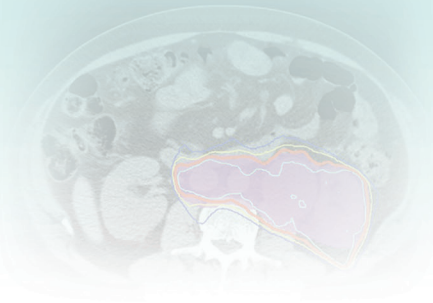
Overview



Rashmi K. Murthy, Vicente Valero, and Thomas A. Buchholz

INCIDENCE AND MORTALITY

Breast cancer is the most common cancer in women, and it is estimated that one in eight women in the United States will develop breast cancer in their lifetime. Every year more than 40,000 women die from breast cancer, making it the second-leading cause of cancer-related deaths in women. Historically, the increase in breast cancer incidence was thought to be a reflection of changes in reproductive patterns, such as delayed childbearing and nulliparity, which are recognized as risk factors. Since the early 1980s, the incidence of breast cancer among older women was steadily rising because of improved early detection with the widespread use of mammography. The rates stabilized in the late 1990s and then started to decrease. In contrast the incidence of breast cancer in younger women has remained stable. With a rapidly aging population in the United States, the number of breast cancers is expected to increase over the next 20 years. Fortunately, screening, early detection, and advances in multidisciplinary treatment have led to continuous declines since 1990. Survivorship is a growing issue and research into the late effects of treatment will become even more relevant as the population of breast cancer survivors continues to increase. In this chapter, we will provide an overview and highlight the general considerations necessary in formulating a multimodality treatment plan for the management of a patient with breast cancer.

ETIOLOGY, RISK FACTORS, AND GENETICS

Breast cancer results from a series of genetic and epigenetic events that lead to dysregulation of cell growth, circumvention of apoptosis, and development of the ability to invade. The causes of these events remain largely unknown, although epidemiologic studies have implicated lifestyle, environmental, and germ-line genetic factors in predisposition to this disease.

Accepted risk factors for breast cancer include female sex, increasing age, personal or family history of the disease, exposure to ionizing radiation, nulliparity, hormone replacement therapy, alcohol intake, germ-line mutations in the *BRCA1* gene or *BRCA2* gene, and other more unusual inherited conditions. Up to 10% of breast cancers are caused by germ-line mutations that are passed down in families.

Advances in molecular genetics have identified several genes associated with an inherited susceptibility to breast cancer (i.e., *BRCA1, BRCA2, PTEN, TP53, CDH1*), and identification of a mutation has major implications for prevention, screening, and treatment. Formal risk assessment and genetic counseling takes into account a detailed family pedigree, an evaluation of the patient needs and concerns, past medical and surgical history, and any active cancer diagnoses.

PROGNOSTIC AND PREDICTIVE FACTORS

Several features help to predict the probability of successful outcome after treatment for breast cancer. The most powerful prognostic factor is disease stage at diagnosis, which is determined by the status of regional lymph nodes and the size of the primary tumor. Additional tumor-related prognostic factors include tumor grade, estrogen and progesterone receptor status, HER2/neu (ERBB2) status, and proliferative index. The most important patient-related factor is age, with young patients with breast cancer typically having the worst outcomes.

The genetic heterogeneity of breast cancer is increasingly being appreciated. New molecular tumor assays, including cDNA microarray classifications and molecular-based predictive assays, are enhancing the understanding of tumor biologic characteristics, prognosis, and predictors of treatment response. Several have moved into the marketplace and are used for treatment decisions (i.e., Oncotype-DX, PAM50, Mamaprint). Ultimately, it is hoped that continued research into the molecular biology of breast cancer will continue to identify new therapeutic targets and increase the personalization of breast cancer therapy.

TREATMENT

Breast cancer therapy requires a multidisciplinary team consisting of surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, reconstructive surgeons, and supportive care personnel. Each aspect of multidisciplinary care should occur in a coordinated fashion. Most patients with breast cancer receive surgery, radiation, and systemic treatment. All three therapeutic specialties have seen significant advances, and each component of these treatments has been shown to independently offer survival benefit for selected patients. For patients with early-stage breast cancer, the outcomes associated with breast-conservation surgery, sentinel lymph node dissection, radiation, and systemic treatments are excellent. Treatment advances have also improved the prognosis for patients with more advanced disease at presentation. A particularly exciting advance has been the use of anti-HER2–directed therapies for patients with HER2-positive disease. In the future, additional molecularly targeted treatments are likely to further improve breast cancer outcomes.

INTRODUCTION

Breast cancer is one of the most common cancers seen and treated by radiation oncologists. Radiation plays an important role in the management of breast cancer at all stages, including ductal carcinoma in situ, early-stage disease (as a component of breast conservation), and locally advanced disease (as an adjuvant treatment after mastectomy). Radiation is also a highly effective palliative modality for patients with metastatic disease progressing within a localized area that adversely affects their quality of life.

This section of the textbook consists of this overview introduction, followed by chapters highlighting the role of radiation in ductal carcinoma in situ, early-stage disease, and locally advanced disease. This overview component reviews important aspects of breast cancer anatomy, breast cancer epidemiology and statistics concerning incidence and mortality, risk factors for the disease, screening, staging, prognostic and predictive factors, including the molecular classification of disease, and a summary of the role of surgery, radiation, and systemic therapies for breast cancer.

ANATOMY

A comprehensive understanding of the anatomy of the breast and its regional lymphatics is imperative for radiation oncologists to appropriately design radiation therapy fields that optimally cover targeted areas at risk for disease while sparing uninvolved normal structures. Historically, radiation treatment fields were designed based on standard external landmarks, but such techniques risked inadequate treatment of sites at risk of containing disease. Treatment planning based on computed tomography (CT) imaging has optimized the planning process and heightened the importance of radiation oncologists' familiarity with anatomy, particularly with respect to the breast's lymphatic drainage pathways.

The breast typically extends medially to the midline and laterally to near the midaxillary line. The cranial and caudal borders of the breast are typically the second and sixth anterior ribs, respectively, although the breast may extend higher into the axillary region (known as the *tail of Spence*). Breast parenchymal tissue is supported by fibrous septa (Cooper's suspensory ligaments) and connective tissue that contains blood vessels, nerves, lymphatics, and adipose tissue. The deep boundary of the breast is the fascia of the pectoralis major muscle. The chest wall, which consists of the rib cage and interosseous muscles and fascia, lies underneath the pectoralis major muscle. Microscopically, the breast parenchyma consists of lobules and ducts. The ductal system of the breast is divided into branching segments that converge into major lactiferous ducts near the nipple-areola complex. The interface between the lobules and the ducts, the *terminal ductal-lobular unit*, is the most common location for the development of breast cancer.

The breast has a rich lymphatic plexus that drains to lymph nodes of the axilla, internal mammary chain (IMC), and supraclavicular fossa (Figure G-1). Drainage can also occur to lymph nodes within the breast itself (intramammary nodes) and those between the pectoralis major and minor muscles (interpectoral or Rotter's lymph nodes). Sentinel lymph node surgery has helped to identify the most common drainage pathways of the breast lymphatics. Most individuals have lymphatic drainage to one or more lymph nodes in the low axilla. Axillary lymph nodes are customarily divided into three levels according to their anatomic location relative to the pectoralis minor muscle: level I axillary lymph nodes are located inferolateral to the pectoralis minor muscle; level II lymph nodes are beneath the pectoralis minor muscle; and level III lymph nodes (also called infraclavicular lymph nodes) are those superior and medial to the pectoralis minor muscle but below the clavicle. Figure G-2 shows an axial positron emission tomography (PET) image combined with a CT image of a patient with involvement of level I, II, and III lymph nodes. Patients with advanced disease are also at risk of having involvement of Rotter's nodes, an example of which is shown in Figure G-3.

Breast cancer can also involve lymph nodes within the IMC. Lymphatic channels that drain to internal mammary lymph nodes tend to run close to the pectoralis fascia, and therefore a sentinel lymph node procedure that is done with a superficial or subdermal injection of blue dye or radiocolloid will rarely reveal drainage to the IMC. To demonstrate drainage in such cases, these injections must be done within the tumor bed or deep near the pectoralis muscles. When breast cancer involves lymph nodes in the IMC, the nodes are usually within the first three intercostal spaces. These anatomic areas are easily visualized with CT scans, on which the internal mammary artery and vein are apparent just lateral to the sternum within the thoracic cavity. One study involving lymphoscintigraphy before sentinel lymph node surgery indicated that the frequency of drainage to the IMC was highest for lower inner quadrant tumors (43%), followed by lower outer quadrant tumors (32%) and central tumors (28%).[1] An axial PET/CT slice of a patient who presented with involvement of an internal mammary lymph node and concurrent disease within the ipsilateral breast and level I axilla is shown in Figure G-4. The frequency of internal mammary lymph node involvement depends on the status of the axillary lymph nodes and the anatomic location of the primary tumor. An important study from China reported the rates of IMC involvement in 2269 patients who had had dissection of this region as a component of an extended radical mastectomy.[2] The rates of IMC involvement were highest when axillary disease was also present (Table G-1).

Finally, breast cancer can also spread to the supraclavicular nodes, although this typically occurs only when axillary lymph nodes are also involved. The risk of supraclavicular lymph node involvement depends greatly on the number of positive axillary lymph nodes; clinical outcome data suggest that supraclavicular involvement for patients with one to three positive axillary lymph nodes is rare, but more than 15% of patients with four or more positive axillary lymph nodes

TABLE G-1 Pathologic Rates of Involvement of Internal Mammary Lymph Nodes According to Tumor Location and Pathologic Status of the Axilla

Tumor Location	Axillary Lymph Node (ALN) Status	Rates of Involvement of the Internal Mammary Lymph Node(s)
Medial/central	0 + ALN	6% (27/428)
	1-3 + ALN	26% (41/160)
	4-6 + ALN	43% (21/49)
	≥7 + ALN	40% (44/110)
Lateral	0 + ALN	3% (12/456)
	1-3 + ALN	14% (34/238)
	4-6 + ALN	20% (18/90)
	≥7 + ALN	43% (63/148)

Data from Huang O, Wang L, Shen K, et al: Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis. Analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat 107(3):379–387, 2008.

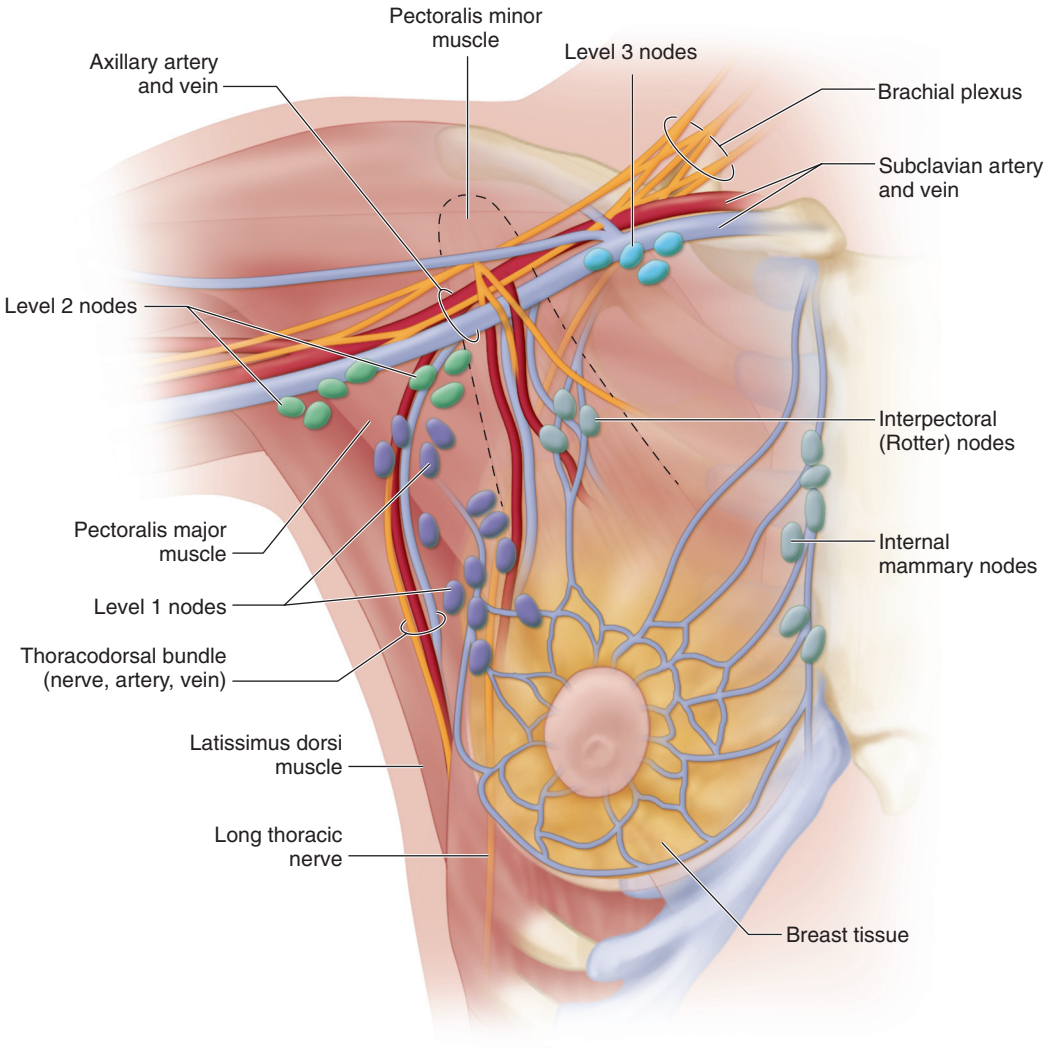


Figure G-1 Pictorial depiction of anatomic landmarks of the axilla and lymphatic drainage of the breast.

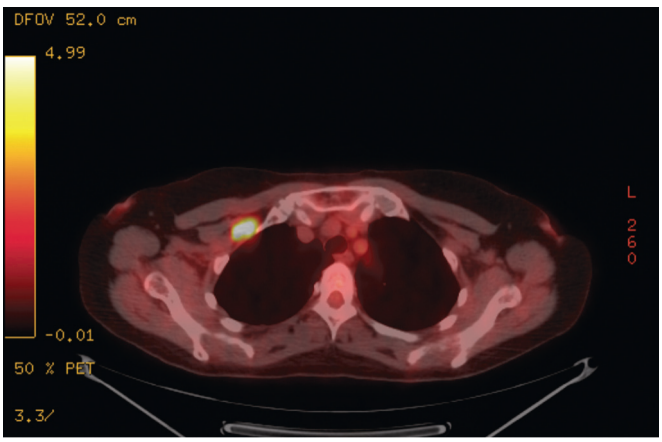


Figure G-2 Axial PET/CT slice of a patient with a right breast cancer that involved the level III axilla and infraclavicular fossa. The involved lymph node is below and medial to the pectoralis minor muscle. *CT,* computed tomography; *PET,* positron emission tomography.

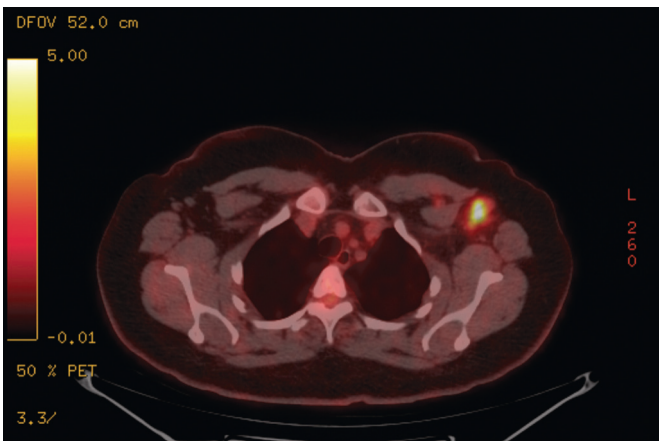


Figure G-3 Axial PET/CT slice of a patient with a left breast cancer that involved the level I axilla and Rotter's lymph nodes. The level I adenopathy is located lateral to the pectoralis minor muscle, and the involved Rotter's lymph nodes are anterior to the pectoralis major muscle. *CT,* computed tomography; *PET,* positron emission tomography.

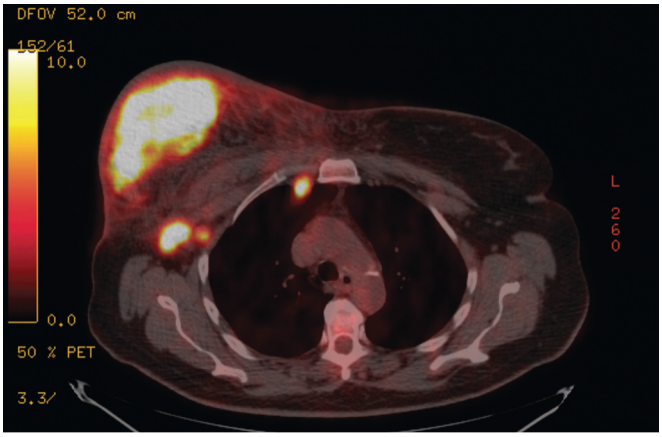


Figure G-4 Axial PET/CT slice of a patient with an inflammatory carcinoma of the right breast showing increased activity diffusely through the breast and involvement of both axillary level I and internal mammary lymph nodes. *CT*, Computed tomography; *PET*, positron emission tomography.

will have recurrence in the supraclavicular fossa if this region is not treated.[3] However, a recent study indicated that specific subsets of patients with one to three positive axillary lymph nodes may be at higher risk of recurrence in the supraclavicular fossa and may therefore benefit from treatment to this region. Those subsets include patients with high-grade disease, estrogen receptor–negative disease, and younger patients.[4] Disease that presents with involvement of supraclavicular lymph nodes at diagnosis has a particularly poor prognosis and represents the highest-risk category of nodal disease.

When designing radiation fields, a comprehensive understanding of anatomic relationships in the area to be targeted is essential for the radiation oncologist. Contouring, the process by which the target is delineated from normal tissue is subject to significant levels of inter- and intraobserver variability in terms of accuracy and reproducibility.[5] Guidelines have been developed for high-risk breast cancer to reduce this variability and to guide the delineation of the primary and lymph node clinical target volumes.[6] A recent advance in radiation treatment planning is the use of automated atlas based segmentation (AABS), a technology that uses CT-based atlases as a template to help delineate target volumes with more consistency.[7-9] This technology allows for increased reproducibility among radiation oncologists in delineating the regions of interest.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality Rates

The American Cancer Society estimated that in 2013 an estimated 232,340 new cases of invasive breast cancer and 39,620 breast cancer deaths would occur[10] making it the second-leading cause of cancer-related deaths in women, exceeded only by lung cancer. Historically, the increase in breast cancer incidence was thought to be a reflection of changes in reproductive patterns, such as delayed childbearing and giving birth to fewer children, which are recognized as risk factors.

Starting in the early 1980s, the incidence of breast cancer among older women began rising as a result of improved detection with the widespread use of mammography. The rates stabilized in the late 1990s and then started to decrease; it has been hypothesized that the decline occurred because of a reduced use of hormone replacement therapy following the 2002 publication of the Women's Health Initiative randomized trial results.[11,12] In contrast the incidence of breast cancer in younger women has remained stable. Although breast cancer is a rare disease in young women, it is the most common cancer occurring in the age group. When it occurs in women younger than 35, it brings forth unique clinical challenges for the clinician and personal challenges for the patient, especially when associated with pregnancy.[13,14]

With a rapidly aging population in the United States, the number of breast cancers is expected to increase over the next 20 years. Fortunately, breast cancer mortality rates have declined continuously since 1990, probably because of screening leading to early detection and advances in multidisciplinary treatment.[15] Survivorship is a growing issue and research into the late effects of treatment is of relevance given that more than 2.9 million U.S. women with a history of breast cancer are expected to be alive in 2012.[16]

Risk Factors

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (1 in 8 women).[10] Table G-2 lists risk factors for developing breast cancer. The strongest risk factor for breast cancer is being female; only about 1% of all new breast cancer cases occur in men.[10] The second-most important risk factor is an individual's age, with 95% of all new breast cancer cases developing in women aged 40 years or older.[10] The annual risk of developing breast cancer increases exponentially from age 40 until menopause, at which time the rate of increase in annual risk slows considerably. After the age of 80, the annual incidence of breast cancer begins to show a slight decline. The risk of developing breast cancer as a function of age for females is shown in Table G-3.

The risk of breast cancer development is influenced by estrogen exposure over the course of one's life. Specifically, risk factors for breast cancer development include young age at menarche, nulliparity or older age at first pregnancy, and older age at menopause. In a large study of Swedish women, the risk of breast cancer increased approximately 13% for every 5-year increase in age at first birth.[17] Postmenopausal estrogen replacement therapy also has been shown to increase the risk of breast cancer. In a meta-analysis of 51 studies that included 52,705 women with breast cancer and 108,411 women without breast cancer, receipt of postmenopausal hormone replacement therapy was found to increase the annual relative risk of developing breast cancer by 2.3% for each year of hormonal therapy.[18] In 2000, a study of 46,000 women reported that the combined use of estrogen and progesterone increased the relative risk of breast cancer by 8% compared with the risk in nonusers, whereas the use of estrogen alone increased the relative risk by only 1%.[19] These data have been confirmed by two large prospective studies conducted through the Women's Health Initiative.[20,21]

Many patients and family members are interested in whether they can modify their risk for developing breast cancer through diet or exercise, or both. Evidence in support of any association between dietary fat content and breast cancer development has been weak and inconsistent.[22,23] Because of conflicting findings, it has been difficult to make strong nutritional recommendations for breast cancer prevention. Use of omega-3 polyunsaturated fatty acid (PUFA) supplements has gained attention in preclinical studies as a potential protectant against breast cancer.[24] In contrast, alcohol intake seems to be more consistently associated with increased breast cancer risk.[25,26] Exercise and body weight have a moderate impact on breast cancer risk. Relatively large studies have demonstrated that daily exercise, particularly early in life, can reduce the risk of breast cancer for both premenopausal and

TABLE G-2 Breast Cancer Risk Factors

Risk Factors Used in the National Cancer Institute Breast Cancer Risk Assessment Tool*	Other Known Risk Factors	Unlikely Risk Factors
Personal history of lobular carcinoma in situ or ductal carcinoma in situ	Female sex	Higher fat intake
Older age	Personal history of breast cancer	Fibrocystic breast disease
Family history of breast cancer and number of first-degree relatives with breast cancer	Germ-line mutation in *BRCA1* gene or *BRCA2* gene	Fibroadenoma
Nulliparity and age at first birth	Higher alcohol consumption	Simple breast cysts
Older age at menarche	Low amounts of exercise	Use of oral contraceptives
History of a breast biopsy and number of breast biopsies	Use of hormone replacement therapy	Use of tobacco
Personal history of atypical ductal hyperplasia	History of radiation treatments to the chest for Hodgkin's disease	
White race	Lack of breast-feeding	

*See also www.cancer.gov/bcrisktool.

TABLE G-3 Risk of Being Diagnosed with Breast Cancer in 10, 20, and 30 Years and in the Remaining Lifetime*

Current Age	+10 yrs	+20 yrs	+30 yrs	Eventually
0	0.00	0.00	0.05	13.39
10	0.00	0.05	0.49	13.54
20	0.05	0.49	1.95	13.57
30	0.44	1.91	4.57	13.59
40	1.49	4.18	7.64	13.31
50	2.79	6.36	9.77	12.21
60	3.83	7.49	9.63	10.11

yrs, *Years.*
**Given cancer-free status at the current age, lifetime risk (%) of being diagnosed with cancer was determined according to 12 Surveillance, Epidemiology, and End Results (SEER) areas; the lifetime risk of dying of cancer was 2.98% (determined for U.S. totals, 1999 to 2001).*

postmenopausal women.[27,28] Some recent evidence suggests that exercise and body weight can influence the outcome after breast cancer treatment as well.[29,30]

Genetic Factors and Breast Cancer Etiology

Breast cancer develops from breast epithelial tissue with abnormalities in several cellular processes as a result of genetic and epigenetic events. Some patients have inherited germ-line genetic conditions, such as a mutation in a relevant tumor suppressor gene, but in most cases the genetic events leading to breast cancer are somatic or sporadic. Approximately 20% to 25% of women diagnosed with breast cancer have a family history of the disease, and approximately 10% of patients have a family history showing an autosomal dominant pattern of breast cancer inheritance.

Epidemiologic studies of families with a history of breast cancer led to the discovery of germ-line mutations in two important tumor suppressor genes, the *BRCA1* and *BRCA2* genes. Individuals who inherit a mutation in the *BRCA1* gene or *BRCA2* gene from one of their parents have a high lifetime risk of developing a breast cancer that is associated with certain aggressive tumor characteristics. Mutation in the *BRCA1* gene is associated with triple negative cancers, medullary cancer, young age at diagnosis, and ovarian cancer.[31] Patients with mutations in the *BRCA2* gene more commonly develop ER-positive breast cancer, and although they are still at increased risk of ovarian cancer relative to the general population, this risk is less than for those with the *BRCA1* gene mutation. The *BRCA2* gene is also associated with male breast cancer.[31] Table G-4 highlights the main features of BRCA-linked tumors and the prevalence of second malignancies in *BRCA1* and *BRCA2* gene mutation carriers.[13,32-35]

The mutations of interest are point mutations that are found during traditional Sanger sequencing of the *BRCA1* and *BRCA2* genes. Large rearrangements in BRCA1 and BRCA2 (BART) occur in a small percentage (<1%) of all patients tested for hereditary breast or ovarian cancer syndrome.[36] Since 2008, BART testing has been included as part of Comprehensive BRCA*analysis* tests for patients with a strong personal and family history of breast and ovarian cancer and in individuals meeting criteria for automatic BART testing, the prevalence of mutations in a high-risk population is higher (7.5%) than in the normal population.[37]

For all patients diagnosed with breast cancer, a preliminary risk assessment should be performed to determine if a more formal evaluation is needed. The degree of risk for a familial syndrome increases with the number of affected family members, the closeness of the relationship, and the younger the age at diagnosis of the affected member.[38] Formal risk assessment and genetic counseling takes into account a detailed family pedigree, an evaluation of the patient needs and concerns, and the past medical and surgical history as well as any active cancer diagnoses.

The National Cancer Center Network (NCCN) panel recommends that patients with a personal history of breast cancer in addition to one or more of the criteria listed in Box G-1 should undergo testing. Furthermore, mutations should be suspected and tested for in cases of male breast cancer at any age, ovarian cancer at any age, and in high-risk ethnic backgrounds (e.g., Ashkenazi Jewish heritage). In addition to hereditary breast and ovarian cancer syndrome (BRCA1/BRCA2), advances in molecular genetics have identified several genes associated with an inherited susceptibility to breast cancer (e.g., *PTEN*, *TP53*, *CDH1*) and identification of a mutation has implications for prevention, screening, and treatment.[39]

New genetic testing panels use next-generation sequencing to detect hereditary breast, ovarian, and other cancer for patients who have tested negative for high penetrance genes such as *BRCA1* and *BRCA2* in light of a suggestive family history. These panels should not be routinely ordered without an expert cancer geneticist consultation as guidelines on risk assessment and management of variant mutations is not clearly defined.

Breast Cancer Screening

Breast cancer screening is performed in asymptomatic women so that disease can be detected earlier. Irrespective of risk level,

TABLE G-4 Features of BRCA-Linked Tumors

	BRCA1	*BRCA2*
Tumor biology	High proliferation rates Low differentiation Increased prevalence of grade-3 tumors Reduced ER/PR expression Increased rate of p53 mutations Higher degree of aneuploidy Reduced Her2/neu expression	Higher frequency of medullary tumor Increased rate of p53 mutation Higher degree of aneuploidy Reduced HER2/neu expression
Estimated lifetime breast cancer risk	47%-66%	40%-57%
Female breast cancer risk according to age	2% by age 30 20% by age 40 37% by age 50 55% by age 60	Same as *BRCA1*
Ovarian cancer risk	21% by age 50 40% by age 60	2% by age 50 6% by age 60

Adapted from references 13, 32, and 35.
ER, *Estrogen receptor;* HER2, *human epidermal growth factor receptor 2;* PR, *progesterone receptor.*

BOX G-1 Hereditary Breast and Ovarian Syndrome Testing Criteria

HEREDITARY BREAST AND OVARIAN SYNDROME TESTING CRITERIA (*BRCA1/BRCA2*)

A personal history of breast cancer plus one or more of the following:

1. Diagnosed at age 45 or younger
2. Having two breast primaries with the first breast cancer diagnosed at younger than age 50
3. Diagnosed at younger than age 50 with one or more close relative with breast cancer at any age.
4. Diagnosed with triple negative breast cancer at younger than age 60
5. Diagnosed at any age with two or more close relatives with breast cancer at any age; diagnosed at any age with one or more close relative with epithelial ovarian cancer diagnosed at any age
6. Diagnosed at any age with 2 or more close relatives with pancreatic or aggressive prostate cancer (Gleason ≥7) at any age

Adapted from Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines 2014. Accessed on 2/21/14.

a routine physical examination including a clinical breast examination (CBE) should be performed in all women. Following a complete medical history, women may be stratified into two risk groups: those at average risk and those at increased risk to determine further testing. Although controversies are unresolved regarding the timing interval of screening and the benefit of screening in particular age groups (i.e., ages 40 to 49), it is recommended that average risk women age 40 or older should undergo yearly screening bilateral mammogram based on a consensus statement from the American Cancer Society.[40-43] In the guidelines, there is no strict upper age limit for screening. However, if a patient has severe comorbidities that limit her life expectancy and if no intervention will be planned on the basis of the screening findings, then a recommendation should be made against screening in those clinical situations.

Much of the controversy over breast cancer screening stems from the concern that mammography may be overdiagnostic. This term refers to the fact that some cancers detected at screening may grow so slowly or not at all and that they may never result in death even if left undetected and untreated.[44] In these cases, patients are being subjected to unnecessary biopsies, surgeries, radiation therapy, and subsequent systemic treatments. This results in psychosocial and financial costs for patients, families, and society at large.

Table G-5 shows the recognized risk factors that place women at a higher risk of breast cancer and highlights the appropriate screening recommendations for them. The modified Gail model is a risk assessment tool, which calculates the 5-year and lifetime predicted risk of developing invasive breast cancer as a function of several known risk factors.[45,46] However, this risk tool should not be used in women with a predisposing gene mutation, a strong family history, a history of prior thoracic radiation, or for those with lobular carcinoma-in situ (LCIS). Additionally, models that rely on family history (i.e., Claus,[47] Tyrer-Cuzick,[48] and BRCAPRO[49]) can identify women with a greater than 20% lifetime risk of breast cancer based on these models and are instrumental in directing screening and identifying women who are candidates for risk reduction strategies.

The routine use of magnetic resonance imaging (MRI) screening for the general population is not recommended because of the high cost and high false-positive rate associated with MRI. Among the high-risk populations, clear evidence exists to recommend annual MRI screening in addition to mammography for BRCA carriers. In general, screening for hereditary breast cancer begins at age 25 and includes annual mammography, annual breast MRI, and biannual clinical breast exams. Because of the high incidence of "interval" cancers in BRCA carriers, alternating the imaging techniques (mammogram and MRI) every 6 months is suggested to attempt to provide more coverage. Women who received radiation treatment for prior diagnosis of lymphoma are screened similarly with mammography and MRI starting 10 years after completing radiation. Other high-risk characteristics such as a personal previous history of breast cancer, LCIS, or average familial risk do not warrant the adjunct use of MRI.

Breast Cancer Prevention Strategies

Women who are at increased risk of developing breast cancer can reduce this risk through prevention strategies. Specific lifestyle changes with the potential to modify risk include reducing or eliminating alcohol consumption, maintaining ideal weight, and exercising on a regular schedule. All women regardless of age or risk status should be recommended to

TABLE G-5 Breast Cancer Screening: Increased Risk Category

High-Risk Factor	Screening Recommendation
Prior history of breast cancer, Hx of lobular carcinoma in situ (LCIS) or familial risk	Encourage breast awareness, CBE every 6-12 months, annual mammography
≥35 years of age with a 5-year risk of invasive breast carcinoma ≥1.7% by Gail Model*	Encourage breast awareness, CBE every 6-12 months, annual mammography
Lifetime risk of breast cancer >20% based on family history models	Encourage breast awareness beginning at age 30, CBE every 6-12 months, annual mammogram; consider reduction strategies
History of previous therapeutic thoracic radiation (e.g., mantle radiation) between the ages of 10-30 years	Age ≥25: encourage breast awareness, annual mammograms, annual MRI as adjunct to mammograms, to be initiated 8-10 years after radiation exposure or at age 40, whichever comes first Age <25: encourage breast awareness, risk counseling, and annual CBE; annual mammography and MRI to be initiated 8-10 years after radiation exposure
Known genetic predisposition	Encourage breast awareness, CBE every 6-12 months, annual mammography, annual MRI; begin screening at age 25
Family history pedigree suggestive of genetic predisposition	Encourage breast awareness, CBE every 6-12 months, annual mammography, annual MRI; begin screening 10 years earlier than age of youngest woman in family diagnosed with breast cancer, but no later than age 40

From Breast Cancer Screening and Diagnosis. NCCN Guidelines 2014. Accessed on 2/21/14.
CBE, *Clinical breast examination;* Hx, *history;* MRI, *magnetic resonance imaging.*
**Risk Assessment by the Gail Model includes current age, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race.*

maintain a healthy lifestyle. Pharmacologic strategies that affect estrogen and progesterone signaling pathways can also reduce the risk of developing breast cancer. Risk reduction surgeries (i.e., bilateral total mastectomy or bilateral salpingo-oophorectomy) may be beneficial in select high-risk groups.

Risk Reduction Agents

Estrogen and the estrogen receptor (ER) are key regulators in the progression of breast cancer. Drugs that target ER are known as selective estrogen receptor modulators (SERMs) and were first approved as a treatment for metastatic hormone-receptor–positive breast cancer given its antagonistic effects on breast tissue. Tamoxifen is now routinely used to treat all stages of breast cancer. In adjuvant treatment trials, it has been noted that women who have been treated with tamoxifen for primary invasive disease have a lower incidence of ipsilateral and contralateral tumor recurrences.[50,51] This clinical finding as well as preclinical studies showing that tamoxifen has anti-initiator and antipromoter properties served as the basis for exploring the preventative effects of tamoxifen.[52,53]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial was a randomized placebo-controlled study of tamoxifen that enrolled 13,388 women predicted to have a 1.67% or higher risk of developing breast cancer within 5 years. The results showed that tamoxifen reduced the rates of invasive and noninvasive ER-positive breast cancer by 49% and 50%, respectively.[54] In the International Breast Cancer Intervention Study I (IBIS-I) trial, women at high risk were treated with tamoxifen for 5 years and were found to have a reduced incidence in ER-positive breast cancer by 48% with a persistent benefit for at least 10 years after discontinuing therapy.[55,56] Although highly effective for breast cancer prevention, a side effect profile including hot flashes, night sweats, vaginal symptoms, and more serious effects such as endometrial cancer and thromboembolism has been associated with tamoxifen use. The rate of endometrial cancer was higher in women over the age of 50, and the risk for thromboembolism increased with age as well. Because of tamoxifen-related side effects, efforts were undertaken to consider alternative agents. Raloxifene (another SERM) was evaluated and found to reduce the rate of invasive ER-positive breast cancers becoming available as an alternative option in women who are postmenopausal.[57,58] Based on the collective results of the tamoxifen and raloxifene clinical prevention trials, the STAR (P-2) trial, conducted by the NSABP, compared the effectiveness of treatment with tamoxifen or raloxifene for 5 years on reducing breast cancer risk in 19,474 women who were postmenopausal and high risk.[59] The long-term follow-up of the STAR trial showed that although there were fewer cases of thromboembolism and uterine cancers in the raloxifene group, it was ultimately less effective at prevention of invasive breast cancer.[60]

More recently, the portfolio of choices for prevention strategies among patients who are high risk and postmenopausal has been further expanded. Aromatase inhibitors such as letrozole, anastrozole, and exemestane block the biosynthesis of estrogen from androgens by inhibiting the aromatase enzyme, which results in a decrease of circulating estrogen levels in the serum, tissue, and tumor cells.[61] Aromatase inhibitors have been shown to be more effective at preventing breast cancer recurrence and reducing second breast cancers than tamoxifen in the adjuvant setting.[62-64] These data led to the evaluation of aromatase inhibitors in the preventative setting. Two randomized placebo-controlled trials have demonstrated that exemestane (a steroidal aromatase inhibitor) and anastrozole (a nonsteroidal aromatases inhibitor) appear to be more effective than placebo at reducing the incidence of invasive and ductal carcinoma in situ cancers in women who are postmenopausal.[65,66] It is important to note, however, that the effects of tamoxifen have been shown to last for at least 10 years, and further follow-up is needed in the IBIS-II and MAP.3 trials to evaluate whether the effects of exemestane and anastrozole on breast cancer risk reduction will be sustained. At the current time, for women who are older than 35 years of age and who are at increased risk of breast cancer, oncologists may select among the available pharmacological strategies for breast cancer risk reduction based on the patient's hormonal status and the side effect profile of the drug.[67] Table G-6 highlights the available pharmacologic breast cancer risk reduction strategies.

The diagnosis of ductal carcinoma in situ (DCIS) has become a more common entity since the widespread use of screening mammography has been adopted, and it is recognized to be a risk factor for development of invasive breast

TABLE G-6 Highlights from Select Pharmacological Breast Cancer Prevention Trials

Trial	Study Design	Patient Population	Results	Toxicity Pearls
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)				
Tamoxifen				
NSABP-P-1[54]	Tamoxifen vs. placebo	*N* = 13,388, HR, PPM	49% reduction in all BC	Decreased risk of bone fractures* Increased risk of thromboembolism† Increased risk of uterine cancer†
IBIS-I[55]	Tamoxifen vs. placebo	*N* = 7154, HR, PPM	27% reduction in all BC and 31% reduction in ER+BC	
Raloxifene				
MORE[57]	Raloxifene (60 or 120 mg) vs. placebo	*N* = 7705, NR, PM	65% reduction in all BC and 90% reduction in ER+BC	
CORE[58]	Extension of MORE	*N* = 5213‡	50% reduction in all BC and 66% reduction in ER+BC	
Tamoxifen vs. Raloxfene				
STAR-P-2[60]	Tamoxifen vs. raloxifene	*N* = 19,747, HR, PM	5 years: raloxifene = tamoxifen 81 months: raloxifene is 75% as effective as tamoxifen	Raloxifene: decreased risk of thromboembolism and uterine cancers compared to tamoxifen
AROMATASE INHIBITORS (AIS)				
Exemestane				
MAP3[65]	Exemestane vs. placebo	*N* = 4560, HR, PM	65% reduction in all BC at 3 years follow-up and 75% reduction in ER+BC	Increased risk of bone fractures, skeletal symptoms and vasomotor symptoms with AIs
Anastrazole				
IBIS-II[66]	Anastrazole vs. placebo	*N* = 6000, HR, PM	53% reduction in all BC at 5 years and 58% reduction in ER+BC	

AIs, *Aromatase inhibitors;* BC, *breast cancer;* ER+BC, *ER-positive breast cancer;* HR, *high-risk women;* NR, *normal-risk women;* PM, *post-menopausal;* PPM, *post-menopausal and pre-menopausal.*
**Tamoxifen has bone building effects.*
†*Increased risk of uterine cancer is more clinically relevant in older women (>age 50) with an intact uterus; increased risk of thromboembolism is worse in older age groups.*
‡*From MORE trial.*

cancer. It is unclear, however, which lesions will progress and develop invasive properties and which will not. Currently management of this entity includes a combination of surgical resection, radiation, and tamoxifen. For women with DCIS, the NSABP B-17 study reported a significantly better overall 5-year event-free survival attributed to a lower incidence of invasive and noninvasive ipsilateral breast cancer among women who underwent lumpectomy and radiation therapy compared to lumpectomy alone or lumpectomy and tamoxifen. The NSABP B-24 trial showed that the combination of lumpectomy, radiation, and tamoxifen was more effective in the prevention of invasive cancer in women with DCIS compared to lumpectomy and radiation alone.[68] A retrospective subset analysis of NSABP B-24 showed that women with ER-positive DCIS benefit from intervention with tamoxifen, whereas women with ER-negative disease do not.[69] Therefore, tamoxifen is recommended for women with ER-positive DCIS who have remaining breast tissue following locoregional management. Second-generation trials of endocrine therapy with aromatase inhibitors (NSABP-35 and International Breast Cancer Intervention Study II) have been limited to women with hormone-receptor positive DCIS.

Risk Reduction Surgeries

Bilateral risk-reduction mastectomy has a role in carefully selected patients after an appropriate workup, multidisciplinary consultation, and genetic counseling. Bilateral mastectomy is proven to be an effective risk reduction strategy for women with a germline mutation in the *BRCA1* or *BRCA2* gene.[70-72] When it is performed for the purpose of risk reduction, it should involve removal of all breast tissue. Axillary evaluation is not required unless there is invasive disease identified when the mastectomy specimen is evaluated pathologically.[73] For *BRCA 1* and *BRCA2* gene mutation carriers, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing as a highly effective preventative measure against ovarian cancer risk.[74]

Diagnostic Overview

In most cases, breast cancer is diagnosed after abnormalities are found on screening mammography or after detection of a palpable mass. Some patients may present with an isolated painless lump in the breast. Others may have discharge or bleeding from the nipple. In some, the mass may have gone unnoticed, ignored, or neglected for some time and the presenting signs and symptoms may include nipple retraction, pain, ulceration, inflammation, or malodor with fixation to the skin or chest wall on physical examination. All patients should undergo a careful history with attention given to risk factors and family history. Next, a detailed physical examination should be performed with focus on the involved breast, the opposite breast, all regional lymph node areas, the lungs, bone, and liver. Bilateral diagnostic mammography, including additional views that highlight the noted abnormality should be performed to assess the extent of involvement and to

evaluate for additional ipsilateral or contralateral disease. Most patients should also have diagnostic ultrasonography of the breast and regional lymph nodes to further delineate the locoregional extent of disease.

For patients with a suspicious abnormality on physical examination or on mammography or sonography, tissue from the abnormality should be obtained to rule out cancer. The recommended biopsy procedure is a percutaneous core biopsy usually done under sonographic guidance. For patients who present with suspicious calcifications that cannot be well visualized with sonography, a stereotactic biopsy is recommended. A stereotactic biopsy is done under mammographic localization. In any biopsy procedure, it is important to leave a clip or other marker near the abnormality to help localize the tumor bed for subsequent surgery. Once the diagnosis of breast cancer is established further pathological testing should be done on the tumor tissue to determine important features such as histology, grade, presence of lymphovascular invasion, and receptor status (ER), progesterone receptor [PR], and HER2/neu receptor). Fine-needle aspiration of any suspicious regional lymph nodes can also be valuable for determining the initial extent of disease. When indicated, appropriate staging studies should be performed to rule out the presence of distant metastatic disease. However, most patients with early-stage disease do not require staging studies.

STAGING

Breast cancer is staged according to the size and characteristics of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of metastatic disease (M).

Table G-7 shows the breast cancer staging system from the seventh (2010) edition of the *American Joint Committee for Cancer (AJCC) Staging Manual*.[75] That system comprises both a clinical staging system, based on physical examination and radiographic studies, and a pathologic staging system, based on examination of surgical specimens. Pathologic staging after initial systemic treatments before surgery should be annotated with a *yp* before the assigned stage. All practitioners involved in breast cancer care should be familiar with the AJCC staging

TABLE G-7 American Joint Committee on Cancer Staging System for Breast Cancer[75]

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular ductal carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor[a]
T1	≤2 cm in greatest dimension
T1mi	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor >0.1 cm but not >0.5 cm in greatest dimension
T1b	Tumor >0.5 cm but not >1 cm in greatest dimension
T1c	Tumor >1 cm but not >2 cm in greatest dimension
T2	Tumor >2 cm but not >5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to the chest wall, not including only pectoralis muscle invasion
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin modules confined to the same breast
T4c	Both (T4a and T4b)
T4d	Inflammatory carcinoma
REGIONAL LYMPH NODES (N)	
Clinical Disease	
NX	Regional lymph node(s) cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I to II axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent[b] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically apparent[b] ipsilateral internal mammary lymph nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastases in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[b] ipsilateral internal mammary node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

TABLE G-7 American Joint Committee on Cancer Staging System for Breast Cancer—cont'd

Pathologic Disease (pN)[c]			
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)		
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells[d]		
pN0(i–)	No regional lymph node metastasis histologically, negative immunohistochemical staining		
pN0(i+)	Isolated tumor cells identified histologically or by positive immunohistochemical staining, no cluster >0.2 mm		
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[e]		
pN0(mol+)	No regional lymph node metastasis histologically or by immunohistochemical staining, positive molecular findings (RT-PCR)e		
pN1	Metastasis in 1 to 3 axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1mi	Micrometastasis (>0.2 mm or >200 cells, none >2 mm)		
pN1a	Metastasis in 1 to 3 axillary lymph nodes		
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1c	Metastasis in 1 to 3 axillary lymph nodes[g] and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN2	Metastasis in 1 to 3 axillary lymph nodes or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit >2 mm)		
pN2b	Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis		
pN3	Metastases in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes		
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit >2 mm), or metastasis to the infraclavicular lymph nodes		
pN3b	Metastasis in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes		
DISTANT METASTASIS (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
cM0(i+)	No clinical or radiographic evidence of distant metastasis but molecular or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue no larger than 0.2 mm in a patient without symptoms		
M1	Distant metastasis		
STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1[h]	N0	M0
Stage IIA	T0	N1	M0
	T1[h]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[h]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al, eds: AJCC cancer staging manual, ed 3, New York, 2010, Springer, pp 345–376.

[a]*Paget's disease associated with a tumor is classified according to the size of the tumor.*

[b]Clinically apparent disease *is defined as disease detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or is disease that is grossly visible pathologically.*

[c]*Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(i+)(sn).*

[d]*Isolated tumor cells are defined as single tumor cells or small cell clusters ≤0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin staining. Isolated tumor cells do not usually show evidence of metastatic activity (e.g., proliferation or stromal reaction).*

[e]*Reverse transcriptase-polymerase chain reaction.*

[f]Not clinically apparent disease *is defined as disease not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.*

[g]*If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.*

[h]*T1 includes T1mic.*

system, and it is critical that each case be assigned a tumor-nodes-metastasis (TNM) stage before any treatment is begun. For patients with clinical stage I or II disease, the staging workup should include a physical examination, diagnostic mammography, ultrasonography, and routine serum studies. For patients with locally advanced disease, screening tests for metastatic disease should include a bone scan and liver imaging with CT or PET/CT.

The TNM staging of breast cancer has evolved over time. Some of the more important changes in recent staging systems have included:

- Considering the number of positive lymph nodes in assigning the pathologic N stage
- Considering the size of positive lymph node metastasis in assigning the pathological N stage (micrometastasis versus macrometastasis)
- Changing involvement of infraclavicular lymph nodes from N1 to N3 disease
- Changing involvement of supraclavicular lymph nodes from M1 to N3 disease
- Considering isolated tumor cells detected with immunohistochemical staining of sentinel lymph nodes, which is denoted as N0(i+)

Although it is important to establish the clinical stage before breast cancer, this is preliminary and following surgery a more definitive stage will be decided based on pathological examination of the postsurgical specimen. The pathologic stage is important for prognosis, to understand tumor biology, and to direct future systemic therapies. In up to one third of patients who have no clinically evident axillary nodes at diagnosis, histological examination of the nodes after surgery reveals cancer.

BREAST CANCER BIOLOGIC CHARACTERISTICS

Breast cancer is a biologically heterogeneous disease. Recent advances in genomics and molecular biology techniques have permitted more comprehensive assessments of its genetic heterogeneity. DNA microarray expression profiles have led to classification of breast cancer into molecular subtypes that correspond with distinct prognostic groups based on biology and aggressiveness of the disease.[76,77] Interestingly, these molecular classes are strongly influenced by the genes controlling expression of the ER and HER2/neu receptor.

Molecular Classification

The molecular profiles of estrogen-enriched cancers tend to be similar to those of luminal ductal cells, whereas estrogen-negative breast cancers have molecular phenotypes similar to cells in the basal layers of the breast ductal epithelium. Tumors that overexpress HER2/neu have unique signatures. Recent molecular classifications often group diseases into four classes that overlap but are not synonymous with variations in ER, PR, and HER2/neu status: luminal A tumors, which include most ER-positive, PR-positive, HER2-negative tumors; luminal B tumors, which include most ER-positive, PR-positive, HER2-positive tumors; HER2 tumors, which include most ER-negative, PR-negative, HER2-positive tumors; and, finally, basilar cancers, which overlap significantly with triple-negative (ER-negative, PR-negative, HER2-negative) breast cancers.

Luminal A disease expresses more ER-related genes, carries the best prognosis and predicts response to hormonal therapy. Luminal B tumors express more cellular proliferation and HER2-related genes and often have a higher grade and a worse prognosis compared to luminal A. A subgroup (30% to 50%) of basal-type cancer tends to be chemoresponsive but is nevertheless an aggressive molecular subtype with an overall poor prognosis. Finally, the inherent aggressive biology of HER2-positive disease has been transformed with the use of trastuzumab and other HER2-directed therapies—lapatinib, pertuzumab, and recently ado-trastuzumab. Increasing numbers of reports suggest that molecular subtypes and genetic factors can also affect the outcome after radiation and other locoregional treatments. For patients treated with breast conservation, recent studies from Harvard, British Columbia, and the M. D. Anderson Cancer Center suggest that triple-negative or basilar-like cancers are at increased risk of local recurrence after treatment with lumpectomy and whole-breast radiation.[78-80] These findings are consistent with reports from the Danish randomized trials and the M. D. Anderson Cancer Center indicating that triple-negative disease is also associated with locoregional recurrence after postmastectomy radiation.[81,82]

Predictive Markers and Selection of Therapy

In addition to classification, molecular markers are used to select patients for systemic treatment (e.g., chemotherapy, endocrine therapy, and targeted therapy) and to predict those who are most likely to benefit from the therapies. The quintessential example of a predictive marker is ER; since its discovery, all breast tumors are pathologically assessed for ER and patients with ER-positive tumors benefit from antihormonal treatments such as tamoxifen. A second important predictive factor was discovered in 1985 as the HER2 or erbB2 protein and is found to be amplified in 20% of breast cancers leading to protein overexpression.[83,84] HER2/neu is a transmembrane cell surface receptor with an internal domain that activates downstream signaling pathways. Overexpression has been associated with increased proliferative capacity, enhancement of metastatic potential, and increased rate of tumorigenesis. Trastuzumab is a humanized monoclonal antibody against the extracellular domain of the surface receptor and is an effective treatment in HER2–positive breast cancer in both the metastatic and adjuvant settings (adjuvant therapy as discussed later).[85] HER2 testing by immunohistochemistry to measure protein expression or fluorescent in situ hybridization (FISH) to measure HER2 gene copies is standard for all breast tumors and is predictive of response to targeted therapy.[86]

Furthermore, gene products may be combined to provide a picture of the molecular phenotype of the individual's cancer and thereby predict recurrence or response to chemotherapy. The Oncotype DX assay (Genomic Health) is a 21-gene recurrence score assay that was originally designed to predict the recurrence of ER-positive, node-negative breast cancer after treatment with adjuvant endocrine therapy. The test estimates 10-year risk of recurrence using formalin-fixed, paraffin-embedded tumor tissue. The gene expression is analyzed and a risk score (RS) is assigned based on a weighted algorithm. The assay was validated in 668 patient samples from patients treated with ER-positive, node-negative, tamoxifen who were enrolled in the NSABP B-14 clinical trial.[87] It has now been clinically adopted to determine whether women with high-risk, node negative, HER2-negative, ER-positive breast cancer should receive adjuvant chemotherapy in addition to endocrine therapy (see discussion in this chapter) as it is able to predict the magnitude of benefit.[88]

The assay categorizes patients into three risk groups: (1) A low-risk group (RS, 0-18), distant recurrence risk of less than 10%; (2) intermediate-risk group (18 < RS < 31), distant recurrence risk between 10% and 20%; (3) high-risk (RS > 31), distant recurrence risk greater than 20%. Chemotherapy is generally recommended for patients with intermediate and

high risk for recurrence.[89] Other multigene assays have been identified such as Mammaprint and PAM50; however, Oncotype-DX is widely used in the United States because of its practical attributes and ability to predict response to chemotherapy.

The prognostic and predictive capabilities of the Oncotype DX assay are continually being evaluated. In the prospective, randomized TAILORx clinical trial, patients assigned an intermediate RS were randomized to receive either chemotherapy and hormonal therapy or hormonal therapy alone. This trial enrolled more than 11,000 patients and closed to accrual in October 2010. Results are eagerly anticipated and will refine the utility of the test for the intermediate-risk group. A similar trial for patients who are node-positive (RxPONDER; SWOG S1007) is currently enrolling patients to determine whether there is a subset of patients who are node-positive, HER2-negative, hormone receptor–positive who may be spared from chemotherapy. As discussed later in this chapter, according to current guidelines, patients who are node-positive should be offered chemotherapy outside of a clinical trial.[89]

TREATMENT OVERVIEW

For invasive breast cancer in stages I to III, the goals of treatment are curative. Treatment decisions are ultimately made with regard to patient comorbidities, after weighing the potential benefits and harms of therapy, and based on the patient's personal preferences. Often, several extended discussions between the patient and a multidisciplinary team including medical oncology, surgical oncology, plastic surgery, and radiation oncology are needed to determine the best treatment plan. Multimodality therapy (Figure G-5) has had a profound impact on the outcomes of breast cancer because it has allowed for improved disease-free survival and overall survival.

Locoregional Treatments

Surgery and radiation have important roles in the curative management of most breast cancers and greatly determine the level of local control achievable. For patients with early-stage invasive disease, surgery can either be a breast-conserving resection of the primary tumor (e.g., a lumpectomy, segmental mastectomy, wide local excision) or a mastectomy. As highlighted in the subsequent chapter on early-stage breast cancer, numerous randomized prospective clinical trials have indicated that breast-conserving surgery with whole-breast radiation provides long-term outcomes equivalent to those of mastectomy. The goal of breast-conserving surgery should be to remove the primary tumor with surgical margins that are free from either invasive or in situ disease. A secondary goal is to provide the best possible cosmetic outcome, without retraction, nipple displacement, or excess volume loss from the procedure. For some women with larger breasts, several centers are now advocating oncoplastic surgery, in which local tissue rearrangements are performed at the time of surgical resection to maintain optimal breast aesthetics.[90,91]

Breast Surgery

Mastectomy is performed when the tumor is too large or locally advanced to allow breast conservation, although neoadjuvant systemic therapy can sometimes convert a patient into becoming eligible for breast-conserving surgery. Furthermore, mastectomy is indicated if the tumor is multicentric or multifocal, if the patient has a contraindication to radiation therapy, if the lesion is an ipsilateral recurrence in a previously irradiated breast, or if margin-free status cannot be achieved. Mastectomy is also a highly effective local treatment modality for early-stage disease and often precludes the need for radiation if the patient has lymph node-negative disease.

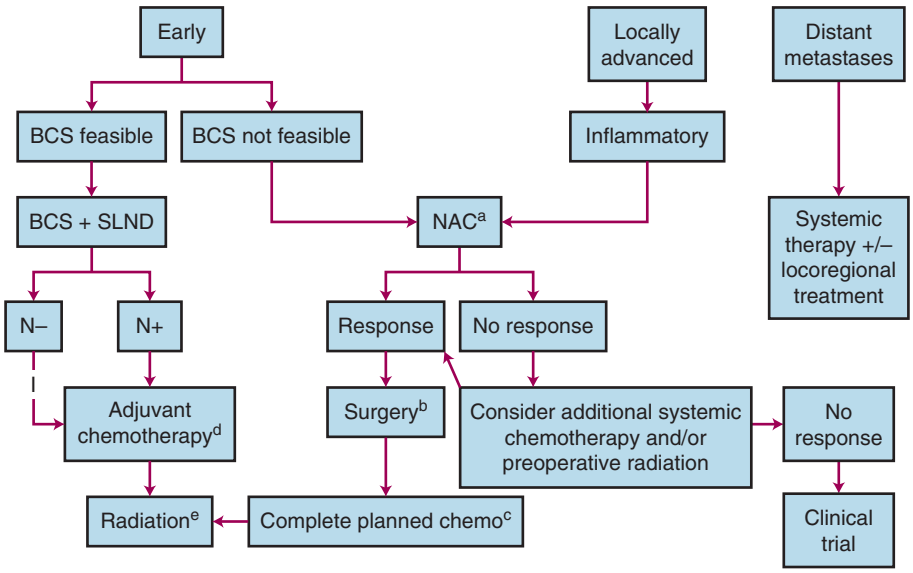


Figure G-5 Overview of multimodality therapy for breast cancer. *ALND,* axillary lymph node dissection; *BCS,* breast-conservation surgery; *ER,* estrogen receptor; *NAC,* neoadjuvant chemotherapy; *PR,* progesterone receptor; *SLND,* sentinel lymph node dissection. [a]Anthracycline- and taxane-based therapy is preferred. For Her2-positive tumor, add dual anti-HER2 blockade to the taxane portion. [b]The extent of surgery is determined by response but always includes an ALND. In inflammatory breast cancer, the surgery is always mastectomy + ALND. [c]Complete planned chemotherapy regimen if not completed preoperatively. Add endocrine treatment if ER-positive or PR-positive. Complete up to 1 year of trastuzumab in HER2-positive disease; may be administered concurrently with radiation therapy and with endocrine therapy if indicated. [d]Adjuvant chemotherapy is indicated in triple negative and HER2-positive tumors >5 mm. In hormone receptor–positive, HER2-negative tumors, chemotherapy is beneficial in patients with a high recurrence score on Oncotype-DX testing and is currently offered as standard of care in patients with intermediate recurrence score. [e]Whole-breast radiation with or without chest wall and lymph node basins as clinically indicated. For inflammatory breast cancer, radiation should include chest wall, level I/II axillary lymph nodes, supraclavicular nodes, and internal mammary lymph nodes if involved.
Adapted from NCCN guidelines and the ASCO-SEP Medical Oncology Self-Evaluation Program.

Skin-sparing mastectomy can preserve significant breast skin, which can allow plastic surgeons to use the breast's natural scaffolding to optimize the cosmetic results of an immediate reconstruction. If the normal inframammary sulcus is maintained, the breast can be reconstructed with excellent symmetry to the contralateral breast. Immediate breast reconstruction can be performed at the time of mastectomy for patients with noninvasive or early-stage disease and can be accomplished with tissue expanders and implants or autologous tissue flaps. Reconstruction may also be delayed for a period of up to 1 to 2 years.

Axillary Management

In addition to treating the primary breast tumor, surgery is important for staging and treatment of the axillary lymph nodes. For patients with invasive disease but no clinical evidence of spread to axillary lymph nodes, sentinel lymph node surgery is the gold standard approach for initial axillary disease staging. Sentinel lymph node biopsy is based on the concept that there is a reproducibly identifiable node (or nodes) that drains the breast and predicts the status of the remaining axillary lymph nodes.[92] This procedure entails injection of azusulfan blue dye or a radiocolloid, or both, into the periareolar or peritumoral subcutaneous tissue. Drainage to the first-echelon lymph nodes in the axilla is then detected by visual inspection of afferent lymphatic channels to a blue node or by use of a handheld gamma probe to detect lymph nodes showing radioactivity. Randomized trials have indicated that sentinel lymph node surgery is highly accurate, with identification and detection rates of 97%, equivalent to those of standard axillary dissection.[93] Axillary recurrence rates are less than 1% after a negative sentinel lymph node biopsy.[94] Currently, sentinel lymph node biopsy is the standard of care for staging the axilla in women with T1-T3, clinically node negative breast cancer.

The sentinel lymph node biopsy procedure represents a significant advance in surgical management that reduces the morbidity of axillary dissection in patients with node-negative disease by reliably differentiating between patients who are node-negative and node-positive disease. One of the main clinical questions after standardization of this approach is to ask whether there is a need for axillary dissection for local control and survival in the era of multimodality therapy. The ACOSOG Z11 trial randomized women with clinically node-negative with cancer <5 cm in size and positive sentinel lymph node(s) (<3 in number) treated with lumpectomy and radiation to completion axillary dissection versus no further surgery. At a median follow-up of 6 years, there were no differences in local control or survival between the groups.[95] Although these results are impressive, much discussion has occurred and the consensus is that further investigation is necessary. A key question is whether whole breast radiation played any role in the low recurrence rates and whether the axilla was actually untreated as all patients in the study received adjuvant breast radiation as a part of their breast-conservation surgery. Furthermore, long-term follow-up is needed as the majority of patients in the Z11 study had ER-positive, HER2/neu–negative postmenopausal disease making them more susceptible to late recurrences. Given that axillary burden is a reflection of tumor biology, these results should be applied within context and carefully to a select group of women who meet the Z11 criteria (Box G-2).[96] In patients who meet the strict criteria for the trial, discussion of these data should ensue with a focus on the questions that remain and the need for long-term follow-up.[97]

Radiation

The role of radiation in the locoregional management of breast cancer is reviewed in the three chapters on ductal carcinoma in situ, early-stage invasive disease, and locally advanced disease. Investigations of the use of radiation for breast cancer date back to some of the first randomized prospective trials in medicine, conducted during the 1950s and 1960s. As such, radiation is one of the most comprehensively investigated aspects of breast cancer care. A unique aspect of these investigations is that the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in Oxford, England, which has done meta-analyses of the compiled data every 5 years, has centralized all of the data from each randomized trial investigating radiation treatments. Data from the EBCTCG analyses have yielded important and conclusive information about the benefits and risks of radiation treatments for breast cancer. For many decades, radiation was clearly shown to reduce the probability of locoregional recurrence for patients treated with breast-conserving surgery and for patients with positive lymph nodes who underwent mastectomy. The 2005 publication of the EBCTCG meta-analysis, which was able to assess 15-year outcome data, further demonstrated that use of radiation could reduce rates of breast cancer death and improve overall survival rates.[98] Included in that study were individual patient data from 42,080 patients with breast cancer treated in 78 clinical trials that investigated locoregional treatments between 1952 and 1995. Among those patients were 7311 patients treated in 10 trials comparing radiation versus no radiation after breast-conserving surgery and 9933 patients treated in 25 trials comparing radiation versus no radiation after modified radical mastectomy. In the trials that investigated radiation as a component of breast-conservation therapy, radiation was shown to reduce the risk of local recurrence by two thirds and to improve the absolute 15-year overall survival rate by 6% (41% versus 35%). Similarly, for patients with positive lymph nodes treated with modified radical mastectomy, radiation reduced the locoregional recurrence rate by 21% at 15 years (29% versus 8%), which was associated with a 5% decrease in the 15-year breast cancer mortality rate (60% versus 55%). A more recent update of these analyses continues to demonstrate locoregional and survival advantages for radiation therapy.[98]

The time course of the survival advantages from radiation is quite different than that seen from adjuvant systemic treatments. Specifically, survival advantages from systemic treatments tend to become evident within the first 5 years, probably reflecting the eradication of micrometastatic disease present at the time of adjuvant treatment. In contrast, the survival benefits from radiation reflect the eradication of persistent locoregional disease. For persistent locoregional disease to cause death, it must first repopulate and then successfully metastasize, after which the metastases must grow and become life-threatening. This concept is supported by data from the EBCTCG analyses; specifically, the locoregional advantages associated with radiation were found to occur early,

BOX G-2 ACOSOG Z0011 Criteria

"Z11 CRITERIA"[95,96]

Clinical T1 or T2 tumors
Clinically node negative
Breast conserving surgery and whole breast radiation
One or two positive sentinel lymph nodes
The following patients should be excluded:
Mastectomy
Breast conservation surgery with accelerated partial-breast radiation
Neoadjuvant chemotherapy
Three or more positive sentinel lymph nodes

with separation of the radiation versus no radiation curves developing during the first 5 years. However, the survival curves continued to overlap during these first 5 years, separating only later to become clearly evident by 15 years.[98,99]

The EBCTCG data also have been valuable in clarifying potential risks associated with radiation. Long-term outcome data from randomized trials indicate that coincidental radiation of the heart increased the risk of subsequent death from cardiovascular disease.[43] Indeed, in the first generation of randomized radiation trials, the percentage of patients dying from cardiovascular disease was roughly proportional to the decrease in risk of death from breast cancer after radiation therapy. These findings highlighted the importance of developing new radiation techniques to avoid irradiating the heart. Fortunately, with improvements in radiation techniques and improvements in the management of cardiovascular disease, the risk of cardiac toxicity associated with radiation has decreased over time.[100,101]

In general, the survival benefits associated with radiation treatments depend on four factors: (1) the risk of persistent locoregional disease after surgery and adjuvant systemic therapy; (2) the success of radiation in eradicating any persistent locoregional disease; (3) the risk of radiation-related death from normal tissue effects; and (4) the risk of dying of micrometastatic disease present at the time of locoregional treatment and outside of the radiation treatment volume. The success of radiation in eradicating persistent locoregional disease has increased and the risk of radiation-related toxicity has declined with the development of new treatment techniques that more accurately deliver the appropriate radiation doses to intended targets while avoiding radiation of normal tissues. Remarkably, the benefits of radiation have been relatively consistent over time: generally, radiation can reduce the risk of recurrence in all clinical settings by 65% to 75%.[98] In addition, with the advent of modern radiation techniques, the risk of radiation-associated death from normal tissue effects should be quite small.

Clinical research continues in attempts to identify, before treatment if possible, which patients will have clinically relevant persistent locoregional disease after surgery and adjuvant systemic therapy. The current standard is to recommend adjuvant radiation therapy for patients with invasive disease who are treated with breast-conserving surgery with the possible exception of women older than the age of 70 years with stage I ER-positive breast cancer. In addition, women with pathologic stage III breast cancer and some patients with pathologic stage II breast cancer who are treated with systemic therapy and surgery should receive postmastectomy radiation because of the clinically relevant risk of persistent locoregional disease. The risk of persistent disease is also interrelated with the risk of dying from micrometastatic disease that is present at the time of locoregional treatment and is outside of the radiation treatment volume. Specifically, having more than one involved lymph node and having an advanced primary tumor are predictive for both locoregional recurrence and distant metastases. Correspondingly, the probability of achieving a survival advantage with radiation may change over time as new systemic therapies are developed that have a much higher probability of reducing the competing risk of dying from micrometastatic disease.

Systemic Treatments

Systemic treatments are added to the treatment regimen of locally advanced or early-stage breast cancer based on a balance between the risk of distant metastasis and the benefit of therapies to reduce the risk of relapse early in the disease course (within the first 5 years). Data from a meta-analysis of adjuvant chemotherapy trials conducted by the EBCTCG indicate that systemic therapy provides a survival benefit for patients with lymph node-positive disease, those with lymph node-negative disease, and those with ER-positive tumors.[102] As you read further in this section, it will be helpful to refer to Figures G-5 and G-6. With increasing stage of disease, there is an associated increased risk in the development of systemic recurrence. In addition, to the extent of disease present at diagnosis, the underlying biological characteristics of the tumor are vital to determine the risk of recurrence or existence of micrometastatic disease. Age is an independent prognostic feature and younger women are at a higher risk of local and distant recurrence. In the setting of a young patient population, adjuvant systemic therapy is offered at a lower risk-to-benefit threshold. In comparison, for women older than age 70, there are no strict guidelines because few of them are included in clinical trials and decisions to proceed with systemic treatment should consider patient comorbidities and toxicity related to treatments. Treatment for breast cancer with cytotoxic agents may impair fertility and all patients who are premenopausal should be informed of the potential impact of chemotherapy on fertility. It is appropriate to consider fertility preservation before breast cancer treatment in young women who desire to bear children in the future.

Selection of Therapy

To help physicians and patients make treatment decisions and understand prognosis, Adjuvant! (www.adjuvantonline.com) was designed to determine the risk of relapse and death and to estimate the benefit of adjuvant systemic therapy based on patient age, comorbid conditions, tumor grade, ER status, tumor size, and the number of involved lymph nodes.[103] Systemic therapy should be considered for all patients when the tumor size is larger than 0.5 cm regardless of nodal status, or when there is lymph node involvement regardless of tumor size. The only patients who may not be at sufficient risk to warrant systemic treatment are those with small stage I tumors (<6 mm) that do not overexpress HER2/neu (Figure G-6).

The NCCN guidelines recommends consideration of Oncotype DX testing in patients with hormone receptor–positive, HER2/neu–negative, node-negative disease to help identify patients who are predicted to obtain the most benefit from adjuvant hormonal therapy alone and those who may or may not require adjuvant chemotherapy.[89] Tumors larger than 1.0 cm or tumors measuring 6 mm to 1.0 cm with unfavorable features including angiolymphatic invasion, high nuclear grade, or high histological grade, triple receptor negative and HER2/neu–positive should be considered for systemic adjuvant therapy, Tumors with a high RS (>31) have a predicted benefit from chemotherapy in addition to hormonal therapy. Patients in the low risk group (RS, 0-18) with a distant recurrence rate of less than 10% are predicted to have marginal benefit if any from adjuvant chemotherapy and should be offered hormonal therapy alone. Patients who are in the intermediate RS group (19-31) and those who are node positive (1-3) are currently being advised to receive chemotherapy followed by hormonal therapy; the clinical utility of Oncotype-DX test in these groups is being further defined in clinical trials (TAILORx and RxPONDER, respectively).

Cytotoxic Therapies

Several regimens are considered appropriate standard treatment for early and locally advanced disease (Tables G-8 and G-9). In general, a combination of two or more drugs is more effective than single agents. The NSABP B-18 trial showed that the administration of chemotherapy in the neoadjuvant setting did not improve or affect disease-free survival or overall survival in comparison to adjuvant administration.[124] Given that

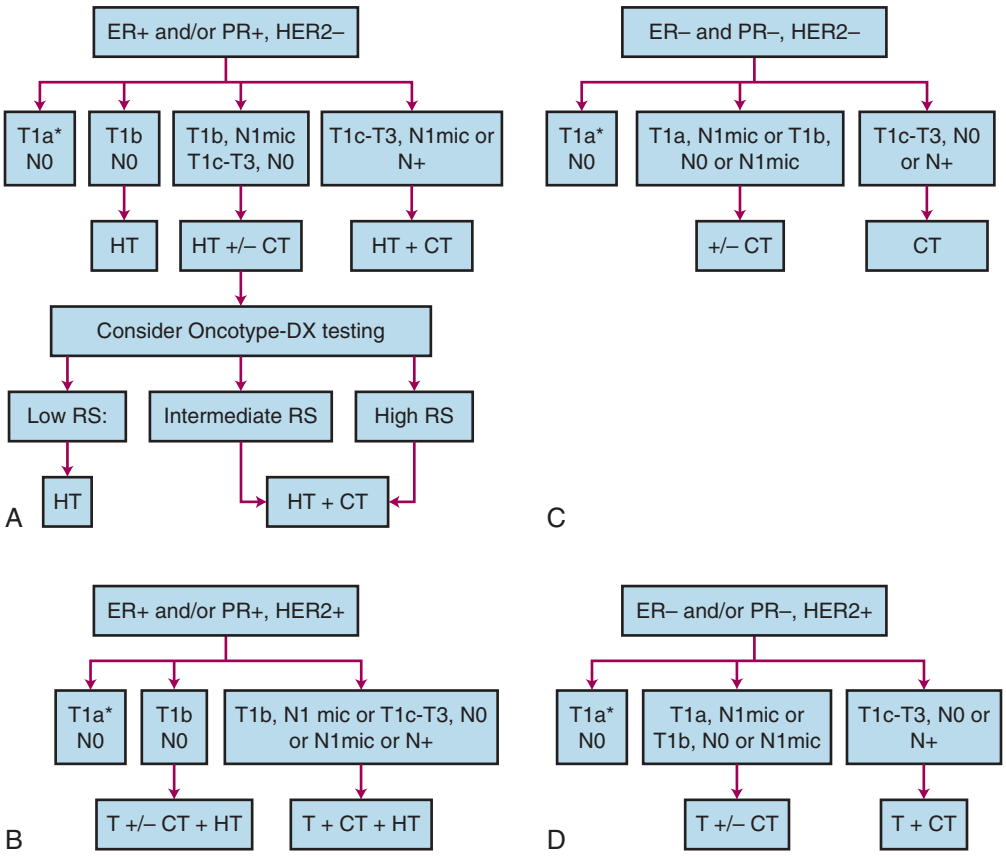


Figure G-6 Guidelines for adjuvant systemic therapy for **(A)** hormone receptor–positive, HER2-negative disease **(B)** hormone receptor–positive, HER2-positive disease **(C)** hormone receptor–negative, HER2 negative, and **(D)** hormone receptor–negative, HER2-positive disease. *CT,* Chemotherapy; *ER,* estrogen receptor; *HT,* hormonal therapy; *N+,* node positive; *PR,* progesterone receptor; *RS,* recurrence score; *T,* trastuzumab. *No adjuvant therapy; consider hormonal therapy in hormone receptor positive tumors for disease prevention.
Adapted from NCCN guidelines and the ASCO-SEP Medical Oncology Self-Evaluation Program.

TABLE G-8 Adjuvant or Neoadjuvant Chemotherapy Options

HER2-Negative Disease[a]	HER2-Positive Disease[c]
Adjuvant or Neoadjuvant	**Adjuvant**
Doxorubicin/cyclophosphamide (AC) × 4 cycles followed by 12 weeks of paclitaxel (p × 12)[b,104]	AC × 4 cycles followed by 12 weeks of paclitaxel and trastuzumab ± pertuzumab (pH ± P)[d] followed by trastuzumab (H) (over a 40-week duration)[114]
Dose-dense doxorubicin/cyclophosphamide (ddAC) × 4 cycles followed by dose-dense paclitaxel (ddp) × 4 cycles[105]	Docetaxel/carboplatin/trastuzumab ± pertuzumab (TCH ± P)[d] × 6 cycles followed by H (over a 34-week duration)[115]
Docetaxel/doxorubicin/cyclophosphamide (TAC) × 6 cycles[106]	Paclitaxel (p) and trastuzumab (H) (pH) × 12[e] followed by trastuzumab (H) (over a 40-week duration)[116]
Doxorubicin/cyclophosphamide (AC) × 4 cycles followed by docetaxel (D) ×4 cycles[107-109]	**Neoadjuvant**[d]
Other:	Non-anthracycline containing:
Docetaxel/cyclophosphamide (TC)[f] × 4 cycles[110]	Docetaxel/trastuzumab/pertuzumab (THP) × 4-6 cycles followed by adjuvant H (over a 40-week duration)[117]
Cyclophosphamide/methotrexate/fluorouracil (CMF)[g] × 6 cycles[111]	Docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) × 6 cycles followed by adjuvant H (over a 40-week duration).[118]
The following may be substituted for AC in the regimen AC × 4 → p × 12:	Anthracycline containing:
Fluorouracil/Adriamycin/cyclophosphamide (FAC) × 4 cycles[112]	AC/FAC/FEC/EC × 3-4 cycles, followed by preoperative THP × 3-4 cycles followed by adjuvant H (over a 40-week duration).[118,119]
Fluorouracil/epirubicin/cyclophosphamide (FEC) × 4 cycles[113]	

[a]*In Her2-negative disease, adjuvant systemic regimens are equally effective administered as adjuvant or neoadjuvant.*
[b]*The following substitutions may be made for AC: fluorouracil/epirubicin/cyclophosphamide (FEC); fluorouracil/adriamycin/cyclophosphamide (FAC).*
[c]*For patients with Her2-positive and axillary node-positive breast cancer, trastuzumab should be a component of their adjuvant systemic therapy. Trastuzumab should be highly considered for patients with HER2-positive node-negative tumors ≥1 cm. Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Anti-Her2 therapy should not be given in combination with an anthracycline.*
[d]*A pertuzumab containing regimen should be administered to patients with HER2-positive breast cancer preferably in the neoadjuvant setting for tumors >2 cm that are locally advanced and operable. Patients who have not received a neoadjuvant pertuzumab-containing regimen may receive adjuvant pertuzumab.*
[e]*Paclitaxel with trastuzumab may be considered for patients with low-risk stage I, Her2-positive disease, particularly if not eligible for other standard adjuvant regimens because of comorbidities. Preliminary results from the Adjuvant Paclitaxel and Trastuzumab (APT) study were presented at San Antonio Breast Cancer Symposium 2013.*
[f]*Can be considered in patients who are low-risk and node negative; if node positive, anthracycline-containing regimen is preferred.*
[g]*Can be considered in patients who are low risk, those who have underlying cardiac dysfunction, or those with recurrent breast cancer or new breast primary who have previously received anthracycline-based therapy.*

TABLE G-9 Adjuvant Endocrine Therapy in Hormone Receptor-Positive Disease

Study	Endocrine Therapy/Duration	RR Recurrence	RR Mortality
	Primary Therapy		
EBCTC[120]	Tamoxifen (5 yrs)	0.61 (0.57-0.65)	0.70 (0.64-0.75)
ATAC[121]	Anastrozole vs. tamoxifen (5 yrs)	0.90 (0.82-0.99)	1.00 (0.89-1.12)
BIG 1-98[122]	Letrozole vs. tamoxifen (5 yrs)	0.88 (0.78-0.99)	0.81 (0.69-0.94)
	Sequential Therapy		
BIG 1-98	Tamoxifen/letrozole vs. letrozole Letrozole/tamoxifen vs. letrozole	1.05 (0.84-1.32) 0.96 (0.76-1.21)	1.13 (0.83-1.53) 0.90 (0.65-1.24)
	Extended Therapy		
NCIC CTG MA. 17[123]	Tamoxifen × 5 yrs followed by letrozole × 5 yrs	0.68 (0.55-0.83)	0.98 (0.78-1.22)

RR, *Relative risk;* yrs, *years.*

there is no efficacy advantage in progression-free or overall survival, systemic therapy regimens may be considered for administration in the adjuvant or neoadjuvant settings.[125] For locally advanced or inflammatory breast cancers, chemotherapy with or without targeted therapy is routinely administered in the neoadjuvant setting. The key advantages of neoadjuvant chemotherapy (NAC) include the ability to enable breast conserving surgery by downstaging tumors before surgery and the ability to assess in vivo response to chemotherapy.[126] In addition to increasing the likelihood of tumor control, more recently, a cited advantage of administering chemotherapy in the neoadjuvant setting has been accelerated drug approval. Pathological complete response has been proposed as a surrogate endpoint predictive of long-term clinical benefit and neoadjuvant trials allow for rapid assessment of drug efficacy.[127,128]

The most widely adopted regimens include combinations of an anthracycline and a taxane (either paclitaxel or docetaxel). This recommendation is based in part on an intergroup trial that randomly assigned patients who had been treated with four cycles of doxorubicin and cyclophosphamide (AC) to receive either four cycles of paclitaxel or no additional chemotherapy. Results of that trial showed a disease-free survival benefit for patients treated with paclitaxel.[129] These results are supported by those of a similar study conducted by the NSABP (the B-28 trial), which also found that patients who received four cycles of AC plus four cycles of paclitaxel had higher disease-free survival rates than those who received four cycles of AC alone.[130] Subsequent chemotherapy trials have investigated various combinations of taxane and anthracycline chemotherapy. An intergroup trial revealed that giving four cycles of AC followed by four cycles of paclitaxel in a dose-dense fashion improved disease-free survival rates relative to the usual 3-week dosing schedule of the same chemotherapy.[131] Finally, the Breast Cancer International Research Group conducted a trial that randomly assigned patients with lymph node-positive breast cancer to receive either six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) or six cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC) and found an improvement in disease-free survival rates among those given TAC.[132] Collectively, these findings suggest that for patients with high-risk disease features (e.g., lymph node-positive disease, and node-negative with unfavorable features including large tumor size, high histological grade, triple receptor negative), any of the following third-generation chemotherapy regimens can be considered acceptable: dose-dense scheduling of AC with paclitaxel, weekly paclitaxel followed by AC, AC followed by docetaxel every 3 weeks, or TAC.[104,107,131,133,134] For patients with lower-risk breast cancer who desire a shorter course of chemotherapy, giving four cycles of docetaxel and cyclophosphamide (TC) has become more common after a recent randomized prospective trial found that this regimen produced better disease-free survival and overall survival rates than did four cycles of AC.[135]

Triple-negative breast cancer (TNBC) lacks expression of ER and PR and lacks overexpression or amplification of HER2 and is worth some focused attention because it is associated with a poor prognosis and poor overall response to standard anthracycline and taxane-based chemotherapy. Standard chemotherapy when administered in a neoadjuvant (NAC) fashion and results in a pathological complete response (pCR) of 20% to 34%.[128,136,137] A pCR is associated with increased survival and those who do not achieve this status are at high risk for disease recurrence.[138] Recent studies have shown that the pCR may be improved in TNBC with the addition of platinum-based NAC; however, this continues to be a topic of debate across TNBC.[139] Continued research efforts are under way to improve local and systemic control in this molecular subtype.

Endocrine Therapies

For most patients with ER-positive or PR-positive disease, hormonal therapy is indicated (Table G-9). Before selection of hormonal therapy, it is important to establish the patient's menopausal status. Premenopausal women whose ovaries continue to function after chemotherapy should receive tamoxifen for 5 years to 10 years as the preferred therapy.[140,141] Cytotoxic therapy may induce menopause; however, for the purpose of adjuvant hormonal therapy selection, the patient's menopausal status at the time of diagnosis is most relevant. Patients who were perimenopausal at the time of diagnosis should receive tamoxifen for 2 years to 3 years and may be switched to an aromatase inhibitor when they achieve menopause. For women who are postmenopausal, the use of an aromatase inhibitor is most effective. There are several options for patients who are postmenopausal, including an aromatase inhibitor for 5 years, initial tamoxifen for 2 years to 3 years followed by an aromatase inhibitor, aromatase inhibitor for 2 years to 3 years followed by tamoxifen for 2 years to 3 years or tamoxifen for 5 years followed by 5 years of an aromatase inhibitor.[142-144] Results of a recent EBCTCG meta-analysis of trials that compared breast cancer outcomes with adjuvant aromatase inhibitors versus tamoxifen for women who are postmenopausal with ER-positive breast cancer demonstrated that the use of aromatase inhibitors was associated with a breast cancer recurrence rate that was 3% lower than that with tamoxifen within 3 years to 5 years of follow-up.[64] A recent consensus statement from the American Society of Clinical Oncology that also reviewed published and ongoing trials of

adjuvant aromatase inhibitors recommends that women who are postmenopausal with ER-positive breast cancer consider incorporating an aromatase inhibitor at some point during adjuvant treatment.[145]

HER2 Targeting

The introduction of trastuzumab (Herceptin) for the adjuvant treatment of tumors with amplification of HER2/neu has been one of the most exciting advances in systemic treatment in the history of breast cancer. Randomized prospective trials demonstrated substantial improvements in disease-free and overall survival rates for patients with HER2/neu-overexpressing tumors when trastuzumab was added to adjuvant chemotherapy.[146-148] Specifically, the combined results from two randomized trials involving 3351 patients (94% of whom had lymph node-positive disease) indicated that four cycles of AC followed by weekly paclitaxel or 3-week paclitaxel with concurrent trastuzumab followed by 1 year of trastuzumab achieved a 52% reduction in the relative risk of recurrence compared with chemotherapy without trastuzumab.[147] The absolute reduction in risk of recurrence at 3 years was 12%. The European Herceptin Adjuvant (HERA) trial randomly assigned 5081 patients who had received at least four cycles of chemotherapy for HER2/neu-positive breast cancer (68% of whom had positive lymph nodes) to receive no further treatment, trastuzumab for 1 year, or trastuzumab for 2 years.[146] Trastuzumab reduced the relative risk of recurrence over chemotherapy alone by 46% (8.4% absolute reduction of the risk at 3 years). Finally, the Breast Cancer International Research Group trial 006 randomly assigned 3174 patients with HER2/neu-positive breast cancer (71% of whom had lymph node-positive disease) to receive chemotherapy with or without trastuzumab. That trial again confirmed that the addition of trastuzumab reduced the relative risk of recurrence or death over chemotherapy alone by 39%.[148] The incorporation of adjuvant trastuzumab based therapy has transformed the natural history of HER2-positive disease.

Neoadjuvant treatment with HER2 blockade has been found to significantly improve the pCR rate for patients treated with chemotherapy plus trastuzumab compared to chemotherapy alone.[149,150] More recently, neoadjuvant dual HER2 blockade has been evaluated.[117,118,151] The NeoSPHERE and NeoALLTO studies demonstrated that double HER2 blockade increased the pCR rate from 29% to 45% with pertuzumab plus trastuzumab and from 29% to 51% with lapatinib plus trastuzumab.[117,151] In NeoSPHERE, patients with hormone receptor–negative disease had a greater benefit when treated in the arm with dual HER2 blockade and chemotherapy. Of note, 17% of patients in the dual HER2 blockade–only arm achieved a pCR. It has recently been shown that achievement of a pCR specifically in the NeoALLTO study translates to an event-free survival and overall survival benefit.[152] In 2014 the results of ALTTO, NeoALTTO's "sister" trial in the adjuvant setting became available showing no additional benefit for the addition of lapatinib to trastuzumab in the adjuvant treatment of HER2 positive breast cancer.[152a]

For HER2-positive tumors that are large (>2 cm), operable, and locally advanced, the preferred treatment approach currently is dual HER2 blockade in the neoadjuvant setting with trastuzumab and pertuzumab in combination with a taxane with or without sequential anthracycline-based therapy.[117,118] Pertuzumab recently gained Food and Drug Administration (FDA) approval in the neoadjuvant setting in October 2013 and is recommended for use in one of the combinations as listed in Table G-8. A trial known as the Adjuvant Pertuzumab and Herceptin in Initial Therapy of Breast Cancer (APHINITY) will provide further data, disease-free survival, and results are eagerly anticipated in 2016. Further clinical investigation will be required to further examine the role of dual HER2 blockade alone and to identify the subset of patients that achieve pCR with a less toxic regimen.[117]

Sequencing of Therapies

The choice of sequence of systemic therapy in relation to surgery and radiation is optimally made by a multidisciplinary team. The decision is based on disease stage, the need for "up front" pathologic staging information, patient eligibility and desire for breast conservation, and coordination of the treating disciplines. Sequences in which chemotherapy is given before surgery (neoadjuvant therapy) are becoming increasingly more common for patients with stage II or III breast cancer. Trials investigating neoadjuvant hormonal therapy and chemotherapy with or without targeted therapy and its use to increase rates of breast conservation are reviewed in an upcoming chapter. For those patients who undergo surgery to be followed by adjuvant chemotherapy and adjuvant radiation, most centers in the United States recommend that the chemotherapy be completed first and then the radiation be given. A randomized prospective trial comparing 12 weeks of adjuvant chemotherapy given either before or after radiation for patients treated with breast-conservation therapy found no significant differences between the two treatment groups in time to any event, distant metastasis, or death.[153] The findings from this trial indicated that plans to delay radiation so that adjuvant chemotherapy could be completed first should be considered only for those patients with negative surgical margins. The sequencing of hormonal therapy and radiation has not been studied in a randomized comparative trial, but retrospective analyses suggest that concurrent and sequential treatments probably provide similar outcomes.[154-156] Finally, concurrent radiation and trastuzumab treatment also seems to be safe, although information on long-term outcome is not yet available. Randomized trials investigating the use of adjuvant trastuzumab have involved giving radiation and trastuzumab concurrently; findings from these trials on normal tissue effects, including short-term cardiac toxicity, suggest that giving trastuzumab concurrently with radiation does not increase the risk of injury.[157,158]

FINAL REMARKS

In the past 20 years, there has been tremendous growth in knowledge regarding the pathogenesis and treatment of breast cancer. Many of these advances have been possible because of collaborative focused efforts among radiologists, pathologists, genetic counselors, radiation oncologists, surgical oncologists, and medical oncologists. In this introductory chapter to the breast cancer section, we provide a broad overview that ranges from incidence and mortality to anatomy, biological characteristics, risk assessment, screening, diagnosis, staging, prognosis, selection of therapies, and multimodality treatment (surgery, radiation, and systemic therapy). We hope to have provided a strong foundation that will help you in your study moving forward. In the chapters to follow, there will be a more detailed discussion of early breast cancer, postmastectomy radiation, and DCIS from a radiation oncology focused perspective.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

3. Strom EA, Woodward WA, Katz A, et al: Clinical investigation: Regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys 63:1508–1513, 2005.
4. Truong PT, Jones SO, Kader HA, et al: Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence

risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73:357–364, 2009.
6. Kirova YM, Castro Pena P, Dendale R, et al: Simplified rules for everyday delineation of lymph node areas for breast cancer radiotherapy. Br J Radiol 83:683–686, 2010.
13. Anders CK, Johnson R, Litton J, et al: Breast cancer before age 40 years. Semin Oncol 36:237–249, 2009.
14. Litton JK, Theriault RL: Breast cancer and pregnancy: Current concepts in diagnosis and treatment. Oncologist 15:1238–1247, 2010.
20. Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 291:1701–1712, 2004.
21. Chlebowski RT, Hendrix SL, Langer RD, et al: Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. JAMA 289:3243–3253, 2003.
25. Smith-Warner SA, Spiegelman D, Yaun SS, et al: Alcohol and breast cancer in women: A pooled analysis of cohort studies. JAMA 279:535–540, 1998.
39. Daly MB, Axilbund JE, Buys S, et al: Genetic/familial high-risk assessment: Breast and ovarian. J Natl Compr Canc Netw 8:562–594, 2010.
43. Smith RA, Cokkinides V, Eyre HJ, et al: American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin 53:27–43, 2003.
46. Gail MH, Costantino JP: Validating and improving models for projecting the absolute risk of breast cancer. J Natl Cancer Inst 93:334–335, 2001.
50. Fisher B, Costantino J, Redmond C, et al: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 320:479–484, 1989.
54. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371–1388, 1998.
55. Cuzick J, Forbes J, Edwards R, et al: First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial. Lancet 360:817–824, 2002.
56. Cuzick J, Forbes JF, Sestak I, et al: Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99:272–282, 2007.
60. Vogel VG, Costantino JP, Wickerham DL, et al: Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 3:696–706, 2010.
61. Buzdar AU, Robertson JF, Eiermann W, et al: An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer 95:2006–2016, 2002.
62. Baum M, Buzdar A, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 98:1802–1810, 2003.
63. Breast International Group 1-98 Collaborative G, Thurlimann B, Keshaviah A, et al: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747–2757, 2005.
64. Dowsett M, Cuzick J, Ingle J, et al: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28:509–518, 2010.
68. Fisher B, Dignam J, Wolmark N, et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353:1993–2000, 1999.
73. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer Risk Reduction. Version 1. 2013.
75. Edge SB, Byrd DR, Compton CC, et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer.
78. Albert JM, Gonzalez-Angulo AM, Guray M, et al: Estrogen/progesterone receptor negativity and HER2 positivity predict locoregional recurrence in patients with T1a,bN0 breast cancer. Int J Radiat Oncol Biol Phys 77(5):1296–1302, 2010.
79. Nguyen PL, Taghian AG, Katz MS, et al: Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26:2373–2378, 2008.
81. Kyndi M, Sorensen FB, Knudsen H, et al: Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group. J Clin Oncol 26:1419–1426, 2008.
82. Woodward WA, Strom EA, Tucker SL, et al: Locoregional recurrence after doxorubicin-based chemotherapy and postmastectomy: Implications for breast cancer patients with early-stage disease and predictors for recurrence after postmastectomy radiation. Int J Radiat Oncol Biol Phys 57:336–344, 2003.
83. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177–182, 1987.
85. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792, 2001.
88. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726–3734, 2006.
89. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer. Version 2. 2014.
92. Giuliano AE, Dale PS, Turner RR, et al: Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 222:394–399, discussion 399–401, 1995.
94. Veronesi U, Viale G, Paganelli G, et al: Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. Ann Surg 251:595–600, 2010.
95. Giuliano AE, McCall L, Beitsch P, et al: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 252:426–432, discussion 432–433, 2010.
96. Caudle AS, Hunt KK, Kuerer HM, et al: Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: A practice-changing trial. Ann Surg Oncol 18:2407–2412, 2011.
98. Group EBCTC: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 366:2087–2106, 2005.
99. Punglia RS, Morrow M, Winer EP, et al: Local therapy and survival in breast cancer. N Engl J Med 356:2399–2405, 2007.
102. Group EBCTC: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687–1717, 2005.
103. Ravdin PM, Siminoff LA, Davis GJ, et al: Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 19:980–991, 2001.
120. Early Breast Cancer Trialists' Collaborative G: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687–1717, 2005.
121. Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62, 2005.
123. Jin H, Tu D, Zhao N, et al: Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: Analyses adjusting for treatment crossover. J Clin Oncol 30:718–721, 2012.
124. Wolmark N, Wang J, Mamounas E, et al: Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 30:96–102, 2001.
125. Mauri D, Pavlidis N, Ioannidis JP: Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. J Natl Cancer Inst 97:188–194, 2005.
126. Graham LJ, Shupe MP, Schneble EJ, et al: Current approaches and challenges in monitoring treatment responses in breast cancer. J Cancer 5:58–68, 2014.
127. Prowell TM, Pazdur R: Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 366:2438–2441, 2012.
128. Cortazar P, Zhang L, Untch M, et al: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384(9938):164–172, 2014.
129. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976–983, 2003.
130. Mamounas EP, Bryant J, Lembersky B, et al: Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. J Clin Oncol 23:3686–3696, 2005.
131. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431–1439, 2003.
132. Hugh J, Hanson J, Cheang MC, et al: Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol 27:1168–1176, 2009.
138. von Minckwitz G, Untch M, Blohmer JU, et al: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796–1804, 2012.
140. Davies C, Pan H, Godwin J, et al: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805–816, 2013.
141. Gray RG, Rea DW, Handley K, et al: ATTom: randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—preliminary results. Proc Am J Clin Oncol 26(10):513, 2008.

145. Burstein HJ, et al: American society of clinical oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 28(23):3784–3796, 2010.
147. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673–1684, 2005.
148. Slamon D, Eiermann W, Robert N, et al: Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat 94(Suppl 1):abst 1, 2005.
149. Buzdar AU, Ibrahim NK, Francis D, et al: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676–3685, 2005.
150. Buzdar AU, Valero V, Ibrahim NK, et al: Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 13:228–233, 2007.
153. Bellon JR, Come SE, Gelman RS, et al: Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: Updated results of a prospective randomized trial. J Clin Oncol 23:1934–1940, 2005.

REFERENCES

1. Shahar KH, Buchholz TA, Delpassand E, et al: Lower and central tumor location correlates with lymphoscintigraphy drainage to the internal mammary lymph nodes in breast carcinoma. Cancer 103:1323–1329, 2005.
2. Huang O, Wang L, Shen K, et al: Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: Analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat 107:379–387, 2008.
3. Strom EA, Woodward WA, Katz A, et al: Clinical investigation: Regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys 63:1508–1513, 2005.
4. Truong PT, Jones SO, Kader HA, et al: Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73:357–364, 2009.
5. Li XA, Tai A, Arthur DW, et al: Variability of target and normal structure delineation for breast cancer radiotherapy: An RTOG Multi-Institutional and Multiobserver Study. Int J Radiat Oncol Biol Phys 73:944–951, 2009.
6. Kirova YM, Castro Pena P, Dendale R, et al: Simplified rules for everyday delineation of lymph node areas for breast cancer radiotherapy. Br J Radiol 83:683–686, 2010.
7. van Mourik AM, Elkhuizen PH, Minkema D, et al: Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. Radiother Oncol 94:286–291, 2010.
8. Reed VK, Woodward WA, Zhang L, et al: Automatic segmentation of whole breast using atlas approach and deformable image registration. Int J Radiat Oncol Biol Phys 73:1493–1500, 2009.
9. J W: Book Breast Cancer Atlas for Radiation Therapy Planning. Consensus Definitions, editor. RTOG; 2009. Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions.
10. Society AC: Breast Cancer Facts and Figures 2013-2014. 2013.
11. Ravdin PM, Cronin KA, Howlader N, et al: The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356:1670–1674, 2007.
12. Marshall SF, Clarke CA, Deapen D, et al: Recent breast cancer incidence trends according to hormone therapy use: The California Teachers Study cohort. Breast Cancer Res 12:R4, 2010.
13. Anders CK, Johnson R, Litton J, et al: Breast cancer before age 40 years. Semin Oncol 36:237–249, 2009.
14. Litton JK, Theriault RL: Breast cancer and pregnancy: Current concepts in diagnosis and treatment. Oncologist 15:1238–1247, 2010.
15. Berry DA, Cronin KA, Plevritis SK, et al: Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792, 2005.
16. Siegel R, DeSantis C, Virgo K, et al: Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62:220–241, 2012.
17. Lambe M, Hsieh C, Tsaih S, et al: Maternal risk of breast cancer following multiple births: A nationwide study in Sweden. Cancer Causes Control 7:533–538, 1996.
18. Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 350:1047–1059, 1997.
19. Schairer C, Lubin J, Troisi R, et al: Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 283:485–491, 2000.
20. Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 291:1701–1712, 2004.
21. Chlebowski RT, Hendrix SL, Langer RD, et al: Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. JAMA 289:3243–3253, 2003.
22. Holmes MD, Hunter DJ, Colditz GA, et al: Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 281:914–920, 1999.
23. Prentice RL, Caan B, Chlebowski RT, et al: Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295:629–642, 2006.
24. Iyengar NM, Hudis CA: Gucalp A: Omega-3 fatty acids for the prevention of breast cancer: An update and state of the science. Curr Breast Cancer Rep 5:247–254, 2013.
25. Smith-Warner SA, Spiegelman D, Yaun SS, et al: Alcohol and breast cancer in women: A pooled analysis of cohort studies. JAMA 279:535–540, 1998.
26. Scoccianti C, Lauby-Secretan B, Bello PY, et al: Female breast cancer and alcohol consumption: A review of the literature. Am J Prev Med 46:S16–S25, 2014.
27. Carpenter CL, Ross RK, Paganini-Hill A, et al: Lifetime exercise activity and breast cancer risk among post-menopausal women. Br J Cancer 80:1852–1858, 1999.
28. Shoff SM, Newcomb PA, Trentham-Dietz A, et al: Early-life physical activity and postmenopausal breast cancer: Effect of body size and weight change. Cancer Epidemiol Biomarkers Prev 9:591–595, 2000.
29. Daley AJ, Crank H, Saxton JM, et al: Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol 25:1713–1721, 2007.
30. Milne HM, Wallman KE, Gordon S, et al: Effects of a combined aerobic and resistance exercise program in breast cancer survivors: A randomized controlled trial. Breast Cancer Res Treat 108:279–288, 2008.
31. Buchholz TA, Weil MM, Story MD, et al: Tumor suppressor genes and breast cancer. Radiat Oncol Investig 7:55–65, 1999.
32. Klauber-DeMore N: Tumor biology of breast cancer in young women. Breast Dis 23:9–15, 2005.
33. Petrucelli N, Daly MB, Feldman GL: Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. Genet Med 12:245–259, 2010.
34. Breast Cancer Linkage C: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91:1310–1316, 1999.
35. Evans JP, Skrzynia C, Susswein L, et al: Genetics and the young woman with breast cancer. Breast Dis 23:17–29, 2005.
36. BRAC: Analysis Large Rearrangement Test (BART), Salt Lake City, 2013, UMG, Inc.
37. Judkins T, Rosenthal E, Arnell C, et al: Clinical significance of large rearrangements in BRCA1 and BRCA2. Cancer 118:5210–5216, 2012.
38. Colditz GA, Willett WC, Hunter DJ, et al: Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA 270:338–343, 1993.
39. Daly MB, Axilbund JE, Buys S, et al: Genetic/familial high-risk assessment: Breast and ovarian. J Natl Compr Canc Netw 8:562–594, 2010.
40. Deleted in review.
41. Armstrong K, Moye E, Williams S, et al: Screening mammography in women 40 to 49 years of age: A systematic review for the American College of Physicians. Ann Intern Med 146:516–526, 2007.
42. van Schoor G, Broeders MJ, Paap E, et al: A rationale for starting breast cancer screening under age 50. Ann Oncol 19:1208–1209, 2008.
43. Smith RA, Cokkinides V, Eyre HJ, et al: American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin 53:27–43, 2003.
44. Bleyer A, Welch HG: Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 367:1998–2005, 2012.
45. Gail MH, Brinton LA, Byar DP, et al: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 81:1879–1886, 1989.
46. Gail MH, Costantino JP: Validating and improving models for projecting the absolute risk of breast cancer. J Natl Cancer Inst 93:334–335, 2001.
47. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643–651, 1994.
48. Tyrer J, Duffy SW, Cuzick J: A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 23:1111–1130, 2004.
49. Parmigiani G, Berry D, Aguilar O: Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 62:145–158, 1998.
50. Fisher B, Costantino J, Redmond C, et al: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 320:479–484, 1989.
51. Fisher B, Redmond C: New perspective on cancer of the contralateral breast: A marker for assessing tamoxifen as a preventive agent. J Natl Cancer Inst 83:1278–1280, 1991.
52. Jordan VC, Allen KE: Evaluation of the antitumour activity of the non-steroidal antioestrogen monohydroxytamoxifen in the DMBA-induced rat mammary carcinoma model. Eur J Cancer 16:239–251, 1980.
53. Jordan VC: Effect of tamoxifen (ICI 46,474) on initiation and growth of DMBA-induced rat mammary carcinomata. Eur J Cancer 12:419–424, 1976.
54. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371–1388, 1998.
55. Cuzick J, Forbes J, Edwards R, et al: First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial. Lancet 360:817–824, 2002.
56. Cuzick J, Forbes JF, Sestak I, et al: Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99:272–282, 2007.
57. Cummings SR, Eckert S, Krueger KA, et al: The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. JAMA 281:2189–2197, 1999.
58. Martino S, Cauley JA, Barrett-Connor E, et al: Continuing outcomes relevant to Evista: Breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 96:1751–1761, 2004.
59. Vogel VG, Costantino JP, Wickerham DL, et al: Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295:2727–2741, 2006.
60. Vogel VG, Costantino JP, Wickerham DL, et al: Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 3:696–706, 2010.
61. Buzdar AU, Robertson JF, Eiermann W, et al: An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer 95:2006–2016, 2002.

62. Baum M, Buzdar A, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 98:1802–1810, 2003.
63. Breast International Group 1-98 Collaborative G, Thurlimann B, Keshaviah A, et al: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747–2757, 2005.
64. Dowsett M, Cuzick J, Ingle J, et al: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28:509–518, 2010.
65. Goss PE, Ingle JN, Ales-Martinez JE, et al: Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 364:2381–2391, 2011.
66. Cuzick J, Sestak I, Forbes JF, et al: Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): An international, double-blind, randomised placebo-controlled trial. Lancet 2013.
67. Visvanathan K, Hurley P, Bantug E, et al: Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 31:2942–2962, 2013.
68. Fisher B, Dignam J, Wolmark N, et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353:1993–2000, 1999.
69. Allred DC, Anderson SJ, Paik S, et al: Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: A study based on NSABP protocol B-24. J Clin Oncol 30:1268–1273, 2012.
70. Hartmann LC, Schaid DJ, Woods JE, et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77–84, 1999.
71. Hartmann LC, Sellers TA, Schaid DJ, et al: Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 93:1633–1637, 2001.
72. Rebbeck TR, Friebel T, Lynch HT, et al: Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol 22:1055–1062, 2004.
73. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer Risk Reduction. Version 1. 2013.
74. Rebbeck TR, Lynch HT, Neuhausen SL, et al: Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346:1616–1622, 2002.
75. Edge SB, Byrd DR, Compton CC, et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer.
76. Sorlie T, Perou CM, Tibshirani R, et al: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869–10874, 2001.
77. Sorlie T, Tibshirani R, Parker J, et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 100:8418–8423, 2003.
78. Albert JM, Gonzalez-Angulo AM, Guray M, et al: Estrogen/progesterone receptor negativity and HER2 positivity predict locoregional recurrence in patients with T1a,bN0 breast cancer. Int J Radiat Oncol Biol Phys 77(5):1296–1302, 2010.
79. Nguyen PL, Taghian AG, Katz MS, et al: Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26:2373–2378, 2008.
80. Voduc KD, Cheang MC, Tyldesley S, et al: Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28:1684–1691, 2010.
81. Kyndi M, Sorensen FB, Knudsen H, et al: Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group. J Clin Oncol 26:1419–1426, 2008.
82. Woodward WA, Strom EA, Tucker SL, et al: Locoregional recurrence after doxorubicin-based chemotherapy and postmastectomy: Implications for breast cancer patients with early-stage disease and predictors for recurrence after postmastectomy radiation. Int J Radiat Oncol Biol Phys 57:336–344, 2003.
83. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177–182, 1987.
84. Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707–712, 1989.
85. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792, 2001.
86. McCormick SR, Lillemoe TJ, Beneke J, et al: HER2 assessment by immunohistochemical analysis and fluorescence in situ hybridization: Comparison of HercepTest and PathVysion commercial assays. Am J Clin Pathol 117:935–943, 2002.
87. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817–2826, 2004.
88. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726–3734, 2006.
89. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer. Version 2. 2014.
90. Berry M, Fitoussi AD, Curnier A, et al: Oncoplastic breast surgery: A review and systematic approach. J Plast Reconstr Aesthet Surg 63(8):1233–1243, 2010.
91. Chen CY, Calhoun KE, Masetti R, et al: Oncoplastic breast conserving surgery: A renaissance of anatomically-based surgical technique. Minerva Chir 61:421–434, 2006.
92. Giuliano AE, Dale PS, Turner RR, et al: Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 222:394–399, discussion 399–401, 1995.
93. Krag DN, Ashikaga T, Harlow SP, et al: Surgeon training, protocol compliance, and technical outcomes from breast cancer sentinel lymph node randomized trial. J Natl Cancer Inst 101:1356–1362, 2009.
94. Veronesi U, Viale G, Paganelli G, et al: Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. Ann Surg 251:595–600, 2010.
95. Giuliano AE, McCall L, Beitsch P, et al: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 252:426–432, discussion 432–433, 2010.
96. Caudle AS, Hunt KK, Kuerer HM, et al: Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: A practice-changing trial. Ann Surg Oncol 18:2407–2412, 2011.
97. Gatzemeier W, Mann GB: Which sentinel lymph-node (SLN) positive breast cancer patient needs an axillary lymph-node dissection (ALND)—ACOSOG Z0011 results and beyond. Breast 22:211–216, 2013.
98. Group EBCTC: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 366:2087–2106, 2005.
99. Punglia RS, Morrow M, Winer EP, et al: Local therapy and survival in breast cancer. N Engl J Med 356:2399–2405, 2007.
100. Giordano SH, Kuo YF, Freeman JL, et al: Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 97:419–424, 2005.
101. Patt DA, Goodwin JS, Kuo YF, et al: Cardiac morbidity of adjuvant radiotherapy for breast cancer. J Clin Oncol 23:7475–7482, 2005.
102. Group EBCTC: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687–1717, 2005.
103. Ravdin PM, Siminoff LA, Davis GJ, et al: Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 19:980–991, 2001.
104. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663–1671, 2008.
105. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431–1439, 2003.
106. Martin M, Pienkowski T, Mackey J, et al: Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 352:2302–2313, 2005.
107. Bear HD, Anderson S, Smith RE, et al: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast And Bowel Project Protocol B-27. J Clin Oncol 24:2019–2027, 2006.
108. Bear HD, Anderson S, Brown A, et al: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 21:4165–4174, 2003.
109. Gradishar WJ, Wedam SB, Jahanzeb M, et al: Neoadjuvant docetaxel followed by adjuvant doxorubicin and cyclophosphamide in patients with stage III breast cancer. Ann Oncol 16:1297–1304, 2005.
110. Jones SE, Savin MA, Holmes FA, et al: Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 24:5381–5387, 2006.
111. Goldhirsch A, Colleoni M, Coates AS, et al: Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: Are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 9:489–493, 1998.
112. Buzdar AU, Kau SW, Smith TL, et al: Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. Am J Clin Oncol 12:123–128, 1989.
113. Martin M, Rodriguez-Lescure A, Ruiz A, et al: Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. J Natl Cancer Inst 100:805–814, 2008.
114. Perez EA, Romond EH, Suman VJ, et al: Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29:3366–3373, 2011.
115. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273–1283, 2011.
116. Tolaney S: A phase II study of adjuvant paclitaxel(T) and trastuzumab(H) (APT trial) for node-negative, HER2-positive breast cancer (BC). 2013 San Antonio Breast Cancer Symposium. San Antonio, TX (Abstract S1-04).

117. Gianni L, Pienkowski T, Im YH, et al: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncol 13:25–32, 2012.
118. Schneeweiss A, Chia S, Hickish T, et al: Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 24:2278–2284, 2013.
119. Buzdar AU, Suman VJ, Meric-Bernstam F, et al: Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): A randomised, controlled, phase 3 trial. Lancet Oncol 14:1317–1325, 2013.
120. Early Breast Cancer Trialists' Collaborative G: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687–1717, 2005.
121. Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62, 2005.
122. Regan MM, Price KN, Giobbie-Hurder A, et al: Interpreting Breast International Group (BIG) 1-98: A randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. Breast Cancer Res 13:209, 2011.
123. Jin H, Tu D, Zhao N, et al: Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: Analyses adjusting for treatment crossover. J Clin Oncol 30:718–721, 2012.
124. Wolmark N, Wang J, Mamounas E, et al: Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 30:96–102, 2001.
125. Mauri D, Pavlidis N, Ioannidis JP: Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. J Natl Cancer Inst 97:188–194, 2005.
126. Graham LJ, Shupe MP, Schneble EJ, et al: Current approaches and challenges in monitoring treatment responses in breast cancer. J Cancer 5:58–68, 2014.
127. Prowell TM, Pazdur R: Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 366:2438–2441, 2012.
128. Cortazar P, Zhang L, Untch M, et al: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384(9938):164–172, 2014.
129. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976–983, 2003.
130. Mamounas EP, Bryant J, Lembersky B, et al: Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. J Clin Oncol 23:3686–3696, 2005.
131. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431–1439, 2003.
132. Hugh J, Hanson J, Cheang MC, et al: Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol 27:1168–1176, 2009.
133. Martin M, Segui MA, Anton A, et al: Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med 363:2200–2210, 2010.
134. Swain SM, Jeong JH, Geyer CE, Jr, et al: Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 362:2053–2065, 2010.
135. Jones S, Holmes FA, O'Shaughnessy J, et al: Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 27:1177–1183, 2009.
136. Liedtke C, Broglio K, Moulder S, et al: Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol 20:1953–1958, 2009.
137. Carey LA, Dees EC, Sawyer L, et al: The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329–2334, 2007.
138. von Minckwitz G, Untch M, Blohmer JU, et al: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796–1804, 2012.
139. Petrelli F, Coinu A, Borgonovo K, et al: The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: A systematic review and meta-analysis. Breast Cancer Res Treat 144(2):223–232, 2014.
140. Davies C, Pan H, Godwin J, et al: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805–816, 2013.
141. Gray RG, Rea DW, Handley K, et al: ATTom: randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—preliminary results. Proc Am J Clin Oncol 26(10):513, 2008.
142. Coombes RC, Hall E, Gibson LJ, et al: Intergroup Exemestane Study. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081–1092, 2004.
143. Forbes JF, Cuzick J, Buzdar A, et al: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 9:45–53, 2008.
144. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349:1793–1802, 2003.
145. Burstein HJ, et al: American society of clinical oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 28(23):3784–3796, 2010.
146. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659–1672, 2005.
147. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673–1684, 2005.
148. Slamon D, Eiermann W, Robert N, et al: Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat 94(Suppl 1):abst 1, 2005.
149. Buzdar AU, Ibrahim NK, Francis D, et al: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676–3685, 2005.
150. Buzdar AU, Valero V, Ibrahim NK, et al: Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 13:228–233, 2007.
151. Baselga J, Bradbury I, Eidtmann H, et al: Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): A randomised, open-label, multicentre, phase 3 trial. Lancet 379:633–640, 2012.
152. Piccart-Gebhart M: The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer: Survival follow-up analysis of the NeoALTTO study (BIG 1-06). 2013 Breast Cancer Symposium. San Antonio, TX (Abstract S1-01).
152a. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al: First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone, trastuzumab alone, their sequence, or their combination in the adjuvant treatment of HER2-positive early breast cancer. ASCO Annual Meeting. Abstract LBA4. Presented June 1, 2014.
153. Bellon JR, Come SE, Gelman RS, et al: Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: Updated results of a prospective randomized trial. J Clin Oncol 23:1934–1940, 2005.
154. Ahn PH, Vu HT, Lannin D, et al: Sequence of radiotherapy with tamoxifen in conservatively managed breast cancer does not affect local relapse rates. J Clin Oncol 23:17–23, 2005.
155. Harris EE, Christensen VJ, Hwang WT, et al: Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. J Clin Oncol 23:11–16, 2005.
156. Pierce LJ, Hutchins LF, Green SR, et al: Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. J Clin Oncol 23:24–29, 2005.
157. Halyard MY, Pisansky TM, Dueck AC, et al: Radiotherapy and adjuvant trastuzumab in operable breast cancer: Tolerability and adverse event data from the NCCTG Phase III Trial N9831. J Clin Oncol 27:2638–2644, 2009.
158. Tan-Chiu E, Yothers G, Romond E, et al: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 23:7811–7819, 2005.