Breast Cancer

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Faculty

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Faculty Disclosure

Contributing faculty, Jacqueline Houtman, RN, MA, CDP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses and allied healthcare professionals invested in the care, delivery of treatment, and relevant education of patients with breast cancer.

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Course Objective

The purpose of this course is to provide nurses and allied health professionals with the information necessary to accurately diagnose and effectively treat patients with breast cancer according to established guidelines, with the ultimate goal of improving patient care and quality of life.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the incidence and epidemiology of breast cancer.
2. Discuss the risk factors for breast cancer, identifying which factors are nonmodifiable versus modifiable.
3. Review hereditary breast cancers with *BRCA1* and *BRCA2* mutations and inherited syndromes.
4. Outline the models used to determine these risks.
5. Review the anatomy and physiology of normal breast development and the lymphatic system.
6. Identify screening recommendations for the early detection of breast cancer.
7. Identify the pathology of benign and malignant breast tumors.
8. Discuss the diagnostic work-up, incorporating the physical examination, imaging, biopsy, and pertinent family history.
9. Analyze the various classifications of breast cancer according to pathology and extent of tissue involvement.
10. Review the staging and grading systems for breast cancers.
11. Analyze surgical options and interventions as primary treatment, including reconstruction and prostheses.
12. Discuss lymphedema and measures to avoid this chronic morbidity.
13. Describe the role of radiation therapy and potential side effects.
14. Evaluate endocrine therapy for the treatment of estrogen- and progesterone-receptor positive breast cancer.
15. Review available systemic chemotherapy for breast cancer.
16. Summarize male breast cancer, outlining risk factors differing to those identified in women.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The same questions have been debated repeatedly over the centuries: Is breast cancer confined to breast tissue with regional involvement? Is breast cancer a systemic disease? Is the malignancy a combination of both? Research indicates that breast cancer is a complex disease with many possible etiologies.

As early as the 1700s, the mechanism by which the lymphatic system disperses cancer cells was acknowledged. Progressing into the 1800s, more refined surgical techniques and anesthesia evolved, with evidence that advanced breast cancer could be slowed by removing the ovaries, paving the way for endocrine therapy. For the first 60 to 70 years of the 20th century, radical mastectomies were the gold standard of treatment. Today, breast-conserving approaches have minimized surgical interventions, emphasizing survival achievable by treating micrometastases with radiation and systemic chemotherapy. Despite significant strides forward, treatment side effects, toxicities, and chronic morbidities such as lymphedema still lag behind in progress.

The heterogeneity of breast cancer presents a treatment challenge. This challenge is being met with targeted therapies to interrupt molecular pathways, biologics, chemotherapy, and radiation. The ability to switch chemotherapy modalities and combine agents to circumvent drug resistance has enabled a small percentage of women with metastatic disease to survive for as long as 20 years [1].

In the inpatient oncology setting, nurses are more accustomed to caring for patients with advanced or metastatic breast cancer as opposed to patients with early-onset disease, who receive their treatments on an outpatient basis. Inpatient nurses may not have an opportunity to appreciate the thousands of women (and hundreds of men) diagnosed with breast cancers who deal with this disease on a daily basis. These patients' lives may revolve around radiation treatments, chemotherapy, and ongoing procedures for breast reconstruction. Simultaneously, women maintain careers, run households, and raise their children; many are also care providers for extended family members. In essence, these courageous women are "getting on with life" [2].

INCIDENCE AND EPIDEMIOLOGY OF BREAST CANCER

The increasing number of women undergoing breast cancer screenings, with resultant detection of malignancies and treatment initiated at an earlier stage, is very encouraging. Breast cancer incidence has been steadily decreasing since 1999, although in recent years it has increased slightly (by 0.5% per year) [3]. However, breast cancer deaths declined by 1% per year from 2013 to 2018 [3]. As of 2022, there are more than 3.8 million breast cancer survivors in the United States, and more than 339,000 additional women will be diagnosed with the disease [3].

Breast cancer is diagnosed more frequently in women than any other cancer (with the exception of skin cancer) and carries the second highest mortality rate after lung cancer [3; 4; 5; 6; 7]. An estimated 287,850 women will be diagnosed with an invasive breast cancer in 2022, and an additional 51,400 women will be diagnosed with carcinoma in situ (CIS) breast cancer [3].

The probability of a woman developing breast cancer if she reaches the age of 85 years is one in eight, or about 12.5%. As noted, rates are much higher in women than in men, with female breast cancer 100 times more common than male breast cancer. Still, an estimated 2,710 men will be diagnosed with breast cancer in 2022 [8; 254].

In 2022, the number of expected deaths from breast cancer in women is 43,250, which equates to approximately 30% of all cancer-related deaths in women [3]. The total number of annual deaths from breast cancer in men is an estimated 530 [9].

The 5- and 10-year relative survival rates are 90% and 84%, respectively, for invasive breast cancer, partly because almost two-thirds of women (65%) are diagnosed with localized-stage disease [10]. Declines in mortality have been more favorable in women with estrogen receptor/progesterone receptor (ER/PR)-positive cancer as opposed to ER/PR-negative disease.

In the United States, non-Hispanic White women have the highest incidence rate overall, although rates vary by age [9]. For example, Black women younger than 45 years of age have a greater incidence rate than their White counterparts [3; 5; 11; 12; 13]. African American women are generally diagnosed with a more advanced and aggressive disease, including triple-negative cancers, which carry a poorer prognosis and lower survival rates [13].

RISK FACTORS

Certain risk factors associated with breast cancer cannot be modified, including age, sex, ethnicity, family history/inherited gene mutations, and hormonal influences. The most significant risk factors for developing breast cancer are female sex, increasing age, and familial breast cancer [4; 12; 14; 15; 16].

It is essential to differentiate between a history of breast cancer in a family and the risk of inheriting a genetic mutation. There is a misguided fear and assumption of being "at risk" when a related family member has a diagnosis of breast cancer. For every woman diagnosed with breast cancer, 20% to 30% will have a relative with this disease. In reality, however, only 5% to 10% of all breast cancers are caused by a mutation in the breast cancer tumor suppressor genes, denoted as *BRCA1* and *BRCA2* [5; 13; 17; 18].

An evaluation of risk may be helpful in identifying persons likely to develop breast cancer and to establish a prognosis. However, it is important to remember that not everyone at risk will ultimately develop breast cancer. Types of calculated risk may be categorized as absolute, relative, or attributable based on modifiable and nonmodifiable factors.

NONMODIFIABLE RISK FACTORS

Sex

The most significant nonmodifiable risk factor for the development of breast cancer is female sex. As discussed, women comprise 99% of breast cancer diagnoses and deaths [19]. Male rates are higher in some countries but are not ever recorded to be greater than 15% of female cases.

Age

Aging increases a woman's risk of developing breast cancer, with age-specific incidence increasing throughout a woman's lifetime and correlating with decreased ovarian activity. The probable cause of a breast cancer diagnosis before 40 years of age is a genetic predisposition. For most women with an average risk, the usual age of onset is after 50 years of age, with most cancers diagnosed in women between 62 and 79 years of age [13; 19; 20].

Race/Ethnicity

As noted, breast cancer incidence and mortality rates vary significantly across racial/ethnic groups. According to data from the Surveillance, Epidemiology, and End Results (SEER) program, American Indian/Alaska Native, Asian Indian/Pakistani, Black, Filipino, Hawaiian, Mexican, Puerto Rican, and Samoan women have higher odds of presenting with stage IV breast cancer compared to non-Hispanic White women [21]. Almost all groups were more likely to be diagnosed with ER/PR-negative disease, with Black and Puerto Rican women having the highest odds ratios (2.4- and 1.9-fold increases, respectively) compared with non-Hispanic Whites. Lastly, Black, Hawaiian, Puerto Rican, and Samoan patients had 1.5- to 1.8-fold elevated risks of breast cancer-specific mortality [21].

Overall, *BRCA1* mutations are estimated to be present in 1 in 500 to 1 in 800 women. However, in Jewish women of Ashkenazi descent, the risk runs much higher at 1 in 40. For Jewish women diagnosed with breast cancer before 40 years of age, at least 20% will have the *BRCA1* mutation [22; 23].

Genetic Predisposition/Family History

Inherited gene mutations are a significant risk factor for the development of breast cancer [19]. An experienced healthcare professional will quickly associate the probability of a genetic mutation with a family history revealing several first- and second-degree relatives reportedly having been diagnosed with ovarian and/or breast cancer. A breast cancer diagnosis established in a younger family member, reports of bilateral breast cancer, or the unusual occurrence of a male family member developing breast cancer implicate a genetic mutation, particularly when the history illustrates no identifiable environmental factors [12; 24].

Breast cancer susceptibility genes *BRCA1* and *BRCA2* are autosomal dominant tumor suppressor genes responsible for 5% to 10% of all cases [23]. *BRCA1* is located on chromosome 17q21, consisting of 1,863 amino acids within 24 coding regions. *BRCA2* was identified on chromosome 13ql2. It has 27 coding regions, producing a protein more prolific than *BRCA1*, with 3,418 amino acids [12; 14; 23; 25].

Carriers of mutated *BRCA1* and *BRCA2* are reduced to one functioning allele on the genes, as one of the wild type (normal) alleles has been lost [23]. When *BRCA1* or *BRCA2* is unable to repair damaged DNA, mutations can potentially result in one or more malignancies.

BRCA1 and *BRCA2* are high penetrance genes, but not 100%. They are seen more predominately in Eastern European populations. As discussed, Jewish women of Ashkenazi descent possess what is termed the "founder effect." This founder effect mutation has stayed within a certain population that has been geographically or culturally isolated; outsiders have not been integrated within this specific population. Three founder mutations have been located with *BRCA1* (187delAG and 5385insC) and *BRCA2* (617delT). Populations possessing a founder effect have been identified in Sweden, Holland, Iceland, Hungary, and France; ethnic groups include African Americans and Hispanics [14; 22; 23].

BRCA1 and *BRCA2* are inherited by both men and women (i.e., are not in sex-linked chromosomes) and confer a 50% chance any offspring will inherit the mutation [23]. For reasons as yet unknown, not everyone who inherits the mutation will go on to develop hereditary breast or ovarian cancer. In these individuals, the risk then becomes comparable to that of the general population. This germ line (inherited) mutation cannot skip a generation. Even if the mutation does not manifest as breast cancer, it is still passed on [18].

According to the American Society of Clinical Oncology, women at high risk for familial breast cancer syndromes should be referred for genetic counseling. Criteria to recommend referral include: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before 50 years of age; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative.

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Level of Evidence: Expert Opinion/Consensus Statement

Women who inherit the breast or ovarian cancer gene have a lifetime risk of 50% to 85% of developing breast cancer. There is an 11% additional risk of developing a contralateral breast malignancy within five years, rising to 25% to 27% by 10 years after diagnosis [24; 26]. First-degree relatives have a 50% chance of inheriting the gene, and second-degree relatives have a 25% chance of this inheritance [18]. *BRCA1* mutations confer an additional risk of uterine, pancreatic, cervical, and gastric cancers. *BRCA2* risks include pancreatic, stomach, gallbladder, and bile duct cancers [23; 25].

Genes other than *BRCA1* and *BRCA2* have also been implicated in increased breast cancer susceptibility [27]. Rarer inherited genetic mutations include those associated with Cowden, Li-Fraumeni, and Peutz-Jeghers syndromes and ataxia telangiectasia [4; 28]. Of these, Cowden and Li-Fraumeni syndromes are the most common [29].

Cowden Syndrome

Cowden syndrome, also known as multiple hamartoma syndrome, is a rare autosomal dominant disorder. The tumor suppressor gene is the major phosphatase and tensin homolog gene (*PTEN*) located on chromosome 10q23.3. Although it is a benign disease, considerable morbidity is experienced. Several distinct features characterize this disease, including macrocephaly and hamartomas, benign tumors that manifest on various sites. These tumors include trichilemmomas (roughened papules) on the face, papillomas on the lips and mucous membranes, acral skin keratosis, and palmar-plantar lesions. In all, 90% of individuals with inherited *PTEN* mutations exhibit skin changes by 20 years of age.

Hamartomas may also develop on the thyroid gland, with early-onset thyroid cancer common. Most women with Cowden syndrome (75%) will develop fibrocystic breasts, fibroadenomas, ductal hyperplasia, and/or lobular atrophy. In premenopausal women, 25% to 50% will develop breast cancer, usually invasive ductal, with the potential for bilateral and multifocal lesions [14; 18; 23; 25; 30].

Vigilance is required with screening for men and women. Beginning with a very thorough physical examination at 18 years of age, or five years previous to the reported age a family member was diagnosed, a clinical breast examination (CBE) should occur every six months starting at 20 years of age, followed by an annual mammogram and magnetic resonance imaging (MRI) beginning at between 30 and 35 years of age. Genetic screening and counseling should be offered [30].

Li-Fraumeni Syndrome

Li-Fraumeni syndrome was initially identified in 1969 in young adults with sarcomas. Early-onset breast cancer, soft tissue and bone sarcomas, brain tumors, and leukemia are associated with this syndrome. In 1990, the tumor suppressor gene *TP53*, located on chromosome 17p13.1, was implicated in this condition. In patients with Li-Fraumeni syndrome, 70% have the *TP53* mutation. *TP53* plays a vital role in slowing the progression of the cell cycle when damaged DNA is in need of repair.

This autosomal dominant mutation is highly penetrant, with a lifetime risk for women of 100%. Breast cancer can occur as early as 15 years of age for patients with Li-Fraumeni syndrome, and tumors are human epidermal growth factor receptor-2 (HER2)-positive in the majority of cases.

Beginning at 18 to 20 years of age, an annual physical and neurologic examination is necessary. Monthly breast self-examination (BSE) and bi-annual CBE are also recommended. Annual mammogram should begin at 20 to 25 years of age.

If breast cancer is diagnosed, full mastectomy is advised rather than partial mastectomy (lumpectomy) and radiation in order to decrease the risk of a secondary primary and/or subsequent radiation-induced malignancy. Genetic counseling is essential due to the complexity of genetic heterogeneity [14; 18; 22; 25; 31; 32].

Hormonal Influences

Years of exposure to endogenous estrogen and progesterone, plus sporadic changes in breast tissue, play a major role in the risk of developing breast cancer. Early menarche and late menopause increase the risk, implicating the total number of menstrual cycles women experience as the contributing factor [5; 13; 33].

Breast Density

Breast density has been established as a predicted risk for breast cancer, with very dense tissue increasing the risk three- to fivefold. Adding to this increased risk is the impact of greater breast density on the interpretation of imaging studies. Dense breast tissue images as white enhancements on mammograms, as opposed to black, posing a challenge to identifying masses [13; 15; 26; 34; 35].

Exposure to Mantle Radiation

Women who received mantle radiation to the chest before 15 years of age (typically for Hodgkin lymphoma) are at increased risk for developing breast cancer. Younger age at exposure and a higher dose of radiation correlate with risk level. The risk continues for 25 years, with an estimated 12% to 20% of women developing breast cancer by 45 years of age. Childhood survivors of Hodgkin lymphoma mirror the disease course seen in women with *BRCA1* mutations, with diagnosis usually occurring between 32 and 35 years of age [13; 36; 37; 38].

Existing Breast Cancer

Women who have had breast cancer have a three- to fourfold increased risk of developing a new cancer in the other breast or in another part of the same breast, which is considered different from a recurrence of the original malignancy. Invasive or in situ breast cancer can result in a contralateral breast malignancy, although estimates of this likelihood vary widely. Approximately 5% of women with in situ tumors will progress to an invasive contralateral malignancy within 10 years, with a greater risk in premenopausal than postmenopausal women [39].

Benign Breast Disease

Caution is warranted when discussing benign breast disease as a risk factor for cancer development, as it can cause unnecessary panic on the part of patients. Many documented benign breast diseases are purely benign and present no risk for malignancy. However, some conditions are linked to an increased risk, particularly those with histologic findings consistent with atypical hyperplasia [40]. Atypical hyperplasia, whether lobular or ductal, confers a risk more than four times greater than among women without breast disease. Proliferative lesions without atypia (e.g., fibroadenoma, sclerosing adenosis) raise a woman's risk of breast cancer slightly (about 1.5 times the usual risk). These changes can affect one or both breasts, and a familial history further increases the risk [4; 28; 40].

MODIFIABLE RISK FACTORS

Obesity

In postmenopausal women, overweight and obesity are risk factors for breast cancer. Increased adipose tissue correlates with greater circulating estradiol, although it is questionable as to the timing when excess weight may actually influence estrogen storage [41]. An additional concern is whether excess body fat can mask clinical findings, causing a delay in making a diagnosis, in particular with disease recurrence [42]. Higher mortality has been noted in inactive, obese women than active, slimmer women [3].

Alcohol Consumption

Consumption of two or more alcoholic beverages per day is associated with a 20% higher breast cancer risk in pre- and postmenopausal women, an effect attributed to alcohol's stimulatory action on the carcinogen acetaldehyde [41]. In addition, DNA repair is suboptimal when poor nutrition accompanies an excess intake of alcohol [4; 13; 14; 29].

Parity

Women who are younger than 18 years of age when they deliver their first full-term infant have a lower risk of developing breast cancer than women who are 30 years of age or older when delivering their first full-term child. Risk increases after pregnancy for approximately 10 years, changing then to a more sustained protective effect. Overall, the relative risk is higher for women who give birth at an older age than for women who remain nulliparous [13].

Lactation

Breastfeeding confers a protective effect against developing breast cancer. Research indicates the total amount of time breastfeeding correlates with risk level. One year or more of breastfeeding reduces the risk by 26%, with an additional 7% reduced risk with each live birth [14; 43].

Hormone Replacement Therapy

Postmenopausal women on combination hormone replacement therapy (HRT) appear to have an increased risk for the development of breast cancer, although those taking estrogen alone (and not progesterone) do not. Increased risk is seen in women in as little as two years after initiation of combination HRT. In addition, these women develop denser breast tissue, which presents a challenge with mammogram interpretation [14].

RISK PREDICTION MODELS

It is natural for women to question the risk to her personally of developing breast cancer. Before embarking on any risk assessment, it is prudent to determine the extent of the patient's knowledge relating to her family history, her understanding of what the family member(s) experienced, and how much she is willing to learn. All patients will approach this experience from different backgrounds, with cultural and ethnic beliefs helping guide personal decisions [44].

Some women will independently pursue answers conducting their own basic research, while others will accept guidance and input solely from the healthcare team; both are acceptable [6]. This may be an opportune moment to ascertain what beliefs or stories women have been exposed to, reassuring them that diagnostics are less intrusive and surgical procedures will aim to minimize the amount of tissue removed.

Several breast cancer risk prediction models exist, and many are available online. Decisions for selecting a particular model are based on an individual woman's history, with two major pathways [23]. Is the risk very low or average for developing breast cancer, or is there a known or suspected familial history or hereditary trait of breast cancer? If the prediction model determines a risk exists, this will provide a mechanism to either treat preventively or make the necessary referral for genetic testing [4].

There are no clearly defined criteria to determine "high" risk. Models designed for women at higher risk require more detailed information about personal and family history of breast and ovarian cancers, including ages at onset of cancer and/or carrier status of specific breast cancer-susceptibility alleles [23]. The general consensus is that a genetic mutation, such as *BRCA1* or *BRCA2*, and presence of a high number of first- and second-degree relatives with a breast cancer diagnosis fit into the category of "high" risk [4; 24; 28]. Models used to determine risk are not all-inclusive tools, but they can provide a good basis for practitioners to work from. A risk assessment can be confusing for patients and may prove to be a challenge for some practitioners as well. Any doubt on the practitioner's part as to their personal ability to complete a risk model should be acknowledged and the appropriate referral made to those with the expertise.

Breast Cancer Risk Assessment Tool

Empiric models are appropriate tools for assessing risk when it is improbable there is a hereditary predisposition, which would require genetic testing [4; 45]. The National Cancer Institute (NCI) developed the familiar Breast Cancer Risk Assessment Tool (BCRAT), better known as the Gail model, in 1989. The BCRAT predicts the risk of invasive breast cancer within the next five years and up until 90 years of age by incorporating the following data [13; 15; 45; 46; 47]:

- Age at menarche
- Age at delivery of first live birth
- Breast biopsies performed previously (negative result)
- First-degree relatives with breast cancer
- Race/ethnicity
- Age of patient
- History of any breast cancer

The established cut score for the BCRAT is 1.66%; women who score lower are considered at lower risk, while those who score at or above this are high risk.

Although the BCRAT has been validated for White women, Black/African American women, Hispanic women and for Asian and Pacific Islander women in the United States, it may underestimate risk in Black women with previous biopsies and Hispanic women born outside the United States. Additionally, because data on American Indian/Alaska Native women are limited, their risk estimates are partly based on data for White women and may be inaccurate [47]. Additional disadvantages of the BCRAT include that it is designed only for women 35 years of age or older. No questions are related to a personal or family history of ovarian cancer, and there is no inquiry into distant family members or the age of onset of those with a breast cancer diagnosis. The role of race/ethnicity for African American women and other specific populations is excluded. Finally, the pathology report pertaining to a biopsy is excluded, even though the biopsy report is significantly more valid than the fact a biopsy was performed [18; 47].

The Claus Model

The Claus model is well suited for risk assessment when there is a significant family history of breast cancer. This model calculates risk at 10-year increments based primarily on items assessing family history [23]. The Claus model has the disadvantage of excluding ethnicity, hormonal/reproductive factors, personal breast disease, and ovarian cancer. *BRCA1* and *BRCA2* mutations are not calculated [18].

The BRCAPRO Model

The BRCAPRO is the most widely used and studied model to assess the probability of a genetic mutation, focusing on *BRCA1* and *BRCA2* plus any family history of breast cancer. The BRCAPRO combines components of several risk assessment models including the Couch model, the Claus model, the Shattuck-Eidens model, and the Frank model. The model cumulatively builds on several variables, including age at diagnosis and first- and second-degree family members with any relevant history of breast or ovarian cancer. Race/ethnicity is also incorporated into this model [4; 18; 22].

AN OVERVIEW OF BREAST AND LYMPH ANATOMY

BREAST ANATOMY AND DEVELOPMENT

Approximately five weeks after conception, embryonic breast tissue begins to develop. Cells at this early stage appear as little more than a ridge or thickened area of tissue. At approximately 10 to 16 weeks, more defined tissue forms the foundation for glands for milk production. Muscle cells form the nipple, with the darkened area of areola containing sebaceous glands surrounding the nipple protrusion. As pregnancy advances with hormonal influence from placenta to fetus, the glands with the ability to produce milk form as lobules. From birth to puberty, the 10 to 12 rudimental ducts formed beneath the nipple and areola slowly continue to form into more mature ductal structures.

From the onset of puberty, the female breast takes approximately three to four years for glandular maturation. However, full breast differentiation is only achieved with pregnancy and lactation. At puberty, the hypothalamus releases gonadotropin-stimulating hormones, which act on the anterior pituitary gland. The anterior pituitary in turn releases follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH promotes ovarian follicular maturity, with the subsequent production of estrogen, mainly in the form of 17-beta estradiol. Breast tissue enlarges due to the influence of estrogen and the allied growth hormones of glucocorticoids [48; 49].

During a woman's lifetime, breast tissue undergoes many changes influenced by the fluctuating hormone levels of estrogen and progesterone. After formation, maturation, and differentiation, tissue regresses with menopause and aging [48].

Breast tissue is primarily composed of epithelial and fibrous connective tissue. The mature breast, or mammary gland, lies on the anterior chest wall, on a vertical axis between the second and sixth rib, and on a horizontal line between the sternum and mid-axilla. The tail of Spence extends into the axilla.

Enveloping the breast is the superficial pectoral fascia; underlying supporting muscles are the pectoralis major and serratus anterior muscle. The fascia from these two muscles is connected by Cooper ligaments weaving between the lobes throughout the breast tissue. These suspensory ligaments lend form and anchorage to the breast tissue. The internal mammary artery supplies blood to the majority of breast tissue, but the upper outer quadrant of the breast receives its supply from the lateral thoracic arteries. The superficial lymphatic vessels, which can only propel lymph in one direction, drain into deeper lymphatics and subsequently to the axillary nodes. The axillary nodes receive 97% of the lymph; the remaining 3% drains into the internal mammary node.

Approximately 15 to 25 lobes are arranged in a circular pattern in the round protuberant breast. These lobes contain ducts that end in tiny branches or clumps of acini (which become alveoli when milk is produced) and are known as the terminal duct lobular unit (TDLU). The TDLUs are linked by smaller ducts that then merge into 5 to 10 ducts opening on the surface of the nipple. The nipple has surrounding pigmented areola with sebaceous glands for lubrication. The superficial portion of the ducts is lined with epithelium, transitioning to glandular epithelium distally. The ductules of the TDLUs are lined by two different types of cells: the luminal cells, which are responsible for secreting milk, and the myoepithelial cells, which function to eject the milk. The myoepithelial cells, as the name suggests, are epithelial cells and smooth muscle and are sandwiched between the basement membrane and luminal cells, constituting the basal layer [49; 50].

THE LYMPHATIC SYSTEM

The lymphatic system has some similarities to the vascular system. Smaller lymphatic vessels drain into increasingly larger vessels, leading to the blood capillary-interstitial-lymphatic vessel interface. Varying pressures dictate how much fluid from arterial capillaries enters the interstitium, including the osmotic colloid pressure from both the plasma and interstitial fluid and pressure exerted from the capillary itself. The filtration pressure from these components working simultaneously is 13 mm Hg. A pressure of 7 mm Hg from the venous capillaries counteracts this, allowing approximately 90% of filtered fluid to return to the venous system [51; 52; 53]. The function of the small lymphatic vessels in the interstitium is to remove the remaining 10% of large protein molecules and fluid the venous system cannot accommodate.

Lymphatic vessels differ from those of the circulatory system, as they function within a low pressure system supported by the close proximity of pulsating arteries (with smooth muscle within the larger lymphatic vessels promoting peristalsis). The valves (lymphangions) within the vessels permit the lymph to be transported in one direction only.

The body is divided into the right and left lymphatic systems. The right lymphatic duct receives lymph from the right side of the head and neck, the right arm, and the right side of the upper trunk. This lymphatic duct then drains into the right venous angle, located between the right internal jugular and right subclavian vein. The right subclavian vein returns lymph to the heart, where it subsequently flows back into the systemic circulation as plasma. The left side of the lymphatic system carries a far greater load and is responsible for the lower extremities, the pelvic area, the left side of the head and neck, the left chest, and the left arm. Lymph returning from the lower extremities and pelvis collects into the cisterna chyli in the mid-abdominal region before being propelled on to the thoracic duct. From the thoracic duct, the lymph continues to the final drainage area in the left venous angle. Parallel with the right, the left subclavian vein returns lymph to the circulation as plasma [52; 53; 54; 55; 56; 57].

There are approximately 600 to 700 lymph nodes throughout the body, and damaged nodes cannot regenerate. When a malfunction occurs in the lymphatic system, caused by injury from a surgical intervention or as a side effect from radiation therapy, lymphedema can result. Lymphedema occurs in 5% to 9% of patients undergoing sentinel lymph node biopsy (SLNB) and up to 40% of patients who have had axillary lymph node dissection (ALND) [51; 52; 54].

SCREENING FOR BREAST CANCER

Screening for breast cancer begins with a routine history and physical examination. Information pertaining to the health of the patient and any family history of breast or ovarian cancer is included. Subsequent office visits require an update of any new and relevant information. Nurses should take every opportunity to educate and emphasize the goal of breast cancer screening: early detection reduces mortality. In addition to the history and physical, screening includes BSE, CBE, and mammography [35; 46; 58; 59].

BREAST SELF-EXAMINATION

Less emphasis is placed on BSE today compared to previous years, as BSE has not demonstrated any significant difference in mortality rates [60]. It is equally acceptable for women to perform self-exams on a routine basis or sporadically; the technique is the most valuable component. Care providers should request a return demonstration from patients to ensure the BSE is performed correctly. More importantly than whether or not BSE is performed, patients should develop an awareness of any changes in their breasts [15]. Any pain, detectable lumps or masses, skin changes (especially in or around the nipple), or evidence of bleeding or discharge should be reported as soon as detected [7; 46; 61].

CLINICAL BREAST EXAMINATION

CBEs are performed by skilled healthcare professionals, usually at each yearly appointment, with women examined in both upright and supine positions. The examination should be very thorough, focusing on both breasts and including the axillary, infraclavicular, and supraclavicular node beds. This examination, with the same criteria applicable to mammograms, should be scheduled around the first and second weeks after menstruation to avoid changes in breast tissue related to hormonal fluctuations [61].

MAMMOGRAPHY

Mammography serves a twofold purpose: to screen and to diagnose. In particular, mammograms are used to detect tumors that are too small to palpate, allowing for earlier diagnosis and more effective treatment (e.g., ductal carcinoma in situ [DCIS]) [46; 61; 62]. This section will focus on the use of mammography in screening for breast cancers.

The outcome of a consortium headed by the NCI in 1977 resulted in the breast cancer screening guidelines evolving into the standard currently endorsed today. Beginning at 40 years of age, women at average risk for breast cancer should undergo a yearly screening mammogram, reimbursable by Medicare or private insurance [7]. Mammograms are subsequently scheduled for intervals of at least one year and one day to be eligible for insurance coverage. Screening guidelines are evidence-based, with a general consensus from governing bodies such as the NCI and the American Cancer Society (ACS). Revisions generally occur every five years, depending on relevant research. Shared decision making drives any changes, with a focus on the potential for harms and benefits derived from screening [7; 46; 63].

Some controversy arose in 2009, when the U.S. Preventive Services Task Force (USPSTF) recommended mammograms for screening purposes to begin at 50 years of age, continuing every two years until 74 years of age, a recommendation they reaffirmed in 2016. As of 2022, an update was in progress [64]. Other organizations (i.e., the Centers for Disease Control and Prevention, ACS) recommend that women 45 to 54 years of age and those 40 to 44 years of age who choose to begin screening before 45 years of age, should be screened annually, and women 55 years of age and older should transition to biennial screening or continue annual screening, if that is their preference [65; 66].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Obstetricians and Gynecologists recommends offering annual or biennial mammography screening starting at age 40 years of age. They recommend initiation of screening between 40 and 49 years of age after counseling, if the patient desires. Shared decision making that incorporates patient values regarding relative benefits and harms is stressed.

(https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2017/07/breast-cancer-risk-assessment-and-screening-in-average-risk-women. Last accessed July 21, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

With the use of screening mammography, approximately 75% of breast cancers are detected in women 40 to 49 years of age and 90% are detected in women in their 60s. These statistics are encouraging, but research indicates thousands of women without insurance, of certain racial/ethnic minorities, and with lower levels of education undergo screening either sporadically or not at all. These groups require targeted outreach to improve screening rates and prognosis [7; 29]. For all women, it is important to schedule mammograms to accommodate home and work obligations. Flexibility with scheduling and timely reminders prior to appointments will help increase compliance.

Preparing for a Mammogram

Premammogram instructions should discourage the use of deodorant, talcum powder, lotion, or perfume prior to the examination, as the presence of these substances can cause light particles on the images, mimicking calcifications [67]. Women are counseled that the actual time taking the images amounts to a few seconds, although it may feel longer due to discomfort of the breast tissue being so firmly compacted. Two views are taken of each breast: cranial-caudal and mediolateral-oblique [46].

Mammogram Interpretation

Mammograms are interpreted through the Breast Imaging Reporting and Data System (BI-RADS). Women receive a written report of their mammogram results, in terms they can understand, within 30 days of their screening. The four descriptions of breast tissue range from fatty to dense. The detection of abnormalities (or lack thereof) is categorized as [67; 68; 69; 70]:

- 0: Readings are inconclusive; requires further imaging.
- 1: Findings are negative; continue routine screenings.
- 2: Findings are benign (e.g., fibroadenoma, cyst); continue routine screenings.
- 3: Abnormality is presumed benign. Follow-up mammogram in six months, the findings of which may rarely necessitate a biopsy. Possibility of malignancy is less than 2%.
- 4: Abnormality is suspicious. Biopsy required for histology as malignancy detected in 25% to 50% of masses.
- 5: Highly suspicious requiring intervention. If first tissue biopsy is benign, re-sample from a different site, as there is a 95% malignancy rate.
- 6: Imaging with biopsy yielded positive malignancy.

Errors in mammogram interpretation do occur, with variations in breast density, extremes of body type (obese or underweight), HRT, and the skill of the radiologist all impacting the findings [67]. In particular, this modality has a general inability to distinguish cysts from solid masses. False-positive results requiring a follow-up study can provoke anxiety, not only during the time before the re-screening but also while waiting for the subsequent results. False-positive results can also result in an unnecessary biopsy and/or overtreatment of a non-aggressive benign lesion. In reality, of the 11% of mammograms requiring further investigation, 90% prove to be benign [62].

The cost of a mammogram is relatively inexpensive, at approximately $150, yet a large number of women continue not to be screened. There are many barriers other than cost that contribute to this discrepancy. Pain and embarrassment have been noted to contribute to lack of compliance with screening recommendations, with anxiety before appointments a significant factor [71]. Language barriers, lack of transportation, lack of health insurance, and low income have also been identified as impedances. In addition, long office wait times and lower mammography capacity have been found to decrease screening rates [72]. Some women have an exaggerated sense of the amount of radiation exposure from a mammogram. In reality, the amount of exposure is insignificant.

The majority of women who undergo mammography do so due to healthcare professionals' recommendations and endorsements [36]. If 5% more women underwent mammography each year, as many as 560 deaths could be prevented annually. Nurses and other healthcare professionals have an obligation to educate and endorse the guidelines for breast cancer screening recommendations in order to improve the screening rate and overall survival [35; 71].

SCREENING RECOMMENDATIONS

Average-Risk Women

Counseling should begin at 20 years of age and include information on the early signs and symptoms of breast cancer and a recommendation for CBE at least every three years. This should continue until 45 years of age, after which annual CBE and mammography should begin. Women 40 to 44 years of age should have the opportunity to begin annual screening [65].

High-Risk Women

Beginning at 30 years of age, annual mammography and MRI are recommended for women if they have [65; 73]:

- A risk assessment score greater than 20% to 25% (e.g., using BRCAPRO)
- A known history of breast cancer in a first-degree family member
- An established *BRCA* mutation

The USPSTF recommends that high-risk women should receive genetic counseling and, if indicated after counseling, genetic testing for *BRCA1/2* [74].

Childhood Cancer Survivors

Women 25 years of age and older who received mantle radiation for childhood Hodgkin lymphoma should be followed very closely by a skilled healthcare professional. Intensified surveillance for survivors involves CBE every six to 12 months, continual breast awareness, and scheduled yearly mammograms. Mammograms should begin within eight to 10 years after the radiation ceased or at 25 years of age. Annual MRI is also recommended, although the efficacy of this continues to be debated [15; 36; 58].

PATHOLOGY OF BREAST LESIONS

Most benign breast lesions are diagnosed in women between 20 to 50 years of age, amounting to 90% of diseases of the breast [58]. Although it is rare to be diagnosed with a malignancy prior to 30 years of age, it should never be presumed that symptoms of masses or lesions in younger women will be nonmalignant. Any and all clinical findings denoting changes in breast tissue should be investigated. Invariably, a diagnosis of breast cancer is established when a biopsy is performed for diagnostic purposes [58].

Benign lesions are classified as proliferative or non-proliferative. Non-proliferative lesions do not raise cause for concern, but proliferative disease plus atypical hyperplasia confers a risk of developing breast cancer. Women with atypical hyperplasia who have a family history of breast cancer are at greater risk than those with no family history of the disease [4]. Close surveillance with a CBE every six months, an annual mammogram, and an emphasis on a healthy lifestyle with a nutritious diet and avoidance of alcohol is strongly advocated [75; 76]. HRT and the use of oral contraceptives should be avoided in these patients.

Fibrocystic changes are identified more frequently than any other benign breast mass, and fibroadenoma, comprised of both glandular and structural tissue, is the most common type of benign tumor diagnosed in women 20 to 35 years of age. These tumors arise in the intralobular fibrous stroma of breast tissue. Surveillance with routine screening is usually sufficient treatment if there is absolute assurance that it is not a phyllodes tumor [77].

Phyllodes tumors are similar to fibroadenomas, but the benign epithelial cells are proliferated, requiring close surveillance. Tumors with no metastases should be removed with clear margins to prevent a recurrence; however, even borderline low-grade phyllodes that exhibit no metastases have the potential to recur [77]. High-grade tumors mimic sarcomas, and metastatic spread may present years after initial diagnosis with the disease discovered in the bone, lung, and pleura.

Sclerosing adenosis, a benign condition of the breast in which extra tissue develops within the breast lobules, is typically detected when breast biopsies are performed. Sclerosis of the lumens of the glands occurs with overgrowth of benign lobular tissue [77].

Women may experience pain associated from enlarged cysts due to microcalcifications. Increased symptoms correlating with menstrual hormonal fluctuations are not uncommon, and palpable nodules or a ropey texture felt within the breast tissue may be reported. Discharge from the nipples may also be experienced. Any bilateral brown or green discharge is deemed physiologic, but if the discharge is bloody, it warrants further investigation to rule out any pathologic process [76].

DIAGNOSTIC EVALUATION

When women present with a suspected breast malignancy, it is essential to establish a good rapport and for practitioners to be attentive, sensitive listeners. While this may be the beginning of a long process of establishing trust and developing a mutual respect, it is evident that this professional relationship can be invaluable for patients and their families. Patients experience many challenges during their cancer survival journey, setting goals and achieving milestones with courage. The tertiary stage of screening and surveillance has its own set of challenges [2].

INITIAL PRESENTATION

The leading symptom experienced by women presenting with a suspected breast cancer is discovery of a lump or abnormality in their breast. This may be a palpable lump detected by the patient or the result of an abnormality detected by a screening mammogram requiring further workup [78]. Far less frequent presentations include discharge from the nipple, pain, or change in the size or shape of the breast. The first step at this stage is obtaining a thorough patient history that explores personal history of breast, ovarian, or childhood cancer; family-related history; current medications, including any oral contraceptives; and the date of their last menstrual cycle and cycle regularity. Younger women present a challenge with

diagnostics, as breast tissue changes with fluctuating hormone levels and younger women tend to have denser breast tissue [69]. In older women, the focus changes to include questions regarding menopause and any prescribed HRT [67].

PHYSICAL EXAMINATION

A thorough examination of both breasts requires the patient to undress to the waist. This initial inspection checks for any asymmetry in the breasts, which may be chronic or a new development. Any edema noted is usually detected below the nipple line, invariably caused by tumor cells invading the dermal lymphatics, as seen with inflammatory breast cancer, or metastatic disease spreading to the axillary lymph nodes. In women with pendulous breasts, it is not abnormal to detect some edema while upright, but it should resolve when the patient is supine. Nipples are assessed for any inversion, discharge, skin abnormalities, or eczematous skin changes. This part of the examination is undertaken with the patient in the sitting position, arms relaxed, hands placed on hips to flex the underlying pectoral muscles. Arms are then raised and finally stretched out in front, which permits observation of any skin puckering or dimpling or any retracted areas of breast tissue [69].

Lymph nodes in the axilla and clavicular area should be palpated. Pain is an abnormal finding. The detection of any clumped, fixed, inflamed, immobile, soft, or firm nodes should be clearly documented in the record. A minor infection in the hand or arm can result in some nodes becoming mildly inflamed, so this should be explored if nodes appear changed.

The examination will be completed with the patient in the supine position, with the breasts palpated in a circular pattern, pressing as firmly as permitted. Pushing on the nipple should not yield any resistance [58; 79].

Patients should be informed of the various imaging tests and biopsies included in the diagnostic work-up. Some of the simpler tests, such as a chest x-ray and blood work, including a complete blood count (CBC), comprehensive metabolic panel (CMP), and liver function tests, are obtained to establish a baseline. If there is a nurse navigator or breast care specialist on site, these clinicians prove to be a valuable resource to patients and their families throughout the course of their treatment [2; 6; 80].

GENETIC TESTING

There are resources available to identify genetic profiles of persons with possible breast cancer or an increased risk, including the 21-gene recurrence score (Oncotype DX) and the Amsterdam 70-gene prognostic profile (MammaPrint). Online prognostic tools, such as Adjuvant! and Predict, give an estimated prognosis, examining the likelihood of recurrence and mortality associated with chemotherapy, hormone therapy, or both after surgery. These tools are geared toward early unilateral disease with no metastases, with axillary nodes staged; radiation should be included in the treatment plan with breast-conserving surgery [81]. Predict is available at https://breast.predict.nhs.uk; as of 2022, the Adjuvant! site (http://www.adjuvantonline.com) was under construction [45; 82; 83; 84; 85].

IMAGING

Diagnostic Mammography

Although the same scanner and technique apply to a diagnostic mammogram as with a screening mammogram, there is more deliberation with the diagnostic imaging. This involves taking a series of pictures of breast tissue, capturing as many nodes as possible. The radiologist, who may even be accompanied by a second radiologist for additional input, is present during the scanning, reading each image until a decision is reached to either schedule a follow-up appointment within three to six months or recommend proceeding with an ultrasound-guided biopsy. Ideally, the biopsy should be obtained as soon as possible following the diagnostic mammogram.

If a defined mass is known to be malignant, it is imperative to complete the mammogram before the biopsy, as changes occur in the breast tissue after the biopsy has been completed. For women with a history of breast-conserving surgery and prior radiation treatments, mammograms are less sensitive and more challenging to read due to scar tissue [61].

Ultrasound

After the initial mammogram, an ultrasound may be completed, if necessary [86]. The main utility of ultrasound is its ability to distinguish a cyst from a solid mass. The order for an ultrasound should summarize the location of the detectable lump and describe the findings. If the mass is solid, the location (described by placement on a clock face) and distance from the nipple should be noted. The order should also indicate if the mass should be aspirated or biopsied.

Ultrasound is noninvasive and painless, although patients may experience some discomfort with pressure from the scanner if the breast is tender or inflamed. The patient is positioned in a semi-reclining position with her wrist over her forehead to enable the area of breast tissue to be thinned as much as possible. Women with larger breasts may need to sit more upright, allowing gravity to help with positioning of pendulous breasts. As with scheduling mammograms or breast examinations, the ideal time for ultrasound for premenopausal women is one to two weeks after their menstrual cycle. Having the radiologist present to evaluate the images in real time is preferable.

In patients with suspected inflammatory breast cancer, ultrasound is preferred over mammography. For these patients, ultrasound will determine if the lymphatic vessels and nodes are engorged and will ascertain the thickness of the skin [7; 86].

Magnetic Resonance Imaging

MRIs are costly but invaluable in showing the extent of the breast tumor. MRI is used for both screening and diagnostic purposes, although the CDC and the ACS only recommend both annual mammogram and MRI for high-risk women [62; 66]. Prior to an MRI being performed, patients are routinely screened for any implanted metal objects, questioned as to whether they are claustrophobic, and cautioned they will need to remain still. The scanner is loud, and patients are offered ear plugs or headphones to muffle the sound. If contrast is ordered with the MRI, a renal panel will be obtained to check creatinine and blood urea nitrogen. The contrast injected for the MRI is gadolinium diethylenetriamine penta-acetic acid (DTPA), which has the potential to cause nephrogenic sclerosing fibrosis if any renal impairment exists [61; 68].

TUMOR BIOPSY

MRI-Guided Core Biopsy

In patients with suspicious mammography findings or a palpable breast mass, biopsy may be indicated. An MRI-guided core biopsy requires the use of a breast biopsy coil and a specialized table for the procedure. For the biopsy, women are placed prone on the table and informed that additional time is required to move them in and out of the magnet field and to exchange metal with plastic equipment for safety within the scanner. A needle biopsy may be sufficient, or a vacuum-assisted device can be used when obtaining a larger tissue sample. After the biopsy has been obtained, a titanium clip is placed in the breast to mark the lesion. If the biopsy is highly suspicious for a malignancy, a repeat MRI may be necessary [87].

It is imperative that the images are captured within the first minutes after the gadolinium is injected, when the vascular tumor is highlighted and before there is any detectable uptake of the contrast by any benign lesions. The downside to using contrast with an MRI is that normal breast tissue may appear abnormal due to hormonal influence. Fibroadenomas, mastitis, necrotic areas, and atypical hyperplasia will also be highlighted, potentially resulting in an unnecessary biopsy being performed [68].

Fine-Needle Aspiration

Percutaneous fine-needle aspiration (FNA) is used when a mass, usually a cyst, is palpable and does not require imaging to locate the site. An FNA is used to biopsy BI-RADS category 3, 4, or 5 lesions.

The procedure is minimally invasive and inexpensive, requiring small-gauge needles size 23 to 27 and a 10- to 20-mL syringe. The needle is inserted in the lesion and twisted to obtain cells. Once retrieved, the tissue is deposited in preservative solution and sent for cytology. The downside of FNA is its inability to distinguish between an invasive and an in situ lesion; it should not be performed for suspected DCIS. There is also a possibility of an insufficient number of cells being obtained, resulting in an equivocal diagnosis [88; 89]. An estimated 10% to 20% of malignancies are undetected with FNA due to false-negative findings [90; 91].

Caution is warranted when benign cysts are aspirated on a fairly regular basis (e.g., for women with cystic breasts). Fluid removed should be assessed for consistency and color and compared to any previously obtained aspiration. Any change in the color of the aspirate or the presence of blood indicates the fluid should be sent for cytology [91].

Core-Needle Biopsy

A core-needle biopsy is appropriate for BI-RADS category 4 lesions with suspicious, nonpalpable masses. A core sample is more substantial compared to the amount of tissue obtained with FNA. The procedure is minimally invasive, and anticoagulants do not need to be put on hold. The area is numbed with local anesthesia, and a large-gauge needle and an automated biopsy gun obtain the core tissue. Women generally prefer this method to the stereotactic biopsy, as it is less time consuming and no x-ray is required. Ultrasound can be used for guidance if needed [68; 88; 89; 90].

Stereotactic Biopsy

A stereotactic biopsy may be performed for microcalcifications, nonpalpable lesions, locally advanced breast cancer, and DCIS. Some preparation is required prior to the biopsy being performed as it is a more extensive procedure.

Anticoagulants may be held a few days prior to the biopsy, under the guidance of the patient's primary care provider, with prothrombin time/international normalized ratio checked prior to the biopsy. Additionally, any routine use of vitamin E, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs) should be halted. Prophylactic antibiotics may be required for patients with a history of mitral valve replacement. Patients with chronic back pain, chronic obstructive pulmonary disease, obesity, persistent cough, or history of anxiety may not be eligible for stereotactic biopsy.

When undergoing a stereotactic biopsy, patients are required to lie prone and must be able to remain still for approximately 15 to 20 minutes, or longer if an MRI scanner is used [92]. Of note, the table has a weight limit of 350 pounds. Lying prone, patients are shielded from seeing the equipment housed below the table. The patient is prepped for the sterile procedure, and the area is numbed with local anesthetic. A 14-gauge needle is inserted into the breast, running parallel to the chest wall to prevent needles being propelled into the chest wall and subsequent pneumothorax. Women with small breasts may require a different approach to achieve the 2-cm thickness of compressed breast tissue required to safely obtain the stereotactic biopsy [92]. A core-needle biopsy with a vacuum-assisted device, using 8- or 11-gauge needles, can be used if a number of sites are to be biopsied; the 8-gauge needle allows for a larger sample size of tissue to be evacuated. Clips are placed in the area of the mass to mark the biopsy site; this is particularly imperative if the entire mass is removed. Clips have the potential to migrate, so additional documentation of placement is necessary if future surgical intervention is planned [61; 88; 89; 92; 93].

Following the procedure, women should be instructed to avoid heavy lifting for a few days. Hematomas may form, and patients should be informed they will gradually resorb over time [68].

Surgical Biopsy

Incisional and excisional biopsies were historically mainstays of breast cancer diagnosis. Incisional biopsies require the removal of a wedge of tissue to be examined in pathology. These biopsies are seldom performed today, as more accurate and sophisticated methods have made the use of this invasive method nearly obsolete [90].

The goal of an excisional biopsy is to remove the entire mass; however, it is associated with a high probability of the lesion having to be re-excised. An excisional biopsy is no longer the preferred method or the standard of care to obtain a breast tissue biopsy. It was often perceived as a way to obtain a "quick answer" for the patient, but the less invasive options are the preferred first-line approaches. It is important to remember that women have the right to elect to undergo the procedure, having the benign tumor removed and minimizing their anxiety [90].

LYMPH NODE BIOPSY

Before dialogue occurs between the patient and the healthcare team regarding a treatment plan, the next step in the diagnostic process is an SLNB and/or an ALND.

Sentinel Lymph Node Biopsy

SLNB is an integral part of the diagnostic work-up. Major improvements have been made in mapping lymph nodes, a method used to determine if any metastatic disease has spread from the breast lesion to the lymph system in the axilla. An SLNB as a preoperative staging procedure is a very accurate prognostic indicator [94]. If the SLNB yields positive results, an ALND will follow, contingent on the treatment plan [95].

The axilla houses approximately 40 lymph nodes. Among these, three levels of lymph nodes have been identified [96]:

- Level I nodes: Approximately 65% of nodes are lateral and inferior to the pectoralis minor muscle. Most sentinel nodes (83%) are identified in this area.
- Level II nodes: About 30% of nodes are located posterior to the pectoralis minor muscle, with the axillary vein below this cluster. More than 15% of sentinel nodes are identified in this area.
- Level III nodes: Fewer than 10% of nodes are located medially to the pectoralis minor muscle below the clavicle and against the chest wall. Rarely is a sentinel node detected here.

The number of positive nodes, as opposed to the location, is the prognostic indicator. Because lymph nodes lie buried in fatty tissue, a dye or radioisotope is required to highlight and track nodal location.

Different methods of SLNB can be utilized, with two types of dye, methylene blue or isosulfan blue vital dye, available. Various sites in the breast may be selected for injection: subareolar, subdermal, or peritumoral. Radioactive isotopes are an alternative mapping method, but uptake of the isotope can take up to 24 hours. In some cases, isotopes are injected the day prior to the procedure [88].

After being surgically prepped for the SLNB, 3–5 mL of dye is injected around the tumor, avoiding the mass or any previous biopsy sites. The breast is massaged to encourage the flow of dye and dilate the lymphatic vessels. Less than an hour is required for the uptake of the selected dye. Dye and radioisotope may be used simultaneously in order to increase the accuracy of identifying the sentinel node and decrease the likelihood of false-negative results.

The technique and accuracy in obtaining the biopsies relies on the skill and competency of the surgical team. Precision is needed to track any blue-stained lymph vessels leading to the designated nodes. Dye will not be taken up by any nodes that have been replaced by tumor. It is imperative that the node proximal to the tumor staining the bluest be identified as the sentinel node. If the nodes are negative, there is generally no need to pursue ALND. However, any palpable nodes in the axilla, even if they fail to stain, should be removed.

There are several advantages of SLNB, and it is considered the gold standard of lymph assessment. The procedure is minimally invasive, requiring a small incision and no drain. SLNB may be completed on men and women and is associated with less pain than more invasive procedures. It is considered accurate and is associated with decreased morbidity relative to a lower occurrence of lymphedema [94].

Current evidence does not support SLNB in pregnant or lactating women [94]. Preoperative education is necessary to prepare patients for the procedure, particularly potential side effects. The isosulfan dye causes discoloration of the skin. Urine will be tinged green, and changes in stool color may be observed. These changes will fade with time. Methylene blue dye can cause skin necrosis, although this is not common. Should it occur, silver sulfadiazine dressings are recommended.

Anaphylaxis can occur as a reaction to isosulfan blue dye, although this is a rare occurrence. Treatment involves IV fluids, corticosteroids, diphenhydramine hydrochloride, and epinephrine.

Axillary Lymph Node Dissection

In the majority of cases, an ALND will be conducted after the sentinel node has been identified. However, ALND may supersede SLNB when nodes are palpable in the axilla or if inflammatory breast cancer has been diagnosed. With inflammatory breast cancer, the flow of lymph to the axilla is obstructed, which can result in a false-negative result with SLNB. Women who are pregnant or breastfeeding will require ALND, as they are ineligible for SLNB [94; 96]. A decision not to pursue ALND may be appropriate if the plan is to proceed with a mastectomy while simultaneously removing the nodes.

ALND is a more involved procedure than SLNB and usually requires general anesthesia. If comorbidities prohibit this, moderate sedation is an acceptable alternative. Approximately ten level I and level II nodes are excised, and at least three positive nodes must be present for a definitive diagnosis [49].

Any level III nodes requiring excision should be removed individually to reduce morbidity, although this is rarely necessary. Patients undergoing ALND may require an overnight stay in the hospital if a mastectomy is scheduled to follow the dissection [49].

Prior to discharge, patients should be taught how to empty and record the drainage amount from their bulb-type wound drain. A timely return to normal activities is encouraged, with patients receiving instructions for shoulder and arm mobility and the amount of activity permitted [63].

There are several potential side effects that may arise after ALND. Intercostal brachial or thoracodorsal nerve injury can result in numbness in the axilla. Pain with loss of arm and shoulder movement arises from damaged latissimus dorsi or serratus anterior muscles; these injuries may require physical therapy. A seroma may develop after the drain has been removed, in which case, periodic aspiration may be required. Some patients may develop lymphedema or, infrequently, infection.

Axillary web syndrome can occur from trauma to the lymphatic and venous system. With this syndrome, superficial, painful "threads" run from the area of nodal dissection down the inner arm, with pain restricting arm movement. No treatment is necessary, and the complication resolves itself within eight weeks following surgery [63; 96].

CLASSIFICATION OF BREAST CANCERS

Adenocarcinomas make up the majority of breast malignancies and are classified as ductal or lobular. The in situ ductal or lobular masses are confined; there is no metastatic spread to surrounding tissues and no invasion through the basement membrane. Invasive tumors spread beyond the primary mass.

CARCINOMA IN SITU

Ductal Carcinoma In Situ

DCIS constitutes 20% of all newly diagnosed breast cancers [75]. The malignancy arises in the TDLUs; the malignant epithelial cells tend to grow in medium to larger-sized ducts but do not extend through the basement membrane [88; 93].

DCIS is usually diagnosed between the ages of 49 and 69 years. The challenge with DCIS is not only whether the in situ mass will progress to an invasive tumor, but when the progression will occur. DCIS is considered a precursor to invasive breast cancer and is related to a mutation in the *BRCA* genes and the allied risk factors of familial breast cancer, obesity, increased breast density, and nulliparity. Survivors of childhood Hodgkin lymphoma are usually diagnosed with this form of tumor if they develop breast cancer [37].

The goal of treatment with DCIS is to prevent the in situ mass from progressing to an invasive breast cancer [75]. Depending on the amount of tumor involvement, the standard of care is total mastectomy or breast-conserving surgery followed by radiation therapy and endocrine therapy. An SLNB is not indicated in this plan of care [63; 95].

The morphology of DCIS may be broadly categorized as either comedo or non-comedo. Non-comedo DCIS includes the subgroups of cribriform, papillary, micropapillary, and solid.

In comedo-type DCIS, the TDLU is filled with pleomorphic malignant cells. Invariably, calcifications formed from a central core of necrotic material are seen on mammogram. The extent of necrosis corresponds to the prediction of an increased risk of a recurrent ipsilateral malignancy, with a higher grade of malignancy predicting a higher rate of invasion. The cells usually lack estrogen and progesterone receptors, with an overexpression of HER2, a known proto-oncogene. A mutation in the *TP53* tumor suppression gene is also detected [49; 97].

As noted, there are several types of non-comedo DCIS, each with its own characteristic presentation and cytology. In the cribriform type, malignant cells are smaller and uniform, appearing in a pattern resembling a sieve. If any necrosis develops, it is found within small clusters of cells or within single cells. The TDLU is not full, as is seen in comedo-type DCIS. Papillary cancers are distinguished by neoplastic cells projecting intraluminally, with a fibrovascular core. Most papillary breast cancers eventually spread to the lymph nodes. In the micropapillary form, small clusters of cells extend into the lumens. The base of the papillae is small, expanding to a larger apex.

Solid non-comedo DCIS is characterized by breast ducts becoming solidly packed with malignant cells, causing distention. Cells range from small to large and are less defined. No necrosis is identified [49; 97].

Lobular Carcinoma in Situ

As with other breast lesions, lobular carcinoma in situ (LCIS) is often an incidental finding, discovered when biopsies are performed pursuing other diagnoses. The majority of women diagnosed with LCIS are premenopausal, usually between 40 and 50 years of age. Although infrequently diagnosed, the incidence has increased over the last 20 years in postmenopausal women [98]. The abnormal cells found in LCIS are not cancerous, and therefore, it is not a precursor or a type of breast cancer.

There are no clinical signs or mammographic findings typical of LCIS, and it is distinguished from atypical lobular hyperplasia only by degree of distention of involved spaces. The noninvasive in situ mass arises in the TDLUs of the breast tissue, and the carcinoma is usually found to be multifocal and bilateral. LCIS predicts risk for both lobular and ductal invasive carcinomas. The goal of treatment of LCIS is similar to DCIS: surveillance with timely intervention. If LCIS does progress to an invasive tumor, there is a greater possibility of it being ductal as opposed to lobular [98]. When necessary, intervention requires tumor removal and possible radiation therapy [97].

Although LCIS is classified as predicting risk and not as a precursor, the variant of pleomorphic LCIS (PLCIS) is much more likely to develop into invasive carcinoma. In PLCIS, the cells have central necrosis, calcification, and discohesive cells with lack of uniformity in the large nuclei; massive acinar distention is common. PLCIS has a worse prognosis than classic LCIS, with some suggesting that it should be treated more like high-grade DCIS [98; 99]. Because it is so rare, treatment recommendations are not well defined. Complete excision with margins, nodal staging, and possibly adjuvant therapy are common approaches.

INVASIVE BREAST CANCERS

Invasive or infiltrating breast cancers extend to affect the surrounding tissue, and these carcinomas most often arise in the upper outer quadrant of the breast. The invasive ductal and lobular carcinomas are more prominent than the subtypes of mucinous (colloid), medullary, tubular, or papillary types.

Invasive Ductal Carcinoma

Invasive ductal carcinomas make up approximately 70% to 80% of all invasive breast cancers. With this breast cancer, malignant cells have extended beyond the ducts and the TDLUs into the breast parenchyma, and a dense mass is detectable on mammogram or ultrasound [97; 100].

Breast examination may reveal a fixed, immobile mass. The firmness of the mass results from a fibrous response that ultimately produces the hard gritty tumor. Pathologically, the tumors have a gray-white appearance. The invasive ductal carcinomas are histologically graded as [88; 97]:

- Well differentiated (grade 1): The cells are usually ER/PR-positive and HER2 is not overexpressed. Solid clusters of cells infiltrate the supporting breast tissue. Mitotic activity is absent, and the nuclei are uniform.
- Moderately differentiated (grade 2): A solid cluster of cells plus differentiation in the glandular tissue. There is evidence of pleomorphic nuclei and increased mitotic activity.
- Poorly differentiated (grade 3): The tumors are solid clusters or nests; there is no gland formation. Atypical nuclei and mitotic activity are very evident.

Invasive carcinomas are subtyped in order to assist in developing a treatment plan and projecting a prognosis. Tubular carcinoma consists of very small, low-grade tumors that seldom metastasize and have a favorable prognosis. The stroma is infiltrated by tubular columns with protruding areas of cytoplasm. DCIS is detected in 75% of these tumors [49; 88; 97].

Medullary carcinoma is relatively rare, occurring in fewer than 2% of cases [101]. These soft, fleshy, tan-brown tumors with necrotic or hemorrhagic areas constitute a well-defined mass, presenting as an aggressive lymphoplasmacyte infiltrate. Although high-grade and poorly differentiated, tubular carcinomas have a more favorable prognosis than the infiltrating ductal type.

An estimated 1% to 2% of invasive cancers are mucinous (colloid), which is characterized by tumors composed of clumps of cells within pools of extracellular mucin. Masses are well circumscribed, with a slow growth pattern and favorable prognosis; there is less likelihood of metastasizing to the axilla. Tumors

are ER/PR-positive and HER2-negative. There may also be cells from DCIS found within the tumor [49; 88; 97]. Mucinous carcinomas are most commonly diagnosed in women 60 to 70 years of age.

Invasive Lobular Carcinoma

Invasive lobular carcinomas amount to approximately 6% to 9% of all invasive breast cancers [101]. Invariably, invasive lobular carcinoma is diagnosed in older women.

Reaching a definitive diagnosis of invasive lobular carcinoma with mammogram interpretation alone is a challenge. The problem arises when breast tissue is dense and there is no definable mass. Tumors form in an irregular pattern and may be found bilaterally and in several quadrants of breast tissue. The cells of the invasive lobular tumor and those of LCIS are identical. Approximately 60% of invasive lobular tumors progress from LCIS, but they can also stem from DCIS. This type has the distinguishing feature of preferential metastases to the meninges, gastrointestinal tract, and peritoneum. Pathologically, the distinguishable cells form a single line and invade the supporting stoma. Well-differentiated tumors rarely overexpress HER2 and are found to be ER/PR positive, but the reverse is found in poorly differentiated tumors. In families with a known E-cadherin (*CDH1*) gene mutation, there is a higher incidence of invasive lobular malignancies [49; 88].

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer is a locally advanced, stage III breast cancer. Inflammatory breast cancer can unfortunately be mistaken for an infectious process, causing a delay in reaching a diagnosis. Upon presentation, however, there is no evidence of any elevated temperature or leukocytosis indicative of sepsis. Primary inflammatory breast cancer is referred to as de novo, distinguishing it from secondary inflammatory breast cancer, which typically presents on the chest wall site of a prior mastectomy.

African American women have higher rates of inflammatory breast cancer compared to White women and tend to be younger at diagnosis. However, rates appear to be increasing for White women. High body mass index (BMI) is also a risk factor.

Inflammatory breast cancer accounts for approximately 2% of all invasive breast cancers; the tumors are rare and very aggressive. By the time a diagnosis of inflammatory breast cancer is established, the majority of women will have involvement in lymph nodes and 30% will have distant metastatic disease [69].

The outward appearance of the affected breast reveals a purplish-red bruise and swelling. The tissue is firm and painful, and some nipple changes may be apparent. Edema and stretched hair follicles creates the *peau d'orange* (orange peel) appearance [69]. In inflammatory breast cancer, emboli within the dermal lymphatics are actually tumor cells, creating the characteristic appearance [49; 69; 88]. Histology reveals more than 50% are ER negative; of these, 33% are found to be triple-negative breast cancers [102].

The criteria established by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control for the diagnosis of inflammatory breast cancer include [73; 102; 103]:

- A time frame of six months or less
- Biopsy-confirmed invasive carcinoma
- May or may not have a palpable mass
- Erythema, warmth, and *peau d'orange* are included in the rapidly presenting symptoms

In conjunction with an MRI and positron emission tomography (PET) scan to rule out metastatic disease, full thickness skin biopsies are required. Two skin punch biopsies a minimum of 6 mm apart are obtained distally from the scattered area of infiltrated stroma.

Newer treatment modalities, with neoadjuvant chemotherapy followed by mastectomy to halt the aggressive progression of inflammatory breast cancer, have yielded promising results compared to the previously projected dismal five-year survival rate [73; 102; 104].

Paget Disease of the Breast

Paget disease of the breast accounts for 1% to 3% of breast malignancies in women and less than 1% in men. Paget disease is identified by ulcerated, raw, scaly vesicular lesions visible on the nipple and extending to the areola. Paget cells, classified as large, high-grade adenocarcinoma, are present within the nipple epidermis. Advanced disease may manifest with some nipple retraction, but this is an infrequent finding [49; 69; 88]. The malignancy is generally ipsilateral.

The average age at diagnosis is 50 to 60 years of age. Any appearance of eczematous skin changes, nipple involvement, or discharge from the nipple should be investigated to rule out the possibility of an underlying malignancy [69]. Initial symptoms of pain and itching may exist for months and precede any visible signs of the disease. Steroids or antibiotics may provide a temporary improvement in the skin appearance; a biopsy is necessary to confirm the diagnosis. In 85% to 88% of patients who present with typical symptoms, an invasive or in situ malignancy will be detected [90]. Roughly 50% have a detectable mass within 2 cm of the affected nipple. An estimated 25% have an intraductal occult malignancy, with no abnormality seen on mammogram and no detectable mass. Another 20% have no palpable mass but an abnormality is detectable on mammogram; this finding confers a greater risk for invasive cancer. Paget disease must be distinguished from malignant melanoma and Bowman disease, a type of squamous cell carcinoma [105].

TRIPLE-NEGATIVE/BASAL-LIKE BREAST CANCERS

Gene expression analysis has identified intrinsic subtypes, and this profiling is integral for treatment planning. The most common subtypes are [1; 106; 107; 108; 109; 110]:

- Luminal A: Luminal (epithelial) cells proliferate at a low level and are usually ER-positive and HER2-negative. This subtype is associated with a generally good prognosis. Approximately 40% of tumors are luminal A.
- Luminal B: Highly proliferative cells are present and are ER-positive. These cancers have a poorer prognosis and tend to recur. Approximately 20% of tumors are luminal B.
- Triple-negative/basal-like (Though triple-negative breast cancers are more similar to basal-like than other tumors, basal-like and triple-negative breast cancers are not synonymous.)
- HER2 type

Triple-negative breast cancer is diagnosed if a tumor lacks estrogen, progesterone, and human epidermal growth factor receptors (EGFRs). Triple-negative and basal-like breast cancers account for approximately 15% to 20% of all breast cancers [111]. It invariably arises as an interval tumor, detected upon clinical examination between regular mammograms, emphasizing the aggressive nature and rapid growth of the tumor.

Approximately 85% of basal-like breast cancers are triple-negative, and these cancers generally originate in ducts. *BRCA1* mutations are found in 20% of triple-negative breast cancers. This type of cancer is associated with larger tumors, higher grades, and a poor prognosis. They are also highly aggressive, with a tendency for visceral metastases, particularly to the liver and soft tissue. Early brain metastasis is a significantly poor indicator. In fact, central nervous system involvement at all projects a prognosis of six months or less. The risk for recurrence within three years compounds considerably; after three years, risk decreases [25; 78; 106].

Triple-negative breast cancers are more common among premenopausal women and are diagnosed with greater frequency in African American and Hispanic women [111]. Other risk factors, some of which are modifiable, include:

- A younger age at the onset of menstruation
- Full-term pregnancy at a younger age
- A short interval of breastfeeding
- Lactation halted through medication
- Obesity

Although there is no definitive data to date, it has been suggested that if abdominal obesity could be reduced and extended breastfeeding promoted, the risk of basal-like breast cancers could be significantly reduced among African American women. As with any breast cancer, ongoing surveillance for disease recurrence or metastatic disease is paramount [102].

Due to the unique properties of the tumor, several treatment challenges arise. Triple-negative breast cancer does not respond to either endocrine or targeted therapies. Therefore, it is reliant upon systemic chemotherapy (doxorubicin and cyclophosphamide, followed by paclitaxel) and mastectomy to slow the disease process [106; 108; 111].

STAGING AND GRADING BREAST CANCERS

Breast cancer staging is crucial in determining a treatment plan, the extent of surgical intervention required to remove the tumor, and the appropriateness of endocrine therapy, neoadjuvant chemotherapy and radiation, or a combination of both. The first step to staging is to establish a diagnosis through diagnostic imaging and biopsy. Cytology to categorize the cancer and to determine the extent of the disease is necessary. Testing for estrogen and progesterone receptors is done by immunohistochemical (IHC) assays, and all invasive primary cancers are tested for these receptors [17]. IHC results are expressed through an Allred score [17]. A possible total score of 8 quantifies two components: the intensity of staining (ranging from absent to strong) and the proportion of cells staining positive (ranging from none to all or nearly all). As few as 1% of stained cells may be sufficient to justify treatment with endocrine therapy. A negative result applies to results less than 1% [112; 113]. Stringent quality controls ensure timeliness and accuracy from the initial tissue procurement to subsequent fixation of the specimen in the laboratory [17; 114].

After clinical staging is finished, pathologic staging is completed. The results of both are recorded using the AJCC staging system, which is accessible at https://www.facs.org/quality-programs/cancer-programs/american-joint-committee-on-cancer/cancer-staging-systems [69; 115].

TNM STAGING SYSTEM FOR BREAST CANCER

The AJCC uses the primary tumor, node, distant metastasis (TNM) system to establish an anatomic breast cancer stage and associated prognostic group. The AJCC has been examining and upgrading the TNM system for more than 50 years. While the most recently revised edition validates the progress made with the accomplishment of less invasive surgeries, refined radiation, and combination systemic and targeted therapies, the AJCC also emphasizes the significance of molecular profiling. It will be interesting to see whether any significant changes will be made to the TNM staging system in the future based on the current research with molecular profiling. The 8th edition of the *AJCC Cancer Staging Manual* was implemented in 2018 and includes an updated breast cancer staging system [116].

AMERICAN JOINT COMISSION ON CANCER TUMOR CLASSIFICATION FOR BREAST CANCER		
Grade	**Evidence**	
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma in situ	Tis (DCIS): Ductal carcinoma in situ
		Tis (Paget): Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension	T1mi: ≤1 mm in greatest dimension
		T1a: >1 mm but ≤5 mm in greatest dimension
		T1b: >5 mm but ≤10 mm in greatest dimension
		T1c: >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension	
T3	Tumor >50 mm in greatest dimension	
T4	Tumor of any size with direct invasion to the chest wall and/or to the skin (ulceration or skin nodules)[a]	T4a: Extension to the chest wall, not including only pectoralis muscle adherence/invasion
		T4b: Ulceration and/or ipsilateral satellite nodules and/or edema (including *peau d'orange*) of the skin, which does not meet the criteria for inflammatory breast carcinoma
		T4c: Both T4a and T4b
		T4d: Inflammatory carcinoma[b]
[a] Invasion of the dermis alone does not qualify as T4. [b] Inflammatory breast cancer is clinically defined when one-third or more of the skin is involved; this requires a tissue diagnosis to determine tumor markers.		
Source: Reprinted with permission from Amin MB, Edge SB, Greene FL, et al. (eds). AJCC Cancer Staging Handbook. 8th ed. New York, NY: Springer; 2017. *Table 1*		

Primary Tumor (T)

The classification of the primary tumor is the same regardless of whether it is assessed by clinical or pathologic criteria or both (***Table 1***). Size prior to the removal of tissues for assessment should be measured to the nearest millimeter. If biopsies have been obtained and a significant amount of tissue removed, a reconstruction of the actual tumor size is necessary to avoid inaccurate staging and suboptimal treatment of the disease. If the tumor size is slightly less than or greater than a cutoff for a given T classification, the measurement should be rounded to the millimeter closest to the cutoff. Designation should be made with a subscript "c" or "p" modifier to indicate whether the classification was determined by clinical (physical or radiologic) or pathologic measurements, respectively. In general, pathologic determination of tumor size should take precedence over clinical determination.

AMERICAN JOINT COMISSION ON CANCER LYMPH NODE CLASSIFICATION FOR BREAST CANCER		
Grade	**Evidence**	
Clinical[a]		
NX	Regional lymph nodes cannot be assessed (prior removal)	
N0	No regional lymph node metastases	
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)	N1mi: Micrometastases (approx. 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)[b]
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases	N2a: Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
		N2b: Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph nodes 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)
Pathologic (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 identified histologically	pN0(i+): ITCs only (malignant cell clusters in regional lymph node(s) no larger than 0.2 mm)
		pN0(mol+): Positive molecular findings (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy	pN1mi: Micrometastases (approx. 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
		pN1a: Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
		pN1b: Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
		pN1c: pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the *absence* of axillary lymph node metastases	pN2a: Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
		pN2b: Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary lymph nodes

Table 2 continues on next page.

AMERICAN JOINT COMISSION ON CANCER LYMPH NODE CLASSIFICATION FOR BREAST CANCER *(Continued)*		
Grade	**Evidence**	
pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the *presence* of one or more positive level I, II axillary nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases detected by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes	pN3a: Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
		pN3b: pN1a or pN2a in the presence of N2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
		pN3c: Metastases in ipsilateral supraclavicular lymph nodes
[a]The suffixes (sn) and (f) should be added to the N category to denote confirmation of metastasis by sentinel lymph node biopsy or FNA/core-needle biopsy, respectively, with no further resection of nodes. [b]N1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely in cases treated with neoadjuvant therapy. [c]Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.		
Source: Reprinted with permission from Amin MB, Edge SB, Greene FL, et al. (eds). AJCC Cancer Staging Handbook. 8th ed. New York, NY: Springer; 2017. *Table 2*		

Regional Lymph Nodes (N)

The involvement of the regional lymph nodes is an important prognostic indicator. Staging is based on whether nodes are fixed or mobile, the area detected, and whether the determination is made by clinical examination, imaging, or SLNB (***Table 2***). The axillary lymph node status supersedes any other indicator in determining survival and likelihood of remaining free of disease. If no nodes test positive for disease, the 10-year survival rate is estimated to be 70% to 80%; this rate decreases by 50% when one to three nodes test positive, and drops to 10% to 15% when 10 or more nodes are detected [49].

Distant Metastasis (M)

The metastasis (M) classification is an expression of the spread of tumor cells, via blood or lymph, beyond the regional nodes (***Table 3***). The sites most commonly involved are the brain, liver, bone, and lung.

Anatomic Stage/Prognostic Groups

The combined TNM score is used to stage the breast cancer, which is used to guide treatment decisions and determine prognosis (***Table 4***). The higher stages have lower associated overall survival.

HISTOLOGIC AND NUCLEAR GRADE

The Nottingham modification of the Scarff-Bloom-Richardson system is the most widely used tool for histologic grading of breast cancer and, according to the AJCC, is a required element for assigning breast cancer stage for invasive cancer [103]. This system is based on the assessment of three factors [117]:

- Tubule formation: The level of differentiation in the cells (particularly the formation of tubules in nests of tumor cells) compared to other differentiated tissue (e.g., papillary, tubular, glandular). The greater the similarity (expressed as a percentage), the better the prognosis.

AMERICAN JOINT COMMISSION ON CANCER DISTANT METASTASIS CLASSIFICATION FOR BREAST CANCER	
Grade	**Evidence**
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distance metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
cM1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm
pM1	Any histologically proven metastases in distant organs, or if in nonregional nodes, metastases greater than 0.2 mm

Source: Reprinted with permission from Amin MB, Edge SB, Greene FL, et al. (eds). AJCC Cancer Staging Handbook. 8th ed. New York, NY: Springer; 2017. *Table 3*

AMERICAN JOINT COMMISSION ON CANCER ANATOMIC STAGE/PROGNOSTIC GROUPS FOR BREAST CANCER			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
IA	T1[a]	N0	M0
IB	T0 T1[a]	N1mi N1mi	M0[c] M0
IIA	T0 T1[a] T2	N1[b] N1[b] N0	M0 M0 M0
IIB	T2 T3	N1 N0	M0 M0
IIIA	T0 T1[a] T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 M0 M0
IIIB	T4 T4 T4	N0 N1 N2	M0 M0 M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

[a] T1 includes T1mi.
[b] T0 and TI tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
[c] M0 includes M0(i+)

Source: Reprinted with permission from Amin MB, Edge SB, Greene FL, et al. (eds). AJCC Cancer Staging Handbook. 8th ed. New York, NY: Springer; 2017. *Table 4*

- Nuclear grade: the uniformity of cell shape and nuclei (e.g., edges, density, size, shape). This factor is assigned a grade of low, intermediate, or high that correlates to disease advancement and prognosis.
- Mitotic index: Determination of the degree of proliferation or rapid growth of a tumor based on the number of cell divisions seen in 10 microscopic fields.

Each of the factors is allotted 1 to 3 points, with 3 conferring the poorest prognosis and 1 the most favorable. These points are totaled to obtain the histologic grade [49; 103]:

- 3–5: Well differentiated, low grade 1
- 6–7: Moderately differentiated, grade 2
- 8–9: Poorly differentiated, high grade 3

The subjective use of grading alone is discouraged [103].

HEALTH PROMOTION

Obtaining a complete history at the first appointment serves as an opportunity to ascertain the lifestyle to which the patient is accustomed and possible areas of improvement. Health promotion involves essential changes to patients' everyday lives to prevent illness, maintain health, or re-establish healthfulness. The stress of these changes together with a new diagnosis can be overwhelming, but the implications of maintaining a healthy lifestyle, projecting that future treatment may possibly incorporate chemotherapy and radiation, provides an opportunity for education [13; 58].

Encouraging the patient to take steps to improve her or his overall health is of benefit during and after breast cancer treatment. Health promotion interventions should be based on the needs of the individual and generally focus on healthy dietary choices, avoidance of potentially harmful activities/substances, and social engagement. Limiting alcohol intake, stopping smoking, exercising, and eating a nutritious diet are all important aspects of health promotion for women with breast cancer.

Breast cancer is a life-altering diagnosis characterized by physical limitations, significant psychosocial impact, and inevitable financial burdens. Sensitivity is necessary when scheduling appointments, as women may be trying to juggle work and caring for family, associated comorbidities, and limited mobility, all of which can affect scheduling screening and follow-up appointments [6; 44; 63].

SURGICAL INTERVENTIONS

With any new diagnosis of breast cancer, one of the first considerations is whether surgery is necessary and appropriate, and if so, which type. This decision is guided primarily by the stage and type of cancer and patient preferences.

The majority of breast cancers are diagnosed at stage I or stage II, but approximately 10% are at a more advanced stage when they are identified. Women with locally advanced breast cancer (stage III) generally require neoadjuvant chemotherapy and/or radiation prior to any surgery to promote tumor shrinkage and allow for a more manageable surgical procedure [62; 63; 118]. Surgery may also be indicated for metastasized stage IV breast cancer, but primarily only for palliation of pain or prevention/amelioration of symptoms of the disease. It is important to note that surgery with radiation therapy is generally not curative for these patients.

No surgical intervention should be planned or undertaken without in-depth discussion, at appointed intervals, with the patient, surgeon, plastic surgeon (if reconstruction is planned), medical oncologist, radiation oncologist, and nurses involved in the preoperative teaching [63; 119; 120; 121].

Patients will be given medical clearance preoperatively. Preoperative teaching should include rationale for antibiotic coverage and, if an inpatient stay is required, the use of deep vein thrombosis (DVT) prophylaxis [119; 121].

The breast care nurse specialist or nurse navigator has a crucial role in educating the patient after the plan of care has been established. Psychologically, women have been observed to have better outcomes when they actively participate in decision making, and this should be a consideration during patient teaching. Issues related to breast reconstruction, impact on relationships, and family planning, particularly if an oophorectomy is a future consideration, should all be addressed. Genetic counseling is a critical component of care for younger women with hereditary breast cancer if a prophylactic bilateral mastectomy is planned. Patients with advanced cancers, extensive metastases, and/or debilitating comorbidities may ultimately make the decision not to undergo any surgical intervention [16; 63; 118; 122; 123].

Surgical options for breast cancer fall under the general categories of breast-conserving surgeries or total mastectomy, although this encompasses a wide range of techniques. One of the major goals of breast cancer treatment, aside from remission, is to preserve as much breast tissue as possible to produce an acceptable cosmetic outcome [46; 63; 93; 118; 119; 122; 124]. However, preserving tissue may account for local recurrences in younger women (35 to 40 years of age) with more aggressive disease [121]. At 10 years, the local recurrence rate after mastectomy is 1%; after breast-conserving surgery, the recurrence rate is 20%. This rate decreases to 10% for patients who undergo breast-conserving surgery plus radiation. Although the recurrence rates vary, the overall long-term survival rates are no different with mastectomy versus breast-conserving surgery with or without radiation [125; 126; 127; 128; 129; 130; 131].

As with total mastectomy, tumor size relative to remaining breast tissue is a consideration when planning a breast-conserving approach. There must be adequate tissue to support radiation therapy, if this is planned. The overall goal is to obtain negative margins, which may be difficult with invasive cancers [62; 121; 132; 133]. Some women who are eligible for breast-conserving surgery choose instead to undergo a simple mastectomy in order to avoid postoperative radiation therapy, reduce the risk of recurrence and the associated biopsies and surgeries, and engage in less intensive surveillance [119; 134; 135].

Mastectomies may be radical, modified radical, or simple. Radical mastectomy is rarely performed today due to the morbidity associated with removal of the entire breast and skin. With this approach, level I, II, and III axillary nodes plus the pectoralis major and minor muscles are removed. A modified radical mastectomy involves removal of the entire breast, the fascia underlying the pectoralis major muscle, and level I and II axillary nodes. A modified radical mastectomy is appropriate for patients with two or more primary tumors in the same breast but in separate quadrants and malignant microcalcifications in diffuse areas. The tumor(s) should be large in relation to the area of breast tissue. Re-excision of breast tissue that fails to produce negative margins is an indication for this type of surgery. It is the surgical intervention of choice for patients previously administered radiation therapy for breast cancer or mantle radiation therapy for childhood Hodgkin lymphoma.

In simple (total) mastectomy, the entire breast is removed, leaving the axillary nodes and the pectoralis major and minor muscles intact. This procedure is guided by SLNB, which allows for a less invasive surgical procedure. Approximately 33% of women with DCIS undergo simple mastectomy.

There are other subtypes of mastectomy that preserve certain tissues in anticipation of reconstruction. Skin-sparing mastectomy, first performed in 1991, requires precision to dissect the breast tissue from the skin and ensure a minimum of residual breast tissue. The majority of skin covering the breast remains intact, including the nipple and areola. Skin-sparing mastectomy also provides an opportunity to remove any biopsy scars during the surgery [118; 122]. Following the tumor excision, the cavity is filled with autologous tissue. This procedure is an option for women with hereditary breast disease

electing prophylactic surgery, as the reconstruction can be performed immediately. Women with stage I and stage II cancer and DCIS meet the criteria for skin-sparing mastectomy, but women with inflammatory breast disease are not eligible.

With nipple-sparing mastectomy, the ducts lying beneath the nipple and areolar area are removed, but the nipple and areola themselves remain. This modality can incorporate immediate reconstruction and is particularly appropriate for prophylactic surgery and smaller breasts with minimal ptosis [118; 122]. The tumor must be solitary, less than 2 cm in size, and located at least 2 cm from the nipple. No positive nodes should be present.

BREAST RECONSTRUCTION

Having discussed surgical options, the next step is to explore breast reconstruction. If reconstruction is a viable option, it should to be timed simultaneously with the surgery or delayed until after completion of radiation or chemotherapy [136]. The National Comprehensive Cancer Network (NCCN) guideline recommends radiation therapy be completed prior to any autologous reconstruction in order to achieve optimal outcomes [120; 137]. Patient preference for an autologous reconstruction, alloplastic with an implant, or prosthesis should also be considered, and all patients should be given information regarding available options and given time to make a decision. Despite the 1998 Women's Health and Cancer Rights Act mandating insurance to provide coverage for breast reconstruction, including contralateral breast surgery for symmetry if required, many women are unaware of this benefit. Other reasons reconstructive breast surgery is underutilized include [63; 120; 122; 138; 139]:

- Lack of patient information and education regarding reconstruction, prosthesis, and implants
- Patient desire to avoid the additional surgery and lengthy recovery times
- Low number of referrals to plastic surgeons

Patient Expectations and Decision Making

For the approximately 40% of patients electing to have breast reconstruction, it is essential to determine the expectations women have, what are they hoping to achieve, and what is realistically feasible [120]. Women should be cautioned that, with aging, the contralateral breast will naturally alter in shape, size, and ptosis and may no longer match the reconstructed breast. The sensation in a reconstructed breast will also be different. An excellent cosmetic outcome can be achieved but will never be as good as prior to surgery [138]. An earlier trend of allowing a grieving period to adjust to the loss of a breast while awaiting reconstruction is no longer advocated [120]. Instead, physicians should opt for earlier reconstruction, timed simultaneously with the surgery if possible [140].

The choice to undergo breast reconstruction is based primarily on a patient's desire to maintain body image, preserve sexuality, and negate the need for external prostheses, and the appearance of the breast is more natural [140]. For some women, reconstruction provides an opportunity for breast augmentation. Being able to wear attractive clothes may be an essential component of a patient's self-perception and femininity, and intact breasts may provide less of a reminder of the disease [122; 123].

Factors that impact the decision to have breast reconstruction surgery include [56; 63; 120; 122; 123; 138; 139; 141]:

- The number of surgeries involved
- Prolonged surgery under general anesthesia
- Wound care
- Drain care
- Pain management
- Limitation of activities and the need for physical therapy to minimize arm morbidity
- Time away from work and recovery period
- Child care issues
- Comorbidities
- Timing of radiation therapy

Patients tend to have a better appreciation of what lies ahead if given the opportunity to meet with someone who has undergone reconstruction to discuss expectations [140; 142]. Healthcare professionals should also have educational materials available with detailed explanations and graphics to help women understand the extent and time involved with the surgical procedures [63; 123].

Autologous Reconstructions

Transverse Rectus Abdominus Myocutaneous (TRAM) Flap

The pedicled transverse rectus abdominus myocutaneous (TRAM) flap is an autologous reconstruction requiring two areas of surgical intervention. Initially, a mastectomy, preferably a skin-sparing mastectomy in order to produce a superior cosmetic outcome, is performed. Then, a lower hip-to-hip transverse abdominal incision is made and a flap of muscle, fat, and skin is excised (similar to an abdominoplasty or "tummy tuck"). This resected flap is rotated, tunneled under the skin, and used to create the mound of the reconstructed breast or a pocket for an implant. Although the flap is separated from the lower abdomen, it remains attached to the rectus abdominus muscle, which will subsequently form the pedicle. The pedicle receives vascular support through an intact blood supply from the superior epigastric artery [63; 120; 124; 136; 139; 141].

The pedicled TRAM flap has the advantage of being completed in one surgery and recreating a breast that appears and feels more natural than an implant. However, there are many drawbacks and potential complications as well. The surgery usually lasts four to six hours, and patients are required to remain at the hospital for three to five days, with at least eight weeks before the patient may return to work. Pain management is an issue, and chronic pain can be exacerbated with an existing history of low back pain. Drain and wound care are necessary after the procedure and can be extensive. Some patients will experience a pulling sensation in the abdomen [120; 123].

Full or partial flap loss will occur in some patients, although full loss occurs in fewer than 1% of cases. Additional surgery may be required for the removal of necrotic tissue, but most patients can be managed with dressings. Nearly all patients will experience loss of abdominal strength to some degree, with an increased risk of hernia that may require surgery in the future; lifting over a certain weight must be avoided [63; 120; 122; 138; 141]. Seromas may also develop, although most reabsorb over time. Due to these potential complications, TRAM flap procedures have generally been abandoned for more effective and safer approaches [143].

Free TRAM Flap

Similar to the pedicled TRAM flap procedure, the free TRAM flap involves a mastectomy and resection of a portion of the lower rectus abdominus muscle, skin, and fat for the reconstructed breast. However, the tissue is fully resected and transplanted; no pedicle is included. Microvascular anastomosis connects the perforators to either the internal mammary or thoracodorsal blood vessels, enabling the transplanted breast tissue to remain viable [120; 124].

This procedure is associated with longer surgery times and a risk for partial or total flap loss (2% to 5% of surgeries). It also requires specialized nurses to monitor for flap necrosis in the postoperative period. As with the pedicled TRAM flap, the free TRAM flap may result in seromas, hematomas, and abdominal wall weakness [120; 122; 136; 138].

Reconstructive TRAM flap surgeries are complicated, and additional challenges arise with patients who are obese or who are long-term smokers. In patients with large breasts, harvesting the entire rectus abdominus muscle may be required to form the flap. Other factors that place patients at higher risk for complications include [144]:

- Cardiac disease
- Pulmonary disease
- History of DVT
- Collagen-vascular disease, lupus, scleroderma

- Age (>70 years)
- Prior surgery that has interrupted blood supply to the TRAM flap
- Contraindications to anticoagulation therapy

Some institutions enforce strict smoking cessation guidelines, insisting patients be free of any nicotine products, including gum or patches, for a minimum of four to six weeks prior to surgery and confirming this with blood work preoperatively. For patients with a long history of smoking, the TRAM flap may be completed in two surgical procedures, with an interval of several days between. The first surgery would involve dividing and re-routing the inferior epigastric vessels to perfuse the subcutaneous tissue in the infraumbilical area. With an augmented blood supply, this tissue can then be resected to form the breast mound in the final surgery, completing the TRAM [63; 120; 122; 138; 139].

Deep Inferior Epigastric Perforator (DIEP) Flap

The deep inferior epigastric perforator (DIEP) flap procedure uses the lower transverse abdominal area of fat and skin to create a usable flap, but the rectus abdominus muscle remains intact. The deep inferior epigastric perforators are used, and the transplanted tissue is dependent on the perforators for viability; a variant uses the superficial inferior epigastric artery (SIEA flap) and tissue from the lower abdomen. If circulation is deemed to be inadequate during surgery, the DIEP can be converted to a TRAM flap procedure. A DIEP cannot be performed if there is a pre-existing history of liposuction; obesity and smoking may also be contraindications [120].

DIEP flap has the advantages of being less painful and resulting in less abdominal weakness (with a corresponding decrease in the risk of hernia). The recovery time is also shorter than with a TRAM procedure, but DIEP requires a lengthy surgery to establish microvascular connections. Patients may develop fat necrosis, seroma, or hematoma following the surgery [63; 120; 122; 141].

Latissimus Dorsi Flap (LDF)

The latissimus dorsi flap (LDF) involves resecting the skin and fat from the upper back and tunneling it through the axilla. The latissimus dorsi muscle usually acts as a pedicled flap, with blood supply via the thoracodorsal artery and vein. The flap generally requires a saline or silicone implant to augment the muscle and provide contour to the breast, with tissue expansion prior to placement of the implant. However, in many patients, the flap can be used without an implant, restoring volumes of up to 1.5 L in larger patients or with the use of modified techniques [145]. This form of reconstruction is suitable for women ineligible for a TRAM flap due to obesity, smoking, or a previous breast reconstruction that resulted in flap failure. It is also of benefit in patients who previously have undergone irradiation. Contraindications include posterior thoracotomy, severe cardiac or pulmonary disease, or patient desire to avoid implants [145].

After LDF, patients will experience some loss of function, but it is usually insignificant. Over time, the muscle over the implant may atrophy, causing the implant to become very prominent. Within 10 years, as many as 50% of women will undergo additional reconstruction. Seroma, hematoma, and flap necrosis are potential complications [63; 120; 136; 138; 139].

Gluteal Free Flap

One alternative to using abdominal or back muscles is to use the gluteal muscle from the buttock to create a flap. This may be a good option for women with insufficient abdominal fat or who prefer a less visible scar.

The gluteal free flap procedure involves removing the superior or inferior gluteal fat, skin, and some muscle. The superior gluteal artery perforators will supply the superior muscle, and the inferior gluteal artery perforators supply the inferior muscle. Due to the proximity of the sciatic nerve, the microvascular anastomosis involved, and the repositioning required during surgery, the procedure is a lengthy one, totaling 8 to 10 hours. A long hospital stay (four

to five days) and lengthy recovery time are common. If a bilateral reconstruction is planned, two separate procedures will be required. There is a good possibility the reconstructed breast will feel firmer than the natural breast [120; 138].

Precision and expertise are required with this surgery to preserve the sciatic nerve and complete microvascular anastomosis, and nerve damage can occur. Even without damage, the sciatic nerve will have less protective padding after the procedure, and pain is common. If the superior gluteal muscle is used, there may be less contour to the hip. Similar to the other procedures, flap loss, seroma, and infection may develop [63; 120; 122; 138].

Transverse Upper Gracilis (TUG) Flap

For women with insufficient lower abdominal fat and with smaller breasts, an alternative option for reconstruction involves use of the upper gracilis muscle. Although the lower buttock and upper thigh may have a minimum of fat, it may be sufficient for certain women.

The scars associated with TUG flap are less visible than on the abdomen, and hip contour should be maintained. A lengthy surgery is necessary to allow for microvascular anastomosis [63].

ALLOPLASTIC RECONSTRUCTION

While patients generally express higher levels of satisfaction with autologous breast reconstructions due to the more natural look and feel, this may not be an option or choice for many women. Women with less time to invest in surgery or those involved in athletics may choose alloplastic reconstruction. It is also a viable option for older women with comorbidities, as it involves less of a commitment than autologous reconstruction. There is no donor site, so the recovery period is shorter and less complicated.

If radiation is included in the treatment plan, NCCN guidelines suggest timing alloplastic reconstruction before initiating radiation therapy [137]. Radiation causes fibrosis, and attempting to expand irradiated tissue to accommodate expanders creates problems. However, capsular contraction can occur if the breast is irradiated following placement of the implant [120; 136; 137; 140].

Alloplastic reconstruction is achieved using a shell composed of silicone polymer filled with saline, silicone, or a combination of the two. A two-part implant and expander procedure, termed secondary, has superseded the older method of a primary implant in the majority of cases. The older method involved placing the implant in the breast cavity during surgery, with no augmenting tissue and no opportunity for expansion, which produced an inferior breast reconstruction.

Using a secondary implant provides an opportunity for skin and muscle to gradually expand before a permanent implant is placed. It is crucial the implant is not inserted too soon following the initial surgery in order to avoid losing the inframammary fold that lends natural contour to the breast. The shell device can be inserted through the original mastectomy incision and positioned beneath the pectoralis major.

At weekly or bi-weekly intervals for approximately two months, saline is injected through a self-sealing portal, allowing for gradual expansion [120; 122; 138]. Upon reaching the desired breast size, a waiting period of three to four weeks follows, after which the temporary device is removed and a permanent implant, either silicone or saline, replaces the expander [63; 138; 139].

This approach requires frequent trips to the office for injections and a second surgery to replace the expander. The results are less natural in look and feel than autologous approaches; the breast is firmer with no natural movement [120]. Potential complications include pain, infection, seroma, hematoma, capsular contraction, and deflation of the capsule (requiring removal and replacement) [63; 119; 120; 138].

NIPPLE/AREOLA RECONSTRUCTION

Prior to any surgery or reconstruction, patients should be aware of the timeline for reconstruction of the nipple and areola. This is the final stage in reconstruction, taking place after the breast has healed and swelling subsided. Creating a nipple is achieved using skin grafts and may be completed in the outpatient setting. The biggest challenge is placing the nipple on the breast mound symmetrically with the contralateral breast. After situating the protruding nipple and surrounding areola, tattooing is used to augment the appearance [122; 136; 138; 139].

POSTOPERATIVE CARE

Major and minor surgical breast interventions require similar postoperative monitoring and care to achieve optimal outcomes. The breast and donor site should be monitored for wound integrity, checking for signs and symptoms of infection. Dressings should be changed regularly per policy.

Patients with same-day discharge should be instructed to report any temperature of 100.4°F or greater. Dramatic changes in the color, warmth, drainage, turgor, or tissue perfusion at the surgical, reconstruction, and donor sites should be reported and documented. Tissue must be monitored for viability and perfusion.

Patients will empty and record wound drainage. Premature removal of the drain and/or vigorous exercise can result in a seroma. A seroma can be a precursor to several complications, including delayed wound healing, wound dehiscence, or flap necrosis. Most patients will develop seroma to some degree, particularly those who choose breast-conserving therapies, but it is imperative to control it, if possible [121]. Any unresolved seroma requires aspiration or the placement of a drain [119].

Patients will be repositioned in order to relieve pain and to prevent compromising circulation. If used, abdominal binders should also be monitored for signs of restricted circulation. Analgesics should be prescribed and administered on a schedule in order to prevent breakthrough pain. If unresolved acute pain becomes chronic, follow-up is necessary to rule out disease recurrence or metastases.

Physical therapy for maintenance of arm mobility is recommended. Patients should be advised of the maximum amount of weight permitted to be lifted and to clear all exercise programs with their physician. Pulmonary toileting is often necessary, and the use of an incentive spirometer is considered mandatory for smokers. Early ambulation and DVT prophylaxis are strongly recommended [63; 119; 121; 122]. Upon discharge, all patients who have undergone a reconstructive procedure should be cautioned to protect their chest area when wearing car seat belts.

Although elective breast surgery is considered relatively "clean," there is always a risk for complications. Cellulitis and abscess are particular risks. Any fat residue in the cavity will become necrotic and form an abscess. This usually occurs at about five months postoperatively, but it can develop at any time between one and eight months after surgery [63; 121].

The American Society of Clinical Oncology recommends that women treated with breast-conserving surgery should have their first post-treatment mammogram no earlier than six months after definitive radiation therapy. Subsequent mammograms should be obtained every 6 to 12 months for surveillance of abnormalities. Mammography should be performed yearly if stability of mammographic findings is achieved after completion of locoregional therapy.

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Level of Evidence: Expert Opinion/Consensus Statement

PROSTHESIS

For women who choose not to undergo breast reconstruction, prostheses are an option. Breast prostheses are silicone or fiber filled and range from a whole breast to a partial breast, with individual nipples in varying skin tones. A partial prosthesis may be required to augment a previously reconstructed breast and/or for women who have undergone multiple breast biopsies [146]. Some prostheses attach directly to the skin, which enables them to be worn

during swimming or vigorous exercise. Swimwear is also available to accommodate a detachable prosthesis [63; 146].

It may seem that having a prosthesis fitted following mastectomy is less challenging, with fewer psychologic issues than with reconstruction. However, time, attention, and a great deal of sensitivity are required when helping women choose and be fitted for breast prosthesis. Although women may have actively participated in the decision not to undergo an allogeneic or autologous reconstruction, the prosthesis will always be a visual reminder of the disease [146].

At approximately six weeks following surgery, when the wound is healed and swelling has subsided, a fitting can be scheduled. The cost of prostheses varies and can range from less than $100 to as much as $3,000. Patients should be informed that insurance companies, including Medicare and Medicaid, are mandated to cover prosthesis, bras, and subsequent replacements to some extent.

Professional fitters are available, and the fit and reassurance associated with one-on-one attention from a fitter may be preferable to obtaining a prosthesis through mail order. The ACS's Reach to Recovery program has breast cancer survivor volunteers with the appropriate training to help with prosthetic fittings. As supplies permit, the volunteers may be able to supply and fit the initial temporary prosthesis at no cost [122; 147].

Deciding on a bra or camisole comfortable for everyday wear is the first priority. The weight of the prosthesis should match the weight of the contralateral breast for balance and to prevent shoulder deformity from developing over time. If a patient gains or loses weight, replacing the prosthesis may be necessary. Women are advised to wear the prosthesis for short periods of time initially, increasing the time gradually until they are confident they can wear the prosthesis for the entire day. Advising women not to settle and accept an ill-fitting prosthesis can make a huge difference in their quality of life.

LYMPHEDEMA

Lymphedema occurs when the volume of interstitial lymph exceeds the capability of the lymphatic transporting system. It is a frequent complication of surgical interventions and radiation therapy administered for the treatment of breast cancer, an association that was documented as early as 1898. When radical mastectomies were the primary surgical treatment option for breast cancers, 80% of women developed lymphedema. Today, the prevalence of lymphedema two years following breast cancer treatment is 20% to 36%, increasing to 30% to 45% after 15 years [34; 139; 148; 149].

There are two forms of lymphedema: primary and secondary. Primary lymphedema is diagnosed when it is not directly attributable to another medical condition and is relatively rare. The lymphedema associated with breast cancer is secondary lymphedema, resulting from injury or insult to the lymph nodes or lymphatic vessels [51; 52; 56; 150].

The impact of lymphedema related to breast cancer is evident in physical morbidity, and the quality of life is poorer for patients with significant disabilities, but there is also a psychologic and emotional burden. Women with lymphedema often become reluctant to socialize and uncomfortable dressing to accommodate their swollen arm. For many breast cancer survivors, lymphedema serves as a constant reminder of their disease. Work and activities of daily living are impacted. Financially, women who develop postsurgical lymphedema can incur additional costs of $14,887 to $23,167 compared to women who do not develop lymphedema [34; 51; 150; 151].

Lymphedema can arise within a few months of surgery and resolve without progression to a chronic morbidity. Or, with no apparent trigger, lymphedema can abruptly manifest after many years and persist indefinitely; it is not uncommon for lymphedema to develop 20 to 30 years after surgery. Because once lymphedema has developed it can become chronic and irreversible, early intervention is required to prevent lifelong morbidity [52; 54; 56; 57; 150].

There is a lack of consensus regarding the best way to define, measure, and treat this complication. The paucity of research has not produced sufficient evidence for the efficacy of any approach in preventing or eradicating lymphedema. As breast cancer survival rates have increased and the rate of lymphedema occurs in higher percentages in older women, the overall risk of developing lymphedema has increased [52; 57; 149; 152].

PATHOPHYSIOLOGY

In patients with breast cancer, lymphedema is caused by an inability of the lymphatic system to transport lymph back into circulation. The fluid and hydrophilic protein constituting lymph becomes trapped in the interstitial spaces, causing a swollen arm or breast tissue. The overabundance of fluid should not be confused with edema, which can be treated with diuretics and reversed in a much shorter time than lymphedema [52; 57; 150; 153; 154].

CAUSES OF LYMPHEDEMA

Surgery, SLNB, and ALND are prime causes of lymphedema in breast cancer patients. Contributing factors include the number of nodes removed and the extent of surgery. Lymph nodes and vessels within radiation fields can be damaged directly, or inflammation from radiation therapy can cause constriction and fibrosis; either factor can cause lymphedema. Other possible causes include [52; 53; 54; 55; 56; 57; 150]:

- Arm injury on the affected breast side
- Inflammatory changes
- Aging
- Metastatic disease spreading to the lymph nodes
- Tumor located in the upper outer quadrant of the breast
- Implanted central venous access device (CVAD)
- Scarring from chemotherapeutic agents (e.g., bleomycin)

While damage to nodes and vessels may be irreparable, there are some contributing factors that can be modified to help minimize symptoms. Blood pressure recordings, blood draws, and vaccinations should be avoided on the affected side. Patients should be advised to refrain from strenuous exercise, as increased blood flow increases lymph production. If possible, cuts and injuries should be avoided, reducing the risk of infection; lymphostasis, with protein-rich lymph, provides a perfect medium for pathogens, which is compounded by the impedance of lymphocytes and macrophages. Maintaining a BMI of less than 30 is ideal. Patients should avoid constricting garments that impede lymph drainage. Observational studies have demonstrated that air travel is not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary [155; 156; 157]. Finally, extremes of temperature can be damaging, and increases in skin temperatures from very hot showers or baths, soaking in spas or hot tubs, or sunbathing should be avoided [51; 53; 56; 57; 150; 151; 154]. More research is needed to determine the effect of these procedures on the risk of lymphedema [155].

DIAGNOSIS

Early subtle changes in the initial development of lymphedema may go unnoticed. Feelings of aching or heaviness may be attributed to overextending oneself physically. Skin may feel taut, with less mobility in the affected arm.

While there is an urgency to diagnose lymphedema in the very early stages, practitioners should not automatically assume lymphedema is present, although in the majority of cases it will be. The possibility of congestive heart failure, metastatic disease, or disease recurrence warrants investigation. An increase in the circumference of both arms with overall weight gain can be misleading, subsequently causing a delay in diagnosing lymphedema [51; 56; 150; 154].

Lymphedema is not solely confined to a limb. Although more prominent in the upper arm, as opposed to the forearm or hand, lymphedema can also occur in the thorax and breast area as well. Clinical findings and reported symptoms are generally sufficient to make a definitive diagnosis; however, careful patient history and physical examination may be necessary for differential diagnosis, and an ultrasound may be necessary to rule out the possibility of a thrombus [52].

The preoperative period is an ideal opportunity for education. The goal is not to add to the patient's distress but to emphasize that prevention, early recognition, reporting, and timely intervention make a significant difference in determining whether lymphedema is a manageable complication or progresses to a challenge that can persist for a lifetime.

Careful inspection of the skin for color, texture, loss of skin integrity, or more pronounced skin folds due to excess fluid should be noted. Non-pitting edema may be present. Patients may report that jewelry feels tighter or clothing fits less comfortably. The affected arm may feel taut with decreased mobility. Pain is not usually an issue, but there is often a feeling of discomfort and heaviness [54; 57]. Prior to any surgical intervention, however minor, or the administration of radiation, the circumference of both upper extremities should be measured and documented for future reference.

Lymphedema can be measured in a variety of ways. The easiest and least expensive method is with a flexible, non-stretchable tape measure. Measurements of both upper extremities are made at defined intervals, then recorded and compared. A 2-cm difference in the affected arm is sufficient for diagnosis. Other methods include measurement of volume with water displacement, recording limb shape and volume with the use of a perometer (which uses infrared technology), or measurement and comparison of fluid and protein composition in both arms via bioimpedance spectroscopy [52; 54; 56; 150; 158].

STAGES OF LYMPHEDEMA

The International Society of Lymphology uses a staging system to help guide treatment decisions and prognosis for lymphedema. The established stages are [51; 53; 54; 150; 155]:

- Stage 0: Lymph flow is impaired, although there is no clinical evidence of swelling.
- Stage I: Limb elevation may reduce the (reversible) edema, the tissues are soft, and some pitting may be evident.
- Stage II: Elevating the affected limb has no impact on swelling (irreversible). Fibrotic tissue may prohibit pitting. It is probable that the lymphedema will persist for 12 months or longer. This stage may present with a positive Stemmer sign (i.e., an inability to lift the skin of the dorsum of the fingers or toes).
- Stage III: Skin thickens, with chronic inflammation and lymph stasis that culminates in elephantiasis. This infrequently seen stage is formidable, usually resulting from lymphedema that was neglected and not treated in a timely manner. Fibrotic skin changes are evident, with cysts and hyperkeratosis.

Of note, patients who have breast-conserving surgery are automatically categorized as stage 0, a latency stage, due to the interruption of lymph vessels and flow.

TREATMENT

As discussed, it is imperative to report the earliest signs and symptoms of lymphedema so treatment can be started as soon as possible. After the diagnosis is established, patients should be referred to a breast care center or clinic specializing in lymphedema therapy [158]. One of the most universally accepted treatments for lymphedema is complete decongestive therapy. This therapy, also referred to as complex decongestive therapy, consists of two treatment phases: (1) skin care/manual lymphatic drainage, including compression bandaging, and (2) maintenance treatment at home, which consists of continuously wearing compression garments or sleeves, which may also include bandaging, if necessary [158].

There are five components to the first phase of complete decongestive therapy [158]:

- Skin and nail care
- Therapeutic exercise
- Manual lymph drainage
- Multi-layer, short-stretch compression bandaging
- Patient education in lymphedema self-management and elastic compression garments

The initial goal is to maintain the integrity of the skin and underlying structures, reducing the fluid volume in the affected arm until a plateau is reached. Manual lymphatic drainage is a massage therapy designed to gently propel fluid forward, allowing superficial lymph vessels to fill and larger conduits to open, thereby promoting drainage of lymph back into the circulation. This generally requires treatment sessions five days per week for two to four weeks. Therapy begins with the lower forearm, gradually working upwards to the axilla and shoulder. Compression bandages may be worn overnight, but are removed prior to therapy [158].

Contraindications for manual lymphatic drainage include any signs or symptoms of infection, cellulitis, thrombosis, and heart failure. Caution should be exercised when considering manual lymphatic drainage for patients with pre-existing comorbidities. For example, diabetes patients with neuropathy may be unable to identify bandaging that is too constricting, causing further damage. For patients with asthma, therapy is initiated slowly, building up gradually to the normal treatment protocol. Hypertension should be monitored and treatment tailored. Caution is required with any existing paralysis and contractures to prevent further constriction of lymph flow and drainage [51; 52; 54; 150].

For the second (maintenance) phase of the treatment, a compression sleeve and gauntlet with a selected range of pressures is worn during waking hours. Depending on the extent of the lymphedema, compression bandages may need to be continued, as in the first phase, and worn at night [51; 52; 54; 56; 57; 153; 154; 159]. Short-stretch compression bandages are supplemented with padding to form multilayers of bandaging, so pressure is applied with any arm movement and muscle contraction. Intermittent pneumatic compression devices may also be useful. These devices pump sequentially to promote lymph flow and drainage. For patients unable to perform self-manual lymphatic drainage and bandaging, a pneumatic compression device acts as a supplement to compression garments. Surgical options to reverse lymphedema are limited, and long-term benefits derived from any interventions appear to be minimal.

During this phase, the majority of the responsibility for continuing therapy shifts to the patient. It is clearly evident that the management of lymphedema is dependent upon patients investing in their own care to minimize this morbidity [34; 153].

Education outlining the treatment plan should emphasize compliance with follow-up appointments, which will be scheduled every six to nine months. Case managers will assist in obtaining replacement compression garments to ensure a consistently good fit.

Establishing a Skin Care Routine

Patients at risk for or who have developed lymphedema should adopt habits to maintain healthy skin. A daily routine of lubricating skin to keep it supple and prevent cracks also provides an opportunity to inspect for cuts or scratches. Nail and cuticle care should be nontraumatic, and patients are advised to wear a thimble if sewing. Gloves are recommended for washing dishes and any outside garden work. Water not exceeding 102°F should be used for cleansing, and temperature should be tested with the elbow of the unaffected arm; soaking in hot tubs and taking very hot showers should be avoided. Clothing and jewelry should be loose and non-constricting. The affected arm should not hang in a dependent position for any longer than 30 minutes; carrying heavy bags should be discouraged [51; 52; 54; 150; 153; 154; 159].

RADIATION THERAPY

Having successfully undergone surgery, the next step for many patients is radiation therapy. Radiation therapy with whole breast irradiation has been the mainstay of breast cancer treatment for nearly 100 years. But in a manner similar to surgery, radiation treatment has evolved to focus more on breast conservation [132]. Morbidity and mortality rates have decreased as a result of earlier detection, allowing for less invasive procedures and increased control of microscopic disease. Breast-conserving surgery followed by radiation therapy has become the standard of care for stage I, stage II, and locally advanced stage III breast cancers [133; 139; 160].

Radiation targeting a tumor results in the destruction of double-strand DNA; single-strand DNA destruction is insignificant. Malignant cells are damaged by ionizing radiation via chemical changes from the production of free radicals within tissues [161]. Rapidly dividing cells, those in late G2 and M (mitosis) phase, cells that are well-oxygenated, and poorly differentiated tumors are all susceptible to radiation, although poorly differentiated tumors generally carry a poorer prognosis. Normal tissue can repair relatively quickly, recovering from the effects of radiation therapy in approximately six hours. Therefore, a six-hour interval is scheduled between hyperfractionated twice daily treatments in accelerated partial breast irradiation [133; 160].

Larger tumors present a problem; the required tumoricidal dose may prove too lethal to sustain normal tissue. In these cases, the potential and expected side effects of the DNA destruction and chromosomal damage can cause loss of tumor suppressor genes or activation of oncogenesis.

Radiation for stage III tumors encompasses a large area, including all of the chest wall plus any remaining breast tissue, the skin, and regional lymph nodes. Intense planning is required when such a large area is involved to minimize exposure to the heart, lung fields, spinal cord, and brachial plexus [160].

Radiation is administered via a linear accelerator (delivering radiation through an external beam) or via sealed sources, and the route prescribed varies depending on the clinical presentation. Radiation may focus solely on breast tissue, the chest wall following mastectomy, and/or lymph nodes to eradicate microscopic disease. With recurrent or metastatic disease, radiation therapy is invaluable for palliating symptoms [121; 161].

Whichever modality is deemed appropriate, the ultimate goal of radiation therapy is to destroy as much tumor as possible, eradicate any microscopic disease, preserve normal tissue (by shielding the contralateral breast and protecting vital organs), decrease the risk of recurrence, and achieve long-term survival [162].

ELIGIBILITY

Not every woman is eligible or will choose to undergo radiation therapy. The decision may reflect a woman's priorities in life, particularly if significant and debilitating comorbidities currently impact her quality of life. This is particularly relevant in older women with node-positive disease requiring whole breast and nodal radiation therapy. Radiation to the nodes in the three upper intercostal spaces, the supraclavicular space, and the apex of the axilla results in considerable morbidity [139; 162].

Guidelines indicate that some women may not require radiation therapy. The NCCN recommends that women 70 years of age or older with tumors 2 cm or smaller and ER-positive and node-negative disease be treated with prescribed hormone therapy and lumpectomy [132; 137; 139].

While the majority of women are able to make decisions that reflect their personal preferences, others are ineligible due to absolute or relative contraindications relating to existing health issues. Absolute contraindications to radiation therapy include [118; 139]:

- Pregnancy: Women during their third trimester can undergo breast-conserving surgery, but radiation therapy is delayed until after delivery. After receiving radiation, women should be advised to wait two years before conceiving.

- Multi-centric tumors in more than one quadrant of the breast (i.e., unable to be removed with a single excision)
- Prior malignancy requiring radiation to the chest, as additional radiation therapy could result in toxic cumulative doses

Relative contraindications to radiation are [121; 160]:

- Acute scleroderma or systemic lupus erythematous (due to the increased risk for late-onset brachial plexus damage, breast fibrosis, and chest wall necrosis)
- Tumor measuring 5 cm or greater
- Repeated positive margins
- Premenopausal women with an established *BRCA1* or *BRCA2* mutation

SIMULATION

Surgical reports, PET scans, MRIs, and any relevant computed tomography (CT) scan information should be available prior to beginning radiation therapy. Patients are positioned supine on the CT simulation table with arms rotated externally and abducted away from the chest area [132]. The simulator will compute the entire area within the treatment field, delineating healthy tissue and vital organs and the area to be targeted. Tattoos (resembling tiny beads) or skin markings will be placed strategically. Individualized immobilization blocks are created to ensure the patient remains immobile during daily repetitions of radiation to the targeted area(s). For left-sided breast tumors, steps are taken to minimize cardiac exposure [133; 139; 162].

With this simulated information, the dosimetrists formulate a precise treatment plan that is approved by the radiation oncologist and physicists before initiation. This will include confirmation of the:

- Total and fractionated doses
- Planned number of treatments
- Energy
- Prescribed location target

An area around the tumor site is included in the treatment field in order to obtain clear margins. The target area will encompass 1 cm beyond the palpated breast tissue from sternum to axilla in patients receiving breast-conserving surgery. For postmastectomy patients, radiation should be delivered beyond the scar. The contralateral breast inframammary fold is the inferior delineation, extending superiorly to the base of the head of the clavicle. Prior to the first treatment and then on a weekly basis, a portal film is obtained to confirm the accuracy of the designated treatment area [32; 160].

DOSING

The radiation oncologist is responsible for determining the prescribed radiation dose necessary to maximize tumor destruction while also allowing normal tissues to survive and subsequently repair [160]. Radiation is divided into fractionated doses, allowing normal tissues time to repair and realigning malignant cells' cycles to enhance the effects. Radiation doses are measured in grays (Gy); the older term of "radiation absorbed dose" (RAD) is no longer used. For whole breast radiation, the NCCN recommends a hypofractionated dose of 40–42.5 Gy in 15 to 16 fractions; in selected cases, 45–50 Gy in 25 to 28 fractions may be considered. The dosing is delivered five days per week over a period of four to five weeks. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy divided between four to eight daily fractions [132; 133; 137; 139; 160].

ACCELERATED PARTIAL BREAST IRRADIATION

Accelerated partial breast irradiation has been in use for several years, although some experts still consider it to be in the investigational stage. A debate remains whether shorter treatment modalities and fewer side effects outweigh the increased risk for recurrence, but it has been added to the treatment options for breast cancer.

Accelerated partial breast irradiation delivers a sealed source of condensed radiation to patients who have undergone lumpectomy. With this approach, a finite area of breast tissue is targeted, either through multi-catheter interstitial accelerated partial breast irradiation or balloon catheter brachytherapy [16; 135; 163; 164]. Another option is intensity-modulated radiation therapy, which uses a linear accelerator to focus radiation intensely on a very specific area. The use of intensity-modulated radiation therapy increases dose homogeneity and reduces tissue damage. While this concept is practiced, there is little evidence to support its use in breast cancer irradiation [162; 164; 165]. Doses prescribed for accelerated partial breast irradiation are the same for both the interstitial and intracavity methods of administration [164].

Following tumor removal, the tumor bed and a surrounding area of 1 to 2 cm is targeted; the majority of breast tissue is not irradiated. Patients eligible for accelerated partial breast irradiation include those with early-stage breast cancer and those with a low risk for recurrence.

Advantages of accelerated partial breast irradiation include a shorter treatment period (five days compared to five to six weeks) and greatly reduced cost. Toxicity is minimized due to the finite area being irradiated. All of these factors also result in increased compliance [137; 166].

However, there are disadvantages as well. The smaller treatment area results in a greater risk for recurrence if microscopic cells are missed. Fractionated doses are higher, with increased potential for inhomogeneity and the possibility of increased toxicities (e.g., fat necrosis) at a later date. There is also a risk of infection due to the introduction of catheters [134; 164]. Patients are instructed to keep the catheter(s) dry and the dressing clean throughout the five days of treatment and for two to three days following the removal of the catheters [164].

The American Brachytherapy Society, the American Society of Breast Surgeons, and the American Society for Radiation Oncology have established the following eligibility guidelines for partial breast irradiation [167; 168]:

- Age 50 years or older (Women 40 to 49 years of age who meet other criteria should be considered "cautionary".)
- Tumor 2.5 cm or less in diameter
- Node-negative disease, as determined by SLNB
- Clear surgical margins 3 mm or larger
- DCIS or invasive ductal carcinoma

Patients with any of the following are considered ineligible [167; 168]:

- Age younger than 40 years
- Pregnancy
- *BRCA1* or *BRCA2* mutation
- Positive lymph nodes
- Tumor 3 cm or larger
- Positive margins
- Malignancy in lymphovascular space
- More than one tumor site within the breast(s)

Though not an absolute contraindication, patients with small breasts may be considered ineligible.

Interstitial Brachytherapy

If interstitial brachytherapy is desired, small hollow catheters are threaded through the breast tissue following lumpectomy. These catheters are placed either at the time of surgery or several days later in the outpatient setting. The area may require 15 to 20 catheters to encompass the tumor site, spaced 1 to 1.5 cm apart [164]. Although this method is accelerated, dosing is challenging and requires precision and expertise. Treatments are scheduled twice a day, with a six-hour interval in-between, for a total of five days. The catheters are loaded with iridium-192 for the defined treatment time. After the five-day course of radiation is completed, the catheters are removed [139; 166].

Intracavity Brachytherapy

The preferred timing for the insertion of an intracavity catheter or balloon for the delivery of brachytherapy is in the days to weeks following surgery. This closed technique affords ample time to review the final pathologic report and decreases the risk of infection. The balloon can also be placed during surgery, but there is an added risk of infection using this open method [135; 164; 165].

The dual lumen catheter is placed under CT, ultrasound, or stereotactic mammogram guidance. The catheter has a red port and blue port that remain positioned on the outside of the breast. The ports terminate in a balloon seated within the tumor cavity.

The dimensions must be evaluated to ensure correct placement of the balloon, with a goal distance of 7 mm from the skin and less than 10% of air or fluid around the balloon (i.e., a "snug" fit within the tumor space). The balloon is filled with saline or CT contrast via the blue port, while the red port accommodates the iridium-192 seed. Treatment takes approximately 10 minutes per session, twice a day for five days. Dressings over the exit site are changed daily by the nursing staff in the radiology department. The catheters are removed when treatment is completed [135; 160; 165; 166].

Possible complications to intracavity brachytherapy include [160]:

- Fat necrosis
- Wound infection
- Pain
- Edema within the breast tissue
- Catheter rupture or failure
- Seroma
- Skin toxicity

Intraoperative Brachytherapy

Intraoperative brachytherapy is delivered with a one-time dose during surgery, targeting the margins and limiting exposure to the skin. This method is widely used in Europe and is gradually being used more often in the United States. The disadvantage of administering radiation therapy during surgery is the final pathologic report has not been reviewed, a longer time is required in the operating room, and there is less accuracy with the delivered dose [164].

Radiation may be delivered to the tumor bed during surgery via an applicator or a linear accelerator [166]. In the first case, an applicator is temporarily sutured into the cavity, where 20 Gy is administered directed at the surface where the applicator is placed. An additional 5 Gy is applied at 1 cm for approximately 20 to 45 minutes.

The alternative method involves the delivery of radiation therapy via the linear accelerator in a single 21 Gy dose. The chest wall and lungs are protected by a shield.

According to the literature, most women undergoing accelerated partial breast irradiation tolerate the placement of the catheters or balloon without problems. Relevant patient education includes reporting any fevers, malaise, or potential skin issues, and keeping scheduled follow-up appointments.

RADIATION-INDUCED SIDE EFFECTS

As noted, various side effects will manifest as a result of radiation therapy. The severity of these side effects will depend to some extent on the overall health of the patient. For those who lack adequate nutrition, who are overweight, who have a history of diabetes or renal failure, who continue to smoke, or who fail to comply with a skin care regimen, potential side effects may be compounded.

Two of the most commonly experienced side effects are skin reactions and fatigue; fortunately, both are manageable [139; 169]. The onset of fatigue is predictable, beginning within two to three weeks of initiation of radiation therapy and gradually worsening. Some patients cope by allowing more relaxation periods and enlisting help from family and friends; others may need to adjust their work schedules. Treating insomnia and anemia and prescribing moderate exercise (e.g., walking) should be considered. Psychologic and psychosocial issues may also contribute to fatigue. If fatigue does not resolve within two to three weeks of radiation therapy being completed, further investigation as to etiology is warranted [132; 133; 162; 169; 170; 171].

Skin reactions can occur as early as 10 to 14 days into treatment, with 90% to 95% of women eventually experiencing some reaction [162; 172]. Late occurrence, developing six months or even years after radiation therapy is completed, may rarely occur. Certain factors increase the risk for adverse skin reactions. Women requiring a pendulous breast to be moved away from the abdominal wall during radiation therapy are at greater risk, as are women receiving a higher dose of radiation. Women with fair skin are more prone than women with darker skin to develop skin reactions [162; 172].

Radiation dermatitis can vary widely in severity. Pruritus occurs after about three weeks of treatment of 30 Gy. In some cases, sebaceous glands are damaged, resulting in less perspiration. Dry desquamation results from damaged stem cells in the epidermis. This can progress to moist desquamation as it invades the dermis, usually with doses of 45 to 60 Gy. Chemotherapy and friction in skin folds can exacerbate these symptoms. In severe cases, patients may require a break in radiation therapy until symptoms subside [173]. Extreme moist desquamation seldom occurs, but it can be a cause of tissue necrosis.

Fibrosis may result in a loss of movement in the chest and shoulder area. Pigmentation is also altered in the radiation field, as melanocytes shift to the skin's surface; this may result in skin flaking [133; 160; 162; 170]. Atrophied skin has greater potential for injury.

A non-productive cough and fever may result from interstitial inflammation associated with radiation pneumonitis. This may appear up to six to 18 months after radiation therapy is completed, particularly if the axillary and supraclavicular nodes were irradiated. Steroids are generally sufficient to resolve symptoms [139; 162; 170].

Higher doses of radiation to left-sided tumors may result in cardiac ischemia [139]. However, improvements in technology and the ability to shift the heart away from the treatment field have greatly reduced cardiac toxicity [170]. Vigilance is required as systemic therapy with trastuzumab and anthracyclines can compound the potential toxicity [133].

Brachial nerve damage can result from radiation therapy to axillary, infraclavicular, or supraclavicular nodes. Surgical resection renders nerves more vulnerable to radiation and the associated nerve damage [34]. Doses totaling 55 Gy or greater produce nerve damage in 73% of patients; doses of 51 Gy result in nerve damage in 15% of patients. Onset of symptoms can occur within months to years of treatment. Arm and hand numbness, pain, and weakness may be treated with physical therapy. Caution is warranted to prevent additional injuries if paresthesia is present [170].

Edema of the soft tissues of the chest can result in skin tautness and a feeling of heaviness. Signs of cellulitis, exhibited by warmth and fever, may be evident. Wearing a supportive bra and taking NSAIDs will alleviate some of the discomfort [133; 170].

Rib fractures may occur spontaneously or as result of a fall or trauma to the chest wall in patients receiving radiation. In some cases, the fractures are asymptomatic and detected only on x-ray, but other patients may have signs of hemoptysis, increased pain, and shortness of breath. Fractures will heal without any required intervention [133; 160; 162; 170].

As discussed, lymphedema is another significant side effect of breast irradiation, developing in many patients and having an adverse effect on quality of life, even in long-term survivors. The course and treatment is identical whether it occurs secondary to surgery, radiation, or the cancer itself.

FOLLOW-UP

All patients who have received radiation therapy will require follow-up and additional screenings throughout their lifetimes. A physical examination, including assessment of lymph nodes, should be conducted every three to six months for three years, then every six months thereafter. Mammograms should be scheduled every six months for two years, then annually.

Undergoing radiation for any duration requires a commitment to attend daily appointments, be diligent with skin care, and invest in a healthy lifestyle. Support and encouragement from family and caregivers should not be underestimated, as there are benefits derived from not being alone during this stressful period [142].

SKIN CARE

Basic daily skin care is affordable and achievable, and it is of utmost importance for patients receiving radiation therapy. An emphasis on early reporting of symptoms and reassurance that skin will heal is important. Radiation departments will have their own protocols and recommendations for individualized skin care based on current evidence-based practice.

Skin areas in the treatment field should be cleansed of any lotion, perfume, powder, or deodorant at least four hours prior to radiation therapy. Patients should be advised to use mild soaps and avoid extremes of water temperatures and sun exposure. Friction can cause skin breakdown, so skin should be patted dry and constricting clothing should be avoided.

Any pain or discomfort may be relieved with NSAIDs. If pruritic areas develop, the use of antihistamines can relieve symptoms, help patients avoid scratching, and promote bedtime sleep. Small areas of bleeding can be controlled with silver nitrate sticks. If dressings are necessary, tape should be avoided, as removal could result in additional tissue damage [56; 172; 174].

PATIENT EDUCATION

Women may express some frustration having to wait the six weeks of healing time following surgery before beginning radiation therapy. However, this is an opportune time for education and it allows patients time to adjust to the healing process. After the informed consent for radiation therapy is obtained, the education process can begin [174]. Patients should be advised that the initial simulation is a lengthy process. At the first appointment, setting up the treatment will be outlined and the areas to be irradiated marked.

Subsequent treatments last about 15 to 30 minutes, with the majority of the time dedicated to positioning on the table and the placement of shields [161]. The patient will be alone in the treatment room, and she must be able to remain absolutely still while the beam is on. Background music may be used to encourage relaxation. The radiation therapist will also communicate to the patient via intercom and may reassure the patient she is in constant view on a monitor. Patients should be reassured they will not become "radioactive" or pose a danger to themselves or others after treatment.

Radiation treatments are scheduled Monday through Friday. Weekends are scheduled breaks, allowing healing and minimizing fatigue. Daily appointments require a commitment from the patient and last a total of five to six weeks, including the final boost.

Treatments are painless, although there will likely be predictable, expected side effects. Overall wellness should be promoted during the treatment period, including adequate nutrition, smoking cessation, dealing with fatigue, diligent skin care, and management of comorbidities. Pregnancy must be avoided. Patients are permitted to shower but should be advised to pat skin dry to prevent friction. Tattoos and skin markings made to guide treatment must remain intact [162].

During the treatment period, weekly check-ups are scheduled with the radiation oncologist and nurse, at which time weight and vital signs are recorded and the skin is examined, checking entry and exit sites on the chest and back for any signs of adverse reactions. Medications can be adjusted and reconciled as needed during this period.

ENDOCRINE THERAPY

Following radiation and surgery, adjuvant endocrine chemoprevention therapy may be prescribed to reduce the risk of any disease recurrence, prevent the development of a contralateral breast malignancy, and treat any metastatic disease. The purpose of endocrine therapy, prescribed as a daily oral medication or monthly intramuscular injection, is to block or interrupt molecular pathways and reduce the levels of estrogen fueling tumor growth. If appropriate, endocrine therapy is preferential to the more toxic chemotherapy if the disease is stable and not overly aggressive.

Approximately 70% to 80% of women with breast cancer have tumors that are ER positive [16]. Tumors that are ER/PR positive respond more favorably to endocrine therapy than any other combination of these receptors. Tumors negative for estrogen and progesterone receptors require treatment with chemotherapy or targeted therapies [175].

In postmenopausal women, despite the decline in the production of estrogen and progesterone by the ovaries, small amounts of the hormone are still produced in the brain, breast tissue, breast tumors, subcutaneous fat, skin, and muscle. Androgens produced by the adrenal cortex are synthesized by the enzyme aromatase, thus producing a source of estrogen, albeit in low levels [107]. Therefore, this approach may be used by women of any age with susceptible tumors.

Women who are identified as being at high risk for breast cancer may also be offered risk-reducing medications (e.g., tamoxifen, raloxifene, aromatase inhibitors) if they are at low risk for medication side effects [176].

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs), previously called anti-estrogens, are a mainstay in the treatment of breast cancer. The two SERMs most frequently used are raloxifene (Evista) and tamoxifen (Nolvadex); the latter is probably more widely recognized than any other breast cancer treatment [177]. A third SERM, toremifene (Fareston), is approved for the treatment of advanced breast cancer in postmenopausal women with ER-positive or ER-status-unknown tumors; however, the drug is not commonly used in the United States [178; 179].

Tamoxifen

The use of tamoxifen has evolved over time, and today it is considered the criterion standard for the endocrine treatment of postmenopausal women with ER-positive tumors. Tamoxifen was initially used as a contraceptive, but starting in the 1970s, it has been used as a treatment for advanced breast cancer in postmenopausal women, gaining approval from the U.S. Food and Drug Administration (FDA) in 1977. By 1987, tamoxifen became a common adjuvant therapy for node-positive disease. Studies show that 30% to 40% of women with newly diagnosed metastatic disease remain stable for several years with no disease progression or regression if prescribed tamoxifen [180].

To date, tens of thousands of women worldwide have been enrolled in trials comparing various doses and durations of tamoxifen and regimens involving aromatase inhibitors (AIs) [107; 181]. Despite the multitude of trials, there does not appear to be a definitive answer as to whether AIs should be administered prior to tamoxifen, alone or in combination, or the optimal time frame for combination therapy [182].

Tamoxifen is currently prescribed to men and pre- and postmenopausal women, regardless of age or node status, for [177; 178; 182]:

- Newly diagnosed metastatic disease
- Prevention of recurrence following breast-conserving surgery/radiation therapy for DCIS
- Prevention of contralateral breast disease
- Adjuvant therapy preceding the possible need for chemotherapy

DVT, pulmonary embolism, atrial fibrillation, hypertension, transient ischemic attacks, and uncontrolled diabetes are considered contraindications for tamoxifen use [178].

Research indicates that five years of tamoxifen versus no treatment yields an annual reduction in the risk of recurrence of 41%. Risk reduction continues up to 10 years following completion of the treatment, although the cause of this continued efficacy remains unclear [160].

Treatment with tamoxifen is usually initiated after radiation therapy and chemotherapy are completed, approximately four to six weeks following surgery. The daily prescribed dose is 20 mg orally for up to five years [178]. Five years has been determined to be the optimal time for prolonging disease-free survival and overall survival in women with ER-positive cancer [107; 175; 183].

The benefits and risks associated with tamoxifen should be clearly outlined to patients. Yearly gynecologic check-ups are strongly encouraged, with patients instructed to report any new symptoms, including shortness of breath, pain and swelling in their legs, vaginal bleeding, or abdominal bloating and weight gain [68; 107; 177; 183].

Mechanism of Action and Resistance

Tamoxifen is a nonsteroidal SERM that competitively binds to estrogen receptors on tumor cells and other tissue targets, decreasing DNA synthesis and inhibiting the systemic effects of estrogen. Tamoxifen causes cells to remain in the G0 and G1 phases of the cell cycle. Because it prevents malignant cells from dividing but does not cause cell death, it is considered cytostatic rather than cytocidal [178].

The liver produces two drug metabolizing enzymes in the cytochromes, P450 2D6 (CYP2D6) and CYP3A4/5, that convert tamoxifen to the active metabolite endoxifen. Tamoxifen is metabolized initially to *N*-desmethyl-tamoxifen through the action of CYP3A4/5, and then converted to endoxifen via CYP2D6 [178]. As such, tamoxifen is a prodrug; it is the conversion of tamoxifen to endoxifen that allows for greater binding affinity to estrogen receptors.

Any reduction in an individual's ability to convert tamoxifen to endoxifen, either from a genetic predisposition or the co-administration of certain medications, results in little benefit being derived from this drug [107; 184; 185]. Medications that inhibit CYP2D6 function are often the cause of tamoxifen ineffectiveness, and this includes drugs prescribed to treat hot flashes and depression, such as selective serotonin reuptake inhibitors (SSRIs) [178]. The strong inhibitors of CYP2D6 include bupropion (Wellbutrin), fluoxetine (Prozac), and paroxetine (Paxil); moderate inhibitors are diphenhydramine (Benadryl), amiodarone (Cordarone), cimetidine (Tagamet), trazodone (Desyrel), sertraline (Zoloft), and duloxetine (Cymbalta) [107; 185]. If possible, these medications should be avoided in patients taking tamoxifen.

Tamoxifen is a partial agonist, binding estrogen to estrogen and competing with estrogen receptors on tumors; however, tamoxifen also possesses antagonist properties and promotes estrogen activity. The agonistic effects contribute to bone mineral density, reducing the risk of osteoporosis and associated fractures. However, tamoxifen can cause serious adverse effects as a result of its antagonism, including a doubled risk for both endometrial cancer and thromboembolic events. Leg cramps and the development of cataracts may also occur [16; 107; 178; 186; 187].

Compliance

A major drawback of tamoxifen is the lack of compliance stemming from the long treatment period. An estimated 22% of women discontinue tamoxifen treatment within one year; by 3.5 years, 35% will have stopped, and only 49% of women complete the full five-year treatment plan. It is important to assure patients that half of all recurrences are halted and mortality is reduced by 65% when tamoxifen is taken for five years [1]. If women appreciate the positive results achieved with tamoxifen, there may be more of an inclination to continue treatment.

Aside from the daily reminder and time commitment, reasons stated for discontinuing the medication include the cost (approximately $22 per month) and the side effects experienced. In addition to the risk of endometrial cancer and thromboembolic events, side effects can also include [93; 98; 107; 174; 175; 177; 178; 187; 188]:

- Nausea, vomiting, loss of appetite, and weight loss
- Hot flashes
- Decreased libido, vaginal dryness, and dyspareunia
- Reduced cognition and memory impairment
- Rash and skin changes
- Fluid retention
- Irregular menstruation or amenorrhea in premenopausal women
- Vaginal bleeding

Raloxifene

Raloxifene was initially designed for the treatment of osteoporosis, and its beneficial effects on bone health are one reason some prefer it to tamoxifen. Raloxifene has been determined to be as effective as tamoxifen, but it carries a smaller risk of endometrial cancer and thromboembolic side effects [183]. As a SERM, it has a similar action to tamoxifen, although it displays fewer estrogen-like effects than tamoxifen.

Raloxifene is appropriate for high-risk postmenopausal women (e.g., women with an intact uterus, a risk score of 1.66% or greater on the BCRAT, women treated for osteoporosis, and a history of LCIS), reducing the risk of recurrence in this population by 50%. Due to the potential teratogenicity, premenopausal women should not be prescribed raloxifene [58; 98; 107; 177; 178].

SELECTIVE ESTROGEN RECEPTOR DOWN-REGULATORS

Fulvestrant (Faslodex) is a selective estrogen receptor down-regulator (SERD) used as a second-line breast cancer treatment for postmenopausal women who are ER-positive with metastatic disease or disease progression following previous endocrine or chemotherapy. As a pure estrogen antagonist, the action of fulvestrant differs from that of tamoxifen. Estrogen signals are inhibited and estrogen receptors are degraded by fulvestrant, preventing estrogen from reaching the nucleus [178; 181; 182; 189].

Increased compliance is possible with this medication because it is administered on a monthly basis in a clinic or office. These appointments also provide patients with an opportunity to discuss any issues with their healthcare provider.

Fulvestrant is approved to be administered monthly at a dose of 500 mg via intramuscular injection. The drug is refrigerated for storage and brought to room temperature 30 minutes prior to being slowly administering via the Z-track method. The injection may be administered at one site in a muscle able to accommodate the volume, usually the dorsal gluteus maximus or deltoid, or the dose can be divided and administered in two separate injections. Patients will experience some discomfort at the injection site(s), but this should subside relatively quickly. Other side effects from fulvestrant use are consistent with menopausal symptoms: hot flashes, night sweats, fatigue due to interrupted sleep, vaginal dryness, and dyspareunia [181; 182; 189].

In 2019, the FDA approved alpelisib (Piqray) for use in combination with fulvestrant to treat postmenopausal women and men with HR-positive or HER2-negative breast cancer with a PIK3CA mutation [190]. Alpelisib is approved to be administered once daily at a dose of 300 mg orally, in combination with fulvestrant [178].

Alpelisib is a phosphoinositide 3 kinase (PI3K) inhibitor with strong, selective activity against PI3Kα. Mutations in the gene encoding the catalytic α-subunit of PI3K (*PI3KCA*) lead to activation of PI3Kα and Akt-signaling, cellular transformation, and tumor generation. The combination of alpelisib with fulvestrant has synergistic antitumor activity in *PI3KCA*-mutated, ER-positive models [178].

The American Society of Clinical Oncology Update Committee recommends alpelisib in combination with endocrine therapy should be offered to postmenopausal patients in combination with fulvestrant, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced breast cancer, or metastatic breast cancer following prior endocrine therapy including an aromatase inhibitor, with or without a CDK4/6 inhibitor. Careful screening for and management of common toxicities are required.

(https://ascopubs.org/doi/full/10.1200/JCO.21.01392. Last accessed July 21, 2022.)

Level of Evidence: High

The FDA also approved a companion diagnostic test, the therascreen PIK3CA RGQ PCR Kit, which enables detection of the PIK3CA mutation in a tissue and/or liquid biopsy. Patients who screen negative with liquid biopsy should undergo tumor biopsy for PIK3CA mutation testing [190].

Common side effects of alpelisib include rash, nausea, vomiting, fatigue, decreased appetite, stomatitis, and weight and hair loss [190]. Severe cutaneous reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in a small percentage of patients [178]. Alpelisib is contraindicated in patients with a history of Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis. Severe diarrhea may commonly occur, sometimes resulting in dehydration and acute kidney injury. Severe hyperglycemia, including ketoacidosis, particularly in patients 65 years of age and older, has been reported with alpelisib [178].

AROMATASE INHIBITORS

AIs halt the production of estrogen by inhibiting the action of the P450 cytochrome aromatase, preventing androstenedione and testosterone from being converted to estrogen. The AIs were initially prescribed for metastatic breast disease in postmenopausal women with ER-positive tumors, but are now used for early breast disease as well. There are two types of third-generation AIs approved for the treatment of breast cancer: steroidal and nonsteroidal. Exemestane (Aromasin) is a steroidal androgen inhibitor that binds to and halts the action of the aromatase enzyme, and its effects are irreversible. Exemestane is indicated for the adjuvant treatment of ER-positive breast cancer that has progressed despite treatment with tamoxifen or for women who wish to replace tamoxifen for the last two or three years of a five-year endocrine therapy plan [177; 178]. Exemestane is dosed at 25 mg daily and costs approximately $607 per month. Patients are advised to take this medication following a meal [178].

As with exemestane, nonsteroidal competitive aromatase inhibitors bind to the heme group of aromatase, which leads to inhibition of the enzyme and a significant reduction in plasma estrogen levels. However, these medications do not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens, and the effects are reversible. Available nonsteroidal AIs include letrozole (Femara) and anastrozole (Arimidex), with letrozole the most potent of the group. The 2.5-mg daily dose of letrozole should be reduced by 50% if there is any hepatic impairment. Anastrozole is dosed as 1 mg daily. Both of these drugs may be taken prior to meals [178; 181; 191].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In postmenopausal women at increased risk, the American Society of Clinical Oncology asserts that the choice of endocrine therapy includes anastrozole (1 mg/day) in addition to exemestane (25 mg/day), raloxifene (60 mg/day), or tamoxifen (20 mg/day) for five years. The decision regarding choice of endocrine therapy should take into consideration age, baseline comorbidities, and adverse effect profiles. Clinicians should not prescribe anastrozole, exemestane, or raloxifene for breast cancer risk reduction to premenopausal women. Tamoxifen 20 mg/day for five years is still considered standard of care for risk reduction in premenopausal women who are at least 35 years old and have completed childbearing.

(https://ascopubs.org/doi/full/10.1200/JCO.19.01472. Last accessed July 21, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Side Effects

Side effects are reported in 35% to 50% of patients taking an AI and can manifest as early as four to 12 weeks after initiation of therapy. In many patients, activities of daily living are greatly impacted due to bone pain. Joints in the hands, wrists, feet, and ankles may become stiffened, resulting in as many as 10% to 15% of patients discontinuing treatment. Decreased estrogen levels increase patellar cartilage damage, resulting in joint erosion and pain [192]. A bisphosphonate may be prescribed concurrently to counter the adverse effects on bone mineral density and reduce skeletal morbidity.

Bone pain should not automatically be presumed to be a side effect from AIs; imaging may be necessary to rule out fractures and the possibility of bone metastases. Treating the symptoms may include physical therapy with range of motion exercises. Acetaminophen and NSAIDs may provide some relief, but if NSAIDs are prescribed, monitoring for gastric irritation is warranted. Low-impact bone strengthening exercise, such as walking, should be encouraged in moderation.

In addition to arthralgia and bone pain, patients may experience headaches, nausea, vomiting, and hot flashes. The risk for endometrial cancer or thromboembolic events is lessened with AIs compared to tamoxifen [16; 107; 177; 184; 191; 193; 194; 195].

Focusing on nutrition and a healthy lifestyle is worth pursuing. Any vaginal bleeding not related to menstruation should be reported immediately in light of the risk of endometrial cancer. Patients may not feel comfortable discussing side effects impacting sexual activity (e.g., vaginal dryness, decreased libido), so creating a trusting relationship in which patients feel safe sharing their concerns can allow for an honest discussion. Referral to a counselor may prove beneficial [14; 182; 194].

In women who have undergone induced menopause, AIs may stimulate premenopausal levels of estradiol, with some patients reporting their menses have resumed. This is due to the negative feedback loop to the pituitary and hypothalamus. If menses begins, the agent should be discontinued. Although the side effects manifested from AIs differ from those of tamoxifen, they do have the potential to severely impact quality of life and treatment compliance [98; 107; 177; 181; 186; 196].

LUTEINIZING HORMONE-RELEASING HORMONE AGONISTS

Another class of medications used in the treatment of ER-positive breast cancer is the LH-releasing hormone agonists, of which available agents include goserelin (Zoladex) and leuprorelin acetate (Lupron). These agents act by inhibiting ovarian activity and suppressing estrogen [107]. This class of medications may diminish the effects of antidiabetic agents, so therapy and blood glucose levels should be monitored [178].

Goserelin

Goserelin is administered as a tiny pellet implanted via a large bore needle into the subcutaneous abdominal tissue below the navel. The usual dose is 3.6 mg every 28 days [178]. To buffer the painful implanting of the pellet, a local anesthetic is applied prior to the procedure. Goserelin can cause hot flashes, headaches, depression, vaginal dryness, and edema.

Leuprorelin

More well known as an established treatment for prostate cancer, leuprorelin is being evaluated for its use in ovarian ablation in premenopausal women with breast cancer; as of 2019, this use was off label [178]. Leuprorelin is administered by intramuscular injection at a dose of 3.75 mg every 28 days or 11.25 mg every three months for up to 24 months [178]. Side effects include breast discomfort, hot flashes, increased perspiration, peripheral edema, and dizziness [107].

TARGETED THERAPIES

All normal adult epithelial tissue contains low levels of the gene *ERBB2*, also known as neu-oncogene or HER2. The HER family includes HER1, HER2, HER3, and HER4 with intracellular tyrosine kinase receptors [88]. HER1, HER3, and HER4 are capable of ligand binding in the intracellular and extracellular domain. Extracellular and intracellular signals to promote cell activity travel via various molecular pathways and have the ability to influence one another's signals. Extracellular signaling includes insulin-like growth factor 1 receptor and the *ERBB2* family. Intracellular signaling involves PI3K, mammalian target of rapamycin (mTOR), RAS, RAF, and mitogen-activated protein kinase (MAPK).

HER2 is encoded by *ERBB2*, which is located on chromosome 17q21-q22. Overexpression of HER2 is detected in 25% of all women with breast cancer. Even aside from node status, tumor size, histologic grade, and ER/PR receptor status, presence of this genetic mutation carries a poor prognosis. Overexpression of HER2 causes increased cell division, sustained angiogenesis, and the promotion of metastases. These combined factors, if not halted by interrupting the signaling pathways promoting tumor growth, result in decreased overall survival [112; 114].

TRASTUZAMAB

Interrupting the HER2 extracellular domain molecular pathway signals can be achieved with the recombinant humanized monoclonal antibody (MoAb) trastuzumab. Trastuzumab was approved by the FDA in 1998 for the treatment of HER2-positive disease. The drug acts on the extracellular membrane where HER2 is located, inhibiting cell proliferation, promoting cell death, and preventing angiogenesis. It is given with paclitaxel as first-line treatment for advanced breast cancer and for metastatic disease following prior therapy [114; 133; 178; 197; 198; 199].

Trastuzumab is administered intravenously either weekly or every three weeks, typically for one year [102; 178]. The most significant possible side effect of this agent is congestive heart failure resulting in a reduced left ventricular ejection fraction (LVEF) [88; 178]. Prior to the initiation of trastuzumab, a multigated acquisition (MUGA) scan or echocardiogram are required to establish a baseline. The LVEF must be subsequently measured every three months during treatment, then every six months for two years after completion of the therapy. If there is any significant decrease in the LVEF that necessitates holding the treatment for a total of three doses, the therapy will be discontinued. Congestive heart failure resulting from trastuzumab can be treated with diuretics, with the patient monitored according to medical protocol. This therapy is not contraindicated in the elderly providing their cardiac function is adequate and they are medically stable. Cardiologic monitoring should be performed in elderly patients, as trials have shown an increased risk for cardiotoxicity [178; 200; 201; 202].

The initial treatment with trastuzumab is administered over 90 minutes; subsequent treatments can be infused over 30 to 60 minutes. Premedication with acetaminophen and diphenhydramine can help curb the side effects of fever or chills. The patient's vital signs should be appropriately monitored during the infusion. Of note, the drug is not compatible with dextrose [88; 107; 178].

Patient education is twofold: to encourage compliance with the regimen, particularly if dosed weekly, and to alert patients to the signs and symptoms of developing congestive heart failure. Patients should be advised to report any weight gain, edema, shortness of breath, or elevations in blood pressure. A heart healthy diet limiting sodium intake, smoking cessation, and participation in some form of exercise are all part of the extended treatment plan.

It is important to determine who will derive maximum benefit from trastuzumab, as resistance to the drug can occur. An accurate indicator that resistance is likely to occur is a *PTEN* deficiency, found in 50% of all patients with breast cancer [198].

ADO-TRASTUZUMAB EMTANSINE

In 2013, the FDA approved the HER2-targeted antibody drug conjugate ado-trastuzumab emtansine (Kadcyla) for use in the treatment of patients with HER2-positive, metastatic breast cancer who have previously been treated with trastuzumab and a taxane (alone or in combination) [203]. This combination agent includes both trastuzumab and the drug DM1, a small-molecule cytotoxin and microtubule inhibitor. Clinical trials have shown that patients treated with ado-trastuzumab emtansine have significantly improved overall and progression-free survival compared to treatment with lapatinib plus capecitabine [203].

The initial dose is IV 3.6 mg/kg infused over 90 minutes every three weeks until disease progression or unacceptable toxicity; however, to control toxicities, the dose may be reduced by 0.6 mg/kg twice prior to discontinuation [178; 203]. Subsequent doses may be administered over 30 minutes if the initial dose was well tolerated. The most common side effects reported are nausea, fatigue, pain in the muscles or joints, thrombocytopenia, increased liver enzymes, headache, and constipation. Black box warnings regarding the possibility of LVEF reductions, serious hepatotoxicity, and embryo-fetal death have been issued, and patients taking this agent should be closely monitored. Effective contraception is also recommended while on this medication and for six months following for women of childbearing age [178; 203].

PERTUZUMAB

Pertuzumab (Perjeta) is a MoAb aimed at preventing signals travelling from HER3 to HER2. Trials have examined the efficacy of trastuzumab plus pertuzumab, and a combination of these two drugs has been found effective against tumors. A triple regimen adding docetaxel has also been studied [198; 204].

Pertuzumab was originally approved in 2012 for the treatment of patients with advanced or late-stage (metastatic) HER2-positive breast cancer. However, in 2013, pertuzumab became the first drug approved as part of a complete treatment regimen for patients with early-stage breast cancer before surgery [205]. For either use, the dose is 840 mg IV over 60 minutes followed by a maintenance dose of 420 mg over 30 to 60 minutes every 3 weeks [178; 205]. As part of the neoadjuvant treatment, this is continued for three to six cycles. As a treatment for metastatic disease, treatment continues until disease progression or unacceptable toxicity.

ATEZOLIZUMAB

In 2019, the FDA approved atezolizumab, an MoAb agent, for the treatment of unresectable, locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1 (i.e., PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area) [206]. It should be prescribed in combination with paclitaxel protein-bound.

FAM-TRASTUZUMAB DERUXTECAN

Also in 2019, the FDA granted accelerated approval to fam-trastuzumab deruxtecan (Enhertu) for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting [207]. Fam-trastuzumab deruxtecan is a HER2-directed antibody and topoisomerase inhibitor conjugate and is administered at a dosage of 5.4 mg/kg once every three weeks until disease progression or unacceptable toxicity. The most serious risks with this agent are interstitial lung disease and embryo-fetal toxicity [207].

SACITUZUMAB GOVITECAN

In 2020, the FDA approved the topoisomerase I inhibitor sacituzumab govitecan for the treatment of treatment-resistant metastatic triple-negative breast cancer [178; 208]. This agent is administered intravenously at a dosage of 10 mg/kg on days 1 and 8 of a 21-day treatment cycle (maximum: 10 mg/kg/dose) [178].

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors (TKIs) are instrumental in regulating molecular pathways that govern cell proliferation, differentiation, metabolism, and migration. They are of particular use in patients with tamoxifen-resistant ER-positive tumors. There are 18 available TKIs, but only one, lapatinib, is approved for the treatment of breast cancer [178].

Lapatinib

Lapatinib (Tykerb) is a reversible TKI capable of interrupting intracellular activity. Lapatinib is not a MoAb but is a small molecule that competes with adenosine triphosphate for binding sites, blocking signals to intracellular tyrosine kinase. The interrupted pathways include PI3K and EPK1/2 [199; 209; 210].

Lapatinib is currently prescribed for [107]:

- First-line therapy
- Patients with resistance to trastuzumab
- Locally advanced or metastatic disease progression following taxanes, anthracyclines, or trastuzumab
- Recurrent inflammatory disease

Lapatinib is being investigated for its effectiveness in treating brain metastases as well [211].

Due to the targeted effect of lapatinib, less toxicity is experienced than seen with chemotherapy, but side effects do occur. Although the risk for congestive heart failure with lapatinib is low, any prior treatment with an anthracycline may cause some heart damage and predispose a patient to heart failure. A serious side effect experienced with lapatinib is severe diarrhea, requiring treatment with antidiarrheals and adequate fluid intake to combat dehydration [178]. Loperamide 4 mg initially followed by 2 mg after each loose stool, reaching a maximum of 16 mg in 24 hours, is recommended. Any diarrhea not responding to this regimen may require antibiotics [178].

An acriform rash (not acne) found on the upper trunk and face is a possible side effect. It may respond to simple moisturizing creams with frequent hygiene to prevent skin infections. If the rash becomes very troublesome, steroid intervention and antibiotics may be necessary; however, steroids produce additional side effects, with elevated blood glucose levels and weight gain. Fatigue, mouth sores, and palmar-plantar erythrodysesthesia (PPE) are less common side effects. Patients should be advised to take lapatinib one hour prior to meals or two hours after they have eaten [107; 178; 197; 198; 210; 212].

CYCLIN-DEPENDENT KINASE INHIBITORS

In 2015, the FDA approved the first cyclin-dependent kinase inhibitor, palbociclib (Ibrance), for the treatment of metastatic breast cancer [213]. Palbociclib acts by blocking the action of cyclin-dependent kinases, which inhibits the growth of cancer cells. This agent is indicated for postmenopausal women with ER-positive, HER2-negative metastatic breast cancer who have not yet received an endocrine-based therapy but also may be used (in conjunction with fulvestrant) in patients with disease progression following endocrine therapy [178; 213].

The usual oral dose is 125 mg once daily for 21 days, followed by a seven-day rest period to complete a 28-day treatment cycle [178]. It is prescribed in conjunction with continuous letrozole.

The most common side effects of palbociclib are neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, and diarrhea [213]. The FDA recommends that the patient's blood count be monitored regularly while taking the drug [213].

In 2017, the FDA approved abemaciclib (Verzenio) and ribociclib (Kisqali) for the treatment of ER-positive, HER2-negative advanced or metastatic breast cancer in men and postmenopausal women [178]. Abemaciclib and ribociclib have a similar mechanism of action as palbociclib. The agents may be used as initial endocrine-based therapy (in combination with an AI) or following disease progression on endocrine therapy [178]. The recommended starting oral dose of abemaciclib is 150 mg twice daily. Common side effects include alopecia, abdominal pain, anemia, decreased appetite, and infection [178]. The recommended starting oral dose of ribociclib is 600 mg once daily for 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle [178]. The American Society of Clinical Oncology recommends hepatitis B screening prior to beginning therapy with abemaciclib or ribociclib. The patient's blood count also should be regularly monitored [178; 214].

FAM-TRASTUZUMAB DERUXTECAN-NXKI

In 2022, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu), an antibody-drug conjugate consisting of the humanized monoclonal antibody trastuzumab covalently linked to the topoisomerase I inhibitor deruxtecan, for the treatment of patients with unresectable or metastatic HER2-low breast cancer [264]. HER2-low is a newer category of tumors defined as those whose cells contain lower levels of HER2 protein on their surface. It is estimated that about 60% of patients previously classified as having HER2-negative subtype can now be considered as HER2-low, and fam-trastuzumab deruxtecan-nxki is the first agent specifically approved for this population [264].

Fam-trastuzumab deruxtecan-nxki is administered via IV infusion at a dosage of 5.4 mg/kg once every three weeks until disease progression or unacceptable toxicity [178]. A randomized, multicenter, open-label clinical trial that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The results showed improvement in both progression-free survival and overall survival in people with unresectable or metastatic HER2-low breast cancer treated with fam-trastuzumab deruxtecan-nxki compared with other chemotherapy (eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel) [264].

The most common adverse reactions are nausea, fatigue, alopecia, vomiting, constipation, decreased appetite, musculoskeletal pain, and diarrhea. The prescribing information includes a boxed warning to advise health care professionals of the risk of interstitial lung disease and embryo-fetal toxicity [264].

CHEMOTHERAPY

When considering chemotherapy for any patient with early-onset, locally advanced, recurrent, or metastatic breast cancer, there is a very basic but salient question: What benefit is to be gained in relation to the predicted risks and toxicities associated with the planned treatment? Other important considerations include the risk for recurrence and the overall performance status of the patient. Treatment planning should also consider whether hormone therapy alone is adequate or if chemotherapy is warranted, taking into account considerable toxicities [15; 139; 199].

With early breast disease, the goal of chemotherapy is to treat any micrometastasis and prevent disease recurrence. In patients with advanced or metastatic disease, chemotherapy can act to manage symptoms, stabilize the disease, and prolong survival [83; 187]. The average survival for women with metastatic disease ranges from 18 months to three years, although 2% of women have been known to survive up to 20 years on up to five varied chemotherapy modalities. These long-term survivors have a better overall performance status and tend to be younger premenopausal women with less aggressive disease [113; 195; 199; 215]. Chemotherapy for advanced breast and metastatic disease carries with it significant toxicities, so it is important to establish if the patient's expectations are in line with what can realistically be accomplished.

As with many cancer treatments, when one regimen fails due to drug resistance (from the possibility of a genetic mutation, altered cell signals, or the disease progressing at a more rapid rate than can be treated), patients can be offered alternative modalities and the treatment switched accordingly. However, this is not as straightforward as implied. While there are multiple combinations available, there is no established protocol or criteria for exchanging one modality for another or switching from hormone therapy to chemotherapy. The NCCN guideline lists single and combined agents but does not stipulate which combinations are preferable in specific situations [137].

Decisions for specific chemotherapy agents are based on HER2 status, tumor size and nodes, grade, ER/PR receptor status, whether the tumor is a triple-negative breast cancer or an inflammatory malignancy, and the overall performance status of the patient [137]. Younger women may derive significantly more benefit from chemotherapy than older women, most likely due to the greater prevalence of comorbidities that occurs with aging [59; 83]. It is essential to make an individualized assessment and plan appropriately, examining functional and mental capacity, social structure and support, nutritional status, and any current polypharmacy [82; 88; 216]. Elderly women with a projected life expectancy of 5 to 10 years or longer should receive treatment using a similar regimen to that used for younger postmenopausal women [107; 217].

Although there appears to be many chemotherapeutic options to treat breast cancer, in essence the number is relatively finite. There are, however, a substantial number of combinations of two or three agents. For example, FEC is comprised of fluorouracil, epirubicin, and cyclophosphamide. Exchanging the epirubicin for doxorubicin results in the new regimen FAC. For the most part, the same agents are selected in neoadjuvant (prior to surgery) and adjuvant (following surgery) treatments and in the treatment of metastatic disease.

Recurrent and metastatic disease present challenges regarding the timing of treatment intervals. A break of more than one year may allow the same agent to be administered for a second course of treatment [196]. New drugs are constantly being trialed, and any patient eligible for inclusion in a clinical trial should be referred by the oncologist to the appropriate team [137].

Adjuvant chemotherapy is generally initiated four to six weeks following surgery, preferably within 12 weeks and prior to any planned radiation. The dosing schedule and route of administration will depend on the regimen prescribed, and certain therapies require the support of colony-stimulating factors. The typical treatment duration is four to six months [82; 107; 133; 199; 216].

PREPARATION FOR CHEMOTHERAPY

Due to the vesicant properties of the agents frequently prescribed, most notably doxorubicin (Adriamycin), a CVAD will be surgically implanted prior to initiating therapy. Depending on comorbidities and the disease process, the CVAD may also be used for IV fluids, IV antibiotics, and/or blood transfusion support, if required.

Health promotion is of utmost importance during this time, and steps should be taken to avoid illness throughout chemotherapy, particularly during nadirs. Steps can be taken to plan for side effects. Child care, a leave from work or school, and arrangements for additional help can be made. All of these points may be stressed at patient teaching prior to the initiation of chemotherapy.

CHEMOTHERAPEUTIC AGENTS

Using combined agents reduces drug resistance, and monotherapy is now rarely used in the treatment of breast cancer. Selected drugs are used to interrupt the cell cycle or damage double-strand DNA, producing the desired tumoricidal effects. Small tumors grow at a more rapid rate than larger tumors, and for these cases, administering higher doses of chemotherapy over a shorter time interval effectively destroys more cells and allows malignant cells less time to recover. With less genetic instability in smaller tumors, there is less of an opportunity for drug resistance to emerge [83].

There are at least 20 regimens to treat HER2-negative disease. The focus here, however, will be on the individual agents routinely used, reviewing the short- and long-term side effects and toxicities [107].

Alkylating Agents

Cyclophosphamide (Cytoxan) is cell cycle nonspecific, effecting breaks in double-strand DNA and prohibiting DNA repair and replication. Cyclophosphamide, administered either orally or intravenously, is a major component of many regimens. Oral cyclophosphamide should be taken with an antiemetic in the early morning with plenty of fluids. Patients should be instructed to empty their bladder frequently and report any signs of blood

in their urine, although it is unlikely with the dose prescribed for breast cancer that hemorrhagic cystitis would occur.

More common side effects include alopecia, nausea, and vomiting, with patients frequently reporting a metallic taste. The anticipated nadir occurs within 8 to 14 days. A potentially harmful side effect is a secondary hematologic malignancy with myelodysplastic syndrome potentially progressing to acute myelocytic leukemia, although this is dose dependent. Radiation to the chest area or any prior treatments with an anthracycline may potentiate some cardiotoxicity [93; 107; 133; 184; 199; 218].

Anthracyclines

Anthracyclines prescribed to treat breast cancer are doxorubicin, liposomal doxorubicin (Doxil), and epirubicin (Ellence). Anthracyclines (antitumor antibiotics) are used frequently in combination regimens, definitely with a taxane as first-line treatment for metastatic breast disease. Anthracyclines are cell cycle non-specific, binding with DNA and interrupting the synthesis of DNA and RNA [107; 133; 178; 195; 218].

Doxorubicin is a vesicant administered preferably via a CVAD. Due to the potential cardiotoxicity, the lifetime cumulative dose is 550 mg/m^2 [219]. If radiation therapy or cyclophosphamide has been previously administered, the cumulative dose is reduced to 450 mg/m^2. The potential for heart damage may be lessened if doxorubicin is given as a continuous infusion over 96 hours or in lower doses administered more frequently. Higher doses of doxorubicin correlate with greater toxicity, resulting in irreversible heart damage. Early toxicity can occur during treatment and continue for one year; late-onset toxicity may occur years later, manifesting with worsening LVEF [178]. Additional side effects from doxorubicin include anemia, nausea and vomiting, anorexia, fatigue, alopecia, diarrhea or constipation, and neutropenia [93; 107; 219]. Due to the potential cardiotoxicity associated with doxorubicin, a cardiac MRI (preferred) or baseline MUGA scan must be obtained [178; 219].

Liposomal doxorubicin, equally as effective as the nonliposomal agent, helps reduce cardiotoxicity, although even in this form elderly patients may require a dose reduction. Similar side effects to doxorubicin are experienced; a higher incidence of PPE, also known as hand-foot syndrome, and mucositis occur with the liposomal form of the drug [107; 178]. Liposomal doxorubicin for the treatment of metastatic breast cancer is an off-label use in the United States [178].

When doxorubicin and trastuzumab are prescribed concurrently, nurses should be cognizant that trastuzumab can increase the risk for heart damage [178]. Healthcare professionals should assess other medications prescribed for comorbidities for their role in potentiating or decreasing the action of doxorubicin; several classes of drugs are implicated [199; 220].

Dexrazoxane is a cardioprotectant given prior to dosing with doxorubicin when the dose accumulates to 300 mg/m^2, thereby enabling therapy to continue. It is selected for patients who have previously been heavily treated with other cytotoxic agents. Dexrazoxane is dosed at a 10:1 ratio and infused within 30 minutes of doxorubicin or epirubicin administration [178; 199].

As approximately 5% of doxorubicin is excreted via the kidneys, patients should be cautioned their urine will be reddish tinged from the coloring of the drug. Any signs or symptoms of congestive heart failure, including weight gain, shortness of breath, edema, or chest pain, must be reported. Liver function studies should be monitored regularly. The usual nadir with doxorubicin is between 10 to 14 days [178]. It is imperative to monitor for fever or chills, as the possibility of infection is greatest at this time. Nausea and vomiting, diarrhea, alopecia, and hyperpigmentation of the nail beds can also occur. Dietary instructions should focus on limiting sodium intake and avoiding alcohol. Emphasizing the need to refrain from smoking remains a constant.

Epirubicin is an anthracycline given in combination with other agents. It is dosed at 60–90 mg/m^2 over 10 minutes every 21 days [178]. The side effects are similar to those of doxorubicin, but with less severity. A dose reduction is required with any known hepatic disease. Caution is required with epirubicin and cimetidine, as there is a potential for increased toxicity [199].

Antimetabolites

The antimetabolites gemcitabine (Gemzar), capecitabine (Xeloda), 5-fluorouracil (5-FU or brand name Adrucil), and methotrexate (MTX) are cell cycle-specific antimetabolite chemotherapy agents. These drugs interfere with DNA and/or RNA synthesis via various actions and ultimately inhibit cell growth.

Gemcitabine is administered by IV weekly, either as monotherapy or in combination with other agents. When given with paclitaxel, the regimen is 1,250 mg/m^2 over 30 minutes on days 1 and 8, repeating the cycle every 21 days. The monotherapy dose, which is off label, is 800 mg/m^2 over 30 minutes on days 1, 8, and 15 of a 28-day treatment cycle [178]. Dose limiting may be necessary in anticipation of thrombocytopenia. Additional side effects include nausea and vomiting, rash, and flu-like symptoms [107].

Capecitabine is a fluorouracil pro-drug converted through the actions of enzymes to 5-FU. Tumor tissue has elevated levels of thymidine phosphorylase, which completes the conversion of capecitabine to 5-FU. This oral medication is administered twice daily for 14 days and cycled every three weeks, which produces less toxicity than if administered IV but is equally efficacious [88; 178]. Patients older than 65 years of age may require a dose reduction. Capecitabine is given as monotherapy for women with metastatic disease who have failed anthracycline and taxane therapy. The usual dose is 1,000–1,250 mg/m^2 twice daily on days 1 to 14, with the cycle repeated every 21 days [178]. Side effects include nausea and vomiting and PPE; alopecia and myelosuppression seldom occur. Capecitabine should be taken following a meal and with plenty of water. It is imperative to monitor for any interactions with capecitabine, phenytoin, folates, or warfarin. Renal function should also be monitored [107; 178; 221].

5-FU is administered IV in combination with other agents. The dose varies dependent on the regimen chosen, but ranges from 500–600 mg/m^2 on days 1 and 8 of a 21- or 28-day cycle [178]. Adequate hydration and nutrition are essential, and patients are urged to report diarrhea not responding to antidiarrheal medications. Diarrhea caused by 5-FU can be severe and debilitating, leading to dehydration, hypotension, weakness, and dizziness; a similar protocol with loperamide prescribed for patients taking lapatinib should be followed. Mucositis is problematic, further compounding the potential for dehydration. A darkened streak on the skin tracking the vein where the drug was infused is a possible side effect, along with alopecia, photosensitivity, and PPE. A nadir at around 10 to 14 days is normal [178; 199].

Methotrexate, one of the oldest of the antimetabolites, is an analog of folic acid. It is seldom used as a single agent and is generally combined with cyclophosphamide and 5-FU. If it is chosen, the dose is 30–60 mg/m^2 on days 1 and 8 every three to four weeks [178]. Any renal impairment should be closely observed in patients taking this agent, with attention to potential drug-drug interactions with several classes of drugs, including aminoglycosides, NSAIDs, and phenytoin [107; 199].

Vinca Alkaloids

Vinorelbine (Navelbine) is a vinca alkaloid and a microtubular inhibitor that prevents cell replication. Vinca alkaloids (spindle poisons) do not mimic the actions of taxanes and are prescribed for patients previously treated with anthracyclines and taxanes. Vinorelbine as a single agent is administered at 25 mg/m^2 every 7 days; when used with trastuzumab, it is given at 30–35 mg/m^2 on days 1 and 8 every three weeks [178]. It is considered relatively safe for elderly patients with comorbidities. The most frequently experienced side effect is neutropenia, with nausea/vomiting and alopecia being insignificant [88; 178; 199].

Taxanes

The taxanes are microtubule stabilizers, binding to B tubulin proteins. Taxanes available for the treatment of breast cancer include paclitaxel (Taxol), docetaxel (Taxotere), and nab-paclitaxel (Abraxane). Taxanes administered intravenously require polyethylene-lined tubing with an in-line filter.

Paclitaxel is an established agent for first- or second-line therapy, as a single or combined agent, and for recurrent or metastatic disease. Premedications are required when paclitaxel is used due to the medium polyoxyethylated castor oil used to reconstitute the drug. Frequent monitoring during the infusion is required, and the majority of adverse reactions occur within the first 10 minutes. Bradycardia, hypotension, dyspnea, wheezing, or complaints of chest pain require the infusion be stopped and treated appropriately with steroids, IV fluids, and antihistamines. If appropriate, the drug can be slowly restarted when the patient recovers. However, patients who experience severe reactions should not be re-challenged with the drug [107; 178; 215].

Nab-paclitaxel can be administered for subsequent treatments following a hypersensitive reaction to paclitaxel. Nab-paclitaxel does not require premedication, but it is considerably more expensive than paclitaxel [107; 178; 199; 215]. Potential side effects include alopecia, myelosuppression, and neurotoxicity producing peripheral neuropathy.

Docetaxel is administered 60–100 mg/m^2 IV over one hour every three weeks. In order to help counteract the side effects of fluid retention, weight gain, and respiratory difficulties, patients may be prescribed 8 mg of dexamethasone for a total of three days: one day prior to treatment, the day of treatment, and the day after. Nausea and vomiting, mucositis, peripheral neuropathy, and PPE are potential side effects. Onycholysis of the fingers and toes can be unsightly and painful [107; 178; 199].

Epothilones

In 2007, the FDA approved ixabepilone (Ixempra) for patients who developed resistance to anthracyclines, taxanes, and capecitabine. Ixabepilone is the first of the epothilones, a class of drugs that acts like an antitubular agent but can target cells that have developed a resistance to the taxanes. Ixabepilone is given as 40 mg/m^2 over three hours every three weeks as monotherapy or in conjunction with capecitabine [178]. It has a six-hour window of stability once reconstituted. Similar to the taxanes, premedication and close monitoring are required for possible hypersensitive reactions [178]. Studies have shown that epothilones may have better efficacy and milder adverse effects than taxanes [107; 215].

PARP Inhibitors

In 2018, olaparib was approved by the FDA for the treatment of HER2-negative metastatic breast cancer with a germline *BRCA* mutation [222]. Olaparib, the first PARP inhibitor approved for the treatment of breast cancer, acts by blocking an enzyme involved in repairing damaged DNA, allowing cells with damaged *BRCA* genes to die and potentially slowing or stopping tumor growth. This agent is administered orally 300 mg twice daily until disease progression or unacceptable toxicity. Also in 2018, a second PARP inhibitor, talazoparib, was approved by the FDA for patients with HER2-negative locally advanced or metastatic breast cancer with a germline *BRCA* mutation. Patients must be selected for therapy based on an FDA-approved companion diagnostic for talazoparib [178; 223]. Talazoparib is administered orally 1 mg daily until disease progression or unacceptable toxicity [178]. The prescribing information includes warnings and precautions for myelodysplastic syndrome/acute myeloid leukemia, myelosuppression, and embryo-fetal toxicity. Common adverse reactions include fatigue, anemia, nausea and vomiting, neutropenia, thrombocytopenia, and decreased appetite [178].

SIDE EFFECTS RELATED TO CHEMOTHERAPY

Side effects and toxicities differ to some degree among the available chemotherapeutic agents. Some side effects are more manageable than others and subside after treatments are completed with no residual long-term effects. However, some toxicity is irreversible and persists for a lifetime. Both types of adverse effects require diligence and appropriate treatment in order to improve patients' quality of life.

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) has historically been one of the most highly anticipated side effects associated with chemotherapy [139; 216]. Although nausea and vomiting still present a challenge, it is a treatable condition.

CINV is invariably more problematic in younger women, women with a history of motion sickness or morning sickness, and women prone to anxiety. Nausea and vomiting occur when the release of dopamine-2, neurokinin-1, or serotonin 5-hydroxytryamine (5-HT) triggers the vagus nerve to stimulate the chemoreceptor trigger zone. Due to the complexity of various signals and triggers, a combination of antiemetics is often required for effective prevention and treatment [107; 148; 224; 225].

The majority of chemotherapy agents administered for breast cancer fall into the moderate-to-high range of emetogenicity, including 5-FU, cyclophosphamide, paclitaxel, epirubicin, and docetaxel. Cyclophosphamide, doxorubicin, and methotrexate fall into the moderate category, and 30% to 60% of patients taking these medications will experience CINV without premedication. High-dose cyclophosphamide (>1,500 mg/m^2) and the anthracyclines fall into the highly emetogenic category, with as many as 90% of patients experiencing CINV if insufficient premedication is administered. The lowest potential risk (10% to 30%) for CINV results from the administration of the taxanes, 5-FU, and gemcitabine [2; 224; 225].

CINV is further classified by the timing and intervals of occurrence. Acute CINV, as implied, can manifest with chemotherapy initiation, lasting up to 24 hours. Combined agents and those rapidly infused may potentiate a more severe emetogenic response compared to single agents or infusions given over longer periods of time.

As many as 54% of patients experience anticipatory nausea and vomiting as a result of initial treatments being poorly controlled. Investigating the triggers associated with anticipatory CINV, such as the smell of food, can provide some insight. For hospitalized patients, having meal trays "aired out" prior to being delivered to their room may prove beneficial. Incorporating alprazolam and lorazepam into a patient's medication regimen is warranted to reduce anxiety.

Delayed nausea and vomiting can continue for approximately one week, with the onset beginning 24 hours after the completion of chemotherapy. Two agents known to cause delayed CINV are cyclophosphamide and doxorubicin. Breakthrough nausea and vomiting may require around-the-clock dosing with antiemetics with a thorough investigation into previously administered antiemetics clearly proven to be ineffective.

CINV can be controlled and managed with effective antiemetics. According to American Society of Clinical Oncology guidelines, a 5-hydroxytryptamine type 3 (5-HT3) antagonist, dexamethasone (Decadron), olanzapine (Zyprexa), and a neurokinin 1 (NK1) receptor antagonist (such as aprepitant [Emend]) should be used as prophylaxis for a highly emetic chemotherapy agent or combination (e.g., an anthracycline and cyclophosphamide) [226]. Palonosetron (Aloxi), in combination with dexamethasone, is recommended for patients taking chemotherapy agents with moderate emetic risk, and dexamethasone is recommended before the first dose of chemotherapy with a low emetic risk. In addition to pharmacologic management of nausea and vomiting, other supportive approaches include maintenance of oral hygiene, regular baths to reduce unpleasant odors, and small meals at regular intervals. Cold foods may be better tolerated than hot foods because of decreased smells.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Clinical Oncology asserts that adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of a neurokinin 1 (NK1) receptor antagonist, a serotonin (5-HT3) receptor antagonist, dexamethasone, and olanzapine.

(https://ascopubs.org/doi/10.1200/JCO.2017.74.4789. Last accessed July 21, 2022.)

Strength of Recommendation/Level of Evidence: Strong/High

Overall quality of life is impacted if CINV is not controlled; patients are less productive, and work and home life are disrupted. Patients should be reassured they will receive antiemetics prior to treatments, throughout the course of therapy, and as needed to use at home [56; 181; 224; 225].

Alopecia

Alopecia, a very visible side effect of chemotherapy, can be daunting. Hair loss typically begins as early as two to three weeks into treatment, and in addition to the head and eyebrows, hair is also lost from the pubic and axillary areas as well. Although alopecia may significantly impact quality of life, most women appear to adapt well, opting to wear a head covering or wig. A short haircut early in the course of treatment prevents hair from being noticeably shed on clothing and bedding and falling into food or meal trays. For all women, undoubtedly, new hair growth will begin after treatments are completed, although hair color or texture may be different [2; 107; 139; 181; 216].

Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy results from agents targeting microtubules, which includes the taxanes, vinca alkaloids, and epothilones [139; 227; 228]. Approximately 40% to 70% of women will develop this debilitating side effect, with patients with pre-existing neuropathy caused by diabetes or alcohol abuse at risk for more severe symptoms. Patients may be reluctant to report chemotherapy-induced peripheral neuropathy, as one of the interventions to relieve symptoms is a dose reduction or lengthening of the time interval between treatments. Patients understandably fear that if they miss a treatment, it could allow for disease progression. Reassurance should be given this is not an accurate assumption.

Early symptoms begin with numbness or tingling in the toes or fingers [215; 228]. Neuropathy is painful, and the numbness and tingling result in the loss of fine motor skills, making simple tasks such as buttoning clothes a challenge. Skin sensations are diminished, posing a danger of injury. Gait disturbances create safety issues with ambulation, requiring physical therapy and the use of assistive devices [227].

Remedial efforts, such as dose reduction or retiming treatments, are the mainstay in treating chemotherapy-induced peripheral neuropathy. In approximately one-third of patients, long-term chemotherapy-induced peripheral neuropathy may be relieved with amitriptyline, gabapentin, and glutamine taken on a regular basis. Topical analgesics and creams may afford some relief, but focusing on safety becomes a priority [2; 181; 216; 228].

Chemotherapy-Induced Cognitive Impairment

Chemotherapy-induced cognitive impairment (CICI) or dysfunction, also termed "chemo brain" or "chemo fog," occurs in up to 23% of women undergoing chemotherapy for breast cancer; overall, the estimated prevalence of CICI varies from 15% to 82% depending on the patient population and the definition of impairment [229; 230]. It manifests as an alteration in cognitive abilities, with a decreased attention span and ability to learn, word-finding difficulty, and short-term memory loss [139; 231]. The mechanism responsible for CICI is not fully understood. Many possibly etiologies have been described, and the underlying mechanism is believed to be multifactorial [230; 232]. The direct neurotoxic effects of chemotherapy may cause damage to neurons or surrounding cells, with some studies indicating structural changes in white matter [233].

Oxidative stress and DNA damage may cause a slowing of cell division in the subventricular zone, impairing cognition. Changes in hormone levels and/or immune dysregulation may also contribute [232]. Genetic predisposition (e.g., impaired DNA repair capability) may result in an exaggerated level of cognitive impairment. Other factors include the possibility of brain metastases, electrolyte or metabolic imbalances, and polypharmacy [56; 216; 234; 235; 236]. Cognitive impairments have also been shown to occur prior to chemotherapy, making it difficult to determine causality [229; 237; 238; 239]. CICI may also be a result of common problems faced by cancer survivors (e.g., pain, insomnia, depression, fatigue) [240].

It is possible that this side effect will continue in some women for as long as 10 years after treatment. Alerting patients to the possibility of CICI and helping to prepare them with suggested coping strategies may relieve some of the frustration experienced. Restructuring the day, compiling lists and calendars, and learning to pace activities are useful approaches that can enable patients to continue with life as normal as much as possible. Being driven to appointments and help with running errands can provide a safety net for affected women. However, careers can be significantly challenged [241; 242; 243].

There are no defined modalities to reverse this impairment. Coping mechanisms and support are crucial. Adequate rest is also important, as fatigue may contribute to CICI cycling with depression. If anemia is present, it should be addressed fully. Methylphenidate and modafinil have been suggested for the treatment of CICI, and research regarding the utility of these drugs for such patients is ongoing [231; 236; 244]. Various nonpharmacologic approaches to managing CICI have been suggested, including mental exercises, yoga, meditation/guided imagery, exercise, stress management techniques, probiotic supplementation, and acupuncture. Although evidence supporting any of these approaches is lacking, many survivors report that they find them to be helpful and empowering [239].

Myelosuppression

Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is further classified based on the factor affected as anemia, thrombocytopenia, or neutropenia. These are anticipated side effects from chemotherapy, but they can be addressed and corrected. Patients should report any shortness of breath, dizziness, tachycardia, or headaches indicative of anemia. When myelosuppression is present, there is a heightened risk for infection during patients' nadirs, so reporting 100.4°F or higher and other signs of infection is important. Febrile neutropenia requires hospitalization, with fever work-up to determine the cause and subsequent treatment with appropriate IV antibiotics. Crowds should be avoided during the nadir period; if this is not feasible, patients should be advised to wear a mask when in public.

The treatment of anemia can be complicated. Many studies have provided evidence to recommend the use of erythropoiesis-stimulating agents (e.g., erythropoietin [Epogen], darbepoetin [Procrit]) for anemia in people with cancer because of the benefits of increasing the hemoglobin level, improving exercise tolerance, reducing symptoms, and decreasing the need for blood transfusions [245; 246]. However, safety concerns led the FDA to require a boxed warning on the label of erythropoiesis-stimulating agents regarding the increased risk of several adverse events (e.g., death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence) among people with chronic kidney disease or cancer [178; 247]. The FDA recommends using the lowest dose sufficient to avoid red blood cell transfusion [178; 247]. The overall goal is to protect patients against infection, maintain safety when there is a potential risk for bleeding, and keep patients on track with the scheduled treatment plan [139; 181; 212; 216; 235; 247].

Fatigue

Fatigue has been suggested to be the sixth vital sign for cancer patients and can severely impact quality of life [248]. Fatigue experienced during and following cancer treatments is multifactorial, with physical, psychologic, and emotional manifestations [148; 171; 216; 249]. As many as 70% to 100% of patients undergoing chemotherapy will experience fatigue, and it has been known to persist up to five years in 30% to 40% of women; for some, this debilitating side effect may last as long as 10 years [2; 56; 171; 181; 249]. Fatigue is more pronounced with higher doses of chemotherapy, dose density scheduling, and concurrent administration of chemotherapy and radiation.

Ideally, all patients should be assessed prior to starting chemotherapy for any existing fatigue, but this is often overlooked in the push toward starting treatment [169; 171; 181]. Fatigue experienced prior to the beginning of any treatment is a predictor of increased severity with ongoing therapy [234]. The NCCN has established guidelines for screening and treatment of cancer- and chemotherapy-related fatigue [250].

Anemia is a major cause of fatigue, although its treatment is a complex issue, as discussed. Shortness of breath and profound weakness can cause significant increases in fatigue and anxiety, with some presuming this signals disease progression. Focusing on nutrition, iron supplements, and pharmacologic management to correct deficiencies will add to a sense of well-being and decrease fatigue [171]. Electrolyte imbalances (e.g., hypercalcemia, hyponatremia, hypokalemia, hypothyroidism) should be assessed and corrected appropriately.

When medications are the underlying cause of the fatigue, nonessential medications should be discontinued, and changing medications or the time of dosing may reduce tiredness during the day. Appropriate management of infection, cachexia, depression, and insomnia may also help reduce fatigue [246; 250; 251].

Most patients will try to manage fatigue by resting and/or sleeping more often, and many healthcare professionals will also recommend this strategy. However, additional rest and/or sleep usually does not restore energy in patients who have fatigue related to cancer or cancer treatments; continued lack of exercise may even promote fatigue [246]. Aerobic exercise has been found to alleviate fatigue among cancer survivors. A meta-analysis demonstrated a significant effect of exercise in the treatment of fatigue during and after cancer treatment [252]. An update of the meta-analysis confirmed this finding but concluded that additional research is needed to determine the optimal type, intensity, and timing of exercise as an intervention for cancer-related fatigue [253].

Although an exercise program is recommended, decreasing activity to conserve energy is also encouraged [246]. Clinicians should talk to the patient and family about the importance of the patient conserving energy by adjusting daily activities to correspond to times of peak energy, setting priorities for activities, following a normal wake-sleep cycle, using assistive devices, and delegating less important tasks [246].

Pharmacologic treatment of fatigue should be undertaken only after potential causes of fatigue have been ruled out [246; 250]. Methylphenidate may reduce fatigue, and the NCCN recommends it as a first-line option in the cancer care setting [250]. This recommendation is based on systematic reviews showing a significant effect of methylphenidate for the treatment of fatigue in people with cancer or HIV/AIDS or for opioid-induced sedation [246; 246]. An optimal dose of methylphenidate has not been defined, but an initial dose of 5–10 mg (given in the morning) has been used, with the dose titrated to 40–60 mg per day (given once in the morning and once at midday) [246; 250]. Among the side effects are nervousness, jitteriness, agitation, arrhythmia, and tachycardia. Though used in the past, modafinil is no longer recommended by the NCCN for the treatment of cancer-related fatigue [250].

Palmar-Plantar Erythrodysesthesia

PPE is an inflammatory process of unknown etiology that begins on the soles of the feet and the palms of the hands. Early manifestations are usually painless, itchy patches of dry skin, but the condition progresses to edematous, painful areas affecting activities of daily living and quality of life; intervention is necessary. Some relief from the discomfort can be achieved by elevating the extremities, limiting pressure on the soles of feet, avoiding heavy bedcovers, applying cold compresses and/or creams, and using corticosteroids and analgesics. The drugs capecitabine and pegylated doxorubicin are the major causal agents in PPE, and if these are part of a patient's chemotherapy, dose reduction may be necessary to control symptoms [88; 107; 199; 212].

PATIENT EDUCATION

Prior to initiating chemotherapy, patients should be counseled regarding the importance of keeping scheduled treatment appointments and subsequent follow-up clinic visits to check blood work, weight, and vital signs. These appointments provide an opportunity to discuss any problems and to monitor compliance with oral chemotherapeutic agents. It is important to assess compliance with medications as prescribed, timing related to food intake, avoiding drug interactions, and monitoring and managing side effects. Patients should be advised not to double doses if one is missed. Calendars are especially helpful when the regimen is not based on daily dosing. Fixed incomes and prohibitive costs of the drugs create a further burden; social workers, case managers, and counselors can be helpful in these cases [188; 221].

Printed educational materials pertaining to each chemotherapy agent prescribed will be provided. Printouts are a good resource, enabling patients and care providers to refer back periodically. With any subsequent changes in the plan or the introduction of new drugs, further education and counseling is warranted [221].

Health Maintenance During Chemotherapy

It is essential for patients undergoing chemotherapy to optimize overall health and avoid illness if at all possible. Health maintenance goals should be set as part of the treatment protocol and reinforced during patient teaching. Avoiding infection is key during chemotherapy, particularly during patients' nadirs. This entails adhering to proper hand hygiene, avoiding crowded areas (especially during flu season), and being vigilant for signs of infection.

Patients should check their temperature at around the same time daily and report any temperatures of 100.4°F or greater. Signs and symptoms of infection of the skin surrounding a CVAD site (e.g., pain, redness, swelling, drainage) should also be reported.

Teeth or dentures should be brushed after every meal; mouth rinses may help to remove any food debris. Mouth sores, a sore throat, or symptoms of mucositis should be promptly reported.

Nutrition must be adequate, with plenty of fluids and the avoidance of alcohol. Protein supplements may be ordered to augment intake. Diarrhea can lead to dehydration and electrolyte imbalance if not controlled. Any sudden weight gain or edema should be reported. Smoking cessation and mobility and exercise within safe boundaries are strongly encouraged [38; 139; 212; 220].

Timely reporting from patients as they experience side effects ensures prompt intervention and treatment, preventing toxicities from accelerating to more serious complications. As such, reporting symptoms is a large aspect of patient teaching. Pain, redness, or swelling in the upper or lower extremities may be indicative of thrombosis and should be addressed. Any new onset of increased shortness of breath indicating cardiac toxicity or the possibility of a pulmonary embolism requires immediate reporting. It is understandably difficult for patients to comprehend and retain everything they hear from one or two teaching sessions. With ongoing treatments and as side effects emerge, teaching should be reiterated. Having patients repeat what they have heard is an excellent way of determining how much they comprehend.

MALE BREAST CANCER

Breast cancer in men is rare; an estimated 2,710 new cases will be diagnosed in the United States in 2022, and an estimated 530 men will die of the disease [254]. These figures represent less than 1% of all breast cancer diagnosed in this country. Although the numbers are low, the prevalence has increased 26% since the early 1980s, prompting increased attention and highlighting the need to emphasize to men—and their healthcare providers—that breast cancer is not confined to women [255]. The lack of awareness of the disease in men has led to a longer time between the development of symptoms and diagnosis and to a later age (mean age: 67 years) and stage of disease at the time of diagnosis compared with women [255; 256; 257].

Male breast cancer has not been extensively studied, and research is difficult because of the small numbers of men with the disease. Reviews of the literature have been helpful in identifying risk factors, clinical and pathologic characteristics, and the role of genetics [255; 256; 258]. Studies have shown that male breast cancer differs from female breast cancer in many ways. For example, some risk factors unique to men include [257; 258]:

- Undescended testes
- Orchiectomy
- Infertility
- Gynecomastia
- Mastitis
- Breast trauma
- Klinefelter syndrome
- Radiation to the chest wall

BRCA2 mutation is found in approximately 4% to 16% of men with breast cancer [258].

A painless subareolar lump or swelling is the most common presenting symptom, occurring in approximately 85% of men with breast cancer [255; 259]. Other common symptoms are nipple retraction, localized pain, or nipple ulceration, bleeding, or discharge [257]. About 1% to 2% of men will have no symptoms [255; 259]. In diagnosing male breast cancer, the primary consideration is to distinguish cancer from gynecomastia, which is present in about 30% of healthy men [256].

The approach to the diagnostic evaluation of male breast cancer is the same as for female breast cancer. A history and physical examination will help determine potential risk factors and identify the clinical features. Mammography has good sensitivity and specificity, and ultrasonography may be useful, especially for detecting involvement of the lymph nodes [256; 257]. Biopsy is essential for elucidating the pathologic characteristics. In male breast cancers, the overexpression of ER and PR is likely. Approximately 85% of all male breast cancers are ER-positive, and 70% are PR-positive [110; 257; 258].

As noted, data on male breast cancer are limited, and recommendations for treatment have been extrapolated from the literature on female breast cancer and from small series of men with the disease. Modified radical mastectomy is used most often, with lumpectomy rarely performed [257; 258]. SLNB has also been effective in men [260; 261]. Adjuvant radiation therapy has been associated with a lower local recurrence rate and a higher survival rate [256; 258]. Adjuvant chemotherapy has been carried out according to guidelines for women at high risk for recurrence. Adjuvant hormone therapy has a clear role in the treatment of men with hormone receptor-positive cancer, with reductions in recurrence and death [259; 262]. In addition, tamoxifen has led to a 50% response rate for metastatic breast cancer [256].

Five-year survival rates for men with breast cancer have been reported to be between 40% and 65% [255; 256]. In one retrospective study, the median survival was 87 months (83 months for men with invasive disease) [258]. Older age, higher stage of disease, and increasing tumor size have been associated with shorter survival [258]. The risk of second cancers (breast and nonbreast) appears to be high [263].

CONCLUSION

It is difficult to imagine the anxiety and anguish experienced with an initial diagnosis of breast cancer. Patients are expected to absorb information and education pertaining to diagnostics, treatment plans, and the anticipated toxicities during this period, which is difficult. Nurses and clinicians within their respective roles of expertise, caring for men and women with breast cancer throughout the disease trajectory, should offer support and provide guidance. Anticipating educational needs to prevent or minimize chronic complications, with appropriate referrals made for counseling, ensures the provision of seamless care. Emphasis on compliance with oral therapies and attending scheduled follow-up appointments for surveillance of benign and malignant masses cannot be overstated. Providing quality care to transition women and men from the initial diagnosis of breast cancer through the diagnostic process, surgery, and subsequent treatments is the responsibility of the entire team of healthcare providers.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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