Breast cancer is the most common cancer among women worldwide and it accounts for 23% of all cancer diagnosed among women. It is also the most common cancer diagnosed in women in North America, and is second only to lung cancer as the leading cause of death from cancer in women. When diagnosed early, breast cancer can be treated primarily using surgery, radiation, and systemic therapy. In Western countries at the time of diagnosis more than 90% of patients will have only localized disease.

**EPIDEMIOLOGY**

- In the United States, in 2013, an estimated 232,340 women and 2,240 men will be diagnosed with breast cancer.
- In 2013, about 39,620 women and 410 men are expected to die from breast cancer in the United States.
  - About 1.5 million women will get a diagnosis of breast cancer worldwide and about half a million will die globally from breast cancer.
- A US woman's lifetime risk of developing breast cancer is one in eight.
- There are currently more than 2.9 million breast cancer survivors in the United States.

**RISK FACTORS**

The risk factors for developing breast cancer in women are listed in Table 12.1. The etiologies of most breast cancers are unknown and sporadic. About 5% to 10% of breast cancers are familial or hereditary.

**Genetics**

- About 5% to 10% of all women with breast cancer may have a specific mutation in single genes that are passed down in a family, and the most common mutations are those of the genes BRCA1 or BRCA2. Other genes implicated with breast cancer are PTEN, TP53, and CDH1.
Increasing age
Family history of breast cancer at a young age
Genetic mutations such as BRCA1 or BRCA2 mutations
Increased mammographic breast density
Early menarche
Late menopause
Nulliparity
Older age at first child birth
Atypical lobular hyperplasia or atypical ductal hyperplasia
Prior breast biopsies
Long-term postmenopausal estrogen replacement
Early exposure to ionizing radiation

<table>
<thead>
<tr>
<th>Table 12.1 Risk Factors for Breast Cancer in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Family history of breast cancer at a young age</td>
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</tr>
<tr>
<td>Early exposure to ionizing radiation</td>
</tr>
</tbody>
</table>

- Mutations of BRCA1 (chromosome 17q21) and BRCA2 (chromosome 13q12–13q13) are responsible for 85% of hereditary breast cancer.
- Specific mutations of BRCA1 and BRCA2 are more common in women of Ashkenazi Jewish ancestry.
- Overall prevalence of disease-related mutation is BRCA1 has been estimated at 1 in 300, while BRCA2 is 1 in 800.
- Mutations of BRCA1 or BRCA2 can be highly penetrant, with estimates of 45% to 84% lifetime risk for breast cancer, as well as an increased risk for contralateral breast cancer.
- Mutations in either gene also confer about 11% to 62% lifetime risk of developing ovarian cancer.
- See also Chapter 45.

**Indications for Genetic Testing**

Genetic testing is available commercially (Myriad Genetics). All patients should undergo genetic counseling before undergoing the test. There are three possible outcomes of genetic testing for the BRCA mutations: positive, variant of uncertain significance, or negative. A negative result indicates no increased risk of breast cancer due to a germ-line mutation of the BRCA1/2 genes. A variant of uncertain significance (indeterminate) test result indicates that no conclusive evidence exists to indicate that the mutation does or does not carry an increased risk of the development of breast cancer due to an inherited genetic mutation. A positive result indicates that there exists a mutation in the BRCA1 or 2 genes that have been associated with an inherited risk of developing breast cancer.

As per NCCN guidelines (accessed January 2013), patients with breast cancer with one or more of the following should undergo further genetic risk evaluation:
- Early-age onset breast cancer
- Triple negative breast cancer (ER−, PR−, HER-2/neu−)
- ≥2 breast primaries in a single individual or two different individuals from the same side of the family
- ≥1 close blood relative (first-, second-, or third-degree relative) with breast cancer ≤50 years of age
- ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age
- Population at increased risk (i.e., women of Ashkenazi Jewish descent)
- Male breast cancer

**Management of Patients with Positive BRCA Test**

Management recommendations for patients with a known genetic mutation are highly individualized and should be made by an expert. Recommendations include the following:
- Breast self-examination training and education starting at age 18.
- Clinical breast examination every 6 to 12 months, starting at age 25.
- Annual mammogram and breast magnetic resonance imaging (MRI) starting at age 25 or earlier based on family history.
- Discuss options of bilateral prophylactic mastectomy on a case-by-case basis, since it could prevent breast cancer in 90% to 100%.
■ Recommend bilateral salpingo-oophorectomy (BSO) ideally between the ages of 35 and 40 or after completion of child bearing. BSO alone will reduce breast cancer risk by 50% and prevents ovarian cancer by 95%.
■ Patients who defer BSO may consider concurrent trans-vaginal ultrasound with CA-125 lab draw every 6 months starting at the age of 30 or 5 to 10 years prior to the earliest age of ovarian cancer in the family.

CHEMOPREVENTION

Risk Assessment
■ The Gail model (http://www.nci.nih.gov) is a statistical model that calculates a woman’s absolute risk of developing breast cancer by using the following criteria: age, age at menarche, age at first live birth, number of previous biopsies, history of atypical ductal hyperplasia (ADH), and number of first-degree relatives with breast cancer. This model is not intended to be used in patients with an existing history of invasive cancer, DCIS, or lobular carcinoma in situ (LCIS). The Gail model underestimates the risk of breast cancer in a person with hereditary breast cancer.

Prevention Studies

The National Surgical Adjuvant Breast and Bowel Project
■ The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study showed a 49% reduction in the incidence of invasive breast cancer in high-risk subjects who took tamoxifen at a dose of 20 mg daily for 5 years.
■ Women eligible for this trial were at least 35 years old and were assessed to have an absolute risk of at least 1.67% over the period of 5 years using the Gail model or a pathologic diagnosis of LCIS.
■ Use of tamoxifen for breast cancer should be individualized, and must be considered after weighing the risk:benefit ratio for each patient.
■ Women with a life expectancy of ≥10 years and no diagnosis/history of breast cancer considered at increased risk of breast cancer should receive individualized counseling to decrease breast cancer risk.

NSABP P-2: Study of Tamoxifen and Raloxifene
In the NSABP P-2 study, tamoxifen 20 mg daily was compared with raloxifene 60 mg daily in postmenopausal women with high risk of developing breast cancer (Gail risk model 1.66%). The results of the study revealed that raloxifene was equivalent to tamoxifen in preventing invasive breast cancer (about a 50% reduction). Raloxifene did not reduce the risk of DCIS or LCIS unlike tamoxifen.
Raloxifene has a better side effect profile, which resulted in a lower incidence of uterine hyperplasia, hysterectomy, cataracts, and a lower rate of thromboembolic events. In postmenopausal patients, due to equal efficacy and better side effect profile, raloxifene 60 mg daily could be used instead of tamoxifen for breast cancer prevention.

Aromatase Inhibitors for Risk Reduction
The Arimidex, Tamoxifen alone, or in Combination Trial (ATAC Trial) showed a nonsignificant reduction in contralateral breast cancers in women treated with anastrozole alone when compared with tamoxifen ($P = 0.62$). A significant reduction ($P = 0.04$) was noted in contralateral breast cancers in a subset of women with hormone receptor-positive first cancers.
The Breast International Group (BIG) 1-98 trial compared postmenopausal women with early-stage breast cancer to those who underwent 5 years of therapy and found that risk of breast cancer recurrence was lower in women in the letrozole arm when compared to the tamoxifen arm.
The MAP.3 trial evaluated the role of exemestane in a risk reduction setting, randomizing women to either exemestane or placebo. A median follow-up of 3 years showed that exemestane reduced the relative incidence of breast cancers by 65% when compared to placebo. It was not associated with any significant serious side effects and only minimal changes in quality of life.
Summary

In premenopausal women with increased risk of breast cancer as per the Gail model it is reasonable to recommend tamoxifen 20 mg daily for 5 years. In postmenopausal women raloxifene and tamoxifen are equally effective, but raloxifene has been shown to have less side effects. Exemestane can also be considered; however, the FDA has not approved exemestane in this setting at this time. Any risk reduction approach should be carefully decided after a detailed risk versus benefit discussion with the patient.

There are only limited data for chemoprevention in patients with BRCA mutation. One study showed that tamoxifen can reduces the risk by 62% compared to placebo; however, tamoxifen use was not associated with reduction in risk in those patients with a BRCA1 mutation. Clinical trials are addressing the role of AIs in breast cancer prevention in mutation carriers.

Screening Mammograms and MRI

- The National Cancer Institute, American Cancer Society, and American College of Radiology all recommend mammography for women aged 40 years and older.
- Women aged 40 years and older at an average risk of breast cancer should have mammograms every 1 to 2 years.
- Women who are at higher than average risk of breast cancer (those with a family history of breast cancer or with either the BRCA1 or the BRCA2 gene) should discuss with their health care providers about whether to have mammograms before the age of 40 and how often to have them.
- Mammograms should be continued regardless of a woman’s age, as long as she does not have serious, chronic health problems such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, and moderate to severe dementia. Age alone should not be the reason to stop having regular mammograms. Women with serious health problems or short life expectancies should discuss with their doctors whether to continue having mammograms.
- Screening mammograms help reduce death in patients between the ages of 40 and 70 years.
- Potential harm of screening includes false-negative and false-positive results, over diagnosis and overtreatment.
- There is considerable controversy among various experts regarding the risk and benefit screening mammogram, especially women between 40 and 50 years.

Digital Mammography

The diagnostic superiority of digital mammography was demonstrated in the Digital Mammographic Imaging Screening Trial (DMIST). This study concluded that pre- or perimenopausal women under the age of 50, or women at any age with dense breasts, had a more accurate detection of breast cancer with the digital mammogram. The amount of radiation exposure in digital mammograms is less than film mammograms.

Magnetic Resonance Imaging

Breast MRI has been shown to have a higher sensitivity than mammography. Specificity is however lower, which will result in more false positives and therefore more biopsies. In a high-risk population, MRI and mammogram (92.7%) have a higher sensitivity than mammogram and ultrasound combined (52%). In high-risk women, breast MRI is cost effective, specifically those women with BRCA gene mutations (along with untreated first-degree relatives) and women whose lifetime risk of breast cancer exceeds 20%. Patients need to be carefully selected for additional screening with MRI. MRI is recommended in patients with prior radiation therapy who are ≥25 years of age, and women with a genetic predisposition for breast cancer starting at the age of 25.

Clinical Features of Breast Cancer

Clinical features may include a breast lump, skin thickening or alteration, peau d’orange, dimpling of the skin, nipple inversion or crusting (Paget disease), unilateral nipple discharge, and new onset pain. Patients may instead present with signs and symptoms of metastatic disease.
DIAGNOSIS

1. History and physical examination
2. Bilateral mammogram (80% to 90% accuracy)
3. Biopsy: Any distinct mass should be considered for a biopsy, even if the mammograms are negative.
   The standard methods of diagnosis for palpable lesions are
   - Core-needle biopsy
   - Incisional or excisional biopsy
The options in nonpalpable breast lesions are
   - Ultrasound-guided core-needle biopsy
   - Stereotactic core-needle biopsy under mammographic localization
   - Needle localization under mammography, followed by surgical excision
   - MRI-guided biopsy
4. Laboratory studies
   - Complete blood count, liver function tests, and alkaline phosphatase level.
   - Routine use of breast cancer markers such as CA 27:29 and 15:3 is not recommended.
5. Pathology and special studies
   - Histology and diagnosis (invasive vs. in situ)
   - Pathologic grade of the tumor
   - Tumor involvement of the margin
   - Tumor size
   - Lymphovascular invasion
6. Estrogen receptor/progesterone receptor (ER/PR) status should be done in all tumors (both invasive and noninvasive) and biopsies of metastatic or recurrent (patients who relapsed) lesions.
   - As per the ASCO/CAP guidelines (2010) ER/PR is considered as positive if 1% of tumor cell nuclei are immunoreactive.
7. HER-2/neu- testing (as per ASCO/CAP Guidelines 2013)
   - Positive for HER-2/neu- is either IHC 3+ (defined as uniform intense membrane staining of more than 30% of invasive tumor cells) or FISH amplified (ratio of HER-2/neu- to CEP17 of more than 2.0 or average HER-2/neu- gene copy number more than six signals/nucleus for those test systems without an internal control probe).
   - Equivocal for HER-2/neu- is defined as either IHC 2+ or FISH ratio of <2 or average HER-2/neu-gene copy number of 4 to 6 signals/nucleus for test systems without an internal control probe.
   - Negative for HER-2/neu- is defined as either IHC 0–1+ or FISH ratio of less than 2 with an average HER-2/neu- gene copy number of less than 4 signals/nucleus for test systems without an internal control probe.
8. Indices of proliferation (e.g., mitotic index, Ki-67, or S phase) can be helpful. Ki-67 can be helpful in distinguishing luminal A versus B in ER/PR-positive lesions.
9. Radiographic studies are performed on the basis of the findings of the history and physical examination and blood tests.
   Appropriate imaging studies such as CAT scan, ultrasound, MRI, or CT/PET scan can be considered as per the clinical indications. They are not routinely recommended for all patients.
10. Breast MRI is indicated in the following (American College of Radiology Guidelines):
    - Evaluating the extent of disease in known cancer patients
      - Multifocal and multicentric disease
      - Pectoralis and chest wall involvement
      - Contralateral breast cancer
    - Evaluating response to neoadjuvant chemotherapy
    - Axillary adenopathy, primary unknown
    - Postlumpectomy for residual disease (close or positive margins)
    - Suspected recurrence of breast cancer
      - Inconclusive mammographic/clinical findings
      - Reconstruction with tissue flaps or implants
    - Lesion characterization
      - Inconclusive findings on mammogram, ultrasound, physical examination
11. Positron emission tomography (PET) scan. PET scans are of low yield in patients with early (stage I and II) breast cancer. CT/PET scan may be useful in patients with locally advanced or metastatic breast cancer.

**PATHOLOGY**

Infiltrating or invasive ductal cancer is the most common breast cancer histologic type and comprises 70% to 80% of all cases (Table 12.2).

**STAGING OF BREAST CANCER**

For staging of breast cancer the American Joint Committee on Cancer (AJCC) manual, seventh edition, should be followed.

**Prognostic Factors**

Anatomic features such as tumor size and lymph node status are important prognostic features. But biologic features of the tumor are equally important or possibly even more important than anatomic features.

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**Table 12.2 Pathologic Classification of Breast Cancer**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>Intraductal (in situ)</td>
</tr>
<tr>
<td></td>
<td>Invasive with predominant intraductal component</td>
</tr>
<tr>
<td></td>
<td>Invasive, NOS</td>
</tr>
<tr>
<td></td>
<td>Comedo</td>
</tr>
<tr>
<td></td>
<td>Inflammatory</td>
</tr>
<tr>
<td></td>
<td>Medullary with lymphocytic infiltrate</td>
</tr>
<tr>
<td></td>
<td>Mucinous (colloid)</td>
</tr>
<tr>
<td></td>
<td>Papillary</td>
</tr>
<tr>
<td></td>
<td>Scirrhous</td>
</tr>
<tr>
<td></td>
<td>Tubular</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Other</td>
<td>Undifferentiated</td>
</tr>
<tr>
<td>Lobular</td>
<td>In situ</td>
</tr>
<tr>
<td></td>
<td>Invasive with predominant in situ component</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td>Nipple</td>
<td>Paget disease, NOS</td>
</tr>
<tr>
<td></td>
<td>Paget disease with intraductal carcinoma</td>
</tr>
<tr>
<td></td>
<td>Paget disease with invasive ductal carcinoma</td>
</tr>
<tr>
<td>Other types (not typical breast cancer)</td>
<td>Phyllodes tumor</td>
</tr>
<tr>
<td></td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td></td>
<td>Primary lymphoma</td>
</tr>
</tbody>
</table>

NOS, not otherwise specified.
1. Number of positive axillary lymph nodes
   - This is an important prognostic indicator. Prognosis is worse with increasing number of lymph nodes.
2. Tumor size
   - In general, tumors smaller than 1 cm have a good prognosis in patients without lymph node involvement.
3. Histologic or nuclear grade
   - Patients with poorly differentiated histology and high nuclear grade have a worse prognosis than others.
   - Scarff-Bloom-Richardson grading system and Fisher nuclear grade are commonly used systems. The modified Scarff-Bloom-Richardson grading system assigns a score (1 to 3 points) for features such as size, mitosis, and tubule formation. These scores are added and tumors are labeled low grade (3 to 5 points), intermediate grade (6 to 7 points), or high grade (8 to 9 points).
4. ER/PR status
   - ER- and/or PR-positive tumors have better prognosis and these patients are eligible to receive endocrine therapy.
5. Histologic tumor type
   - Prognoses of infiltrating ductal and lobular carcinoma are similar.
   - Mucinous (colloid) and tubular histologies have better prognosis.
   - Inflammatory breast cancer is one of the most aggressive forms of breast cancer.
6. HER-2/neu expression
   - HER-2/neu-overexpression is a poor prognostic marker and patients with HER-2/neu-overexpression are candidates for HER-2/neu-targeted therapies. Availability of effective HER-2/neu-targeted therapies has revolutionized the treatment and outcome of HER-2/neu-positive breast cancer. Because of targeted therapies, for all practical purposes, HER-2/neu-positivity can be considered as a good prognostic feature now. It is important to remember that patients with a FISH ratio between 2.0 and 2.2 were considered as HER-2/neu-positive and were eligible for treatment in the early adjuvant trastuzumab trials. So patients with FISH ratio more than 2 should be considered for treatment with HER-2/neu-targeted drugs, especially trastuzumab in adjuvant settings.
7. Gene expression profiles
   - Oncotype DX is a diagnostic genomic assay based on RT-PCR on paraffin-embedded tissue (Fig. 12.1). This assay was initially developed to quantify the likelihood of cancer recurrence in women with newly diagnosed, stage I or II, node-negative, ER-positive breast cancer. Patients are divided into low-risk, intermediate-risk, and high-risk groups on the basis of the expression of a panel of 21 genes. The recurrence score determined by this assay is found to be a better predictor of outcome than standard measures such as age, tumor size, and tumor grade. Studies have validated the role of Oncotype DX

![Oncotype DX assay](image-url)
patients with node-positive and ER-positive tumors and it can be used in selected settings. It is being studied in DCIS also.

MammaPrint is a DNA microarray assay of 70 genes designed to predict the risk of recurrence of early-stage breast cancer. In February 2007, the FDA approved the use of MammaPrint in patients less than the age of 61, with a tumor size less than 5 cm and lymph node negative.

Several distinct types of breast cancer are identified by gene expression studies. They differ markedly in prognosis and in the therapeutic targets they express (Table 12.3).

- **Luminal subtypes**: Luminal A and luminal B, which express genes associated with luminal epithelial cells of normal breast tissue and overlap with ER-positive breast cancers defined by clinical assays. The luminal A subtype amounts to about 40% of cancers and they have the best prognosis. About 20% of breast cancers are of luminal B subtype and they have worse prognosis compared to luminal A.

- **HER-2/neu-enriched subtype** (previously the HER-2/neu-positive/ER-negative subtype): The HER-2/neu-enriched subtype comprises the majority of clinically HER-2/neu-positive breast cancers. It accounts for 10% to 15% of breast cancers. Not all HER-2/neu-positive tumors are HER-2/neu-enriched. About half of clinical HER-2/neu-positive breast cancers are HER-2/neu-enriched; the other half can include any molecular subtype including HER-2/neu-positive luminal subtypes.

- **ER-negative subtypes**: There are several ER-negative subtypes characterized by low expression of hormone receptor-related genes. These include the basal-like, claudin-low, interferon-rich, androgen receptor, and normal-like subtypes. They are mostly triple negative breast cancer and they have a more aggressive clinical course.

### MANAGEMENT

#### High-Risk Lesions

Patients with high-risk lesions may be eligible for breast cancer prevention studies. Tamoxifen and raloxifene are two FDA-approved drugs for breast cancer prevention in high-risk settings. As per the MAP.3 study exemestane was found to be effective in breast cancer prevention.

**Atypical Ductal Hyperplasia**

- There is a four- to fivefold increase in the risk of developing breast cancer in patients with ADH.
- There is wide variation in the criteria used in the diagnosis of ADH.
- ADH is managed by close follow-up of patients.
- Clinical breast examination and mammogram are the preferred screening methods.
- Tamoxifen 20 mg PO for 5 years: The NSABP P-1 study showed 86% reduction in the risk of developing invasive breast cancer in patients who received tamoxifen.
The NSABP P-2 study showed similar efficacy for raloxifene 60 mg daily for 5 years, but with fewer adverse effects. Hence, in postmenopausal patients, raloxifene could be considered as the preferred treatment option.

**Lobular Carcinoma In Situ**
- LCIS is not considered a form of cancer, but a marker of increased risk of developing invasive breast cancer.
- It is usually multicentric and bilateral.
- There is a 21% chance of developing breast cancer in patients within 15 years of developing LCIS.
- It is managed by close follow-up of patients.
- Patients can be followed up by clinical breast examination every 4 to 12 months, annual mammogram, and/or MRI.
- Tamoxifen or raloxifene (postmenopausal) may be used for prevention of breast cancer (56% reduction in risk as per the NSABP P-1 and P-2 studies).

**Noninvasive Breast Cancer**

**Ductal Carcinoma In Situ**
- The extensive use of mammograms has led to the diagnosis of ductal carcinoma in situ (DCIS) increasing over the last several years.
- Microcalcification or soft tissue abnormality is seen in the mammogram of DCIS.
- Comedocarcinoma has a poor prognosis.
- Noncomedocarcinoma includes micropapillary, papillary, solid, and cribriform carcinoma.

**Treatment**
- Lumpectomy followed by radiation treatment followed by tamoxifen for 5 years is the standard treatment option.
- Other treatment options are:
  - Total mastectomy with or without tamoxifen
  - In patients who previously had lumpectomy and radiation, tamoxifen reduced the risk of breast cancer recurrence (ipsilateral and contralateral; NSABP B-24). The benefit is limited only for patients with ER/PR-positive DCIS.
  - The role of AIs in receptor-positive DCIS is being investigated in many clinical trials, some of which have closed for accrual (NSABP B-35). Another phase 3 clinical trial, the CRUK-IBIS-II-DCIS, is still accruing patients.
  - NSABP B-43 is evaluating the role of trastuzumab in HER-2/neu-positive DCIS.

**Invasive Breast Cancer**

Breast cancer should be managed in a multidisciplinary approach with the input from the surgeon, medical oncologist, pathologist, radiologist, and radiation oncologist. After the diagnosis of breast cancer with a core needle biopsy or fine-needle aspiration cytology, it is important to confirm the histology, prognostic markers, and receptors. Various treatment options should then be discussed with the patient before the treatment plan is finalized.

**Surgery**
- As per NSABP B-06 and EORTC 10801, no survival difference is seen in patients who are treated with modified radical mastectomy versus lumpectomy and radiation therapy (breast conservation therapy [BCT]). BCT is the preferred treatment for early-stage breast cancer.
- As per NCCN guidelines contraindications for breast-conserving therapy requiring radiation therapy include:
  - Prior radiation therapy to the breast or chest wall
  - Radiation therapy during pregnancy
• Diffuse suspicious or malignant-appearing microcalcifications
• Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result
• Positive pathologic margin

Relative:
• Active connective tissue disease involving the skin (especially scleroderma and lupus).
• Tumors >5 cm.
• Focally positive margin.
• Women with a known or suspected genetic predisposition to breast cancer: May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast-conserving therapy. Prophylactic bilateral mastectomy for risk reduction may be considered.

Axillary Lymph Node Dissection

■ Axillary lymph node dissection (ALND) primarily provides prognostic information. It has minimal therapeutic benefit, especially in clinically negative axilla.
■ Among patients with clinically negative axillary lymph nodes, 30% will have positive histology after dissection.
■ A complete axillary node dissection is associated with approximately 10% to 25% risk of lymphedema, which can be mild to severe.

Sentinel Node Biopsy

“The SLN is defined as any node that receives drainage directly from the primary tumor, therefore, allowing for more than one SLN.” Injection of technetium-labeled sulfur colloid, vital blue dye, or both around the tumor, biopsy cavity, or in the subareolar area is taken up into the lymphatic system with a predominant pattern into the axilla. Nodes that contain dye or technetium are identified as the SLN. Identification rates of 92% to 98% of patients are the standard. Studies have shown a 97.5% to 100% concordance between SLN biopsy and complete ALND.

The ACOSOG Z 0011 clinical trial showed that there is no difference in overall survival (OS) and disease-free survival in doing a complete axillary node dissection in patients with clinical T1–T2 invasive breast cancer without palpable adenopathy and pathologic evidence of 1 to 2 SLNs-containing metastases. So in patients who meet the criteria for this trial, a complete axillary node dissection can be potentially avoided, even with a positive SNL metastasis.

Reconstruction

Reconstructive surgery may be used for patients who opt for a mastectomy. It may be done at the time of the mastectomy (immediate reconstruction) or at a later time (delayed reconstruction). Patients diagnosed with stage I and IIA disease and electing to undergo a mastectomy should be offered immediate reconstruction as long as their comorbid conditions do not preclude this intervention. For patients with stage IIB or III breast cancer and undergoing mastectomy, delayed reconstruction may be the more appropriate management option.

Reconstruction can be done in one of two ways: implant-based or an autologous tissue graft. Examples of autologous tissue grafts include TRAM (transverse rectus abdominis myocutaneous) flaps, the latissimus dorsi flap, and the DIEP (deep inferior epigastric perforator) flap. The latter is the preferred method as it is analogous to the TRAM flap; however, the rectus muscle is not raised to the breast site, thereby allowing quicker recovery of abdominal strength. The latissimus dorsi flap may be safer in patients who are obese or have compromised vasculature due to diabetes mellitus or smoking.

Radiotherapy

■ Radiotherapy (RT) is an integral part of breast-conserving treatment (lumpectomy). It is associated with a large reduction in local recurrence and a positive impact on survival.
■ Standard radiation is 45 to 50.4 Gy at 1.8 to 2 Gy per fraction to the whole breast. A boost is recommended in patients at higher risk for local failure (based on age, pathology, and margin status). The boost dose is 10 to 16 Gy at 2 Gy per fraction. An alternative hypofractionation schedule is 42.5 Gy
at 2.66 Gy per fraction to the whole breast. This treatment method has been demonstrated to provide comparable results following breast conserving surgery in patients with clear surgical margins and negative lymph nodes.

- RT is usually done after chemotherapy when systemic chemotherapy is indicated.
- Postmastectomy radiation treatment to the chest wall and supraclavicular lymph nodes decreases the risk of locoregional recurrence and improves survival in patients with multiple positive lymph nodes and patients with T3 or T4 tumors.
- Two randomized trials showed improvement in OS for postmastectomy radiation in patients with one to three positive lymph nodes, and is being evaluated in more clinical trials. In selected patients, this should be discussed.

**Accelerated Partial Breast Irradiation**

The primary goal of accelerated partial breast irradiation (APBI) is to shorten the duration of radiation therapy while maintaining adequate local control. There are several APBI techniques currently under study; however, brachytherapy is the most widely used. Brachytherapy methods are designed to irradiate the tumor bed or cavity while sparing normal breast tissue. Patients should be selected according to published criteria since the whole breast is not treated. The standard dose for balloon catheter brachytherapy is 34 Gy in 10 fractions delivered twice daily.

**Adjuvant Systemic Therapy**

Adjuvant therapy decisions are made based upon the stage, nodal status, and tumor biology. Important tumor biologic factors are ER/PR, HER-2/neu-, tumor grade, and risk stratification based upon gene expression profiles (e.g., Oncotype DX or MammaPrint) (Fig. 12.2). Age, comorbid conditions, performance status, patient preference, risk–benefit discussion, and life expectancy should be incorporated in adjuvant treatment decision-making.

![Algorithm for systemic adjuvant therapy](image-url)
General Principles of Adjuvant Therapy (Table 12.3)

1. All patients with breast cancer should be screened for potential clinical trials.
2. ER/PR-positive patients should be considered for antiestrogen therapy.
3. HER-2/neu-positive patients should be considered for HER-2/neu-targeted therapy.
4. Chemotherapy should be considered for the following patients:
   a. ER/PR-negative patients
   b. Triple negative patients
   c. HER-2/neu-positive patients
   d. Node-positive patients
   e. High-risk patients based upon Oncotype DX, MammaPrint, or other prognostic classification
   f. Patients under the age of 35 years

Adjuvant Therapy in HER-2/neu-Negative Patients

A variety of adjuvant regimens have been used across the world. Depending upon the biology of the tumor, stage of the disease, patient’s health status, comorbid conditions, and chance of recurrence, an optimal regimen can be chosen (Table 12.4). There is no major difference in efficacy among the regimens.

Table 12.4 Non–Trastuzumab-Containing Combinations

<table>
<thead>
<tr>
<th>Commonly Used Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dense AC followed by paclitaxel chemotherapy</td>
</tr>
<tr>
<td>• Doxorubicin 60 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cyclophosphamide 600 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cycled every 14 d for 4 cycles</td>
</tr>
<tr>
<td>• Followed by</td>
</tr>
<tr>
<td>• Paclitaxel 175 mg/m² by 3 h IV infusion day</td>
</tr>
<tr>
<td>Cycled every 14 d for 4 cycles (All cycles are with filgrastim support)</td>
</tr>
<tr>
<td>Dose-dense AC followed by weekly paclitaxel chemotherapy</td>
</tr>
<tr>
<td>• Doxorubicin 60 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cyclophosphamide 600 mg/m² IV day 1</td>
</tr>
<tr>
<td>Cycled every 14 d for 4 cycles</td>
</tr>
<tr>
<td>Followed by</td>
</tr>
<tr>
<td>• Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wk</td>
</tr>
<tr>
<td>TC chemotherapy</td>
</tr>
<tr>
<td>• Docetaxel 75 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cyclophosphamide 600 mg/m² IV day 1</td>
</tr>
<tr>
<td>Cycled every 21 d for 4 cycles</td>
</tr>
<tr>
<td>AC chemotherapy</td>
</tr>
<tr>
<td>• Doxorubicin 60 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cyclophosphamide 600 mg/m² IV day 1</td>
</tr>
<tr>
<td>Cycled every 21 d for 4 cycles</td>
</tr>
<tr>
<td>TAC chemotherapy</td>
</tr>
<tr>
<td>• Docetaxel 75 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Doxorubicin 50 mg/m² IV day 1</td>
</tr>
<tr>
<td>• Cyclophosphamide 500 mg/m² IV day 1</td>
</tr>
<tr>
<td>Cycled every 21 d for 6 cycles (All cycles are with filgrastim support)</td>
</tr>
<tr>
<td>Other Regimens</td>
</tr>
<tr>
<td>FAC chemotherapy</td>
</tr>
<tr>
<td>• 5-Fluorouracil 500 mg/m² IV days 1 and 8 or days 1 and 4</td>
</tr>
<tr>
<td>• Doxorubicin 50 mg/m² IV day 1 (or by 72-h continuous infusion)</td>
</tr>
<tr>
<td>• Cyclophosphamide 500 mg/m² IV day 1</td>
</tr>
<tr>
<td>Cycled every 21 d for 6 cycles</td>
</tr>
<tr>
<td>CAF chemotherapy</td>
</tr>
</tbody>
</table>

(Continued)
**Table 12.4 (Continued)**

- Cyclophosphamide 100 mg/m² PO days 1–14
- Doxorubicin 30 mg/m² IV days 1 and 8
- 5-Fluorouracil 500 mg/m² IV days 1 and 8

Cycled every 28 d for 6 cycles

**CEF chemotherapy**
- Cyclophosphamide 75 mg/m² PO days 1–14
- Epirubicin 60 mg/m² IV days 1 and 8
- 5-Fluorouracil 600 mg/m² IV days 1 and 8

Cycled every 28 d for 6 cycles

**AC followed by docetaxel chemotherapy**
- Doxorubicin 60 mg/m² IV on day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 d for 4 cycles

Followed by
- Docetaxel 100 mg/m² IV on day 1

Cycled every 21 d for 4 cycles

**EC chemotherapy**
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 830 mg/m² IV day 1

Cycled every 21 d for 8 cycles

**FEC followed by docetaxel**
- 5-Fluorouracil 500 mg/m² IV day 1
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 d for 3 cycles

Followed by
- Docetaxel 100 mg/m² IV day 1

Cycled every 21 d for 3 cycles

**FEC followed by weekly aclitaxel**
- 5-Fluorouracil 600 mg/m² IV day 1
- Epirubicin 90 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 d for 4 cycles

Followed by
- 3 wk of no treatment

Followed by
- Paclitaxel 100 mg/m² IV

Cycled every 21 d for 8 cycles

**FAC followed by weekly paclitaxel**
- 5-Fluorouracil 500 mg/m² IV days 1 and 8 or days 1 and 4
- Doxorubicin 50 mg/m² IV day 1 (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 d for 6 cycles

Followed by
- Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wk
Adjuvant Therapy in HER-2/neu-Positive Patients (Table 12.5)

Incorporation of trastuzumab in the adjuvant therapy is the most important development in the treatment of breast cancer in the past 10 years. Many trastuzumab-containing regimens have been tested and all are equally effective. Clinical trials have shown more than 50% improvement in DFS and more than 30% improvement in OS for patients who received trastuzumab in an adjuvant setting. The major difference is in the cardiac toxicity. Non-anthracycline-containing regimen, such as TCH (BCIRG 006) and HERA trial (sequential herceptin), had less cardiac toxicity compared to other anthracycline-containing regimens.

Several ongoing clinical trials are evaluating the role of pertuzumab, ado-trastuzumab emtansine (TDM-1), lapatinib, and other HER-2/neu-targeted agents in adjuvant breast cancer treatment.

Neoadjuvant or Preoperative Chemotherapy

Neoadjuvant or preoperative chemotherapy can be considered for any patients with locally advanced breast cancer (IIB, IIIA, IIIB, IIIC), and inflammatory breast cancer. But in IIIA, IIIB, and IIIC, and inflammatory breast cancer it is the treatment of choice.

- Initial surgery is limited to biopsy to confirm the diagnosis and to identify the ER/PR, HER-2/neu-status, and other prognostic features.

**Table 12.5 Trastuzumab-Containing Regimens**

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC followed by T chemotherapy with trastuzumab</td>
<td>Doxorubicin 60 mg/m² IV day 1, Cyclophosphamide 600 mg/m² IV day 1, Cycled every 21 d for 4 cycles, Followed by Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wk, With Trastuzumab 4 mg/kg IV with first dose of paclitaxel, Followed by Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment</td>
</tr>
<tr>
<td>TCH chemotherapy</td>
<td>Docetaxel 75 mg/m² IV day 1, Carboplatin AUC 6 IV day 1, Cycled every 21 d for 6 cycles, With Trastuzumab 8 mg/kg IV day 1, Followed by Trastuzumab 6 mg/kg IV every 3 wk to complete 1 y of trastuzumab therapy</td>
</tr>
<tr>
<td>Dose-dense AC followed by paclitaxel chemotherapy</td>
<td>Doxorubicin 60 mg/m² IV day 1, Cyclophosphamide 600 mg/m² IV day 1, Cycled every 14 d for 4 cycles, Followed by Paclitaxel 175 mg/m² by 3 h IV infusion day 1, Cycled every 14 d for 4 cycles (All cycles are with filgrastim support), With Trastuzumab 4 mg/kg IV with first dose of paclitaxel, Followed by Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment (Cardiac monitoring is recommended at baseline, 3, 6, and 9 mo)</td>
</tr>
</tbody>
</table>

Modified from NCCN guidelines 2013.
Preoperative evaluation of the breast mass by mammogram, ultrasound, or MRI is recommended. Potentially, the neoadjuvant chemotherapy can reduce the size of the primary tumor, so breast conserving surgery can be performed.

HER-2/neu-negative patients:
- Usually, a preoperative regimen contains an anthracycline and a taxane. Any adjuvant regimen can be used in a neoadjuvant setting.
- One of the largest neoadjuvant clinical trials is the NSABP B-27 trial (four cycles of AC followed by docetaxel for four cycles given every 3 weeks).

HER-2/neu-positive patients:
- An M.D. Anderson study has shown that trastuzumab with paclitaxel for four cycles followed by FEC with trastuzumab for four cycles is highly active.
- Any adjuvant trastuzumab regimen can be used in a neoadjuvant setting.
- Several clinical trials have shown an advantage for combination of HER-2/neu-targeted agents such as pertuzumab (NEOSPHERE) or lapatinib (NEOALTO) with trastuzumab.

Adjuvant Endocrine Therapy

Unless there is a contraindication, endocrine therapy should be considered for all patients with ER-positive and/or PR-positive tumors. As per the Oxford overview analysis, tamoxifen can decrease mortality by about 30% recurrence by 50% in hormone receptor-positive patients (Fig. 12.3 and Table 12.6).

![Adjuvant endocrine therapy diagram](image_url)
Postmenopausal Women

Several large randomized studies have shown superiority of AIs over tamoxifen in adjuvant settings. If the patient has no contraindication, AIs are the preferred agents in postmenopausal patients. Anastrozole, letrozole, and exemestane are three third-generation AIs approved by the FDA for adjuvant use. The major side effects include arthralgia, ostopenia, osteoporosis, and fracture.

**Anastrozole** One of the largest adjuvant breast cancer trials, comparing tamoxifen with anastrozole and combination of both anastrozole and tamoxifen (ATAC), has shown that anastrozole is superior to tamoxifen in improving DFS, reduction in contralateral breast cancer, and has a favorable side-effect profile. For postmenopausal patients, the recommended dose is anastrozole 1 mg PO daily for 5 years.

**Letrozole** BIG 1-98 showed a similar magnitude of improvement (like the ATAC trial) in DFS and a reduction of distant metastasis with letrozole. For postmenopausal patients, the recommended dose is letrozole 2.5 mg PO daily for 5 years.

**Switching from Tamoxifen to an Aromatase Inhibitor** In the IES study, exemestane therapy after 2 to 3 years of tamoxifen therapy significantly improved DFS and reduced the incidence of contralateral breast cancer as compared with the standard 5 years of tamoxifen therapy. The FDA has approved exemestane 25 mg daily after 2 to 3 years of tamoxifen in postmenopausal patients (total of 5 years of endocrine therapy).

The Italian Tamoxifen Anastrozole (ITA) trial, Austrian Breast Colorectal Study Group (ABCSG 8), and Arimidex, Noveldex (ARNO) study have shown an improvement in DFS and OS in patients who were initially treated with 2 to 3 years of tamoxifen and subsequently randomized to 2 to 3 years of anastrozole.

**Extended Adjuvant** The MA-17 study showed approximately 43% reduction in recurrence in postmenopausal patients receiving 2.5 mg of letrozole after completing 5 years of tamoxifen (extended adjuvant therapy). The NSABP B-42 clinical trial is looking at the role of extended use of AIs beyond 5 years.
**Endocrine Therapy: Premenopausal Patients (Fig. 12.3)**

Hormone receptor-positive, premenopausal patients are in general treated with tamoxifen. Combination of ovarian ablation or suppression with endocrine therapy (tamoxifen or aromatize inhibitors) is being investigated in many clinical trials.

**Tamoxifen**

Tamoxifen is a selective estrogen-receptor modulator (SERM), with both estrogen agonist and antagonist potential. In premenopausal patients, tamoxifen 20 mg daily is the treatment of choice, unless the patient has any contraindications such as history of thromboembolic disease, stroke, and endometrial cancer. Major adverse effects include a higher incidence of cerebrovascular accidents, thrombosis, endometrial cancer, hot flashes, mood changes, and weight gain.

In general, tamoxifen is recommended for 5 years. But a recent study (ATLAS) showed a continued benefit of tamoxifen for 10 years. In selected patients, tamoxifen should be considered for 10 years.

**Ovarian Ablation or Ovarian Suppression**

The Oxford overview and several studies have found that premenopausal patients who stopped having periods after completion of chemotherapy have better survival than those who continued to have periods. Ovarian ablation can be achieved by surgery, radiation, or with LHRH agonists (goserelin, triptorelin). The definite roles of ovarian suppression or ablation in patients who are receiving tamoxifen or AIs are not clear yet. Several ongoing phase 3 clinical trials using LHRH agonists (SOFT, TEXT, PERCHE) will answer this question.

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**BREAST CANCER IN PREGNANCY**

- Breast cancer during pregnancy was thought to be more aggressive, but the overall poor outcome is likely related to the advanced stage at the time of diagnosis.
- Breast biopsy is safe in all stages of pregnancy and should be done for any mass concerning cancer.

**Treatment**

- Lumpectomy and axillary dissection can be performed in the third trimester, and radiation therapy can be safely delayed until after delivery.
- Modified radical mastectomy is the treatment of choice in the first and second trimesters because radiation treatment is contraindicated during pregnancy.

**Chemotherapy**

- Chemotherapy should not be administered during the first trimester.
- No chemotherapy agent has been found to be completely safe during pregnancy.
- An anthracycline combined with cyclophosphamide (e.g., AC given every 3 weeks for four cycles) has been used safely in the adjuvant setting during the second or third trimesters.
- Chemotherapy should be scheduled to avoid neutropenia and thrombocytopenia at the time of delivery.
- Paclitaxel is teratogenic and should not be used during pregnancy.
- Tamoxifen is teratogenic and should not be used in pregnant women.
- Therapeutic abortion does not change the survival rate.

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**MALE BREAST CANCER**

- Male breast cancer is uncommon.
- Risk factors are family history, BRCA2 germ-line mutation, Klinefelter syndrome, and radiation to the chest wall.
Presence of gynecomastia is not a risk factor for breast cancer.
It is first seen as a mass beneath the nipple or ulceration.
The mean age of occurrence is 60 to 70 years.
Eighty percent of male breast cancer is hormone-receptor positive.

Treatment
- Modified radical mastectomy.
- Lumpectomy is rarely done because it does not offer any cosmetic benefit.
- Systemic treatment with chemotherapy and endocrine therapy should follow the general guidelines for female patients.
- None of the adjuvant treatment modalities has been tested in a randomized clinical trial setting in men.

Phyllodes Tumor
A phyllodes tumor is clinically suspected when the tumor is growing rapidly and clinical and radiologic features suggestive of fibroadenoma. It is treated with wide excision without an axillary node dissection. In patients who have recurrent phyllodes tumor, radiation therapy can be considered after wide excision.

Paget Disease of the Nipple
Patients should be evaluated for any evidence of invasive or noninvasive breast cancer by appropriate imaging and biopsy. If the patient has only Paget disease of the nipple areolar complex (NAC), the patient can be treated with mastectomy with ALND or wide excision of the NAC and axillary node surgery with whole-breast radiation. Patients with invasive or noninvasive breast cancer should be managed appropriately.

METASTATIC BREAST CANCER (FIG. 12.4)
Principles of Treatment
1. Repeat biopsy to confirm the diagnosis of recurrent/metastatic breast cancer.
2. Strongly recommend to repeat all markers including ER/PR and HER-2/neu-.
3. All patients should be considered for clinical trials.
4. HER-2/neu-positive patients could be treated with HER-2/neu-targeted agents such as trastuzumab, ado-trastuzumab emtansine (TDM-1), pertuzumab, or lapatinib.
5. ER/PR-positive patients should be treated with antiestrogen therapy if they have nonvisceral disease or slow growing disease.
6. Combination chemotherapy regimens have not shown significant DFS or OS benefit, so patients should be treated with single, sequential agents if possible.
7. All patients with metastatic disease involving the bone should be considered for a bisphosphonates (zolendronic acid/pamidronate) or denosumab (RANK ligand inhibitor).
8. A detailed discussion of the comorbid conditions, performance status, patient preference, toxicities of the treatment, and risk versus benefit should be done with the patient.
9. Goal of treatment should be discussed in detail with the patient, since it is palliative for majority of the patients.

Targeted Therapy
Trastuzumab (Herceptin®)
This is a monoclonal antibody, which is found to be highly effective in metastatic and adjuvant breast cancer therapy. The dose is usually 4 mg/kg as a loading dose and 2 mg/kg weekly. It can also be given every 3 weeks, with a loading dose of 8 mg/kg followed by 6 mg/kg. The addition of 1 year of adjuvant trastuzumab improves DFS and OS among women with HER-2/neu-positive breast cancer. In general, trastuzumab is given in combination with chemotherapy in adjuvant and metastatic settings.
Trastuzumab is well tolerated; rarely it can cause infusion reaction and pulmonary toxicity. The major side effect from trastuzumab is cardiac toxicity when it is used with or after anthracyclines. With anthracycline-containing regimen, the congestive heart failure rate is about 2% to 4%. Nonanthracycline regimens such as TCH did not show increased cardiac toxicity. It is important to monitor cardiac function with an ECHO cardiogram or MUGA scan baseline and every 3 months, for patients who are receiving trastuzumab.

Ado-trastuzumab emtansine (Kadcyla®)
Ado-trastuzumab emtansine is an antibody–drug conjugate composed of trastuzumab linked to a highly potent cytotoxic derivative of maytansine (DM1) by a stable linker. DM1 is a microtubule inhibitor. Trastuzumab targets the conjugate to HER-2/neu- receptors and the stable linker releases the cytotoxic agent only when the compound is internalized through receptor endocytosis. Ado-trastuzumab emtansine has been found to be active in trastuzumab- and lapatinib-resistant metastatic breast cancer, as well as in trastuzumab-naïve tumors. Results of the phase 3 EMILIA trial that compared trastuzumab emtansine with capecitabine plus lapatinib in advanced HER-2/neu-positive breast cancer showed a substantial improvement in progression-free survival (PFS) and OS with the conjugate.

The dose of ado-trastuzumab emtansine is 3.6 mg/kg IV every 3 weeks and it is extremely well tolerated in clinical trials.

Side effects include thrombocytopenia and liver function abnormalities. No significant increase in cardiomyopathy or peripheral neuropathy was seen. It is being evaluated in several clinical trials including neoadjuvant (NSABP B 50), adjuvant, and metastatic. Some of the trials are looking at the role of ado-trastuzumab emtansine in combination with pertuzumab.

Pertuzumab (Perjeta®)
Pertuzumab is a humanized monoclonal antibody that binds HER-2/neu- at a different epitope of the HER-2/neu- extracellular domain than that of trastuzumab. It prevents HER-2/neu- from dimerizing with HER3. Similar to trastuzumab, pertuzumab causes antibody-dependent, cell-mediated cytotoxicity. Since pertuzumab and trastuzumab bind to different HER-2/neu- epitopes and have complementary mechanisms of action, when pertuzumab is combined with trastuzumab, it provides a more comprehensive blockade of HER-2/neu- signaling and results in greater antitumor activity in clinical trials.
the CLEOPATRA study, when pertuzumab was given with trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, in first-line treatment for HER-2/neu-positive metastatic breast cancer, it significantly prolonged progression-free survival. No additional cardiac toxicity was seen. The FDA-approved dose of pertuzumab was 840 mg, followed by 420 mg every 3 weeks.

**Lapatinib (Tykerb®)**
A potent, small molecule inhibitor of the HER1 and HER-2/neu- tyrosine kinases. The inhibitory effects, though reversible, result in blockade of receptor-mediated activation and propagation of downstream signaling involved in regulation of cell proliferation and cell survival. It is a dual tyrosine kinase inhibitor, which blocks both EGFR (HER1) and HER-2/neu- pathway intracellularly. The FDA-approved dose of lapatinib is 1,250 mg daily PO. The side effects include diarrhea and rash.

**Other HER-2/neu-Targeted Agents**

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**Other Relevant Agents**

**nab-Paclitaxel (Abraxane®)**
Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a novel paclitaxel formulation that does not require Cremophor or polysorbate 80 for solubilization, thus reducing solvent-related toxicity and micelle formation. The FDA-approved dose of nab-paclitaxel is 260 mg/m² every 3 weeks for the treatment of metastatic breast cancer. The side effects include neutropenia, peripheral neuropathy, nausea, etc. Due to lack of cremophor, nab-paclitaxel does not require premedication with steroids.

**Ixabepilone (Ixempra®)**
This drug belongs to a novel class of drugs called epothilones. Epothilones are nontaxane microtubule-stabilizing agents. The tubulin-polymerizing activity of ixabepilone is stronger than paclitaxel. It has proven efficacy in taxane-resistant settings. Ixabepilone has low susceptibility to tumor resistance mechanisms such as P-glycoprotein (P-gp) and multidrug-resistance protein-1 (MRP1). The FDA approved ixabepilone in combination with capecitabine in patients with metastatic or locally advanced breast cancer, who are resistant to or refractory to a taxane and anthracycline. Ixabepilone is also approved as a monotherapy in patients who are resistant or refractory to taxane, anthracycline, and capecitabine. The dose is 40 mg/m² administered over 3 hours every 3 weeks. Patients should be premedicated with diphenhydramine and cimetidine an hour prior to the infusion with ixabepilone.

**Eribulin (Halaven®)**
Eribulin mesylate is a nontaxane, tubulin- and microtubule-targeting chemotherapeutic agent binds directly with tubulin disrupting mitotic spindles and inhibits microtubule polymerization. A phase 3 study, which compared eribulin to treatment of physician’s choice (TPC) in patients with locally recurrent or metastatic breast cancer with previous treatment with an anthracycline and taxane, showed improvement in PFS and OS with eribulin. The most common side effects were neutropenia and peripheral neuropathy. Eribulin is the only chemotherapy agent that has shown a survival advantage in late lines of therapy for breast cancer. The FDA-approved dose of eribulin is 1.4 mg/m² administered on days 1 and 8 of a 21-day schedule.

**Capecitabine (Xeloda®)**
Capecitabine (Xeloda) is a fluoropyrimidine carbamate and it is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. It is indicated as a monotherapy for metastatic breast cancer. The FDA-approved dose is 1,250 mg/m² twice a day given...
for 2 weeks and 1 week off, then repeating every 21 days. For practical purposes most clinicians use 1,000 mg/m² twice a day 2 weeks on 1 week off. The most common side effects are hand–foot syndrome and diarrhea. Patients should be educated about management of the hand–foot syndrome.

**Faslodex (Faslodex®)**

Fulvestrant (FASLODEX) is an ER antagonist (ER downregulator) and it is indicated in the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly on days 1, 15, and 29 and once monthly thereafter. Side effects are mainly related to pain and injection site reaction.

**Everolimus (Afinitor®)**

The FDA approved everolimus tablets (Afinitor®) for the treatment of postmenopausal women with advanced hormone receptor-positive, HER-2/neu-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. A randomized study with everolimus 10 mg per day plus exemestane 25 mg per day showed improvement in PFS compared to placebo plus exemestane 25 mg per day. The most common adverse reactions in patients receiving everolimus plus exemestane were stomatitis, infections, rash, fatigue, diarrhea, hyperglycemia, and pneumonitis.

**Supportive Care Agents**

**Bisphosphonates**

- Bisphosphonates should be used in patients with bony metastatic disease because they prevent progression of lytic lesions, delay skeletal-related events, and decrease pain. However, the optimal frequencies of administration and duration of therapy are not known.
- Zoledronic acid (4 mg by 15-minute infusion) and pamidronate (90 mg by 2-hour infusion) are two available bisphosphonates approved for bony metastatic disease.
- Osteonecrosis of the jaw (ONJ) is a very rare but a potential complication of long-term treatment with intravenous bisphosphonates.

**Rank Ligand Inhibitor**

**Denosumab (XGEVA®)** The receptor activator of nuclear factor-κB (RANK), the RANK ligand (RANKL), and osteoprotegerin, a decoy receptor for RANKL, regulate osteoclastogenesis and may play a key role in bone metastasis. Denosumab (XGEVA), a fully human monoclonal antibody that binds to and neutralizes RANKL, inhibits osteoclast function, prevents generalized bone resorption and local bone destruction, and has become a therapeutic option for preventing or delaying first on-study skeletal-related events in various malignancies.

It is approved for patients with bone metastasis from breast cancer, prostate cancer, and other solid tumors. The dose is 120 mg subcutaneous every 4 weeks. It can cause significant hypocalcemia. So patients should take appropriate calcium replacement. The incidence of osteonecrosis of the jaw is about 2.2% with denosumab. It does not have to be adjusted for renal impairment.

**Central Nervous System Metastasis**

Central nervous system (CNS) metastasis may consist of either parenchymal or leptomeningeal metastasis. The control of systemic disease is crucial to improving the survival of patients with resectable brain metastasis.

The standard treatment for multiple brain lesions remains whole-brain radiation (WBR) for symptom control, with no improvement in survival. The therapy for a single-brain metastasis remains either surgery or radiosurgery (Gamma Knife), with conflicting information as to the benefit of prior WBR. Leptomeningeal metastasis is conventionally treated with intrathecal chemotherapy, and may provide short-term symptom control. The superiority of intrathecal versus systemic chemotherapy in leptomeningeal metastasis is controversial. About 30% of HER-2/neu-positive patients will develop brain metastatic disease, and lapatinib-containing regimen is an option in these patients.
LOCALLY RECURRENT BREAST CANCER

After mastectomy:
- Eighty percent of local recurrences occur within 5 years.
- Treatment of choice is surgical excision and radiation therapy.
- Systemic therapy may be considered, although the survival advantage is not clear.

After lumpectomy:
- Mastectomy is the treatment of choice for patients who have only isolated breast cancer recurrence.

FOLLOW-UP FOR PATIENTS WITH OPERABLE BREAST CANCER (BASED ON ASCO GUIDELINES)

1. History and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually.
3. Annual mammogram of the contralateral and ipsilateral (remaining breast after lumpectomy) breast.
4. Annual Papanicolaou smear and pelvic examinations in women who are taking, or who have taken, tamoxifen.
5. Blood tests including a complete blood count, liver function tests, and alkaline phosphatase levels are not routinely recommended.
   - Serum tumor markers (CA 27-29, and CA 15-3) are not recommended.
   - Bone scan and imaging of the chest, abdomen, pelvis, and brain or PET scans are not recommended routinely, but they are done if symptoms or laboratory abnormalities are present.
6. Rectal examination, occult blood testing, and skin examination must be performed annually or every 2 years.

REVIEW QUESTIONS

1. A 29-year-old white female of Irish ancestry was seen in the high-risk clinic. Her father was diagnosed with pancreatic cancer at the age of 45, her paternal grandmother was diagnosed with ovarian cancer at the age of 38, and her paternal aunt was diagnosed with breast cancer at the age of 48. There is no other family or personal history of breast cancer. In addition to genetic counseling and genetic testing, what is the next step?
   A. Bilateral mastectomy and prophylactic oophorectomy
   B. CT/PET scan for ovarian or pancreatic cancer screening
   C. Breast MRI and pelvic ultrasound
   D. CA 125 and CA 19-9
   E. Wait for the genetic testing results to come before decide about the next step

2. A 55-year-old patient is seen in the medical oncology clinic after having a lumpectomy and sentinel lymph node dissection for an invasive ductal cancer. The tumor size is 1.8 cm and ER/PR strongly positive and HER-2/neu- negative. One of the two sentinel lymph nodes examined was positive for cancer. Her management options are
   A. She should proceed with complete axillary node dissection, for local control, since one sentinel lymph node is positive.
   B. She should get chemotherapy, because one node is positive.
   C. May be a candidate for Oncotype, radiation therapy, and endocrine therapy, if she is in the low-risk group.
   D. Since she has a lymph node involvement, she is not a candidate for Oncotype.
3. A 65-year-old patient with invasive ductal cancer had a left modified radical mastectomy and 2 lymph nodes were positive for invasive cancer. Her tumor size was 2.7 cm and she was staged as T2 N1 M0 (IIB). ER/PR was 90% to 100% positive and K1 67 was 5%. HER-2/neu- was negative by immunohistochemistry. She is in your office to discuss about adjuvant therapy options. She is otherwise very healthy.

A. Since she has a IIB tumor, strongly recommend chemotherapy with TC for four cycles.
B. Chemotherapy may not add much value to her treatment; her maximum benefit will be from endocrine therapy.
C. She should receive radiation therapy since she had a 2.7 cm tumor and one lymph node positive.
D. It is up to the patient to decide about her therapy since she is older than 65.

4. A 44-year-old school teacher was diagnosed with a stage IIIB, ER/PR-negative and HER-2/neu-negative breast cancer in 2002. In 2007 the patient presented with chest pain and shortness of breath. Chest x-ray followed by a CT scan of the chest showed a 4 cm left lower lobe lesion, which was biopsied and was confirmed as breast cancer. The repeat ER/PR was negative, but HER-2/neu-testing by immunohistochemistry was 3+ . The patient was started on multiple trastuzumab- and lapatinib-containing regimens. She continues to work and has an excellent cardiac function and ECOG performance status. The last restaging scan showed progression of the cancer compared to the previous scan. The patient clearly wishes to continue with the treatment. Her options are

A. Supportive care only, since she had multiple treatments in the past.
B. Pertuzumab, trastuzumab, and docetaxel as per the CLEOPATRA study.
C. Avoid HER-2/neu-targeted therapy, since it has worked in the past.
D. Ado-trastuzumab emtansine (TDM-1) is a very reasonable option for her.
E. Keep her on trastuzumab and change to different chemotherapy.

5. A 56-year-old woman with metastatic breast cancer, on treatment with exemestane and everolimus, presented to the walk-in clinic with new onset fever, cough, and shortness of breath. The chest x-ray showed diffuse patchy infiltrate. The patient's blood pressure was 134/86 mmHg and heart rate was 84 per minute. Her pulse oxymetry was 94% on room air. Her sites of metastatic disease were L4 and L5 lesions. The patient's last dose of zolendronic acid was about 3 weeks back. Her management options include

A. She has lymphangiatic spread of breast cancer, so consider stopping the current medicine and start her on chemotherapy.
B. It is everolimus-induced pneumonitis, so she should be immediately taken off the treatment and never put back on it again.
C. If it is only a grade 2 toxicity, we can interrupt the everolimus and restart at a lower dose, once the toxicity is improved to grade 1 or less.
D. She needs a bronchoscopy to confirm the diagnosis.

Suggested Readings


