonstrate an increase in cardiovascular events. 453

One provocative study reported that patients who experienced treatment-emergent symptoms, either AIMSS or hot flashes, within the first 3 months of AI therapy had improved disease outcomes. 454 Subsequent analyses of other large trials were mixed, with some reporting similar findings for some or all symptoms, 455–458 and others reporting no association. 459, 460 These analyses were limited by the lack of information about either baseline symptoms or symptom severity, and therefore it remains unknown how to apply these findings clinically.

**Long-Term Follow-Up**

A number of evidence-based guidelines have been published describing appropriate follow-up for breast cancer survivors. 455, 461 Breast cancer survivors should undergo evaluation with history and physical examination every 3 to 12 months, depending on time since diagnosis, and annual mammography. Available evidence does not support use of any surveillance blood tests (e.g., complete blood counts, liver function tests, tumor markers) or imaging studies other than mammography in patients with no signs or symptoms concerning for recurrence. 456, 461 Depending on the presence of long-term or late toxicities, patients should be referred to mental health providers, rehabilitation specialists, cardiologists, and endocrinologists, as indicated. Cancer specialists should ensure adequate coordination of care in a shared care model with gynecologists and primary care physicians, who will have an increasingly important role in the long-term care of these breast cancer survivors (Table 88.10). In addition to surveillance for possible late complications resulting from local and systemic therapies given as part of their breast cancer treatment, 462 breast cancer survivors also require age-appropriate routine health maintenance care. In many settings, noncancer specialists may assume the primary long-term follow-up care of these patients, 463 but it is critical that good communication be maintained with cancer specialists, especially for patients with hormone receptor–positive disease who receive endocrine therapy for at least 10 years. Accreditation bodies now require survivorship care plans to facilitate communication, 464 although minimal data exist to demonstrate the effectiveness of these plans for improving patient care. 465

**New Strategies in Adjuvant Treatment**

Greater understanding of the biologic subtypes of breast cancer is helping with the selection of treatment strategies targeting specific tumor subtypes. ER, PR, and HER2 remain the most useful markers at present, although, as noted previously, gene expression profiles are being tested prospectively as prognostic and predictive markers to ensure the optimal identification of the patients most likely to benefit from a specific strategy, including treatment with adjuvant chemotherapy and/or the use of extended endocrine therapy. For patients with HER2-positive disease, adjuvant trials are in progress to examine the use of additional anti-HER2 agents, including pertuzumab, ado-trastuzumab emtansine, and neratinib, in conjunction with trastuzumab. 466

As noted earlier, whether or not a patient achieves a pCR with primary systemic therapy is predictive of long-term disease outcomes, especially in those patients with TNBC or HER2-positive disease. Therefore a number of clinical trials are ongoing to evaluate the use of additional cytotoxic agents or novel targeted drugs in patients with residual disease at the time of surgery. One trial that was recently reported was the randomized phase III CREATE-X trial, which demonstrated a benefit from the addition of capecitabine in patients with
with TNBC with residual disease after primary systemic therapy, as described earlier. Other trials using this strategy are currently in progress, including trials to evaluate targeted therapies such as PARP inhibitors and mTOR inhibitors, and immunotherapies such as PD-L1 inhibitors (NCT02954874, NCT02032823).

Much attention has also been directed toward the study of bisphosphonates as adjuvant therapy to reduce the risk of breast cancer recurrence, distinct from their use to support bone health. Although initial studies of adjuvant clodronate demonstrated a survival benefit and reduction in bony recurrences, a larger randomized NSABP trial of adjuvant clodronate versus placebo failed to show any overall benefit. Mixed results have also been observed with adjuvant zoledronic acid. In the ABCSG-12 trial, in which premenopausal women treated with goserelin were randomized to zoledronic acid or no therapy for 3 years, treatment with the bisphosphonate improved DFS (HR, 0.68 [95% CI, 0.51–0.91]; P = .046). These findings were stronger for patients with hormone receptor–negative breast cancer.

### MANAGEMENT OF METASTATIC DISEASE

Because most patients with metastatic breast cancer ultimately die of their disease, the primary goal of therapy is palliation of symptoms and prolongation of life. At the same time, there has been an improvement in the survival of patients with metastatic disease over the last few decades as a result of more effective therapies. Historically, median survival of patients after the diagnosis of metastatic breast cancer was 2 to 3 years. However, some patients survive long term, and a very small number of patients with “oligometastatic” disease may even benefit from multimodality therapy that includes surgical resection of an isolated visceral metastasis with curative intent.

Also, specific therapies such as trastuzumab have dramatically changed the natural history of HER2-positive metastatic breast cancer for a subset of patients.

Approximately 75% of metastases occur within the first 5 years after the diagnosis of early-stage disease, especially among patients with hormone receptor–negative disease. Unfortunately, patients with hormone receptor–positive disease have a significant residual risk of recurrence beyond the first 5 years, and metastases have been documented as late as 20 to 30 years after the initial diagnosis.

Although most patients with metastatic disease are expected to experience progression of disease at some point, certain clinical and tumor characteristics are useful in predicting prognosis. Patients with a long interval since initial diagnosis, excellent performance status, hormone receptor–positive disease that primarily involves bone or soft tissue, and only a few sites of visceral involvement are likely to have a better long-term prognosis. In addition, some patients with HER2-positive disease can also have prolonged survival, even after the diagnosis and treatment of brain metastases. Available locoregional, systemic, and supportive care treatments can result in significant regression of disease, relief of symptoms, and, in some cases, prolongation of survival. However, the goal of treatment of metastatic breast cancer is not a cure, but palliation with improved quality of life can be achieved in many patients.

Preliminary evidence indicates a role for combined multimodality therapy in patients with small-volume metastatic disease.
confirmed, this could have significant implications for the current recommendations for no surveillance in the absence of specific symptoms.\textsuperscript{325} Previous exposure to adjuvant therapy predicts a lower response to first-line chemotherapy in patients with metastatic breast cancer. However, retrospective data suggest that patients who have a recurrence long after completing adjuvant therapy may respond to similar regimens.\textsuperscript{462} IBCSG data also suggest that quality-of-life scores may correlate with outcome in metastatic breast cancer,\textsuperscript{474} and improvement in symptoms such as pain and shortness of breath may correlate with greater response to therapy.\textsuperscript{484}

Prompt initiation of supportive measures and specific anticancer therapy in patients with significant symptoms or life-threatening complications (e.g., spinal cord compression, destructive bone lesions in weight-bearing areas, hypercalcemia, and symptomatic pleural or pericardial effusions and ascites) can offer significant palliation of symptoms. Management of oncologic problems common to cancer and its therapy is described in detail elsewhere in this book.

Evaluation of Suspected Metastases

At the time of recurrence, many patients have nonspecific symptoms, such as new pain, weight loss, or dyspnea. Guidelines now recommend tissue acquisition for diagnostic confirmation of recurrent breast cancer and reassessment of biomarker status (ER, PR, and HER2) to guide treatment decision making.\textsuperscript{485} Biopsy is particularly important in the setting of solitary lesions, which may be due to a disease process other than breast cancer. In addition, recent studies have demonstrated considerable discordance between primary and metastatic breast tumors,\textsuperscript{486,487} and this can also have substantial implications for treatment. One caveat is patients with primary hormone receptor–positive disease who are found to have ER-negative disease at bone biopsy. It is possible that the lack of ER expression is due to a laboratory artifact related to bone decalcification, and therefore frontline endocrine therapy could still be considered in this context.\textsuperscript{488}

Circulating tumor markers such as CA15-3, CA27.29, and CEA, although not diagnostic for breast cancer, can provide useful information for disease monitoring in a subset of patients, and a baseline value can be useful for assessing trends.\textsuperscript{199} Imaging studies, including bone scintigraphy and contrast computed tomography (CT) scan, fluorine-18 fluorodeoxyglucose–positron emission tomography (FDG-PET)/CT, and/or plain radiographs, provide a baseline for the evaluation of response to the planned treatment modality. Skeletal scintigraphy (bone scan) remains a reasonable option to screen for bone metastasis, although scintigraphic flare response can make the interpretation of changes with treatment challenging.\textsuperscript{489,490} Other metabolic studies such as FDG-PET may have a role, especially when integrated with conventional CT imaging for anatomic information, although it remains unclear whether FDG-PET can replace bone scintigraphy scan,\textsuperscript{491} and cost remains a barrier. Recent reports also suggest an apparent increase in the prevalence of central nervous system metastases in breast cancer, especially in patients with HER2-positive disease.\textsuperscript{492} This increase is in great part a result of improved control of systemic disease and lack of penetration of antibody therapy in sanctuary sites.

Endocrine Therapy

Endocrine therapy is often very effective with minimal associated toxicity, and therefore should be considered the primary option over cytotoxic chemotherapy for frontline therapy in patients with bone-only or asymptomatic visceral metastatic hormone receptor–positive disease.\textsuperscript{493,494} Patients in visceral crisis, however, should be considered for frontline multitargeted cytotoxic chemotherapy because of its faster onset of action. The majority of patients whose tumors coexpress HER2 benefit from HER2-based therapies in the frontline setting, but single-agent oral therapy with an endocrine agent remains an option for a selected subset of patients.\textsuperscript{495} Fig. 88.23 lists a treatment algorithm for palliative endocrine regimens.

Selective Estrogen Receptor Modulators

Tamoxifen, 20 mg daily, is a SERM that has been in clinical use for decades, and was the standard-of-care endocrine therapy for treatment of metastatic disease until the advent of AI therapy. Toremifene, which

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is also available for use, has a similar profile and is cross-resistant with tamoxifen. In general, tamoxifen is no longer used in the first-line setting, especially for postmenopausal women, and instead is used in the second-line or later setting. Minimal data are available regarding tamoxifen in the second-line setting, in which approximately 10% of patients had an objective response and the clinical benefit rate was almost 50%.496

Acquired resistance to tamoxifen is multifactorial and can be due to a variety of mechanisms, including activation of alternate growth pathways, mutations in ER, alterations in tamoxifen metabolism, inadequate concentrations of intracellular tamoxifen, and differential expression of steroid-receptor transcriptional coactivators and corepressors.497 As an example, recently there has been a recognition that mutations in the ligand-binding domain of ER develop in as many as 30% to 40% of patients treated with endocrine therapy in the metastatic setting and result in resistance to endocrine therapy, including tamoxifen and AIs.498 Interesting to note, very few ER mutations have been identified in primary tumors or after treatment with adjuvant endocrine therapy.

Aromatase Inhibitors
In postmenopausal women with no or distant previous exposure to antiestrogen agents, the AIs show similar or modestly superior efficacy compared with tamoxifen.499 Therefore these drugs are often used in the frontline setting for postmenopausal women, and for premenopausal women in combination with ovarian suppression or ablation. Although letrozole appears to more potently suppress both total-body aromatization and plasma estrogen levels than anastrozole,500,501 direct comparison as second-line therapy in metastatic breast cancer showed no convincing clinical advantage of one AI over the other.502 AIs should be avoided as second-line therapy in metastatic breast cancer showed no convincing versus 48.4 months; recently, data from the phase II FIRST trial demonstrated improved OS compared with anastrozole; OS data are not yet mature.511 The metastatic setting and result in resistance to endocrine therapy, including tamoxifen and AIs.503 Interesting to note, very few ER mutations have been identified in primary tumors or after treatment with adjuvant endocrine therapy.

Ovarian Ablation
The preferred endocrine therapy in premenopausal women with endocrine-responsive disease and recent exposure to tamoxifen is AI therapy plus OFS with surgical or chemical techniques (LHRH agonist).504 Radiation ablation is less reliable and technically more challenging, and the results are not as immediate.505 Available data show both an OS advantage and a progression-free survival (PFS) advantage with the addition of tamoxifen to an LHRH agonist,506 but there are limited data on OFS and an AI in the metastatic setting.507

Other Antiestrogens
The pure antiestrogen fulvestrant downregulates ER and lacks the agonistic activity of tamoxifen. The standard dose of fulvestrant is 500 mg intramuscularly every 2 weeks for three doses then monthly based on data that demonstrated improved PFS when compared with the previously recommended dose of 250 mg intramuscularly monthly.508 It has also been shown to have a comparable clinical benefit rate compared with the steroidal AI exemestane in women whose ER-positive disease progressed on prior nonsteroidal AI.509 More recently, data from the phase II FIRST trial demonstrated improved PFS and OS with frontline fulvestrant versus anastrozole (OS, 54.1 versus 48.4 months; \(P = .04\)).510 Data reported from the phase III FALCON trial similarly demonstrated a PFS benefit of fulvestrant compared with anastrozole; OS data are not yet mature.511

Combination Regimens With Antiestrogens for Postmenopausal Patients
In addition to the option of using antiestrogens as monotherapy, since 2012 new data have been reported regarding combinations of antiestrogens. In addition, more recent data have been published supporting combinations of antiestrogens with other targeted agents in the first and later lines of therapy. Examples include CDK4/6 inhibitors, inhibitors of the PI3K-AKT-mTOR pathway, and anti-HER2 agents. Most patients will be treated with all three classes of antiestrogen therapy at some point, in addition to at least a subset of the targeted therapies. However, there are few data regarding the optimal sequence of therapy, either monotherapy or combination regimens.

Two studies have evaluated anastrozole alone versus in combination with fulvestrant in previously untreated metastatic disease. One trial showed similar outcomes,512 whereas the second showed an improved PFS favoring the combination, possibly related to prior tamoxifen exposure.513 In the latter trial there was no required crossover to fulvestrant following anastrozole monotherapy, so it is unknown whether the combination is superior to sequential therapy. CDK4/6 inhibitors regulate cell cycle progression and arrest cells in the G1 phase.514 In patients with ER-positive and HER2-negative disease, data have demonstrated a PFS advantage for adding the CDK4/6 inhibitor palbociclib to letrozole for treatment of metastatic disease. In the PALOMA-2 phase III trial, the addition of palbociclib to letrozole resulted in a 10-month improvement in DFS compared with letrozole alone (24.8 versus 14.5 months; \(P = .0004\)) in postmenopausal women with previously untreated metastatic disease, with an HR for disease progression or death of 0.58 (95% CI, 0.46–0.72; \(P < .001\)).515 No OS benefit has been reported. In addition, similar results were seen with the combination of a different CDK4/6 inhibitor, ribociclib, and letrozole compared with letrozole alone, with an improvement in 18-month PFS from 42.2% to 63%.516 In the second-line setting in patients with progression on a nonsteroidal AI, there was an improvement in PFS with the addition of palbociclib to fulvestrant, from 4.6 to 9.5 months \((P < .0001)\).517,518 Based on these data, palbociclib received accelerated approval from the FDA in 2015, and other CDK4/6 inhibitors are also being considered for approval.

Activation of the mTOR pathway may represent a mechanism of resistance to antiestrogens in ER-positive disease. A PFS benefit has been shown with the addition of the mTOR inhibitor everolimus to exemestane in patients with ER-positive and HER2-negative disease that is refractory to a nonsteroidal AI, from 4.1 months with exemestane alone to 10.6 months with the combination.519 However, no PFS or OS benefit was observed when the mTOR inhibitor temsirolimus was added to letrozole as first-line therapy in otherwise AI-naive patients, even though approximately half of these patients had prior exposure to adjuvant tamoxifen.520

As described later, chemotherapy plus anti-HER2–directed therapy is recommended as frontline therapy for most patients with ER-positive and HER2-positive metastatic breast cancer.593 However, there are data to guide the use of anti-HER2 therapy plus AI therapy in the frontline setting for metastatic disease from at least two large trials.521,522 No predictors of response to therapy have yet been identified. Based on these data, palbociclib received accelerated approval from the FDA in 2015, and other CDK4/6 inhibitors are also being considered for approval.

Chemotherapy
Palliative chemotherapy should be considered for patients with symptomatic visceral disease, ER- and PR-negative disease, or hormone receptor–positive disease that is resistant to endocrine therapy. Given the palliative goal and need to appropriately balance the benefits and toxicities of cytotoxic therapy, the challenge for the oncologist is in deciding when to initiate chemotherapy and with which regimen. Many appropriate chemotherapy regimens are available, including both single-agent and multiagent regimens, and there is little evidence to support use of combination therapy over sequential single-agent chemotherapy (Table 88.11).
There often is a fine line between premature use of chemotherapy in the asymptomatic patient without disease-related complications versus delaying therapy until deterioration of performance status significantly decreases the likelihood of response to or tolerance of therapy. There is considerable interest in identifying biologic parameters that may predict the success of specific chemotherapy regimens. The organ distribution of metastases and the patient’s symptoms, history of exposure to chemotherapy, and general medical condition are helpful considerations in determining the time of initiation of chemotherapy. Age alone should never be a contraindication to treatment. Similarly, lack of response or clinical benefit after a few sequential chemotherapy (as few as three) regimens and/or a poor performance status of 3 or worse may identify patients who are unlikely to benefit from further standard chemotherapy and in whom the primary focus should be on other palliative measures for symptom management.

**Single-Agent Chemotherapy**

Commonly used single-agent chemotherapy drugs in patients with advanced disease include microtubule inhibitors, anthracyclines, and capecitabine. Because no data suggest a markedly strong benefit of one class of drugs over another, decisions should be made based on patient convenience and toxicity profile. Other active agents include gemcitabine, 5-fluorouracil, platinum compounds, and etoposide.

Multiple agents act via inhibition of microtubules, including taxanes, epothilones, vinorelbine, and eribulin. The activity of taxanes in patients with anthracycline-resistant disease is well documented \(^524\) and may extend to patients previously treated with another taxane. Taxanes appear to have a better toxicity profile compared with doxorubicin. \(^525\)

The epothilone B analogue ixabepilone also has clinical activity in patients with disease resistant to paclitaxel, doxorubicin, and capecitabine. \(^526,527\) However, although the nanoparticle albumin formulation of paclitaxel (nab-paclitaxel) had shown a PFS benefit versus paclitaxel \(^528\) and docetaxel \(^529\) in the metastatic setting, a trial comparing these agents in the frontline setting in combination with bevacizumab demonstrated that weekly ixabepilone was inferior to paclitaxel, and there was a trend toward inferiority for weekly nab-paclitaxel as well. \(^530\)

Such data suggest that nab-paclitaxel might be of primary interest in patients with metastatic disease with allergy to paclitaxel or poor tolerance to dexamethasone premedication that is often routinely used with paclitaxel.

The nontaxane microtubule inhibitor eribulin was shown to offer an OS benefit when compared with best clinician choice for patients with prior exposure to at least two chemotherapy regimens for metastatic disease (13.1 versus 10.6 months; \(P = .041\)). \(^531\) However, in a randomized phase III trial of eribulin versus capecitabine in patients with metastatic disease, 75% of whom had received no or one prior chemotherapy regimen, there was no difference in the coprimary end points of DFS and OS, \(^532\) which leaves uncertainty regarding the optimal use of this drug.

As described earlier, anthracyclines are commonly used in the adjuvant setting, but they can also be used for treatment of metastatic disease. Because of concern for heart failure with cumulative exposure, the amount that can be given in the metastatic setting is sometimes limited. However, there is the option of giving liposomal doxorubicin, which has been shown to have equivalent efficacy to standard doxorubicin in the first-line setting. \(^533,534\)

Capecitabine is an oral prodrg of 5-fluorouracil that is active in patients who showed disease progression after previous taxane regimens. \(^535\) In addition to having benefit similar to eribulin in the frontline setting, \(^532\) it has also been shown to have similar activity to liposomal doxorubicin. \(^536\) Because it is oral and usually associated with minimal alopecia and peripheral neuropathy, it is generally a convenient option for patients.

Platinum analogues such as cisplatin and carboplatin, which act via cross-linking DNA, interfere with DNA replication. Although it is unclear which subtypes of breast cancer are most sensitive to treatment with platinums, a subset of TNBCs including those associated with BRCA1 mutations appears to be susceptible to the action of platinum salts because of defects in the DNA double-strand break repair mechanism. \(^537\) Although previously published data are mixed, a phase II trial of cisplatin for metastatic breast cancer demonstrated a relatively high response rate, especially in patients who harbored BRCA1 or BRCA2 germline mutations or whose tumors had a BRCA-like genomic instability signature. \(^538\)

**Combination Chemotherapy**

Combination regimens that are administered in the adjuvant setting can also be considered for use in the metastatic setting. In addition, gemcitabine plus paclitaxel was shown to significantly improve OS when compared with paclitaxel alone (18.6 versus 15.8 months; \(P = .0489\)). \(^538\) Subsequently, a similar study design demonstrated that the combination of ixabepilone plus capecitabine resulted in superior PFS compared with capecitabine alone (5.8 versus 4.2 months), which led to FDA approval in 2007 of ixabepilone in combination with capecitabine. \(^539\) No OS benefit was identified. However, although these combination regimens were superior to treatment with a single agent, it is unknown whether the use of two drugs in combination would lead to improved PFS or OS compared with use of the same two drugs in sequence. In addition, combination regimens are often associated with increased toxicity compared with sequential single agents, which may not be appropriate given the palliative intent of the treatment.

High-dose chemotherapy with autologous or allogeneic stem cell support remains investigational. Available data from multiple randomized trials do not support its use as a standard approach. \(^539\)

**HER2-Targeted Therapy**

Anti-HER2 therapy is another example of targeted therapy. Available data demonstrate that the potential benefits of trastuzumab are restricted to patients whose tumors overexpress HER2; current evidence does not support its use against HER2-negative disease. \(^540\) Single-agent therapy with trastuzumab results in an objective response rate of 26% in the first-line setting for HER2-positive disease. \(^541\) Although the initial phase II trial of combination regimens demonstrated a DFS and OS benefit when the anti-HER2 monoclonal antibody trastuzumab was added to anthracycline and cyclophosphamide or paclitaxel, excessive cardiac toxicity limits the ability to combine anthracyclines

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**Table 88.11 Commonly Used Cytotoxic Chemotherapy and Anti-HER2 Therapy Drugs in Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>CYTOTOXIC CHEMOTHERAPY</th>
<th>Anti-HER2 THERAPY</th>
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<tr>
<td>Albumin-bound paclitaxel</td>
<td>Ado-trastuzumab emtansine</td>
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<tr>
<td>Capecitabine</td>
<td>Lapatinib</td>
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<tr>
<td>Cisplatin</td>
<td>Pertuzumab</td>
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<tr>
<td>Carboplatin</td>
<td>Trastuzumab</td>
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<td>Docetaxel</td>
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<td>Doxorubicin</td>
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<td>Eribulin</td>
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<td>Gemcitabine</td>
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<tr>
<td>Ixabepilone</td>
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<tr>
<td>Vinorelbine</td>
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\(^{1599}\)
with trastuzumab. Additional small studies have been conducted to support the use of trastuzumab in combination with other cytotoxic chemotherapies. In addition, there are limited data to support continuation of trastuzumab during subsequent regimens.

The dual tyrosine kinase inhibitor lapatinib is approved in combination with capecitabine for the treatment of patients who previously were treated with trastuzumab, and improves OS when combined with paclitaxel versus paclitaxel alone in the frontline setting. In addition, the combination of two HER2-directed agents, trastuzumab and lapatinib, is superior to lapatinib alone in patients whose cancer progressed on trastuzumab-based therapy for HER2-positive metastatic breast cancer. In addition to the effect of lapatinib on extracranial disease, data also suggest that lapatinib in combination with chemotherapy has activity against HER2-positive brain metastases.

Perutzumab, a second anti-HER2 monoclonal antibody, has no meaningful clinical activity as a single agent or against HER2-negative disease. It was granted FDA approval based on the results of a phase III randomized trial (CLEOPATRA) comparing docetaxel and trastuzumab with and without pertuzumab in the first-line setting, which demonstrated a PFS and OS benefit. Of note, enrolled patients had received no prior trastuzumab therapy or had received it at least 6 months prior to enrollment. OS increased by 15.7 months, from 40.8 months to 56.5 months (HR, 0.68 [95% CI, 0.56–0.84]; P < .001). A number of clinical trials are currently underway to investigate the use of pertuzumab in later lines of therapy.

Ado-trastuzumab emtansine, originally known as T-DM1, is an antibody-drug conjugate that links the microtubule inhibitor DM1 to trastuzumab. It binds HER2 at the same site as trastuzumab and delivers the cytotoxic agent to the HER2-overexpressing cancer cells. T-DM1 has been shown to have activity in trastuzumab-refractory HER2-positive disease, and was shown to provide both PFS and OS benefit when compared with the combination of capecitabine and lapatinib. Similarly, T-DM1 demonstrated an improvement in PFS compared with physician’s choice for those with prior trastuzumab and lapatinib therapy. However, initial results of a phase III trial of first-line treatment with a taxane plus T-DM1 with pertuzumab or T-DM1 with placebo demonstrated noninferiority of PFS between the T-DM1–containing arms and controls; T-DM1 was associated with less toxicity. Therefore for now, the use of docetaxel, trastuzumab, and pertuzumab remains the standard of care for first-line therapy.

Therapies Targeting Angiogenesis

Although the humanized monoclonal antibody bevacizumab, which targets the vascular endothelial growth factor–A ligand, was originally granted accelerated approval by the FDA for the treatment of metastatic breast cancer, the approval was revoked when confirmatory studies failed to demonstrate a sufficient PFS benefit given the toxicities, and also demonstrated no OS benefit. First-line data showed a significant increase in PFS when the drug was added to paclitaxel in a randomized first-line trial in women with metastatic disease (ECOG 2100). However, other confirmatory studies failed to show a similar PFS or any OS benefit. Therefore although bevacizumab is still available for treatment of other malignancies, is it not approved for treatment of breast cancer in the United States.

Bisphosphonates

Bone is the most common site of metastasis in breast cancer. Monthly injections of antosteoclast inhibitors, including bisphosphonates and the receptor activator of nuclear factor–κB ligand (RANKL) inhibitor denosumab, for up to 2 years can reduce the risk of skeletal events in patients who have lytic bone metastases and are receiving systemic therapy. Zoledronate is an effective alternative to pamidronate because of its shorter infusion time, and denosumab is convenient because it is a subcutaneous injection. Preliminary data from the OPTIMIZE-2 trial suggest that after 1 year of monthly bisphosphonate therapy, switching from every 4 weeks to every 12 weeks was noninferior to continuing infusion every 4 weeks (NCT00320710). Similarly, preliminary data from CALGB 70604 demonstrated that administration every 12 weeks starting at the time of diagnosis of bone metastases was noninferior to administration every 4 week. These more potent third-generation bisphosphonates and denosumab are associated with an increased risk of osteonecrosis of the jaw, and long-term safety data beyond 1 or 2 years are not available. Use of oral supplementation with calcium and vitamin D is recommended, along with a baseline preventive dental evaluation before therapy is started.

UNUSUAL PROBLEMS ENCOUNTERED IN BREAST CANCER

Inflammatory Disease

Inflammatory breast cancer is the most aggressive form of nonmetastatic breast cancer. Although it accounts for only 1% to 4% of breast cancers in the United States, its presentation is striking. Characteristics essential to the clinical diagnosis include rapid enlargement and generalized induration of the breast, often without an associated mass. Diffuse skin erythema affecting more than one-third of the breast is the most distinctive clinical feature of the disease. Retraction of the nipple, diffuse breast warmth, and peau d’orange skin changes are commonly observed. Not infrequently, patients are thought to have mastitis and are treated with antibiotics.

Pathologically, inflammatory cancer is not a distinct histologic entity, although studies are ongoing to try to identify a signature specific for inflammatory breast cancer. Inflammatory breast cancer can be hormone receptor–positive or –negative, and HER2 positive or negative. At present, total lymphatic involvement is the pathologic hallmark of the disease. Since the first description by Bryant in 1887, many studies have associated the clinical findings with carcinoma in the lymphatics of the skin. Thorough examination of mastectomy specimens confirms dermal lymphatic involvement in as many as 70% of women with clinical signs of inflammatory carcinoma.

Dispute exists in the literature about the criteria necessary to diagnose inflammatory breast cancer. Although some believe that clinical findings alone are adequate to make the diagnosis, others argue that a skin biopsy confirming dermal lymphatic involvement is needed. Both presentations share a similar poor outcome.

Combined modality therapy with primary systemic chemotherapy, modified radical mastectomy, and postmastectomy radiation therapy has become the standard approach to the treatment of inflammatory breast cancer, similar to the evolution of treatment for other types of LABC. Retrospective data are convincing for a survival benefit and support the routine use of systemic therapy in this disease. Depending on the choice of chemotherapeutic and locoregional treatment, DFS rates at 5 years generally exceeded 25% to 30%, with 5-year survival rates approaching 40%.

Male Breast Cancer

Male breast cancer is rare, accounting for 0.2% of male cancers and less than 1% of new breast cancers. Mutations in the BRCA2 gene predispose men to breast cancer and may account for up to 40% of all cases. Most present as infiltrating ductal carcinoma with unilateral, firm, painless masses. Nipple discharge should be taken seriously and is an indication for FNA or core or excisional biopsy. Mammography and ultrasond may help to differentiate breast cancer from gynecomastia. A negative finding on FNA or core biopsy necessitates an excision procedure, and cytologic findings that show gynecomastia mandate close follow-up. The tumor phenotype appears similar to that observed in women.

Treatment is similar to that for female breast cancer. There is evidence that SLN biopsy can be safely applied in male breast cancer. Because most patients have endocrine-responsive disease, oophorectomy
Male breast cancer accounts for only approximately 1% of all cases of breast cancer, and men with DCIS only are estimated to be 7% of that already small group. Little information exists on the management of DCIS in men. Total mastectomy or wide excision with free margins may be considered a reasonable treatment.

**Breast Cancer and Pregnancy**

**Breast Cancer During Pregnancy**

Carcinoma of the breast, although rare in pregnant women, occurs in about 1 to 3 patients per 10,000 deliveries and is the most common malignancy associated with pregnancy. European data suggest that the prognosis of breast cancer during pregnancy is similar to that of breast cancer diagnosed in women who are not pregnant. Diagnosis and staging are more difficult in pregnant women because of physiologic changes in the mother and radiation risk to the fetus. Mammograms are not routinely performed because little information can be gained because of pregnancy-related increased breast density. Ultrasound and MRI can be used, although based on currently available data, gado-linium should be avoided.

In terms of local therapy, methylene blue dye should not be used for SLN biopsy because of risks to the fetus, although radiolabeled sulfur colloid appears to be safe.

Similarly, radiotherapy to the breast is not performed while the patient is pregnant. Therefore systemic chemotherapy is often given before surgery because a subset of the chemotherapeutic agents (doxorubicin and cyclophosphamide) appear to be able to be given safely after the first trimester, although there is some debate about the safety of taxanes. Tamoxifen and trastuzumab are not recommended during pregnancy because of concerns about teratogenesis.

**Pregnancy After Breast Cancer**

Many women now maintain fertility after breast cancer treatment, and some will become pregnant. There is increasing evidence that in contrast to women diagnosed with breast cancer during pregnancy, those diagnosed with breast cancer during the first few years after pregnancy have an approximately threefold increased risk of developing metastatic disease and dying from breast cancer. The biologic reasons for this distinction remain unclear.

**Axillary Metastases With Occult Breast Cancer**

A woman with clinically suspicious axillary lymph nodes despite negative breast examination findings and mammogram requires careful evaluation for breast cancer. FNA often allows the diagnosis of adenocarcinoma versus other tumor types. The breast is the most common primary source when dealing with adenocarcinoma, although gastrointestinal, pulmonary, or thyroid sources should also be considered. Breast imaging with ultrasound and MRI should be performed, although if no breast primary is identified, then additional imaging with CT scan of the chest and abdomen should be considered.

The definition of “occult breast carcinoma” is a breast cancer manifesting with metastatic axillary nodes without evidence of the primary tumor. Occult breast carcinoma manifesting as axillary metastases is rare, accounting for less than 0.4% of primary operable breast cancer. A large single-institution study of 69 patients with an occult primary showed that breast MRI was able to depict a primary carcinoma in 63% of the patients, and no carcinoma was found in the mastectomy specimen when the MRI finding was negative. Such patients should be managed with axillary dissection and may receive either mastectomy of the breast or whole-breast radiation therapy for breast conservation; breast conservation should be considered because local recurrence rates are very low.

**Phyllodes Tumors of the Breast**

Phyllodes tumors are uncommon breast tumors, accounting for less than 0.5% of all breast malignancies, that have a diverse range of biologic behaviors. These can range from benign tumors with a propensity to recur locally to a malignant sarcoma that can metastasize. The term phyllodes means leaf-like, and these tumors characteristic have leaf-like papillary projections at pathologic assessment. Although in the past these were called cystosarcoma phyllodes, this is no longer an appropriate term because these are not true sarcomas and rarely have a cystic component.

Phyllodes tumors have characteristics very similar to those of fibroadenomas; most patients have smooth, well-defined mobile masses. One-fifth of patients will have nonpalpable mammographic abnormalities. What typically distinguishes these fibroadenomas clinically is their rapid growth pattern, and phyllodes should be suspected in any patient with a large or rapidly growing mass. Core needle biopsy is required in order to make the diagnosis because FNA is not accurate for differentiating fibroadenomas and phyllodes tumors.

Histologically, phyllodes tumors are categorized as benign, borderline, or malignant. Benign lesions have circumscribed tumor margins, mild to moderate cellular atypia, a low mitotic rate, and a lack of stromal overgrowth. Phyllodes tumors are described as borderline when they have a greater degree of atypia and a higher mitotic rate (4–9 mitoses per 10 high-power fields) but still a lack of stromal overgrowth. Malignant tumors are characterized by marked atypia, high mitotic rate (>10), and the presence of stromal overgrowth.

Complete surgical excision with negative margins is the standard of care for phyllodes tumors. Positive margins are associated with high local recurrence rates. Margins of 1 cm are generally recommended for borderline or malignant tumors, because margins less than 1 cm have been associated with a higher recurrence rate. As long as appropriate margins can be obtained with a satisfactory cosmetic outcome, mastectomy is not necessary. Axillary metastases are extremely rare, so neither SLN biopsy nor ALND is indicated.
Radiation therapy is not necessary for benign phyllodes tumors but is recommended after excision for borderline or malignant phyllodes tumors. In a meta-analysis of eight studies, adjuvant radiation therapy was associated with a significantly decreased risk of local recurrence (HR, 0.31 [95% CI, 0.10 to 0.72]) but had no impact on OS.165 Hormonal therapy is not effective, and there are few data regarding the efficacy of chemotherapy for malignant phyllodes tumors. Patients with benign or borderline phyllodes are cured with local therapy alone, whereas patients with malignant phyllodes tumors have a 5-year survival rate between 60% and 80%.135 Patients with large (>5 cm), high-risk recurrent malignant phyllodes tumors may be considered for chemotherapy.

FUTURE STRATEGIES

As noted earlier, a greater understanding of the biologic subtypes of breast cancer is helpful with the selection of treatment strategies targeting specific tumor subtypes. Although considerable progress has been made, new treatment strategies will be required in both the curative and metastatic settings. Research is ongoing to identify effective treatments for patients with residual disease after preoperative systemic therapy, and those with endocrine-sensitive tumors who are at risk of late recurrence of disease. In the advanced-disease setting, there are active areas of research examining both new cytotoxic agents and combinations of chemotherapy, targeted therapy, and/or immunotherapies to treat refractory cancers. Finally, with the increasing number of cancer survivors across the globe, it will be important to evaluate symptom management and survivorship strategies to reduce long-term and late effects of therapy and to improve coordination of care for patients and providers. Overall there has been tremendous progress in both the understanding and management of breast cancer in the past decade, and there is considerable promise for increased knowledge and new treatment approaches in the future.

The complete reference list is available online at ExpertConsult.com.

KEY REFERENCES


51. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in...


Surg invasive analysis of acquired resistance to cancer


Part III: Specific Malignancies


64. Monkaeva A, Henry NL. Paclitaxel for the treatment of estrogen-negative, HER2-negative meta-


74.帕拉德斯 R, 賢勳 L, 賢明 P, 等. Paclitaxel versus doxorubicin as first-line single-agent chemothera-


76. Thomas NS, Comey HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer pro-


553. Macdonald OK, Lee CM, Tward JD, Chappell CD, Gaffney DK. Malignant phyllodes tumour of the female breast: association of primary therapy with cause-specific survival from the surveillance, epidemiology, and end results (SEER) program. Cancer. 2006;107(9):2127–2133.


Part III: Specific Malignancies


