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Editors

Breast Disease

Management and Therapies, Volume 2

Second Edition

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Preface

The goal of *Breast Disease: Management and Therapies* is to provide a comprehensive, scholarly appraisal of contemporary therapy. We have attempted to provide useful and explicit recommendations on management, but we must stress that these recommendations are subject to change. Some of the recommendations are controversial and the subject of ongoing clinical trials. The gold standard for breast cancer care includes an integrated multidisciplinary team approach, comprising pathologists, radiologists, surgical oncologists, medical oncologists, radiation oncologists, oncology nurses, and plastic surgeons. This book is organized into 9 sections and 51 chapters, and we give a brief summary of its content below.

Diagnostic *breast biopsy* is one of the most common medical procedures, and a variety of methods have been developed in the last 30 years to augment classic surgical incisional and excisional biopsies. Fine-needle aspiration (FNA) has an important historical role and remains among the most cost-effective methods. However, this technique is limited by the weakness of current breast cytology to adequately reproduce all information provided by traditional histopathology. Core biopsies, ranging from the use of simple needle cores to larger coring devices to remove spaghetti- to macaroni-sized pieces, have become the mainstay of current biopsy techniques for most palpable and non-palpable lesions. Surgical incisional and excisional biopsies, which are classic standards, are reserved for a few exceptional circumstances, including the removal of symptomatic benign lesions or when coring biopsy tools fail to provide adequate diagnostic information and material.

After diagnosis, in the *evaluation of patients for metastases prior to surgery*, preoperative ultrasonography (US) and needle biopsy have emerged as effective methods for axillary staging for triaging women with breast cancer directly to axillary surgery for sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) or to neoadjuvant chemotherapy (NCT) in those with axillary node-positive disease. However, no perfect modality is available to identify metastatic disease in breast cancer; every diagnostic test has its own advantages and limitations. The available evidence suggests routine evaluation for stage III and possibly stage II breast cancer using imaging techniques, including positron emission tomography-computerized tomography (PET-CT). The workup of abnormal findings in breast cancer patients is by patient signs and symptoms, including history and physical examination, laboratory tests, imaging, biopsy of suspicious finding in imaging studies, and monitoring serum markers.

Breast-conserving surgery (BCS) and mastectomy are two options for surgical treatment. SLNB has replaced *axillary lymph node dissection* (ALND) in clinically node-negative early-stage breast cancer patients. ALND is considered mandatory in sentinel node-positive patients, but recent data have demonstrated that BCS and radiotherapy are the equivalent of ALND for micro−/macrometastatic sentinel lymph nodes (SLNs). This approach reduces the morbidity of dissection without decreasing overall survival (OS).

Breast reconstruction provides closure to many women who have been treated for breast cancer by increasing their comfort in clothing and providing a psychological benefit. Patients who choose reconstruction must navigate a reconstructive pathway guided by their plastic surgeons, which include decisions regarding the timing, type, and extent of reconstruction.

After surgery, *adjuvant endocrine therapy* is a pivotal component of treatment for women with hormone receptor-positive early-stage breast cancer; this therapy delays local and distant relapse and prolongs survival. Patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive invasive breast cancers should be considered for adjuvant endocrine therapy regardless of age, lymph node status, or adjuvant chemotherapy use. Features indicative of uncertain endocrine responsiveness include low levels of hormone receptor immunoreactivity, PR negativity, poor differentiation (grade 3), high Ki67 index, human epidermal growth factor receptor 2 (HER2) overexpression, and high gene recurrence score. Adjuvant hormonal manipulation is achieved by blocking the ER in breast tumor tissues with tamoxifen in premenopausal and postmenopausal women, lowering systemic estrogen levels with luteinizing hormone-releasing hormone agonists in premenopausal women, or blocking estrogen biosynthesis in non-ovarian tissues with aromatase inhibitors in postmenopausal women.

All patients with invasive breast cancer should be evaluated to assess the need for *adjuvant cytotoxic therapy*, trastuzumab therapy, and/or endocrine therapy. If patients must receive endocrine therapy (either tamoxifen or aromatase inhibitor) and cytotoxic therapy as adjuvant therapy, chemotherapy should precede endocrine therapy. Molecular subtypes of breast cancer can be distinguished by common pathological variables, including ER, PR, HER2, and Ki67 index. The inclusion of chemotherapy in the adjuvant regimen depends on the intrinsic subtype. Multigene expression array profiling is not always required for subtype definition after clinicopathological assessment. Young age, grade 3 disease, lymphovascular invasion, one to three positive nodes, and large tumor size are not adequate features to omit molecular diagnostics in the decision of adjuvant chemotherapy. Any lymph node positivity should not be a sole indication for adjuvant chemotherapy. However, patients with more than three involved lymph nodes, low hormone receptor positivity, positive HER2 status, triple-negative status, high 21-gene recurrence score (RS), and high-risk 70-gene scores should receive adjuvant chemotherapy. A high Ki67 proliferation index and histological grade 3 tumors are acceptable indications for adjuvant chemotherapy.

In patients with HER2-positive early-stage breast cancer, the monoclonal antibody trastuzumab has been approved as the first molecularly targeted agent for the adjuvant treatment. Current *adjuvant anti-HER2 therapies* must be refined for different patient subsets with HER2-positive tumors to provide personalized, effective, and minimally toxic treatment.

Mastectomy can remove any detectable macroscopic disease, but some tumor foci might remain in the locoregional tissue (i.e., chest wall or lymph nodes), potentially causing locoregional disease recurrence. *Postmastectomy adjuvant radiotherapy* (PMRT) has the potential to eliminate such microscopic disease. PMRT has been recommended for patients with $\geq$4 positive axillary lymph nodes but is not administered to most women with node-negative disease. Patients with one to three positive axillary lymph nodes constitute a gray zone.

Breast irradiation after BSC is an essential component of breast conservation therapy for maximizing local control and overall survival. The optimal dose and fractionation schedule for radiation therapy after BCS has not yet been defined. There is renewed interest in hypofractionation for whole-breast irradiation, and this approach has important practical advantages and biological implications. Irradiating only the tumor-bearing quadrant of the breast instead of irradiating the entire breast after BCS has also increased in popularity in the last decade.

Preoperative systemic chemotherapy (PSC), also known as "neoadjuvant chemotherapy," is an important therapeutic option for most patients with breast cancer and is becoming increasingly popular in the breast oncology community for the treatment of earlier-stage disease. Moreover, it is a valuable research tool for identifying predictive molecular biomarkers and is a valid treatment option for patients with early-stage breast cancer.

The principles of *surgery after* PSC remain the same. Monitoring the response to therapy is important for surgical planning and prognostic information. Preoperative marking of the tumor is essential for guiding BCS after PSC and should be performed in all patients. Axillary staging can be performed prior to or after PSC, and both methods are associated with specific risks and benefits. Early literature supported the use of pre-PSC SLNB, but current literature suggests

increased accuracy and decreased use of axillary dissection in patients who undergo SLNB after PSC.

Chemotherapy can be particularly toxic for elderly postmenopausal patients, and *neoadjuvant hormonal therapy* (NHT) is an alternative for patients with hormone receptor-positive, locally advanced, postmenopausal breast cancer. This treatment is also highly beneficial for patients with comorbidities and can comprise tamoxifen and steroidal or nonsteroidal aromatase inhibitors (AIs). The best activities in clinical trials have been observed with AIs. NHT produces good response rates and adequate downstaging of tumor size such that BCS may become an option. The optimal duration of such treatments should be at least 4 months and may be continued for as long as 8 months.

Neoadjuvant therapy is administered with the objective of improving surgical outcomes in patients with *locally advanced breast cancer* for whom a primary surgical approach is technically not feasible and in patients with operable breast cancer who desire breast conservation but for whom either a mastectomy is required or a partial mastectomy would result in a poor cosmetic outcome. Patients treated with *neoadjuvant chemotherapy* are significantly more likely to undergo BCS without a significant increase in local recurrence compared with patients who are treated with surgery first. In addition, neoadjuvant chemotherapy is appropriate for patients with HER2-positive or triple-negative breast cancer who are most likely to have a good locoregional response to treatment, regardless of the size of their breast cancer at presentation.

The decision to treat patients with *radiotherapy after preoperative chemotherapy* is still largely based on the initial clinical staging of the patients. The use of three-field radiotherapy, including the chest wall/breast and regional lymphatics, after surgery in locally advanced, node-positive patients receiving neoadjuvant systemic chemotherapy is well-established. A pooled analysis is the only prospective dataset that can assist radiotherapy decisions in the neoadjuvant setting. Well-designed randomized, controlled studies are urgently needed in this controversial area.

Inflammatory breast carcinoma (IBC) is the most aggressive, lethal, and rare form of breast cancer. It is characterized by the rapid development of erythema, edema, and peau d'orange over one-third or more of the skin of the breast due to the occlusion of dermal mammary lymphatics by tumor emboli. Plugging of the dermal lymphatics of the breast finding is not mandatory for diagnosis. The most striking progress in the management of IBC has been the sequential incorporation of preoperative systemic chemotherapy [an induction regimen containing an anthracycline and a taxane (plus trastuzumab in *HER2*-positive patients)] followed by surgery and radiation therapy.

Breast cancer risk increases with age, and life expectancy continues to increase; therefore, *breast cancer in older women* has become a significant public health concern. The basic principles of imaging, diagnosis, and treatment remain the standard for all women with breast cancer. However, in the elderly population, comorbid conditions, life expectancy, and quality of life take on particular importance for the clinician to consider and balance with treatment decisions. Historically, older women have been poorly represented in breast cancer trials, and their surgical and adjuvant treatment often differs from that of younger women. *Breast cancer is observed in men* 100-fold less often than in women. Previous studies have shown that metastatic breast cancer (MBC) cases significantly differ from female cases, whereas new studies have reported that breast cancer has similar characteristics at the same stages in both genders.

Pregnancy-associated breast cancer is defined as breast cancer that is diagnosed during gestation, lactation, or the first postpartum year. Surgical treatment can be undertaken during any phase of the pregnancy. Chemotherapy can potentially be administered during the second or third trimester. Radiotherapy is reserved for the postpartum period.

Paget's disease of the breast is characterized by eczema-form changes accompanied with erosion and ulceration of the nipple and areolar epidermis. This condition is primarily correlated with ductal carcinoma in situ (DCIS); additionally, it can be accompanied by invasive ductal carcinoma (IDC). The diagnosis is determined upon the microscopic observation of

Paget cells in a skin biopsy. The width of the lesion is evaluated via mammography and MRI in patients for whom breast-preserving surgery is planned. Depending on the extent of the lesion, SLNB and axillary curettage for those having axillary metastases are treatment alternatives to breast-preserving surgery or mastectomy.

Phyllodes tumors, also termed phylloides tumors or cystosarcoma phyllodes, are rare fibroepithelial neoplasms of the breast that remain challenging for both surgeons and pathologists. The World Health Organization (WHO) established the name phyllodes tumor and the following histological types: benign, borderline, and malignant. Breast imaging studies may fail to distinguish the phyllodes tumor from a fibroadenoma. A core needle biopsy is preferable to fine-needle aspiration for tissue diagnosis. The common treatment for phyllodes tumors is wide local excision. Mastectomy is indicated for patients with a large lesion. The benefits of adjuvant chemotherapy and radiotherapy are controversial.

Breast sarcomas are rare clinical entities. Surgical excision with clear margins is the primary treatment for localized tumors. Lymph node sampling and dissection are not recommended. Adjuvant or neoadjuvant therapy should be considered for high-risk patients. Angiosarcomas are the most common sarcomas of the breast. These lesions can be associated with lymphedema or irradiation. Surgery is the primary treatment, and wide negative margins are essential for a long-term cure. Primary breast lymphoma is a rare entity that arises from the periductal and perilobular lymphatic tissue and intramammary lymph nodes. Surgery is limited to biopsy. Metastatic involvement of the breast most often originates from the contralateral site. The most common malignancy of the body that metastasizes to the breast is *malignant melanoma*. Hematological malignancies, such as *leukemia and lymphoma*, also frequently occur.

Reducing estrogen production and preventing estrogen from interacting with the ER pathway have been the focus of several preclinical and clinical trials and are the commonly used *endocrine treatment* strategies for treating HR+ *MBC*. Because the ovaries are the main source of estrogen in premenopausal women, ovarian ablation or functional suppression is the primary means of decreasing circulating estrogen. In postmenopausal women, the peripheral conversion of androgens to estrogen is the predominant source of estrogen. Thus, the inhibition of the conversion of androgens by an AI or via the interaction of estrogen with its receptor is the most frequently used approach to treat postmenopausal women with HR+ breast cancer.

In ER-positive/*HER2-negative MBC*, endocrine therapy is preferred, even in the presence of visceral metastasis. Chemotherapy should be reserved for patients with combination chemotherapy indications or proven endocrine resistance. Regarding the use of chemotherapy, sequential monotherapy is the preferred choice for MBC. Combination chemotherapy should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control. HER2-targeted therapies have radically altered the prognosis of *HER2-positive MBC*. However, resistance to these therapies frequently leads to treatment failure and new tumor progression. The most promising new anti-HER therapies are T-DM1 and pertuzumab, which has been evaluated in trastuzumab-resistant patients as well as in a first-line setting with trastuzumab. The dual blockage of HER appears to be a favorable approach for these patients; however, downstream signaling steps can be activated to overcome *tyrosine kinase inhibition*. Because tumor cells can adapt themselves by using alternative pathways to maintain proliferation, providing a sufficient treatment approach also requires the consideration of possible escape mechanisms in tumor cells.

Immunomodulation appears to be a promising strategy for breast cancer. High immunogenicity has been described in breast cancer subtypes with a high proliferation index. Immune checkpoints are one of the major mechanisms of immune escape. Expression of PD-L1 on tumor cells leads to lower activity of CD8+ T cells. Antibodies against PD-1 or PD-L1 are being investigated in clinical trials. The first results are promising, but predictive markers are urgently needed to select patients who have the best chance for receiving an effective treatment. One possible avenue is immuno-molecular therapy, which integrates immune and

molecular features to devise novel combinatorial approaches based on targeting intracellular molecular alterations and modulating the immune response.

Although antiangiogenic therapies, including anti-vascular endothelial growth factor (VEGF) antibodies and tyrosine kinase inhibitors, have become important components of the standard of care for the treatment of many solid tumors, the results of clinical trials investigating the efficacy of *antiangiogenic agents* in breast cancer are contradictory.

Breast cancer during pregnancy must be managed with a multidisciplinary approach that should follow standard protocols for nonpregnant patients as much as possible while considering the safety of the fetus. Various assisted reproductive technology approaches are available for breast cancer patients who wish to preserve fertility after cancer treatment. These approaches can be utilized before or after the initiation of adjuvant breast cancer treatment. Hence, adequate counseling should be provided to premenopausal breast cancer patients prior to cancer treatment.

Cancer is a chronic, life-threatening disease that greatly impacts all spheres of life. Cancer patients develop various emotional, mental, and behavioral reactions regarding their illness during diagnosis, treatment, and palliative period. Some of these reactions are normal and may even tend toward adaptation in some cases. The treatment team must understand such reactions and support them. Disordered or maladaptive reactions, however, require psychiatric evaluation and treatment. It is essential to encourage the patient to express her feelings, support the patient, and provide her with security. Health-care professionals should be aware of and respect women's coping strategies and encourage them to use these strategies to reduce psychological symptoms. Health-care professionals should also make family members and friends aware of their role in supporting and encouraging coping strategies.

We have summarized some important points of this book above. We would like to dedicate this book to postgraduate physicians in training to become breast cancer specialists. We hope this book stimulates today's young doctors to contribute to the basic and clinical research on which future books will be based.

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Part I

Invasive Breast Cancer

Biopsy Techniques in Nonpalpable or Palpable Breast Lesions

1

William C. Dooley

Fine-Needle Aspiration Biopsy–Core Needle Biopsy

Fine-Needle Aspiration (FNA) Biopsy

Fine-needle aspiration has a long history in breast cancer diagnosis. It has been popularized as a part of the "triple test" for the evaluation of palpable abnormalities preceding the modern mammographic screening era [1]. FNA is a common tool in many European clinics, where breast cytology is a more refined and practiced art. One of the inherent weaknesses of breast cytology is the substantial overlap in cytological appearance of many very early lesions and malignant, premalignant, and common benign lesions [2]. Further, if cancerous cells are observed, FNA cannot be used alone with cytology to definitively determine whether the lesion is in situ or invasive [3, 4]. These critical issues have limited its use in the USA in favor of coring needle techniques. Globally, however, FNA remains a cost-effective tool with much value and efficiency.

FNA is typically performed to evaluate palpable abnormalities and asymmetric breast tissue in a perceived high-risk situation, to screen high-risk patients for biological markers indicative of current active proliferation to evaluate temporal breast cancer risk, or to monitor trials of prevention agents. FNA is typically performed with a 22–25 G needle on a 10 cc syringe. Local anesthesia is induced by dermal injection and installation into the region of biopsy. Rigorous rapid jiggling of the biopsy needle in and out under vacuum and releasing the vacuum before extracting the needle provides the best specimen and can be rapidly mastered by the immediate evaluation of specimen cellularity by the operator (Fig. 1.1). Initially, air-dried smears were prepared, but increasingly, the aspirate material is injected into a liquid transport fixative such as those used for cervical cytology. The cellular architecture is often less disrupted in liquid media [5]. Occasionally, the pH of the local anesthesia may impact the cellular appearance. This can be minimized by buffering the initial local anesthetic immediately prior to injection. The specimens can be adequate for routine cytology, immunohistochemistry, and molecular techniques in both clinical and research settings. Usually, FNA results are considered highly specific but variably sensitive.

The use of FNA for nonpalpable abnormalities is more complex. When aspirating under image guidance, there is a slightly increased risk of parallax issues in which the aspiration is immediately in front or behind the target lesion. Because this leads to insufficient removal of the target for image confirmation, much hope is placed on the initial accuracy of the first few needle passes. The local anesthesia and hematoma from the biopsy typically rapidly interfere with imaging quality as the FNA continues. The results for nonpalpable lesions are always confounded by these issues.

The most important use of FNA remains as a part of the triple test [1]. This technique has stood the test of time as highly reliable predating mammographic screening through the current plethora of new imaging technologies to evaluate palpable breast lesions. Most palpable breast lesions will have imageable lesions, which are then amenable to coring biopsy techniques. However, there are always some patients with odd asymmetric thickening, regionally focused reproducibility, worrisome history, or other factors that make the breast clinician suspicious of a significant abnormality in spite of negative breast imaging [6]. In this situation, the use of FNA as the third and final arm of a triple test is well justified by the medical literature and is considered highly accurate. Under this circumstance, the goal of screening is to confirm the presence or absence of significant glandular proliferation. If proliferative cells are not observed in an adequate cellular specimen, the probability of breast cancer is exceedingly low. If, however, proliferative ductal epithelial cells are observed, open surgical biopsy of the region is required to exclude an image-occult neoplastic change.

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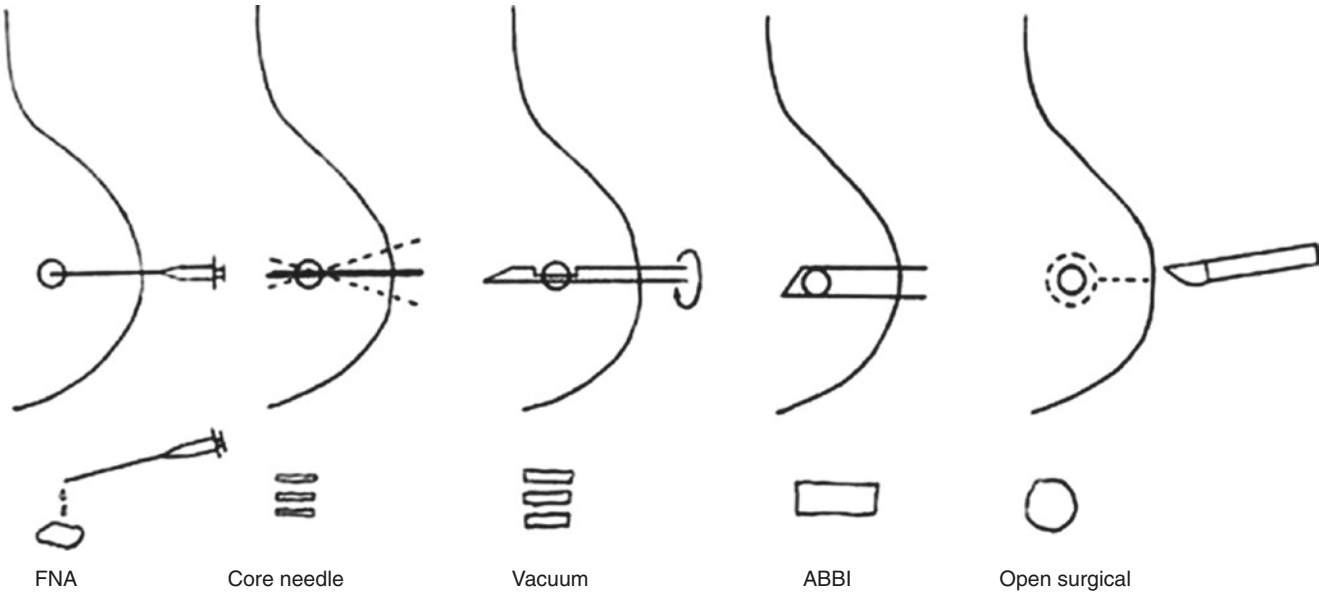

Fig. 1.1 Different types of biopsies. (Reproduced with kind permission from Imaginis, Copyright 2000, Imaginis.com)

Core Needle Biopsy

Core needle biopsies were developed as a limited method of performing an incisional biopsy for diagnosis. Early coring needle technologies were cumbersome and were often used primarily for tiny biopsies of solid organs, such as the liver and kidney. In the late 1980s, the technology improved substantially with the introduction of automated coring needles. These needles typically cored 14 G, 16 G, or 18 G samples approximately 1–2 cm in length [7]. With improving mammographic imaging and increased facility with breast ultrasound, these new coring needles were applied to breast diagnostic work in the early 1990s. A series of trials demonstrated that these mini incisional biopsies by needle under image guidance could accurately diagnose many breast lesions. Because of the small diameter and rapid fixation of these biopsies, the time from biopsy to diagnosis began to decrease rapidly [8]. Establishing the diagnosis prior to the initial surgical procedure dramatically improved the chances of obtaining surgically clear margins during the initial operation and expanded the use of breast conservation dramatically. This was a crucial event in the evolution of the diagnostic process for breast cancer [9, 10].

Core biopsy methods vary slightly in specific needle design and the imaging used to direct the biopsy. As the popularity of core biopsy has increased, this method is now used not only for nonpalpable lesions, but also for palpable lesions combined with imaging to ensure biopsy of the center of the target lesion. After pressing a button or trigger, each of the coring needles usually throws out a coring section up to 2 cm in length and then rapidly covers the entire coring section and tissue core with a larger hollow needle of the final core size. This basic mechanism underlies many of the shortcomings of this method. The rapid-fire mechanism can allow a hard lesion in the midst of soft breast tissue to bounce off, and thus, the core will be of the tissue side of the target and not the target itself. Similarly, the cores are relatively small in the imaged lesions, and imaging is usually inadequate to visualize the actual hole or tract after needle removal. This introduces two possibilities: that the target bounced off the needle or that the parallax issues of imaging led to a false assurance of central target biopsy. A single core in the center of the target should be histologically adequate for nearly all lesions except borderline atypia versus in situ disease. Clearly, early experience demonstrated that one core was not adequate, and multiple cores are now obtained to reduce the possibility of underdiagnosis due to sampling bias [11–13]. Based on specific histologies and imaging characteristics, 4–15 cores to assure an adequate diagnosis are common [14] (Figs. 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, and 1.12). However, when substantial proliferative changes, such as atypia and papillary changes,

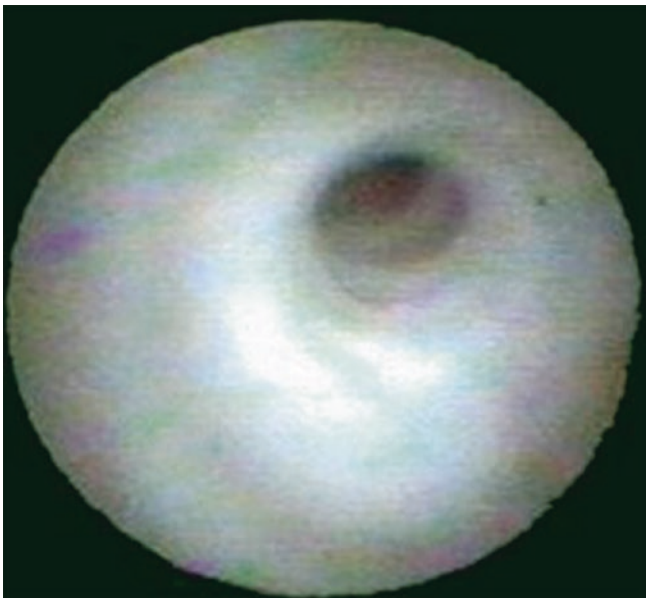

Fig. 1.2 Clean duct

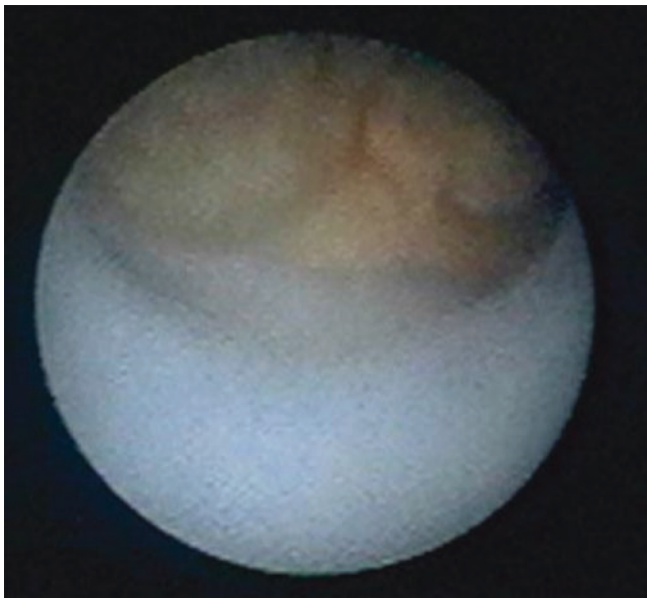

Fig. 1.4 Papilloma

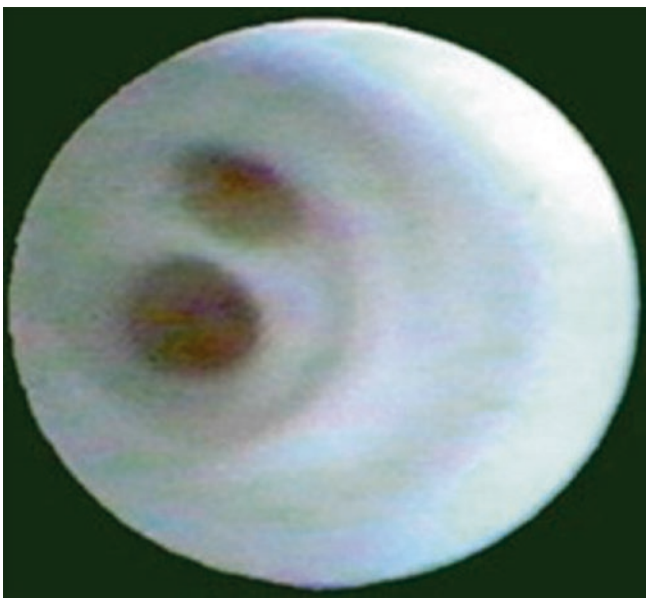

Fig. 1.3 Bifurcation

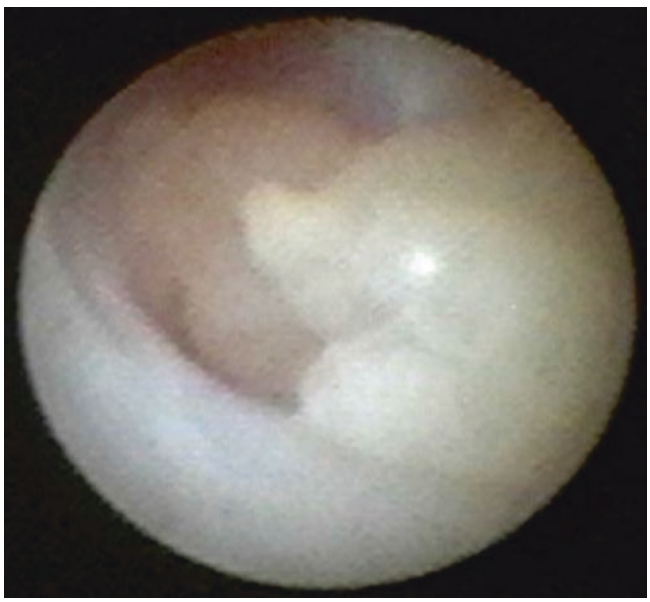

Fig. 1.5 Papillomas

are observed, the core diagnosis is not reliable and requires open surgical excisional biopsy.

Core biopsy needles today are usually used in larger and advanced tumors where issues of sample bias are markedly diminished. Their importance in the evolution of modern breast diagnostic biopsy cannot, however, be understated. Reducing the number of breast cancers diagnosed by surgical biopsy has dramatically increased successful breast conservation and revolutionized the last two decades of breast cancer care in North America and Europe [15].

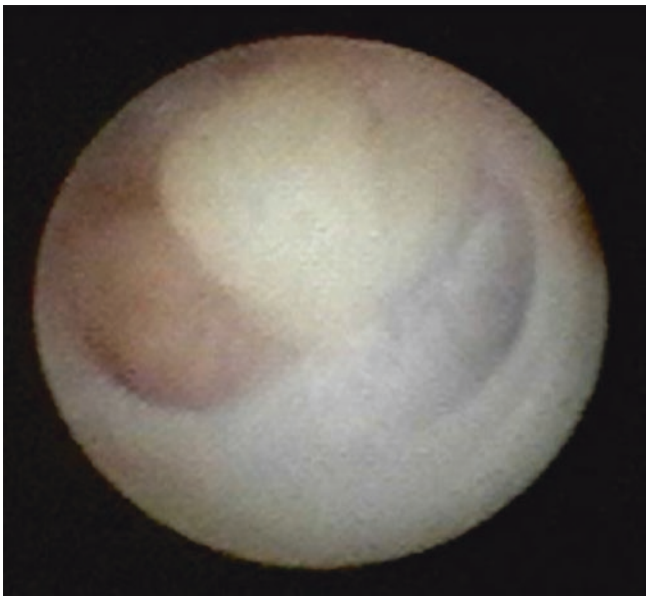

Fig. 1.6 Papillomas

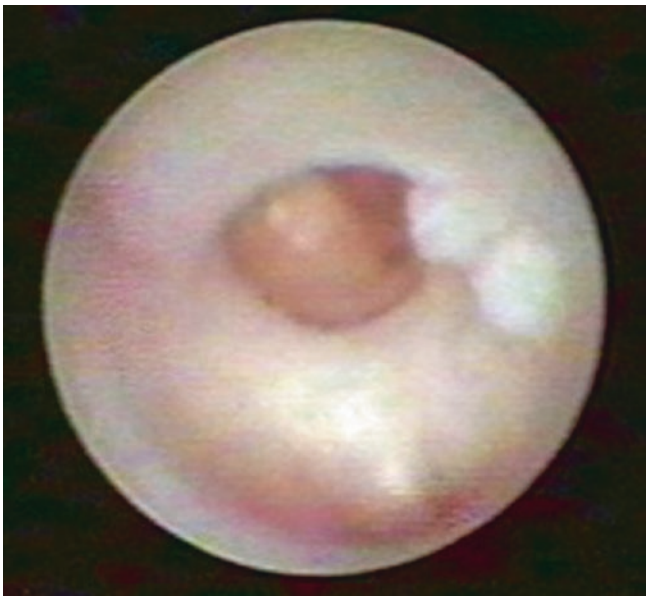

Fig. 1.8 Low-grade DCIS

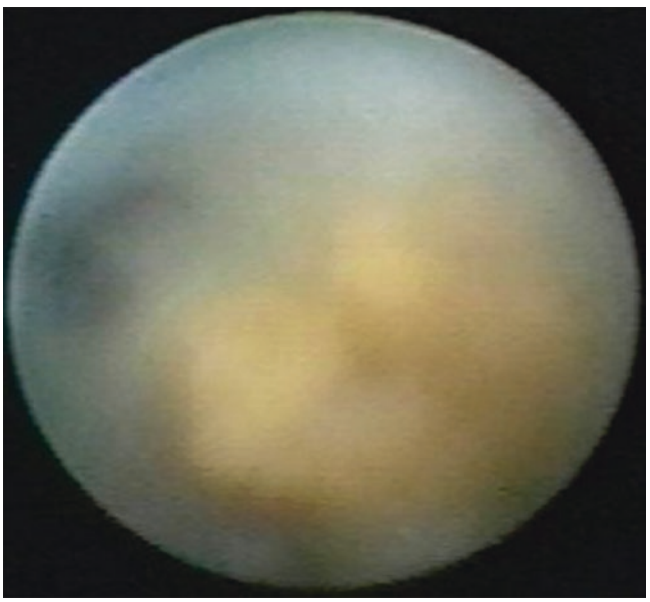

Fig. 1.7 DCIS

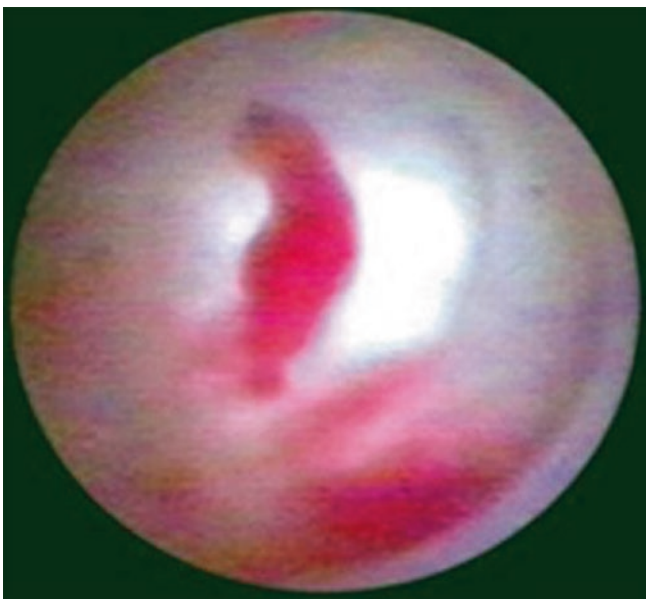

Fig. 1.9 High-grade DCIS

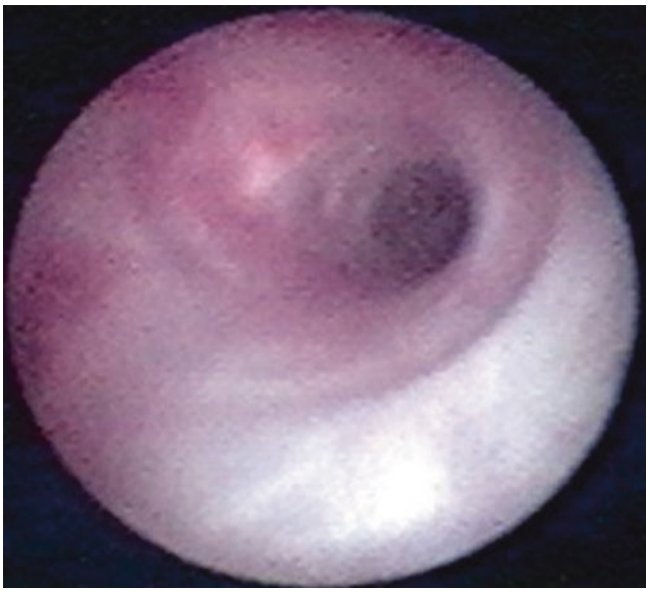

Fig. 1.10 DCIS

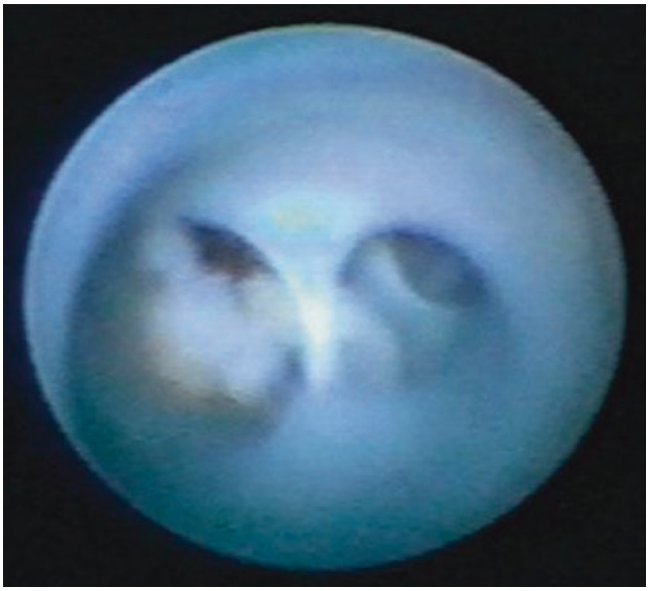

Fig. 1.12 High-grade DCIS

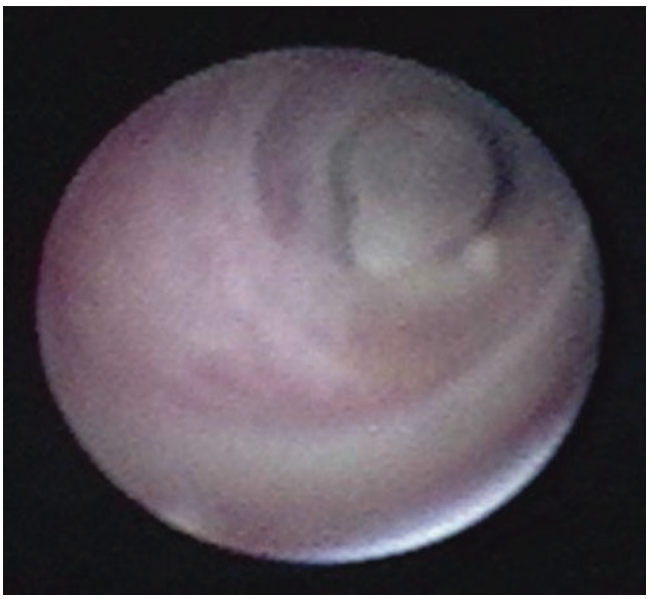

Fig. 1.11 DCIS

Vacuum-Assisted Breast Biopsy, Rotating Core Biopsy, and Radiofrequency Minimal Access Incisional Biopsy

The problem of throwing cores limited the safe use of older core needles to the axilla close to vessels or close to the chest wall. A new generation of coring devices have been developed to address the movement of the coring needle during biopsy to allow visualization of the biopsy in real time and increase the volume of tissue removed, thereby reducing the number of cores required to make a diagnosis and increasing the percentage of cores with actual pieces of the target lesion [12] (Fig. 1.12). The first versions were 10 G or larger solid-appearing needles inserted into the breast. Once inserted into or beside the target lesion, a trap door opens, allowing suction to be applied to pull the tissue into the center of the needle. A rotating core inside the needle is then deployed to remove a larger core of tissue. Most of these needles allow the outer needle shaft to be left in place as cores are pulled out and new cores are taken. Reduced movement of the

coring needle clearly reduces issues of biopsy pain but also allows sufficient excision of tissue in one location to confirm the adequacy of sampling by imaging before needle withdrawal.

This technique works well, but some of the hardest lesions within the softest breast tissue still cannot be sucked into the vacuum section of the needle. Alternatives, such as the insertion of a 19 G cold core needle into the lesion, followed by freezing of the lesion with liquid CO_2 and removal of a larger rotating core around the central needle within the ice ball, enable the biopsy of even the hardest lesions. Another approach to small hard lesions is to use radiofrequency (cautery) with an excision device introduced through a large needle with a hole 5–8 mm in diameter. Rings of RF wire are deployed from the tip of such devices and, under image control, can be used to excise pieces of tissue up to 2 cm in diameter. Such techniques approach minimal access surgical incisional biopsy. Early enthusiasts believed that surgical lumpectomy might be accomplished on small subcentimeter lesions; success of this type has been limited, which likely reflects the joint technical limitations of the RF devices and real-time imaging in 3-D during the biopsy.

These techniques have dramatically reduced the number of cores required for diagnostic accuracy. However, more than one core is still required in the majority of cases, and when there is histological atypia or worrisome changes, wide excision of the region surgically is required to prevent missed cancers. All of these techniques can be performed stereotactically with mammography or MRI. Because of their complexity and logistical setup issues and positioning, using mammography or MRI extends the duration of each biopsy procedure to 40–60 min, with multiple staff to support the equipment and patient needs. As ultrasound imaging has improved, the majority of image nonpalpable lesions can be observed sufficiently well to direct one of these coring techniques without difficult patient positioning and minimal additional staff. The vast majority of breast biopsies today of palpable or nonpalpable lesions are ultrasound-directed and continuously imaged vacuum core biopsies. Although small lesions less than 1 cm may be completely removed, imaging cannot be used to adequately predict which patients have received adequate histological excision without actually examining the exterior margin of an intact en bloc resection or its equivalent.

Surgical Biopsy: Incisional Biopsy–Excisional Biopsy

Excisional surgical biopsy of palpable or nonpalpable image-visible lesions will always be considered the gold standard. Even when surgical excision occurs, the missed cancer rate is approximately 2% or 1/50. Because breast biopsy is one of the most common medical procedures, this rate translates into many missed cancers. Even when the palpable lesion is obvious or the image lesion is clearly observed in specimen radiography, it is always necessary to ensure all potential abnormal targets are identified. In the case of palpable lesions, this requires adequate pre- and postoperative imaging to ensure any allied lesions are removed and never assuming that the imaged lesion is the palpable lesion without adequate proof. In the case of imaged lesions, the surgeon must carefully bimanually palpate the surrounding breast tissue to ensure all abnormalities have been identified. Similarly, postoperative imaging within 6 months or sooner revealing no additional lesions or residual lesions is needed.

Surgical incisional biopsy has been commonly used for more than a century for the diagnosis of large breast lesions and lesions that involve the skin [15]. Coring tools can often replace formal open surgical biopsies. There are circumstances in which incisions are still required, such as a mass coexistent with an abscess for which diagnostic biopsy can be accomplished by incision of the wall of the abscess during abscess drainage. Inflammatory breast cancer is a clinical diagnosis, but it is occasionally useful for clinical practice or research stratification to determine the involvement of dermal lymphatics. Such involvement was typically determined with an incision in a small region of inflamed skin. Today, 3- to 5-mm dermal punch core biopsy tools allow a "needle-like" approach to these diagnostic biopsies. Because a smaller sample is taken, sample bias is introduced, as with needle core biopsies. The region most likely to have dermal lymphatic involvement is the skin at the areolar edge in the same quadrant as the inflammatory lesion. Small core biopsies in this region can avoid the removal of skin requiring suturing required in older times. Similarly, the same dermal cores can be used to assess lesions of the nipple papilla for both Paget's disease and nipple adenomas.

Surgical excisional biopsy can be directed by palpation or use of an imaging adjunct. Ultrasound provides an almost direct extension of physical exam and can often localize well the majority of nonpalpable abnormalities. For years, the ultrasound equipment available in imaging suites has had much greater resolution than those available in operating rooms. As more surgeons become adequately trained to use ultrasound equipment, intraoperative imaging with the highest quality devices has transformed breast surgery and especially added to our ability to achieve adequate margins during the initial therapeutic operation. When the target lesion is not clearly visible by ultrasound or palpable, we must resort to some marking of the target region that can be used by the surgeon because excision between plates of a mammogram device or in the magnet of an MRI is difficult. The core biopsy world has introduced a series of markers to leave behind for future imaging post biopsy. Any of these markers can be used in this circumstance, the most useful of

which are ultrasound-visible postcore markers that can be intraoperatively imaged with ultrasound during the surgical procedure. The classic method, however, has been to deploy a wire, needle, and/or dye injection into the target region under image guidance for the surgeon to use to find the lesion in question. In the case of malignant core biopsies, this has even evolved into leaving a small radioactive bead in the biopsy cavity to guide later wide excision lumpectomy. Whichever method is used, imaging the extracted tissue or the residual breast immediately post procedure is the best but not an absolutely infallible method to assure the excision of the correct tissue target. The most efficient method is to either ultrasound the specimen or radiograph the specimen in the operating room. Using this immediate image information, the surgeon can most likely identify and remove the target lesion even if the first specimen was inadequate.

Ductoscopy

Mammary ductoscopy has evolved from initial experimentation in Japan, where pathological nipple discharge is a more common symptom of early-stage breast cancer [16]. American innovations in submillimeter endoscopes and the recognition of the safety and improved endoscopic potential when saline distension is used have prompted new interest in this technique to identify some of the earliest lesions in situ long before traditional imaging would allow detection. It is now possible to find nearly all lesions intraductally that give rise to bloody nipple discharge, atypical cells in nipple fluid, or extensive intraductal carcinoma around small early-stage breast cancers [17–22]. Biopsy tools and scope modifications that can allow biopsy under direct vision are being developed. Currently, clinically clear indications are relatively restricted. However, researchers now have a method that will repeatedly allow access to the ductal epithelium in high-risk patients. As molecular markers begin to replace traditional cytology, which has limitations as discussed before with FNA, we can expect anatomic mapping of the field defects of genetic changes that predispose to cancer and a crucial new understanding of how anatomy and molecular events interact in breast carcinogenesis [23–28]. These new understandings will hopefully shape the future of breast cancer prevention, which is beginning to replace our current standards of screening and treatment.

The most common indication for mammary ductoscopy is solitary duct spontaneous bloody nipple discharge. Occasionally, high-risk women produce abundant nipple fluid. Some prior research trials have indicated that there is increased risk if a nonlactating female is easily producing fluid [26, 29, 30]. If these high-risk women have nipple fluid cytology that is suspicious, this may appear sinister even in the absence of any imaging findings. The ducts that are producing fluid are usually quite large and can be easily cannulated with lachrymal duct probes and/or sutured with 22–24 G angiocaths. First, the duct is anesthetized and dilated by topical local anesthesia distention. Ductoscopy is readily performed with any available submillimeter endoscope. Most series of pathological nipple discharge reveal that 7–9% are related to cancer [18, 19, 30].

Many stage 0–2 breast cancers (particularly if the invasive component is <2.5 cm) will have expressible nipple fluid [16, 28]. These ducts may produce less fluid but, if identified, can usually be used to locate the cancer and its allied proliferative changes in the region. Core biopsies performed on the nipple side of the target lesion usually disrupt the ducts making fluid, so if ductoscopy is of interest, it is important that diagnostic biopsies be performed from the deep non-nipple side of the target lesion. With some practice, ductoscopy at the time of therapeutic lumpectomy can be an important adjunct to achieving clear margins and can theoretically aid the selection of patients with limited region disease that may be ideal for partial-breast irradiation techniques.

Final Considerations

It is important to remember the 2% miss rate of diagnostic breast biopsy in the USA. No biopsy procedure should be considered complete without a metachronous physical exam and repeat imaging after healing of the biopsy procedure. These procedures are usually performed after 6 months, and scientific data suggest that there is no decrease in survival if missed lesions are identified and removed within that initial 6-month period. This is of most crucial importance in image-guided nonpalpable lesion biopsies. Any smaller incisional technique that yields pathological information that is unexpected or discordant with clinical expectations requires immediate confirmation by surgical excisional biopsy. Any surgical excision that does not clearly contain the lesion on specimen radiograph is difficult to resolve. Immediate postoperative (within the first month) imaging can be used, but edema and healing changes may substantially interfere with accurate target detection. If the pathology is concordant in these cases, 6-month imaging and exam follow-up seem prudent.

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Evaluation of Patients for Metastases Prior to Primary Therapy

2

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Introduction

Diagnostic and therapeutic modalities for breast cancer continue to improve, and the ultimate goal of achieving disease-free and long-term survival is increasingly feasible. Tumor-node-metastasis (TNM) staging, which quantifies the physical extent of disease, has been the mainstay of prognosis prediction [1]. The accurate staging of breast cancer is crucial for clinical decision-making because the extent of the disease has a direct impact on the patient's prognosis and consequently alters therapeutic choices, for example, locoregional versus systemic therapy [2].

As with any patient, a comprehensive history and systemic physical examination are essential to identify metastasis, and the examination should focus on the chest wall, skin, contralateral breast, regional and distant lymph nodes, skeletal system, lungs, liver, and central nervous system. Laboratory testing should include complete blood count (CBC), serum calcium, and alkaline phosphatase, as well as liver and renal function tests. Diagnostic tests and staging procedures are selected based on the organ sites that are most frequently involved in metastatic breast cancer and patient signs and symptoms.

The preoperative assessment should aim to predict the N stage (lymph node metastases) and M stage (distant metastases).

Workup for Axillary Metastases

Axillary lymph node status has long been considered the most important prognostic indicator of recurrence and survival for newly diagnosed breast cancer patients [3–5]. The accurate prediction of axillary lymph node status is the primary objective of physical examination and imaging and is essential in developing a treatment plan, which may include neoadjuvant chemotherapy, immediate reconstruction, and/or intraoperative accelerated partial breast radiotherapy [5].

Physical examination is a primitive and rudimentary method for the detection of axillary metastasis. Although palpation of enlarged lymph nodes in the axilla may indicate metastasis, differentiating a metastatic lymph node from an inflamed or reactive one by physical examination is extremely difficult. The sensitivity of detection via physical examination is very low, with a range of 25–39% in various reports [6–9]. Metastatic deposits have been reported to be found in approximately 40% of patients with clinically negative lymph nodes after sentinel lymph node biopsy (SLNB) [10]. Furthermore, 25% of clinically suspicious lymph nodes may ultimately be negative for metastasis after definitive pathology [11], thus requiring imaging techniques to evaluate axillary lymph node status prior to surgery [12].

The standard imaging method for the detection of breast cancer is mammography (MMG). Although the imaging of axillary lymph nodes is not consistent, lymph nodes in the lower part of the axilla can be visualized [13]. Valente et al. have reported a high likelihood of malignancy if suspicious nodes are identified in the axilla, with 99.5% specificity [8]. As a complement to MMG, axillary ultrasound (US) is a simple test that has been increasingly used in the preoperative setting to detect axillary metastases. Fine-needle aspiration biopsy (FNAB) or core biopsy (CB) of the suspicious lymph node has also been suggested to decrease the number of patients undergoing SLNB and subsequent axillary lymph node dissection (ALND) and, consequently, reduce healthcare costs [14].

The criteria to label a lymph node as suspicious in US evaluation include size, cortical thickening (>3 mm), a multilobulated cortex, the absence of the fatty hilum, and the presence of nonhilar blood flow (which reflects increased vascularity) [15–19]. Because lymph flows through the

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cortex toward the hilum in a normal lymph node, malignant cells are first deposited in the cortex and cause early architectural destruction that can be observed by US, followed by changes in the hilum [18]. Moore et al. have reported that cortical abnormalities are most predictive of N1a disease, whereas the loss or compression of the hyperechoic region or cortical hilum along with abnormal lymph node shape is more commonly observed in N2–N3 disease [19].

However, US alone is insufficient to accurately stage the axilla and is therefore combined with either FNAB or CB of the suspicious lymph node. The reported sensitivity and specificity of axillary US and percutaneous biopsy range from 45.2–86.2% to 40.5–99%, respectively [18–22]. This variability may be due to the application of nonuniform morphological criteria across different studies and the heterogeneity of study designs. In a systematic review conducted by Alvarez et al., the average sensitivity of US was 68%, whereas the average specificity was 75.2% if size (<5 mm or visible nodes on US) was used as the only criterion for malignant involvement. However, the average sensitivity was 71% with 96% specificity when morphological criteria were used. In patients with nonpalpable axillary lymph nodes, sensitivity and specificity were 60.9% and 75.2%, respectively, when size was the only parameter. The corresponding values when morphological criteria were used were 43.9% and 92.4%, respectively.

In a meta-analysis of 21 studies by Houssami et al., the median US sensitivity and specificity were 61.4% [with an interquartile range (IQR) of 51.2–79.4%] and 82% [IQR 76.9–89%], respectively. In these studies, for the subset of 1733 subjects who then were selected for US-guided needle biopsy based on US features, the median sensitivity and specificity were 79.4% and 100%, respectively [23, 24]. The authors suggested that preoperative US and needle biopsy could be used to effectively triage women with breast cancer directly to axillary surgery.

Diepstraten et al. conducted a meta-analysis of pooled data from 31 studies to estimate the false-negative rate of US and percutaneous biopsy; this rate was defined as the proportion of women with a negative US with or without aspiration biopsy in whom axillary nodal metastases were detected at SLNB [25]. For 50% of the breast cancer patients with metastasis in the axilla, axillary involvement could be identified preoperatively by axillary US-guided FNAB or CB. However, 25% of the patients (one in four women) with a negative US and biopsy result had axillary metastases at subsequent SLNB. Thus, a negative US and biopsy result for metastasis cannot preclude an operative intervention in the axilla for precise staging.

New techniques have been evaluated to increase the sensitivity and specificity of axillary US. Sever et al. [26] have demonstrated that contrast-enhanced US can be used to identify the sentinel lymph node, thus enabling targeted biopsy, which may reduce the false-negative rate. US elastography for the detection of metastatic lymph nodes by measuring stiffness on US examination has shown promise for increasing the sensitivity of conventional US, although reports are limited in number and patient sample size [27, 28].

Magnetic resonance imaging (MRI) has been the best method to show the anatomy in relation to pathology [8]. Level 1–2 axillary lymph nodes as well as internal mammary and level III lymph nodes are visualized. The reported sensitivity of MRI is 36–78%, with higher specificity (93–100%) [7, 20, 29, 30]. However, some studies have failed to demonstrate the superiority of MRI over axillary US; the sensitivity of MRI for axillary lymph node metastases was <40%, whereas accuracy was similar to axillary US for the detection of axillary metastasis [8, 31].

Valente et al. have reported a trade-off in sensitivity and specificity for the prediction of lymph node involvement in breast cancer patients using a combination of physical examination, MMG, US, and MRI. If any of these modalities is suspicious, there is a 56% chance of metastatic disease in the patient, which increases to nearly 100% if three or four modalities are suspicious for metastatic disease [8]. The major flaw in combining various modalities is that the specific axillary lymph nodes detected by different imaging modalities cannot be correlated when the modality that initially detected the suspicious lymph node cannot be used as a guide to perform percutaneous biopsy of the suspicious node.

The methods for sampling and pathological assessment of the sample retrieved by percutaneous biopsy are also subject to limitations. Percutaneous FNAB only samples a portion of the node, and a negative FNAB or CB result does not exclude axillary metastasis. In a comparison of FNAB and CB in a series of 178 patients, Rautiainen et al. observed a sensitivity of 72.5% and 88.2%, respectively, and a specificity of 100% for both methods [32]. The overall accuracy in this study was 78.8% for FNAB and 90.9% for CB. Additional histopathological examination was tested to improve the accuracy of CB of the morphologically abnormal lymph node but failed to provide a benefit [33]. Despite attempts to decrease the number of patients referred to the operating room for SLNB by increasing the accuracy of US and percutaneous biopsy, one major issue remains—the correlation of the suspicious lymph nodes with the sentinel nodes is only 64–78.3% in perioperative frozen sections [17, 34].

The ACOSOG Z0011 trial provided insights into the management of the axilla in patients with T1-2N0 breast cancer by demonstrating that ALND can be omitted in patients with one or two positive sentinel lymph nodes (SLNs) without negative impact on disease-free survival or disease recurrence [35, 36]. In this group of patients, the value of US and percutaneous biopsy becomes questionable because the presence of ITCs or micrometastases in SLN core biopsy

specimens may not correlate with the actual size of the LN metastatic disease on final surgical histology [37]. Therefore, the ACOSOG Z0011 trial casts doubt on the desirability of US-guided percutaneous biopsy in cT1-2N0 patients. However, US-guided percutaneous biopsy might be helpful to exclude patients with a higher lymph node ratio (LNR; defined as the number of positive nodes/number of nodes dissected).

Neal et al. reported that preoperative negative ultrasound findings could exclude advanced nodal disease in 96% of patients with invasive ductal carcinoma [38]. Reyna et al. reported a negative predictive value of 71% in minimal nodal disease in invasive ductal carcinoma patients compared to 44% for invasive nonductal carcinoma types [39]. In a retrospective series, the ACOSOG Z0011 criteria were used to detect axillary lymph node positivity by axillary US+/− FNAB. The authors found SLN metastasis ≥6 mm in only 2% of patients and >7 mm in only 1%. Although the authors did not provide precise breakpoints for disease burden or markers of excessive disease virulence that might be best treated with ALND, they suggested that at least 10% of patients committed to ALND could be treated with whole-breast radiation, SLNB, and adjuvant therapy [40]. Considering the operator-dependent nature of ultrasonography, MRI was suggested to be more valuable by Hyun et al., who reported that advanced nodal staging could be excluded in 98.2% of patients by preoperative axillary staging with MRI [41].

Proceeding with ALND in the presence of a positive SLNB has become questionable, at least in a certain group of patients, after two phase III noninferiority trials [42, 43]. The IBCSG 23-01 trial showed that no axillary dissection was noninferior to axillary dissection in terms of locoregional control or survival in patients with one or more micrometastatic (≤2 mm) sentinel nodes and a maximum tumor diameter of 5 cm treated with breast-conserving surgery, whole-breast irradiation, and adjuvant systemic treatment. Thus, these patients can be spared axillary lymph node dissection without compromising locoregional control or survival [42]. Similarly, the AMAROS trial randomized patients with tumors up to 3 cm with no palpable lymphadenopathy in the axilla to ALND versus axillary radiotherapy after a positive SLNB. There were no significant differences between the treatment groups in terms of disease-free survival and overall survival [43]. In light of increasing doubts about the role of SLNB itself, a new trial (SOUND) is ongoing at the European Institute of Oncology of Milan to compare SLNB with observation when axillary ultrasound is negative in patients with small breast cancer who are candidates for breast-conserving surgery. Until then, the role of axillary ultrasound plus FNAB or core needle biopsy of the suspicious lymph node should be revised, and each patient should be handled on an individual basis by the tumor board [44].

Furthermore, the accuracy and oncologic safety of the SLNB procedure in patients with cN+ locally advanced breast cancer is an ongoing concern. Both the ACOSOG Z1071 and SENTINA trials investigated the role of SLNB after downstaging of the axilla with NAC. These studies demonstrated that as the number of sentinel nodes removed increases, the false-negative rate (FNR) decreases, and at least two or three nodes should to be taken as SLNs [45, 46]. The ACOSOG Z1071 trial evaluated the FNR of SLN surgery for patients with clinical T0-4, N1-2 disease treated with NAC and found that the FNR was 12.6% for N1 patients with two or more resected SLNs. Furthermore, the FNR decreased to 9.1% when surgeons identified three SLNs in addition to using radiolabeled colloids with blue dye. Similar results were published in the SENTINA trial, showing an overall FNR of 14.2%.

There is a tendency to reduce the FNR of SLNB by placing clips in the most suspicious lymph node or nodes before initiating neoadjuvant chemotherapy [47]. Caudle et al. reported that adding an evaluation of the clipped node along with the SLNs reduced the FNR to 1.2%. Cabioglu et al. [48] reported an overall FNR of 11.4% for patients who presented with node-positive cT1-4/cN1-3 disease and received NAC after placement of clips into the metastatic node. This FNR appears to be better than the rates observed in the randomized SENTINA and Z1071 trials, with included patient accrual from more than 100 centers, but similar to the FNR in single-institution series, with the MD Anderson Cancer Center showing an FNR of 10.1%, as reported by Caudle et al. [47]. In concordance with the SENTINA and Z1071 trials, use of the combined technique or excision of two or more SLNs reduced the FNR to 0% for cN1 patients in the series of Cabioglu et al. For patients with cN1 before NAC, the FNR was 4.2% when the clipped node was identified as an SLN. Cabioglu et al. concluded that axillary dissection could be omitted for patients who present initially with N1 disease and a negative clipped node as the SLN after NAC due to the low FNR. Targeted axillary dissection may be required for patients with a clipped node as the non-SLN in addition to SLNB.

FDG PET/CT is a recently evolving technique used to stage patients pre- and postoperatively. Several studies have reported variable sensitivities of FDG PET/CT of 37–95% for the detection of axillary metastases [49–54]. The accuracy decreases for small (<10 mm) metastatic lymph nodes and micrometastatic disease. Other studies have reported high sensitivity and specificity in detecting axillary metastasis and that FDG PET/CT could modify the TNM staging in 47% of patients with breast cancer [49, 50]. The specificity and positive predictive value of FDG PET/CT are better (96% and 88%, respectively) for the prediction of axillary disease and correlate well with SLNB. However, the relatively poor sensitivity of FDG PET/CT must be considered

in treatment planning [50, 53]. In a meta-analysis, Cooper et al. [55] reported that a high false-negative rate precludes the recommendation of FDG PET/CT for routine application in cases of clinically negative axilla. The clinical value of false-negative axilla has not been established because reported involvement has been limited to the sentinel node, some of which were micrometastases [56].

The sensitivity of FDG PET/CT for assessing the primary lesion and axilla may be increased by performing the examination in a prone position. In a prone position, the tumor can be more clearly distinguished from adjacent structures, enabling a more extensive evaluation of the axillary fat and its lymph nodes. More studies are needed to assess the efficacy of these protocols in increasing the sensitivity of FDG PET/CT in detecting axillary disease (Fig. 2.1a) [57, 58].

A tumor burden threshold must be met to detect metastatic lymph nodes using current imaging modalities, particularly FDG PET/CT. Fujii et al. reported a significant correlation between FDG uptake and the size of lymph node metastases, whereas the number of nodal metastases did not correlate with FDG uptake [54]. The findings imply that a preoperative FDG-PET evaluation of lymph nodes is not sufficient to predict lymphatic spread or micrometastasis [54]. Instead, the power of PET/CT should be viewed as being able to detect unexpected extra-axillary regional lymph node involvement [59].

Van Nijnatten et al. [60] investigated the feasibility and potential added value of dedicated axillary 18F-FDG hybrid PET/MRI compared to those of standard imaging modalities (i.e., US, MRI, and PET/CT) for axillary nodal staging in patients with clinically node-positive breast cancer.

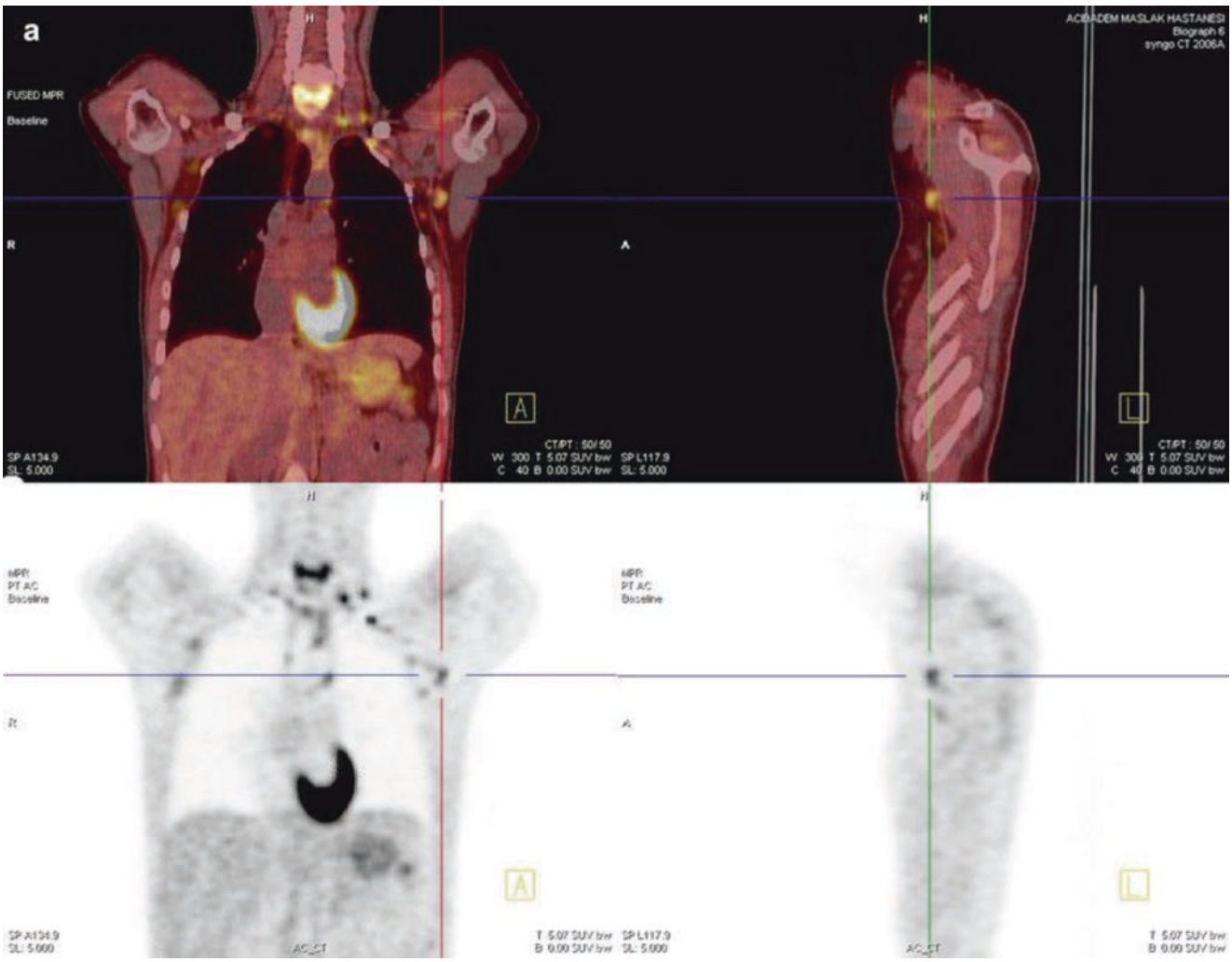
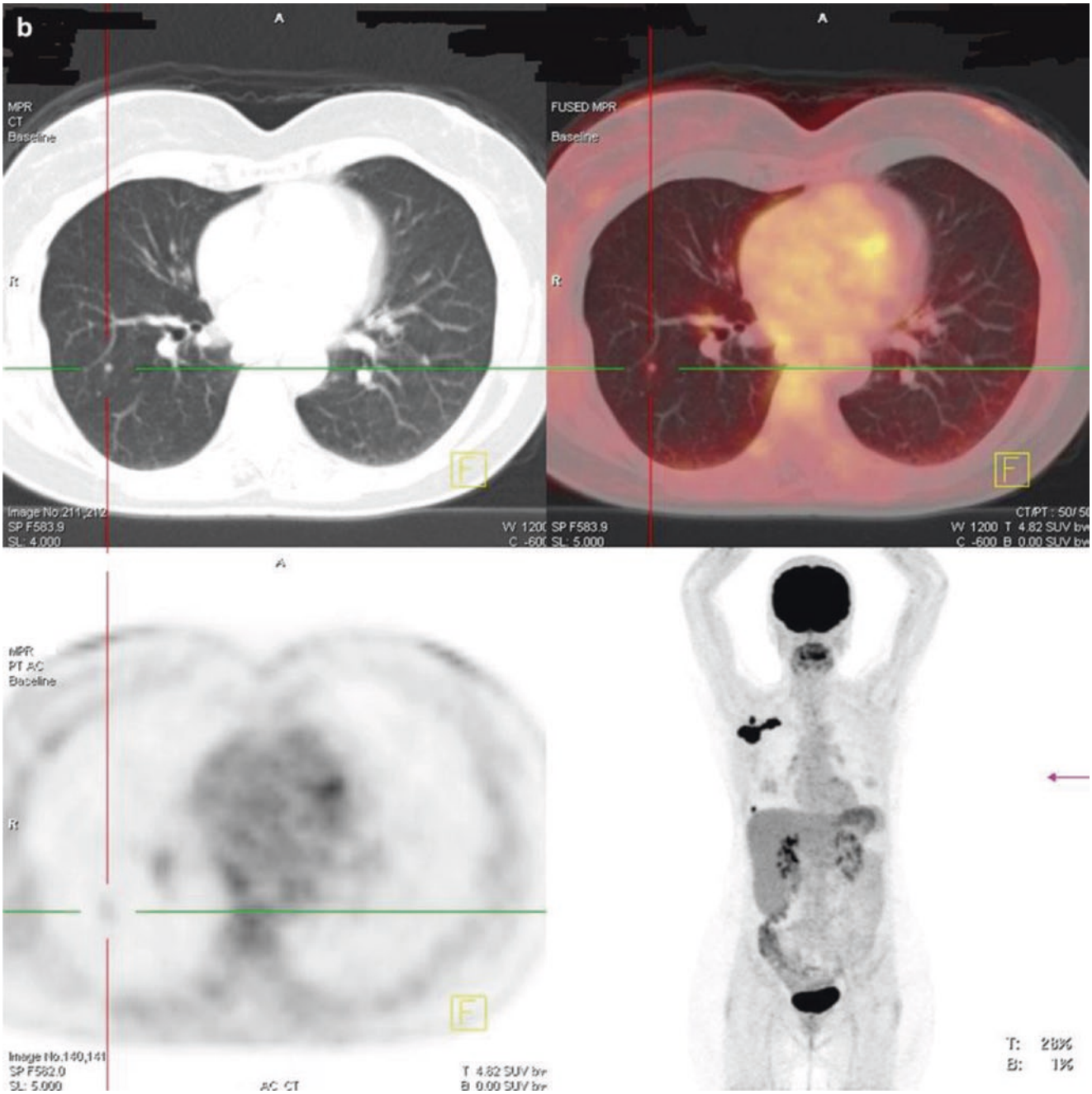


Fig. 2.1 (**a**) FDG PET/CT of a patient with increased SUV in the left axillary lymph nodes suspicious for metastases. (**b**) FDG PET/CT of a patient with increased SUV in the right axillary lymph nodes and the right pulmonary nodule suspicious for metastases. (**c**) FDG PET/CT of a patient with increased SUV in the left internal mammary lymph nodes suspicious for metastases. (**d**) NAF PET/CT of a patient with disseminated bone metastases in the calvarium, ribs, spine, pelvis, right humerus, and right femur suspicious for metastases



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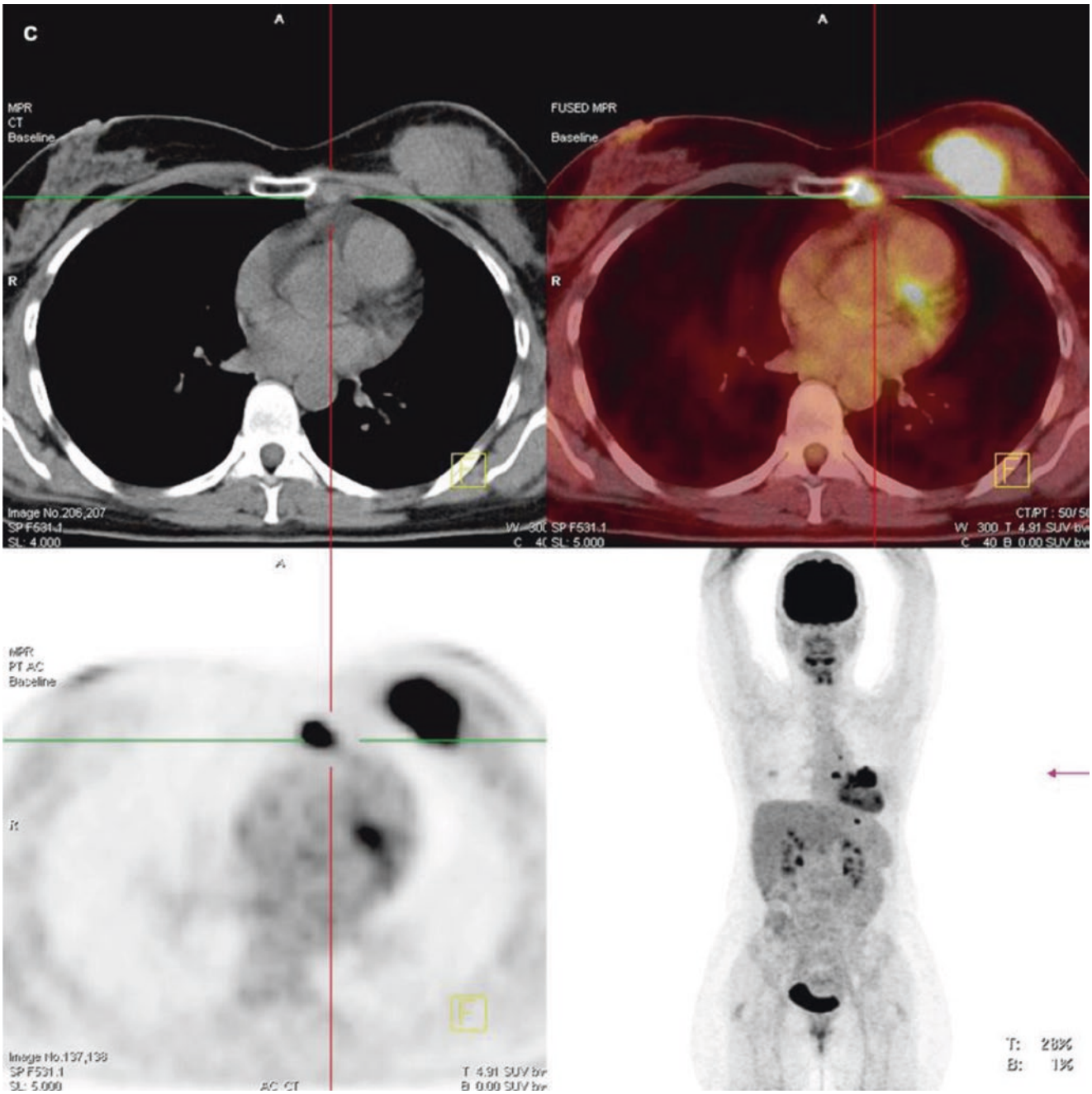

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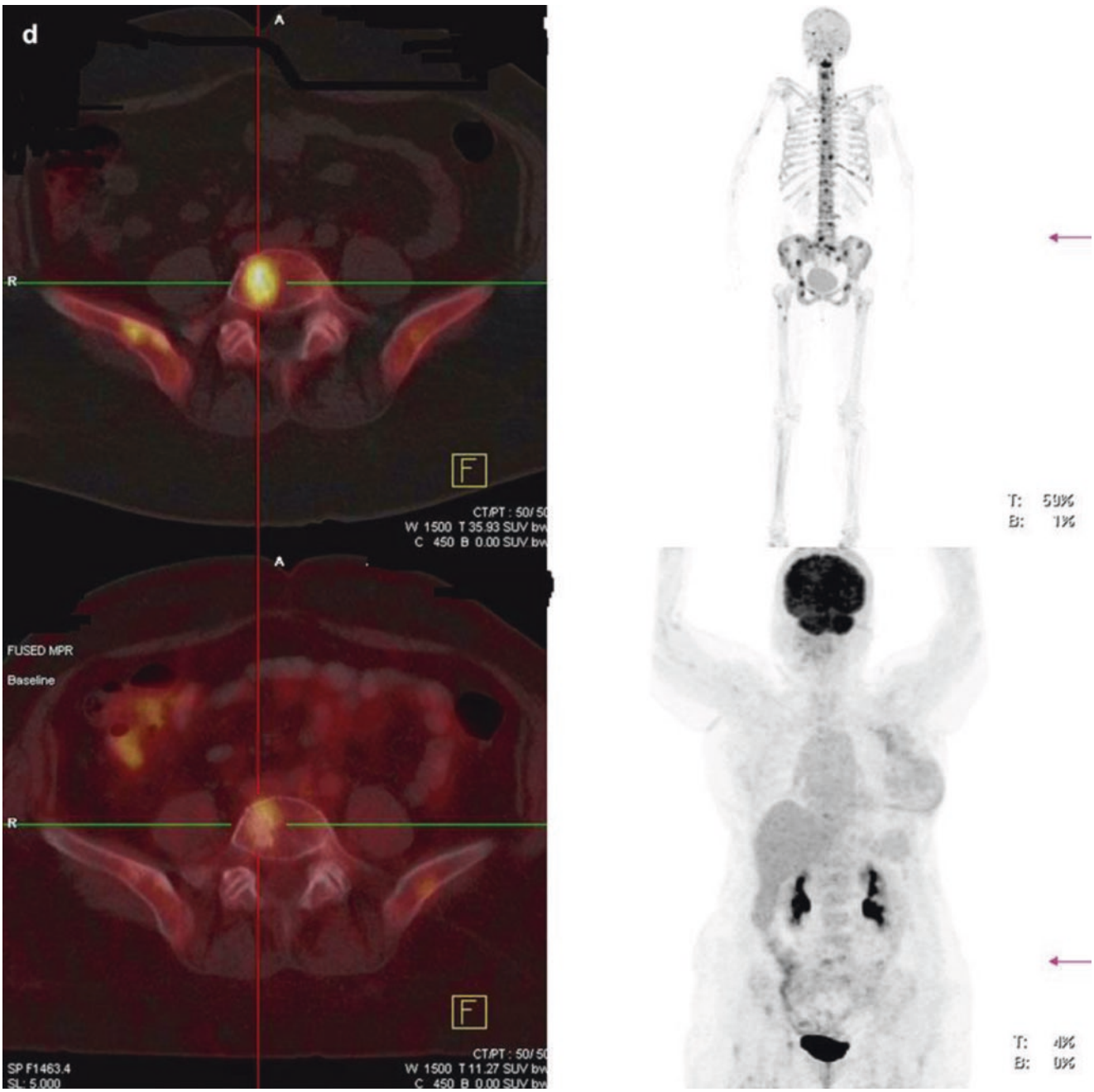

Fig. 2.1 (continued)

Compared to standard imaging modalities, dedicated axillary hybrid PET/MRI resulted in the following changes to clinical nodal status: 40% according to US findings, 75% according to T2W MRI findings, 40% according to CE-T1W MRI findings and 22% according to PET/CT findings. The differences between PET/CT and PET/MRI findings were due to the better delineation of the lymph nodes on the MRI component. The results of the study showed that dedicated axillary 18F-FDG hybrid PET/MRI is clinically feasible and resulted in a change in nodal status in 40–75% of patients compared to that of US or MRI. Compared to PET/CT only, the nodal status changed in 22% of patients, although the SUVmax measurements were comparable between the imaging modalities. In conclusion, dedicated axillary 18F-FDG hybrid PET/MRI appears to improve diagnostic performance for axillary nodal staging in clinically node-positive breast cancer patients. Further studies are needed to investigate the accuracy of this hybrid modality.

Currently, there is no imaging modality or combination of modalities that can reach the accuracy of and replace SLNB. In addition, there is also no modality that can be used to preclude SLNB where it is found to be negative. Furthermore, it should be kept in mind that omission of ALND is not associated with inferior outcomes in a certain subset of patients with a limited axillary metastatic burden.

Workup for Distant Metastases

The presence of distant metastases is an adverse prognostic factor for survival [61]. The identification of unexpected distant metastases in a patient with a newly diagnosed breast cancer usually alters the management strategy. Approximately 4% of patients with a diagnosis of breast cancer will have distant metastases at the time of presentation, and the majority of them will have signs and symptoms of metastasis [62]; 10% of these patients have multiple lesions at multiple sites [63].

Noninvasive radiological workup targets the most common sites of distant metastasis: the bones, lungs, and liver [64]. The commonly employed tests are bone scan, chest radiography (which is replaced by diagnostic chest CT), and liver US. The sensitivity of these tests has been questioned in several studies that report inappropriateness in the subgroup of patients with small tumors and absent or minimal involvement of the axillary lymph nodes [54–66]. NCCN guidelines recommend CBC, liver function tests, alkaline phosphatase, bilateral mammography, and US/MRI (as needed) for all patients, whereas additional tests are required in the presence of specific signs or symptoms for stages I–II B [67]. However, for stage IIIA disease (T3N1M0) or locally advanced breast cancer, chest CT, abdominal ± pelvic CT or MRI, bone scan or sodium fluoride (NaF) PET/CT (optional), and FDG PET/CT (optional) are suggested.

As the number of early breast cancer patients has increased, the detection of possible distant metastasis remains to be addressed. Guidelines lack consensus about whom to evaluate and how to evaluate patients with primary operable breast cancer [64–66, 68, 69]. It is crucial to define a subgroup of patients in whom positive findings on staging tests would alter the treatment plan and provide more efficient local and systemic treatment to save healthcare costs and ensure optimal use of resources. Unnecessary examinations constitute physical, psychosocial, and financial burdens for both the patient and the healthcare providers.

The presence of detectable metastatic disease in breast cancer patients at the time of primary diagnosis is exceedingly low and increases from stages I to III [64, 65]. Bone is the most common site of metastasis; according to a systematic review by Myers, the incidence of positive bone scan across studies is 0.9–40% for all stages, with the lowest incidence in stage I patients (0.5%, 95% confidence interval 0.1–0.9) and highest in stage III patients (8.3%, 95% CI 6.7–9.9) [65]. The incidences of liver and lung metastasis are even lower than that of bone metastasis. The incidence of liver metastasis is 0%, 0.4%, and 2% for stage I, II, and III diseases, respectively. The detection of lung metastases by chest X-ray is similar, with incidences of 0.1%, 0.2%, and 1.7% for stage I, II, and III disease, respectively. Chen et al. found a prevalence of lung metastasis of 0.099% in early breast cancer patients who were upstaged to stage IV by chest X-ray in a series of 1493 subjects [70]. Puglisi et al. found no pulmonary or liver metastases but only bone metastases in only 5% of 516 patients using traditional modalities (i.e., bone scan, liver US, and chest X-ray) [64].

As radiological modalities have evolved and are more commonly applied in general practice, chest X-ray has been replaced by diagnostic chest CT. However, the clinical value of preoperative chest CT in clinically operable and asymptomatic patients has not been established. Recently, Kim and colleagues investigated the clinical value of preoperative chest CT in 1703 patients and detected abnormal CT findings including suspected metastases and indeterminate nodules in the lung or liver, in 266 patients (15.6%) [71]. Among these, 1.5% of all patients and 9.8% of patients with abnormal CT findings had true metastases, including 17 lung, 3 liver, and 6 lung plus liver metastases. True metastases were detected in 0.2%, 0%, and 6% of patients with stage I, II, and III disease, respectively. The authors concluded that in the absence of symptoms/signs suggestive of metastatic disease, the incidence of metastases is low, and false-positive findings are more common than true-positive findings, thus failing to compensate the high cost and exposure to ionizing radiation.

FDG PET/CT is an alternative technique that is becoming more widely used to encompass all diagnostic staging in a single study. Data for its use in staging primary breast cancer are accumulating, and recent studies have addressed the added value of FDG PET/CT over conventional techniques for staging primary breast cancer (Fig. 2.1b) [57, 72–74]. In several studies, FDG PET/CT has been reported to be more effective than conventional imaging methods in detecting occult distant metastases [49, 50, 75].

FDG PET/CT is important in the detection of extra-axillary involvement, such as supraclavicular, internal mammary, and mediastinal lymph nodes [49, 76]. Bernsdorf et al. reported that FDG PET/CT alone detected six cases of distant metastases and 12 cases of extra-axillary LN involvement in a comparison with conventional imaging of early breast cancer larger than 2 cm [77]. The detection of internal mammary lymph node metastases may have significant prognostic and therapeutic value because these patients are likely to have worse prognosis than those without malignant involvement of these nodes (Fig. 2.1c). Similarly, in a study by Garami et al. of 115 breast cancer patients for whom traditional diagnostic modalities showed no signs of distant metastases or extensive axillary and/or extra-axillary lymphatic spread, FDG PET/CT indicated nine distant metastases that were confirmed by direct sampling in eight patients [50]. The total yield was 7–8% and was particularly relevant for stage II disease.

Despite different study designs, all studies have demonstrated the value of PET/CT for staging and treatment planning of breast cancer [59]. None of the studies described cases with positive conventional imaging but negative findings on PET/CT. In all studies, PET/CT showed additional sites of metastases and newly detected distant metastases (including extra-axillary regional nodes) in patients. PET/CT led to a change of management in 8–18% of patients [59]. In early breast cancer, the change in the management of the patient may be even lower (3.9%) than in clinically node-negative patients, and it is reported to be 1.1% when the change in management was confined to breast cancer treatment alone [78].

FDG PET/CT can also be used to detect bone metastases. Some authors have reported that FDG PET/CT is more efficient than bone scintigraphy in detecting lytic and mixed bone metastases and bone marrow involvement but may lack sensitivity for sclerotic bone metastases, and a multimodality approach is suggested [75, 79]. NaF PET/CT is another scintigraphic imaging technique that was reported to have superior image quality and ability to evaluate skeletal disease extent compared to FDG PET/CT and 99mTc-MDP in a pilot study (Fig. 2.1d) [80].

Another issue for the routine use of FDG PET/CT for staging is low specificity. Active granulomatous infections such as tuberculosis and sarcoidosis can exhibit increased FDG uptake [81, 82]. Functional ovaries in premenopausal women can also lead to false-positive results. Increased FDG uptake represents ovarian malignancy in postmenopausal patients, whereas the results should be handled carefully in premenopausal patients, in whom the uptake may be functional or malignant [49, 81, 82].

However, the sensitivity of FDG PET/CT is limited and decreased in small and/or low-grade tumors, particularly when the tumor size is <1–2 cm [49, 50]. At this time, FDG PET/CT is not a routine imaging modality for early breast cancer staging; instead, it is recommended as an adjunctive method to evaluate distant metastasis and regional lymph nodes in advanced breast cancer [49, 67, 78]. FDG PET/CT is an important adjunct to conventional studies when the results are equivocal or suspicious, particularly in locally advanced or metastatic disease. However, its use has been increasing widely over bone scan and liver US in early-stage breast cancer, particularly in patients with lobular histology and receptor-negative tumors [83]. Future studies should evaluate the impact of more specific tumor characteristics on the value of PET/CT for initial breast cancer staging [60].

The genetic heterogeneity and subsequent different clinical courses of breast cancer have been revealed by molecular subtype classification, a breakthrough in breast cancer research [84–86]. Different subtypes have different clinical courses and responses to treatment, which means that the clinician should consider distinct subtypes before selecting appropriate therapeutic strategies. Major molecular subtypes in breast cancer differ in their ability to metastasize to distant organ(s) and share biological features and pathways with their preferred distant metastatic sites [87]. Moreover, recent studies have found that the molecular subtypes of breast cancer may change at relapse [88, 89]. The correlation of the molecular characteristics of the tumor with baseline staging tests was addressed by Chen et al., who suggested preoperative baseline staging tests for every stage III cancer but limited tests for stage II patients based on histological subtypes [90]. They recommended bone scans for HER2-positive luminal B, nonluminal HER2-overexpressing, and basal-like subtypes; preoperative liver US for Her-2-positive luminal B and nonluminal HER-2-overexpressing subtypes; and chest X-ray for basal-like subtypes for the early detection of distant metastases.

Finally, some novel PET tracers that have been already tested in humans, such as 18F-fluoroestradiol (which binds to ER) [91], 18F-FFNP (a progesterone analog) [92] and 68Ga-ABY-002 (a molecular imaging agent with high specificity and affinity for HER2) [93], and new emerging techniques such as hybrid 18F-FDG PET/MRI may provide additional useful information about tumor heterogeneity and responsiveness to therapy and staging, particularly in the case of stage IV disease at the time of diagnosis [94, 95, 96].

Conclusion

For axillary staging, preoperative US and needle biopsy have emerged as the most effective methods for triaging women with breast cancer directly to axillary surgery for SLNB or ALND or to neoadjuvant chemotherapy for those with axillary node-positive disease. Furthermore, placement of clips into the most suspicious lymph node during needle biopsy of the lymph nodes prior to chemotherapy for axillary staging may be useful for targeted axillary dissection. Retrieving the clipped node as the SLN has also been shown has been shown to improve the false-negative rates of SLNB after NAC.

There is no perfect modality for identifying metastatic disease in breast cancer; every diagnostic test has its own advantages and limitations. The current evidence still supports the use of FDG PET/CT for routine evaluation of metastatic disease in advanced clinical stage, including stage III and possibly stage II, breast cancer with aggressive molecular subtypes, including HER2-positive or triple-negative tumors. The development and validation of new molecular markers, including liquid biopsies or circulating tumor cells, or novel hybrid technologies, including PET/MRI, may be beneficial for the diagnostic and therapeutic workup of patients with breast cancer in the future.

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Breast Cancer Staging

3

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Introduction

The TNM staging system for breast cancer described by the American Joint Committee on Cancer (AJCC) applies to invasive and in situ carcinomas with or without microinvasion [1, 2]. This classification system was introduced to reflect the risk of recurrence and for use as a standard prognostic assessment tool for patients with newly diagnosed breast cancer. The improved understanding of prognostic and predictive biological marker overexpression, such as estrogen receptor (ER) and human epidermal growth factor receptor-2 (HER-2), has been used to predict the response to systemic therapies (antiestrogen, anti-HER-2) [3, 4]. The use of these factors as predictive rather than prognostic markers is fundamentally important in the management of patients with newly diagnosed breast cancer, but there might be difficulties incorporating these biomarkers into the TNM system. Therefore, rapid advances in both clinical and laboratory science along with translational research have raised questions about the feasibility of TNM staging as a guide to determine whether to apply systemic therapy based on anatomic prognosis.

Multigene expression assays, such as the 70-gene prognostic signature or Oncotype DX tests, may provide additional prognostic and predictive information beyond anatomic TNM staging and the ER/progesterone receptor (PR) and HER-2 status. A recently reported validation study has emphasized that the prognostic stage provides more accurate prognostic information than the anatomic stage alone, thus supporting the use of the prognostic stage in breast cancer staging [5]. In 2017, the 8th revised edition of the TNM system was published [2]. Clinical and pathological stage (PS) tables were incorporated in addition to the traditional anatomic prognostic stage tables. The pathological stage table is based on clinical information, biomarker data including multigene genomic assays, and findings from surgery and resected tissue. As breast cancer therapy has evolved with the increasing application of neoadjuvant therapy, additional pretreatment and post-treatment staging have also been incorporated into the TNM staging system to determine chemotherapy response and treatment efficacy.

Summary of Changes in Breast Cancer Staging

Due to advances in personalized medicine, the last update of AJCC Breast Cancer Staging incorporated more molecular gene assays and new prognostic and predictive markers [6–9]. Lobular carcinoma in situ was removed from TNM staging and treated as a benign high-risk lesion. An anatomic stage table, clinical prognostic stage table, and pathological prognostic stage table were added in the eighth edition. As in previous editions, *the Anatomic Stage* table includes the anatomic extent of cancer as defined by the T, N, and M categories for use around the world where biomarker analysis of tumors is not available. *The Clinical Prognostic Stage* table is used to determine the clinical T, N, and M stages based on the findings of physical examination and imaging studies and the tumor characteristics of relevant biopsies, including the grade (G) and ER, progesterone receptor (PR), and HER-2 status. Finally, *the Pathological Prognostic Stage* table is based on clinical information, biomarker data, and findings from the initial surgery and resected tissue before any systemic or radiation treatment.

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Tumors >1 mm and <2 mm should be reported by rounding to 2 mm. Therefore, tumors between 1 and 1.5 mm should be treated as 2 mm invasive cancer and should not be considered microinvasive cancer. T1mi is defined as an invasive tumor foci ≤1 mm.

The cNx category is not considered a valid classification unless the nodes in the relevant node basin have been removed and cannot be examined by imaging or clinical examination.

The largest contiguous tumor or tumor deposit is used for pT and pN; for the primary tumor, the sizes of multiple tumors or lymph node–adjacent satellite tumors are not added. Among skin or dermal tumor satellite nodules, only those with epidermal ulcers or skin edema (clinical peau d'orange) are categorized as T4b, whereas classification of satellite nodules without any clinical findings of edema or ulcers is based on tumor size.

The last edition clarified the post-neoadjuvant therapy pathological T category (ypT) and pathological N category (ypN), which is based on the largest contiguous focus of residual invasive cancer, if present. When multiple foci of a residual tumor are present, the (m) modifier is included. Treatment-related fibrosis adjacent to residual invasive carcinoma or between foci of residual carcinoma is not included in the ypT or ypN maximum dimension. Furthermore, pathological complete response (pCR) cannot be considered in the presence of any residual cancer in the breast, including cancer within blood or lymphatic vessels, or in the lymph nodes. If a cancer is categorized as M1 (clinical or pathological) prior to or during preoperative systemic therapy, the cancer is categorized as M1, regardless of the observed response to therapy.

Although multigene expression assays may provide additional prognostic and predictive information beyond anatomic TNM staging and the ER/PR and HER-2 status, incorporating these biomarkers into the TNM system may be difficult. In the AJCC eighth edition, for patients with T1 and T2 hormone receptor-positive, HER-2 negative, and lymph node-negative tumors, a multigene panel is included in pathological prognostic staging. In the low-risk range, these tumors are placed in the same prognostic group category as T1a-T1bN0M0 regardless of T size. (Tables 3.1, 3.2, 3.3, and 3.4)

TNM Classification

Clinical Staging

Clinical staging involves a combination of physical examination and imaging findings. Physical examination includes inspection and palpation of the skin, mammary glands, and lymph nodes (axillary, supraclavicular, and cervical) before

Table 3.1 TNM primary tumor definitions

T: TNM primary tumor definitions[a]
Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
Tis (DCIS)[b]: Ductal carcinoma in situ
Tis (LCIS): Lobular carcinoma in situ *(LCIS is treated as a benign entity and was removed from TNM staging in the AJCC eighth edition)*
Tis (Paget): Paget's disease of the nipple (without an invasive carcinoma and/or ductal carcinoma in situ (DCIS) in the underlying parenchyma)
T1: T < 2 cm
T1mi: ≤0.1 cm (microinvasive tumor)
Tla: >0.1 cm, <0.5 cm (AJCC eighth edition: Round any measurement >1.0–1.9 mm to 2 mm)
Tlb: >0.5 cm, ≤1 cm
Tlc: >1 cm, ≤2 cm
T2: >2 cm, ≤5 cm
T3: T > 5 cm
T4: Regardless of the size of the tumor: (1) involvement of the thoracic wall: *ribs, intercostal muscles and serratus muscles*; (2) skin involvement (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4b
T4a: Extension to the chest wall including muscularis pectoralis major (invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4)
T4b: Edema, peau d'orange, ulceration, and macroscopic satellite skin nodules in the ipsilateral breast (not an inflammatory carcinoma)
T4c: a + b
T4d: Inflammatory breast cancer

[a]Small microscopic satellite foci of the tumor around the primary tumor do not appreciably alter tumor volume and are not added to the maximum size (AJCC 8th). The 8th edition specifically continues using only the maximum dimension of the largest tumor for cT and pT, and the sizes of multiple tumors are not added
[b]The assigned grade should be nuclear grade

Table 3.2 Clinical classification of regional lymph nodes and distant metastases

Clinical classification of regional lymph nodes (cN)
cNx: Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0: No regional lymph node metastases
c N1: Metastases movable ipsilateral level I, II axillary lymph nodes
cN1mi[a]: >0.2–2 mm, approximately 200 cells
cN2
cN2a: Metastases in the ipsilateral level I, II axillary lymph nodes fixed to one another or to other structures
cN2b: Metastases only in imaging detected ipsilateral internal mammary nodes (excluding lymphoscintigraphy) in the absence of axillary metastases
cN3
cN3a: Ipsilateral infraclavicular lymph node(s) (level III axillary) metastasis
cN3b: Ipsilateral internal mammary lymph node metastasis with axillary lymph node(s) metastases
cN3c: Ipsilateral supraclavicular lymph node metastases
Distant metastases (M)

Table 3.2 (continued)

Mx distant metastasis unknown
M0 no clinical or radiological evidence of distant metastases
cM0 (i+) no clinical or radiological evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are not 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

[a]In cases where sentinel lymph node biopsy is performed before tumor resection (before neoadjuvant therapy)

Table 3.3 Pathological classification of regional lymph nodes

Pathological classification of regional lymph nodes (pN)[a]
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−): No regional lymph node metastases, immunohistochemistry (IHC) (−)
pN0 (i+): Malignant cells in regional lymph nodes no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cells [ITC])
pN0 (mol−): No regional lymph node metastases, negative molecular findings: RT-PCR (−)
pN0 (mol+): Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR) (+); no ITCs detected
pN1
pN1mic: Micrometastases >0.2 mm and/or >200 cells, ≤2 mm
pN1a: Metastases in 1–3 axillary lymph nodes, at least one metastasis greaterthan 2 mm
pN1b: Metastases in ipsilateral internal mammary nodes (excluding ITCs), with micrometastasis or macrometastases detected by sentinel lymph node biopsy but not clinically or by imaging
pN1c Metastases in 1–3 axillary lymph nodes and metastases in internal mammary nodes with micrometastasis or macrometastases detected by sentinel lymph node biopsy but not clinically or by imaging (pN1a and pN1b combined)
pN2
pN2a: Metastases in 4–9 axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b: Metastases in clinically/radiologically detected internal mammary lymph node metastases (except lymphoscintigraphy) with or without microscopic confirmation in the absence of axillary lymph node metastases
pN3
pN3a: Ten or more axillary lymph nodes (at least one tumor deposit >2.0 mm) or metastases to the infraclavicular (level 3 axillary) lymph nodes
pN3b: Metastases in clinically/radiologically detected (except lymphoscintigraphy) ipsilateral internal mammary lymph nodes plus at least one axillary lymph node metastasis, or metastases in more than three axillary lymph nodes and internal mammary lymph node micro- or macrometastases detected by SLNB (not clinically/radiologically)
pN3c: Metastases in ipsilateral supraclavicular lymph nodes
pM1 Any histologically proven metastases in distant organs or, if in non-regional nodes, metastases greater than 0.2 mm

[a]The largest contiguous tumor deposit is used for pN; adjacent satellite tumor deposits are not included in the eighth edition

Table 3.4 Post-neoadjuvant therapy staging

Post-neoadjuvant therapy (yc or ypTNM)
In the setting of patients who received neoadjuvant therapy, pretreatment clinical T (cT) should be based on clinical or imaging findings. Clinical nodal (cN) status is defined by clinical and radiographic findings (with or without histologic examination)
Post-neoadjuvant therapy T should be based on clinical or imaging (ycT) or pathologic findings (ypT)
A subscript is added to the clinical *N* for both node-negative and node-positive patients to indicate whether the *N* was derived from clinical examination, fine-needle aspiration, core needle biopsy, or sentinel lymph node biopsy. The "sn" modifier is used if sentinel lymph node evaluation without axillary dissection was performed after neoadjuvant treatment
The post-treatment ypT is defined as the largest contiguous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. The "m" modifier indicates multiple foci of residual tumor. Note: The definition of post-treatment ypT remains controversial and an area in transition
Post-treatment nodal metastases no greater than 0.2 mm are classified as ypN0(i+) as in patients who have not received neoadjuvant systemic therapy. However, patients with this status are not considered to have pathologic complete response (pCR)
A description of the degree of response to neoadjuvant therapy (complete, partial, no response) is collected by the registrar with the post-treatment ypTNM. The registrars are requested to describe how they defined response (by physical examination, imaging techniques [mammogram, ultrasound, magnetic resonance imaging—MRI], or pathologically)
If a patient presents with inflammatory disease (cT4d) before neoadjuvant chemotherapy, the cancer is still classified as inflammatory breast cancer after therapy, regardless of the response to neoadjuvant therapy. The post-treatment pathological classification (yPT) should reflect the identified residual disease, for example, ypT1a(m)
If a patient presents with Ml prior to systemic therapy, they are considered stage IV and remain stage IV, regardless of the response to neoadjuvant therapy[a]
Post-neoadjuvant therapy is designated with the "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0Cm0
When the only residual cancer in the breast is intralymphatic or intravascular (LVI), the case cannot be classified as pCR, but the ypT0 category is assigned. The presence of in situ cancer after treatment in the absence of residual invasive disease constitutes pCR
Patients with axillary nodal tumor deposits of any size, including isolated tumor foci less than 0.2 mm, are not classified as having pCR

[a]The stage designation may be changed if postsurgical imaging studies reveal the presence of dis tant metastases, provided that the studies are conducted within 4 months of diagnosis in the absence of disease progression and that the patient has not received neoadjuvant therapy

any therapy, including surgery, neoadjuvant chemotherapy, or radiotherapy. Furthermore, clinical staging also includes evaluation by imaging within 4 months of diagnosis in the absence of disease progression. Imaging findings used in clinical TNM staging are obtained by breast mammography, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) to determine the size of the primary tumor, axillary and regional lymph node involvement, chest wall invasion, and presence of any systemic metastasis.

Clinical and imaging findings after neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy should be recorded using the prefix "yc." Furthermore, clinical staging can include the use of fine-needle aspiration (FNA) or core needle biopsy and sentinel lymph node biopsy (SLNB) before neoadjuvant chemotherapy, denoted as "f" for FNA and "sn" for SLNB, respectively. Nodal metastases that were confirmed by FNA or core biopsy are classified as macrometastases, that is, "cN1(f)." Similarly, if the patient has a positive sentinel lymph node, the nodal metastasis is categorized as "cN1(sn)."

Pathological Staging

Pathological staging includes data from the pathological examination of the primary carcinoma or regional lymph nodes (N) after surgery and data regarding core biopsies obtained during surgery at metastatic sites (if applicable) with no macroscopic tumor involvement in any surgical margin along with clinical staging data. A cancer can be classified as pT for pathological staging if there is only microscopic involvement of the margin. If there is a transection in the tumor margin by macroscopic examination, the accurate pathological size of the tumor should be the sum of the sizes of the multiple resected pieces of the tumor.

Pathological stage grouping includes the following two combinations of pathological and clinical classifications: pT pN pM or cT cN cM. If surgery occurs after neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "yp" should be used with the TNM classification, that is, "ypTNM."

Determining Tumor Size

The size of a primary tumor (T) can be determined based on clinical findings, including physical examination and imaging modalities, such as mammography, ultrasound, and MRI; these measurements define the clinical tumor size (cT). The pathologic tumor size (pT) is estimated based on measuring *only the invasive component.* The microscopic measurement is the most accurate method for small invasive tumors submitted in one section/paraffin block, whereas gross measurement is the preferred method to determine pT for a large invasive tumor. The largest contiguous size of a tumor focus is used as an estimate of disease volume, and small satellite foci of the noncontiguous tumor are not added to the size. The cellular fibrous reaction to the invasive tumor is generally included in the measurement of a tumor in resected surgical material before any treatment. However, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the size of the tumor. Furthermore, a cancer can be classified as pT for the pathological stage grouping if there is microscopic but not macroscopic involvement at the margin. If the macroscopic examination indicates that the transected tumor is at the margin of resection, the pathological size of the tumor can be estimated from available information, including imaging studies, but it is not necessarily the sum of the sizes of the multiple resected pieces of the tumor. In cases with prior vacuum or core biopsy, however, the original invasive cancer size should be verified along with imaging, gross, and microscopic histological findings. For patients who receive neoadjuvant systemic or radiation therapy, pretreatment T is defined as cT. Therefore, pretreatment staging is based on clinical findings from a physical examination and imaging (cT), whereas post-treatment (ypT) size should be determined according to the imaging, gross, and microscopic pathological findings.

Tis Classification

Lobular carcinoma in situ (LCIS) has been removed from TNM staging and is considered a benign high-risk lesion. Similarly, "pleomorphic LCIS" is also not included in the 8th edition. The 7th edition recommended that pleomorphic LCIS be treated like ductal carcinoma in situ (DCIS) due to its overlapping features, such as a high nuclear grade and some necrosis. In the 8th edition, due to the low prevalence of high-grade pleomorphic LCIS, the data supporting this approach are considered insufficient, and therefore, LCIS, in both the classic and pleomorphic forms, has been removed from the staging system.

Pure carcinoma in situ is classified as Tis with an additional parenthetical subclassification, including two subtypes: ductal carcinoma in situ (DCIS; or intraductal carcinoma) and Paget's disease of the nipple with no underlying invasive cancer. These are categorized as Tis (DCIS) and Tis (Paget's), respectively.

Paget's disease is characterized by an exudate or crust of the nipple-areola complex caused by infiltration of the epidermis by noninvasive breast cancer epithelial cells. Paget's disease presents in one of the following three conditions [10]:

1. Associated with an underlying invasive carcinoma with T classification according to the size of the invasive disease
2. Associated with an underlying noninvasive carcinoma, usually DCIS with a T classification based on the underlying tumor of Tis (DCIS)
3. Not associated with an identified underlying invasive or noninvasive cancer classified as Tis (Paget's)

Microinvasive Carcinoma

Microinvasive carcinoma is defined as an invasive carcinoma with no foci larger than 1 mm encountered in a setting of DCIS where small foci of tumor cells have invaded through

the basement membrane into the surrounding stroma. In cases with multiple foci, an estimate of the number or a note that the number of foci of microinvasion is too numerous to quantify should be provided. The prognosis of microinvasive carcinoma is generally thought to be favorable, although the clinical impact of multifocal or multicentric microinvasive disease is not well known. Tumors >1 mm and <2 mm should be reported by rounding to 2 mm. Therefore, tumors between 1 and 1.5 mm should be treated as 2-mm invasive cancer and should not be considered microinvasive cancer. T1mi is defined as invasive tumor foci ≤1 mm.

Multiple Simultaneous Ipsilateral Primary Carcinomas

Multiple simultaneous ipsilateral primary carcinomas are defined as multifocal if they are located in the same quadrant or multicentric carcinomas if they are located in different quadrants in the same breast; these tumors are macroscopically measurable, using available clinical and pathological techniques. In these cases, with multiple foci, T-stage classification should be based only on the largest tumor, and not on the sum of the sizes. The presence and sizes of the smaller tumor(s) should be recorded using the "(m)" modifier. In a recent analysis of patients enrolled in the MA.12 clinical trial, worse outcome findings were obtained if a larger single dimension was considered as the T size instead of the larger summation of the largest tumor dimensions [11]. Imaging-guided tissue biopsy can be considered for any additional lesions suspicious for multifocal or multicentric disease that affect clinical management. When the distance between macroscopically apparently distinct tumors with similar histology is small (e.g., <5 mm), they are usually considered one tumor, and their T category should be based on the sum of the sizes. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic (satellite) foci. The largest contiguous tumor or tumor deposit is used for pT and pN; for the primary tumor, the sizes of multiple tumors or lymph node–adjacent satellite tumors are not added.

In cases with simultaneous bilateral primary carcinomas, each carcinoma is staged as a separate primary carcinoma in a separate organ in its own category as specified in the TNM rules. ER, PR, HER-2-neu, and grade should be determined separately for each tumor.

Skin of the Breast and Inflammatory Breast Carcinoma

Skin changes such as dimpling of the skin and nipple retraction, except those that are clinical findings of T4b and T4d disease, may also be observed in Tl, T2, or T3 disease without changing the T category.

T4 is defined as a tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules). T4a is extension to the chest wall. Adherence/invasion to the pectoralis muscle is not considered extension to the chest wall and therefore is not categorized as T4. T4b is defined as edema (including peau d'orange) of the skin, ulceration of the skin of the breast, or satellite skin nodules confined to the same breast. T4c is defined as both T4a and T4b. T4d is inflammatory breast carcinoma.

Inflammatory carcinoma is a clinical-pathological entity, characterized by diffuse erythema and edema (peau d'orange), involving a third or more of the skin of the breast; this is classified as T4d [12]. If the skin alterations, however, involve less than one-third of the skin, the cancer should be categorized as T4b or T4c. On imaging, there may be a detectable mass and thickening of the skin over the breast. A tissue diagnosis should be performed to demonstrate an invasive carcinoma in the underlying breast parenchyma or in the involved dermal lymphatics to assess the status of biological markers such as ER, PR, and HER-2 for planning systemic therapy. The following conditions are not considered inflammatory breast carcinoma: (a) locally advanced breast cancers directly invading the dermis or ulcerating the skin without clinical skin changes, (b) the presence of tumor emboli in dermal lymphatics on tissue biopsy without clinical skin changes, and (c) neglected locally advanced breast cancer in a patient late (at least more than 6 months) in the course of her disease.

Regional Lymph Nodes (N)

Macrometastases

In the 8th edition, cNx is not considered a valid category unless the nodes in the relevant node basin have been removed and cannot be examined by imaging or clinical examination. Patients are classified as cN0 and/or pN0 if the regional lymph nodes are not involved. A cN0 category is used when any evaluation of the axillary lymph nodes is possible, and the imaging and physical examination findings are negative. The classification criteria for clinically node-positive disease are defined in Table 3.2. If tumor involvement of the lymph nodes detected by physical examination or imaging studies is confirmed by an FNA or core biopsy, the lymph nodes are considered to contain macrometastases and labeled cN2a(f) by using the (f) modifier. However, biopsy is not always necessary to categorize a lymph node as positive, and lymph nodes can be classified as malignant by clinical or imaging characteristics alone. If a lymph node or nodes are removed by excisional biopsy or SLNB and examined histopathologically and the primary tumor has not been removed, the N category is recorded as clinical (cN).

Axillary lymph nodes histopathologically examined by surgical excisional biopsy, SLNB, or axillary lymph node dissection (ALND) are classified as described in Table 3.3. Patients with macrometastatic disease in lymph nodes must

have at least one lymph node with a metastasis greater than 2 mm. For patients undergoing SLNB, the additional designation (sn) for "sentinel node" should be used, for example, pNl (sn). Use of the (sn) modifier should be omitted when six or more sentinel nodes are identified on gross examination of pathology specimens. For a case with a standard ALND followed by a positive SLNB, the classification is based on the total results of both SLNB and ALND. When the number of sentinel and nonsentinel nodes is less than six, the (sn) modifier should be used.

In pathological evaluation, the entire lymph node is examined, whereas larger nodes should be bisected or thinly sliced (≤2.0 mm). Certain techniques, such as multilevel sectioning and immunohistochemistry (IHC), may identify additional tumor deposits less than or equal to 2.0 mm (micrometastases and isolated tumor cell [ITC] clusters).

Isolated Tumor Cells (ITCs) and Micrometastases

Small clusters of cells not greater than 0.2 mm in the largest dimension, nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross-section, or single cells with little if any histologic stromal reaction by routine histology or immunohistochemistry (IHC) are defined as ITCs. The lymph nodes should be categorized as pN0(i+) or pN0(i+)(sn) according to the surgery type. Nodes containing only ITCs should be excluded from the total positive node count for N categorization but should be included in the total number of nodes evaluated, and the number of nodes containing only ITC should be noted in the pathology report.

The lymph nodes are more likely to have tumor deposits greater than 0.2 mm but not greater than 2.0 mm in the largest dimension classified as micrometastases (pNlmi) or pNlmi (sn) if more than 200 individual tumor cells are counted as single dispersed cells or as a confluent focus in a single histological section of a node. In cases with multiple tumor deposits in a lymph node, the size of only the largest tumor deposit should be considered to classify the node and not the sum of all tumor deposits. The number of involved nodes should be noted separately for ITCs and micrometastases.

If tumor cells are detected in histologically negative lymph nodes by molecular methods such as reverse transcriptase-polymerase chain reaction (RT-PCR) using epithelial cell markers, the regional lymph nodes are classified as pN0(mol+) or pN0(mol+)(sn) as appropriate. Sacrificing lymph node tissue for molecular analysis that would otherwise be available for histological evaluation and staging is not recommended, particularly when the size of the sacrificed tissue is too small to contain micrometastases.

The prognostic significance of axillary metastases above a 2.0-mm threshold was confirmed by two studies reported over three decades ago [13, 14]. Following the first study, a subcategory for micrometastases was added to the *Cancer Staging Manual.* The introduction of SLNB and the widespread use of immunohistochemistry facilitated the detection of minimal disease in axillary lymph nodes, and the sixth edition of the *Staging Manual* established a lower limit for micrometastases of >0.2 mm, thus creating a new category of minimal nodal disease. Stage I breast cancer is subdivided into Stage IA and Stage IB; Stage IB is defined as the presence of T1 tumors (Tl) with exclusively micrometastases in lymph nodes (Nlmi). This limit was ten times smaller than the upper limit for micrometastases and had been tested in one retrospective study of occult metastases [15]. According to the sixth edition of TNM staging, ITC clusters should be distinguishable from micrometastases on the basis of metastatic characteristics, such as proliferation or stromal reaction [16, 17]. However, in the seventh edition, the Breast Cancer Task Force perceived that this distinction could be highly subjective, and that reproducibility among pathologists and among institutions might be difficult. Therefore, for the seventh and eighth editions, the Breast Cancer Task Force continued to define ITC clusters as not greater than 0.2 mm in diameter and micrometastases as greater than 0.2 mm but not greater than 2.0 mm in diameter. However, pathologists have had difficulty applying the size criterion when a large number of nonconfluent tumor cells are present in a lymph node, such as may occur in some invasive lobular carcinomas [18]. For this reason, additional guidance was incorporated in the seventh edition. When more than 200 nonconfluent or nearly confluent tumor cells are present in a single histological cross section of a lymph node, there is a high probability that more than 1000 cells are present in the node and that the cumulative volume of these cells exceeds the volume of an ITC. Consequently, the node should be classified as containing a micrometastasis. The pathologist should use judgment rather than an absolute cutoff of 0.2 mm or exactly 200 cells in determining the likelihood that the cluster of cells is an ITC or a true micrometastasis. Due to practical and economic constraints in the pathologic evaluation of lymph nodes and the absence of outcome data on the clinical significance of ITC clusters and micrometastases *after* the systematic exclusion of macrometastases, the current thresholds for TNM classifications have not been changed in the eighth edition.

An analysis of the US Surveillance, Epidemiology, and End Results (SEER) national cancer database (NCDB) demonstrated that when nodal tumor deposits no larger than 2.0 mm were the only finding in lymph nodes, and the primary tumor was less than or equal to 2 cm (pTl), the incremental decrease in survival at 5 and 10 years was only 1% compared to patients with no detected nodal metastases [19]. Among patients with pTl, the 10-year survival decreased from 78% to 77% and then to 73% for pN0, pNlmi, and pNla, respectively. Therefore, in the seventh edition, pTl

tumors with nodal micrometastases (pNlmi) are classified as Stage IB to indicate the better prognosis for this particular subset of patients. Furthermore, a recent report demonstrated that occult metastases were detected in 15.9% of 3887 patients with node-negative breast cancer by routine immunohistochemical staining for cytokeratin [20]. Log-rank tests indicated a significant difference between patients in whom occult metastases were detected and those in whom no occult metastases were detected with respect to overall survival (OS) ($P = 0.03$), disease-free survival (DFS) ($P = 0.02$), and distant-disease-free interval ($P = 0.04$). The corresponding adjusted hazard ratios (HRs) for death, any outcome event, and distant disease were 1.40 (95% confidence interval [CI], 1.05 to 1.86), 1.31 (95% CI, 1.07 to 1.60), and 1.30 (95% CI, 1.02 to 1.66), respectively. The 5-year Kaplan-Meier estimates of OS among patients in whom occult metastases were detected and those without detectable metastases were 94.6% and 95.8%, respectively. Occult metastases were an independent prognostic variable in patients with sentinel nodes that were negative on initial examination; however, the magnitude of the difference in outcome at 5 years was small (1.2 percentage points). Based on these data, a clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes in patients with breast cancer could not be demonstrated. Interestingly, a recent analysis of T1 breast cancer further demonstrated that patients with micrometastases and negative nodes showed similar survival outcomes, whereas ER status and grade significantly stratified patients with respect to disease-specific survival (DSS) and OS [21]. These data indicate that tumor biology, including ER status and grade, is a better discriminant of survival than the presence of small-volume nodal metastases.

The detection of ITCs and micrometastases has been enabled by the use of more sensitive molecular assays, such as reverse transcriptase-polymerase chain reaction (RT-PCR). By using this technique, epithelial markers such as cytokeratins were identified in a significant percentage of sentinel nodes that were negative for metastasis by both histological and immunohistochemical staining [22]. However, it seems unlikely that the minimal tumor burden would be as significant as for macrometastases and micrometastases. Furthermore, because lymph node tissue is digested and consumed in preparation for RT-PCR, it is technically challenging to determine the exact size of the original metastatic involvement in the lymph node to justify the completion of ALND if this assay has been found to be positive [23]. A lymph node that is exclusively positive by molecular assay (mol+) may contain ITC clusters, micrometastases, or macrometastases or may be a false-positive result due to sampling, contamination, or features intrinsic to the assay [24]. Since there are currently insufficient data to suggest that RT-PCR assays of lymph nodes should replace the traditional histological evaluation of lymph nodes, the seventh and eighth editions of the *AJCC Cancer Staging* have classified any lesion identified by RT-PCR alone as pN0 that is histologically negative for regional lymph node metastases by using the appended designation (mol+). It is recommended that the first priority in evaluating lymph nodes is the histological identification of macrometastases (metastases larger than 2.0 mm) and N classification based on histological findings and measurements.

Distant Metastases (M)

Patients without any distant metastases (M) evaluated by clinical evaluation, including physical examination, blood workup, and/or radiographic methods, are classified as cM0, whereas cases in which one or more distant metastases are detected by clinical and/or radiographic methods are defined as cMl. Patients with the subsequent development of new metastases as recurrence should be considered as recurrent stage IV even though this does not change the patient's initial stage.

The detection of metastatic disease by clinical examination should include a full physical examination based on evolving symptoms, radiographic findings, and/or laboratory findings. Physical findings alone rarely provide the basis for Ml stage—radiographic studies are almost always required, and pathological biopsy confirmation should be performed whenever feasible. All guidelines suggest that radiographic imaging, such as bone scintigraphy, PET-CT, or anatomic, cross-sectional imaging, is required for symptomatic patients with suspicious findings in the patient's history or physical examination and/or elevated serologic tests for liver or bone function [25]. Staging is also appropriate for patients with stage III disease (clinical or pathological), whereas systemic radiographic staging for metastases is not warranted in asymptomatic patients with normal blood tests who have Tl-2, N0 breast cancer [25]. However, there is no consensus for patients with T2N1 staging. The overuse of PET-CT may result in false-positive findings in patients with newly diagnosed breast cancer, which may result in unnecessary biopsies and delayed initiation of local or systemic therapies.

If the distant metastatic lesion has been confirmed by tissue biopsy, it is defined as pM1. The type of biopsy for a suspicious lesion should be determined by the location of the suspicious metastatic lesion along with patient preference, safety, and operator expertise. FNA may be adequate, especially for visceral lesions, if an experienced cytopathologist is available. Other biopsy techniques such as core needle or open surgical biopsies may be warranted for especially bony or scirrhous lesions. Histopathological examination should include standard hematoxylin and eosin (H&E) staining and additional immunohistochemical staining (ER, PR, HER-2, Ki-67), including fluorescent in situ hybridization (FISH) techniques for HER-2 for some cases with suspicious HER-2

immunohistochemical staining. These biomarker stainings are critical for planning systemic therapies of patients, especially if adequate biomarker data are not available from the primary tumor, and to resolve discordance in biomarker stainings between the primary and metastatic sites. For those patients for whom a tissue biopsy from the metastatic site may not be obtained for reasons such as safety performing the biopsy, follow-up studies after systemic therapies may be required for the final decision depending on whether the suspicious lesion that was present at the time of initial diagnosis has subsequently disappeared.

Patients with abnormal liver function tests should undergo liver imaging, whereas those with elevated alkaline phosphatase or calcium levels or other suggestive symptoms should undergo bone imaging and/or scintigraphy. Anemia and other cytopenias require a full hematological evaluation (e.g., examination of the peripheral smear, iron studies, B12/folate levels), and a bone marrow biopsy may be required during follow-up. The routine use of tumor markers such as CA 15-3, CEA, Ca-125, and CA 27.29 during follow-up has not been shown to improve outcome.

Circulating Tumor Cells, Bone Marrow Micrometastases, and Disseminated Tumor Cells

The demonstration of the prognostic significance of circulating tumor cells (CTCs) in the peripheral blood and bone marrow in patients with both localized and metastatic breast cancer may provide a true biological staging of breast cancer [26–29]. CTCs and microscopic tumor cells detected in the bone marrow are collectively designated disseminated tumor cells (DTCs). Several studies have shown a relationship between bone marrow DTCs and recurrence risk and mortality in M0 stage breast cancer [26, 30, 31]. However, other reports failed to demonstrate prognostic significance of the presence of positive bone marrow micrometastases, which might be due to differences in the techniques used for the detection of bone marrow micrometastases, such as immunofluorescence techniques instead of immunocytochemistry [32, 33]. Similarly, the prognostic value of CTCs detected in breast cancer patients is currently under debate. Most of these studies were small with short follow-up, were confounded by the effects of systemic therapy, and could not demonstrate a significant prognostic effect [34–37]. However, a meta-analysis of 49 articles published between January 1990 and January 2012 enrolling 6825 patients showed that the presence of CTCs was significantly associated with shorter survival in the total population [38]. The prognostic value of CTCs was significant in both early (DFS: HR, 2.86; 95% CI, 2.19–3.75; OS: HR, 2.78; 95% CI, 2.22–3.48) and metastatic breast cancer (PFS: HR, 1.78; 95% CI, 1.52–2.09; OS: HR, 2.33; 95% CI, 2.09–2.60), irrespective of the CTC detection method and time point of blood withdrawal.

In another study, CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System [39]. CTCs were detected in 21.5% of patients (n = 435 of 2026) before chemotherapy and in 22.1% of patients (n = 330 of 1493) after chemotherapy. The presence of CTCs was found to be an independent prognostic marker in multivariable analysis for DFS (HR = 2.11; 95% CI = 1.49–2.99; $P < 0.0001$) and OS (HR = 2.18; 95% CI = 1.32–3.59; P = 0.002). The presence of persisting CTCs after chemotherapy showed a negative influence on DFS (HR = 1.12; 95% CI = 1.02–1.25; P = 0.02) and OS (HR = 1.16; 95% CI = 0.99–1.37; P = 0.06) in a large prospective trial of patients with primary breast cancer, indicating the independent prognostic relevance of CTCs both before and after adjuvant chemotherapy. The worst prognosis in terms of DFS and OS was found in patients with at least five CTCs per 30 cc of blood. Further studies are required to explore the clinical utility of CTCs in breast cancer. In the presence of CTCs in the blood or micrometastases (<0.2 mm) in the bone marrow or other non-regional nodal tissues, the term M0(i+) is used in the eighth edition TNM classification as in the previous edition, if other apparent clinical and/or radiographic findings that correspond to pathological findings are absent. These patients with M0(i+) are staged according to T and N. In patients with overt metastases (Ml), the presence and number of CTCs at the time of diagnosis have also been shown to be prognostic for both disease progression and mortality [40–44]. Changes in CTCs after treatment are also predictive of the response to therapy and prognostic for recurrence and mortality, although the American Society of Clinical Oncology Tumor Marker Guidelines Panel did not recommend the routine use of CTCs in the management of patients with metastatic breast cancer in 2008 because the utility of this assay in patient management decisions has not been demonstrated [27, 34, 40, 41]. Therefore, neither the presence nor the number of CTCs will change the overall classification of patients with M1 disease to further subclassify Ml staging.

In summary, many clinicians consider a palliative rather than curative intent for patients who are designated Ml (stage IV). However, there are no data to suggest that the detection of DTCs in any tissue (bone marrow, blood) in the absence of clinical and/or radiographic findings confers incurability. Therefore, in the absence of overt metastases detected by clinical examination or imaging abnormalities, DTCs should not affect M staging, and the staging category should be M0(i+). For data collection purposes, however, the DTC designation should be expanded to include any cluster of malignant cells no greater than 0.2 mm found in any tissue outside of the breast and surrounding regional lymph nodes in the absence of clinical or radiographic signs of metastases (M0 disease).

Post-neoadjuvant Chemotherapy Classification

The increasing importance of neoadjuvant therapy in breast cancer mandates that the staging system provide the information necessary to assess prognosis in this diverse group of patients. Outcomes after neoadjuvant systemic therapy, either chemotherapy or endocrine therapy, differ among patients, and the staging system should reflect potential prognosis [45–49]. Thus, in the seventh and eighth editions of the AJCC Staging System, post-therapy clinical and pathological staging are recorded using the prefix "yc" and "yp," respectively. Clinical staging (c) is defined by information gathered before neoadjuvant therapy or surgery, including clinical and radiological findings, whereas pathological staging (p) includes information gathered at surgery after NAC (Table 3.4). The last edition clarified that the post-neoadjuvant therapy clinical (ycT) and pathological T (ypT) categories are based on the largest contiguous focus of residual invasive cancer, if present. When multiple foci of a residual tumor are present, the (m) modifier is included. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. The post-treatment ycT and ypT classifications should reflect the extent of residual disease on imaging and pathology, respectively. For example, a patient with a 26.0-mm residual tumor bed containing 11.0 mm and 5 mm tumor foci on a surgical specimen is categorized as ypT1c (m). A cancer classified as inflammatory breast cancer—IBC—(cT4d) before NAC is still classified as inflammatory breast cancer after systemic therapy, even if inflammatory findings including erythema and edema resolve after therapy. However, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0. When the only residual cancer in the breast is intravascular or in the intralymphatic space (LVI), the patient cannot be considered as having pCR but is categorized as ypT0.

Furthermore, the use of FNA and SLNB before neoadjuvant therapy is defined with the subscripts "f" and "sn," respectively. Nodal metastases detected by FNA or core biopsy are classified as macrometastases (Nl) regardless of the size of the tumor focus in the final pathological specimen. For instance, a patient with an ultrasound-guided FNA biopsy of a nonpalpable axillary lymph node that is positive is categorized as cNl (f) and considered clinical stage (CS) IIA. Similarly, a patient with a positive axillary sentinel node detected before neoadjuvant chemotherapy will be categorized as pNl (sn) (pathological stage IIA). Pathological assessment N(ypN) is determined similar to pN. The "sn" modifier is used only if an SLNB without ALND was performed after NAC. If no SLNB or ALND is performed, "ypNx" is used in the classification. In the ypN categories, only the largest contiguous focus of the residual tumor in the lymph node evaluation is used, and treatment-associated fibrosis is not included in estimating the extent of residual metastatic foci.

If a patient has detectable distant metastases before NAC, the patient will be designated as M1 throughout. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastasis is considered progression of disease.

Definition and Clinical Relevance of Complete Response

Pathologic complete response (pCR) has been found to be associated with long-term outcome in several neoadjuvant studies and has therefore been a potential prognostic factor as reported in a recent meta-analysis [50]. However, other studies comparing different neoadjuvant regimens have failed to show an association between the pCR rate and improved outcomes [46, 51, 52]. These discordant findings may mostly be due to the various definitions of pCR used in these studies. Some trials have applied the pCR definition to the breast tumor only, whereas others have also included the axillary lymph nodes [53, 54]. Furthermore, some studies have considered the presence of focal invasive cancer [55] or noninvasive cancer residuals in their pCR definition [54], whereas others have defined pCR as the complete eradication of all invasive and noninvasive cancer [56]. Although an international expert panel proposed that a CR be defined as the absence of invasive and *noninvasive* tumors in the breast [46], in the seventh and eighth editions of the AJCC staging system, pCR is defined as the absence of invasive carcinoma in the breast and the axillary nodes because the presence of DCIS is not a determinant of survival [1, 2].

In a retrospective review from MD Anderson Cancer Center, patients with a pCR with ($n = 199$) and without DCIS ($n = 78$) were found to have similar outcomes but had significantly better survival rates than the patients with invasive cancer ($n = 2025$) [57]. Similar findings were demonstrated by Jones et al. in a study of 435 patients [58]. However, in a study by Minckwitz et al. including 6377 patients with primary breast cancer receiving neoadjuvant anthracycline-taxane-based chemotherapy, DFS was found to be significantly superior in patients with no invasive and no in situ residual disease in the breast or nodes ($n = 955$) compared with patients with residual ductal carcinoma in situ only ($n = 309$), no invasive residual disease in the breast but involved nodes ($n = 186$), only focal invasive disease in the breast ($n = 478$), and gross invasive residual disease ($n = 4449$; $P < 0.001$) [59].

Furthermore, the incidence and prognostic impact of pCR vary among breast cancer–intrinsic subtypes [59, 60]. In a meta-analysis including 20 studies ($n = 8095$), the pooled pCR% was 18.5% (16.2–21.1%) for patients receiving neoadjuvant chemotherapy for primary breast cancer. The subtype-specific pCR% was 8.3% (6.7–10.2%) in HR+/HER-2− [OR 1/referent], 18.7% (15.0–23.1%) in HER-2+/HR+, 38.9% (33.2–44.9%) in HER-2+/

HR− (OR 7.1) and 31.1% (26.5–36.1%) in triple negative (TN) (OR 5.0); pCR% was significantly higher for HER-2+/HR− compared with the TN subtype. Of note, the odds of pCR were highest for the TN and HER-2+/HR− subtypes, with evidence of an influential effect on achieving pCR in the HER-2+/HR− subtype based on inclusion of HER-2-directed therapy with NAC. In a study by Minckwitz et al., pCR was associated with improved DFS in luminal B/HER-2-negative ($P = 0.005$), HER-2-positive/nonluminal ($P < 0.001$), and TN ($P < 0.001$) tumors but not in luminal A ($P = 0.39$) or luminal B/HER-2-positive ($P = 0.45$) breast cancer. Furthermore, pCR in HER-2-positive (nonluminal) and TN tumors was associated with excellent prognosis. Therefore, they concluded that pCR defined as no invasive and no in situ residuals in the breast and nodes can best distinguish patients with favorable outcome from those with unfavorable outcomes. CR in patients overexpressing HER-2 and treated with trastuzumab plus chemotherapy was associated with improved survival compared with those who did not have pCR [61, 62]. Similar findings were obtained in patients treated with trastuzumab in combination with pertuzumab and chemotherapy [63]. However, other studies defining pCR as the absence of invasive cancer in the breast and lymph nodes did not find any survival benefit in patients with pCR [64].

To investigate the immunogenicity of HER-2-positive and TN breast cancers, tumor-infiltrating lymphocytes (TILs) and their associations with pCR, tumors were evaluated for stromal TILs and lymphocyte-predominant breast cancer (LPBC) [65]. GeparSixto investigated the effect of adding carboplatin (Cb) to an anthracycline-plus-taxane combination (PM) on pCR. Increased levels of stromal TILs predicted pCR in both univariate ($P < 0.001$) and multivariate analyses ($P < 0.001$). The pCR rate was 59.9% for LPBC and 33.8% for non-LPBC ($P < 0.001$). pCR rates ≥75% were observed in patients with LPBC tumors treated with PMCb. The presence of stromal TILs might be considered a predictive marker for pCR, especially in TN breast cancer.

The majority of the available data regarding the prognostic significance of pCR has been obtained from patients receiving neoadjuvant chemotherapy, whereas there is limited information about the prognostic significance of the degree of response for neoadjuvant endocrine therapy. pCR is rarely observed in patients receiving 3–4 months of neoadjuvant endocrine therapy, and its absence should not be considered evidence of endocrine resistance or poor prognosis [66, 67]. Further studies including new targeted therapies are warranted to examine the relationship between response to systemic therapy and survival. Therefore, it has been suggested that registrars should collect post-neoadjuvant TNM data.

Assessment of Neoadjuvant Therapy Response

An unresolved problem in defining the yp post-treatment stage is how to determine the best method for measuring tumor size after neoadjuvant chemotherapy. In the absence of a CR, the assessment of response and measurement of tumor size remain problematic. The residual cancer burden method used at MD Anderson Cancer Center (www.mdanderson.org/breastcancer_RCB) can be recommended. The demonstrated prognostic relevance within each molecular subtype of breast cancer provides quantitative information complementary to the yp classification. However, other methods, including Chevallier, the Miller-Payne grading system, and Sataloff, compare the histopathology semi-quantitatively before and after treatment [55, 68–71].

Concerns about reproducibility exist for all of these measures, and none of these methods have been found to predict outcome. In the seventh and eighth editions of the TNM Staging System, the pathological T size was defined by the largest contiguous tumor focus, with a suffix to alert the clinician when multiple scattered tumor foci are observed. When nests of tumor cells in fibrotic stroma are observed after treatment, the T should be determined based on the largest contiguous area of invasive carcinoma, excluding surrounding areas of fibrosis. This method of T measurement has been shown to correlate with survival as reported by Carey et al. [72]

Patients who underwent primary surgery and lymph node evaluation and nodes with ITCs are classified as pN0. However, in patients undergoing surgery after neoadjuvant therapy and presenting with ITCs in lymph nodes, ITCs could represent the presence of minimal nodal disease pretreatment that did not respond to therapy or residual tumor cells of macroscopic nodal disease as a partial response. Until further data are available to address the prognostic significance of ITCs after treatment, those patients with ITCs after neoadjuvant chemotherapy classified as ypN0(i+) are not considered to have a pCR.

To assess the tumor response to chemotherapy, modalities such as physical examination, mammography, ultrasound, and MRI, which may be used to determine the clinical tumor size, have been demonstrated to significantly overestimate and underestimate the extent of the tumor compared with pathological examination [73, 74]. However, a rough estimate of the response should be determined by comparing post-treatment clinical, radiographic, and pathological assessments with those made prior to the initiation of systemic therapy, and this estimate should be recorded. In the seventh and eighth editions, the AJCC response criteria are defined as follows: (1) CR: absence of invasive carcinoma in the breast and node; (2) partial response (PR): decrease in the T and/or N stage; and (3) no response (NR): no change or an increase in the T and/or N stage.

The clinical usefulness of the AJCC response criteria was validated in a study by Keam et al. [75]. A total of 398 consecutive stage II or III breast cancer patients who received NAC were enrolled in this study. The 5-year recurrence-free survival (RFS) rates were 89.6% in CR, 74.1% in PR, and 62.6% in NR ($P = 0.002$). The 5-year OS rates were 97.4% in CR, 88.6% in PR, and 78.3% in NR ($P = 0.012$). After adjusting for potential prognostic factors, the AJCC response criteria were found to be independently associated with RFS and OS. The AJCC response criteria for NAC in breast cancer have clinical usefulness in evaluating the response to NAC and in predicting survival. The authors concluded that the AJCC response criteria could discriminate among patient subgroups with respect to survival.

Carey et al. demonstrated that the AJCC TNM post-treatment (yp) stage was a significant predictor of both 5-year DFS and OS [72]. However, even in patients with pCR, the clinical TNM stage at diagnosis provides valuable prognostic information. Of 226 patients at the MD Anderson Cancer Center with pCR to neoadjuvant therapy, statistically significant differences in 10-year metastasis-free survival were found based on the initial stage at diagnosis before receiving neoadjuvant chemotherapy. At a median follow-up of 63 months, the 10-year distant metastasis-free rate was 82%. Multivariate Cox regression analysis using the combined stage revealed that clinical stages IIIB, IIIC, and IBC (HR, 4.24; 95% CI, 1.96–9.18; $P < 0.0001$) predicted distant metastasis. The clinical relevance of pretreatment stage, post-treatment stage, and degree of response in predicting survival remains to be defined, and, therefore, in the seventh edition of the AJCC Staging System, the pretreatment TNM data are not included in the calculation of post-treatment stage ("yp"), unless the patient was Ml prior to the initiation of therapy. In this case, her M status is considered M1 regardless of the response to therapy.

Other studies have suggested establishing a novel means of determining prognosis for patients treated with neoadjuvant chemotherapy by using clinical and pathological staging parameters, along with biological tumor markers. This novel breast cancer staging system for assessing prognosis after neoadjuvant chemotherapy is based on the pretreatment clinical stage (CS), ER status (E), grade (G), and post-treatment pathological stage (PS). The ability of the CPS + EG staging system based on the scores assigned and summed points for each factor to stratify outcomes was validated in a study by Mittendorf et al. [76]. Application of the CPS + EG staging system facilitated more refined categorization of patients into prognostic subgroups by outcome than presenting CS or final PS as defined by the American Joint Committee on Cancer (AJCC) staging system. By incorporating HER-2-neu status into the previously developed CPS + EG staging system and by using the definition of ER positivity (≥1%), Mittendorf et al. recently validated this updated staging system (Neo-Bioscore) in patients treated with NAC at the University of Texas and MD Anderson Cancer Center between 2005 and 2012 [77]. They concluded that the updated new Neo-Bioscore including HER-2-neu status further improved the stratification with respect to prognosis of patients who received NAC. The authors recommended that biological markers and response to treatment be incorporated into revised and new versions of the AJCC staging system for patients receiving neoadjuvant chemotherapy.

Biomarkers for Prognostic Breast Cancer Staging

Hormone Receptors

ER is a nuclear transcription factor that is a regulator of cellular growth, proliferation, and differentiation in the breast epithelium. PR is an estrogen-regulated gene, and its expression therefore indicates a functioning ER pathway. Immunohistochemical determination of these receptors is the standard tool in current pathology-oncology practice. A cutoff of 1% of tumor cells is recommended for a specimen to be considered positive for ER or PR because clinical data have indicated that these patients can respond to hormonal treatment [3].

Human Epidermal Growth Factor Receptor-2 (HER-2) Test

The most commonly used methods to evaluate HER-2/neu in breast cancer are immunohistochemistry (IHC) and in situ hybridization (ISH). ISH determines the number of HER-2 copies using a DNA probe coupled to a fluorescent (FISH), chromogenic (CISH), or silver (SISH) detection system. In 2013 and 2018, updates of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines were published [4, 78]. In 2015, a short comment on upcoming modifications was released [79].

HER-2 IHC scoring **is reported as follows:**

(a) *Negative:*
Score 0: No staining observed or membrane staining is incomplete, faint/barely perceptible and within ≤10% of the invasive tumor cells.
Score 1+: Incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells.

(b) *Equivocal (Score 2+):* Weak/moderate complete membrane staining in >10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells.

(c) *Positive (Score 3+):* Circumferential membrane staining in >10% of invasive tumor cells that is complete and intense.

Table 3.5 In situ hybridization (ISH) reporting

ISH reporting
Positive
Single-probe average HER-2 copy number ≥6.0 signals/cell
Dual-probe HER-2/CEP 17 ratio ≥2.0 with an average HER-2 copy number ≥4.0 signals per cell
Negative
Single-probe average HER-2 copy number <4.0 signals/cell
Dual-probe HER-2/CEP 17 ratio <2.0 with an average HER-2 copy number <6.0 signals/ cell
Indeterminate
This category was added in the 2013 update. The test should be reported as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Examples include inadequate specimen handling, artifacts (e.g., crushing or marked edge artifacts) that make interpretation difficult, analytical testing failure, or controls that are not as expected. The test should be repeated if possible
2018 Update
The 2018 update on recommendations for HER-2 testing with ISH method cancelled an equivocal result [16, 78]. Instead, it forced pathologists to make a judgment as positive or negative using combination of repeated IHC and dual-probe ISH method. According to final update, if the HER-2/CEP 17 ratio ≥2.0 and average HER-2 copy number is <4.0, the result should be negative after completion of a workup. If the average HER-2 copy number is ≥6.0 and the ratio is <2.0, the result should be positive after completion of a workup.

Table 3.6 Histologic grade scoring and definition

Feature	NGS[a] score
Tubule formation	
Majority of tumor (>75%)	1
Moderate degree (10–75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscopic field area	1–3
G	Grade definition
GX	Grade cannot be assessed
G1	Well-differentiated/favorable; low combined histologic grade: NGS score of 3–5 points
G2	Moderately differentiated/moderately favorable; intermediate combined histologic grade: NGS score of 6–7 points
G3	Poorly differentiated/unfavorable; high combined histologic grade: NGS score of 8–9 points

[a]*NGS* Nottingham Grading System

Samples scoring 3+ are considered unequivocally positive, and those scoring 0/1+ are negative. Equivocal scores (2+) mandate further assessment using ISH. Repeat HER-2 testing on a surgical specimen if the initially tested core biopsy is negative is no longer stated as mandatory. A new HER-2 test *may* (no longer *should*) be ordered on the excision specimen on the basis of some criteria (such as tumor grade 3). (Table 3.5)

In Situ Hybridization Reporting:

- *Positive:*
  - Single-probe average HER-2 copy number ≥6.0 signals/cell.
  - Dual-probe HER-2/CEP17 ratio ≥2.0 with an average HER-2 copy number ≥4.0 signals per cell.
- *Negative*:
  - Single-probe average HER-2 copy number <4.0 signals/cell.
  - Dual-probe HER-2/CEP 17 ratio <2.0 with an average HER-2 copy number <6.0 signals/cell.

The 2018 update on recommendations for HER-2 testing with ISH method cancelled an equivocal result [78], forcing pathologists to make a judgment of positive or negative using a combination of repeated IHC and dual-probe ISH methods. According to the final update, if the HER-2/CEP 17 ratio is ≥2.0 and the average HER-2 copy number is <4.0, the result should be negative after completion of workup. If the average HER-2 copy number is ≥6.0 and the ratio is <2.0, the result should be positive after the completion of workup.

Grade (G)

Histological Grade

Histological grade is used for invasive carcinomas. The Nottingham (Elston-Ellis) modification of the Scarff-Bloom-Richardson (SBR) grading system, also known as the Nottingham Grading System (NGS) [80], is the grading system recommended by professional organizations such as the World Health Organization (WHO) [78], American Joint Committee on Cancer (AJCC), the Royal College of Pathologists (UK RCPath), and CAP [4, 78, 81] (Table 3.6).

NGS is based on the evaluation of three morphological features [80, 82, 83]:

(a) Degree of tubule or gland formation.
(b) Nuclear pleomorphism.
(c) Mitotic count (found in ten consecutive high-power fields (HPFs) in the most mitotically active part of the tumor)

By assigning a value from 1 (favorable) to 3 (unfavorable) for each feature and totaling the scores of the three categories,

Table 3.7 DCIS nuclear grade definition

G	Grade definition
GX	Grade cannot be assessed
G1	Low nuclear grade
G2	Intermediate nuclear grade
G3	High nuclear grade

a combined score of 3–5 points is designated as grade 1, a combined score of 6–7 points is grade 2, and a combined score of 8–9 points is grade 3.

Ductal Carcinoma in Situ (DCIS) Grade (Nuclear Grade)

Most cases of DCIS are positive for ER. Positivity (defined as ≥1% of tumor cells) is observed in 70–85% of cases [84]. Expression correlates with the grade of DCIS. Almost all cases of ER-negative DCIS are of high nuclear grade. PR expression is lower than ER expression. Nuclear grade is used for grading DCIS (Table 3.7) (www.cap.org).

Ki-67

Ki-67 is a nuclear protein associated with cellular proliferation detected by IHC [85]. However, no standard operating procedure or generally accepted cut-off value for Ki-67 is available thus far (AJCC Level of Evidence III). As a single factor, Ki-67 is not reproducible and is therefore not considered a reliable factor for use in clinical practice.

Breast Cancer Biological Subtypes

Breast cancer is a heterogenous disease, and four groups have been defined by gene expression profiling [86, 87]. Instead of molecular gene-expression-based molecular subtypes, clinically defined subtypes based on the expression of ER, PR, HER-2-neu, and Ki-67 are used to assess prognosis and in the therapeutic management of patients as follows:

(a) Luminal A-like tumors (ER+, PR+, Ki-67 low, HER-2-neu−): Usually low-grade tumors with an excellent prognosis and an excellent response to endocrine therapy.
(b) Luminal B-like tumors (ER+, PR±, Ki-67 high, HER-2-neu±): Usually high-grade tumors with an unfavorable prognosis and a high proliferation rate that are less likely to respond to endocrine therapy and more likely to respond to chemotherapy.
(c) HER-2-like (ER−, PR-, Ki-67 high, HER-2-neu +): HER-2-positive with an excellent response to chemotherapy combined with anti-HER-2 therapy including trastuzumab. Usually high-grade tumors with an unfavorable prognosis and high proliferation rate.
(d) Basal-like (ER−, PR−, HER-2-neu−): Triple-negative, generally grade 3 tumors with poor prognosis.

Of these, luminal A tumors have been found to be associated with the most favorable clinical outcome, whereas patients with TN invasive ductal cancer show the worst prognosis [88, 89]. In the St Gallen 2013 guidelines, the breast cancer subtypes based on immunohistochemistry were defined as luminal A, luminal B, nonluminal HER-2, and TN [88]. A useful surrogate definition of luminal A-like as distinct from luminal B-like disease could be made using a combination of ER, PgR, and Ki-67 without requiring molecular diagnostics. The proliferation marker Ki-67 has been suggested as a promising prognostic and predictive breast cancer biomarker, but the best cut points are still under debate. The standardization of Ki-67 remains relevant for diagnostic pathology as a prototype quantitative immunohistochemical biomarker. Several different cut points for Ki-67 have been reported to be significant, and it is very difficult to determine an evidence-based "optimal" cut point. At the 2013 St Gallen Breast Cancer Conference, the majority of the Panel voted that a threshold of ≥20% was clearly indicative of "high" Ki-67 status, and, in 2015, this cutoff was increased to ≥30–35% [89]. These cut points support the view that Ki-67 should be regarded as a continuous marker, reflecting the continuous variation of the proliferation rate in different types of tumors.

The prognostic relevance of the TNM staging system with respect to intrinsic subtype in breast cancer has been studied by Jung et al. [90]. In patients with primary surgery for stages I–III breast cancers ($n = 1145$), the 5-year recurrence-free survival (RFS) rate in HR-positive and HER-2-negative disease with a low Ki-67 staining score (0–25%) was 99%. However, the 5-year RFS rates of patients with HER-2-positive or TN breast cancer were 89% and 83%, respectively. In multivariate analysis, advanced stage (II/III) and unfavorable biology (HER-2-positive or TN) remained as significant predictors of decreased RFS and OS. Patients with stage II or III disease but favorable tumor biology (HR-positive and HER-2-negative and low Ki-67) have been found to have better outcomes than those with stage I disease and unfavorable tumor biology in terms of 5-year RFS (99 vs. 92%, P value = 0.011) and OS (99 vs. 96%, P value = 0.03). These results suggest that the intrinsic subtype has a greater prognostic impact in predicting clinical outcomes in subpopulations of patients with stages I–III breast cancer who show discordance between the stage and biological subtype.

Bagaria et al. investigated whether including the triple-negative phenotype (TNP) could improve the prognostic accuracy of TNM staging for breast cancer [91]. Patients

with invasive ductal breast cancer who underwent primary surgery (n = 1842) were categorized by TNM stage and by the presence or absence of TNP. Multivariable analysis identified TNP status as a powerful prognostic factor, and the study demonstrated that the prognostic accuracy of the TNM staging system that incorporated TNP was superior to that of the current TNM staging system ($P < 0.001$). A TNM staging system that incorporated TNP reduced early-stage compression by 15%. Similarly, the relevance of tumor biomarkers (ER/PR/HER-2) in a recently proposed biological TNM (bTNM) classification system that included TNP for improving the prognostic accuracy of TNM was investigated by Orucevic et al. [92]. Of the 782 patients with invasive ductal breast carcinoma, TNP significantly worsened survival only in more advanced TNM stages (Stage III = HR 3.08, 95% CI 1.88–5.04, Stage IV = HR 24.36, 95% CI 13.81–42.99) and not in earlier stages (I and II). Taken together, these studies along with others suggest that incorporating nonanatomic factors such as ER, PR, and HER-2 status according to the luminal, TNP, and HER-2 subtypes in the TNM staging system (bTNM) could improve the prognostic accuracy of current breast cancer staging [90–93].

Incorporating Biomarkers into TNM-Prognostic Stage Groups

The major changes in the eighth edition of the AJCC staging consisted of integration of biomarkers into the TNM staging. Compared to standard biomarkers such as grade, hormone receptors, and HER-2-neu, there has been great uncertainty about how to accurately integrate prognostic and predictive multigene panels into the AJCC staging system due to the limited prospective data on these expensive panels. The eighth AJCC edition outlines that prognostic staging is not always appropriate for all patients, and in institutions around the world with limited resources for cancer diagnosis and treatment, biomarker determination and/or multigene panels are not routinely performed or available. Moreover, anatomic staging has been a valuable parameter as a common terminology for clinicians and researchers to compare studies and patients, regardless of country or resources. Studies have been performed to investigate whether incorporating biomarkers would improve discrimination over the classic anatomic TNM by using a large database of the University of Texas MD Anderson Cancer Center [94]. In a cohort of 3728 patients who underwent primary surgery, the significance of adding grade (G); lymphovascular invasion (L); estrogen receptor (ER) status (E); progesterone receptor (PR) status; combined ER and PR status (EP); or combined ER, PR, and HER-2 status (M) was tested by using a Cox proportional hazards model. Values of 0–2 were assigned to these disease-specific survival (DSS)-associated factors, and six different staging systems were assessed: PS, PS + G, PS + G L, PS + G E, PS + G EP, and PS + G M. The PS + G E status staging system was the most precise, with a low AIC and high C-index. Compared to the pathological stage alone, this novel staging system resulted in improved discrimination between stages with respect to DSS.

After the use of trastuzumab, another cohort of 3327 patients with 306 HER-2-neu-positive patients was studied to identify factors associated with DSS by using a multivariate analysis [95]. The factors included pathological stage, grade, ER status, PR status, and HER-2-neu status. A score of 0–4 was assigned according to the HR as follows: 1 point for an HR of 1.1–3, 2 points for an HR of 3.1–6, 3 points for an HR of 6.1–10, and 4 points for an HR of >10. An overall staging score defined as the "Bioscore" was estimated by summing the scores for the individual independent predictors of DSS. The risk score was validated in a cohort of 43,938 patients in the California Cancer Registry diagnosed with breast cancer between 2005 and 2008 [8]. The most favorable outcomes were observed for hormone receptor-positive tumors followed by HER-2-positive tumors, and the worst outcomes were observed for TN breast cancer. The risk score system separated patients into four risk groups within each stage category (all $P < 0\,0.05$). Weiss et al. recently reported the results of their validation study of the AJCC eighth edition prognostic stage in 3327 patients treated at MD Anderson Cancer Center between 2007 and 2013 and 54,727 patients of the California Cancer Registry diagnosed with breast cancer between 2005 and 2009 [96]. For the MD Anderson Cancer Center cohort, the prognostic stage upstaged 29.5% of patients and downstaged 28.1% compared with the AJCC anatomic stage, thus providing more accurate staging. Similarly, the prognostic stage was upstaged in 31.0% of patients and downstaged in 20.6% in the California Cancer Registry cohort, thus providing more accurate stratification of patients in terms of prognosis compared to the anatomic stage alone. Similar findings were reported in other validation studies.

Another study reported by Winchester et al. using the National Cancer Database (NCDB) tested the impact of prognostic factors on staging [5]. The analysis incorporated the conventional variables, including TNM categories based on the stage group in the seventh edition, tumor grade, ER status, PR status, and HER-2-neu status combinations. Patients with TN tumors (all grades) and with grade 3 tumors without HER-2-neu overexpression or hormone receptor expression had decreased survival compared to patients at least one stage higher according to the seventh edition criteria. Consistent with the point score developed by the MD Anderson model, patients with ER and PR expression with or without HER-2-neu

overexpression had better survival than others within the same seventh edition stage group.

The clinical prognostic stage should be assigned to all patients, whereas the pathological prognostic stage should be calculated for those patients undergoing surgery as the initial treatment. Prognostic stage groups are defined by combining the anatomic stage group with the grade and HER-2-neu, ER, and PR status. Combining Stages IA and IB and Stages IIIB and IIIC resulted in 120 different categories of patients. Consistent with the anatomic stage tables, the prognostic stage tables also included the subcategories of stages IA, IB, IIA, IIB, IIIA, IIIB, and IIIC in addition to the stage groups for DCIS and metastatic disease, respectively. Those with pT1 or pT2, pN0, M0, ER-positive and HER-2-negative breast cancers and an Oncotype DX score of <11 were assigned as pathological prognostic stage group stage 1A.

The clinical and pathological prognostic stage groups were established for the eighth Edition by the NCBD analyses. For these analyses, survival calculations of patients treated not more than a decade ago were considered to reflect the contemporary management of patients. The incorporation of hormone receptors and HER-2-neu status and grade into the clinical and prognostic stage tables resulted in the reassignment of more than 35% of patients to a stage group higher or lower than the anatomic stage.

In conclusion, although the application of these prognostic stage groups appears to be more complicated than that of the anatomic stage groups, the prognostic stage appears to predict the outcome more accurately [5, 8, 94–97].

Gene Expression Tests (Multigene Panels, Genomic Profiles, Signature Scores)

Several gene expression profiling assays have been developed in an attempt to predict the survival and response of breast cancer patients to therapies [98–108]. These assays are based on the identification of prognostic gene signatures by using microarrays. Many groups have attempted to develop genomic tests based on genomic profiling with the expectation that such tests might better predict clinical outcome than standard pathological and clinical markers. There is growing consensus that multigene expression assays can provide useful complementary information to tumor size and grade in ER-positive breast cancers. First-generation prognostic signatures such as MammaPrint and Oncotype DX are substantially more accurate in predicting recurrence within the first 5 years than in later years [98, 99]. MammaPrint, a 70-gene prognostic signature developed by investigators from Amsterdam, has been used in women younger than 61 years with stage I or II node-negative breast cancer to "assess a patient's risk for distant metastases" [99, 100]. In addition, a second multigene assay based on RT-PCR analysis of the expression of 21 genes (designated the "Oncotype DX 21-gene recurrence score assay") can be used to determine the prognosis in patients with ER-positive breast cancer by assessing the benefit of chemotherapy in addition to hormonal treatment [98, 102, 104–106, 108]. Newer tests (Prosigna, EndoPredict, Breast Cancer Index) appear to possess better prognostic value for late recurrences while also remaining predictive of early relapse [103, 108]. Therefore, the use of genomic/gene expression arrays that also incorporate additional prognostic/predictive biomarkers (e.g., Oncotype DX recurrence score—RS) may provide additional prognostic and predictive information beyond anatomic TNM staging and ER/PR and HER-2 status. The eighth edition strongly recommends the use of these gene expression tests only in patients with hormone receptor-positivity and HER-2-neu negativity and not in patients with more aggressive types, such as TN and HER-2-neu positive tumors. The Expert Panel of AJCC considered incorporating results from the Oncotype DX score into the pathological prognostic stage (2),

The *Oncotype DX test (Genomic Health, Redwood, CA, USA)* is a quantitative RT-PCR assay. This test measures a panel of 21 genes, including 16 cancer-related (prognostic) genes and five reference genes, and generates a recurrence score (RS) that classifies patients as at low (RS <18), intermediate (RS 18–30), or high (RS ≥31) risk of recurrence [98]. The 10-year distant recurrence rates of each category are 6.8%, 14.3%, and 30.5%, respectively. The Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study demonstrated that a group of TAILORx trial participants with low 21-gene recurrence scores (Oncotype DX® Recurrence Score®) of *ten or less* who received hormonal therapy alone without chemotherapy had a less than 1% chance of distant recurrence at 5 years [104–106]. In the TAILORx Clinical Trial, adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone receptor-positive, HER-2-negative, axillary node-negative breast cancer who had a midrange 21-gene recurrence score [106]. However, the chemotherapy benefit for invasive disease-free survival varied with the combination of recurrence score and age ($P = 0.004$), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16–25. For patients with T1 and T2 hormone receptor-positive, HER-2-negative, and lymph node-negative tumors in the low-risk range, these tumors are placed into the same prognostic group category, T1a-T1bN0M0, regardless of T size. These findings from this large-scale prospective trial provided level 1 evidence for incorporating the Oncotype DX score into the pathological prognostic stage table.

Other multigene panels provide similar information that can be used to classify prognostic stage group 1 [99, 103, 108]. Regarding the use of the 70-gene signature assay (MammaPrint), results from the RASTER (microarray-prognoSTics-in-breast-cancER) study in the Netherlands,

a prospectively designed study based on MammaPrint scores in addition to clinical and pathological features, have been reported [100]. In a subset of patients with low-risk clinical (defined by adjuvant! Online) and molecular (MammaPrint score) features, systemic therapy (chemotherapy and/or hormonal therapy) was given to less than 10% of these patients, and the outcome was excellent with distant RFS of 95.3%. Similarly, the MINDACT study, reported in 2016, demonstrated that women with a low genomic risk of recurrence but high clinical risk with ER-positive and HER-2-negative breast cancers might be spared from chemotherapy [107]. Although the MINDACT trial provided sufficient Level 1 evidence for genomic risk as a prognostic factor, its use is limited since it does not predict benefit of chemotherapy and cannot be incorporated into the prognostic stage table since the clinical risk of recurrence used in the MINDACT study was based on survival estimates from the Adjuvant! Online system as of July 2017.

There are more limited data on other gene expression panels. In 2017, the ASCO Clinical Practice Guideline Committee updated the guidelines to use biomarkers to guide decisions on adjuvant systemic therapies for patients with early-stage breast cancer [108]. In summary, studies based on gene expression assays are mostly retrospective in nature, and the follow-up period for assessing prognosis in these studies is 3–5 years. It is also not clear that any of these panels is superior to others with different scoring systems. However, patients with low-risk scores obtained by these multigene panels have clearly been reported to have an excellent prognosis.

Summary and Future Perspectives

Due to advances in personalized medicine, the last update of the AJCC Breast Cancer Staging incorporated recent molecular gene assays and new prognostic and predictive markers (Tables 3.8, 3.9, 3.10, 3.11, 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, 3.19). Clinical and pathological prognostic stage tables were incorporated in addition to the traditional anatomic prognostic stage tables. The pathological stage table is based on clinical information, biomarker data, and findings from surgery and resected tissue.

Table 3.8 Clinical prognostic stage: HER-2-Positive, ER-Positive, PR-Positive

	T0		T1mi		T1		T2		T3		T4	
AJCC 7th												
N0			IA		IA		IIA		IIB		IIIB	IIIB
N1mi	IB		IB		IB		IIB		IIIA	IIIA	IIIB	IIIB
N1	IIA		IIA		IIA		IIB		IIIA	IIIA	IIIB	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G[a]	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
AJCC 8th												
N0			IA		IA		IB		IB		IIIA	IIIB
N1mi	IA		IA		IA		IB		IIA	IIB	IIIA	IIIB
N1	IB		IB		IB		IB		IIA	IIB	IIIA	IIIB
N2	IIA	IIB	IIA	IIB	IIA	IIB	IIA	IIB	IIA	IIB	IIIA	IIIB
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
Differences between AJCC 7 and AJCC 8												
AJCC 7th												
N0							IIA		IIB		IIIB	
N1mi	IB		IB		IB		IIB		IIIA	IIIA	IIIB	
N1	IIA		IIA		IIA		IIB		IIIA	IIIA	IIIB	
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
AJCC 8th												
N0							IB		IB		IIIA	
N1mi	IA		IA		IB		IB		IIA	IIB	IIIA	
N1	IB		IB		IB		IB		IIA	IIB	IIIA	
N2	IIA	IIB	IIA	IIB	IIA	IIB	IIA	IIB	IIA	IIB	IIIA	
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3

[a]*G* histologic grade

Table 3.9 Clinical prognostic stage: HER-2-positive, ER or PR-positive

	T0	T1mi	T1	T2		T3		T4
AJCC 7th								
N0		IA	IA	IIA		IIB	IIB	IIIB
N1mi	IB	IB	IB	IIB	IIB	IIIA		IIIB
N1	IIA	IIA	IIA	IIB	IIB	IIIA		IIIB
N2	IIIA	IIIA	IIIA	IIIA		IIIA		IIIB
N3	IIIC	IIIC	IIIC	IIIC		IIIC		IIIC
G	1,2,3	1,2,3	1,2,3	1,2	3	1,2	3	1,2,3
AJCC 8th								
N0		IA	IA	IIA		IIA	IIB	IIIB
N1mi	IA	IA	IA	IIA	IIB	IIIA		IIIB
N1	IIA	IIA	IIA	IIA	IIB	IIIA		IIIB
N2	IIIA	IIIA	IIIA	IIIA		IIIA		IIIB
N3	IIIB	IIIB	IIIB	IIIB		IIIB		IIIB
G	1,2,3	1,2,3	1,2,3	1,2	3	1,2	3	1,2,3
Differences between AJCC 7 and AJCC 8								
AJCC 7th								
N0						IIB		
N1mi	IB	IB	IB	IIB				
N1				IIB				
N2								
N3	IIIC	IIIC	IIIC	IIIC		IIIC		IIIC
G	1,2,3	1,2,3	1,2,3	1,2	3	1,2	3	1,2,3
AJCC 8th								
N0						IIA		
N1mi	IA	IA	IA	IIA				
N1				IIA				
N2								
N3	IIIB	IIIB	IIIB	IIIB		IIIB		IIIB
G	1,2,3	1,2,3	1,2,3	1,2	3	1,2	3	1,2,3

Table 3.10 Clinical prognostic stage: HER-2-positive, ER-negative, PR-negative

	T0	T1mi	T1	T2	T3	T4
AJCC 7th						
N0		IA	IA	IIA	IIB	IIIB
N1mi	IB	IB	IB	IIB	IIIA	IIIB
N1	IIA	IIA	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
AJCC 8th						
N0		IA	IA	IIA	IIB	IIIB
N1mi	IA	IA	IA	IIB	IIIA	IIIB
N1	IIA	IIA	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
Differences between AJCC 7 and AJCC 8						
AJCC 7th						
N0						
N1mi	IB	IB	IB			
N1						
N2						
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
AJCC 8th						
N0						
N1mi	IA	IA	IA			
N1						
N2						
N3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3

Table 3.11 Clinical prognostic stage: HER-2-negative, ER-negative, PR-negative

	T0			T1mi			T1			T2			T3			T4
AJCC 7th																
N0				IA			IA			IIA	IIA		IIB	IIB		IIIB
N1mi	IB			IB			IB			IIB	IIB		IIIA		IIIA	IIIB
N1	IIA	IIA		IIA	IIA		IIA	IIA		IIB	IIB	IIB	IIIA		IIIA	IIIB
N2	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA			IIIA		IIIA	IIIB
N3	IIIC			IIIC			IIIC			IIIC			IIIC			IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2,3
AJCC 8th																
N0				IB			IB			IIA	IIB		IIB	IIIB		IIIC
N1mi	IB			IB			IB			IIB	IIIB		IIIB		IIIC	IIIC
N1	IIA	IIB		IIA	IIB		IIA	IIB		IIB	IIIB	IIIB	IIIB		IIIC	IIIC
N2	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIC
N3	IIIC			IIIC			IIIC			IIIC			IIIC			IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2,3

(continued)

Table 3.11 (continued)

	T0			T1mi			T1			T2			T3			T4
Differences between AJCC 7 and AJCC 8																
AJCC 7th																
N0				IA			IA				IIA			IIB		IIIB
N1mi											IIB		IIIA		IIIA	IIIB
N1		IIA			IIA			IIA			IIB	IIB	IIIA		IIIA	IIIB
N2	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIB
N3																
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2,3
AJCC 8th																
N0				IB			IB				IIB			IIIB		IIIC
N1mi											IIIB		IIIB		IIIC	IIIC
N1		IIB			IIB			IIB			IIIB	IIIB	IIIB		IIIC	IIIC
N2	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIC
N3																
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2,3

Table 3.12 Clinical prognostic stage: HER-2-negative, ER-positive, PR-positive

	T0		T1mi		T1		T2		T3		T4
AJCC 7th											
N0			IA		IA		IIA	IIA	IIB	IIB	IIIB
N1mi	IB		IB		IB		IIB	IIB	IIIA	IIIA	IIIB
N1	IIA	IIA	IIA	IIA	IIA	IIA	IIB	IIB	IIIA	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIC		IIIC		IIIC		IIIC		IIIC		IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3
AJCC 8th											
N0			IA		IA		IB	IIA	IIA	IIB	IIIB
N1mi	IA		IA		IA		IIA	IIB	IIA	IIIA	IIIB
N1	IB	IIA	IB	IIA	IB	IIA	IIA	IIB	IIA	IIIA	IIIB
N2	IIA	IIIA	IIA	IIIA	IIA	IIIA	IIA	IIIA	IIA	IIIA	IIIB
N3	IIIB		IIIB		IIIB		IIIB		IIIB		IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3
Differences between AJCC 7 and AJCC 8											
AJCC 7th											
N0							IIA		IIB		
N1mi	IB		IB		IB		IIB		IIIA		
N1	IIA		IIA		IIA		IIB		IIIA		
N2	IIIA		IIIA		IIIA		IIIA		IIIA		
N3	IIIC		IIIC		IIIC		IIIC		IIIC		IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3
AJCC 8th											
N0							IB		IIA		
N1mi	IA		IA		IA		IIA		IIA		
N1	IB		IB		IB		IIA		IIA		
N2	IIA		IIA		IIA		IIA		IIA		
N3	IIIB		IIIB		IIIB		IIIB		IIIB		IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3

Table 3.13 Clinical prognostic stage: HER-2-negative, ER or PR-positive

	T0		T1mi		T1		T2		T3		T4	
AJCC 7th												
N0			IA	IA	IA	IA	IIA	IIA	IIB	IIB	IIIB	IIIB
N1mi	IB	IB	IB	IB	IB	IB	IIB	IIB	IIIA	IIIA	IIIB	IIIB
N1	IIA	IIA	IIA	IIA	IIA	IIA	IIB	IIB	IIIA	IIIA	IIIB	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
AJCC 8th												
N0			IA	IB	IA	IB	IIA	IIB	IIB	IIIA	IIIB	IIIC
N1mi	IA	IB	IA	IB	IA	IB	IIB	IIIA	IIIA	IIIB	IIIB	IIIC
N1	IIA	IIB	IIA	IIB	IIA	IIB	IIB	IIIA	IIIA	IIIB	IIIB	IIIC
N2	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIB	IIIC
N3	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
Differences between AJCC 7 and AJCC 8												
AJCC 7th												
N0				IA		IA		IIA		IIB		IIIB
N1mi	IB		IB		IB			IIB		IIIA		IIIB
N1		IIA		IIA		IIA		IIB		IIIA		IIIB
N2		IIIA		IIIA		IIIA		IIIA		IIIA		IIIB
N3	IIIC		IIIC		IIIC		IIIC		IIIC		IIIC	
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3
AJCC 8th												
N0				IB		IB		IIB		IIIA		IIIC
N1mi	IA		IA		IA			IIIA		IIIB		IIIC
N1		IIB		IIB		IIB		IIIA		IIIB		IIIC
N2		IIIB		IIIB		IIIB		IIIB		IIIB		IIIC
N3	IIIB		IIIB		IIIB		IIIB		IIIB		IIIB	
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3	1,2	3

Table 3.14 Pathological prognostic stage: HER-2-positive, ER-positive, PR-positive

	T0		T1mi		T1		T2			T3			T4	
AJCC 7th														
N0			IA		IA		IIA			IIB	IIB		IIIB	IIIB
N1mi	IB		IB		IB		IIB	IIB		IIIA		IIIA	IIIB	IIIB
N1	IIA		IIA		IIA		IIB	IIB		IIIA		IIIA	IIIB	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA		IIIA	IIIA		IIIA	IIIB	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC		IIIC	IIIC		IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3
AJCC 8th														
N0			IA		IA		IA			IA	IB		IIIA	IIIB
N1mi	IA		IA		IA		IA	IB		IB		IIA	IIIA	IIIB
N1	IA		IA		IA		IA	IB		IB		IIA	IIIA	IIIB
N2	IB	IIA	IB	IIA	IB	IIA	IB		IIA	IB		IIA	IIIA	IIIB
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA		IIIB	IIIA		IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3

(continued)

Table 3.14 (continued)

	T0		T1mi		T1		T2			T3			T4	
Differences between AJCC 7 and AJCC 8														
AJCC 7th														
N0							IIA			IIB	IIB		IIIB	
N1mi	IB		IB		IB		IIB	IIB		IIIA		IIIA	IIIB	
N1	IIA		IIA		IIA		IIB	IIB		IIIA		IIIA	IIIB	
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA		IIIA	IIIA		IIIA	IIIB	
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC		IIIC	IIIC		IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3
AJCC 8th														
N0							IA			IA	IB		IIIA	
N1mi	IA		IA		IA		IA	IB		IB		IIA	IIIA	
N1	IA		IA		IA		IA	IB		IB		IIA	IIIA	
N2	IB	IIA	IB	IIA	IB	IIA	IB		IIA	IB		IIA	IIIA	
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA		IIIB	IIIA		IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3

Table 3.15 Pathological prognostic stage: HER-2-positive, ER or PR-positive

	T0		T1mi		T1		T2		T3	T4
AJCC 7th										
N0			IA		IA		IIA	IIA	IIB	IIIB
N1mi	IB		IB		IB		IIB		IIIA	IIIB
N1	IIA	IIA	IIA	IIA	IIA	IIA	IIB		IIIA	IIIB
N2	IIIA		IIIA		IIIA		IIIA		IIIA	IIIB
N3	IIIC		IIIC		IIIC		IIIC		IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3	1,2,3
AJCC 8th										
N0			IA		IA		IB	IIA	IIB	IIIB
N1mi	IA		IA		IA		IIB		IIIA	IIIB
N1	IB	IIA	IB	IIA	IB	IIA	IIB		IIIA	IIIB
N2	IIIA		IIIA		IIIA		IIIA		IIIA	IIIB
N3	IIIB		IIIB		IIIB		IIIB		IIIB	IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3	1,2,3
Differences between AJCC 7 and AJCC 8										
AJCC 7th										
N0							IIA			
N1mi	IB		IB		IB					
N1	IIA		IIA		IIA					
N2										
N3	IIIC		IIIC		IIIC		IIIC		IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3	1,2,3
AJCC 8th										
N0							IB			
N1mi	IA		IA		IA					
N1	IB		IB		IB					
N2										
N3	IIIB		IIIB		IIIB		IIIB		IIIB	IIIB
G	1,2	3	1,2	3	1,2	3	1,2	3	1,2,3	1,2,3

Table 3.16 Pathological prognostic stage: HER-2-positive, ER-negative, PR-negative

	T0	T1mi	T1	T2	T3	T4
AJCC 7th						
N0		IA	IA	IIA	IIB	IIIB
N1mi	IB	IB	IB	IIB	IIIA	IIIB
N1	IIA	IIA	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
AJCC 8th						
N0		IA	IA	IIA	IIB	IIIB
N1mi	IA	IA	IA	IIB	IIIA	IIIB
N1	IIA	IIA	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
Differences between AJCC 7 and AJCC 8						
AJCC 7th						
N0						
N1mi	IB	IB	IB			
N1						
N2						
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
AJCC 8th						
N0						
N1mi	IA	IA	IA			
N1						
N2						
N3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
G	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3

The complexity of the new staging system and the requirement for expensive molecular gene assays to determine the prognostic stage may restrict the widespread clinical use of the new AJCC system throughout the world. Furthermore, the majority of studies regarding prognostic and predictive multigene panels are retrospective in nature, with little prospective data available. Therefore, there has been great concern regarding how to accurately integrate these biomarkers and multigene panels into the AJCC staging system. Future prospective studies are required to outline the importance of these multigene panels to decide on adjuvant treatment and prognosis. It is expected that electronic health record and cancer registry software systems will, in the near future, offer tools to generate clinical and pathological prognostic stage groups from the data entered for the T, N, M, grade, and certain prognostic factors.

Moreover, biological markers, including HER-2-neu, and the response to treatment (Neo-Bioscore) might be incorporated into revised versions of the AJCC staging system for patients receiving neoadjuvant chemotherapy in new editions of the AJCC staging system. With advances in personalized medicine, the increase in available molecular gene assays and new prognostic and predictive markers, such as TILs, or oncoimmunological biomarkers, such as PD-1 (or PDL-1, etc.), might be incorporated into future staging systems. It is anticipated that updates will be made on a more frequent basis than the 6- to 8-year cycle of TNM revisions when relevant validated information is available.

Table 3.17 Pathological prognostic stage: HER-2-negative, ER-negative, PR-negative

	T0			T1mi			T1			T2			T3			T4	
AJCC 7th																	
N0				IA	IA		IA	IA		IIA			IIB	IIB	IIB	IIIB	IIIB
N1mi	IB	IB		IB	IB		IB	IB		IIB		IIB	IIIA	IIIA	IIIA	IIIB	IIIB
N1	IIA			IIA			IIA			IIB		IIB	IIIA	IIIA	IIIA	IIIB	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIB
N3	IIIC	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2,3
AJCC 8th																	
N0				IA	IB		IA	IB		IIA			IIB	IIB	IIIA	IIIB	IIIC
N1mi	IA	IB	IB	IA	IB	IB	IA	IB		IIB		IIIA	IIIA	IIIB	IIIC	IIIB	IIIC
N1	IIA			IIA			IIA			IIB		IIIA	IIIA	IIIB	IIIC	IIIB	IIIC
N2	IIIA	IIIB	IIIC	IIIA	IIIB	IIIC	IIIA	IIIB	IIIC	IIIA	IIIB	IIIC	IIIA	IIIB	IIIC	IIIB	IIIC
N3	IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2,3

(continued)

Table 3.17 (continued)

	T0			T1mi			T1			T2			T3			T4	
Differences between AJCC 7 and AJCC 8																	
AJCC 7th																	
N0					IA			IA						IIB			IIIB
N1mi	IB			IB			IB					IIB		IIIA	IIIA		IIIB
N1												IIB		IIIA	IIIA		IIIB
N2		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA		IIIA	IIIA		IIIB
N3	IIIC			IIIC			IIIC			IIIC			IIIC			IIIC	
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2,3
AJCC 8th																	
N0					IB			IB						IIIA			IIIC
N1mi	IA			IA			IA					IIIA		IIIB	IIIC		IIIC
N1												IIIA		IIIB	IIIC		IIIC
N2		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIB	IIIC		IIIC
N3	IIIB			IIIB			IIIB			IIIB			IIIB			IIIB	
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2,3

Table 3.18 Pathological prognostic stage: HER-2-negative, ER-positive, PR-positive

	T0		T1mi		T1		T2			T3			T4	
AJCC 7th														
N0			IA		IA		IIA	IIA	IIA	IIB	IIB	IIB	IIIB	IIIB
N1mi	IB		IB		IB		IIB	IIB	IIB	IIIA	IIIA	IIIA	IIIB	IIIB
N1	IIA	IIA	IIA	IIA	IIA	IIA	IIB	IIB	IIB	IIIA	IIIA	IIIA	IIIB	IIIB
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIB
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3
AJCC 8th														
N0			IA		IA		IA	IA	IB[a]	IA	IB	IIA	IIIA	IIIB
N1mi	IA		IA		IA		IA	IB	IIA	IB	IB	IIB	IIIA	IIIB
N1	IA	IB	IA	IB	IA	IB	IA	IB	IIA	IB	IB	IIB	IIIA	IIIB
N2	IB	IIB	IB	IIB	IB	IIB	IB	IB	IIB	IB	IB	IIB	IIIA	IIIB
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIA	IIIB	IIIA	IIIA	IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3
Differences between AJCC 7 and AJCC 8														
AJCC 7th														
N0							IIA	IIA	IIA	IIB	IIB	IIB	IIIB	
N1mi	IB		IB		IB		IIB	IIB	IIB	IIIA	IIIA	IIIA	IIIB	
N1	IIA	IIA	IIA	IIA	IIA	IIA	IIB	IIB	IIB	IIIA	IIIA	IIIA	IIIB	
N2	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	
N3	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3
AJCC 8th														
N0							IA	IA	IB[a]	IA	IB	IIA	IIIA	
N1mi	IA		IA		IA		IA	IB	IIA	IB	IB	IIB	IIIA	
N1	IA	IB	IA	IB	IA	IB	IA	IB	IIA	IB	IB	IIB	IIIA	
N2	IB	IIB	IB	IIB	IB	IIB	IB	IB	IIB	IB	IB	IIB	IIIA	
N3	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIA	IIIB	IIIA	IIIA	IIIB	IIIA	IIIB
G	1,2	3	1,2	3	1,2	3	1	2	3	1	2	3	1,2	3

[a]When the Oncotype Dx test result is less than 11 (Level 1 evidence) or a multigene panel, genomic profile, and signature score are in the low-risk category, the case should be assigned as IA

Table 3.19 Pathological prognostic stage: HER-2-negative, ER or PR-positive

	T0			T1mi			T1			T2			T3			T4	
AJCC 7th																	
N0				IA			IA			IIA	IIA		IIB			IIIB	IIIB
N1mi	IB			IB			IB			IIB			IIIA			IIIB	IIIB
N1	IIA	IIA		IIA	IIA		IIA	IIA		IIB			IIIA			IIIB	IIIB
N2	IIIA			IIIA			IIIA			IIIA			IIIA			IIIB	IIIB
N3	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC		IIIC	IIIC	IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2	3
AJCC 8th																	
N0				IA			IA			IB[a]	IIA[a]		IIB			IIIB	IIIC
N1mi	IA			IA			IA			IIB			IIIA			IIIB	IIIC
N1	IB	IIA		IB	IIA		IB	IIA		IIB			IIIA			IIIB	IIIC
N2	IIIA			IIIA			IIIA			IIIA			IIIA			IIIB	IIIC
N3	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB		IIIC	IIIB	IIIC
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2	3
Differences between AJCC 7 and AJCC 8																	
AJCC 7th																	
N0										IIA	IIA						IIIB
N1mi	IB			IB			IB										IIIB
N1	IIA			IIA			IIA										IIIB
N2																	IIIB
N3	IIIC			IIIC			IIIC			IIIC			IIIC			IIIC	
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2	3
AJCC 8																	
N0										IB[a]	IIA[a]						IIIC
N1mi	IA			IA			IA										IIIC
N1	IB			IB			IB										IIIC
N2																	IIIC
N3	IIIB			IIIB			IIIB			IIIB			IIIB			IIIB	
G	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1,2	3

[a]When the Oncotype Dx test result is less than 11 (Level 1 evidence) or a multigene panel, genomic profile, and signature score are in the low-risk category, the case should be assigned as IA

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Surgical Treatment of Early-Stage Breast Cancer

4

Vahit Ozmen and Volkan Dogru

Definition

The term "early-stage breast cancer" is quite controversial. Due to widespread screening with mammography and increased awareness of breast cancer, non-palpable breast cancers account for 75% of all breast cancers. The increasing number of patients with non-palpable breast cancers (cT1a, b, N0 M0) has promoted a new classification in the staging, and "very early-stage breast cancer" has been proposed for this specific group of patients. Accordingly, early-stage breast cancer is classified as stage I (pT1N0) and stage II (T0-2, N0-2, M0). However, today stage I and II breast cancer have been accepted as early breast cancer. Stage II breast cancer is further subdivided into stages IIA and IIB. Patients classified as having stage IIA breast cancer include those with T0-1, N1, and T2, N0 disease. Stage IIB breast cancer includes patients with T2, N1, and T3, N0 disease. However, the current generally accepted definition of early-stage breast cancer includes stage I and stage IIA breast cancer.

Clinical Staging

The revised staging for early-stage breast cancer is presented in this section because the decision to start treatment with either surgery or chemotherapy is based on clinical staging [1].

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Primary Tumor

The diameter of the tumor can be measured via physical examination or radiological evaluation. Radiological evaluations permit more precise measurements.

T1: Defines tumors ≤2 cm and is further divided into four groups according to the diameter of the tumor:

- T1mi: ≤0.1 cm (the size should not be rounded down to nearest millimeter)
- T1a: Tumor >0.1 cm but not more than 0.5 cm
- T1b: Tumor >0.5 cm but not more than 1 cm
- T1c: Tumor >1 cm but not more than 2 cm
- T2 defines tumors >2 cm but not more than 5 cm.
- T3 defines tumors >5 cm.
- T4 defines tumors of any size with direct extension to the chest wall and/or to the skin.

Regional Lymph Nodes

Clinical Evaluation

Regional lymph nodes are evaluated by physical examination.

- NX: Regional lymph nodes cannot be evaluated (previously removed, etc.).
- N0: There are no palpable regional lymph nodes.
- N1: There are mobile and palpable level I–II axillary lymph nodes on the same side.
- N1 mi: This classification is rarely used when the sentinel lymph node has micrometastases (0.2–2.0 mm) before tumor resection.
- N2: There are fixed level I–II axillary lymph nodes on the same side, stuck together or to the surrounding tissue, or there are no palpable lymph nodes in the axilla, but there is a palpable internal mammary lymph node on the same side.

A. Aydiner et al. (eds.), *Breast Disease*, https://doi.org/10.1007/978-3-030-16792-9_4

- N3: There are mobile and palpable level III (infraclavicular) lymph nodes on the same side; simultaneous, clinically evident ipsilateral level I–II axillary and internal mammary lymph nodes; or clinically evident supraclavicular lymph nodes.

Distant Metastasis

- M0: No distant metastasis.
- M1: There is distant metastasis.

Stage I Breast Cancer

Defined as T1 N0 M0 or T0-1 N1mi M0.

If the genomic profile is available and the Oncotype Dx Score is less than 11, ER is positive, HER2 is negative and T1-2 N0 M0, and then the pathologic prognostic stage group is Ia.

Stage IIA Breast Cancer

Defined as T0 N1 M0, T1 N1 M0, or T2 N0 M0

Stage IIB Breast Cancer

Defined as T2 N1 M0 or T3 N0 M0

Because a subset of stage IIB (T3 N0) and stage III breast cancers are regarded as locally advanced breast cancers, initial treatment with neoadjuvant chemotherapy is recommended in these cancers. Surgical treatment, such as breast-conserving surgery (BCS) or mastectomy, is initiated after this treatment.

If the tumor-to-breast volume ratio is appropriate in stage IIB breast cancer patients (T2N1 = tumor size is 2–5 cm, axilla N1), treatment can be initiated with surgery, such as BCS or mastectomy. If the tumor size is 5 cm or more (T3), then treatment should begin with chemotherapy.

For locally advanced breast cancer, BCS can be performed after neoadjuvant chemotherapy in selected cases. This topic is explained elsewhere in a separate section.

Preoperative Evaluation

History, physical examination, chest X-ray, and routine laboratory work-up are sufficient studies for staging in early-stage breast cancer. Computed tomography of the thorax and abdomen, bone scintigraphy, and FDG PET-CT should be used for the evaluation of locally advanced breast cancer and only if the patient has complaints.

Evaluation of the Breast with Tumor

The breast with tumor should be examined in detail, particularly for BCS, because if the tumor is multicentric (tumor in more than one quadrant) in the same breast, BCS may not be performed. If multicentric tumors are close to each other in neighboring quadrants, BCS can be attempted. In multifocal cancers (more than one tumor in the same quadrant), a large excision can be made if the tumor-to-breast volume ratio is appropriate. Careful physical examination and quality mammography with appropriate magnification views should be performed primarily. Ultrasonography and magnetic resonance imaging (MRI) should be added if the patient is young and/or has high breast density. The presence of other tumors in the same quadrant (multifocal) or other quadrants (multicentric) will affect the extent of the surgical treatment.

There are studies suggesting that the screening performance (cancer detection rate and a reduction in recall rate) of digital mammography combined with tomosynthesis is better than that of digital mammography alone, except for patients with extremely dense breasts and at the expense of doubling the amount of radiation that the patients are exposed to [2]. However, innovative radiologic reconstruction and processing methods offer a promising solution for dose reduction [3]. Adjunctive ultrasonography can increase cancer detection, especially in women at an elevated risk of breast cancer, but an increased recall rate and reduced specificity are disadvantages [4]. Nevertheless, in our practice, breast ultrasound is almost routinely added to mammography.

Using MRI routinely in BCS patients is controversial, but an annual screening MRI performed during the second week of the menstrual cycle for premenopausal women is recommended in increased-risk groups [5]. Preoperative MRI of patients who underwent BCS (and radiotherapy afterwards) revealed multifocal/multicentric cancer in 16% of cases; however, the locoregional recurrence (LRR) was <10% in a meta-analysis, which indicated that MRI made no contribution to the survival of patients but increased false positivity, unnecessary biopsies, and mastectomies [6]. However, multivariate analysis from another study showed that multifocal disease detected on preoperative MRI was independently associated with LRR (odds ratio = 11.9) [7]. For this reason, MRI should only be performed in selected cases and when mandatory, and if possible, biopsies should be performed with MRI guidance to enable a histological diagnosis before surgery.

Evaluation of the Other Breast

Patients should also be evaluated carefully for the presence of cancer in the other breast. The incidence of synchronous bilateral breast cancer (<3 months of the first primary) is 1%,

and that of metachronous bilateral breast cancer (>3 months after the first primary) is 7.0% [8]. Ultrasonography and MRI can be useful if suspicious lesions are detected in the physical examination or by mammography.

Histopathological Diagnosis

If there is a suspicion of breast cancer based on history, physical examination, and radiological diagnostic methods, microscopic examination is essential for a definite diagnosis. Preoperative diagnosis aids the planning of the surgical treatment in cooperation with the patient.

Our preferred method for biopsy today is a Tru-Cut (core) biopsy. This method yields adequate material for tissue determination and other required tests (determination of hormonal receptors, etc.). Excisional biopsy for diagnosis is not a preferred method for us because it makes determining surgical borders and performing BCS difficult in the subsequent surgical intervention.

Surgical Procedures for Early-Stage Breast Cancer

1. Mastectomy
2. Breast-conserving surgery (BCS)
3. Skin-sparing mastectomy (explained in another section)
4. Subcutaneous mastectomy (sparing the nipple, areola, and breast skin) (explained in another section)

Mastectomy

History

Mastectomy was first defined and published by William Stewart Halsted and Meyer in the middle of the 1890s as a "radical mastectomy" [9, 10]. This surgical procedure involves en bloc resection of the breast together with the pectoral muscles and all tissues in the axilla. Because the breast skin is broadly excised, a free skin graft is used to close the defect in the thoracic wall. According to the Halsted hypothesis, because breast cancer is a local and regional disease, excision of the breast together with regional lymphatics provides a definitive treatment of the disease. At that time, although the 3-year local/regional recurrence and survival rates were >50% and approximately 20%, respectively, Halsted described these rates as 6% and 40% in his article published in 1907 [11]. These improvements in survival rates and local recurrence led to the performance of Halsted radical mastectomies for nearly a decade for the treatment of breast cancer [12, 13]. This surgical procedure has serious complications, such as thorax deformity, lymphedema, and motor and sensory loss. The addition of radiotherapy to radical mastectomy increases the complications and can also lead to brachial plexopathy (Fig. 4.1). Today, radical mastectomies for the surgical treatment of early-stage breast cancer are not performed. In cases when mastectomies are necessary, modified radical or simple mastectomies that spare the pectoral muscles or BCS in appropriate patients are performed [13].

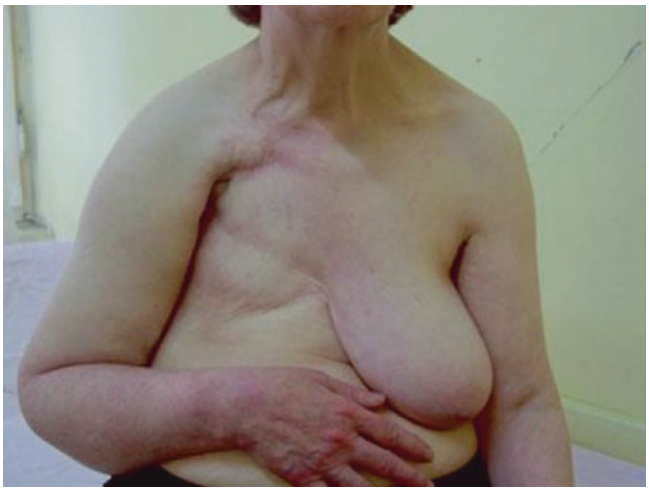

Fig. 4.1 Right arm edema and brachial plexopathy in a patient with pT1N0M0 who underwent radical mastectomy and radiotherapy 35 years ago

Although radical mastectomies provide excellent local regional control, due to the aforementioned high morbidity, modified radical mastectomies evolved in the 1940s. The aim of this surgical procedure was to conserve the major pectoral muscles and, in particular, the long thoracic and thoracodorsal nerves. Patey and Dyson defined a surgical procedure preserving the major pectoral muscle but involving axillary dissection together with the minor muscle [14]. This procedure also helped preserve the medial and lateral pectoral nerves. Later, the technique that is accepted today as a modified radical mastectomy was defined by Auchincloss [15]. Level I and II axillary dissection were found to be satisfactory in this technique, and the major and minor pectoral muscles were preserved.

Modified Radical Mastectomy

Definition

Modified radical mastectomy is defined as the excision of the breast and tumor together with the breast skin (including the nipple areola complex), the pectoral fascia, the lymph nodes in the axilla, and the soft tissue. If the tumor is close to the surface, the incision is adjusted accordingly, and the overlying skin is excised together with the tumor. If the pectoral fascia and/or major pectoral muscle are affected, the tumor-invaded muscle is excised locally to achieve a tumor-free, clean surgical border.

Indications

The generally preferred surgery in early-stage breast cancer is BCS. However, it is not always possible to conserve the breast, and some patients may also choose mastectomy:

1. Patients in whom radiotherapy after BCS is contraindicated: Patients with prior radiation to the thoracic wall, first- or second-trimester pregnancy, collagen disease (scleroderma, active lupus erythematosus, etc.), or ataxia–telangiectasia. Radiotherapy may also not be preferred for social and economic reasons, or patients may refuse radiotherapy. Patients living in a location that is far from the radiotherapy center and patients who do not have sufficient funds for radiotherapy and its complications may also prefer mastectomy.
2. Patient desire: Patients generally accept the surgical treatment suggested by a doctor whom they trust. However, some patients prefer mastectomy to remove a breast to avoid radiotherapy or to complete the treatment in a short time. This desire is more commonly observed in patients who are old and calm and have low educational and economic statuses.
3. Presence of a multicentric tumor or diffuse ductal carcinoma in situ (DCIS) together with an invasive tumor: If there is cancer in more than one quadrant of the breast (multicentricity), BCS may not be possible. In addition, even if the invasive tumor is small in size, the presence of diffuse microcalcifications (DCIS) in its environment requires mastectomy. If the surgical margin is found to be positive and the positivity remains in the recurrent excisions, mastectomy should be performed.
4. Inappropriate tumor-to-breast volume ratio: If the breast is small, conserving the breast can be difficult even if the tumor is small. The cosmetic result after lumpectomy may not be acceptable by the patient or the surgeon. If the breast is very large or hanging loose, application of radiotherapy to the breast after lumpectomy can be difficult. Therefore, it is very important that breast cancer patients are discussed among all specialist physicians (breast surgeon, medical oncologist, radiation oncologist, etc.) and that the treatment plan is prepared accordingly.
5. Patients who have previously undergone BCS with a diagnosis of breast cancer and who have recurrent cancer in the same breast: In patients who have local recurrence in the same breast after BCS, the suggested standard treatment is mastectomy. If axillary dissection was previously performed and there is no axillary recurrence at the time of diagnosis, there is no need for an axillary intervention. Performing sentinel lymph node biopsy (SLNB) in these patients is controversial.
6. Prophylactic mastectomy: For women who are positive for BRCA1 or BRCA2 genes or who are in a high-risk group and desire mastectomy, prophylactic mastectomy can be performed. This topic is explained in a different section.

Prophylactic Antibiotic Administration

Mastectomy incisions are classified as clean wounds because they are located remotely from systems that have a high contamination risk, such as the gastrointestinal, genitourinary, and respiratory systems. Even so, the wound infection rates after modified radical mastectomy are between 2% and 15% [16]. Although Tejirian et al. recommend routine use of antibiotic prophylaxis for breast operations in their meta-analysis [17], the study of Cabaluna et al., alone and when meta-analyzed with data from studies in similar surgical populations, does not support the use of antibiotic prophylaxis in modified radical mastectomy (MRM) [18]. On the other hand, a randomized controlled trial reports that antibiotic prophylaxis significantly decreased surgical site infection incidence after elective breast surgery and was shown to be cost-effective in obese breast cancer patients [19]. For this reason, breast surgeons favor the selective use of preoperative single-dose (i.v.) cephalosporin or ampicillin–sulbactam, which has anti-staphylococcal activity. Single-dose prophylactic antibiotic administration decreases wound infections and, consequently, decreases prolonged wound healing and reduces the risk of delayed chemotherapy. In patients with high infection rates (diabetics, immunosuppressive drug users, reconstruction with expanders or implants, etc.), broader spectrum antibiotics may be used for longer durations. However, other factors, such as increases in cost due to antibiotics, allergic reactions, and increases in bacterial resistance, should also be considered [20].

Surgical Techniques

Today, mastectomies in patients with positive axilla are performed as modified radical mastectomies and include the breast, pectoral fascia, axillary lymph nodes, and soft tissue. In patients with clinically negative axilla, sentinel lymph node biopsy should be performed primarily, and if there is no tumor, axillary dissection is not required. In mastectomies, the surgical borders are formed by the clavicle above, the upper insertion point of the anterior and posterior sheaths of the rectus muscle below, the sternum medially, and the latissimus dorsi muscle laterally.

Incision

In mastectomies, an elliptic Stewart incision is preferred as a standard procedure (Fig. 4.2). Making this incision in a mild oblique way is regarded as a modified Stewart incision, and it extends from the medial side of the sternum to the latissimus dorsi muscle. Some surgeons prefer Orr or modified Orr incisions. If early reconstruction is not performed, the skin should not be left loose. Leaving too much skin increases the risk of ischemia and necrosis, causes an irregular appearance on the thoracic wall, and makes late reconstruction difficult. The postmastectomy breast cancer recurrence rate may also be increased. For the perfect alignment of skin flaps after

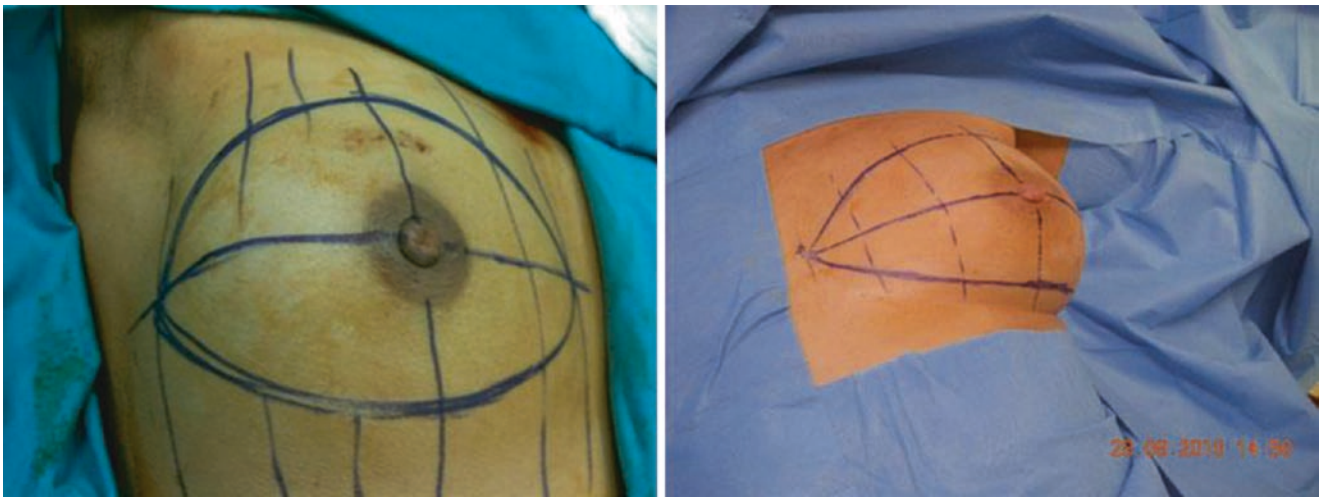

Fig. 4.2 Examples of transverse mastectomy incision (Stewart incision)

Table 4.1 Comparison of local recurrence and overall survival rate of patients who had breast-conserving surgery (BCS) and mastectomy and were followed up for 76 months (İstanbul Faculty of Medicine, The Breast Unit)

Stages of breast cancer	Number of patients	Follow-up time (months)	Tumor diameter (cm)	Surgical margin for BCS (mm)	RT boost	Local recurrence rate		Overall survival rate (%)	
						BCS (%)	Mastectomy (%)	BCS	Mastectomy
Stage I	279 (37%)	76	≤2 cm	2 mm	Yes	6	5	91	91
Stage IIA	243 (38%)	76	2–5 cm	2 mm	Yes	6	5	89	89
Stage IIB	110 (18%)	76	2–5 cm	2 mm	Yes	6	4	82	86
Total	632 (100%)	76	<5 cm	2 mm	Yes	6	4	86	85

Modified from Karanlik et al. [24]

mastectomy, lines that are perpendicular to the incision are drawn with a pen. In addition, a Y-shaped closure with removal of excessive skin can be used to reorient the lateral aspect of the incision to avoid dog ear deformity, especially in obese or large-breasted patients [21].

Dissection

The aim of a mastectomy is to remove as much of the breast tissue as possible such that no breast tissue is visibly left subcutaneously, which minimizes the tumor recurrence rate on the mastectomized side. A retrospective clinical study led by Hartmann et al. at the Mayo Clinic from 1963 to 1990 that included women who were in a high-risk group based on a positive family history and the Gail model and who underwent bilateral prophylactic mastectomy (BPM) revealed that BPM decreased breast cancer risk by 90% in these women [22]. A study by Rebbeck et al. [23] of BRCA1 and BRCA2 carriers indicated that BPM reduces breast cancer risk by 90%. These results indicate that despite mastectomy, breast cancer recurrence probability cannot be eliminated on the same side. In our study conducted at the Istanbul Faculty of Medicine Breast Unit, the local recurrence rate was 4% after 76 months of surveillance in patients who had a mastectomy with a diagnosis of breast cancer (Table 4.1) [24].

After the incision of the cutaneous and subcutaneous tissue with a surgical blade, the superficial fascia overlying the breast parenchyma is exposed. Dissection should be continued along this cleavage between the thin subcutaneous tissue of the breast and the breast parenchyma. When the superior and inferior flaps are being prepared, the skin and the underlying fat tissue and the vessels nourishing it should be protected to a thickness of approximately 5 mm. Electrocautery or a surgical blade can be used during dissection. The risk of ischemia and necrosis of the skin is slightly higher with electrocauterization. The technical skill and experience of the surgeon play a very important role in preparing a flap. Some surgeons aim to facilitate the dissection and reduce blood loss by injecting a solution of lactated Ringer's, lidocaine, and epinephrine into the subcutaneous tissue. However, it is unclear if this technique yields better results.

Skin flaps should be prepared reaching the clavicle above, inferiorly to the origin of the rectus muscle fascia, medially to the sternum, and laterally to the latissimus dorsi muscle. The whole breast tissue is dissected from the skin in this manner. Subsequently, proceeding laterally from the sternum, the fascia overlying the major pectoral muscle together with the breast tissue is skimmed from the muscle to the

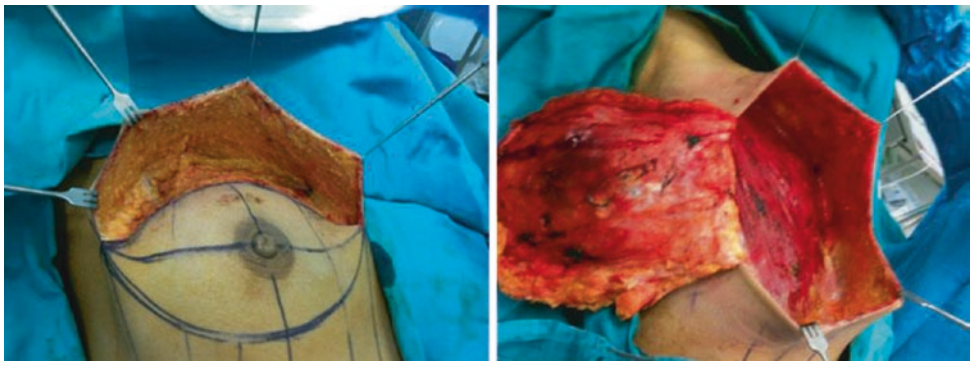

Fig. 4.3 Flap preparation in mastectomy

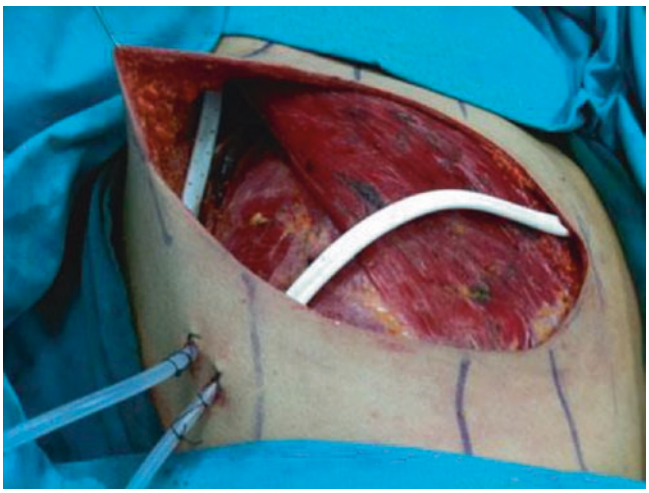

Fig. 4.4 Mastectomy is completed and drains are inserted

latissimus dorsi muscle. If axillary dissection is also performed, axillary tissues between the latissimus dorsi, the major pectoral muscle, and the axillary vein should be removed en bloc together with the breast (Fig. 4.3).

Good hemostasis should be maintained during dissection. In particular, greater caution is required for anticoagulated patients to avoid a hematoma under the flap despite subcutaneous drainage. The use of a surgical blade rather than electrocautery to dissect the pectoral fascia from the muscle helps to reduce necrosis and tissue loss in muscles due to coagulation. However, dissection with a surgical blade causes greater blood loss. In addition, using bipolar electrocautery for hemorrhages over the flaps and muscles minimizes tissue loss.

After the flaps are completely prepared, the breast gland is thoroughly removed, the cavity is rinsed a few times with warm physiological serum, and hemostatic control is repeated. Regardless of axillary dissection, two 10-F Jackson-Pratt drains are placed under the superior and inferior flaps and fixed to the skin with 2-0 silk sutures (Fig. 4.4).

Mastectomy incisions should be closed with subcutaneous and cutaneous sutures. Subcutaneous tissue is sutured with separate sutures using 3-0 absorbable material (polyglactin 910 (Vicryl) or polydioxanone (PDS)). Cutaneous tissue is sutured with continuous intracutaneous sutures using 3-0 or 4-0 fast-absorbing material (Rapide Vicryl or PDS). Any excess skin at the medial or lateral end is excised with a triangular incision.

The closed mastectomy incision is covered vertically with thin Steri-Strips. Surgical gauzes are placed around the drain and over the wound and taped with Hypafix. Because women have more sensitive skin, adhesive plasters should not be left on the skin for too long to avoid the rapid development of erosions and bullous lesions. For this reason, if wound dressings are desired, it can be bandaged in a figure-eight pattern at the end of the day of surgery or the next day.

Complications of Mastectomy

Mastectomy has low mortality and morbidity rates and can be safely performed by a general surgeon. However, as with all surgical procedures, patients should be thoroughly evaluated prior to surgery, careful surgical technique should be applied, good hemostatic control should be maintained, flaps should be prepared free of any breast tissue and to avoid compromising blood flow, and patients should be adequately followed up after surgery. During the preoperative examination, patients should be evaluated for cardiac, respiratory, and other systems and for tolerance to general anesthesia, and medical issues, such as anemia, coagulopathy (particularly long-term anticoagulant usage), diabetes, and hypertension, should be corrected. Immunosuppressant (corticosteroids, antitumor medicine) use should be determined.

After mastectomy, rinsing the surgical site with physiological serum at body temperature is important to reveal any hemorrhages from previously clotted vessels and to remove unnecessary tissue. Bleeding sites on flaps and the major pectoral muscle should preferably be coagulated with bipolar cautery. Compared to monopolar cautery, bipolar cautery burns less tissue and thus reduces skin necrosis and pectoral muscle loss. Good hemostasis prevents the occurrence of hematoma at the surgical site and helps to reduce healing time and the timely initiation of other treatments.

Closed-suction drains (Jackson-Pratt or Blake) should be used to minimize seroma at the surgical site and to prevent hematoma after surgery. These are placed under the flap, conveyed out via a separate incision, and fixed with 2-0 non-absorbable sutures. This incision should be close to the mastectomy incision and, keeping in mind that radiotherapy may be necessary, within the radiotherapy field. Closed-suction drains should be kept in place for 5–10 days. During that time, the catheters should be checked for any clots and fibrin remains and must be cleaned, and drainage should be maintained. Drains can be removed once the drained amount has decreased to 25 ml per 24 h.

After the flaps are covered with a double tissue layer, closed, and adhered with strips, they are dressed with surgical gauze and taped. Tightly dressing the wound and bandaging with compression eliminates seroma-reducing or flap-adhering effects. However, when plasters are left on sensitive skin for too long, they cause erosions and bullous lesions; to keep dressings in place, bandages can be used instead of plaster at the end of the day of surgery or the next day.

We observed that patients generally use the operated extremity very little or sometimes not at all. Patients, who are generally kept in the hospital for 1 day and then discharged, should be advised about the activities they can participate in and their diet both orally and with written instructions at the time of discharge from the hospital. They should be advised that they must use the operated extremity for daily activities and that they should start the arm exercises they performed before the operation as soon as the drains are removed. To restore arm/shoulder movements, they should receive support from physical therapy and rehabilitation polyclinics when necessary.

Wound Infection

The reported wound infection rates after modified radical mastectomy are 2–15% [25]. Infection at the site of incision or in the arm is a cause of serious postoperative morbidity, delaying utilization of the extremity and increasing lymphedema.

Cellulitis is generally responsive to antibiotics. The resulting abscess should be drained early, the wound should be washed, debridement should be performed, and a closed-suction drainage system should be placed again. Antibiotic treatment should be administered according to antibiogram test results. When patient-related adverse factors (uncontrolled diabetes, advanced age, anemia, etc.) are combined with technical problems (flap not well-prepared, necrosis, ischemia, etc.), complications, such as wound infection, necrosis, and abscess, increase. The most common microorganisms causing wound infection are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

Prophylactic antibiotic administration prior to surgery has become a routine procedure. However, some surgeons do not administer antibiotics if the patient is not in a high-risk group. We recommend the administration of a single dose of an anti-staphylococcal antibiotic before mastectomy.

Seroma

The term seroma defines the accumulation of fluid at the surgical site. After mastectomy, the fluid accumulation rate under flaps in the dead space reaches up to 30% despite drainage or after drainage [25]. Broad dissection of the breast disrupts lymphatics, vascular structures, and fatty tissue and causes lymphovascular fluid (transudate) to accumulate in the dead space. The surgical technique performed should aid in the preservation of the vascular nourishment of the flaps and cause less trauma to vascular and lymphatic structures. Seroma can be reduced in this way. In addition, a review of methods reducing the dead space after mastectomy revealed that flap fixation (using sutures or tissue glue) reduces seroma formation [26]. Applying external pressure on the flaps proposed for mechanical fixation did not lead to reduced seroma formation and caused necrosis in the flaps due to pressure [25]. In most cases, careful surgical technique, good hemostasis, and not harvesting flaps larger than needed reduce seroma and thus obviate the necessity for further interventions.

Seroma increases the risk of wound infection, which causes pain and a sensation of fullness at the operation site, delays wound healing, prolongs the hospital stay, and may delay the initiation of chemotherapy. For more than 30 years, the application of closed-suction drainage systems has significantly reduced seroma formation and related complications.

A high body mass index (>30), increased physical activity after the operation, the surgical technique, and improper closed-suction drainage system function are thought to be factors responsible for increasing seroma formation. In a study conducted by Tadych and Donegan [27] in which the amount of drainage was measured with a closed-suction drainage system daily and during the hospital stay, the relationship between the drainage volume and lymphedema formation was investigated. There was no relationship between the total volume drained and patient weight, but a high volume of drainage was directly related to edema in the arm on that side.

Beginning physical activity early after mastectomy is also considered a risk factor for seroma formation. A review of the literature by Shamley et al. revealed that seroma formation was reduced with delayed physical activity [28].

Hemorrhage

Closed-suction drainage systems facilitate the early detection of hemorrhages and decrease hematomas. The reported hemorrhage rates after mastectomy are 1–4% [29]. In hemorrhages that are noticed early, the reactivation of drains by

cleaning and applying dressing to the surgical site with pressure may help stop bleeding. In moderate to severe bleeding, the wound should be opened in the operating room and irrigated, and the bleeding site should be detected and ligated or controlled with suturing. The dead space should then be drained with a closed-suction system. Serious hemorrhages are often due to perforation of branches of the thoracoacromial vessels or the internal mammary artery.

During mastectomy, to prepare the flaps quickly and without bleeding and to reduce postoperative complications, the roles of surgical techniques using monopolar electrocauterization or bipolar electrocauterization, cold blades, hot blades, laser coagulation, and fibrin filling have been investigated [29, 30]. Studies do not indicate that any of these procedures are superior. The aim is to complete the surgery with careful technique and good hemostasis, observe the patient regularly, and prevent hematoma formation.

Pneumothorax

Pneumothorax is a rare complication and is observed more often during radical mastectomy procedures when the major pectoral muscle is removed. Parietal pleura can be torn during the bleeding control of injuries to the intercostal perforating vessels and during dissection. In addition, pneumothorax can occur during the dissection of lymph nodes close to the sternum during internal mammary lymph node biopsy.

When pneumothorax occurs, the torn pleura can be fixed and covered with muscle. Air in the pleural cavity is generally resorbed without intervention. If a serious pneumothorax is observed on the postoperative chest X-ray, a small tube can be placed through the second intercostal space to aspirate the air inside and is then connected to a closed-suction thorax drainage system. The thorax tube is removed once the lung fully expands.

Tissue Necrosis

When subcutaneous vascular structures are not preserved during broad dissection in mastectomy, skin necrosis occurs. Tissue necrosis also develops in uncontrolled seromas and infections. Debridement and wound care are sufficient to manage small necroses.

Current mastectomy techniques seldom require covering the mastectomy space with a free skin graft. However, reconstruction and repair with free pedicled skin grafts may be necessary for necrosis occurring in flaps after mastectomy, advanced-stage breast cancers that do not regress despite chemotherapy, recurrences in the thorax wall, and large breast sarcomas.

Local Recurrence Following Mastectomy

The anatomic sites involved in locoregional recurrence are chest wall muscles, the skin, subcutaneous tissues, and/or ipsilateral regional lymph nodes. Since the 1970s, locoregional control of breast cancer has gradually improved over time. Recently, Keruakous et al. reported 5- and 10-year cumulative incidences of overall LRR after mastectomy (without postmastectomy radiation therapy) in T1-3 pN0 M0 breast cancer of 1.8% and 3%, respectively [31]. Abi-Raad et al. suggested that select patients among T1-2 N0 M0 with multiple risk factors (lymphovascular invasion, tumor size ≥2 cm, close or positive margin, age ≤50, and no systemic therapy) are at higher risk of LRR and may benefit from postmastectomy radiation therapy [32]. Rowell reviewed 22 studies including 18,863 patients. In these studies, 2.5% of mastectomy materials from patients were found to be positive; there was a close surgical border in 8% and pectoral fascia and/or muscle invasion in 7.2% [33]. Some studies defined close surgical borders as 1 mm, some as 2 mm, and others as 4–10 mm.

In this meta-analysis, local recurrence rates in the studies varied between 4% and 30%. The most important risk factor was close surgical borders. The addition of radiotherapy to treatment was found to be imperative for the reduction of local/regional recurrence.

Local/regional recurrences after mastectomy were related to factors such as axillary involvement, the number of positive lymph nodes, extracapsular invasion, hormone receptor positivity, histological grade, tumor diameter, lymphovascular invasion, young age (40 years in some studies, 35 in others), and premenopausal status (Table 4.2) [33–36].

Naturally, one important factor for local/regional recurrence after mastectomy is the experience of the breast surgeon performing the operation. According to "Early Diagnosis, Screening and Treatment Guideline in Breast Cancer" published in the European Union in 2006, breast surgeons should be trained in a "breast unit" in which at least 150 breast cancer patients are treated annually and should perform at least 50

Table 4.2 Local recurrence factors in patients undergoing mastectomy

Local recurrence factors	Relationship with local recurrence		
	Strong (+++)	Fair (++)	Weak (+)
Axilla positivity and the number of nodules	+++		
No systemic treatment		++	
Surgical margin positivity		++	
Close surgical margin (<2 mm)			+
Tumor diameter			+
Age of the patient (<40 or <35)			+
Lymphovascular invasion (+)			+
Extracapsular invasion			+

+++ Relationship consistently reported in literature
++ Relationship frequently reported in literature
+ Relationship occasionally reported in literature

breast cancer operations per year [37]. Surgeons performing less than this number may leave more breast tissue under the flaps, leading to more local recurrence [38].

Breast-Conserving Surgery (BCS)

Definition

BCS is the removal of the tumor (or tumors if multifocal) together with clear/negative surgical margins. This procedure is also called a lumpectomy, broad tumor excision, segmental mastectomy, and tylectomy. After tumor removal, the remaining breast should appear well and acceptable cosmetically.

History

High morbidity due to Halsted's radical mastectomy led surgeons to perform modified radical mastectomies first, preserving the pectoral muscles. Thus, "radical mastectomy," which was first defined in the 1890s and was performed for nearly 100 years, gave way to "modified radical mastectomy" in the 1940s [9–13]. Fischer's hypothesis, which he developed after the results of studies conducted in the 1970s, dictated that breast cancer was a systemic disease and led to surgery to conserve the breast in the treatment of breast cancer [39, 40].

The first prospective randomized clinical trial was conducted in Guy's Hospital (London, UK) and published in 1972 [41]. Because the radiation dose administered to patients in this trial (3800 cGy) was below the standard treatment dosage (6500 cGy), the local recurrence rate was higher in the BCS group.

In the 1970s, BCS was compared to mastectomy in several prospective clinical trials. In the six best known and accepted of these trials and in a meta-analysis of these trials, BCS was shown to yield similar survival rates to mastectomy and had acceptable local recurrence rates and cosmetic and functional results (Table 4.3) [42–48].

Although the results of 20 years of surveillance in the NSABP-B06 and Milan trials showed no significant difference in the mean survival rates in the BCS and mastectomy groups, the local recurrence rates were significantly higher in the BCS group [42, 43]. In the NSABP-B06 trial, the BCS without radiotherapy group had a local recurrence rate of 39.2%, which fell to 14.3% in the BCS + radiotherapy group. This result demonstrated that radiotherapy should be a standard treatment after BCS.

In a study conducted by the EORTC Radiation Oncology Group, in addition to 50 Gy radiation applied to the breast, 16 Gy boost radiation applied to the tumor bed reduced local recurrence from 10.2% to 6.2% [49]. This study together with similar studies indicated the importance of radiotherapy applied to the breast and a boost dose applied to the tumor cavity for reducing local recurrence after BCS [42–49].

The Milan study revealed that cosmetic results of quadrantectomy as BCS were satisfactory in only 60% of patients [43]. Therefore, for patients who have broad tumor excision as BCS and when the cavity is very large, filling the cavity with breast tissue or with latissimus dorsi muscle (oncoplastic surgery) improves the cosmetic appearance.

Patient Selection

To achieve a low local recurrence rate and a good cosmetic appearance in BCS, patients should be carefully selected. After history taking, a careful physical examination, and the necessary radiological examinations, patients should be prepared for BCS. In patients with dense breast texture and who are young, have higher local recurrence probability, and for whom radiotherapy is difficult due to economic or social reasons, mastectomy may be preferred.

For a low local recurrence rate after BCS, multiple tumors should be in the same quadrant (multifocal), surgical borders should be negative, and the appearance of the breast should be cosmetically acceptable after lumpectomy.

Table 4.3 Modern prospective randomized clinical studies comparing breast-conserving surgery and mastectomy

Study	Number of patients	Follow-up time (years)	Tumor diameter (cm)	BCS surgical margin	RT boost	Local recurrence rate (%)		Overal Survival rate (%)	
						BCS	Mastectomy	BCS	Mastectomy
NSABP [42]	1851	20	<4	Without tumor	No	14.3	10.2	46.2	47.2
Milan [43]	701	20	<2	Far	Yes	8.8	2.3	41.7	41.2
NCI [44]	247	10	<5	Gross	Yes	18.0	10.0	77	75
EORTC [45]	903	8	<5	1 cm	Yes	15	10	60	64
Danish [46]	859	6	–	Gross	Yes	3	4	79	82
Gustav-Roussy [47]	179	14.5	<2	2 cm	Yes	11.4	11.0	72	65
EBCTCG [48]	3100	10	All	Differs	+/–	5.9	6.2	50.1	48

NSABP National Surgical Adjuvant Breast Project, *NCI* National Cancer Institute, *EORTC* European Organization for Research and Treatment of Cancer, *EBCTCG* Early Breast Cancer Trialists' Collaborative Group

Table 4.4 Breast-conserving surgery (BCS) contraindications

Breast-conserving surgery
Absolute contraindications
Pregnancy (first and second trimesters)
Multicentricity
Microcalcifications with diffuse malignant appearances
Previous radiotherapy to the chest wall
Ongoing surgical margin positivity despite re-excisions
Relative contraindications
Incompliance of breast/tumor diameter
Collagen vascular diseases
Desire of the patient for mastectomy
Impossibility of radiotherapy treatment (economic reasons, distance from centers)

Contraindications for BCS are summarized in Table 4.4. Multicentric cancers (two or more cancers in more than one quadrant), microcalcifications that show a tendency for diffuse pleomorphic cluster formation, a negative surgical border despite re-excisions, first- or second-trimester pregnancy, and prior radiotherapy to the thorax wall (Hodgkin's lymphoma, thymoma, etc.) all render BCS impossible.

Because the presence of collagen vascular disease in the patient (scleroderma, lupus erythematosus, etc.) will cause wound-healing problems due to the application of radiotherapy in this region, care should be taken in these patients. In women who have low breast volume, the diminished breast after lumpectomy may disrupt its appearance cosmetically. Likewise, BCS may be difficult for cosmetic reasons in women who have a large tumor diameter.

Some patients find the breast with the tumor to be at fault, want to eliminate it, and desire mastectomy. In addition, if the patient is living in a location far from the center where radiotherapy will be administered and cannot travel for economic or other reasons, mastectomy is required.

Surgical Technique

The aim of BCS is to completely remove the tumor from the breast, reduce local recurrence, and achieve a cosmetically acceptable appearance. While locoregional control of breast cancer has improved over the last decade, another major advancement occurred in the field of BCS. There is a growing body of evidence for location-specific oncoplastic BCS interventions to maintain good cosmetic results [50, 51]. These promising innovations have even triggered research on more cosmetic excisional biopsies [52].

Surgical treatment of breast cancer not only reduces local recurrence but also improves survival. In a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), BCS and radiotherapy improved survival by 5.3% by the end of a 15-year period [34]. This rate was approximately 4.4% with mastectomy and radiotherapy [34, 53]. Today, new and more effective chemotherapeutic drugs are also used to decrease local recurrence rates by up to 50% [54].

Prophylactic Antibiotic Administration

Incisions in the breast and axilla make clean wounds and are considered to have a low risk of infection. However, studies have shown that the wound infection rates after breast cancer surgery vary between 1% and 15% [55, 56]. This rate is low after lumpectomy (1–5%) but higher after mastectomy (2–17%) and reconstruction (6–15%). For this reason, we recommend the administration of a single dose of a prophylactic antibiotic that is effective against *S. aureus* and *S. epidermidis* (cephalosporin, ampicillin–sulbactam, etc.).

Incision

Generally, circular incisions that are parallel to the areola and in conformity with the natural lines of Langer are preferred in BCS (Fig. 4.5). However, in some situations, a radial incision can be made for tumors localized at 3, 6, or 9 o'clock. Incisions starting from the sulcus of the breast are a cause of poor cosmesis and should not be made (Fig. 4.6). Incisions should be made just over the tumor and should extend 1 cm proximal and 1 cm distal from the tumor for palpable tumors. If the tumor is close to the skin, it should be removed together with the skin. However, cosmetic appearance may deteriorate in this situation. Today, we prefer a circumareolar incision to reach and excise the tumor with clear surgical margins for better cosmetic appearance.

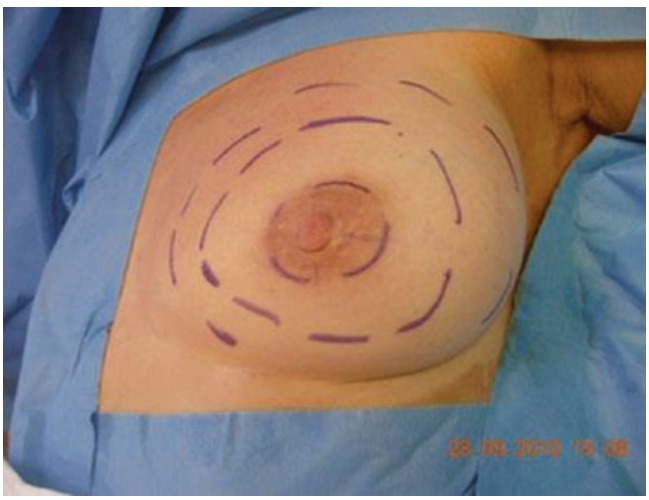

Fig. 4.5 Parallel incisions to the areola for breast-conserving surgery (BCS)

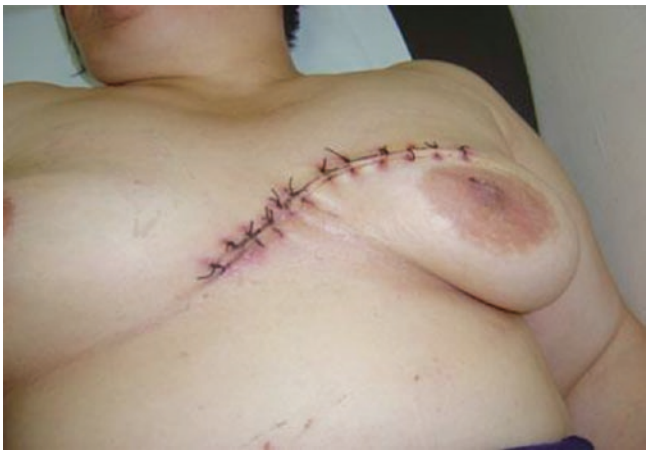

Fig. 4.6 An example of a bad and unacceptable incision in breast-conserving surgery

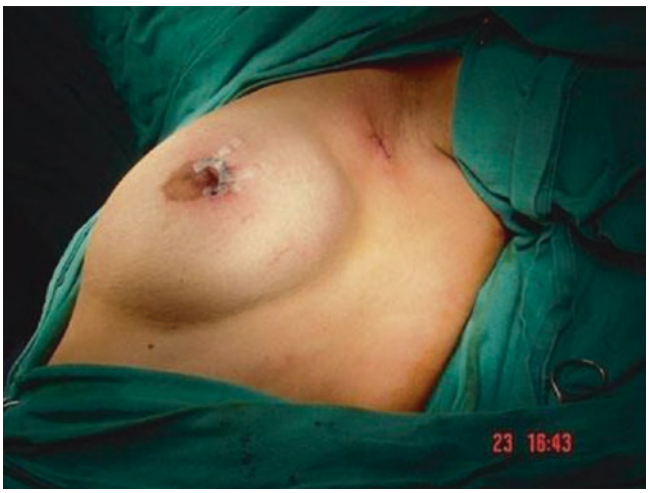

Fig. 4.7 Postoperative view of a patient who had BCS and sentinel lymph node biopsy (SLNB)

To achieve a fine cosmetic result with BCS, for tumors localized in the upper lateral quadrant, separate incisions should be made for the dissection of the tumor and axilla (Fig. 4.7). Incisions that are made radially, including the axilla, could cause increased scar formation and subsequent deformity (Fig. 4.8).

Removal of the Tumor

The tumor should be removed together with the healthy breast tissue around it. Approximately 10 mm macroscopically is sufficient healthy tissue around the tumor. Microscopically, a border of no ink on tumor is generally accepted. The experience of the surgeon is important for identifying healthy tissue around the tumor in palpable lesions and removing the tumor with an adequate border.

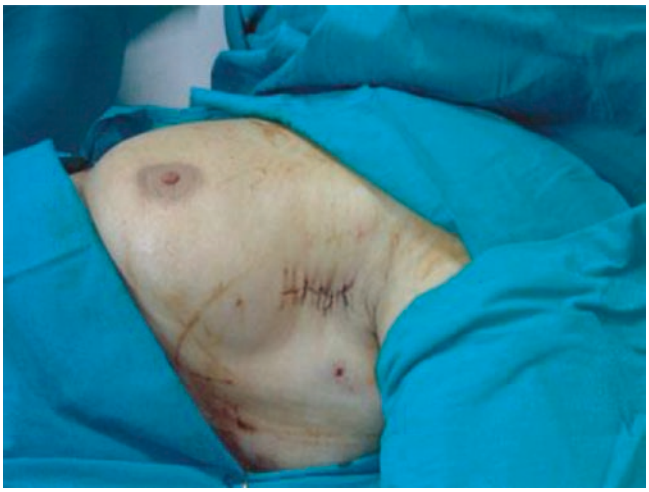

Fig. 4.8 An example of a bad incision in breast-conserving surgery. An incision oblique to the axilla was performed

Morrow et al. investigated 2030 patients who were treated for breast cancer in a population-based study [57]. Mastectomy was performed in 38% of patients, with 9% desiring a mastectomy from the beginning. In 13%, a mastectomy was performed without any effort to perform a re-excision. Re-excision was necessary in 22% of patients who had successful BCS. These results indicate that several factors related to the surgeon, the radiotherapist, and the patient play a role in performing BCS. A survey of "negative borders" was conducted among members of radiation oncology associations in North America and Europe. In North America, 46% of radiation oncologists defined "negative" as tumors cells not in contact with the inked surface, 22% as a 2-mm border, and 15% as ≥5-mm border. Among European radiation oncologists, 28% defined "negative" surgical borders as ink in the border, 9% as 2 mm, and 45% as ≥5 mm [58]. In a survey of 188 surgeons in the USA, 13% found "surgically negative" borders adequate if ink in the border is not in contact with the tumor, 25% if 2 mm or larger, and 55% if >5 mm [59].

The utilization of ultrasonography during surgery also helps to achieve a negative border. In a study conducted by Fine et al., performing lumpectomies in collaboration with intraoperative ultrasonography reduced the excised volume, decreased the length of the incision, and reduced re-excision due to border positivity [60].

In lumpectomies, there is an inverse relationship between the tissue volume excised during lumpectomy and cosmetic appearance, which is more evident in small-sized breasts. However, pathological multifocality and multicentricity rates are higher in tumors that have a diffuse intraductal component and in invasive lobular cancers, and broader excisions are necessary for these tumors.

If a tumor is not close to the overlying skin, the preservation of subcutaneous fat prevents retraction of the skin. In tumors that are close to the skin, tumors should be excised together with the overlying skin.

Surgical Margins in Breast Cancer

The acceptable negative surgical margin width for BC patients undergoing breast-conserving surgery (BCS) for invasive carcinoma is controversial. The Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) published a consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive BC in 2014 [61]. A multidisciplinary panel meta-analyzed the margin width and local recurrence (LR) from a systematic review of 33 studies including 28,162 invasive BC patients to reach consensus [62]. Positive margins (ink on tumor or ductal carcinoma in situ) were associated with a twofold increase in the risk of LR compared with that of negative margins. This increased risk was not related to favorable biology, young age, lobular cancer, extensive intraductal component, endocrine therapy, or a radiation boost. Additionally, negative margins did not significantly decrease the rate of LR compared with that of no ink on tumor. The use of no ink on tumor as a negative margin in invasive cancer was also found to have the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health-care costs.

There is also substantial controversy regarding the clear surgical margin width for ductal carcinoma in situ (DCIS) treated with BCS and radiation therapy. SSO, ASTRO, and American Society of Clinical Oncology (ASCO) organized a multidisciplinary consensus panel on this topic and published in 2016 [63]. The panel used a meta-analysis of margin width and tumor recurrence (TR) from a systematic review of 20 studies including 7883 patients. The results showed that negative margins halved the risk of LR compared that of with positive margins, which were defined as ink on tumor, and a 2-mm margin minimized the risk of LR compared with that of smaller negative margins. However, clear margins did not significantly decrease LR compared with that of 2-mm margins, and negative margins <2 mm alone were not an indication for mastectomy. They concluded that the use of a 2-mm margin in DCIS treated with radiotherapy was associated with low rates of LR and had the potential to decrease the re-excision rates, improve cosmetic outcomes, and decrease health-care costs.

Evaluation of Surgical Margins

Evaluation of surgical margins and sentinel lymph node biopsy intraoperatively by an experienced breast pathologist is essential to reduce histopathological diagnostic discrepancies. Surgical margins should be marked immediately after tumor removal. If different colored inks are used, every border is stained with a different color (Fig. 4.9). At least three borders of lumpectomy material, which is stained with only India ink, are marked with suturing materials of different lengths (Fig. 4.10). Macroscopic (gross) evaluation of the removed specimen is essential for adequate excision of the tumor. Close or positive surgical margins are re-excised and re-evaluated. This procedure is repeated until a negative surgical border is obtained. If a negative surgical margin cannot be achieved, a mastectomy should be performed. Therefore, patients should be informed that the surgical border will be evaluated during the operation and that a mastectomy may be performed if necessary.

In some cases, it can be difficult to evaluate the surgical border; in these patients, the surgeons must wait for the results of the paraffin block, and a re-excision or mastectomy decision is made accordingly. Occasionally, a border that is diagnosed as negative in frozen sections is found positive after the evaluation of paraffin slides, and re-excision or mastectomy is necessary.

In tumors that are distant from the pectoral fascia, there is no need to go deep and remove the pectoral fascia.

After it is certain that the surgical borders are negative in the excised material, the walls of the cavity are marked with four or five metal clips for boost radiotherapy (Fig. 4.11).

Management of the Tumor Cavity

New and modern treatments for BC have increased overall and disease-free survival rates. For these reasons, acceptable and better cosmetic results of BCS have taken on additional significance, and a unique name has been assigned to the collection of these efforts: “oncoplastic breast surgery (OBS).” OBS has generated great excitement over the last two decades and has become an important and unavoidable component of the surgical treatment of breast cancer. Oncoplastic breast procedures should adhere to the best surgical oncologic principles to achieve tumor-free margins with the best principles of plastic surgery to optimize cosmetic outcomes.

Volume Displacement and Replacement Techniques

OBS has been characterized by two fundamental principles: volume displacement and volume replacement.

Volume Displacement Technique

The tumor cavity is filled with local glandular or dermoglandular flaps within the breast, which are mobilized and advanced into the defect. This technique leads to a loss of breast volume, and contralateral surgery is usually required to obtain symmetry. The most commonly used simple oncoplastic techniques utilizing volume displacement are periareolar crescent mastopexy, donut mastopexy (Round block), parallelogram, batwing mastopexy, hemi batwing masto-

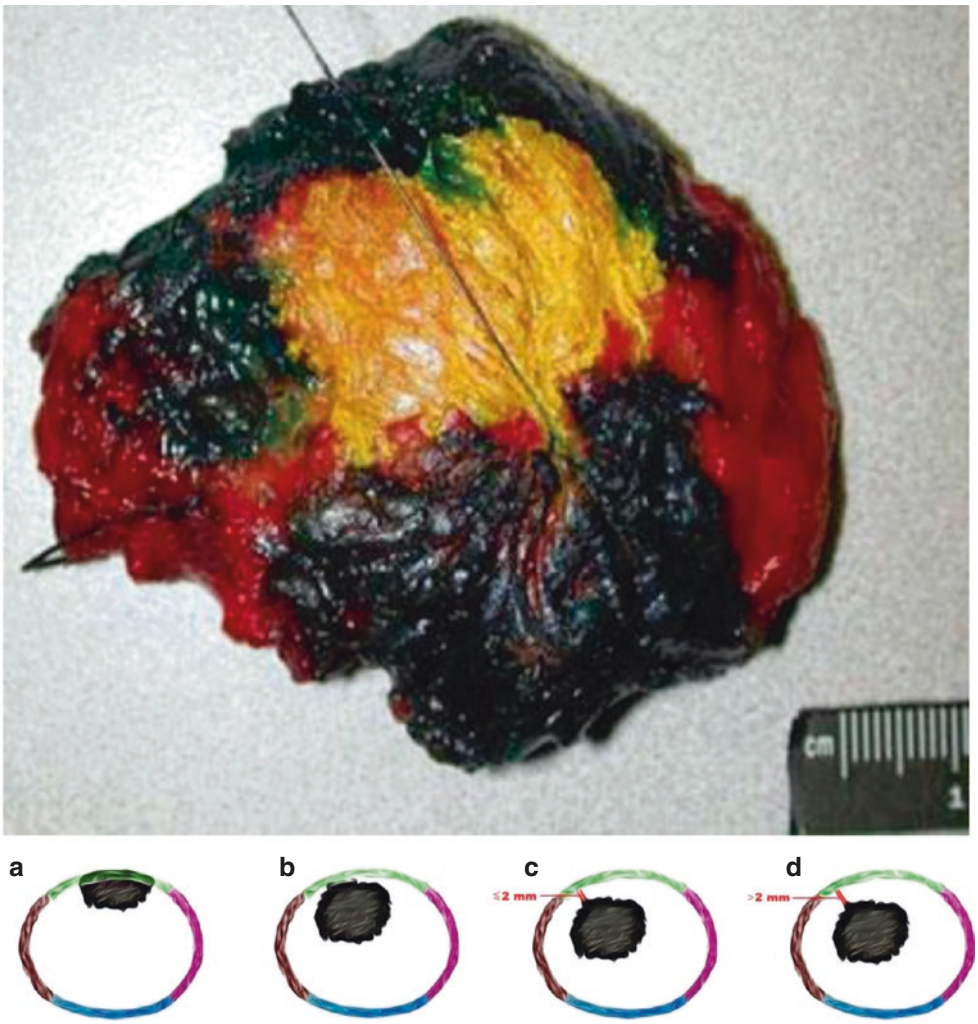

Fig. 4.9 Borders of lumpectomy material dyed with different colors. (**a**) Extensively positive margin. (**b**) Focally positive margin. (**c**) Close margin. (**d**) Negative margin

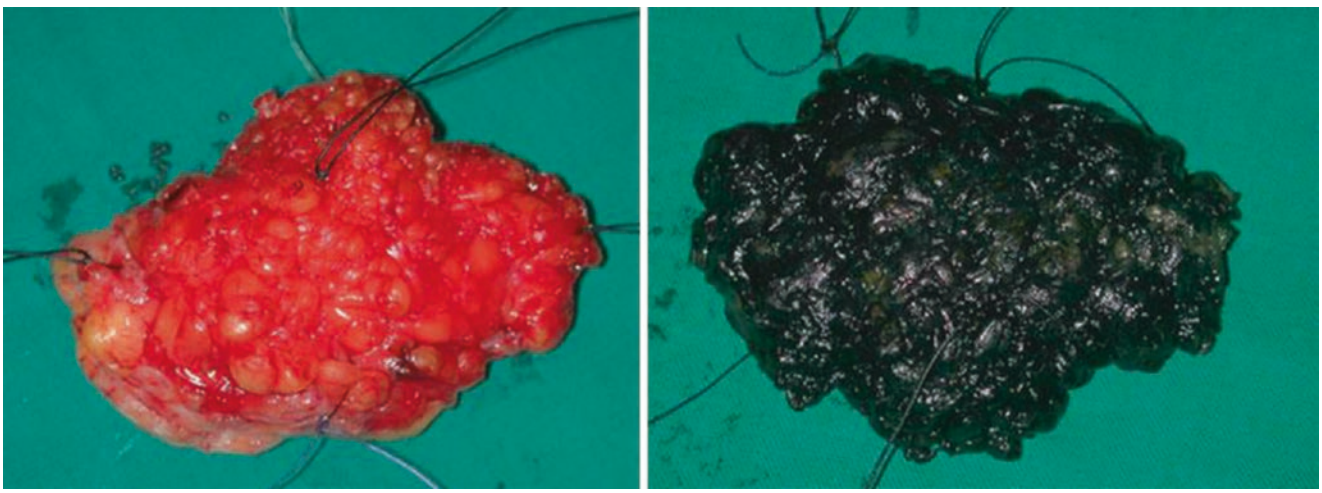

Fig. 4.10 Lumpectomy material marked with different-sized sutures (*left*) and dyed with one color (*right*)

pexy, and radial excision (cosmetic quadrantectomy) [64–66]. Simple oncoplastic techniques utilizing volume displacement are depicted in Fig. 4.12. More advanced techniques (level II oncoplastic techniques) are recommended for those patients for whom a resection of 20–50% is anticipated [50]. There are various quadrant per quadrant algorithms for these techniques [50, 51]. Examples of level II oncoplastic techniques are shown in Fig. 4.13. Volume displacement is also possible for cases with central lesions where removing the nipple areola complex is indicated

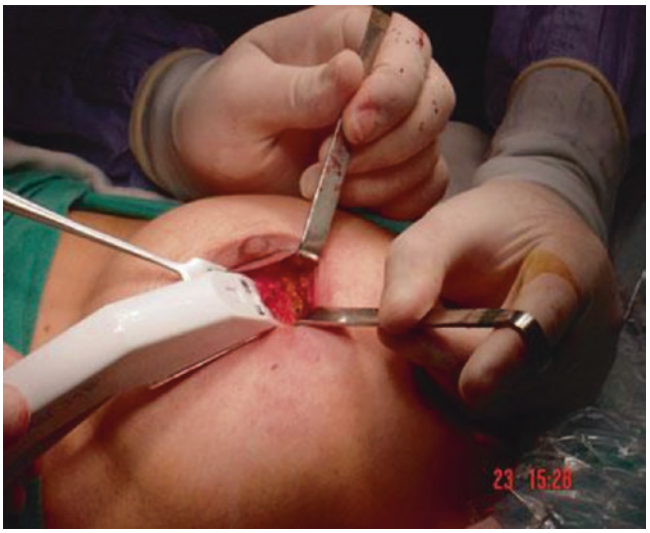

Fig. 4.11 Tumor cavity marked with a metal clip

[67–69]. A summary of techniques suggested for these patients is displayed in Fig. 4.14.

Volume Replacement Technique

If the tumor cavity is too large and the remaining ipsilateral breast tissue that could be employed in the mobilization is not sufficient to fill it, the volume replacement technique is required to conserve the breast. The excision defect is reconstructed by replacing the volume of tissue removed with a similar volume of autologous tissue from an extramammary site. The options include musculocutaneous flaps and perforator flaps that can be transferred on a vascularized pedicle or as a free tissue transfer. The most commonly used flap for immediate reconstruction of the partial mastectomy defect has been the latissimus dorsi musculocutaneous flap. This flap has been effectively used for deformities of the superior, lateral, and inferior aspects of the breasts. Several methods have been

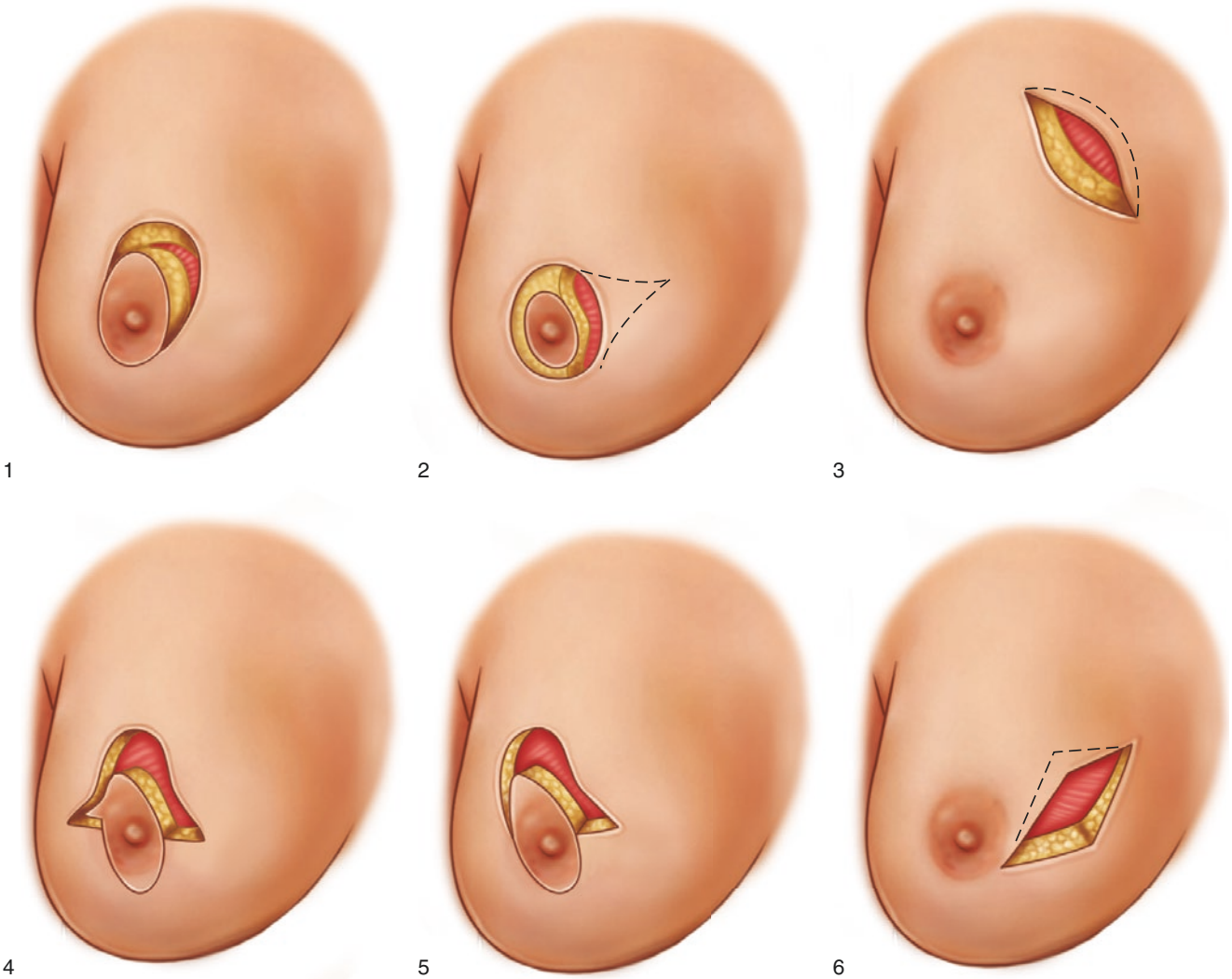

Fig. 4.12 Anterolateral view of left breast (1) periareolar crescent mastopexy, (2) donut mastopexy (Round block), (3) parallelogram, (4) batwing mastopexy, (5) hemi batwing mastopexy, and (6) radial excision, a.k.a. cosmetic quadrantectomy

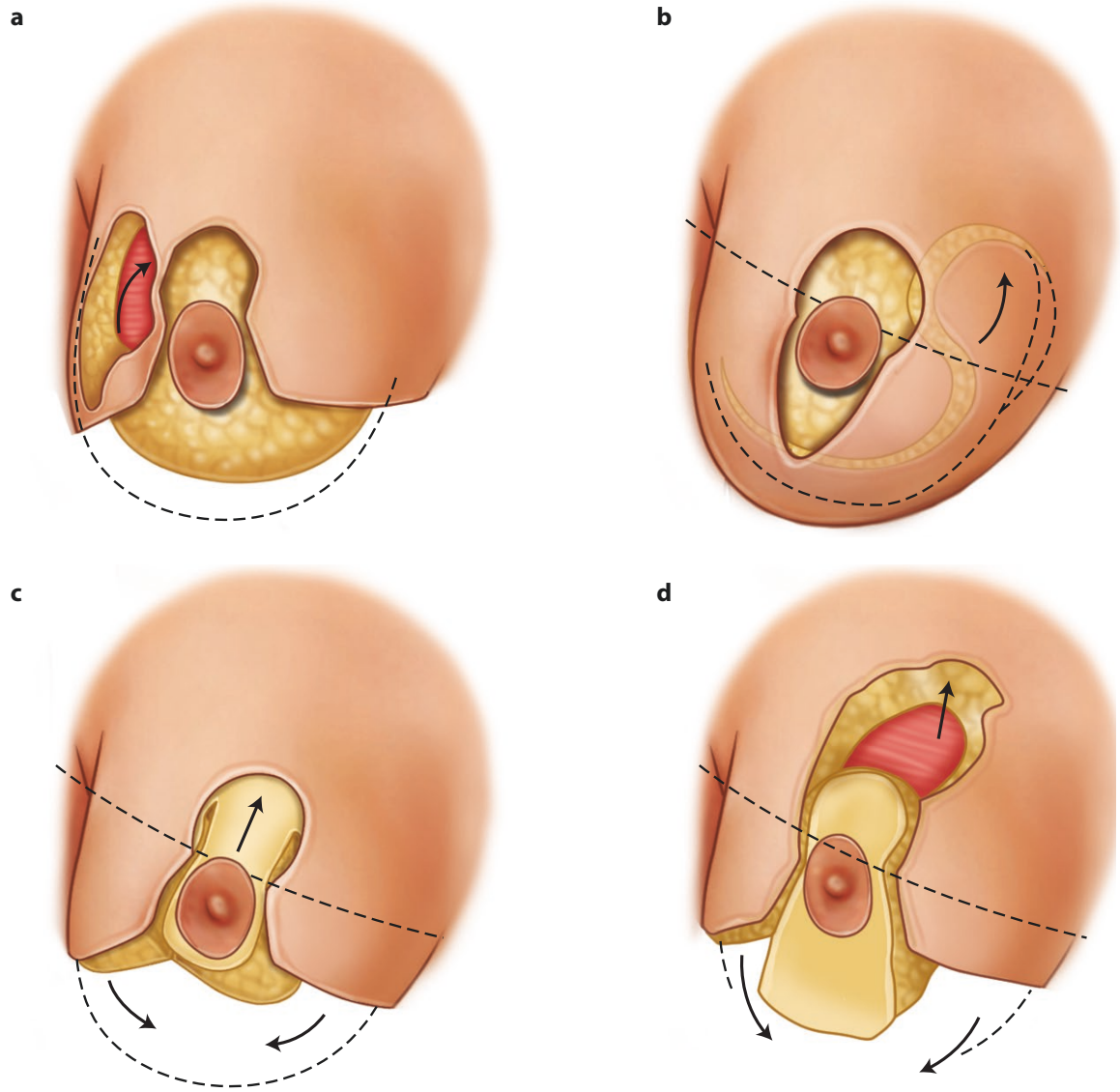

Fig. 4.13 Right breast. (*Upper left*) Reduction mammoplasty with a wide incision and superomedial pedicle displacement for a tumor localized in segment VI. (*Upper right*) Reduction mammoplasty with vertical incision and superolateral pedicle displacement for a tumor localized in segment IX. (*Lower left*) Reduction mammoplasty with a wide incision and superior pedicle displacement for a tumor localized in segment III. (*Upper right*) Reduction mammoplasty with a wide incision and inferior pedicle displacement for a tumor localized in segment VIII

described for harvesting the latissimus dorsi flap. The traditional technique incorporated a posterolateral thoracic incision, whereas the more modern technique utilizes single-incision videoendoscopic surgery for both subcutaneous mastectomy and preparation of the latissimus dorsi muscle [70]. With the videoendoscopic technique, the latissimus dorsi muscle is accessed and totally mobilized through an axillary incision. Another method of harvesting the latissimus dorsi is as a mini-flap. The advantage of the mini-flap is that variable amounts of the latissimus dorsi muscle can be harvested based on the volume requirements of the breast. The flap is generally harvested through an axillary incision that is used for sentinel lymph node biopsy/axillary lymph node dissection as well as the resection of the tumor.

Breast-Conserving Surgery with Mini Latissimus Dorsi Muscle Flap (MLDMF)

The mini latissimus dorsi muscle flap (MLDMF) is a novel approach promising successful cosmetic outcomes after wide excisions for breast cancer surgery. The aim of this technique is to increase the breast-conserving surgery (BCS) rate in challenging patients with large tumors and/or multicentric/multifocal disease. MLDMF has been used as an alternative to subcutaneous mastectomy in our breast center since 2010. This technique provides an opportunity to reconstruct the cavity after segmental mastectomy with a partial muscular flap fed by a thoracodorsal neurovascular bundle [71, 72]. The BCS rate in our center increased from 67% to 78% after implementation of MLDMF in 5 years (2010–

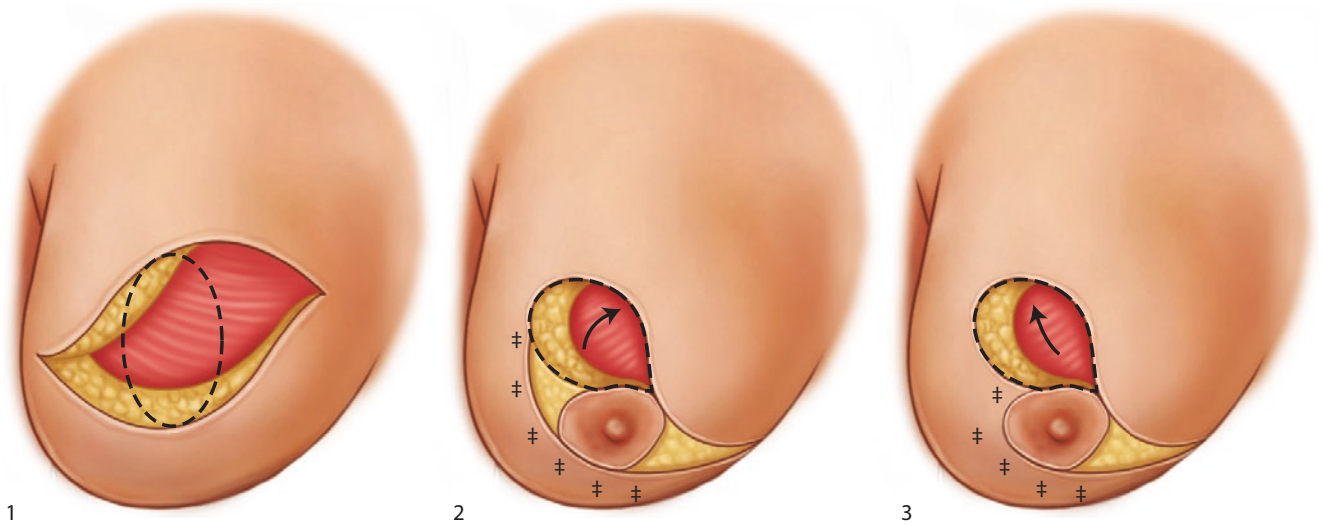

Fig. 4.14 Anterolateral view of the left breast: (1) central lumpectomy, (2) Grisotti flap, (3) Grisotti's E/3 modification. * The full-thickness transection line of the breast parenchyma (medial edge of the dermoglandular pedicle). The breast parenchyma is then displaced in the direction of the arrow

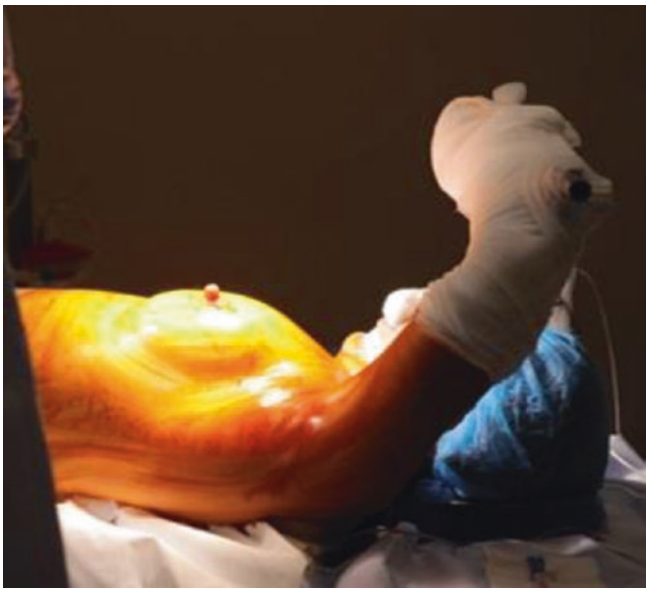

Fig. 4.15 Position of a patient for partial mastectomy with mini latissimus dorsi flap (MLDF)

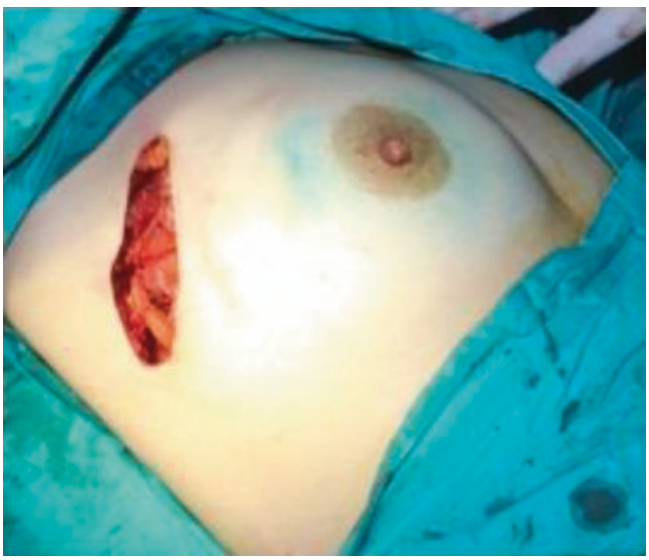

Fig. 4.16 A wide excision is performed through an axillary incision

2015). In our study comparing BCS with and without MLDMF, patients were younger and had larger and more multifocal/multicentric tumors in the MLDMF group [71].

Surgical Technique

Although it was previously described as a two-stage procedure by Dixon et al. [73], we have been using MLDMF to conserve the breast as a one-stage surgery. Following a wide local excision of the tumor with clear margins as reported by the breast pathologist intraoperatively, sentinel lymph node biopsy and/or axillary dissection is performed. If the tumor is localized in the upper outer quadrant of the breast, axillary incision may be sufficient to excise the tumor (Fig. 4.15). The axillary incision is slightly lengthened and deepened over the lateral margin of the latissimus dorsi (LD) muscle while the patient is held in the lateral decubitus position (Fig. 4.16).

The muscle is grasped and retracted from the chest wall to identify the thoracodorsal vessels (Fig. 4.17). The length of muscle required to fill the defect is estimated by measuring from the apex of the axilla to the lower limit of the breast defect. The LD muscle is mobilized from the surrounding structures by using a combination of bipolar scissors and

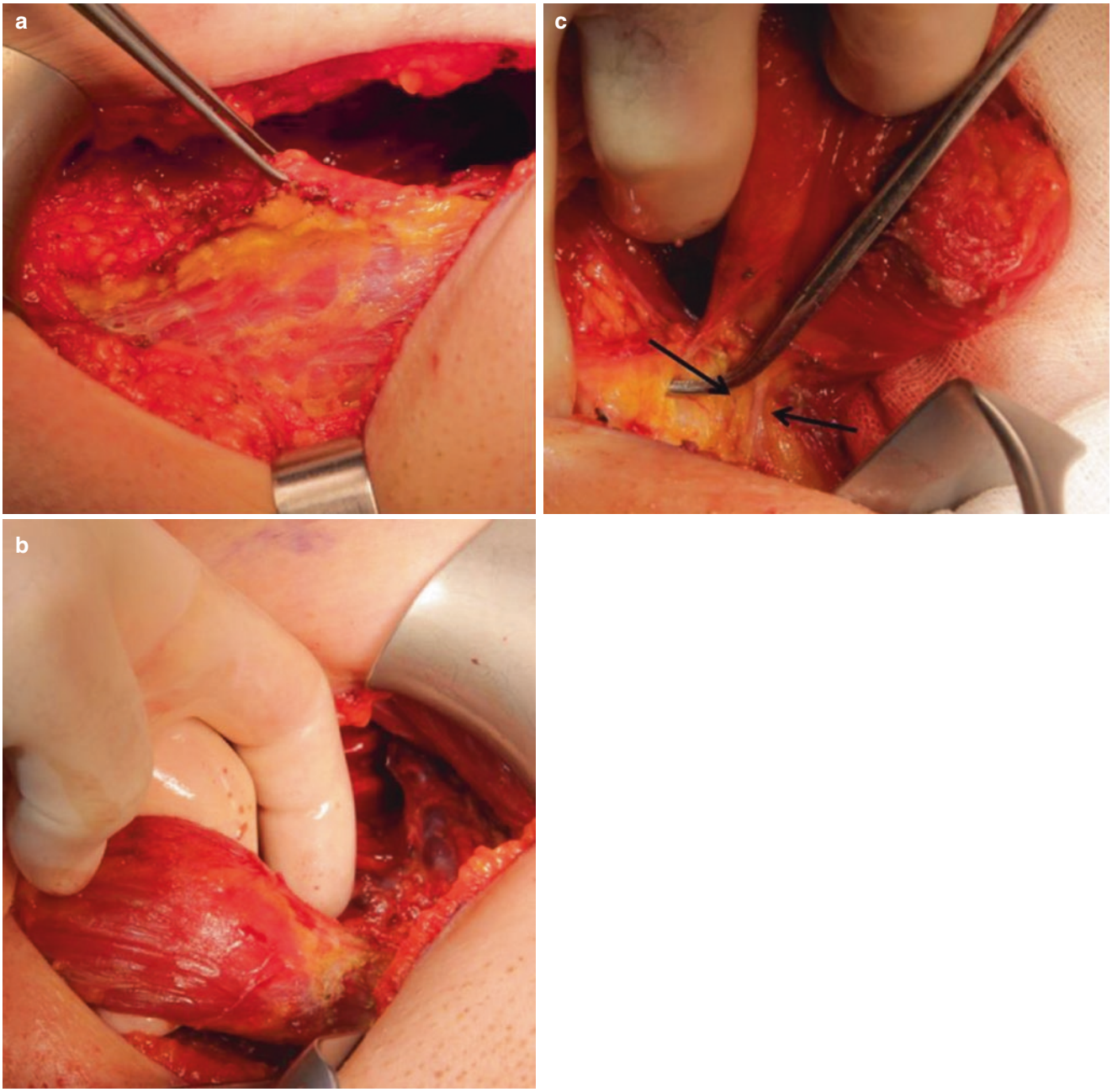

Fig. 4.17 (**a**) Identification of latissimus dorsi muscle. (**b**) Muscle is divided at its insertion on the humerus. (**c**) The thoracodorsal neurovascular bundle should be saved

electrocautery. When a sufficient quantity of muscle has been mobilized, the muscle is divided inferiorly and delivered into the axillary wound (Fig. 4.18). Attention is subsequently turned to the superior part of the muscle, which is divided at its insertion into the humerus, and the LDMF is ready to be transferred into the breast. At this point, the cavity is re-evaluated for any hemorrhaging and is marked with clips. Depending on the site of the wide local excision, a tunnel is created from the axillary wound into the breast defect (Fig. 4.19).

The flap is subsequently passed through the tunnel into the cavity. To remove the tension from the vessels, the flap is secured superolaterally by suturing the tendinous part of the muscle either to the edge of the pectoralis major muscle or to adjacent breast tissue. The muscle is subsequently secured in the breast defect using absorbable sutures to generate a good shape (Fig. 4.20). One suction drain is inserted in the muscle cavity via a separate incision, and the incision is closed with subcutaneous single and intracutaneous continuous absorbable suture materials (Fig. 4.21). Acceptable and good

cosmetic appearance in a patient 6 months after BCS with MLDMF is shown in Fig. 4.22.

Incision Closure

Very careful hemostasis should be applied to the walls of the lumpectomy cavity. For this hemostasis, bipolar cauterization should be used if possible to reduce damage to the breast parenchyma. Serious hematomas can develop if good hemostasis is not maintained, which prolongs wound healing, disrupts the cosmetic appearance, and delays adjuvant treatments.

For good cosmetic appearance, glandular flaps from neighboring breast tissue may be prepared and used to fill the defect in suitable patients (volume displacement). Otherwise,

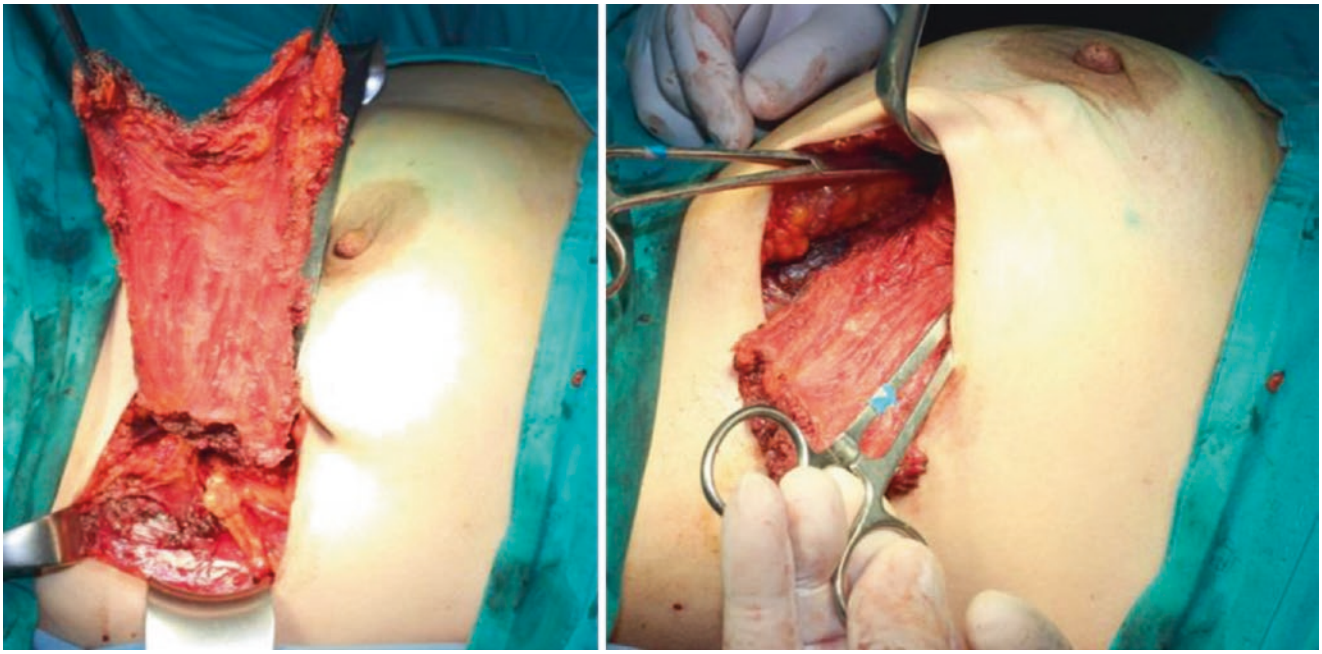

Fig. 4.18 When a sufficient quantity of muscle has been mobilized, the muscle is divided inferiorly and delivered into the axillary wound

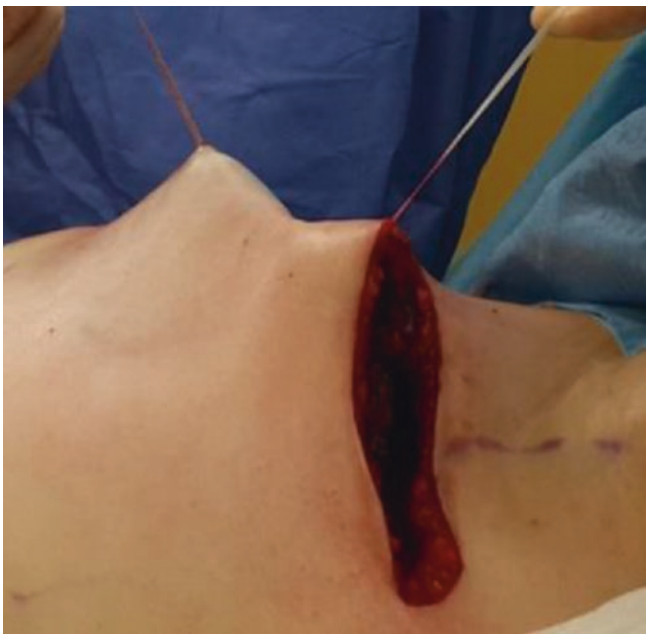

Fig. 4.19 Depending on the site of the wide local excision, a tunnel is created from the axillary wound into the breast defect to circumareolar incision

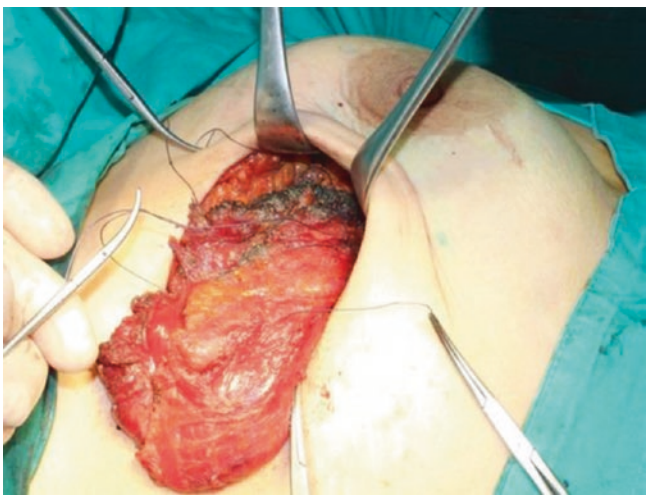

Fig. 4.20 To remove the tension from the vessels, the flap is secured superolaterally by suturing the tendinous part of the muscle either to the edge of the pectoralis major muscle or to adjacent breast tissue

muscular, musculocutaneous flaps may be brought to fill a large tumor cavity to avoid mastectomy. The subcutaneous tissue is sutured with single sutures using absorbable material (3-0–4-0). The skin is sutured with continuous sutures using thinner and absorbable material (3-0, 4-0, or 5-0) and then covered with thin strips.

Re-excision

The finding of positive (ink on tumor) or close margins warrants additional surgery for margin clearance. More than half of re-excision specimens after BCS are found to be free of residual tumor at definitive histology. The adoption of the SSO-ASTRO consensus guidelines has facilitated a dramatic decline in the rates of re-excision from the previous 20–70% range to approximately 13–23% [74] In our study, in 248 patients with initial BCS who underwent one or more re-excisions or mastectomy because of close or positive margins, residual cancer was found in 50% of re-excision(s) or mastectomy specimens. Patients with multifocality, positive axillary lymph nodes, or positive surgical margins were more likely to have residual tumor in re-excision or mastectomy specimens than other patients. We concluded that re-excision or mastectomy could be omitted in patients with close margins with favorable factors such as unifocal tumor or node-negative disease [75].

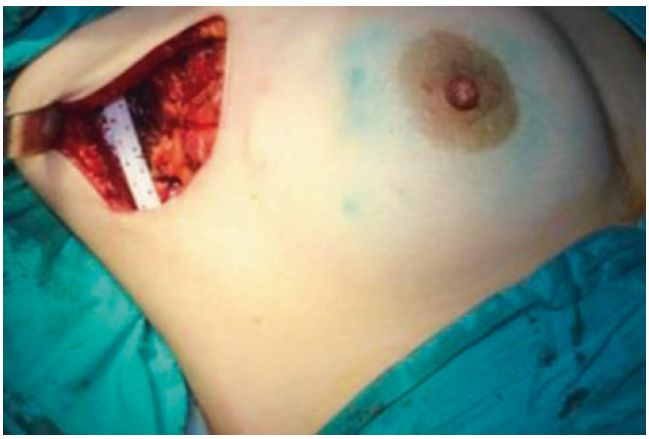

Fig. 4.21 One suction drain is inserted in the muscle cavity via a separate incision, and the incision is closed with subcutaneous single and intracutaneous continuous absorbable suture materials

Quadrantectomy

Quadrantectomy is a method popularized by Veronesi et al. in Milan. In tumors smaller than 2 cm in diameter, the quadrant with the tumor is removed radially, including the surrounding 2–3 cm of tissue, the skin, and the pectoral fascia. The axilla is also removed in tumors that are localized in the upper lateral quadrant. The excised volume was found to be inversely related to local recurrence in the Milan II study [76]. However, as stated previously, because broader excision yields a worse cosmetic appearance, this method is not preferred and not used in surgical practice today (Fig. 4.23).

Local Recurrence Following Breast-Conserving Surgery

The aim of BCS is to completely remove the tumor with negative surgical margins, reduce local recurrence, and achieve an acceptable cosmetic result. As mentioned earlier in the mastectomy section, for a successful result, breast surgery should be performed by a breast surgeon and breast pathologist. The patient should be discussed with other breast specialists, such as the radiologist, pathologist, radiation oncologist, and medical oncologist in a "weekly tumor council," and the patient's suitability for BCS should be determined. The pathologist should evaluate the excised material together with the surgeon, and re-excisions should

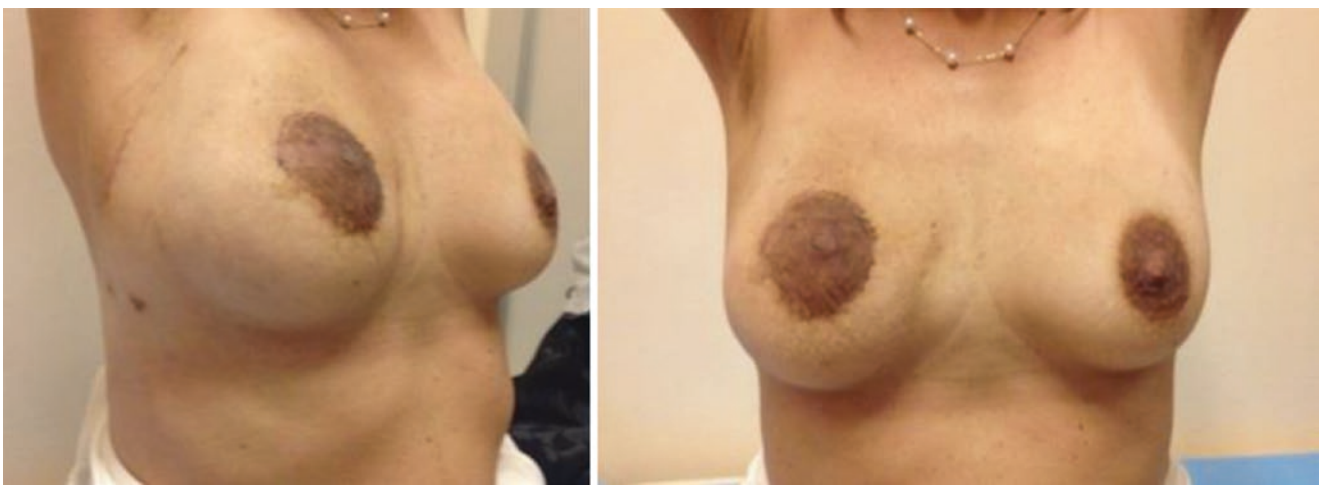

Fig. 4.22 Acceptable and good cosmetic appearance in a patient 6 months after BCS with MLDMF and radiation therapy

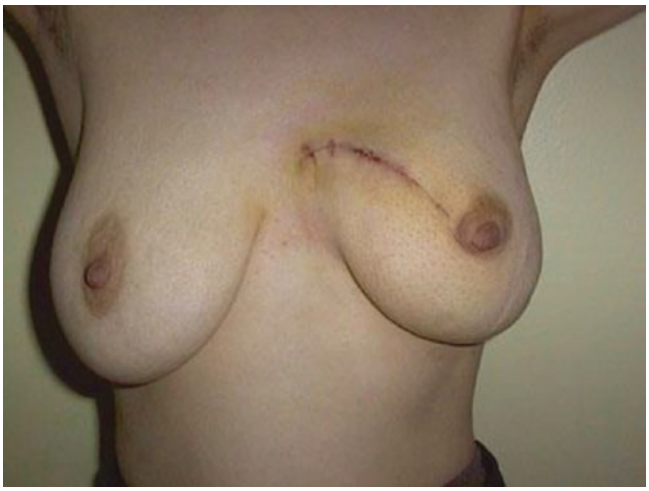

Fig. 4.23 Patient who underwent a quadrantectomy for a localized tumor in the left breast upper inner quadrant (poor cosmetic result)

Table 4.5 Risk factors in patients who undergo breast-conserving surgery

Breast-conserving surgery (BCS)			
	Relationship with local recurrence		
Risk factors	Strong (+++)	Fair (+++)	Weak (+++)
Surgical margin positivity	+++		
Age of the patient (<40 or < 35)		++	
No systemic treatment		++	
Close surgical margin (<2 mm)			+
Lymphovascular invasion (+)			+
Axilla positivity			+

+++ Relationship consistently reported in the literature
++ Relationship frequently reported in the literature
+ Relationship occasionally reported in the literature

be made when necessary. If the surgeon cannot ensure these conditions, he/she should not perform BCS.

To reduce local recurrence after BCS, apart from the experience of the surgeon, the patient should be evaluated carefully by physical examination and radiology prior to surgery, and the size and localization of the tumor and its multifocality/multicentricity should be determined. The indications should not be forced according to the patient's desire.

Available imaging techniques detect a positive surgical border in 20–40% of BCS cases. Risk factors for a positive surgical border are related to tumor biology and patient-related factors. In a meta-analysis conducted by Pleijhuis et al., LRR following BCS was 6–17% [77]. In this study, close or positive surgical margins, tumor size, multifocal tumors, axilla positivity, excisional biopsy for diagnosis (compared with Tru-Cut and fine-needle aspiration biopsies), young patient age (<40 years or <35 years), diffuse intraductal component positivity, lobular histological type, presence of microcalcifications on mammography, and estrogen receptor negativity were related to local recurrence (Table 4.5). Recently, Keruakous et al. reported the 5- and 10-year cumulative incidence of overall LRR after BCS and radiation therapy in T1-3 pN0 M0 breast cancer as 2.4% and 5%, respectively [31]. In addition, Clarke et al. performed a meta-analysis of 78 randomized clinical trials including a total of 42,000 women with breast cancer to analyze the 15-year incidence of LRR and survival; they have found that for every 4 local recurrences prevented, 1 death could be reduced and concluded that the avoidance of local recurrence after BCS and after mastectomy was of comparable relevance to 15-year breast cancer mortality [78].

From the perspective of oncoplastic surgery, there is a paucity of prospective research. However, Lorenzi et al. reported a retrospective study comparing mastectomy and oncoplastic surgery in patients with similar tumor characteristics and showed that the 10-year overall survival and disease-free survival of patients with invasive pT2 tumors treated with the oncoplastic method were similar to those of mastectomy patients [79].

Follow-Up of Patients After Breast-Conserving Surgery

Following BCS, there is an approximately 1–2% risk of cancer development in the treated breast and contralateral breast [80]. Among local recurrences, 75% are observed within 2 years and 95% are observed within 5 years. For this reason, follow-up of breast cancer patients is performed every 3 months during the first 3 years, every 6 months from 3 to 5 years, and annually after the fifth year with physical examination and necessary tests. The recent guidelines published by ASCO did not modify the current approach to follow-up after breast cancer treatment [81].

In patients who have had breast-conserving surgery and radiotherapy, mammography of the treated breast is performed 6 months after radiotherapy. The patient is later followed up with annual mammographies. Scar formation at the site of tumoral excision and its opacity in

X-ray film can make evaluation of this area difficult; Doppler ultrasonography may be helpful. However, gadolinium-contrasted MR imaging has proven to be very helpful in suspected cases for differential diagnosis. Although there is reduced contrast in scar tissue, there is increased vascularization together with increased contrast in recurrent tumoral tissue. If there is a suspicion of recurrence in radiological examinations, this mass should be re-evaluated and biopsied.

Long-Term Complications of Breast-Conserving Treatment

The complications occurring in longer than 5-year surveillance of breast-conserving surgery and radiotherapy, which is the standard treatment for early-stage breast cancer, were edema in the arm, fibrosis in breast skin, limitations in shoulder movements, radiation pneumonia, neuropathy, fat necrosis, and costal fracture, in order of decreasing frequency. In 294 patients who had breast-conserving treatment and were followed up for a mean of 84 months at MD Anderson Cancer Center, the rate of grade 2 or higher complications was 9.9% [82]. Of the 29 patients who had complications, the most common complications were edema of the arm in 13 patients (Fig. 4.13) and fibrosis of the breast skin in 12 patients. Severe fibrosis in the breast causes deformity in the breast (Fig. 4.14). Elderly patients represent the most affected subpopulation of breast cancer survivors in terms of complications. In a study by de Glas NA et al., the odds ratio of postoperative morbidity was higher in older patients (OR 1.85, 95% confidence interval (CI) 1.37–2.50, $p = 0.001$) [83] (Figs. 4.24 and 4.25).

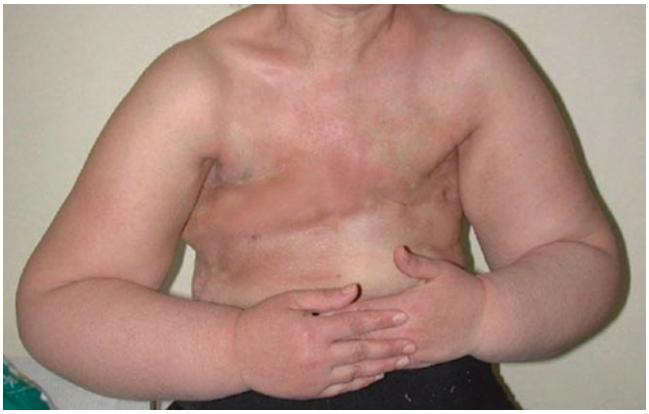

Fig. 4.24 Bilateral arm edema in a patient with breast cancer

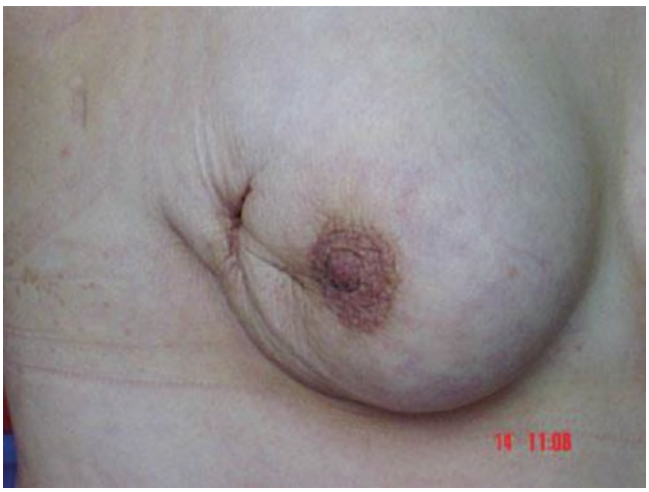

Fig. 4.25 A wider excision, radiotherapy, and fibrosis cause a worse cosmetic outcome

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Evaluation of Axillary Nodes

5

Mahmut Müslümanoğlu

Introduction

Recent studies have demonstrated that the biological characteristics of tumors are more important in determining treatment plans and prognosis than other factors, such as tumor diameter and axillary involvement. Clinical staging is still used to determine the tumor load. Tumor diameter and axillary involvement were used for a long time, and it is difficult for clinicians to abandon these customs. Consequently, tumor diameter and axillary involvement are still considered important major prognostic factors for predicting survival and selecting adjuvant treatment. Although axillary evaluation (sentinel lymph node (SLN), axillary lymph node dissection (ALND)) does not have a profound effect on overall survival (OS), the removal of metastatic lymph nodes from the axilla may contribute to locoregional control and improve quality of life. In the past, axillary staging with ALND was used in clinically node-negative early-stage breast cancer patients; however, this method carries the risk of some arm and shoulder morbidity without any survival benefit. SLN biopsy (SLNB) is equivalent to ALND in clinically node-negative patients in terms of staging, accuracy, disease-free survival (DFS), and OS. Consequently, ALND is not currently advised for patients able to undergo SLNB. SLNB examines the first lymph nodes because the lymphatics of the breast drain to these lymph nodes, which therefore are the site most likely to be reached by tumor cells. If there is no cancer metastasis in the SLN, the other lymph nodes are considered clear (not containing cancer cells); thus, the ALND technique has been abandoned.

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Lymphatic Drainage of the Breast

The lymphatics of the breast comprise interconnected superficial and deep lymphatic vessels. The sub-dermal plexus in the retro areolar space, which is called *Sappey's plexus*, drains the lymphatics of the areola and nipple. The lymphatics of the interlobular connective tissue of the breast and the lymphatics of the walls of the lactiferous channels also drain to this plexus. Efferent lymphatic channels leaving this plexus trace along the lateral border of the major pectoral muscle, penetrate the clavipectoral fascia, and enter the axilla. Axillary lymph nodes collect nearly 75% of the lymphatic drainage of the breast. The remaining lymphatics drain into the internal mammary (parasternal) lymph nodes (IMLNs) accompanying perforated branches of the internal mammary artery; this group generally receives drainage from the medial part of the breast.

Sentinel Lymph Node Biopsy

Sentinel means "sentry," and the SLN is the first lymph node at which cancer cells arrive via lymphatic channels starting from the primary tumor; multiple SLNs may exist. Because these lymph nodes are located on the lymphatic drainage course in breast cancer, they contain cancer cells when lymphatic metastasis has occurred. If metastasis is not detected in the pathological examination of the removed SLNs, the axilla is considered clear, and ALND is not performed.

Radioactive colloid and/or blue dye can be used to detect the SLN. Recently, iron oxide nanoparticles and indocyanine green have been developed for SLNB using the same technique. SLNs that are identified by scintigraphic imaging in the preoperative phase can be detected intraoperatively using a gamma probe and/or by injecting blue dye into the breast tissue; the dyed channel and lymph node can then be detected and removed surgically. There are different practices regarding the choice of agents used (blue dye, radioactive substance,

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or both) and location of injection (periareolar, subareolar, peritumoral). Extra-axillary lymph node (internal mammary group) excision is advised if it is identified as the first draining site by lymphoscintigraphy.

Indications for SLNB

SLNB has been accepted as a standard treatment approach in all clinically node-negative (with physical examination and imaging techniques) early-stage (Fig. 5.1) breast cancer cases, regardless of tumor size (uni- or multiple) and location (central, inner, or outer part of the breast).

Contraindications for SLNB

SLNB is contraindicated whenever a metastatic lymph node is clinically identified in the axilla. This increases the false-negative rate. Diffuse blockage of lymphatic channels in locally advanced breast cancers (LABC)manifesting, as inflammatory breast cancer and dermal edema are also contraindications for SLNB.

Approximately 40% of node-positive patients can be detected with preoperative ultrasonography and needle biopsy [1]. Classically, ALND should be performed directly in this case, or neoadjuvant chemotherapy may be recommended. However, in the near future, axillary tumor load (one or multiple cortical asymmetries or cortical enlargement of the LNs versus multiple gross positive LNs) will become important for deciding further ALND. Whenever any suspicious lymph nodes (hard) (non-SLNs) are palpated in SLNB-negative patients, excision must be considered, especially for those patients in whom core biopsy of the primary tumor was not performed. Core biopsy can cause enlargement and stiffness in some of the axillary nodes, which may cause unnecessary LN excision together with SLNB. If metastasis is detected in SLNs or non-SLNs during

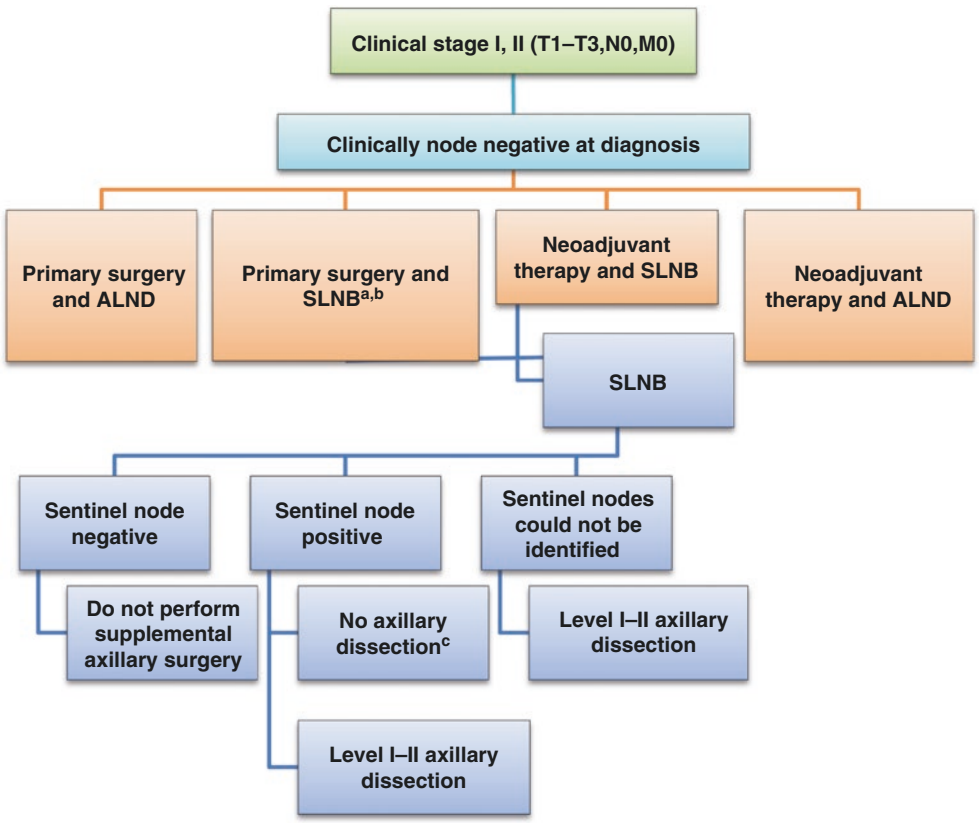

Fig. 5.1 Axillary management of patients with clinical node-negative stage I–II. SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, BCS: breast-conserving surgery. [a]For BCS: In patients with macrometastases in 1–2 sentinel lymph nodes, complete axillary dissection can be safely omitted when "conservative resection with radiotherapy (RT)" is performed. [b]For mastectomy: In patients with macrometastases in 1–2 sentinel lymph nodes, complete axillary dissection must be performed when "no adjuvant RT is planned"; however, in patients for whom RT is planned, no consensus exists for omitting axillary dissection. [c]In patients with T1 or T2 tumors with BCS and 1–2 positive SLNs, if there is no neoadjuvant chemotherapy and whole-breast irradiation is planned, axillary dissection is not needed. Axillary dissection is recommended for SLN-positive patients with triple-negative breast cancer. At least 2–3 SLNs should be assessed in patients receiving neoadjuvant treatment. Consider axillary dissection according to preoperative imaging results. (Neoadjuvant therapy mammography, ultrasonography and positron emission tomography (PET)/CT)

paraffin section examinations, ALND or radiation therapy is decided in a multidisciplinary meeting for each patient according to all factors affecting locoregional recurrence risks and the benefits of adjuvant therapies.

Allergic reactions are observed in approximately 1–3% of cases and can cause serious anaphylactic reactions [2]. Blue dye is not used during pregnancy due to its potentially fatal effects [3]. Some studies have indicated that radioactive substances in low doses can be safely used during pregnancy [4–6].

SLNB in Specific Cases

Ductal Carcinoma In Situ (DCIS)

Metastasis is observed in 1–2% of DCIS cases, suggesting that some DCIS cases can indeed be invasive and that failure to diagnose metastasis is due to a pathologic sampling error [7, 8]. Because invasive foci can be detected in paraffin sections and SLNB is not associated with extensive complications, SLNB should be performed in DCIS patients who have signs on palpation (tumor mass) or a large area of DCIS (calcified areas >2–3 cm) [3]. SLNB is also recommended for patients planning to undergo mastectomy [9].

Multicentric and Multifocal Breast Cancer

In multifocal and multicentric breast cancer cases, SLNB can be safely performed. However, an increase in the false-negative rate has been reported in some studies. Performing the procedure using a radioactive substance may increase the accuracy of SLN [10–13].

SLNB for Patients with Previous Axillary and Breast Surgery

Studies have demonstrated that SLNs can be detected if superficial and deep lymphatic channels are not disrupted via excisional biopsy (particularly together with a large skin incision at the upper lateral quadrant and if the deep pectoral fascia is not affected). However, in patients who have undergone breast-conserving surgery (BCS) and radiotherapy or have undergone ALND, lymphatic flow to the internal mammary glands and contralateral axilla is observed, and these areas are considered the second region for SLNs. The detection of axillary SLNs for the second time in patients who previously underwent SLNB is possible [14–17]. SLNB can be performed after aesthetic interventions and even mastectomy [18–20]. Using tandem methods (blue dye lymphoscintigraphy) during SLNB in patients with previous operations increases the success rate [14].

Male Breast Cancer

Breast cancer in males is rare and constitutes 1% of all breast cancer cases. SLNB should be performed in clinically node-negative male breast cancer to avoid unnecessary ALND. SLNB has the same identification and false-negative rates in males as in females [21–23].

Elderly and Overweight Patients

Although studies report high success rates of SLN detection in elderly and overweight patients, we have observed that this patient group is more problematic in practice; it is particularly difficult to detect SLNs using blue dye alone. The utilization of lymphoscintigraphy along with blue dye in elderly and overweight patients increases the success rate.

Axillary Staging in Patients Treated with Neoadjuvant Chemotherapy

The axilla is clinically negative in approximately 40–50% of patients who are planned to receive neoadjuvant chemotherapy. In cases with a positive axillary node, axillary downstaging occurs at a rate of 30–40% with treatment [24–26]. Research to identify an approach that avoids unnecessary ALND in these two patient groups is ongoing, and the method and timing of axillary staging remain controversial. In clinically axilla-negative cases, SLNB can be performed prior to neoadjuvant chemotherapy, and the need for ALND can be determined after treatment [24].

The opinion that alterations of the breast and lymphatic channels due to chemotherapeutic agents decrease the success rate of SLNB performed after chemotherapy and increase the false-negative rate has essentially been abandoned. In the NSABP-B27 trial, the SLN detection rate after neoadjuvant chemotherapy was 84.8%, and the false-negative rate was 10.6% [27]. Recent trials have shown that the use of radiocolloid alone or together with blue dye significantly enhances accuracy and that SLNB is possible after neoadjuvant chemotherapy [27–29]. ALND should be performed whenever the SLN cannot be detected.

SLNB Technique

Utilization of Radiocolloid and Lymphoscintigraphy

Lymphoscintigraphy is based on the detection of lymph nodes following drainage of the injected radiopharmaceutical agent to the regional lymph nodes via the lymphatic current. Regional lymphatic tracts are mapped using this method and whether an SLN is identified as axillary or extra-axillary using preoperative imaging techniques; during the operation, the SLN is detected by a gamma probe [30].

The most frequently used radiopharmaceuticals are 99mTc-sulfur colloid, 99mTc-nanocolloid, and 99mTc-antimony trisulfide colloid.

Technique During the operation, the tumor mass, including the primary site of injection, is excised first to perform the count correctly and minimize background activity. While the gamma probe is scanned over the skin of the axilla, the site producing the highest activity count is determined, and a small incision is made to enter the axilla. The gamma probe is inserted through the incision, and the lymph node yielding the highest activity count is excised together with its surrounding fat tissue by fine dissection. The activity count of the excised tissue is assessed in a separate location, and after confirming that it is the SLN, the axilla is reevaluated using the probe. If there are any remaining sites producing high activity counts, other SLNs are excised until the activity count is less than 10% of that of the initial node.

Vital Stain

Blue dye injection is another method for visualizing the SLN. The vital stains used for this purpose include patent blue V, isosulfan blue (1% lymphazurin), and methylene blue. Isosulfan blue is the most frequently used agent; however, following injection, reactions ranging from a simple rash to serious anaphylaxis are observed with an incidence ratio of 1:1.1% [31, 32]. Methylene blue is a less expensive alternative that does not bind to plasma proteins and causes fewer anaphylactic reactions. However, methylene blue can cause skin necrosis when intradermally administered, and a dilution ratio of 1:2 is recommended [32]. Studies have yielded similar mapping results using both dyes.

Technique During the operation, approximately 2–5 ml of blue dye is injected by the subareolar routes, and the area is massaged toward the axilla for 2–5 min. Then, the axilla is entered using a 2–3-cm transverse incision just below the axillary hairline. After opening the clavipectoral fascia, the lateral thoracic vein, which extends toward the tail of the breast, is identified. The SLN is generally located where the intercostal nerve crosses this region (axilla, level 1). The blue-stained tract is identified via dissection. When traced either to the axilla or to the breast, a blue-stained lymph node or nodes can be observed. The blue-stained lymph node is removed together with the surrounding thin fat tissue. The results obtained with blue dye are similar to those obtained using radioactive substances [33].

Combination of Vital Stains and Radioisotope Methods

Many studies have reported that blue staining and radiocolloid use are complementary methods that enable the detection of additional SLNs when used together. Moreover, the addition of blue dye to the radiocolloid prevents unnecessary dissections. The SLN detection rate is 95–98% using the radioisotope method [34] and is improved to 95–100% using the combined method. Both methods have high success rates when performed alone, but combined methods should be used in select cases (elderly, overweight, patients who are undergoing SLNB for the second time). We use blue dye (isosulfan blue) in routine practice in our clinic. Lymphoscintigraphy has the advantage of showing extra-axillary drainage.

Determining the Site of Injection

Studies suggest that SLN detection is more successful via the intradermal or subareolar/periareolar routes; however, most studies indicate that the location of injection does not have an effect on SLN detection [33–37]. Each clinic should perform the technique it finds successful. The radioisotope method [32] is improved to 95–100% using the combined method. Both methods have high success rates when performed alone, but combined methods should be used in select cases (elderly, overweight, patients who are undergoing SLNB for the second time). We use blue dye (isosulfan blue) in routine practice in our clinic. Lymphoscintigraphy has the advantage of showing extra-axillary drainage.

Number of SLNs

Frequently, one SLN is removed from the axilla. The false-negative rate drops to 1% when three or more SLNs are removed. However, no benefit is observed when more than four to five SLNs are removed [38–40]. When more than one blue ganglion is detected, and if the lymph channel/channels can be identified and go to a single node, it is sufficient to remove the first 2–3 blue nodes. If channels cannot be identified and the first node is uncertain, it is better to remove all of the blue lymph nodes, which will decrease the false-negative rate.

Behavior of Micrometastases

Detailed SLN examination (multiple sections with several ganglia) has enabled the detection of smaller metastases. Metastases smaller than 0.2 mm are defined as submicro-isolated tumor cells, metastases that are 0.2–2 mm in size are classified as micrometastases, and those >2 mm are macro-metastases. When isolated tumor cells are detected, the axilla is considered negative. When micrometastasis is detected in SLNs, the rate of metastasis in non-SLNs is 10–40%. In macrometastasis, this rate is even higher. Patients with micrometastases in SLNs who did not undergo ALND in BCS and who received radiation therapy were investigated in a randomized trial in Z0011 [41]. This trial followed 446 patients who underwent SLNB and 445 patients who underwent SLNB + ALND. The proportion of patients who had three or more positive LNs was 5% in the SLNB group and 17.6% in the SLNB + ALND group ($p < 0.001$). After an average follow-up of 9.3 years, the 10-year DFS was 80.2%

in the SLNB-alone group and 78.2% in the ALND group. The OS rate was 86.3% in the SLNB-alone group and 83.6% in the ALND group. At 5 years, one nodal recurrence was observed in the SLNB-alone group vs none in the ALND group. Ten-year regional recurrence did not differ significantly between the two groups [41]. According to this study, which was terminated due to difficulties in patient accrual and low recurrence rates, there was no benefit for the patients in the ALND group.

The detection of minimal disease (micrometastasis) in SLNs may be sufficient to initiate adjuvant therapy. In all valid protocols used today, these patients receive adjuvant therapy similar to that used in axilla+ disease (N1a). Therefore, treatment for these patients is not incomplete.

The only difficulty in treating micrometastatic disease is determining the irradiation area for axillary and peripheral lymphatics. The number of involved axillary lymph nodes is a critical component of this decision. Given the availability of effective adjuvant treatment options and the very low axillary recurrence rates (as in ALND), conservative decisions are now made on behalf of the patient when selecting a radiotherapy area; irradiating wide areas, as is done in Nx, appears to be overtreatment.

Internal Mammary Lymph Node Biopsy (IMLNB)

A small percentage (10%) of lymphatics drain into the IMLNs, particularly in centrally and medially located tumors. IMLNB may alter the treatment plan in 0.1% of breast cancer patients and thus is regarded as unnecessary. However, according to the new staging system, only IMLN positivity is classified as N1c; therefore, IMLNB could change the stage for this group of patients. IMLN detection and sampling are necessary to make a decision regarding the adjuvant treatment policy in axilla-negative patients and to determine if IMLNs will be irradiated. For this reason, we recommend performing IMLNB when the axilla is negative in centrally or medially located tumors.

The only method demonstrating lymphatic drainage to this region is lymphoscintigraphy with the utilization of gamma probes. Usually, the second to third intercostal space is explored in selected axilla-negative cases.

Locally Advanced Breast Cancer

In locally advanced breast cancer (LABC), the utilization of axilla-effective systemic treatment modalities (taxane, trastuzumab, etc.) in routine practice has led to increases in complete response rates (breast + axilla) from approximately 10% to 39–70%; for some specific patient groups (ER negative, PR negative, HER2 positive), higher rates of complete response have been achieved. ALND following chemotherapy was the standard axillary approach for LABC, but SLNB is now recommended in patients with axilla positive prior to chemotherapy to obtain a complete clinical response after chemotherapy. According to the results of prospective randomized trials, if two to three lymph nodes are removed using both blue dye and lymphoscintigraphy, the false-negative rate is 14%, and the detection rate is 98% [24–26].

Table 5.1 Nodal pCR after neoadjuvant therapy

	N	Nodal pCR[a]
ACOSOG Z1071 [24]	694	41%
FNAC [25]	145	35%
Mamtani [26]	195	49%

[a]Nodal pCR ranges from 21% in Er+/HER2− to 97% in ER−/HER2+ patients

In cases with a positive axillary node, axillary downstaging occurs at a rate of 30–40% with treatment, and this rate is even higher in triple-negative and Her2-positive patients (Table 5.1) [24, 25, 26, 42]. The identification rate of SLNB may decrease in patients whose axilla become clinically negative after neoadjuvant therapy, and the false-negative rate may increase depending on case selection. The biology of the cancer is also an important factor predicting the response rate. In a prospective study, after neoadjuvant therapy ($n = 195$), nodal pCR rates were overall 49%, "ER+/HER2−" 21%, "ER+/HER2+" 70%, "ER−/HER2+" 97%, and "ER−/HER2−" 47% [26]. The luminal A group has the lowest complete response rate. With neoadjuvant computed tomography (CT), axillary dissection can be avoided in up to 48% of patients [26]. ALND should be performed whenever the SLN cannot be detected (Figs. 5.1 and 5.2).

Examination of the SLN

Paraffin blocks are prepared, and slices are obtained in numbers and thicknesses defined by the laboratory protocol; these sections are then evaluated using hematoxylin and eosin (H&E) and immunohistochemical staining methods. Intraoperative evaluation of the SLN in clinical axilla-negative patients lost its importance following the Z0011 trial based on the equivalent long-term results of ALND versus radiation therapy in axilla 1–2 micro-/macro-positive SLNs [41].

False Negativity

False negativity is defined as the detection of negative SLNs when axillary metastasis is indeed present. SLNs should be detected in at least 85% of patients using the method of choice, and the false-negative rate should be less than 5% [10]. Use of the blue dye and radiocolloid techniques in

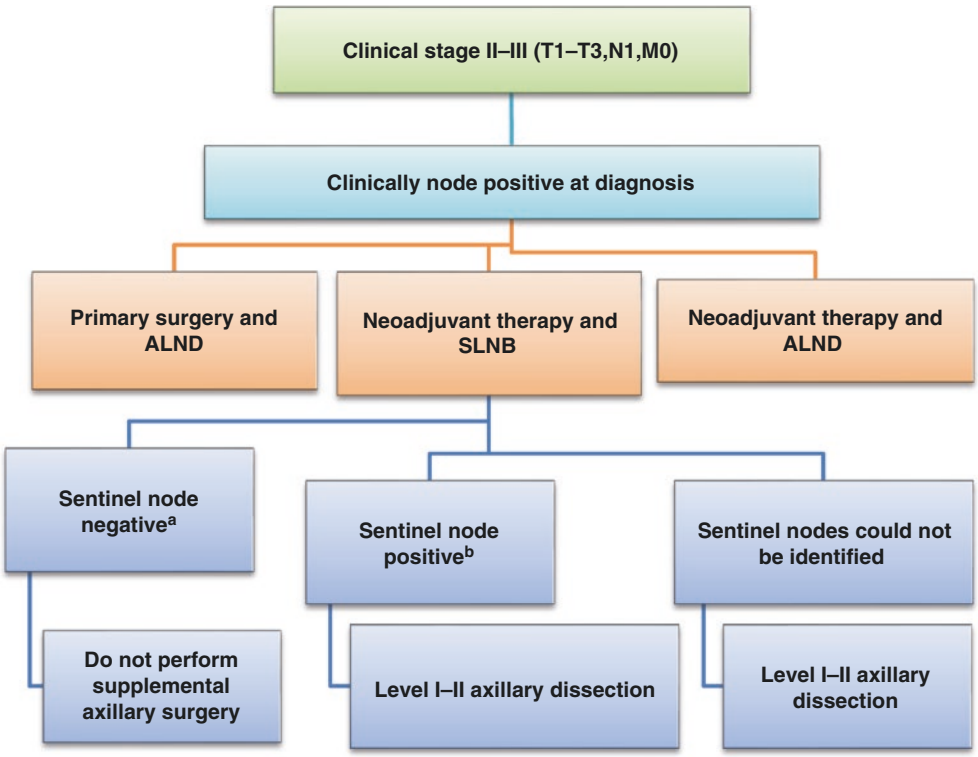

Fig. 5.2 Axillary management of patients with clinical node-positive stage II or III invasive breast cancer. SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection. [a]At least three SLNs should be assessed in patients receiving neoadjuvant treatment. In cases with triple-negative disease, consider ALND. [b]At least three SLNs should be assessed in patients receiving neoadjuvant treatment. After neoadjuvant therapy, if the SLN is positive (macrometastasis), level I–II ALND is recommended. In cases with micrometastases (non-triple-negative), consider ALND. In all cases with triple-negative tumors, ALND is recommended

combination is recommended for surgeons in training to allow them to become familiar with the anatomy and decrease false-negative results.

Axillary Lymph Node Dissection

Indications

ALND was once routinely practiced in breast cancer cases, but the indications for ALND have been revised as SLNB has become standard in early-stage (stage I, II) clinically N0 cases. Today, ALND is performed in clinical N+ early-stage breast cancer and N+ LABC post CT. General attitudes about early-stage N+ breast cancer have changed. Neoadjuvant CT is advised to achieve complete pathologic response to perform SLNB to preserve the axilla. ALND should also be performed when SLN cannot be detected.

Anatomy of the Axilla

Lymph node groups are categorized into three levels according to their orientation to the minor pectoral muscle for the surgeon's convenience. *Level 1* contains the lateral border of the minor pectoral muscle. The central and interpectoral groups, which are located between the medial and lateral borders of the minor pectoral muscle, form *level 2*. The subclavicular group, which is located medially or superiorly to the upper border of the minor pectoral muscle, is categorized as *level 3*.

Axillary Structure

The intercostal brachial and *intercostal thoracic nerves* are sensory nerves; they innervate the skin at the medial part of the upper arm and the posterior part of the axilla. Injury will result in sensory loss at the corresponding skin area.

The long thoracic nerve, which innervates the serratus anterior muscle, originates from C5 to C7, extends inferiorly over the thoracic wall, and branches at the level of the fourth to fifth intercostal. Its injury causes a winged scapula defect.

The thoracodorsal nerve, which innervates the latissimus dorsi, originates from C6 to C8. Preservation of this nerve during dissection is important for subsequent reconstructive interventions.

The Rotter ganglia are in contact with the lateral pectoral pedicle, which is located posteriorly to the major pectoral muscle.

The lateral pectoral nerve, which is located in this pedicle, innervates the medial part of the major pectoral muscle. Its injury results in atrophy of the major pectoral muscle.

The medial pectoral is located anteriorly to the minor pectoral muscle at a distance of 1–2 cm, and the lateral nerve is located more laterally. It originates from the medial chord of the brachial plexus (C8–T1). Its injury results in the atrophy of both muscles.

Atrophy of the pectoral muscles does not cause problems at the early stage but results in cosmetic issues at the chest wall in the long term.

ALND Technique

It is now known that extended lymphatic resection does not provide any benefit for patient survival. Therefore, in routine ALND, only level 1 and level 2 lymph nodes are removed. When lymph nodes are confirmed as positive by preoperative examinations or detected intraoperatively via palpation, level 3 lymph nodes are also included in the dissection. With efficient extraction, level 3 lymph nodes can be removed without sacrificing the minor pectoral muscle.

The incision should be made below the hairline to permit subsequent epilation and should not continue beyond the pectoral muscle anteriorly and the latissimus dorsi muscle posteriorly. Oblique transverse incisions, U-shaped incisions with the gap facing up, and reverse S incisions provide good exposure.

When started medially, the major pectoral muscle is elevated with a retractor. Anterior to the minor pectoral muscle below, the medial pectoral pedicle can be observed 1–2 cm medial of its border. This pedicle should be preserved to avoid atrophy of the major pectoral muscle.

The lateral border of the minor pectoral muscle is freed from the chest wall. This incision is extended upward until the axillary vein is exposed. In most cases, intercostal brachial nerves are sacrificed; however, with fine dissection at T2 and T3 above, the nerves can be separated from the axillary tissue and preserved.

Then, the long thoracic nerve is again identified over the serratus anterior muscle but located deeper (more posterior) than these sensory nerves. At the level of the third intercostal nerve below, it can be found by caressing the serratus anterior muscle with an index finger. It is located inside the fascia of the muscle and should always be preserved. After its exposure, the axillary tissue is dissected laterally from the chest wall. By retracting the major pectoral muscle, palpable lymph nodes are identified in the interpectoral region (Rotter ganglion). The few lymph nodes found here are removed without damaging the lateral pectoral pedicle, which extends anteriorly toward the major pectoral muscle.

There is no need to resect the minor pectoral muscle for a level 3 dissection. For a level 2 dissection, the surgeon should begin from the highest point posterior to the minor pectoral muscle. The surgeon should not extend the incision above the axillary vein; resection of the overlying fatty tissue increases the risk for lymphedema. Below the axillary vein, fatty tissue is skimmed off inferiorly from the chest wall. The dissection is continued inferiorly and laterally, and small branches emanating from the axillary vein are ligated. The lateral thoracic vein (thoracoepigastric vein), which originates from the direction of the axillary vein and enters the axillary tissue, is ligated. The thoracodorsal vein originates distally and posteriorly to the axillary vein and laterally to the lateral thoracic vein. The thoracodorsal nerve occasionally enters more medially, extends more deeply, and distally joins the thoracodorsal vessels. The thoracodorsal nerve can also be observed as a single pedicle adhered to the thoracodorsal vessels. However, it always enters the latissimus dorsi muscle from the medial side.

Fatty tissue between the long thoracic nerve and the thoracodorsal pedicle is skimmed off inferiorly from the axillary vein, and the subscapular muscle is exposed behind. Then, by placing an index finger on the long thoracic nerve, the nerve is traced until its entry site into the serratus anterior muscle (finger dissection). Laterally, the thoracodorsal pedicle is traced until its entry site into the latissimus dorsi muscle; the small venous branches are ligated, and the specimen is removed during this procedure.

While approaching the axilla laterally to medially, the latissimus dorsi muscle is traced upward from its border; at the site where it becomes tendinous, the axillary vein is exposed. Dissection should be continued below to where the latissimus dorsi muscle joins the serratus anterior muscle. Following removal of the tissue, a suction drain is placed in the axillary cavity near the incision.

Complications of ALND

SLNB is now the method of choice to avoid short- and long-term morbidities caused by ALND. Unfortunately, ALND must still be performed in many cases.

Neurovascular Injury

The long thoracic nerve: Injury of this nerve is caused by cutting, traction, or thermal damage; however, it is damaged in less than 1% of cases. Winged scapula defect caused by its injury results in cosmetic problems.

The thoracodorsal nerve: Because this does not cause a significant neurological deficit, this nerve can be excised to obtain a clean axilla if it is invaded by metastatic lymph nodes.

The intercostal brachial nerve: This nerve transverses the axilla and is generally cut during ALND, causing paresthesia at the medial half of the upper arm and adversely affecting quality of life in women.

Injury to *the medial pectoral nerve* does not cause short-term problems but results in cosmetic problems due to atrophy of the major pectoral muscle.

The brachial plexus is located superior to the axillary vein; thus, there is no risk of injury as long as one does not extend the dissection above the axillary vein.

Seroma

Seroma forms in nearly all cases to some extent and is thus not considered a surgical complication. However, prolonged seroma increases the risk of infection and delays adjuvant treatment. A low-pressure suction drain is placed during the operation to inhibit seroma formation. Because prolonged seroma following removal of the drain is a source of infection, it should be emptied via percutaneous aspiration. One effective method is delaying exercise and complete shoulder movements until after the fifth day following the operation. However, some arm and shoulder exercises should be started in the early stage to prevent shoulder problems due to a limited range of movement.

Chronic Pain and Limited Range of Movement

More than 50% of women experience neuropathic pain, which is sometimes severe and interferes with sleep. This pain increases with movement; is localized to the chest wall, axilla, arm, and shoulder regions; and can continue after the third month postoperatively. These pains are thought to be due to nerve injury and to the addition of radiotherapy and/or chemotherapy to treatment [43]. Patients who experience more pain with movement generally limit their shoulder movements, leading to frozen shoulder syndrome. Starting arm movements at the early period postoperatively with the aid of adequate analgesia prevents these complications.

Lymphedema

Lymphatic fluid, which originates in small lymphatic channels, first drains into regional lymph nodes; it is then carried to the systemic circulation via efferent lymphatic channels and the main lymphatic duct. Any obstruction in these channels results in the development of lymphedema in the tissue that could not be drained. Irradiation of the peripheral lymphatics is another factor that increases lymphedema. Recurrent attacks of lymphangitis and cellulitis also increase the risk for lymphedema in the arm. Lymphedema of up to 1–2 cm is considered mild and is observed in 20–30% of patients with level 1–2 ALND. Larger swelling is considered a serious lymphedema and is observed in less than 5% of patients. The risk of lymphedema in patients with level 3 ALND is 30%, and therefore level 3 ALND is not performed without a valid reason. Mild lymphedema can be observed in 5% of patients following SLNB. The aims are to educate patients and prevent lymphedema before it develops. Patients who have undergone ALND should be advised not to strain the affected arm, not to suspend the arm while working, and to avoid procedures that could increase the risk of lymphangitis (skin injury due to manicure, etc.); patients are also recommended not to gain weight.

When lymphedema develops, its severity is first assessed as follows:

- Stage 0: There is only dullness in the arm.
- Stage 1: There is pitting edema (recoverable stage because there is no fibrosis).
- Stage 2: The arm is stretched, and there is fibrosis.
- Stage 3: Elephantiasis is present, with skin signs such as fibrosis, sclerosis, and keratosis.

Treatment and Prevention

Regular trunk cleaning and massage, which is called manual lymphatic drainage, are applied to patients by trained physiotherapists, and bandaging is applied. If no response is obtained using these procedures and if fibrosis has begun in the arm, laser therapy (low-level laser therapy) can be attempted. Laser therapy resolves fibrotic scar tissue by acting on fibroblasts and stimulates lymphatic drainage. This method was demonstrated to have a lymphedema-reducing effect in 52% of cases [43, 44].

The detection and preservation of lymphatics of the arm in the axilla using the injection of blue dye into the upper arm is called reverse axillary mapping. Research on this subject is ongoing.

Conclusion

SLNB is equivalent to ALND in clinically node-negative patients in terms of staging, accuracy, DFS, and OS. ALND has been considered mandatory in sentinel node-positive patients, but recent data with 10 years of follow-up have demonstrated that BCS and radiotherapy are equivalent to ALND of micro/macro-metastatic SLNs. This approach will reduce the morbidity of dissection without decreasing OS. SLNB is also beginning to be used in LABC patients treated with neoadjuvant chemotherapy. In these cases, axilla can be saved, as in early breast cancer. With neoadjuvant CT, axillary dissection can be avoided in up to half of patients. ALND should be performed whenever the SLN cannot be detected.

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Breast Reconstruction

6

Edward H. Davidson, Vu T. Nguyen,
and Kenneth C. Shestak

Introduction

Breast reconstruction provides closure to many women who have been treated for breast cancer by increasing their comfort in clothing and providing a psychological benefit [1, 2]. The role of the plastic surgeon is to guide the patient through the decision tree to select a reconstructive pathway that is safe and meets expectations (Fig. 6.1). The first decision many patients face is whether to embark upon breast reconstruction at all; limited provision of service, concerns regarding cost, and anxiety about the effect on cancer surveillance are commonly cited reasons for forgoing breast reconstruction. The reality, however, is that in the USA, the UK, and many countries in Europe and worldwide, breast reconstruction is part of a holistic approach to breast cancer treatment and hence is "covered" by insurance or under the public health-care provision, thus imparting no financial burden on individual patients. Furthermore, no evidence suggests that any form of breast reconstruction increases the risk of recurrence or impairs oncological surveillance of the breast [3–10]. Patients who choose reconstruction must navigate a reconstructive pathway guided by their plastic surgeons that includes decisions regarding the timing, type, and extent of reconstruction. The gold standard for breast cancer care includes an integrated multidisciplinary team approach comprising surgical oncologists, medical oncologists, radiation oncologists, oncology nurses, and plastic surgeons. Decisions regarding radiation, chemotherapy, and oncological resection all impact the reconstructive approach; thus, the plastic surgery team should be involved as soon as possible rather than as an "afterthought" when oncological treatment is complete.

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Type of Mastectomy and Impact on Breast Reconstruction

The determination of oncological resection is ultimately governed by the surgical oncologist with oncological treatment taking precedence over any reconstructive goals. However, within the confines of safe practice, various options should be considered at the time of mastectomy to ultimately optimize reconstruction.

Total Versus Skin-/Nipple-Sparing Mastectomy

Skin-sparing and now nipple-sparing mastectomies have become a safe clinical reality for many patients [7–9]. Skin-sparing mastectomy provides a reconstructive advantage for both implant-based and autologous reconstruction. Using a native skin envelope to house either a prosthetic or replacement tissue confers an aesthetic advantage by enabling more rapid expansion to the preferred size with the former and avoiding the "artificial construct" appearance of a free flap with the latter (Fig. 6.2).

The ideal candidate for nipple (or rather nipple and areolar)-sparing mastectomies is characterized by small, non-ptotic breasts; an ideal patient would wish to be the same size or slightly to moderately larger. If the patient is a suitable candidate, subsequent nipple-areolar reconstruction is unnecessary. Furthermore, maintenance of the envelope may enable an optimal anatomically shaped autologous reconstruction (Fig. 6.2). Alternatively, in the case of implant-based reconstruction, nipple-sparing mastectomy enables the "direct-to-implant" technique, bypassing the need for preceding expansion in some cases.

As more experience is gained with nipple-sparing mastectomy, pre-mastectomy nipple delay procedures are increasingly advocated for those at high risk of postmastectomy nipple necrosis (i.e., smokers and those with prior periareolar surgery). The nipple-areolar complex (NAC) is surgically

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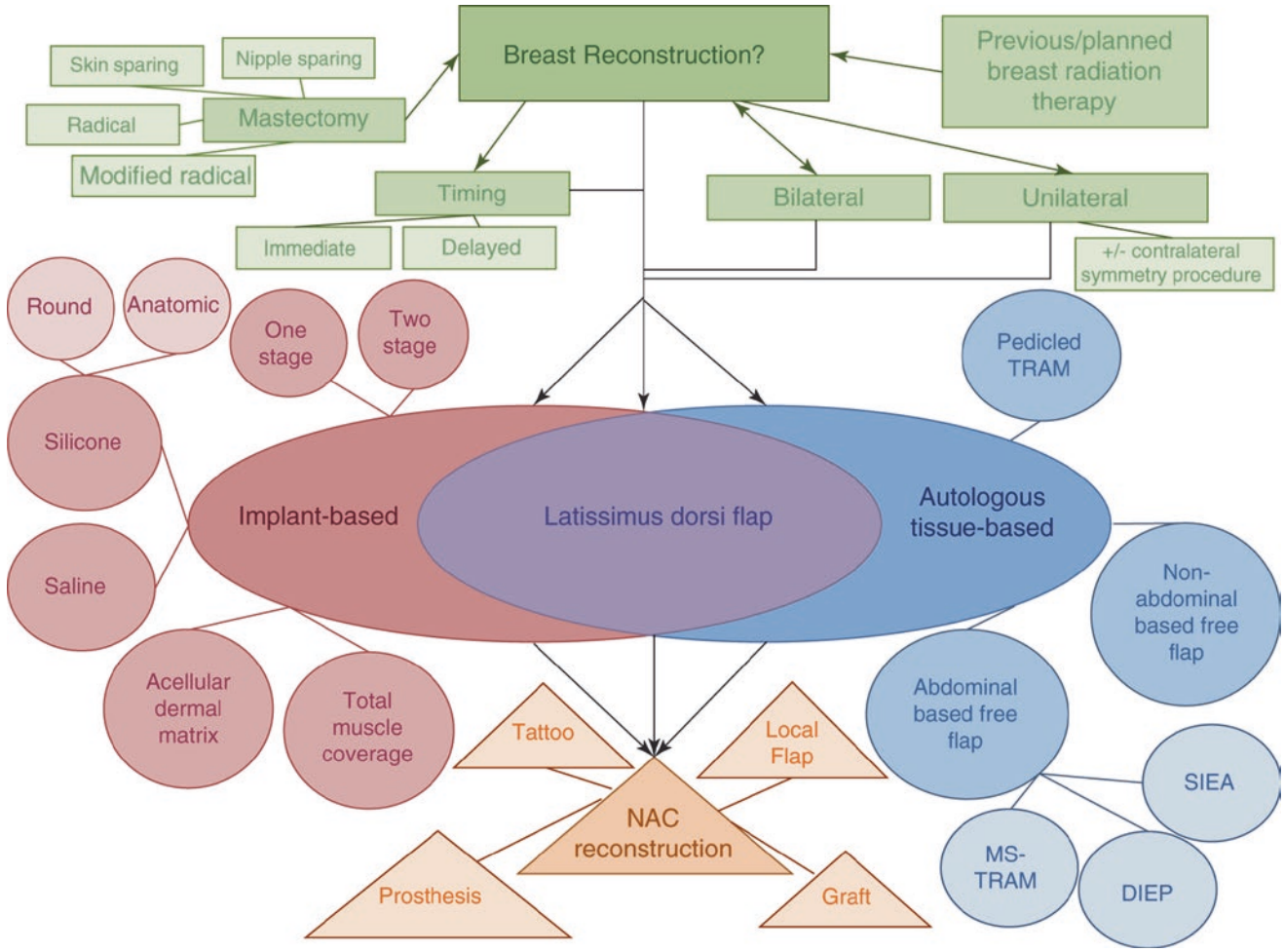

Fig. 6.1 The breast reconstruction decision tree

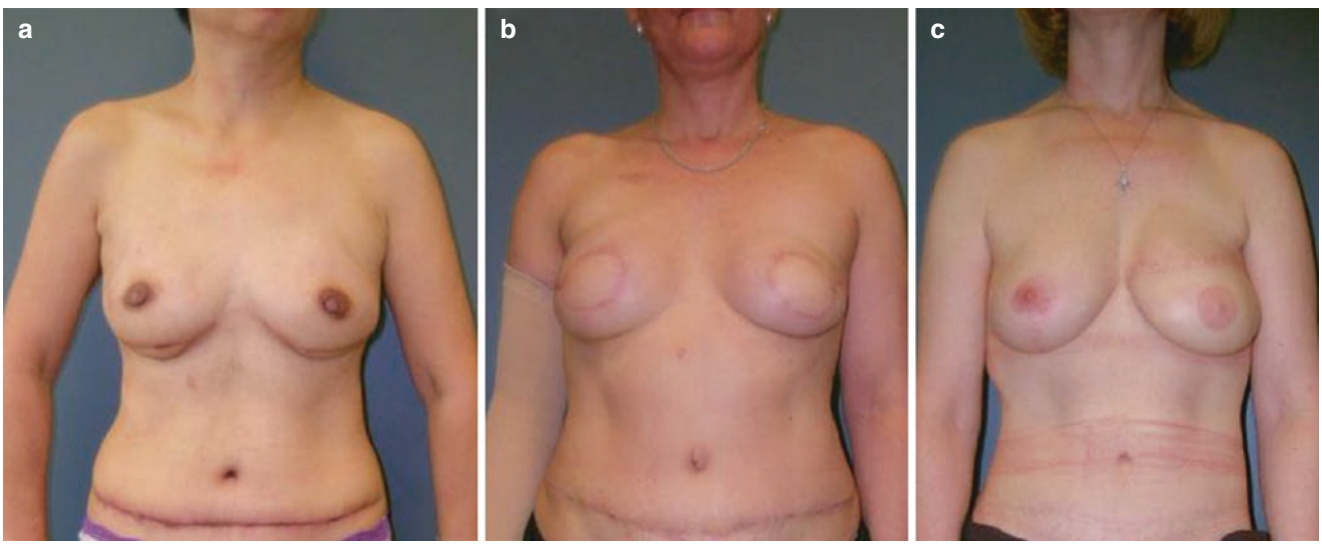

Fig. 6.2 Appearance of nipple-sparing, skin-sparing, and non-skin-sparing mastectomy with autologous reconstruction. (**a**) Early postoperative appearance of bilateral nipple-sparing mastectomy with abdominal-based free-flap reconstruction. The maintained envelope produces an optimal anatomic shape, and the nipple-areolar complex is preserved (note the free-flap skin paddle at the inframammary fold can later be resected but becomes less apparent as scars mature). (**b**) Early postoperative appearance of bilateral skin-sparing mastectomy with abdominal-based free-flap reconstruction prior to nipple-areolar reconstruction. The free-flap skin paddle appears at the center of the breast mound here. (**c**) Postoperative appearance of left mastectomy and delayed abdominal-based free-flap reconstruction with subsequent nipple-areolar reconstruction. Note the "stuck-on" appearance of the breast with a scar across the superior pole

separated from the underlying breast tissue to promote circumareolar blood flow to the nipple-areolar complex from the surrounding skin.

Bilateral Versus Unilateral Mastectomy

In addition to enhancing breast cancer prophylaxis, bilateral rather than unilateral mastectomy may also offer a reconstructive advantage; although not guaranteed, symmetry is easier to achieve when both sides are treated by the same method. However, nipple-sparing mastectomies can better maintain the natural appearance of the contralateral breast, reducing the benefit of bilateral mastectomy.

Delayed Versus Immediate Reconstruction

Breast reconstruction decisions can often be overwhelming for some patients, particularly when confronting the ramifications of a cancer diagnosis. A discussion of implants, the concept of a free flap, and the uncertainties and consequences of the need for radiation therapy can make it very challenging to formulate an informed reconstructive plan. Many patients wish to first focus on achieving oncological clearance prior to proceeding with reconstruction. Delaying reconstruction under these circumstances may be the preferred option. Deferring reconstruction to a later date is also preferred to avoid delaying oncological treatment of patients who are indecisive about reconstruction. Furthermore, when it is unclear if the patient will require postmastectomy radiation, which negatively impacts breast reconstruction, planning for reconstruction becomes easier and better informed after the need for postoperative radiation is determined. Some of this uncertainty can be eliminated if the surgical oncologist is willing to perform a pre-mastectomy sentinel lymph node biopsy ahead of time. In the case of postmastectomy radiation in the USA and other countries, the gold standard is to delay reconstruction until the radiation treatment is completed.

Implant-Based Breast Reconstruction

Breast reconstruction in all forms necessitates volume replacement of the removed breast parenchyma. Implant-based reconstructive methodologies rely on either a silicone or saline prosthetic to achieve volume replacement. Both "silicone" and "saline" implants utilize an outer elastomer shell (envelope) of silicone and either an internal silicone gel or saline fluid, respectively; each is available in different shapes and sizes. Although the discussion of implant-based reconstruction presented herein will focus on these two approaches, it should be recognized that breast implants will continue to evolve, and dozens of different implants and designs will ultimately be available, each championing the benefits of their candidate material and design. The silicone and saline implants discussed herein are the most vigorously tested and most widely used at this time.

Table 6.1 Advantages and disadvantages of implant-based reconstruction

Implant-based breast reconstruction	
Advantages	Disadvantages
Shorter initial surgery	Need for a prosthesis
	Multiple surgeries
Shorter hospital stay	Need for regular office visits for expansion[a]
	Longer time to achieve reconstruction[a]
Shorter recovery	More difficult to recreate a larger/pendulous breast
	Less compatible with radiation therapy
No donor-site scar or morbidity	Risk of implant failure and/or capsular contracture
	Need for future replacement surgery

[a]For two-stage not one-stage implant-based breast reconstruction

The advantages and disadvantages of implant-based reconstruction, particularly compared to tissue-based reconstruction discussed below, are summarized in Table 6.1. Implant-based reconstruction offers the advantage of relatively smaller individual steps, albeit a greater number of steps, to reconstruction, fewer major surgical procedures, a shorter hospital stay, and the avoidance of any secondary donor-site morbidity. However, implant-based reconstruction is often contraindicated in the setting of previous or planned breast radiation therapy, may not permit an adequate symmetrical match to a larger pendulous breast if unilateral reconstruction is desired, and necessitates future replacement surgery because no implant is truly permanent. The most common pathway for implant-based reconstruction is a two-stage approach in which a "tissue expander" is first placed to promote subsequent expansion of the soft tissues to create the desired sized pocket for subsequent placement of the permanent implant (Fig. 6.2).

Two-Stage, Implant-Based Reconstruction

Expander Placement

The precise operative details are beyond the scope of this chapter. However, briefly, either immediately following mastectomy or at a delayed time point (after initially excising the existing scar) following skin-sparing mastectomy, a submuscular pocket for the tissue expander is created by dissecting laterally from the intersection of the pectoralis major muscle and serratus anterior muscle or by splitting the pectoralis major muscle to create a pocket, medially toward the

sternum as well as inferiorly, superiorly, and laterally. Care must be taken not to violate the integrity of the pectoralis major superficially or the chest wall to the plane of dissection. Dissection is preferentially performed medially and inferiorly to ensure subsequent preferential expansion by the device. Inferior dissection proceeds to the level of the inframammary fold and medially to just lateral to the sternum. Completion of the pocket is subsequently dependent on whether "total muscular coverage" or acellular dermal matrix (ADM) is used. With the former, the lateral portion of the pocket is created by dissecting laterally deep to the serratus anterior. Some surgeons are proponents of the use of ADM, citing the advantages of a more malleable, naturally draped expander pocket. Opponents of this technique argue that ADM carries a greater infection risk. However, this is a contentious issue. The completion of the expander pocket when ADM is used is achieved by disinserting the inferior pectoralis major and recreating the inframammary fold (IMF) and lateral aspect of the pocket with a curved triangular sling of ADM sutured inferiorly and laterally to the deep tissues as well as superiorly (after placement of the expander) to the now inferior free edge of the pectoralis major. With either technique, the deflated expander is placed in the pocket. The pocket is then closed by suturing either the serratus anterior or the ADM to the pectoralis major as appropriate. Care must be taken to complete this suture line with direct vision to avoid puncturing the expander. Again, as with implants, a plethora of expanders are available on the market. The author's preference is a low-height anatomically shaped expander with an indwelling port. This expander preferentially expands the inferior pole. Alternatively, a medium-height device can be used. Once closure of the pocket is achieved, the expander is partially inflated. The amount of inflation is dictated by the quality of the overlying tissue, both the muscle of the pocket and the overlying skin. Essentially, the expander is inflated as much as possible without causing undue tension to the overlying muscle or subsequent skin closure. Finally, the skin is then closed over a Jackson-Pratt drain. When using ADM, a drain is commonly placed both in the pocket and in the subcutaneous space due to the increased risk of seroma.

Serial Expansion

Following expander placement, our protocol involves inpatient admission overnight; however, same-day discharge is not inappropriate. Patients routinely receive perioperative antibiotics for 24 h; however, some advocate a longer course of antibiotics, particularly with the use of ADM. This issue is heavily debated and dependent on surgeon preference. Typically, drains are removed 1 week postoperatively if the output has been less than 30 ml/day for two consecutive 24-h periods. Expansion is then commenced 2 weeks postoperatively. A magnet is used to identify the location of the filling port. The skin is marked and prepped with Betadine, and saline is infused percutaneously. Arbitrarily, weekly expansion for 3 weeks is performed, and the time between expansions is subsequently increased with a 30–40-ml infusion at our institution. These smaller volume expansions appear to cause less thinning of the overlying soft tissues. Expansions are largely well tolerated without the need for analgesia. Excessive pain noted post expansion should be addressed by fluid removal.

The expansion protocol is flexible and accommodating to patient convenience and preference; larger more frequent expansions if tolerable and "expansion holidays" are permissible and do not impact the ultimate results. Expansion proceeds in this manner until an endpoint determined by the patient's target breast size is achieved for bilateral procedures, or the contralateral size is achieved in the case of unilateral breast reconstruction. Following the completion of expansion, a 4- to 6-week period of recovery for the soft tissue envelope is provided prior to the exchange of the expander for the implant.

Expander to Implant Exchange

Once expansion is completed, and a further latency period of 4–6 weeks has elapsed to allow tissue recovery, the expander is exchanged for the implant, which remains in place for a lengthy period of time. No implant is permanent. Although extensive and conflicting data are available, patients should be informed that they will likely need to replace the implant at some point in the future as a result of implant failure or capsular contracture. The time frame of this need for replacement is highly variable, but an estimate of a 50% replacement rate at 10 years appears to be easily understood and remembered by both patients and surgeons. Every implant induces periprosthetic capsule formation; over time, this capsule can contract and cause a firm, visibly deformed, and even painful breast. The most extensive form of this problem is not frequently observed. Saline implant failure is immediately obvious in most cases due to deflation. Silicone implant failures are less easy to detect. In the USA, the Federal Drug Administration (FDA) advocates monitoring by magnetic resonance imaging (MRI) 3 years after initial placement and every other year thereafter [11]. The reality is that this advice is largely ignored due to cost issues. Certainly, an MRI is advisable following any trauma to the breast or with symptoms that warrant concern for possible failure.

The choice of either silicone or saline implant is fundamentally a patient's decision. Silicone implants provide a more aesthetic reconstruction and a more natural feel to the reconstructed breast. By contrast, failure of saline implants is more easily detected. Patients are occasionally wary of silicone implants given the 14-year moratorium on their use for cosmetic augmentation by the FDA from 1992 to 2006. Details regarding this moratorium are best explored elsewhere, but, in short, the moratorium was in response to

numerous reports attributing the incidence of different systemic medical issues to silicone prosthesis implantation. Extensive research was unable to identify any association between these ailments and the presence of the implants; thus, the availability of these implants was restored. Although the reputation of silicone implants frequently remains compromised, the extensive scrutiny of silicone implants has established them among the most tested and safe prostheses across all surgical specialties. Notably, silicone implants were only banned in the USA, and this ban did not extend to implant use in reconstruction or research [12–16]. We inform all our patients that all medical evidence emphasizes that implants are safe, but some patients are deterred from their use despite reassurance.

Similar to expanders, silicone or saline implants are available in numerous shapes and sizes with different projection to volume ratios. If choosing silicone implants, the choice is further complicated by the option for newer, so-called fourth-generation anatomically shaped implants. These "teardrop"-shaped implants aim to offer greater projection preferentially at the lower pole and more natural takeoff from the chest wall. If a patient is amenable to fourth-generation implants, the surgeon will consider this option in the selection of an implant at the time of surgery based on the surgeon's judgment of what implant will produce the most aesthetic result. Implant choice is somewhat predetermined by the base width of the original expander pocket; however, the base width can be adjusted at the time of implant exchange and by the volume with which the expander has been infused. Using these two data points, it is prudent to order numerous implants with dimensions that closely resemble these criteria and correspondingly test "sizers" that can be assessed at the time of surgery. It is also wise to order at least two implants of each type of interest for a unilateral reconstruction as well as at least three implants for a bilateral reconstruction in case of iatrogenic implant failure.

The exchange from expander to implant may safely be performed as same-day surgery, and the patient is discharged without the need for an inpatient hospital stay. In brief, the previous intraoperative incision is opened, and the underlying muscle and capsule are incised. The expander is then deflated and removed. Antibiotic solution is used to irrigate the pocket. If necessary, a capsulotomy is performed, and the implant is placed using a minimal touch technique to mitigate infection risk. The placement of the final implant is often preceded by trial placements of reusable implant sizers. The patient sits up on the operating table to judge the aesthetic appearance until the ideal appearance is achieved. With saline implants, the implant shell is placed and then filled with saline. A saline-filled implant has more flexibility in terms of size because it may be under- or overfilled according to the manufacturer's guidelines. In fact, overfilling by 10–20% reduces the risk of implant rippling and failure [17, 18]. The capsule and skin are then closed without the need for drain placement. Perioperative antibiotic practice is again practitioner dependent and contentious, as is instruction regarding return to activity. Wearing a surgical bra or a sports bra that is not overly tight and lacks an underwire in the case of an IMF incision (i.e., following nipple-sparing mastectomy as described below) and avoidance of strenuous activity for 4 weeks is probably advisable.

Single-Stage, Implant-Based Reconstruction

The technique is modified for a nipple-sparing mastectomy. Using an inframammary fold incision, which is the common practice at our institution, the pectoralis is disinserted from its inferior attachments, and the pocket is dissected for placement of the expander. The selected implant is then placed, and the pocket is closed using a sling of ADM to support the inferior pole and maintain the inframammary fold. Nipple-sparing mastectomy, as preciously alluded to, increases the possibility of single-stage direct implant placement and avoids the need for tissue expansion, assuming the patient does not desire a significantly larger cup size than that prior to mastectomy. The maintenance of the full skin envelope can often accommodate immediate implant placement. However, patients should be counseled that the high-tension closure can complicate wound healing and optimal aesthetic results often require a revision procedure.

Radiation and Implant-Based Breast Reconstruction

Previous or proposed breast radiation therapy significantly increases the risk of complications of implant-based reconstruction. For patients with any history of breast conservation treatment with lumpectomy and radiation or planned/completed postmastectomy radiation, the gold standard for reconstruction to date is autologous tissue-based reconstruction, which introduces new, well-vascularized tissue outside the breast to the area of radiation damage. Conversely, expanding radiated tissue carries a high risk of expander extrusion, infection, and dehiscence (Fig. 6.3). Even if radiated tissue is successfully expanded, the risk of wound breakdown following implant exchange is high.

However, implant-based reconstruction pathways and radiation therapy occasionally collide. For example, a patient may choose to proceed with implant-based reconstruction despite the risks, or unanticipated radiation therapy may be required after mastectomy and immediate tissue expander placement have been performed. Some of this uncertainty can be removed if the surgical oncologist is willing to perform a pre-mastectomy sentinel lymph node biopsy prior to

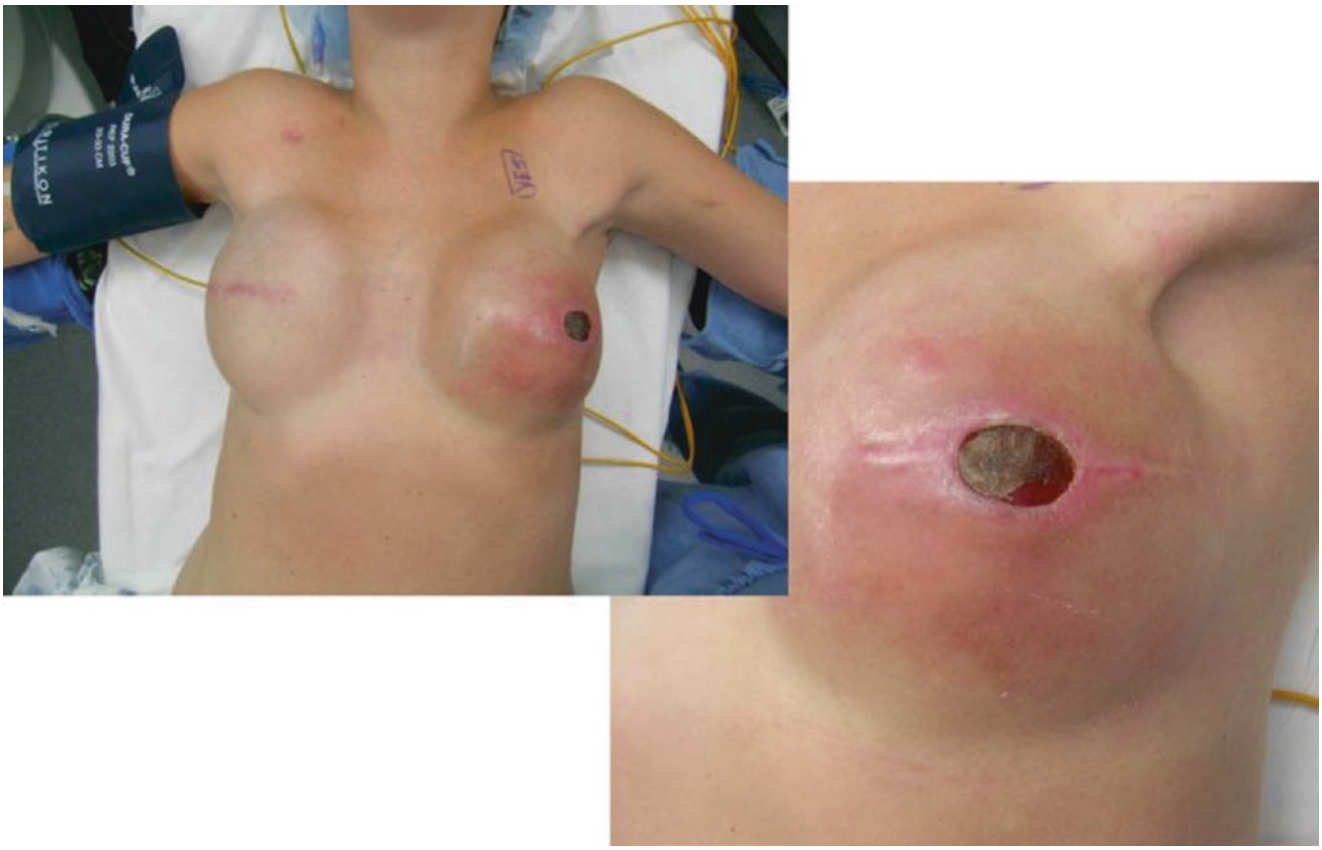

Fig. 6.3 Radiation and implant-based reconstruction; extrusion of a tissue expander in irradiated tissue

the scheduled mastectomy. For patients adamantly opposed to autologous tissue reconstruction or patients with no available autologous options who are appropriately informed of the risks, implant-based reconstruction may be appropriate in individual circumstances. Some surgeons will refuse to proceed with such treatment. In the case of autologous tissue reconstruction, proceeding with implant-based reconstruction is not absolutely precluded if appropriate planning is made. Mitigation of risk can be achieved by avoiding radiation, if oncologically safe, until completion of active expansion. In some centers, particularly those in which adjuvant rather than neoadjuvant chemotherapy is practiced, a timeline of postmastectomy expansion concomitant with chemotherapy, expander-implant exchange, and subsequent radiation of the permanent implant has been championed (Fig. 6.4) [19]. Of course, radiation damage is largely permanent and impacts future implant replacement surgeries. In some clinical circumstances, radiation oncologists are unable to reliably offer adequate radiation therapy in the presence of an implant and may request its removal, representing a surgical "return to square one."

In the event of expander or implant extrusion or threatened extrusion in the context of radiation, the leading options involve salvaging implant-based reconstruction with the supplement of a pedicled latissimus dorsi flap under which an expansion and implant placement can be performed or abandoning implant-based reconstruction and proceeding with a delayed autologous tissue-based reconstruction (both discussed below).

Autologous Tissue-Based Breast Reconstruction

For autologous tissue-based breast reconstruction, volume replacement of the removed breast parenchyma is achieved by transfer of the patient's own tissues from an anatomic site distant from the breast. This procedure necessitates maintenance of the blood supply of the transferred replacement tissue either by preservation of a vascular leash or pedicle carrying the native arterial inflow and venous return or by dissection of a segment of native veins and arteries on the tissue to be transferred. This tissue is subsequently detached from the body, and these donor vessels are inserted in or anastomosed with similarly dissected recipient site arteries and veins to generate a "free flap."

The advantages and disadvantages of autologous tissue-based reconstruction compared to implant-based reconstruction

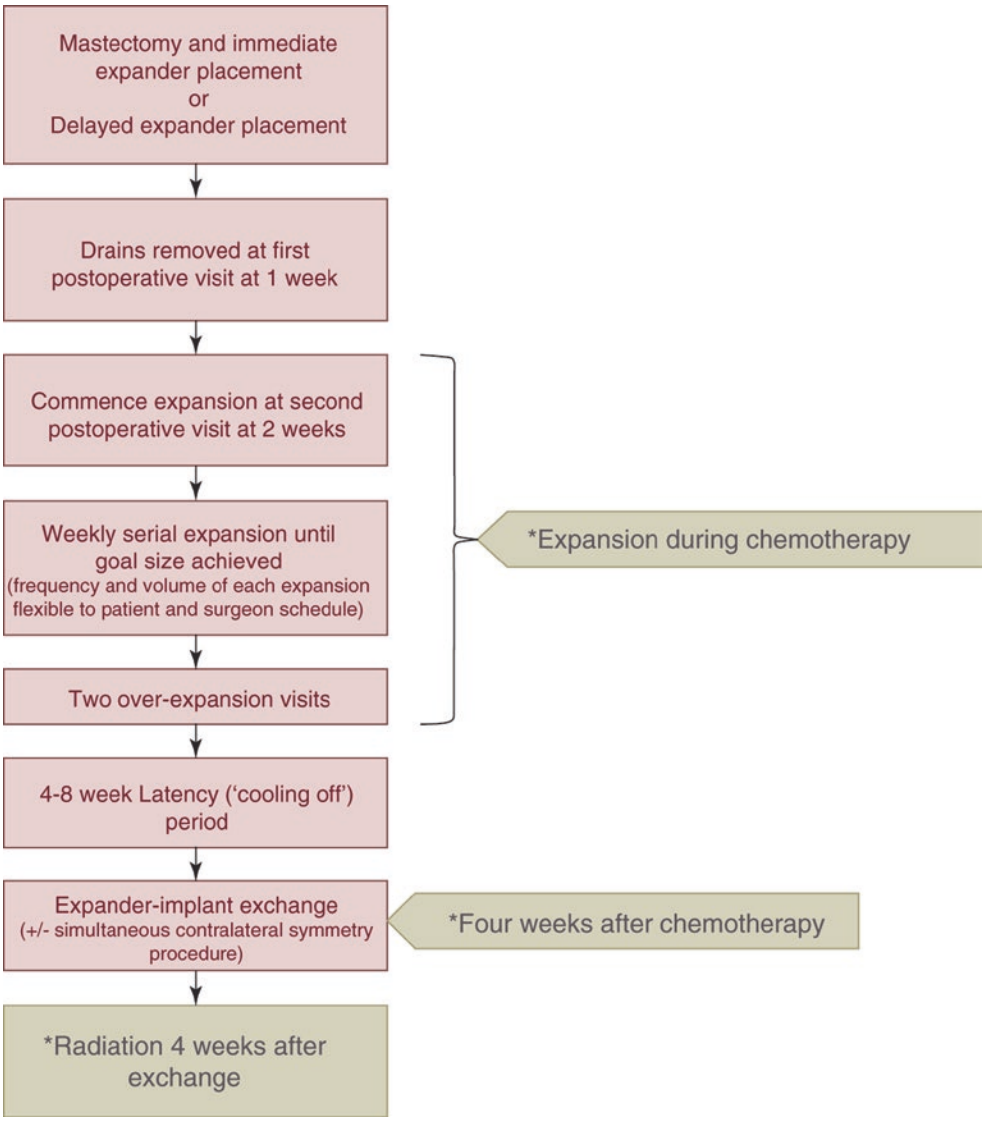

Fig. 6.4 Timeline of two-stage expander-based reconstruction (*and with postmastectomy radiation)

Table 6.2 Advantages and disadvantages of autologous tissue-based reconstruction

Autologous tissue-based breast reconstruction	
Advantages	Disadvantages
One-stage surgery	Longer surgery
No need for future replacement surgery	Longer hospital stay
Mitigates soft tissue injury from radiation	Longer recovery
Use of own tissue that mirrors changes in body habitus	Donor-site scar and risk of donor-site morbidity

are summarized in Table 6.2. Autologous tissue reconstruction enables definitive one-stage breast reconstruction, thus avoiding the need for protracted expansion protocols or future implant replacement surgeries. In the case of radiation therapy, this technique mitigates reconstructive complications with the provision of healthy well-vascularized tissues but requires major surgery and therefore the potential for major complications, requiring longer hospital stays and the risk of donor-site morbidity.

Pedicled Transverse Rectus Abdominus Myocutaneous (Tram) Flap

Pedicle and free TRAM flaps were developed in the late 1970s and early 1980s. Proponents of the pedicled TRAM champion its reliability and reduced operative time and inpatient stay compared with free-tissue transfer and technical ease given the avoidance of microsurgery. The caveat to this technique is the increased risk of donor-site morbidity, namely, abdominal wall bulge or hernia, especially with bilateral reconstruction and segmental disruption of the inframammary fold.

Pedicled TRAM is based on superior epigastric vessels. A transverse ellipse of skin is marked in the lower abdomen from near the anterior superior iliac spine on one side to the other side. This region typically includes the umbilicus, which is ultimately transposed, similar to an abdominoplasty. Skin and subcutaneous tissues are incised down to the external oblique and rectus fascia muscles. The entire rectus or a strip of muscle with superior epigastric vessels, as identified with a 20-mHz handheld Doppler, is dissected off the abdomen either bilaterally or unilaterally as appropriate and tunneled superiorly into the postmastectomy skin envelope. Donor to recipient transfer may follow an ipsilateral or a contralateral path. At our institution, ipsilateral transfer is preferred. This decision is largely based on surgeon preference. The abdomen is closed via transposition of the umbilicus. Synthetic mesh reinforcement of the donor area is needed only if the closure is tight. The flap is inset.

Pedicled flaps do not require Doppler monitoring but rather are assessed based on the clinical appearance of any skin paddle. A healthy flap should appear the same color as the donor tissue, with comparable temperature and capillary refill. An arterially insufficient flap appears pale, may be cooler to touch, and exhibits prolonged capillary refill. Conversely, venous-congested flaps exhibit a blue/purple hue and display rapid capillary refill. With venous congestion, an associated increase in dark red surgical drain output may be noted.

Following the pedicled TRAM flap procedure, patients at our institution typically undergo a two-night inpatient stay. Diet is advanced as tolerated postoperatively, and activity is advanced following initial bed rest overnight. On discharge, patients are counseled to maintain use of a surgical brassiere or loose sports brassiere without an underwire and an abdominal binder at all times for 4–6 weeks and to avoid strenuous activity for 6 weeks. Surgical drains in both the donor and recipient sites are sequentially removed in postoperative office visits at 1, 2, 4, and 12 weeks once output is less than 30 ml in two consecutive 24-h periods.

Some surgeons advocate a practice of flap "delay" to improve the vascularity of the flap; 10 days to 3 weeks prior to flap elevation and inset, which are performed as a short same-day surgery, the ipsilateral deep inferior epigastric vessels are ligated. This procedure has the benefit of increasing blood flow through the superior epigastric artery [20].

Abdominal-Based Free-Tissue Transfer

Although requiring comfort and proficiency with microvascular surgery techniques, abdominal-based free-tissue transfer obviates some of the donor-site morbidity risk associated with the pedicled TRAM flap, particularly in higher-risk patients (i.e., those who are obese and/or smoke). There is a continuum of evolution in free-flap development from free TRAM to muscle-sparing free (MS) TRAM to deep inferior epigastric artery perforator (DIEP) to superficial inferior epigastric artery (SIEA) flaps. At the TRAM flap end of the spectrum, there is the advantage of a relatively more robust blood supply throughout the flap but a greater relative risk of abdominal wall morbidity. Conversely, the SIEA flap marks the most evolved form of abdominal-based, free-tissue transfer in terms of minimizing abdominal wall morbidity yet offering relatively less robust perfusion and subsequent increases in fat necrosis within the flap.

Free TRAM is characterized by harvesting of a full-length strip of rectus muscle. Alternatively, with muscle-sparing TRAM (MS-TRAM), a cuff of rectus muscle with overlying subcutaneous tissue and skin based on the deep inferior epigastric artery and its branches is more commonly harvested (Fig. 6.5). MS-TRAM is further subdivided into MS-I, in which the cuff is on the medial (MS-I-m) or lateral (MS-I-l) border of the rectus, and the more ideal MS-ii, in which a central cuff of muscle is obtained, preserving a lateral and medial band. To harvest a DIEP flap (occasionally referred to as MS-III), the dominant branches of the deep inferior epigastric artery that perforate through the rectus muscle are dissected out along with a minimal cuff of fascia around the perforating vessel. The SIEA flap utilizes the superficial inferior epigastric artery and vein, thus avoiding rectus muscle dissection and harvesting.

At our institution, once a patient has opted for abdominal-based, free-tissue transfer reconstruction, a tentative operative plan is formulated based on a computed tomography (CT) angiogram of the abdomen. Ultimately, the final decision regarding the type of flap vascularization is made at the

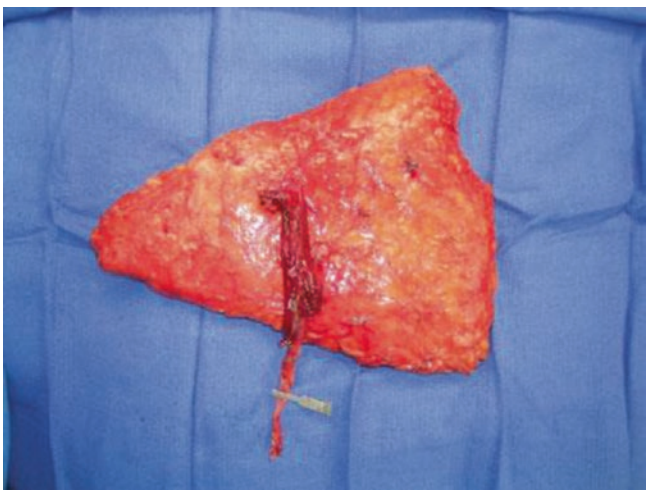

Fig. 6.5 Muscle-sparing TRAM (MS-TRAM); a cuff of rectus muscle with overlying subcutaneous tissue and skin based on the deep inferior epigastric artery and its branches

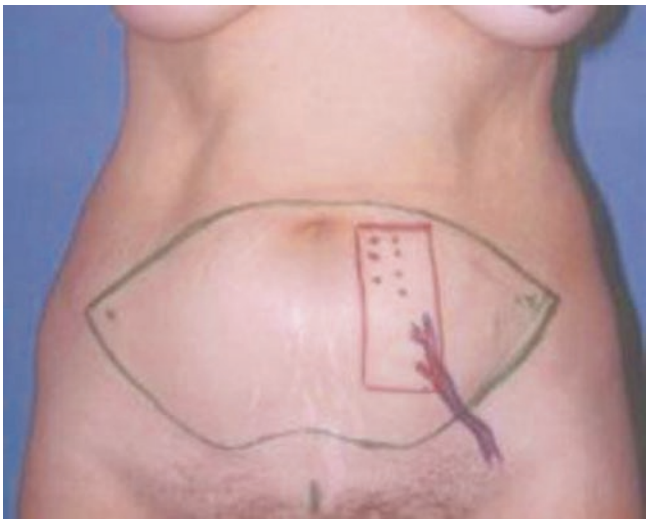

Fig. 6.6 Preoperative marking for abdominal-based free flap indicating the relative positions of skin incisions, strip of rectus muscle, and deep inferior epigastric vessels

time of surgery and is a balance between optimizing perfusion and minimizing abdominal wall morbidity based on each individual's vascular anatomy. If extended to also include the chest, the CT angiogram also enables preoperative assessment of the caliber of the internal mammary vessels. These vessels are our preferred recipients; however, thoracodorsal vessels are preferred by others. The advantage of the internal mammary vessels is that the vessels are generally larger and their use obviates the need to work in a tunnel, in contrast to the use of the thoracodorsal vessels.

A transverse ellipse of skin is marked on the lower abdomen from near the anterior superior iliac spine on one side to the other side, similar in design to an abdominoplasty (Fig. 6.6). Flap elevation can proceed simultaneously to mastectomy if performed in the immediate setting and if acceptable to the surgical oncology team. The skin and subcutaneous tissue are incised down to the external oblique and rectus fascia muscles. Diligence in dissection through the subcutaneous tissues of the inferior incision is required to identify and preserve the SIEA and superior inferior epigastric vein (SIEV). Even if an SIEA flap is not an option, the SIEV is often preserved as a "lifeboat" for a venous-congested flap or as a secondary vein to "supercharge" outflow. Dissection of the subcutaneous tissue off the fascia proceeds laterally to medially with particular care given medial to the linear semilunaris. Perforating branches of the deep inferior epigastric artery are identified and preserved. If an SIEA is planned, the flap can simply be elevated off the fascia via cautery or ligation of all deep perforating branches. Dominant perforators are identified and dissected through the muscle until a pedicle that is sufficiently long to ease microvascular anastomosis is procured for a DIEP flap. Alternatively, the dominant perforator(s) may be harvested en masse with a strip of rectus muscle and a segment of the deep inferior epigastric vessels.

Depending on body habitus, desired flap side, and whether a unilateral or bilateral reconstruction is performed, the abdominal ellipse may be divided at the midline, with each hemi-flap requiring dissection of the donor blood vessels. Alternatively, if supported by the vascular tree, the entire ellipse may be used for a unilateral reconstruction if necessary. Preparation of the recipient vessels may proceed simultaneous to flap elevation, assuming mastectomy is complete. The abdomen is closed via transposition of the umbilicus. Mesh may be necessary only if substantial muscle is resected. Microvascular anastomosis is completed, and the flap is inset.

Free-flap monitoring is an extensive topic in itself. We commonly use an indwelling venous Doppler and an external handheld Doppler to monitor the arterial signal and clinically examine the appearance of any skin paddle. Postoperatively, patients are transferred to a unit with nursing staff trained in free-flap monitoring. Formal "flap checks," which assess venous and arterial signals as well as flap appearance, are performed by nursing staff every hour for the first 48 h and then every 2–4 h thereafter until discharge. Physician staff perform further checks every 6–12 h or immediately in response to any concern highlighted by the nursing staff. There is a low threshold for returning to the operating room to explore and attempt salvage as appropriate for any concern in flap signal or appearance, particularly within the first 48 h postoperatively because 80% of flap jeopardizing complications occur during this time frame. Any intervention "resets" the clock. Patients are not permitted oral intake until flap assessments are completed and deemed satisfactory on the morning of postoperative day 1. At this time, only a clear liquid diet is permitted for a further 24 h. In the absence of any problems, diet and activity are advanced. Patients are confined to bed in the semi-Fowler's position for 24 h. Patients are then allowed out of bed to a chair for 24 h. After this time, patients are allowed out of bed and permitted to shower with assistance. If no complications are encountered, patients are discharged; this typically occurs on postoperative day 4. At discharge, patients are counseled to maintain use of a surgical brassiere or loose sports brassiere without an underwire and an abdominal binder at all times for 4–6 weeks and to avoid strenuous activity for 6–10 weeks. Surgical drains in both the donor and recipient sites are sequentially removed at postoperative office visits at 1, 2, 4, and 12 weeks once output is less than 30 ml in two consecutive 24-h periods.

Non-abdominal Tissue-Based Autologous Free Flaps

Abdominal tissue provides the workhorse flaps described above for autologous tissue-based breast reconstruction. However, microsurgical approaches have evolved such that flaps from other sites have been described and may be offered in certain circumstances. The reconstructive surgeon's willingness to offer options, such as superior or inferior gluteal artery perforator flaps or thigh flaps, is largely influenced by training bias and experience. In addition, options are typically only offered if a patient is not a candidate for abdominally based flap harvest due to prior surgery, or they are adamantly opposed to any risk of abdominal wall morbidity. Typically, the risk of abdominal wall morbidity is traded for a flap that is technically more challenging to shape and one that confers a scar and contour deformity elsewhere, the conspicuity of which is dependent on surgical expertise and patient's body habitus.

The Latissimus Dorsi Flap in Breast Reconstruction

The latissimus dorsi myocutaneous flap was the first flap used for breast reconstruction in the mid-1970s. Its popularity decreased with the introduction of abdominal wall flaps but has once again become popular given its significant utility in various settings.

A pedicled latissimus dorsi flap can serve as a "lifeboat" to salvage implant-based reconstruction complicated by radiation therapy. This flap may be used as an adjunct to implant-based reconstruction in providing a lower pole skin, subcutaneous tissue, and muscle sling to enable implant-based reconstruction of a pendulous breast. In addition, this flap may be an independent option for autologous tissue-based breast reconstruction.

When a tissue expander or permanent implant threatens extrusion or extrudes through radiation-damaged tissue, a pedicled latissimus dorsi flap provides well-vascularized, healthy tissue under which expansion can proceed.

A large pendulous or ptotic breast can be difficult to reconstruct using conventional implant-based methods as the vector of expansion, and therefore, the projection of the implant is horizontal from the chest. Expansion under a latissimus flap draping the inferior fold can recreate the ptotic breast.

An extended or volume-added latissimus has been described in which extensive subcutaneous tissue is harvested beyond that directly overlying the harvested muscle. In some reports, this method provides adequate volume to independently reconstruct an albeit small breast. Other researchers have reported further volume augmentation with supplemental autologous fat grafting (below).

Preoperatively marking the borders of the latissimus is performed with the patient standing. A tunnel through which the flap is passed anteriorly under the breast is also marked just inferior to the axilla. A "no man's land" area in which dissection is prohibited is also typically identified caudal to the tunnel to prevent violation of the lateral border of the breast. Either immediately following mastectomy or after scar excision and undermining of mastectomy flaps in a delayed fashion, the axillary tunnel is dissected with the patient in the supine position. The patient may then be turned prone or to the lateral decubitus position, and the flap is elevated. Sequentially, the skin paddle is incised, and dissection proceeds through the subcutaneous tissue with aggressive beveling to capture a volume of fat until muscle is encountered. The latissimus is traced to its medial, lateral, superior, and inferior borders and is released from its insertions. Care must be taken superomedially to not disrupt the trapezius muscle. The muscle is undermined in a caudal to cranial direction until it is sufficiently free to rotate through the tunnel on the pedicle of the thoracodorsal vessels that enter the undersurface of the muscle superiorly. The donor site skin may then be closed in layers over drains. The placement of at least two drains at the donor site is mandatory given the high risk of seroma. The patient is then turned supine once more, and the flap is inset as appropriate (Fig. 6.7).

Oncoplastic Breast Reduction Surgery

Oncoplastic breast reduction surgery offers something of an intermediate option between breast conservation therapy and breast reconstruction and is an option for a relatively smaller tumor in a relatively larger breast. Essentially, a reduction mammoplasty is performed bilaterally with resection of the tumor along with an adequate margin as part of the excision on the affected side (Fig. 6.8) [21].

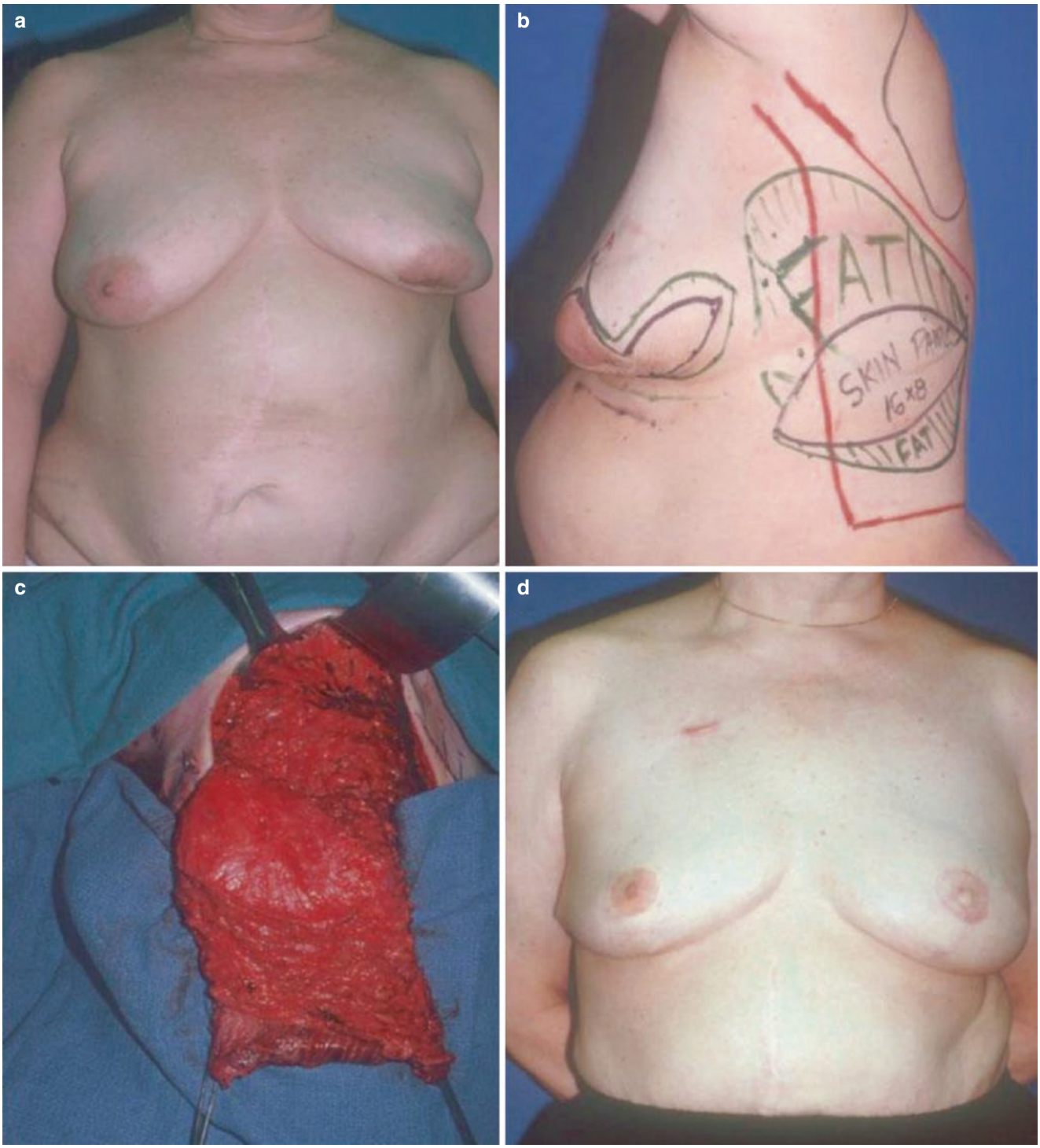

Fig. 6.7 Breast reconstruction with an autologous latissimus dorsi flap. (**a**) Preoperative defect, (**b**) preoperative marking, (**c**) intraoperative elevation of flap, (**d**) postoperative appearance at 2 years

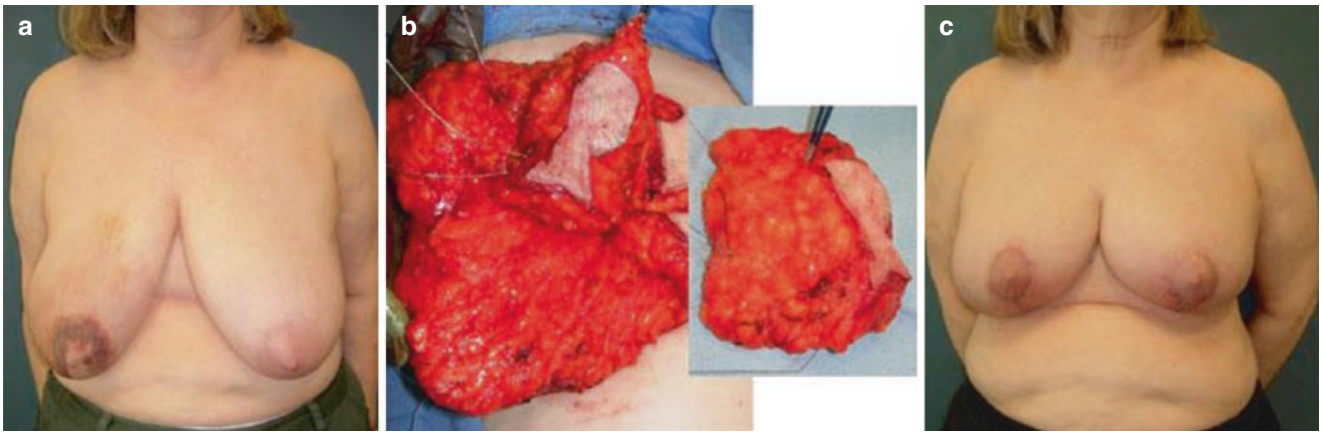

Fig. 6.8 Oncoplastic breast reduction surgery. (**a**) Preoperative appearance of bilateral macromastia with right unifocal breast cancer. (**b**) Intraoperative elevation of breast reduction flaps, resection, and removal of tumor with a large margin of surrounding normal tissue. (**c**) Postoperative appearance at 1 year with contralateral matching reduction mammoplasty

Supplemental Symmetry Procedures

The limitations of reconstructive techniques to recapitulate the native breast in unilateral reconstruction can render an asymmetric mismatch. Asymmetry is typically the result of a smaller and/or less ptotic reconstructed breast compared to the native contralateral breast. A contralateral mastopexy ("breast lift") or reduction mammoplasty can be performed at the time of expander-implant exchange following postoperative recovery after autologous-based reconstruction or at any later point in time. Some patients requiring mastectomy opt for a reconstruction larger than their native breast; thus, a subsequent contralateral augmentation may be offered as a matching procedure.

Nipple-Areolar Complex Reconstruction

For many women, reconstruction of the nipple-areolar complex is the final step of a long journey to overcoming breast cancer treatment. For some women, the restoration of breast parenchymal volume and a normal clothed appearance fulfils their breast reconstruction desires, but many patients opt for completion of breast reconstruction with pursuit of reconstruction of the nipple-areolar complex (NAC). As with restoration of breast volume, a multitude of variations and permutations are available for NAC recreation. Most of the common approaches involve the use of local flaps, skin grafts, or tattooing in isolation or in combination (Figs. 6.9 and 6.10) [22, 23].

Tattooing the nipple and/or areola has the advantage of being an essentially noninvasive, office-based procedure. Results can be variable; however, in skilled hands, this offers a remarkably natural appearance of both the nipple and areola. The shortcoming is the lack of nipple projection.

To create a projected nipple, the following techniques are useful: grafts of the contralateral nipple, auricular tissue, and the use of prosthetics and local flaps. Initial overprojection should be considered with all of these options given the likelihood of loss of projection over time. Techniques for the creation of a projected nipple through local flaps are variants of a similar theme and include the skate flap, the bell flap, the C-V flap, and double-opposing periareolar flap. A caveat to projected nipple creation is that patients should be counseled regarding their constant projection rather than intermittent erection. In addition, these nipples offer no erogenous function.

The surgical solution for areola recreation is skin grafting, for which a plethora of donor sites have been described, including contralateral areola, thigh, groin, and labia.

Nipple preservation may be the premier choice. The nipple can be preserved either through nipple-areolar-sparing mastectomy, which confers the best aesthetics to a reconstructed breast, or in vivo or ex vivo tissue banking with delayed grafting if oncologically sound.

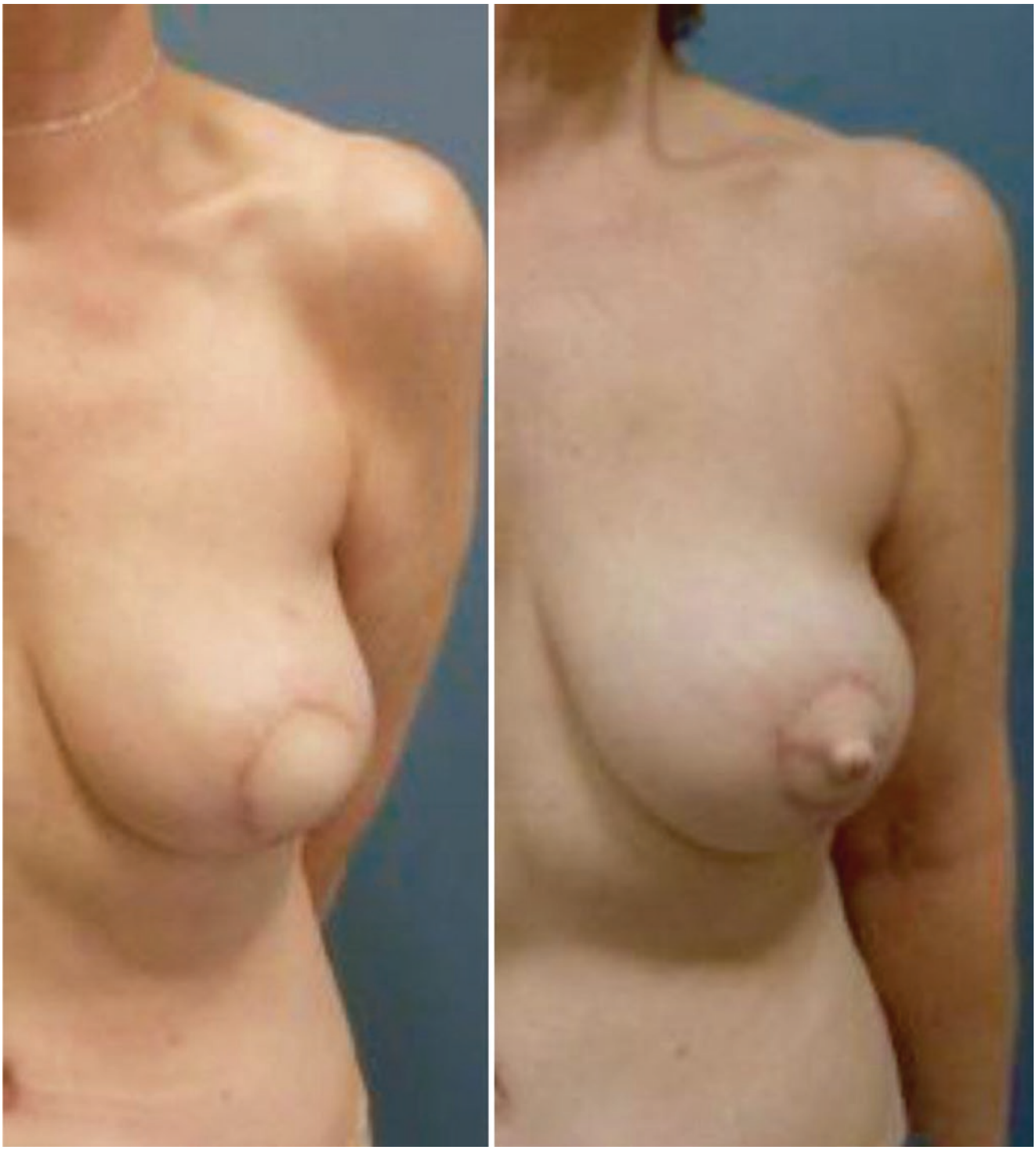

Fig. 6.9 Nipple reconstruction using a local flap method

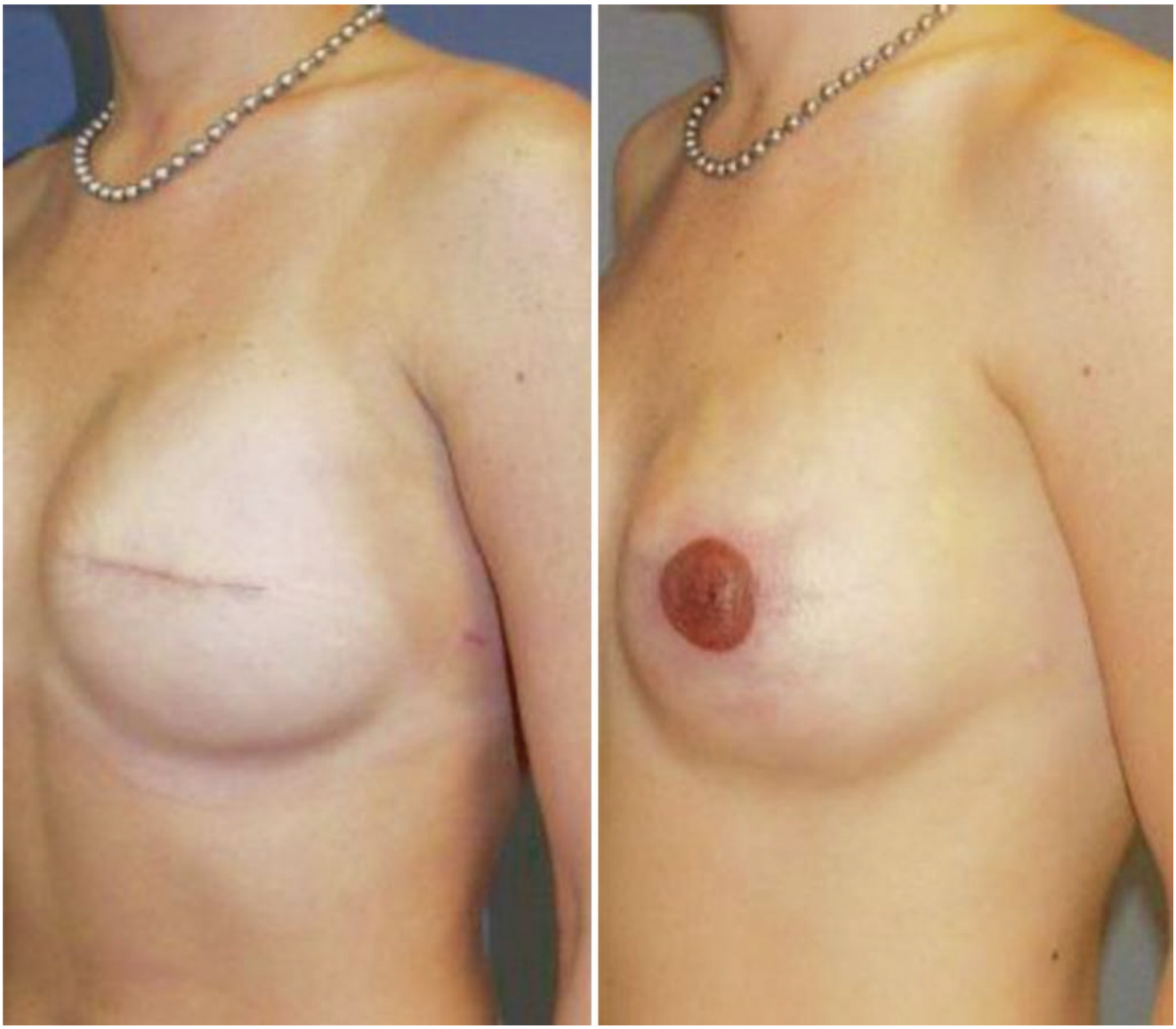

Fig. 6.10 Nipple-areolar complex reconstruction with tattooing

Some authors have advocated NAC reconstruction simultaneously with primary breast reconstruction procedures. NAC reconstruction is commonly delayed until the shape of the reconstructed breast has been achieved to ensure correct and symmetrical positioning.

The Role of Autologous Fat Grafting in Breast Reconstruction

Autologous fat grafting is an evolving treatment modality in plastic surgery for both reconstructive and cosmetic means. Fat is typically harvested from the abdomen, thighs, or buttocks by suction- or syringe-assisted lipoaspiration. Fat is subsequently processed by centrifugation or by rolling on absorbent gauze to remove the aqueous layer and oil. Fat is then transferred into small syringes and carefully injected into the recipient site in small aliquots in a layered lattice by multiple passes. Graft survival can be variable; thus, serial treatments are routinely needed.

In the context of breast reconstruction, this technique is useful for filling post-lumpectomy defects, addressing contour abnormalities following autologous reconstruction (particularly in the upper pole, where the flap "takes off" from the chest wall) and camouflaging implants to hide rippling and the outline of the prosthesis (Fig. 6.11). Experimental and early clinical data support a role for fat grafting in protecting and rescuing skin from radiation injury. Fat grafting is also increasing in popularity for whole-breast reconstruction, with reports of successful cosmetic breast augmentation with fat grafting alone.

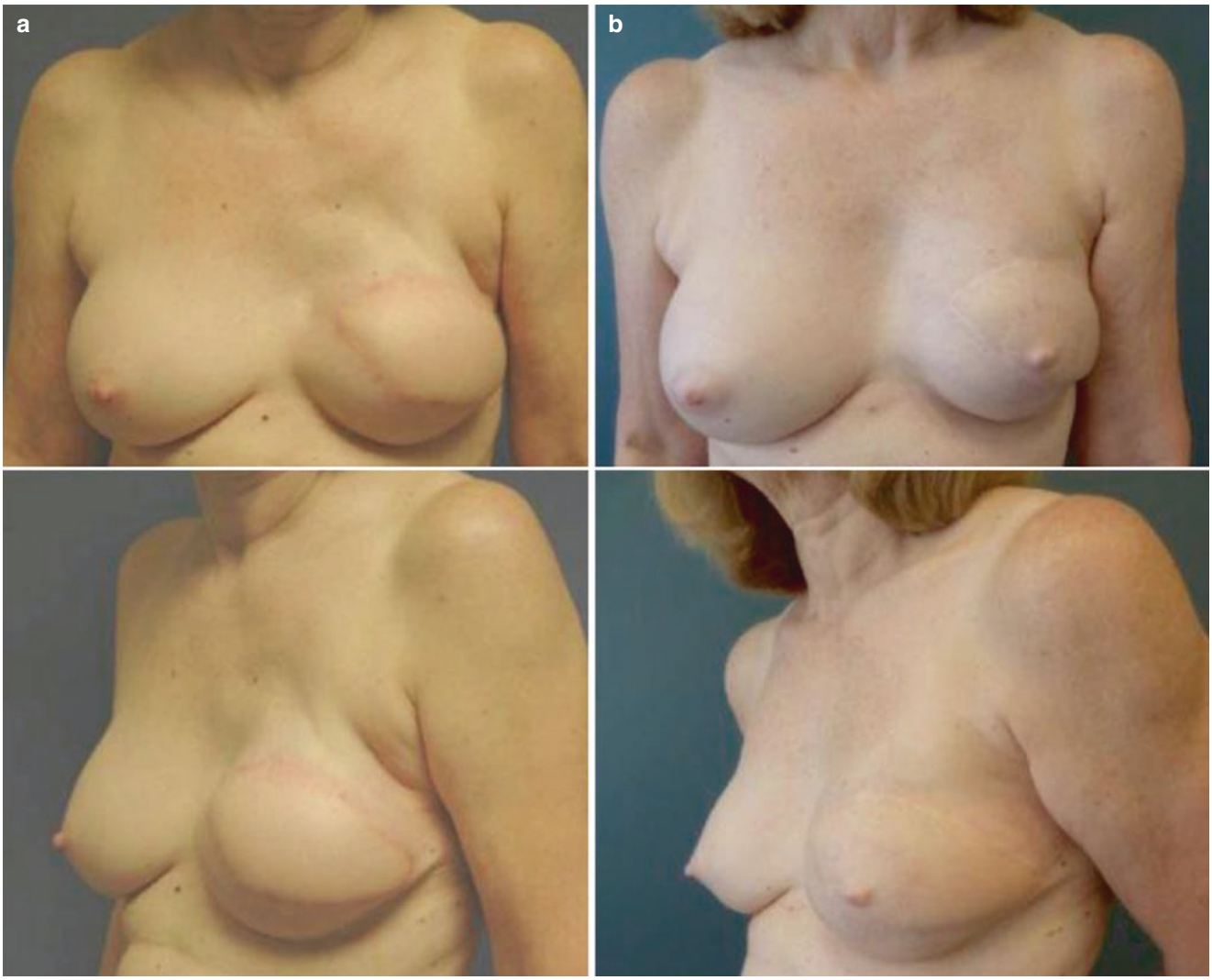

Fig. 6.11 Autologous fat grafting in breast reconstruction. (**a**) Preoperative appearance with significant left breast superior volume and contour deficit. (**b**) Correction with fat; grafting postoperative appearance at 22 months

One additional adjunct to autologous fat-grafting techniques in breast reconstruction involves the development of external expansion, such as with the BRAVA device. Such devices, originally developed for cosmetic breast augmentation, are worn on the chest and exert negative pressure on the chest wall, causing chest wall edema. This edematous tissue not only creates a larger space for fat grafting but may also improve fat graft retention as a result of improved blood supply. Patients are instructed to wear the device as much as possible, typically approximately 12–14 h a day for 4 weeks and 24 h a day for 2–3 days prior to grafting. Patients then undergo fat grafting with a target of approximately 200 ml. The use of the device may be resumed 3 days post grafting, and three to six cycles of expansion and grafting are typically required to achieve an ideal result [24].

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Adjuvant Systemic Therapy: Endocrine Therapy

7

Ibrahim Yildiz and Pinar Saip

Introduction

Adjuvant endocrine therapy (ET) is a major treatment modality for estrogen receptor (ER)-positive breast cancer. Among early-stage breast cancer patients, approximately 60% require adjuvant ET after chemotherapy (CT), 20% only require ET, and 20% only require CT. The antiestrogen drug tamoxifen was first introduced in the 1970s, and over the past 40 years, it has significantly improved overall survival (OS) in women with hormone receptor (HR)-positive early breast cancer. More recently, third-generation aromatase inhibitors (AIs) have been added to the repertoire of adjuvant ETs, and these inhibitors are superior to tamoxifen in reducing recurrence risk and improving OS in postmenopausal women.

Current ETs modulate or disrupt estrogen production or ER function/expression in breast cancer cells. In premenopausal women, the ovarian follicles are the main source of estrogen production. Ovarian estrogen production is regulated by the anterior pituitary gland, which produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts upon thecal cells to stimulate androgen synthesis, whereas FSH acts upon granulosa cells to stimulate the production of the enzyme aromatase, which converts testosterone and androstenedione to estradiol (E_2) and estrone, respectively, through aromatization. Pituitary LH and FSH production is in turn regulated by LH-releasing hormone (LHRH) (also known as gonadotropin-releasing hormone), which is produced in the hypothalamus. In postmenopausal women, estrogen production is dependent on peripheral aromatization, which predominantly occurs in the liver, adrenal glands, and adipose tissue. ET modulates or disrupts ER signaling by blocking pituitary LH/FSH production (LHRH agonists), blocking the ER (tamoxifen), degrading the ER (fulvestrant), or inhibiting peripheral estrogen production (AIs). Given their different modes of action, menopausal status is important in ET selection.

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Rationale of Endocrine Therapy

ERs belong to a family of nuclear steroid receptors that includes thyroid hormone, vitamin D, and retinoid receptors. ER phosphorylation, which occurs upon estrogen binding, induces a conformational change, resulting in receptor dimerization. The receptor complex binds to specific estrogen response elements in the promoters of target genes, resulting in the upregulation of target gene expression [1]. Two ERs, ERα and ERβ, have been described [2]. ERβ is broadly expressed in a variety of tissues, whereas ERα has a more restricted expression pattern (breast, ovary, uterus, and endometrium). The function and role of ERβ in breast cancer are not yet clear; thus, ER generally refers to ERα. The ER exerts both genomic and nongenomic effects in breast cancer. Genomic effects include the transcriptional activation of specific genes that are important for tumor cell growth and survival, whereas nongenomic effects include the activation of growth factor pathways, such as those of human epidermal growth factor receptor 2 (HER2) and insulin-like growth factor receptor, that enhance tumor growth. Growth factor receptor-linked kinases further activate the ER and its coactivators to augment ER-mediated transcriptional activity. This bidirectional crosstalk can cause ET resistance [3]. HR status is currently determined based on the immunohistochemical (IHC) expression of ER and progesterone receptor (PR). Tumors with any detectable (≥1%) ER and/or PR expression are considered HR positive. ER expression correlates with slower tumor growth, better differentiation, and longer natural history. By contrast, the absence of both ER and PR expression is associated with poorer prognosis and reduced OS rate. A positive response to hormone therapy is correlated with higher HR

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protein and mRNA expression levels [4]. For example, 60% of ER-positive/PR-positive patients were responsive to ET, compared with 30% of ER-positive/PR-negative patients and <10% of ER-negative/PR-negative patients. The updated results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) clearly showed that the benefit of ET only occurs in ER-positive tumors and is strongest in tumors with high ER expression [5]. The benefit of adjuvant ET is very small in patients with HR-positive disease who have lymph node-negative cancers ≤0.5 cm or 0.6–1.0 cm in diameter with favorable prognostic features.

Determination of Endocrine Therapy Responsiveness

Endocrine-responsive breast cancer is a heterogeneous disease with a wide spectrum of clinical, pathologic, and molecular features. A variety of prognostic factors associated with recurrence risk in ER-positive breast cancer have emerged (Table 7.1). These factors provide information on the likelihood of tumor recurrence and on risk reduction with adjuvant ET. They may also help to estimate the absolute magnitude of treatment effects. However, to date, no single marker—aside from HR expression—is adequate for identifying patients who may benefit from adjuvant ET. Similarly, no single marker can identify the optimal ET for a given patient. Although molecular typing is an ideal method for assessing recurrence risk and treatment response, routine genetic profiling has not yet been established in clinical practice. IHC typing is still considered state of the art for assessing the risk of relapse and the potential benefits of specific therapies.

The evolving role of endocrine responsiveness in the selection of adjuvant breast cancer therapy is clearly seen in the consensus reports of the St. Gallen International Expert Consensus Meetings. In 2005, St. Gallen Conference panelists included endocrine responsiveness as the decisive criterion in adjuvant therapy selection [6]. Three categories (responsive, uncertain responsive, and unresponsive) were acknowledged and were later renamed as highly endocrine responsive, incompletely endocrine responsive, and endocrine nonresponsive [7]. The definitions of these categories rely mainly, but not exclusively, on the percentages of ER- and PR-positive tumor cells. High ER and PR expression and the absence of adverse biological factors (e.g., HER2 overexpression/amplification, high proliferation index, and high urokinase inhibitor type-1 level) denote highly endocrine-responsive tumors. Incompletely endocrine-responsive tumors are characterized by PR negativity, the presence of adverse biological factors, and extensive axillary lymph node invasion. At St. Gallen 2011, endocrine responsiveness was first linked to the intrinsic molecular breast cancer subtypes (Table 7.2) [8].

Table 7.1 Prognostic factors in HR-positive breast cancer

Tumor size
Nodal status
Tumor grade
Quantitative HR expression
HER2 status
Lymphovascular invasion
Proliferation status (e.g., Ki-67)
Multigene prognostic signatures (e.g., 21-gene recurrence score, PAM 50, Mamma Print)

Gene Expression Profiling

Breast cancer is a heterogeneous disease with diverse morphologies, molecular characteristics, and clinical behaviors. Gene expression profiling studies have identified several distinct breast cancer subtypes that differ markedly in prognosis and therapy response [8–10]. A list of the intrinsic genes that are used to differentiate subtypes includes ER, HER2, and proliferation-related genes as well as a unique cluster of genes called the basal cluster. The molecular subtypes include the following: (1) luminal subtype (luminal A and B) expresses genes associated with luminal epithelial cells of normal breast tissue and overlaps with ER-positive breast cancers as defined by clinical assays, (2) HER2-enriched subtype comprises the majority of clinically HER2-positive breast cancers, and (3) ER-negative subtype expresses low levels of HR-related genes.

The luminal A and luminal B subtypes comprise the majority of ER-positive breast cancers, with luminal A

Table 7.2 Clinicopathologic definitions of the intrinsic subtypes according to the 2011 St. Gallen International Expert Consensus Meeting

Intrinsic subtype	Clinicopathologic definition
Luminal A	ER and/or PR positive
	HER2 negative
	Ki-67 low
Luminal B (HER2 negative)	ER and/or PR positive
	HER2 negative
	Ki-67 high
Luminal B (HER2 positive)	ER and/or PR positive
	HER2 positive
	Ki-67 any

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The 2011 Saint Gallen Consensus Meeting defined as "low proliferation" tumors with a Ki67 index <14%. However, during the 2013 Saint Gallen Conference, the majority of panelists voted that a threshold of ≥20% was indicative of "high" Ki67 status. In March 2015, during the last Saint Gallen Conference, the use of the median Ki67 value from the local laboratory was proposed as the cutoff and accepted by the panel of experts

tumors being more common (40% vs. 20%, respectively, of all breast cancers). These subtypes have certain important molecular and prognostic distinctions. The clinicopathologic definitions of luminal A and B subtypes are shown below (Table 7.2). Luminal A tumors usually have high ER expression, low HER2 expression, and a low proliferation index (Ki-67). Compared with luminal A tumors, luminal B tumors have a lower ER expression, variable HER2 expression, and higher proliferation index. Luminal B tumors carry a worse prognosis than luminal A tumors.

Gene expression profiling has shed light on the complex molecular background of this disease and holds the potential for more accurate prognostication and patient stratification for therapy. Several genomic tests have been developed with the aim of improving prognostic information beyond that which is provided by classic clinicopathologic parameters [11–14]. Some of these tests are currently available in the clinic and are used to determine prognosis and, more importantly, to assist in determining the need for adjuvant chemotherapy, particularly in patients with ER-positive disease. The available data suggest that information generated from genomic tests has resulted in a change in decision-making in approximately 25–30% of cases.

Molecular signatures, such as the 21-gene recurrence score (RS) (Oncotype DX®) [11], the Amsterdam 70-gene prognostic profile (MammaPrint®) [12], Prosigna (PAM50) [14], and the Rotterdam/Veridex 76-gene signature [13], increase the prognostic value of conventional indicators in predicting breast cancer outcomes and treatment response. Oncotype DX is the most widely used of these assays. Oncotype DX can be performed using formalin-fixed paraffin-embedded tissue, whereas the other tests require fresh or frozen tissue. The predictive value of Oncotype DX has been validated in both premenopausal and postmenopausal women, and its use in node-negative, ER-positive breast cancer patients is suggested in the American Society of Clinical Oncology (ASCO) guidelines. MammaPrint and Oncotype DX have a similar predictive ability for clinical outcome [15]. The MammaPrint assay is approved by the Food and Drug Administration (FDA) for the assessment of recurrence risk in ER-positive and ER-negative breast cancer patients.

The Trial Assigning Individualized Options for Treatment (TAILORx) aims to validate the RS prospectively. This study recruited 10,273 node-negative patients with hormone receptor-positive and HER2-negative breast cancer. The RS determined the recommended adjuvant therapy. Of note, the cutoff scores for the respective risk groups were different from earlier studies (low-risk ≤10, intermediate-risk 11–25, and high-risk ≥26). This decision to change the cutoff scores was based on clinical consensus. The primary endpoint was disease-free survival (DFS). Only intermediate-risk patients underwent randomization of treatment. Low-risk patients were recommended endocrine therapy alone, whereas high-risk patients were recommended chemotherapy in combination with endocrine therapy. The results for the low-risk RS have been reported recently. A total of 1629 patients (15.9% of the trial population) had a low-risk RS. With endocrine therapy alone, these patients had excellent 5-year disease-free survival and distant recurrence-free survival rates of 93.8% and 99.3%, respectively [16]. The results for the intermediate-risk RS have also been presented in ASCO 2018. Women with intermediate-risk RS (11–25) were randomized to receive endocrine therapy or chemotherapy. In women with HR-positive, HER2-negative, AN-negative breast cancer and an RS of 11–25, adjuvant endocrine therapy was not inferior to chemotherapy in ITT analysis. According to this study, the findings suggest that chemotherapy may be spared in women with hormone receptor-positive, HER2-negative, node-negative breast cancer older than 50 years with an RS of 0–25 or 50 years or younger with an RS of 0–15, although some benefit of chemotherapy was found in some women 50 years of age or younger. The investigators found that, among patients age 50 or younger with a score of 16–25, there was some benefit of added chemotherapy; there were 2% fewer distant recurrences for those with an RS of 16–20 and 7% fewer for those with an RS of 21–25. Reporting on patients with high RS scores is pending.

The recently published phase 3 study MINDACT trial was designed to offer prospective evidence of the clinical utility of using the 70-gene signature in addition to standard clinical-pathological criteria to select patients for adjuvant chemotherapy. This trial randomized 6693 women with early-stage breast cancer and evaluated both the genomic risk (using the 70-gene signature) and the clinicopathological risk (using a modified version of Adjuvant! Online). Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did. In patients with discordant risk results, either the genomic risk or the clinical risk was used to decide the use of chemotherapy. The 5-year rate of survival without distant metastasis for women deemed to be at high clinical risk, and low genomic risk was 94.7% (95% confidence interval, 92.5–96.2) for those not receiving chemotherapy, above the pre-defined threshold of 92%. The subset of patients who had ER-positive, human epidermal growth factor receptor 2-(HER-2)-negative, and either node-negative or node-positive disease had similar rates of survival without distant metastasis. Women at high clinical risk and low genomic risk for recurrence who were spared chemotherapy based on the 70-gene signature had a 5-year rate of survival without distant metastasis that was 1.5% points lower than the rate with chemotherapy (93.9% vs. 95.5%). These results indicate that approximately 46% of women with breast cancer who are at high clinical risk might not need chemotherapy [17].

21-Gene Recurrence Score in Lymph Node-Negative Patients Treated with Tamoxifen

The 21-gene assay includes 16 tumor-associated genes and five reference genes, which are used to compute an RS. Higher expression of favorable genes (e.g., *ER*, *glutathione S-transferase Mu 1*, and *BCL2-associated athanogene*) results in a lower RS because of a negative coefficient in the RS algorithm. Higher expression of unfavorable genes (CD68 and genes in the proliferation, HER2, and invasion groups) contributes to a higher RS because of a positive coefficient in the RS algorithm (Fig. 7.1). The 21-gene RS was validated in an independent dataset derived from 668 samples collected in the tamoxifen-treated arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, a prospective randomized clinical trial that examined the benefit of adjuvant tamoxifen in HR-positive, node-negative breast cancer. Although this population had a generally good prognosis, the rates of distant recurrence at 10 years were 7%, 14%, and 31% in patients with low (<18), intermediate [18–30], and high (>30) RSs, respectively (Table 7.3) [11]. The sensitivity of RS was 76.9% (95% CI 75.1–80.3), indicating that approximately 77% of patients who developed distant recurrence had a high or intermediate RS. The specificity was 55.4% (95% CI 54.1–56.8), indicating that 55% of patients with no recurrence had a low RS. The NSABP B-20 trial was performed to examine the benefit of concurrent tamoxifen and CT versus tamoxifen alone in node-negative, ER-positive breast cancer patients [18]. Tumor specimens from the tamoxifen-only arm were used as a training set for assay development [19]. In the tamoxifen-only arm, a high RS was almost five times more likely to occur in patients who developed distant recurrence at 10 years, whereas a low RS was five times more likely to occur in patients who did not develop distant recurrence at 10 years. RS sensitivity and specificity were 84% (95% CI 79–98) and 65% (95% CI 63–68), respectively. In a retrospective analysis of the NSABP B-14 and B-20 trials, RS was able to quantify recurrence risk as a continuous variable and predict tamoxifen and CMF responsiveness.

Table 7.3 Risk of distant recurrence at 10 years according to recurrence score in the NASBP B-14 validation study

Recurrence score	Risk group	*n*	10-year distant recurrence % (CI)
<18	Low	338	6.8 (4.0–9.6)
18–30	Intermediate	149	14.3 (8.3–20.3)
≥31	High	181	30.5 (23.6–37.4)

CI Confidence interval

21-Gene Recurrence Score in Lymph Node-Positive Patients Treated with Tamoxifen

In the Southwest Oncology Group (SWOG)-8814 (North American Breast Cancer Intergroup (INT) 0100) study, 1477 postmenopausal women with HR-positive, node-positive

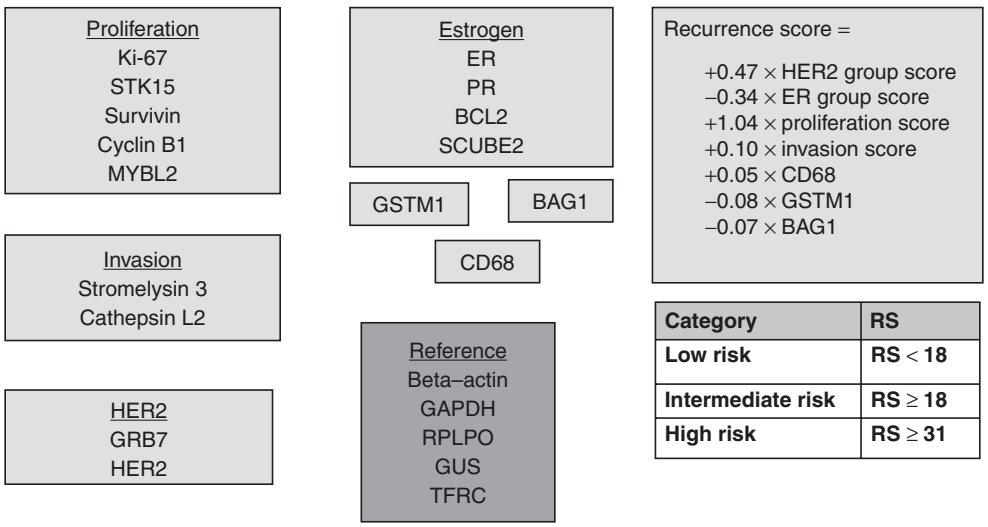


Fig. 7.1 Oncotype DX (Genomic Health, Redwood City, CA) recurrence score (*RS*): genes and algorithm. *HER* human epidermal growth factor receptor, *ER* estrogen receptor, *PR* progesterone receptor. *BAG 1* BCL2 Associated Athanogene 1, *BCL2* associated athanogene: BAG1, B-cell lymphoma 2, BCL2-associated athanogene, *ER* estrogen receptor, *HER2* epidermal growth factor receptor 2, *GAPDH* glyceraldehyde 3-phosphate dehydrogenase, *GRB7* growth factor receptor-bound protein 7, *GSTM1* glutathione S-transferase mu 1, *GUS* glucuronidase, *MYBL2* Myb-related protein B, *PR* progesterone receptor, *RPLPO* ribosomal large protein PO, *RS* recurrence score, *SCUBE2* signal peptide CUB domain EGF-like 2, *STK15* serine/threonine protein kinase 6, *TFRC* transferrin receptor

disease were randomized to receive tamoxifen alone or cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) plus tamoxifen. For patients treated with tamoxifen alone, the 10-year disease-free survival (DFS) rates were 60%, 49%, and 43% in the low, intermediate, and high RS groups, respectively. The continuous RS was prognostic for the first 5 years but not beyond 5 years [20]. Patients with high scores benefitted from CT, whereas those with low scores showed no benefit from CT regardless of the number of positive lymph nodes.

21-Gene Recurrence Score in Lymph Node-Positive and Node-Negative Patients Treated with Tamoxifen or Anastrozole

The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial examined the predictive ability of RS for recurrence in CT-naive postmenopausal breast cancer patients with node-negative (n = 872) or node-positive (n = 432) disease. After combining the treatment arms, the 9-year distant recurrence rates were 4%, 12%, and 25% and 17%, 28%, and 49% for node-negative and node-positive patients in the low, intermediate, and high RS groups, respectively (both $p < 0.001$).

Determination of Menopausal Status

Definitions of menopause-associated terms and biomarkers used to assess menopausal status are provided in Boxes 7.1 [21–23] and 7.2 [24, 25], respectively. Menopausal status is generally assessed using clinical features such as age, menstrual history, and menopausal symptoms, and it may be confirmed by serum FSH and E_2 levels within the menopausal range. Elevated FSH and reduced E_2 levels generally confirm the clinical diagnosis of menopause. However, the use of

Box 7.1 Definitions of Primary Ovarian Insufficiency, Amenorrhea, Menopause, Menopausal Transition, and Perimenopause

Primary ovarian insufficiency (*POI*): Amenorrhea for at least 3 months and serum FSH and E_2 concentrations of >40 IU/L and <10 pg/mL, respectively, obtained twice at least 1 month apart in a woman aged <40 years [21]. The cause of ovarian dysfunction is inherent in the ovary. In most cases, an unknown mechanism leads to premature exhaustion of the resting pool of primordial follicles. POI may also result from genetic defects, autoimmunity, surgery, radiotherapy, or cytotoxic CT.

Amenorrhea: The absence of menses on a permanent, intermittent, or temporary basis. Amenorrhea is classified as primary or secondary. Primary amenorrhea is the failure of menses to occur by age 16 years. Secondary amenorrhea is defined as the absence of menses for more than three cycles or 6 months in a woman with previously normal menses. Amenorrhea may be due to pregnancy or caused by infections, uncontrolled diabetes mellitus, malnutrition, hypothalamic or thyroid dysfunction, hyperprolactinemia, or polycystic ovary syndrome. Secondary amenorrhea in conjunction with increased FSH levels often indicates ovarian insufficiency. However, gonadotropin cutoff values suggestive of ovarian insufficiency onset have not been established, likely due to the intermittent and sometimes erratic decline in ovarian function [21].

Menopause: The permanent cessation of menses resulting from the loss of ovarian follicle activity. Natural menopause can only be retrospectively established after 12 consecutive months of spontaneous amenorrhea. The mean age of natural menopause is 51 years, with a range of 40–60 years [21]. Postmenopause is characterized by markedly high FSH levels, low E_2 levels, and very low or undetectable inhibin-B and anti-Müllerian hormone (AMH) [22]. Varying menopause definitions have been used in breast cancer clinical trials. According to the National Comprehensive Cancer Network (NCCN), menopause is defined as bilateral oophorectomy, age ≥ 60 years, or age < 60 years with amenorrhea for ≥12 months in the absence of CT, tamoxifen, toremifene, or ovarian suppression and FSH and E_2 levels within postmenopausal range.

Menopausal transition: Menopausal transition typically begins in women in their mid-40s and precedes the final menses by 2–8 years (mean duration, 4 years). The endocrine changes underlying menopausal transition are predominantly the consequences of a marked decrease in ovarian follicle numbers. E_2 levels fall considerably, whereas estrone levels remain almost unchanged, reflecting peripheral aromatization of adrenal and ovarian androgens. The increase in FSH is greater than that of LH, presumably due to the loss of inhibins and estrogen feedback. Other significant changes include a decrease in inhibin-B levels during the early phase of the menstrual cycle and AMH levels.

Perimenopause: Perimenopause starts with menopausal transition and lasts throughout the 12 months of amenorrhea [23].

Box 7.2 Biomarkers for the Assessment of Menopausal Status

FSH: FSH is produced by the anterior pituitary gland in response to the pulsatile release of LHRH from the hypothalamus. FSH stimulates the growth of the small antral follicles and finally causes selection of the follicle with the most FSH receptors, which will become the dominant preovulatory follicle. Granulosa cells of the developing preovulatory follicles produce considerable amounts of E_2, which in turn exert negative feedback effect to decrease pituitary FSH secretion. The Stages of Reproductive Aging Workshop proposed FSH as the best predictive marker of menopause but did not establish a precise cutoff value to define menopausal status [24]. Elevated blood FSH levels reflect an age-dependent decrease in the follicle pool. FSH levels rise above 20 IU/L during the late perimenopausal phase; therefore, this level is often used as the cutoff value to determine ovarian reserve depletion. However, tamoxifen treatment in truly postmenopausal women may decrease FSH levels, even into the premenopausal range. Conversely, chemotherapy-induced amenorrhea (CIA) in premenopausal women may temporarily result in highly increased FSH levels; thus, folliculogenesis may resume later. Therefore, no absolute cutoff level of FSH can be provided above which folliculogenesis no longer occurs [25].

E_2: E_2 is mainly secreted by the late antral follicle and the ensuing corpus luteum. E_2 secretion is regulated by FSH and LH. Although E_2 levels <130 pmol/L are considered postmenopausal levels, values of 10–60 pmol/L have been reported. Furthermore, E_2 levels are higher in obese postmenopausal women because of the relatively high aromatase activity associated with the increased number of adipose cells. In contrast, E_2 levels are lower among smokers because nicotine and its metabolite cotinine are strong inhibitors of aromatase. In addition, hormone replacement therapy may lower FSH levels and increase E_2 levels up to 1 year after therapy cessation [25].

LH: LH levels increase with age, independent of E_2 levels, due to increased pituitary sensitivity to LHRH. During menopausal transition, LH increases slowly and reaches moderately elevated levels in postmenopause.

Antral follicle count (AFC), ovarian volume, and blood levels of FSH, E_2, inhibin-B, and AMH are used to evaluate ovarian reserve. AMH and AFC provide the most reliable assessment of the reproductive lifespan of the ovaries, fertility status, and risk of premature ovarian failure. Menstrual cycle irregularity, vasomotor symptoms, significantly elevated basal FSH, and undetectable inhibin-B levels are only short-term predictors of menopause (within 2 years) [27]. Low/undetectable AMH levels, low AFC, poor response to in vitro follicle stimulation, and rise in FSH during the early follicular phase indicate a limited ovarian reserve and risk of early menopause. However, these factors do not predict imminent menopause [27]. Although currently available enzyme-immunometric assays for AMH and FSH are highly sensitive (detection level, 0.05 ng/mL), the lowest level of detection is still not considered an absolute cutoff level to precisely mark menopause.

these biomarkers has several limitations. The transition toward menopause is highly variable, thus making it difficult to define diagnostic cutoff values for FSH/E_2. Therefore, single time point testing of FSH/E_2 levels is not sufficient to confirm menopause. Furthermore, FSH/estrogen levels are influenced by ETs. Tamoxifen increases circulating estrogens and decreases FSH levels [26]. AIs profoundly decrease estrogen levels and increase FSH levels in postmenopausal patients [26, 27]. Therefore, in these clinical settings, FSH/E_2 levels are not reliable surrogate markers of menopause.

Chemotherapy-Induced Amenorrhea/ Menopause

CT can cause significant changes in ovarian function by directly destroying the remaining functional follicles or indirectly promoting the loss of functional follicles through induction of ovarian fibrosis. CT can also lead to amenorrhea by inducing primary or hypergonadotropic hypogonadism [28]. CT is associated with the occurrence of POI. CT-induced POI results from an acceleration of the natural ovarian aging process caused by damage to the steroid-producing granulosa and theca cells and apoptotic death in a fraction of primordial follicles, which mainly impairs follicular development. The sensitivity of the ovaries to CT varies considerably (Table 7.4), with alkylating agents being the most commonly associated with permanent and irreversible gonadal damage [29]. The risk of CT-induced POI has been correlated with CT type, higher cumulative CT dose, and older age, and age > 40 years is the strongest predictor of both CIA and chemotherapy-induced menopause (CIM) [21, 23].

The estimated risk of CIA associated with single and combination CT regimens is shown in Table 7.4 [30]. Transient and prolonged amenorrhea are more frequently observed with CMF and cyclophosphamide, epirubicin, and 5-fluorouracil/CAF regimens compared with doxorubicin

Table 7.4 Estimated risk of permanent amenorrhea associated with single-agent and combination adjuvant regimens in early breast cancer

	Single-agent therapy	Combination therapy
High risk (>80%)	Cyclophosphamide	CMF, FEC, and FAC; six cycles in women aged ≥40 years
Intermediate risk	Cisplatin	CMF, FEC, and FAC; six cycles in women aged 30–39 years
	Carboplatin	AC and EC; four cycles in women aged ≥40 years
	Adriamycin	Taxane-containing combinations
	Taxanes	
Low risk (<20%) or no risk	Methotrexate	CMF, FEC, and FAC; six cycles in women aged <30 years
	5-Fluorouracil	AC and EC; four cycles in women aged <40 years
To be determined	Trastuzumab	
To be determined	Lapatinib	

Adapted from Lee et al. [30] with permission from the American Society of Clinical Oncology

AC adriamycin and cyclophosphamide, *CMF* cyclophosphamide, methotrexate, and fluorouracil, *EC* epirubicin and cyclophosphamide, *FAC* fluorouracil, adriamycin, and cyclophosphamide, *FEC* fluorouracil, epirubicin, and cyclophosphamide

and cyclophosphamide, presumably due to the higher cumulative dose of cyclophosphamide received [28]. The addition of taxanes increases the risk of CIA in many individuals, particularly in the first year of use [23, 31]. Tamoxifen use following CT significantly increases the rate and/or duration of CIA and slightly but significantly increases the CIM risk [23, 28, 32]. However, the mechanism by which tamoxifen influences CIA/CIM remains unclear. Tamoxifen may increase plasma E_2 levels and interfere with the hypothalamic–ovarian feedback loop that regulates estrogen synthesis [23].

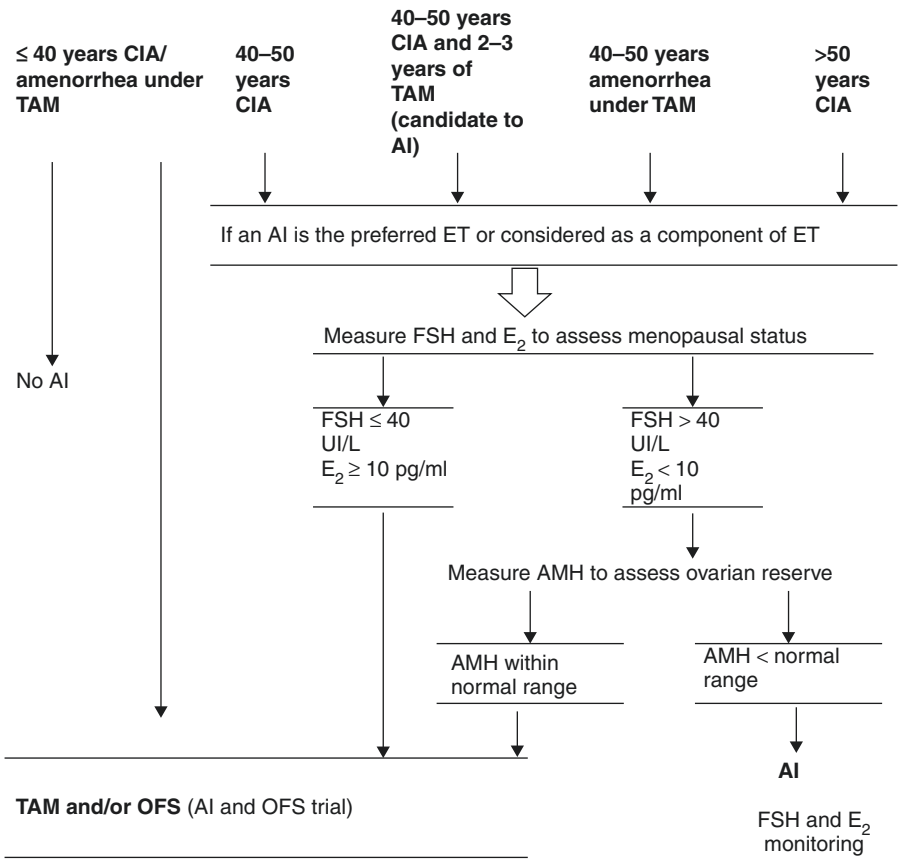
CIA complicates menopause assessment in premenopausal women with early breast cancer. In clinical practice, menopausal status in women with CIA may be determined only using hormonal evaluations and a nonvalidated pool of clinical data, including age, menstrual history, vasomotor symptoms, and the likelihood of gonadal toxicity from CT. The use of such criteria may lead to an inaccurate assessment of menopausal status. Furthermore, although many patients >40 years of age develop CIA, this type of ovarian failure may be temporary in a considerable number of patients. The percentage of women with CIA/oligomenorrhea who will later develop CIM is not yet known. Menstrual cycles and/or fertility may recover months to years after CT withdrawal. Resumption of menses is more likely to occur in younger women, those exposed to less gonadotoxic regimens, and those with a higher basal number of follicles. In fact, the remaining follicles may regrow from the primordial pool in 3–6 months, and gonadotropin levels may return to normal after CT withdrawal, especially in very young women [29]. However, individual CIM risk cannot be predicted. Thus, the use of both pre-CT and post-CT evaluations of ovarian reserve may better predict menopausal status.

Endocrine Therapy Selection According to Menopausal Status

Assessment of ovarian function is important in hormone-sensitive breast cancer patients who are eligible to receive adjuvant ET. Adjuvant AI treatment administered upfront or replacing tamoxifen is superior to tamoxifen alone in postmenopausal patients and has therefore become the standard of care in these patients. In contrast, adjuvant treatment with tamoxifen with or without ovarian suppression is recommended in premenopausal women. Tamoxifen can be safely given to premenopausal women; however, this is not the case for AIs. AIs interfere with androgen-to-estrogen conversion by blocking aromatase, thereby lowering E_2 levels in truly postmenopausal women. However, in the presence of functional ovaries, low levels of estrogen will enhance pituitary FSH production, thereby indirectly stimulating follicular aromatase production and subsequent E_2 production. Consequently, AI treatment in the absence of an LHRH agonist may be ineffective in postmenopausal women who were inaccurately classified as premenopausal. Moreover, in the case of CIA, AIs may promote recovery of ovarian function, leading to therapeutic failure and even to unwanted pregnancy.

The choice of adjuvant ET may be guided by age only in specific patient groups (Table 7.5). Women ≤40 years with CIA should not receive adjuvant ET with AIs alone. Estrogen depletion is the desired endocrine strategy in these patients. Their management should include oophorectomy or chemical ovarian suppression with combined LHRH agonist and tamoxifen. Serial monitoring of E_2 and gonadotropin levels should be performed in women 40–50 years of age with CIA. Women who have FSH and E_2 levels within the premenopausal range (≤40 IU/L and ≥10 pmol/L, respectively) should receive tamoxifen alone or tamoxifen plus ovarian suppression. In patients with hormone levels indicative of postmenopausal status (FSH > 40 IU/L and E_2 < 10 pmol/L), AMH assessment may be useful to detect any residual ovarian function. AI may be cautiously administered to patients whose AMH levels are below the lower limits of normal range. In addition, serial hormone monitoring should be performed (with a reasonable timing of 4 months between consecutive measurements) to achieve ongoing confirmation of menopausal status. For patients whose levels remain within the postmenopausal range, AI can be continued. Otherwise, tamoxifen alone or in combination with ovarian suppression

Table 7.5 Suggested practical approaches to determine the appropriateness of adjuvant AI therapy in breast cancer patients with CIA or tamoxifen-induced amenorrhea



Adapted from Torino et al. [23] with permission from BioScientifica, Ltd.
AI aromatase inhibitor, *AMH* anti-Müllerian hormone, *CIA* chemotherapy-induced amenorrhea, *E2* estradiol, *ET* endocrine therapy, *FSH* follicle-stimulating hormone, *OFS* ovarian function suppression, *TAM* tamoxifen

is the appropriate ET. The same approach should be used in premenopausal women >40 years of age with CIA who may start AI after 2–3 years of tamoxifen. Likewise, in women who develop tamoxifen-induced amenorrhea and are suitable candidates for switching to an AI, it is advisable to perform serial high-quality evaluations of E_2, FSH, and AMH. The switch can only be safely made in cases with confirmed menopausal status. Women >50 years of age at the time of CT with CIA lasting >6 months may receive AI if hormone assessment has provided enough certainty of menopausal status. However, tamoxifen should replace AI in patients whose E_2 levels continue to rise [23].

Adjuvant Endocrine Therapy for Premenopausal Women

Approximately 60% of premenopausal breast cancers are ER positive. Adjuvant ET is an integral component of ER-positive breast cancer therapy. Patients with ER- and/or PR-positive invasive breast cancers should be considered for adjuvant ET regardless of age, lymph node status, or adjuvant CT use [33]. Features that are indicative of uncertain endocrine responsiveness include low levels of HR immunoreactivity, PR negativity, poor differentiation (grade 3), high proliferation index (Ki-67), HER2 overexpression, and high gene RS. In the absence of these features, tumors are considered highly endocrine responsive. Patients with tumors of different degrees of endocrine responsiveness may receive Et alone or in combination with CT. The type of treatment selected is determined by multiple factors including ER and PR status, nodal status, histological grade, and peritumoral vascular invasion (Table 7.6) [34]. Patients with tumors of uncertain endocrine responsiveness are usually treated with a combination of ET and CT. Endocrine strategies in premenopausal women include ER blockade with tamoxifen, temporary ovarian suppression with LHRH agonists, or permanent ovarian suppression with oophorectomy or radiotherapy. Tamoxifen is the mainstay of ET in premenopausal women. The benefit of ovarian suppression has not been clearly demonstrated; however, prospective studies are currently ongoing. The use of AIs as single agents is contraindicated because the reduced feedback of estrogen to the hypothalamus and pituitary may increase gonadotropin secretion and

Table 7.6 Threshold for treatment modalities according to the 2009 St. Gallen Consensus Conference

Clinicopathologic feature	Relative indication for chemoendocrine therapy	Factor not useful for decision	Relative indication for endocrine therapy alone
ER and PR levels	Low		High
Histological grade	3	2	1
Proliferation index[a]	High	Intermediate	Low
Nodal status	Positive (≥4 involved nodes)	Positive (1–3 involved nodes)	Negative
PVI	Present		Absent
pT size, cm	>5	2.1–5	≤2
Patient preference	Use all available treatments		Avoid chemotherapy-related side effects
Multigene signature assay score[b]	High	Intermediate	Low

Adapted from Goldhirsch et al. [34] with permission of Oxford University Press
ER estrogen receptor, *HER2* epidermal growth factor receptor 2, *PR* progesterone receptor, *pT* pathological tumor size (i.e., size of the invasive component), *PVI* peritumoral vascular invasion
[a]Conventional measures of proliferation include assessment of the Ki-67 labeling index (low, ≤15%; intermediate, 16%–30%; high, >30%) and frequency of mitosis. The reliability of these measures will vary in different geographic settings. First-generation gene signatures consist of ER, HER2, and proliferation-related genes. A meta-analysis indicated that much of the prognostic information in these signatures resides in their sampling of proliferative genes, but their respective total scores may be the only form in which information is provided at present and are the only format that could be used in this component of assessment of relative indications for chemotherapy
[b]The European Society for Medical Oncology Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers

stimulate the ovary, thereby leading to an increase in androgen substrates and aromatase. However, concurrent AI and ovarian suppression with an LHRH agonist, surgery, or radiotherapy may also be considered.

Tamoxifen

Until recently, tamoxifen has been the gold standard for the adjuvant treatment of ER-positive breast cancer in both premenopausal and postmenopausal women. The 2011 EBCTCG meta-analysis, which compared 5 years of tamoxifen treatment to no ET in premenopausal and postmenopausal women, was instrumental in establishing the efficacy of adjuvant tamoxifen [5]. Tamoxifen treatment resulted in a 39% reduction in breast cancer recurrence compared with placebo (relative risk [RR] 0.61, 95% CI 0.57–0.65), which translated into a 15-year absolute reduction of 13% (33% vs. 46%, respectively). This outcome was observed in both node-negative and node-positive patients. Tamoxifen treatment also resulted in a 30% reduction in breast cancer mortality risk (RR 0.70, 95% CI 0.64–0.75), which translated into a 15-year absolute reduction of 9% (24% vs. 33% in the placebo group). The magnitude of benefit was similar between women <45 and 55–69 years of age. Tamoxifen also reduced the risks of local recurrence (RR 0.54) and of contralateral breast cancer (RR 0.62).

Timing of Tamoxifen Therapy

Concurrent tamoxifen interferes with the cytotoxicity of CT in cancer cell lines in vitro [35, 36]. The SWOG-8814 (INT 0100) randomized trial investigated the timing of tamoxifen in 1558 patients receiving CT [37]. At a median follow-up of 9.94 years, CAF plus 5 years of tamoxifen was superior to tamoxifen alone, and CAF plus sequential tamoxifen was more effective than CAF plus concurrent tamoxifen. Based on these results, tamoxifen should be given sequentially and not concurrently with CT.

Duration of Tamoxifen Therapy

For decades, tamoxifen for 5 years has been the standard ET for premenopausal women [38]. Tamoxifen for more than 5 years has not been shown to be more beneficial than tamoxifen for 5 years in two North American and Scottish trials [39, 40]. However, the results of the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and Adjuvant Tamoxifen—To Offer More (aTTom) trials have recently changed this paradigm. The ATLAS trial aimed to assess the further benefit of continuing tamoxifen for 10 years in women with HR-positive breast cancer who had completed 5 years of tamoxifen. Premenopausal and postmenopausal women ($n = 6846$) were randomly assigned to receive either 5 years of additional tamoxifen or no further therapy. Extended tamoxifen reduced breast cancer recurrence by 25% (617 vs. 711 patients, respectively; $p < 0.01$) and breast cancer deaths by 29% (331 vs. 397 patients, respectively; $p = 0.001$), but it did not increase nonbreast cancer mortality. These benefits were only observed after 10 years of tamoxifen use. In the extended tamoxifen arm, 1% and 0.2% increases in endometrial cancer incidence and related deaths, respectively, in women aged >50 years were observed [41]. In the aTTom trial, 6953 women with ER-positive ($n = 2755$) or ER-untested ($n = 4198$; estimated to be 80% ER-positive) invasive breast cancer who had completed 5 years of

tamoxifen were randomized to stop tamoxifen or continue tamoxifen to year 10. Extended tamoxifen reduced breast cancer recurrence (580/3468 vs. 672/3485; $p = 0.003$) in a time-dependent manner. The rate ratio was 0.99 (95% CI 0.86–1.15), 0.84 (95% CI 0.73–0.95), and 0.75 (0.66–0.86) during years 5–6, years 7–9, and later years, respectively. Longer treatment also reduced breast cancer recurrence-related mortality (392 vs. 443 deaths; $p = 0.05$) and overall mortality (849 vs. 910 deaths; $p = 0.1$). The rate ratios were 1.03 (95% CI 0.84–1.27) during years 5–9 and 0.77 (95% CI 0.64–0.92) during the later years for breast cancer recurrence-related mortality and 1.05 (95% CI 0.90–1.22) during years 5–9 and 0.86 (95% CI 0.75–0.97) during the later years for overall mortality. Nonbreast cancer mortality was not significantly affected (457 vs. 467 deaths; rate ratio 0.94 [95% CI 0.82–1.07]). However, extended tamoxifen treatment also increased the incidence of endometrial cancer (102 vs. 45 patients; rate ratio 2.20 [95% CI 1.31–2.34]; $p < 0.0001$) and endometrial cancer-related deaths (37 [1.1%] vs. 20 [0.6%] deaths; absolute hazard ratio [HR] 0.5; $p = 0.02$) compared with 5 years of tamoxifen. The aTTom trial also demonstrated that, compared with 5 years of tamoxifen, continuing tamoxifen to 10 years in patients with ER-positive disease yielded further reductions in recurrence from year 7 onward and breast cancer mortality after year 10.

In a recent meta-analysis of extended adjuvant tamoxifen in early breast cancer (eight trials including 29,138 patients), more than 5 years of tamoxifen significantly improved OS (odds ratio [OR] 0.89; 95% CI 0.80–0.99; $p = 0.03$), breast cancer-specific survival (OR 0.78; 95% CI 0.69–0.9; $p = 0.0003$), and recurrence-free survival (RFS; OR 0.72; 95% CI 0.56–0.92; $p = 0.01$) compared with 5 years of tamoxifen. Locoregional and distant relapses were reduced by 36% and 13%, respectively. Compared with 5 years of tamoxifen, additional adjuvant ET reduced the risk of death and relapse in ER-positive breast cancer patients by 10% and 30%, respectively. Combining the results of the aTTom and ATLAS trials enhanced the significance of the recurrence ($p < 0.0001$), breast cancer mortality ($p = 0.002$), and OS ($p = 0.005$) benefits. Taken together, these studies indicate that, compared with tamoxifen for 5 years, 10 years of adjuvant tamoxifen reduces breast cancer mortality by approximately one-third in the first 10 years following diagnosis and by one-half in subsequent years [42].

The optimal duration of ET for premenopausal women to balance the potential benefits and side effects associated with treatment has yet to be determined. ET significantly affects reproductive options in premenopausal women because women are counseled not to become pregnant while undergoing adjuvant ET. Young women receiving ET may also experience menopausal symptoms, such as hot flashes, vaginal dryness, and sexual dysfunction. Tamoxifen is associated with an increased risk of thromboembolic events (1–2% increased risk of deep venous thrombosis and threefold increased risk of pulmonary embolism), increased vaginal bleeding, and threefold increased risk of endometrial cancer. However, the absolute increase in endometrial cancer is <1%, and almost all of the cancers that develop are stage I adenocarcinomas.

Tamoxifen Resistance

The expression of growth factor receptors, such as HER2, is associated with the development of tamoxifen resistance in breast cancer. Selected studies suggest that HER2-positive breast cancers may be less sensitive to some ETs, whereas other studies have failed to confirm this finding [43–46]. A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of ET type [47]. Some studies suggest that PR negativity in ER-positive tumors may be associated with increased growth factor expression, more aggressive tumor phenotype, and tamoxifen resistance. By contrast, higher levels of ER expression predict greater tamoxifen benefits. Other factors that may contribute to tamoxifen resistance include variable expression of ERα and ERβ isoforms, interference with coactivator and corepressor binding, alternative splicing of *ER* mRNA variants, modulators of ER expression (e.g., epidermal growth factor and its receptors, such as epidermal growth factor receptor 1 and HER2), and inherited drug-metabolizing *CYP2D6* genotypes. CYP2D6 converts tamoxifen to endoxifen, the major active tamoxifen metabolite. Over 100 allelic variants of *CYP2D6* have been reported. In the Breast International Group (BIG) 1-98 and ATAC trials, *CYP2D6* genotype status was shown to not influence breast cancer recurrence after tamoxifen use [48, 49]. Given the limited and conflicting evidence at this time, the NCCN Breast Cancer guidelines do not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy.

Ovarian Suppression

The ovaries are the main site of estrogen production in premenopausal women. Therefore, ovarian ablation/suppression is an endocrine therapeutic option to consider in young women with ER-positive disease. Irreversible ovarian ablation may be accomplished by surgical oophorectomy or ovarian irradiation. Radiation is seldom used because of its side effects. Adjuvant CT frequently results in permanent amenorrhea and thus represents an indirect form of ovarian ablation. Chemical castration with LHRH is a reversible approach. Chemical ovarian suppression utilizes LHRH agonists to suppress LH and FSH release from the pituitary and reduce ovarian estrogen production. Goserelin, leuprolide, and triptorelin are also used for chemical ovarian suppression; however, only goserelin has been approved by the FDA. The advantage of chemical suppression is that it is a

simple, reversible outpatient therapy. The disadvantages are restoration of estrogen production at the time of drug withdrawal, injection site reactions, and menopausal symptoms. The optimal form of ovarian suppression (surgical oophorectomy, ovarian irradiation, or chemical suppression) in the adjuvant setting is unknown because of the absence of direct comparison studies. Ovarian ablation therapy is the oldest type of breast cancer therapy. Beatson first reported its use in the palliation of young women with metastatic disease in 1896.

The role of adjuvant ovarian ablation/suppression in premenopausal women with HR-positive breast cancer remains undetermined. The combined analysis of the early studies in the 1995 overview from the EBCTCG demonstrated that ovarian ablation as a single intervention reduces breast cancer recurrence and increases survival in women <50 years of age [50]. Of the 12 randomized trials included in the analysis, 7 trials compared ovarian ablation and no CT, and 5 trials compared ovarian ablation combined with CT. By indirect comparison, the efficacy of ovarian ablation was similar to that of adjuvant CT and tamoxifen. The EBCTCG also performed a meta-analysis of randomized studies of ovarian ablation/suppression alone versus no adjuvant treatment in women >50 years. The annual odds of recurrence and death were reduced in favor of ovarian ablation/suppression over no adjuvant treatment. Reductions of 25% and 29% in recurrence and death rates, respectively, were observed in women <40 years of age, and a 29% reduction in both recurrence rate and death rate was observed in women 40–49 years of age [51]. An analysis of ovarian suppression versus no adjuvant therapy showed no significant reductions in recurrence (HR reduction −28.4; 95% CI −50.5 to 3.5; $p = 0.08$) or death (HR reduction −22; 95% CI −44.1 to 6.4; $p = 0.11$) [52]. The following findings emerged from this meta-analysis. (1) As single agents, LHRH agonists such as goserelin, leuprolide, and triptorelin showed a trend toward a lower risk of breast cancer recurrence compared with no further systemic treatment (HR 0.72, 95% CI 0.49–1.04). A trend toward a reduction in mortality was also observed (HR 0.82, 95% CI 0.47–1.43), although the analysis was likely underpowered for this outcome. (2) The combination of LHRH agonist and tamoxifen showed a trend toward a lower risk of recurrence (HR 0.85, 95% CI 0.67–1.09) and mortality (HR 0.84, 95% CI 0.59–1.19) compared with tamoxifen alone (3). The risks of recurrence (HR 1.04, 95% CI 0.92–1.17) and mortality (HR 0.90, 95% CI 0.79–1.10) did not differ between LHRH agonist plus non-anthracycline-containing adjuvant CT and adjuvant CT alone. These results suggest that LHRH agonists have limited efficacy in patients who receive non-anthracycline-based chemotherapy. This limitation is perhaps due to the high rate of treatment-induced suppression caused by CT regimens such as CMF. However, ovarian suppression may provide an additional benefit for women who are treated with contemporary anthracycline-based regimens. There is no definitive evidence of any additional benefit with the use of LHRH agonists administered as an alternative to or along with tamoxifen. LHRH agonists should be given for at least 2 years. However, the timing and optimal duration of treatment are still a matter of debate. Data comparing the efficacy of monthly and trimonthly formulations of LHRH agonists are lacking. However, monthly goserelin and trimonthly leuprolide have similar effects on E_2 and FSH levels [53]. Thus, to date, selected studies have suggested the benefits of ovarian ablation/suppression in the adjuvant treatment of premenopausal women with HR-positive breast cancer.

Ovarian suppression has also been studied with either tamoxifen or the AI exemestane in premenopausal patients in a combined analysis of the SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) trials; exemestane use was associated with a significant reduction in the risk of recurrence compared with tamoxifen. In women who did not need chemotherapy, 5 years of tamoxifen was sufficient to reduce recurrence risk, and ovarian function suppression is not advised in this group. However, in the cohort that remained premenopausal after CT (average age, 40 years), ovarian suppression added to tamoxifen achieved a 22% reduction in risk of recurrence versus tamoxifen alone. The combination of exemestane plus ovarian function suppression was even better, with a 35% reduction in risk of recurrence versus that in tamoxifen alone. The 5-year event-free survival was 78% for tamoxifen alone, 82.5% for tamoxifen plus ovarian function suppression, and 85.7% for exemestane plus ovarian function suppression [51, 54]. In the SOFT study presented at ASCO 2018, adding ovarian function suppression to tamoxifen significantly decreased the relative risk of disease-free survival events by 24% versus tamoxifen-alone in the overall population after a median of 8 years of follow-up, resulting in a 4.2% absolute benefit at 8 years. The absolute benefit was greater in women who remained premenopausal after receiving chemotherapy before starting ovarian suppression. The clinical benefit was particularly clear in women under age 35, with an 8.6% absolute benefit at 8 years. After a median follow-up of 9 years, the combined analysis of the TEXT and SOFT studies confirmed statistically significant improvements in disease outcomes with exemestane versus tamoxifen used in combination with ovarian suppression. Adjuvant exemestane plus ovarian function suppression, compared with tamoxifen plus ovarian function suppression, showed sustained absolute improvements in disease-free survival and freedom from distant recurrence of 4.0% and 2.1% at 8 years, respectively. Women with HER2-negative breast cancer experienced the greatest clinical benefit, especially those who also received adjuvant chemotherapy due to a higher risk of recurrence. In these higher-risk groups, the

absolute improvements in disease-free survival and freedom from distant recurrence were 7–9% and 5–7% across TEXT and SOFT, respectively, with exemestane plus ovarian suppression. No difference in overall survival after a median follow-up of 9 years was observed when comparing the two groups treated with ovarian suppression [55]. Based on the results of the SOFT and TEXT trials, the NCCN Panel has included ovarian suppression plus an aromatase inhibitor for 5 years as an adjuvant endocrine therapy option for premenopausal women with hormone receptor-positive breast cancer at higher risk of recurrence (e.g., young age, high-grade tumor, lymph node involvement).

In addition, randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant CT in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of CIA.

The abrupt interruption of ovarian function is a significant problem in young premenopausal patients. Adverse events may include severe menopause-related signs and symptoms, psychological distress, impaired quality of life, sexual dysfunction, changes in personal and family relationships, and bone loss. Ovarian ablation alone is not recommended as an alternative to any other form of systemic therapy, except in the specific cases of patients who are candidates for other forms of systemic therapy but who for some reason will not pursue other systemic therapies (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).

Ovarian Ablation/Suppression Versus Chemotherapy

Studies of ovarian ablation/suppression alone versus CMF alone have generally demonstrated similar antitumor efficacy in premenopausal patients with HR-positive tumors, whereas superior outcomes were achieved with CMF in HR-negative patients (Table 7.7) [52, 56–63]. The benefits of ovarian suppression/ablation may be greater in younger premenopausal patients.

Ovarian Ablation/Suppression Plus Tamoxifen Versus Chemotherapy

In general, studies of ovarian ablation/suppression plus tamoxifen versus CT alone have shown no differences in recurrence or survival rates in premenopausal women (Table 7.7) [51, 64–66].

Chemotherapy Plus Ovarian Suppression/Ablation with or Without Tamoxifen

Clinical trials evaluating the efficacy of ovarian suppression as combination or sequential therapy in premenopausal women with HR-positive breast cancer are shown in Table 7.8 [56, 61, 67]. A large intergroup trial compared the efficacy of adjuvant CAF, CAF plus ovarian suppression with goserelin (CAF-Z), and CAF-Z plus tamoxifen (CAF-ZT) in premenopausal women with HR-positive, node-positive breast cancer [56]. Time to recurrence (TTR) and OS were similar between the CAF and CAF-Z groups. TTR (HR 0.73; 95% CI 0.59–0.90; $p < 0.01$), but not OS, was improved in the CAF-Z group compared with the CAF-ZT group (HR 0.91; 95% CI 0.71–1.15; $p = 0.21$). This study did not include a CAF plus tamoxifen arm; therefore, the contribution of goserelin to the improved TTR in the CAF-ZT arm could not be assessed. The addition of ovarian suppression/ablation has also been subjected to meta-analysis by the EBCTCG [51]. They found that the addition of ovarian suppression/ablation to CT did not result in significant reductions in annual recurrence or mortality rates in women <40 and 40–49 years of age.

Currently, there is no evidence that ovarian suppression/ablation is superior to tamoxifen, except perhaps in women

Table 7.7 Randomized trials of adjuvant chemotherapy versus ovarian ablation/suppression with or without tamoxifen

Study	Patients	*n*	Treatment	Outcome
ZEBRA [58]	N^+, $HR^{+/-}$	1640	CMF × 6 vs. Z × 2 years	No difference in HR^+; CMF better in HR^-
IBCSG VIII [61]	N^-, $HR^{+/-}$	706	CMF × 6 vs. Z × 2 years	No difference in HR^+; CMF better in HR^-
Scottish Cancer Trial Breast Group [62]	$N^{+/-}$	332	CMF × 6–8 vs. OA (XRT/surg)	No difference
TABLE [63]	N^+, HR^+	600	CMF × 6 vs. leuprorelin acetate × 2 years	No difference
GROCTA 02 [64]	N^+, HR^+	244	CMF × 6 vs. Z × 2 years + TAM × 5 years	No difference
FASG 06 [65]	N^+, HR^+	333	FEC × 6 vs. triptorelin × 3 years + TAM × 3 years	No difference
ABCSG 5 [66]	Stage I/II, HR^+	1045	CMF × 6 vs. Z × 3 years + TAM × 5 years	DFS better with Z + TAM

ABCSG Austrian Breast Cancer Study Group, *CMF* cyclophosphamide, methotrexate, and fluorouracil, *FAC* fluorouracil, doxorubicin, and cyclophosphamide, *FASG* French Adjuvant Study Group, *FEC* fluorouracil, epirubicin, and cyclophosphamide, *GROCTA* Italian Breast Cancer Adjuvant Study Group, HR^+ hormone receptor-positive, HR^- hormone receptor-negative, *IBCSG* International Breast Cancer Study Group, N^+ node positive, N^- node negative, *OA* ovarian ablation, *surg* oophorectomy, *TABLE* Takeda Adjuvant Breast cancer study with Leuprorelin Acetate, *TAM* tamoxifen, *XRT* ovarian radiation, *Z* goserelin, *ZEBRA* Zoladex Early Breast Cancer Research Association

Table 7.8 Clinical trials evaluating the efficacy of ovarian suppression as combination or sequential therapy in premenopausal women with hormone receptor-positive breast cancer

Study	*n*	Treatment	Outcome
INT 0101 [56]	1503	CAF (6×)[a] vs. CAF (6×) → Z (5 years) vs. CAF (6×) → Z + TAM (both 5 years)	DFS, OS, TTR: CAF → Z + TAM > CAF → Z > CAF
IBCSG VIII [61]	1063	CMF (6×) vs. Z (24 months) vs. CMF (6×) → Z (18 months)	DFS (ER-negative tumors): CMF > Z, DFS (ER-positive tumors): CMF = Z CMF → Z > CMF CMF → Z > Z OS: no difference
ZIPP [67]	2710	After standard CT/RT Z vs. TAM vs. Z + TAM vs. No treatment	RFS and OS: Z > no Z

CAF cyclophosphamide, doxorubicin, and 5-fluorouracil, *CMF* cyclophosphamide, methotrexate, and 5-fluorouracil, *CT* chemotherapy, *DFS* disease-free survival, *ER* estrogen receptor, *IBCSG* International Breast Cancer Study Group, *INT* North American Breast Cancer Intergroup, *OS* overall survival, *RFS* recurrence-free survival, *RT* radiotherapy, *TAM* tamoxifen, *TTR* time to recurrence, *Z* goserelin, *ZIPP* Zoladex in Premenopausal Patients
[a]Six cycles

who have not developed CIM. Ovarian ablation should not be routinely added to systemic CT, tamoxifen, or combined tamoxifen and CT. However, women <40 years of age and patients who do not become amenorrheic after CT may especially benefit from ovarian suppression with an LHRH agonist. The best use of LHRH agonists (concurrent or sequential with CT) is unknown. The combination of LHRH agonist plus AI or AI alone is not indicated in premenopausal patients outside clinical trials. Some women are offered treatment with ovarian suppression in association with AI therapy because of intolerance to or contraindications for tamoxifen.

Adjuvant Endocrine Therapy for Postmenopausal Women

In general, the following three groups of women can safely be considered postmenopausal: women >60 years of age, women who have undergone a bilateral ovariectomy, and women <60 years of age with intact uteri who are not using oral contraceptives or hormone replacement therapy and have been amenorrheic for at least 1 year prior to their breast cancer diagnosis. Women who experience regular menses without using oral contraceptives or hormone replacement therapy can be classified as premenopausal. Strictly stated, in all other cases, ovarian activity cannot be excluded, and menopausal status is therefore considered uncertain. Approximately 75% of breast cancers are diagnosed in postmenopausal women, and 80% of these cancers are HR positive [68]. Third-generation AIs, including anastrozole, letrozole, and exemestane, block estrogen synthesis by inhibiting aromatase. Because these AIs do not block ovarian estrogen production, their use is limited to postmenopausal women.

A number of studies have compared AIs with tamoxifen in the adjuvant setting using either a head-to-head (i.e., randomly assigning patients to 5 years of either drug) or switched schedule approach (i.e., initial tamoxifen for 2–3 years followed by either an AI for 2–3 years or continued tamoxifen for a total of 5 years). The use of AIs in either approach reduces breast cancer recurrence rates compared with tamoxifen alone; however, the effect on survival is less clear [69]. Two large randomized studies showed no significant differences in recurrence or survival between upfront and switching AI therapy [70–72]. Randomized studies have also demonstrated that extended ET with 3–5 years of an AI following 5 years of tamoxifen decreases relapse rates and may improve survival, especially in women with nodal involvement [73–75]. Given the improved outcomes observed with the use of AIs compared with tamoxifen alone, both the ASCO and NCCN recommend the incorporation of AIs at some point in the treatment of postmenopausal women with HR-positive breast cancer [76]. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used. The concurrent use of tamoxifen and anthracyclines has been shown to have detrimental effects, whereas the concurrent use of AIs and CT has not been investigated [8].

Several studies have evaluated AIs as initial adjuvant therapy, sequential therapy following 2–3 years of tamoxifen, and extended therapy following 4.5–6 years of tamoxifen in postmenopausal women with early-stage breast cancer. Two prospective randomized clinical trials have provided evidence of an OS benefit in patients with early-stage breast cancer receiving initial adjuvant ET with tamoxifen followed by sequential anastrozole (HR 0.53; 95% CI 0.28–0.99; $p = 0.045$) or exemestane (HR 0.83; 95% CI 0.69–1.00; $p = 0.05$ [excluding patients with ER-negative disease])

compared with those receiving ET with tamoxifen alone [77, 78]. In addition, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17 trial demonstrated that, compared with placebo, extended letrozole therapy provided a survival advantage in women with axillary lymph node-positive, but not lymph node-negative, ER-positive breast cancer [73]. However, no survival differences have been reported for patients receiving initial adjuvant therapy with an AI versus first-line tamoxifen treatment [79, 80]. Tamoxifen and AIs have different side effect profiles, although both can cause hot flashes, night sweats, and vaginal dryness. AIs are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rates of bone fracture, whereas tamoxifen is associated with an increased risk of uterine cancer and deep venous thrombosis. However, randomized trials have demonstrated that bisphosphonates and denosumab, a receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor, can ameliorate AI-associated bone loss [81, 82].

Upfront Aromatase Inhibitor Therapy

Two large randomized trials, the ATAC [79, 83] and BIG 1-98 [66, 76], compared initial adjuvant ET with either tamoxifen or an AI in postmenopausal breast cancer patients (Table 7.9). In these trials, randomization occurred before the initiation of adjuvant therapy, and analyses included all events during the 5-year period.

The double-blind, placebo-controlled ATAC trial evaluated the efficacy and safety of anastrozole, tamoxifen, or anastrozole plus tamoxifen as initial adjuvant therapy after surgery in 9366 postmenopausal women with localized HR-positive breast cancer. Anastrozole was superior to both tamoxifen and combined tamoxifen and anastrozole [83–85]. At a median follow-up of 120 months, fewer recurrences occurred in patients receiving anastrozole compared with those receiving tamoxifen [79, 83]. DFS, the primary endpoint, was also significantly longer in patients receiving anastrozole (HR 0.86; 95% CI 0.78–0.95; $p = 0.003$). No differences in survival were observed. Although the greatest relative reductions in DFS, TTR, and contralateral breast cancer were observed in the first 2 years of active therapy, these benefits were sustained throughout the entire follow-up period and after treatment completion. Patients in the combined tamoxifen and anastrozole group gained no additional benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near-complete elimination of their endogenous estrogen levels [85]. The ATAC trial subprotocols show a number of important findings, including a lesser effect of anastrozole compared with tamoxifen on endometrial tissue [86]; similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting no significant impairment in overall quality of life [87]; a greater loss of bone mineral density with anastrozole [88]; a small pharmacokinetic interference of anastrozole in the presence of tamoxifen, with unclear significance [89]; and no evidence of an interaction between prior CT and anastrozole [90].

The BIG 1-98 trial, a phase III, double-blind, randomized trial, compared the efficacy of 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, and 2 years of letrozole followed by 3 years of tamoxifen in 8010 postmenopausal women. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first 2 years of treatment only [80]. This analysis (25.8-month median follow-up) showed that 5 years of letrozole significantly improved DFS (HR 0.81; $p = 0.003$) and distant DFS (DDFS) (HR 0.73; $p = 0.001$) compared with 5 years of tamoxifen. These results led to the unblinding of the tamoxifen-alone arm, and 25.2% of patients selectively crossed over to letrozole, which has complicated subsequent intention-to-treat analyses of the monotherapy arms. The updated report (76-month median follow-up) included both an intention-to-treat analysis and a censored weighted modeling analysis at the time of crossover. Significant improvements in DFS and DDFS in favor of letrozole over tamoxifen and a nonsignificant improvement in OS (HR 0.87; 95% CI 0.75–1.02; $p = 0.08$) were still observed. However, in an updated analysis of the BIG 1-98 trial that accounted for women who crossed over from tamoxifen to letrozole after study unblinding, a significant, although modest, improvement in survival was observed in the letrozole arm compared with the tamoxifen arm (HR 0.82, 95% CI 0.70–0.95), resulting in an absolute difference of 1.4% at 5 years [91]. The overall incidence of cardiac adverse events was similar between the letrozole and tamoxifen arms (4.8% vs. 4.7%, respectively). However, the incidence of grade 3–5 cardiac

Table 7.9 Comparative efficacy of upfront aromatase inhibitor for 5 years versus tamoxifen for 5 years in early breast cancer

Study	ATAC [83]	BIG 1-98 [70]
Number of patients	6241	4922
Median follow-up, months	120	76
Disease-free survival		
HR	0.86[a]	0.88
p value	0.003[a]	0.03
Difference in 5-year disease-free survival, %	2.8	2.9
Time to distant recurrence		
HR	0.85[a]	0.85
p value	0.02[a]	0.05
Overall survival		
HR	0.95[a]	0.87
p value	0.4[a]	0.08

ATAC Anastrozole, Tamoxifen, Alone or in Combination, *BIG* Breast International Group, *HR* hazard ratio
[a]ER-negative patients excluded

adverse events was significantly higher in the letrozole arm, whereas the overall incidences of all-grade and high-grade (grade 3–5) thromboembolic events were significantly higher in the tamoxifen arm [92]. In addition, a higher incidence of bone fractures was observed in the letrozole arm than in the tamoxifen arm (9.5% vs. 6.5%, respectively) [93].

The magnitude of any additional benefit from an AI may depend on the risk of relapse. Retrospective analyses of the BIG 1-98 trial suggest that patients with low-risk tumors (i.e., small, low-grade tumors without lymphatic vascular invasion or nodal involvement; strong positive HR expression; and low Ki-67) may do equally well on tamoxifen or an AI [94]; however, this outcome has not been established in a prospective trial. Thus, given the numerous randomized trials demonstrating superior outcomes with AI versus tamoxifen monotherapy, most patients should receive an AI during the first 5 years of adjuvant therapy when possible [95].

Switching from Tamoxifen to Aromatase Inhibitor Versus Continued Tamoxifen

Several trials (Table 7.10) have evaluated the efficacy of switching to an AI after 2–3 years of tamoxifen versus 5 years of tamoxifen alone in an attempt to preempt the potential development of tamoxifen resistance and minimize the long-term side effects of 5-year AI and tamoxifen monotherapies. The largest of these studies, the Intergroup Exemestane Study (IES), compared the switch to exemestane after 2–3 years of tamoxifen versus 5 years of tamoxifen alone. Postmenopausal breast cancer patients who had completed a total of 2–3 years of tamoxifen ($n = 4724$) were randomized to receive either continued tamoxifen or exemestane to complete a total duration of 5 years of ET [96]. At a median follow-up of 55.7 months, sequential exemestane therapy was superior to tamoxifen alone in terms of DFS (HR 0.76; 95% CI 0.66–0.88; $p = 0.0001$). A significant difference in OS was only found in patients with ER-positive tumors (HR 0.83; 95% CI 0.69–1.00; log rank $p = 0.05$). In the most recent update (91-month median follow-up), the benefit in those patients who switched to exemestane has been sustained.

The Italian Tamoxifen Anastrozole (ITA) trial randomized 448 postmenopausal women with breast cancer who had completed 2–3 years of tamoxifen to either continue tamoxifen or switch to anastrozole to complete a total of 5 years of ET [97]. Updated results from this study showed that the HR for relapse-free survival was 0.56 (95% CI 0.35–0.89; $p = 0.01$), and the p value for OS analysis remained at 0.1 [98]. A meta-analysis ($n = 4006$) of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8, Arimidex–Nolvadex (ARNO) 95, and ITA trials showed a significant improvement in OS (HR 0.71; $p = 0.04$) with anastrozole switching therapy in postmenopausal women with hormone-sensitive disease [99, 100]. In the ARNO 95 and ITA trials, only patients who were relapse-free after 2–3 years of tamoxifen were randomized, whereas the ABCSG 8 study randomized patients at diagnosis. An additional meta-analysis of these studies ($n = 9015$) demonstrated that AI switching therapy resulted in a significant 29% proportional decrease in recurrence rate (absolute decrease of 3.1% at 5 years and 3.6% at 8 years), a significant 22% proportional decrease in breast cancer mortality rate (absolute decrease of 0.7% at 5 years and 1.7% at 8 years), and a reduction in overall mortality rate (absolute decrease of 2.2% at 8 years; $p = 0.004$) [69]. An update of the ABCSG 8 trial (60-month median follow-up) showed a modest, statistically nonsignificant improvement in the primary endpoint of RFS and a significant improvement in the defined exploratory endpoint of distant relapse-free survival.

Table 7.10 Comparative efficacy of 2–3 years of tamoxifen followed by 2–3 years of aromatase inhibitor versus 5 years of tamoxifen alone

Study	IES [96]	ARNO 95 [100]	ITA [97, 98]	ABCSG 8 [100]
Number of patients	4724	979	448	3714
Median follow-up, months	55.7	30.1	64	72
Disease-free survival				
HR	0.76	0.66	0.56	0.79
p value	0.0001	0.49	0.01	0.038
Overall survival				
HR	0.83	0.53	0.56	0.77
p value	0.05	0.045	0.1	0.025

ABCSG Austrian Breast Cancer Study Group, *ARNO* Arimidex–Nolvadex, *HR* hazard ratio, *IES* Intergroup Exemestane Study, *ITA* Italian Tamoxifen Anastrozole

Switching from Tamoxifen to Aromatase Inhibitor Versus Upfront Aromatase Inhibitor

The use of upfront or switching AI therapy has been addressed in two large randomized trials, the Tamoxifen Exemestane Adjuvant Multicenter (TEAM) and the BIG 1-98 trials. The TEAM trial evaluated exemestane [72], and the BIG 1-98 trial evaluated letrozole [70, 71]. Neither trial demonstrated any significant difference in recurrence or survival rates between the upfront and switch arms. The TEAM trial compared exemestane alone versus 2.5–3 years of tamoxifen followed by exemestane to complete a total of 5 years of ET [72]. This trial was initially designed to compare 5 years of tamoxifen monotherapy to 5 years of exemestane monotherapy. However, based on the favorable results of the IES, the study design was changed to a switch trial consisting of 9229 postmenopausal patients. At the end of 5 years, 85% of patients in the sequential group versus 86% of patients in the exemestane group were disease-free (HR 0.97; 95% CI 0.88–1.08; $p = 0.60$). This finding is consistent with data from the BIG 1-98 trial, in which tamoxifen followed by letrozole, letrozole followed by tamoxifen, and letrozole alone showed a similar efficacy at a 71-month median follow-up.

Extended Adjuvant Endocrine Therapy

Late recurrences are common in HR-positive breast cancer, and a continual risk of relapse exists throughout a 15-year time span despite 5 years of ET. The risk of breast cancer recurrence after 5 years of endocrine therapy was evaluated in a meta-analysis by the EBCTCG. In that meta-analysis, breast cancer recurrence occurred at a steady rate throughout the study period from 5 to 20 years and was strongly correlated with the original tumor size, nodal status, and tumor grade [101]. The rationale for evaluating AI as extended adjuvant therapy is based on the observation that ER-positive patients continue to exhibit significant residual risk for recurrence and death long after the initial 5 years of tamoxifen therapy. Several trials including the large MA.17 trial and the smaller ABCSG 6 and NSABP B-33 trials have also demonstrated that extended ET with 3–5 years of an AI following 5 years of tamoxifen decreases relapse rates and may affect survival, especially in women with nodal involvement (Table 7.11) [73–75, 102].

The MA.17 trial evaluated the benefit of extended adjuvant ET with letrozole in postmenopausal patients who had completed 5 years of tamoxifen (Box 7.3). At a median follow-up of 2.5 years, extended letrozole treatment resulted in fewer recurrences and fewer new contralateral breast cancers (HR 0.58; 95% CI 0.45–0.76; $p < 0.001$) compared with placebo. No difference in OS was demonstrated (HR 0.82; 95% CI, 0.57–1.19; $p = 0.30$), although a survival advantage was observed in the subset of patients with axillary lymph node-positive disease (HR 0.61; 95% CI 0.38–0.98; $p = 0.04$). However, in an updated analysis (64-month median follow-up) that adjusted for patients in the placebo arm who crossed over to letrozole after study unblinding, a significant 24–39% proportional decrease in mortality was observed in patients who received letrozole after tamoxifen [73]. A formal

Table 7.11 Comparative efficacy of extended adjuvant therapy of 5 years of tamoxifen followed by 3–5 years of aromatase inhibitor versus 5 years of tamoxifen alone

Study	NCIC-CTG MA.17 [73]	ABCSG-6a [74]	NSABPB-33 [75]
Number of patients	5187	852	1562
Median follow-up, months	64	62	30
Disease-free survival			
HR	0.68	0.62	0.68
p value	0.0001	0.031	0.07
Overall survival			
HR	0.98	0.89	NR
p value	0.853	0.57	

ABCSG Austrian Breast Cancer Study Group, *HR* hazard ratio, *NCIC-CTG* National Cancer Institute of Canada Clinical Trials Group, *NR* not recorded, *NSABP* National Surgical Adjuvant Breast and Bowel Project

Box 7.3 Evidence of the Efficacy of Adjuvant AI Therapy from the 2010 EBCTCG Meta-analysis and MA.17 Trial

Single-agent therapy—The 2010 EBCTCG meta-analysis compared adjuvant AI vs. tamoxifen in 9856 women (mean follow-up of 6 years). AI treatment resulted in (1) a reduction in recurrence risk within 5 years (rate ratio 0.77; $p < 0.001$), which translated into a 3% absolute reduction in the 5-year recurrence risk (12% vs. 15%, respectively), and (2) a nonsignificant reduction in the risk of breast cancer death (rate ratio 0.89; $p > 0.1$), which translated into a 1% absolute reduction in the 5-year breast cancer mortality rate (7% vs. 8%, respectively).

Switching therapy—A second analysis compared switching to AI vs. continued tamoxifen in 9015 women (mean follow-up of 4 years). After 2–3 years of tamoxifen, patients were randomly assigned to receive AI or continued tamoxifen to complete a total of 5 years of ET. Switching therapy resulted in (1) a reduction in recurrence risk at 6 years (8% vs. 11%, respectively; rate ratio 0.71; $p < 0.001$) and (2) a reduction in the 5-year breast cancer mortality rate (6% vs. 8%, respectively; rate ratio 0.79; $p = 0.004$).

Extended therapy—A third adjuvant AI strategy is to initiate a 5-year course of AI after the completion of 5 years of tamoxifen. Evidence to support extended therapy comes from the MA.17 trial. In this trial, 5187 postmenopausal women (node-positive, 46%; ER-positive, 98%) who had completed 5 years of adjuvant tamoxifen were randomly assigned to receive letrozole or placebo for 5 years. At a median follow-up of 64 months, letrozole improved DFS (HR 0.68, 95% CI 0.45–0.61) and OS (HR 0.51, 95% CI 0.42–0.61). Interestingly, women in the placebo arm who switched to letrozole after study unblinding still experienced an improvement in DFS despite the substantial interval between therapies (median, 2.8 years).

Similar benefits in DFS have been reported with tamoxifen followed by 3 years of anastrozole and 5 years of exemestane [74, 75]. In the extension study of the ABCSG 6 trial, 852 HR-positive postmenopausal patients who were disease-free and received 5 years of adjuvant tamoxifen were randomized to 3 years of anastrozole ($n = 387$) or no further therapy ($n = 469$). At a median follow-up of 62.3 months, anastrozole significantly reduced the recurrence risk compared with no further treatment (HR 0.62; 95% CI 0.40–0.96; $p = 0.031$) [74]. The results of the ABCSG-6a trial confirmed the benefit

of extended adjuvant anastrozole treatment, showing a 38% decrease in recurrence risk. However, these findings should be viewed cautiously because of the limited statistical power and the lower than expected recruitment rate. Despite the limitations of the NSABP B-33 trial (premature closing and crossover from placebo to exemestane in some patients), the intention-to-treat analysis showed an improvement in DFS at 4 years with exemestane [75].

quality-of-life analysis demonstrated reasonable preservation of life quality during extended ET, although some women experienced ongoing menopausal symptoms and loss of bone mineral density [103, 104]. In conclusion, the MA.17 study demonstrated that extended adjuvant treatment with letrozole after tamoxifen significantly improved DFS and distant metastasis-free survival in lymph node-positive and node-negative patients and extended OS in lymph node-positive patients.

The recently reported MA.17R trial randomized women who had already completed 5 years of aromatase inhibitor therapy with or without previous tamoxifen to a further 5 years of letrozole or placebo. DFS was significantly improved in the extended letrozole group, with similar quality of life, but bone fracture rates were higher. The 5-year DFS rate was 95% for the letrozole arm compared with 91% for the placebo arm [hazard ratio 0.66, 95% CI (0.48–0.91); $p < 0.01$] [105].

Several studies investigated the efficacy and safety of additional treatment with AIs after a sequential regimen of tamoxifen and an AI for 5 years [106, 107]. However, results from NSABP-B42, the DATA trial, and the IDEAL trial have not confirmed the benefit for recurrence-free survival observed in MA17R.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B42 study presented at the San Antonio Breast Cancer Symposium in 2016 investigated the efficacy of 5 years of letrozole after an initial 5 years of endocrine therapy including an AI. This therapy could be either AI monotherapy or sequenced with tamoxifen. In contrast to the findings of the MA.17R trial, the difference in DFS between the control and placebo groups did not reach statistical significance [7-year DFS 84.7% vs. 81.3%, HR 0.85, $p = 0.048$, statistical significance level 0.0418]. For OS, a significant difference between the control and placebo groups was also not observed [91.8% vs. 92.3%, HR 1.15, $p = 0.22$]. However, patients under extended endocrine therapy were significantly less frequently affected by distant recurrence [HR 0.72, $p = 0.03$]; a risk reduction of 28% was observed. Furthermore, a significantly longer BC-free interval (BCFI), defined as time to recurrence or contralateral BC as the first event, was observed in the letrozole group [incidence of BCFI events 6.7% vs. 10.0%, HR 0.71, $p = 0.003$].

The Different Durations of Anastrozole and Tamoxifen (DATA) trial presented at the San Antonio Breast Cancer Symposium in 2016 was designed to investigate the effect of extended AI therapy after TAM. In this multicenter phase III trial, 1660 postmenopausal women with HR^+ EBC who underwent 2–3 years of TAM therapy were randomized to 6 or 3 years of anastrozole daily. The 5-year adapted DFS did not differ significantly [83.1% vs. 79.4%, HR 0.79, $p = 0.07$] [106].

The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) multicenter phase III trial from the Netherlands randomized patients to 2.5 or 5 years of letrozole after 5 years of hormone therapy. The median follow-up was 6.5 years. No significant difference in 5-year DFS was observed between patients with 2.5 years or 5 years of extended letrozole therapy [88.4% vs. 87.9%, HR 0.96, $P = 0.70$]. The 5-year OS also did not differ significantly between these groups [93.5% vs. 92.6%, HR 1.08, $P = 0.59$] [107]. In a recent meta-analysis of extended endocrine therapy that included the abovementioned trials, women with positive nodal status seemed to receive greater benefit from extended endocrine therapy (node-positive HR 0.72 versus node-negative HR 0.83). Similarly, a greater benefit of extended endocrine therapy was observed in women with a larger tumor size and those with both ER and PR expression versus single-receptor expression. A greater effect was also observed in patients who received adjuvant chemotherapy compared with that of those who did not [108].

Other trials have evaluated less intensive extended endocrine regimens and suggested their equivalence with extended therapy for an additional 5 years. The SOLE study was recently presented at the ASCO annual meeting in June 2017. This phase III trial included 4884 postmenopausal women with HR^+, N^+ early-stage BC with the purpose of investigating the effect of a new therapeutic concept of letrozole [109]. The trial was designed to assess the role of continuous versus intermittent letrozole intake. After 5 years of adjuvant endocrine therapy, patients were randomized to 5 years of either continuous ($n = 2441$) or intermittent ($n = 2443$) letrozole administration with mandatory 3-month treatment-free intervals. After 60 months of follow-up, similar 5-year DFS rates were observed in patients with intermittent and continuous letrozole administration [85.8% vs. 87.5%, HR 1.08, $p = 0.31$]. Extending AI after the initial 5 years of any endocrine therapy was also assessed (Table 7.12).

Table 7.12 Extending AI after initial 5 years of any endocrine therapy

Trial	No. of patients	Prerandomization therapy	Randomization	HR for DFS	HR for OS
MA.17R [105]	1918	3–5 ys TAM + 5ys AI	Letrozol (5 ys)	0.66 (p = 0.01)	0.97 (p = ns)
			Placebo		
NSABP B42	3923	5 ys (or TAM sequenced to AI)	Letrozol (5 ys)	0.85 (p = ns)	1.15 (p = ns)
			Placebo		
IDEAL [107]	1824	5 ys AI or TAM or TAM sequenced to AI	Letrozol (5 ys)	0.92 (p = ns)	1.04 (p = ns)
			Letrozol (2.5 ys)		
DATA [106]	1660	2–3 ys TAM	Anastrazol (6 ys)	0.79 (p = 0.07)	0.91 (p = ns)
			Anastrazol (3 ys)		
SOLE [109]	4884	5 ys AI or TAM or TAM sequenced to AI	Letrozol (5 ys-cont)	1.08 (p = ns)	0.05 (p = ns)
			Letrozol (5 ys-int)		

HR hazard ratio, *DFS* disease-free survival, *OS* overall survival, *ns* nonsignificant, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *IDEAL* Investigation on the Duration of Extended Adjuvant Letrozole, *DATA* Different Durations of Anastrozole and Tamoxifen, *ys* years

Table 7.13 Criteria used for adjuvant endocrine therapy selection in postmenopausal women [76, 112]

Adjuvant endocrine therapy	Criteria for therapy selection			
5 years of AI (up to 10 years [76]) Preferred	1. Higher risk of early relapse (e.g., larger tumor size or several positive nodes) 2. History or risk of thromboembolic event 3. Patient on a CYP2D6 inhibitor	→	If muscle/joint discomfort or other adverse effects, use an alternative AI	If unable to tolerate AI, use tamoxifen to complete at least 5 years
Switch from tamoxifen (2–3 years) to AI (2–3 years) to complete a total of 5 years of endocrine therapy (up to 10 years [76]) Preferred	1. Significant osteopenia/ osteoporosis 2. Musculoskeletal and/or joint discomfort 3. Hypercholesterolemia/heart disease	→	AI may be continued up to 5 years if tolerated High proliferative rate (Ki-67) High grade Lower ER/PR level HER2 amplification Presence of LVI	
5 years of tamoxifen (up to 10 years [76]) Less preferred	AI contraindicated or declined by patient	→	5 years of AI if appropriate or consider 5 years of tamoxifen if AI use is still not an option	

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AI aromatase inhibitor, *ER* estrogen receptor, *LVI* lymphovascular invasion, *PR* progesterone receptor

Biomarkers for Endocrine Therapy Selection

No single biomarker can reliably predict the optimal ET for use in a given patient. The prognostic significance of ER and PR levels, PR negativity, HER2 overexpression, Ki-67 level, and 21-gene RS has been examined. In the initial exploratory analysis of the ATAC trial, a greater benefit of anastrozole compared with tamoxifen in the PR-negative subgroup was suggested. A subsequent central analysis using 2006 of 5880 specimens showed that quantitative expression of ER, PR, and HER2 was not useful in identifying patients who would benefit from anastrozole. The TEAM trial showed that, in patients receiving exemestane, ER and PR expression levels predicted DFS, relative risk of relapse increased with decreased ER and PR expression, and PR status did not predict treatment response. In the BIG 1-98 trial, more relapses occurred in the first 2 years in women who received tamoxifen followed by letrozole than in those who received letrozole alone (4.4% vs. 3.1%, respectively). This increased risk of relapse was particularly evident in women with >3 involved nodes ($p < 0.001$), tumors ≥2 cm in size ($p = 0.001$), or vascular invasion ($p = 0.02$). A retrospective analysis demonstrated that these factors in conjunction with ER and PR levels, Ki-67 labeling index, and HER2 status may be useful in guiding the selection of letrozole or tamoxifen [94]. IHC analysis of the nuclear antigen Ki-67 is used to estimate the proliferative activity of tumor cells. Studies have demonstrated the prognostic value of Ki-67 in predicting response and clinical outcomes [110]. One small study suggested that analyzing Ki-67 after short-term ET may be useful in selecting patients who are resistant to ET and may benefit from additional interventions [111]. However, these data require greater analytic and clinical validation. Patients at the highest risk of recurrence benefited the most from AI treatment for 5 years, whereas relapse rates in those at lowest risk did not differ among patients treated with tamoxifen, letrozole, or a switch approach [112]. A summary of the criteria used for adjuvant ET selection in postmenopausal women is shown in (Table 7.13).

Comparison of Letrozole, Anastrozole, and Exemestane Efficacy

According to the evidence to date, AIs exhibit very similar activity. Although letrozole leads to more complete aromatase inhibition [113] and lower serum estrogen levels [104, 114] than anastrozole, the clinical importance of these findings is unclear. To date, indirect comparisons between adjuvant trials suggest that letrozole, anastrozole, and exemestane have similar benefits when compared with tamoxifen. In addition, a neoadjuvant study showed that letrozole, anastrozole, and exemestane similarly suppress the proliferation marker Ki-67 and preoperative endocrine prognostic index scores [115].

The NCIC-CGC MA.27 study compared the efficacy and safety of 5 years of exemestane, a steroidal AI that binds irreversibly to aromatase, to that of anastrozole, a nonsteroidal AI that forms reversible bonds, in 7576 postmenopausal women [116]. At a median follow-up of 4.1 years, the 4-year event-free survival was 91% for exemestane and 91.2% for anastrozole (stratified HR 1.02; 95% CI, 0.87–1.18; $p = 0.85$). The overall DDFS and disease-specific survival rates were also similar. In all, 31.6% of patients discontinued treatment because of adverse effects, concomitant disease, or study refusal. Osteoporosis/osteopenia, hypertriglyceridemia, vaginal bleeding, and hypercholesterolemia were less frequent in response to exemestane, whereas mild liver function abnormalities and rare episodes of atrial fibrillation were less frequent in response to anastrozole. Vasomotor and musculoskeletal symptoms were similar between the arms. Compliance is a major issue for the use of all chronic medications, including adjuvant ET. Given the adverse effects of both tamoxifen and AIs and the uncertain survival benefit of any particular approach, the schedule that leads to better compliance is likely to have the most benefit. For some patients, a switch approach may offer the best balance between efficacy and toxicity [117]. The Femara versus Anastrozole Clinical Evaluation (FACE) trial was recently reported to assess the potential differences in efficacy and safety between the nonsteroidal AIs anastrozole and letrozole in postmenopausal women with HR-positive, node-positive breast cancer. The 5-year estimated DFS rate was 84.9% for letrozole versus 82.9% for anastrozole arm (hazard ratio, 0.93; $P = 0.3$). Exploratory analysis showed similar DFS for letrozole and anastrozole in all evaluated subgroups. The 5-year estimated overall survival rate was 89.9% for letrozole versus 89.2% for anastrozole arm (hazard ratio, 0.98; $P = 0.8$) [118].

Optimal Timing of Aromatase Inhibitor Therapy

Studies have consistently demonstrated that the use of third-generation AIs as initial adjuvant therapy, sequential therapy, or extended therapy lowers recurrence risk, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, in postmenopausal women with HR-positive breast cancer. However, a direct comparison of these strategies is not possible given the differences in design and patient populations among studies. All three adjuvant strategies have shown similar antitumor efficacy and toxicity profiles in randomized studies. The benefit of upfront and switching adjuvant AI therapy was established in the 2010 EBCTCG meta-analysis. Two separate analyses were performed: (1) AI versus tamoxifen monotherapy and (2) switching to AI after 2–3 years of tamoxifen versus continued tamoxifen. The findings of this meta-analysis are summarized in Box 7.3. Upfront or switching AI therapy improved DFS compared with 5 years of tamoxifen. In contrast, AI-containing regimens had no clear impact on OS. However, a modest OS benefit was observed in all switching studies, yielding an absolute gain in survival at 8 years.

The current version of the NCCN Guideline (2019 V1) recommends the following adjuvant ET options for postmenopausal women with early breast cancer: 5 years of AI as initial adjuvant therapy (category 1), 2–3 years of AI followed by tamoxifen to complete 5 years of adjuvant ET (category 1), 2–3 years of tamoxifen followed by an AI to complete 5 years (category 1) or 5 years of AI alone B, or 5 years of tamoxifen followed by 5 years of AI (category 1). The use of tamoxifen alone for 5 years or longer is limited to postmenopausal women who decline AI treatment or have a contraindication to AIs. Patients who experience intolerable adverse effects on the initial adjuvant AI therapy and switch to tamoxifen after 2 years have similar outcomes to those who complete 5 years of AI therapy [71]. Switching to a different AI is reasonable because 39% of patients are able to tolerate an alternative AI [119].

In conclusion, AI use, either upfront or after 2–3 years of tamoxifen, should be recommended for the majority of breast cancer patients. When choosing between upfront and switch strategies, it is reasonable to weigh the potential added benefit of AIs in reducing early relapse in the patients who are most likely to suffer tamoxifen and AI toxicities [120]. Support from prospective studies for the preferential use of upfront AI in patients with greater tumor burdens or more aggressive tumor biology would be extremely useful [94].

Optimal Duration of Adjuvant Endocrine Therapy

Because of the chronic nature of HR-positive disease, the risk of recurrence remains after 5 years. The optimal duration of adjuvant ET is not yet known but should be more than 5 years. It is unclear how the results of the extended adjuvant ET trials, such as the MA.17, should be incorporated into

practice because AIs are used at some point in the first 5 years of breast cancer therapy. Because 5 years of an AI is effective after 5 years of tamoxifen use and because recurrence is decreased every year of AI use, it is logical to assume that 5 years of an AI would also be effective after 2–3 years of tamoxifen. Therefore, up to 5 years of AI treatment is reasonable after switching from tamoxifen regardless of when the switch is made. However, current data support a total of 8–10 years of ET when AIs are used after 2–3 years of tamoxifen. Currently, ASCO 2019 guideline recommends 10 years of therapy for high risk postmenopausal women [76]. Extended duration of tamoxifen has been shown to improve disease-free survival and overall survival in the ATLAS and aTTom trials. However, in postmenopausal women, AIs have been shown to be more effective than tamoxifen. Accordingly, it is recommended that adjuvant endocrine therapy in postmenopausal women with early breast cancer include an AI. Recently, the DATA, IDEAL, and NSABP B42 trials showed that extended adjuvant endocrine therapy with AIs beyond 5 years in postmenopausal women with early breast cancer reduced the occurrence of secondary breast tumors but had no or only a small impact on distant metastasis-free survival. Furthermore, the toxicity of adjuvant AIs led to gradually decreasing compliance rates and long-term toxicities associated with non-breast cancer-related deaths.

Conclusion

Adjuvant ET remains a mainstay of therapy for women with ER-positive breast cancer. A summary of the 2019 NCCN (Version 1.2019) and ASCO 2019 recommendations regarding the use of AIs and tamoxifen in the adjuvant setting is provided in Boxes 7.4 and 7.5, respectively. Adjuvant ET has

Box 7.4 Summary of the 2019 NCCN Breast Cancer Panel Recommendations for Adjuvant Endocrine Therapy (NCCN Guidelines Version 1. 2019 Breast Cancer)

- Endocrine strategies in premenopausal women include ER blockade with tamoxifen, temporary ovarian suppression with LHRH agonists, or permanent ovarian suppression with oophorectomy or radiotherapy. Premenopausal women should not be given AIs as an initial adjuvant therapy outside the confines of a clinical trial. Women who are premenopausal at diagnosis and become amenorrheic after CT may have continued estrogen production from the ovaries without menses. Serial assessment of circulating LH, FSH, and E_2 levels to confirm postmenopausal status is mandatory in this subset of women if AI therapy is considered. Tamoxifen with or without ovarian suppression for 5 years has been the standard ET for premenopausal women (category 1). In women who are postmenopausal at the time of completion of 5 years of tamoxifen (including those who have become postmenopausal during the 5 years of tamoxifen therapy), extended therapy with continued tamoxifen for 5 years (category 2A) or an AI for up to 5 years (category 1) is recommended. For those who remain premenopausal after the initial 5 years of tamoxifen, continued tamoxifen therapy for up to 10 years is recommended based on the data from the ATLAS trial (category 2A). AI for 5 years + ovarian suppression may be considered as an alternative option based on the SOFT and TEXT clinical trial outcomes.
- The following adjuvant ET options are recommended for women who are postmenopausal at diagnosis: initial adjuvant therapy with an AI for 5 years (category 1), AI for 2–3 years followed by tamoxifen to complete a total of 5 years of adjuvant ET (category 1), tamoxifen for 2–3 years followed by an AI to complete a total of 5 years (category 1) or 5 years of an AI (category 2B), or tamoxifen for 4.5–6 years followed by 5 years of an AI (category 1) or consideration of tamoxifen for up to 10 years (category 2A). The use of tamoxifen alone for 5 years (category 1) or up to 10 years (category 2A) is limited to postmenopausal women who decline or have a contraindication to AIs.
- Small, HR-positive tumors (those less than 0.5 cm in greatest diameter that do not involve the lymph nodes) have such favorable prognoses that adjuvant ET is of minimal benefit (category 2B).
- IHC analysis of the nuclear antigen Ki-67 estimates the proliferative activity of tumor cells. Studies have demonstrated the prognostic value of Ki-67 in predicting response and clinical outcome. Standardization of tissue handling and processing is required for improving the reliability and prognostic value of Ki-67 analysis. To date, there is no conclusive evidence that Ki-67 alone, especially baseline Ki-67, is useful in ET selection. Therefore, Ki-67 assessment is not currently recommended.
- The cytochrome P-450 enzyme CYP2D6 converts tamoxifen to endoxifen. Because of the limited and conflicting evidence at this time, CYP2D6 testing for adjuvant ET selection is not recommended. When prescribing a selective serotonin reuptake inhibitor, it is reasonable to avoid potent and intermediate CYP2D6 inhibitors, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Box 7.5 Summary of the ASCO 2019 Recommendations Specific for Adjuvant Endocrine Therapy

1. *Treatment of choice in premenopausal patients with HR-positive early breast cancer*: Women with HR-positive breast cancer who are premenopausal or perimenopausal at the time of diagnosis should be offered adjuvant ET with tamoxifen for an initial duration of 5 years. After 5 years, women should receive additional therapy based on menopausal status. Premenopausal and perimenopausal women and those with unknown or undetermined menopausal status should be offered continued tamoxifen for a total duration of 10 years. Women who have become definitively postmenopausal should be offered the choice of continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an AI to complete a total of up to 10 years of adjuvant ET.
2. *Optimal duration of tamoxifen*: Five trials have evaluated tamoxifen treatment for longer than 5 years; three showed positive results. The two largest studies with the longest reported follow-up now show a breast cancer survival advantage with longer durations (10 years) of tamoxifen use. The beneficial effects of tamoxifen become more pronounced with longer duration. Thus, a minimum of 5 years of extended treatment (i.e., 10 years since diagnosis) is needed to observe clinical benefit. In addition to modest gains in survival, extended therapy with tamoxifen for 10 years was associated with lower risks of recurrence and of contralateral breast cancer compared with 5 years. Extended tamoxifen did not affect non-breast cancer mortality in the studies examined. Consistent with previous reports on the effects of adjuvant ET, only patients with ER-positive tumors appear to benefit from extended therapy with tamoxifen.
3. *What is the appropriate sequence of adjuvant ET in postmenopausal patients*? Postmenopausal women who are intolerant of either tamoxifen or AIs should be offered an alternative adjuvant ET. Women who have received an AI but discontinued treatment at less than 5 years may be offered tamoxifen for a total of 5 years. Women who have received tamoxifen for 2–3 years should be offered the option of switching to an AI for up to 5–8 years to complete a total of up to 7–10 years of adjuvant ET. Women who have received 5 years of tamoxifen or AI as adjuvant ET should be offered additional adjuvant ET. Postmenopausal women should be offered continued tamoxifen for a total of up to 10 years or the option of switching to up to 5 years of an AI to complete a total of up to 10 years of adjuvant ET. Premenopausal and perimenopausal women and those with unknown or undetermined menopausal status should be offered an additional 5 years of tamoxifen to complete a total of 10 years of adjuvant ET.
4. *Determination of ET responsiveness*: Tumor size, nodal status, ER expression, PR expression, and HER2 expression are well-established predictors of breast cancer recurrence. However, robust biomarkers that are capable of predicting early versus late recurrence, the most appropriate ET (tamoxifen vs. AI), and the need for extended adjuvant ET are not available.
5. *Subsets of patients who are more likely to benefit from an AI* versus *tamoxifen*: Currently, no subgroups have been well identified as being more likely to benefit from an AI versus tamoxifen. Most analyses are retrospective and mix predictive and prognostic factors. Tamoxifen is recommended for male patients because of the lack of AI data. The predictive value of CYP2D6 for tamoxifen response is unknown. Thus, CYP2D6 genotype testing is not recommended for treatment selection. However, caution is needed in patients taking tamoxifen with CYP2D6-interacting agents. CYP2D6-interacting agents should not be used in combination with tamoxifen if alternative choices exist.
6. *Risks associated with adjuvant AI therapy*: Toxicity, the presence of comorbidities, and patient preference should be taken into account in treatment selection. Switching therapy should be considered if there is poor adherence or intolerable toxicity. Although serious adverse events are rare, these agents have different and unique toxicity profiles that should be considered when recommending a specific treatment. AI use is associated with increased risk of cardiovascular disease, bone disorders, hypercholesterolemia, and hypertension, whereas tamoxifen is more often associated with gynecologic side effects, flushing, endometrial lesions, and venous thromboembolic events.
7. *Interchangeability of AIs*: There are no clinically relevant differences among AIs. Therefore, patients intolerant of one AI can be switched to another.

made a major contribution in reducing recurrence risk and improving OS in ER-positive disease. In premenopausal women, tamoxifen remains the standard treatment. Currently, up to 10 years of tamoxifen can be safely administered, especially in women who remain premenopausal. The addition of an LHRH agonist to tamoxifen treatment represents another choice. Patients who are considered to be perimenopausal should be initially treated like premenopausal patients. Depending on their serum hormone levels, these patients can be safely switched to an AI therapy once the E_2 and FSH

levels prove the establishment of postmenopausal status. In postmenopausal women, several sequences of endocrine treatment are available. The AI therapy can be induced upfront or sequentially by switching from AI to TAM and vice versa. Because women with ER-positive breast cancer have a long-term risk of relapse, emerging data demonstrating further survival gains with extended adjuvant ET are particularly relevant and indicate that the full potential of currently available endocrine agents has not yet been realized. Ongoing AI studies will further help to define the benefit of extended ET. However, the benefit is likely to vary based on recurrence risk; thus, a move from a one-size-fits-all strategy to a risk-adaptive strategy is needed.

The St. Gallen Consensus Conference 2017 and 2019 panels were almost unanimous that some postmenopausal patients can be treated with tamoxifen alone. Most of the panelists believed that an aromatase inhibitor should be used at some point during the course of adjuvant therapy. Factors that favored the use of an aromatase inhibitor include node positivity, high ki67, high grade, lobular histology, and her two positivity. The Panel recommended longer durations of therapy in women with moderate to high risk of recurrence, typically defined as stage II or III breast cancers.

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Adjuvant Systemic Chemotherapy for HER2-Negative Disease

8

Leyla Ozer and Adnan Aydiner

Introduction

Breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women worldwide [1]. Mammography screening and earlier diagnosis are responsible for at least half of the reduction in breast cancer-related mortality between 1990 and 2003. However, adjuvant systemic therapy accounts, at least in part, for the reduction in cause-specific mortality from breast cancer observed in almost every Western nation [2].

Breast cancer is a heterogeneous, phenotypically diverse disease composed of several biological subtypes that have distinct behaviors and responses to therapy. Chemotherapy probably offers potentially minimal benefits for the 5-year survival rate in women with small endocrine-responsive tumors, although there are considerable data suggesting improvements in both recurrence-free and overall survival for ER-positive or ER-negative tumors ≤1 cm in size [3]. Modest benefits are achieved when each patient is evaluated and grouped according to similar profiles utilizing standard pathological parameters (e.g., nodal status, tumor size, and receptor status) and treated with similar available chemotherapeutic agents. However, these benefits are of great value when applied to large populations with breast cancer. Long-term follow-up from an Oxford overview demonstrated an absolute benefit from chemotherapy, irrespective of age and ER receptor status [4].

One of the current challenges in adjuvant chemotherapy is the selection of the subset of patients who might preferentially benefit from chemotherapy or be spared from adjuvant chemotherapy. Moreover, the chemotherapy dose and schedule must be optimized to achieve the best clinical results and minimize the side effects of treatment. This chapter focuses on these major subjects and the evolution of chemotherapeutic agents.

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Indications for Chemotherapy

Estimating Risks and Benefits

The administration of adjuvant chemotherapy for human epidermal growth factor receptor (HER2)-negative breast cancer requires a consideration of major prognostic factors such as patient age, receptor status (expression of estrogen receptor (ER) and/or progesterone receptor (PR)), tumor size, histology, and nodal involvement.

Algorithms have been published to estimate the rates of recurrence, and a validated computer-based model (Adjuvant! Online (AOL); www.adjuvantonline.com) that incorporates all of the abovementioned prognostic factors except HER2 tumor status is available to estimate 10-year disease-free survival (DFS) and overall survival (OS) [5, 6]. These tools assist clinicians in predicting outcomes for local treatment only and the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy.

Tumor Size

For patients with node-negative breast cancer, tumor size is a known independent prognostic factor [7, 8]. According to statistics from the American Cancer Society, the 5-year relative survival based on tumor size alone is 95%, 82%, and 63% for tumors ≤2 cm, 2.1–5 cm, and >5 cm, respectively [7]. Additional evidence of tumor size as a risk factor for recurrence and death from breast cancer was provided by a European Organization for Research and Treatment of

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Cancer (EORTC) study involving over 1000 patients younger than 40 years. Pathological tumor size (>2 cm) was associated with both worse distant disease-free survival (DDFS; hazard ratio [HR] for recurrence 1.61, 95% CI 1.14–2.25) and OS (HR for mortality 1.68, 95% CI 1.12–2.52) [8]. For young, node-negative patients, tumor size was still a significant prognostic factor for both DFS and OS; however, in a multivariate analysis, molecular subtype was the only factor associated with overall survival (p = 0.02; basal subtype vs. luminal A subtype: HR 0.22, 95% CI 0.08–0.60, p = 0.003) and distant metastasis-free survival (DMFS; p = 0.08; basal subtype vs. luminal A subtype: HR 0.46, 95% CI 0.25–0.85, p = 0.013). According to this study, the established prognostic factors molecular subtype (including hormonal receptor status, histological grade, and HER2 receptor status), tumor size, and nodal status remain independent prognostic factors for disease outcome in young breast cancer patients.

Long-term outcomes and the role of adjuvant therapy in patients with small (<1 cm), node-negative breast cancer remain unclear. Compared with patients with ER-positive tumors, patients with triple-negative tumors have a worse prognosis even when diagnosed at a very small tumor size. This was demonstrated in a study involving 421 breast cancer cases with tumor sizes ≤1 cm, of which 29 (7%) were triple negative [9]. The recurrence rate was 11%, 1%, and 7% among triple-negative, ER-positive, and HER2-positive patients, respectively. Patients with small, node-negative breast tumors usually have a good prognosis, but HER2-positive and triple-negative tumors appear to have a higher recurrence rate, warranting consideration of the broad use and optimization of systemic adjuvant treatments.

Nodal Status

The risk of breast cancer recurrence is substantially increased in patients with pathologically involved lymph nodes (defined as one or more nodes with greater than a 2-mm focus of cancer). Notably, although the staging system for breast cancer includes the presence of isolated tumor cells (a small cluster of cells within the node no greater than 0.2 mm) as node-positive disease, this condition is not clinically significant. However, micrometastases (tumor clusters >0.2 mm but no greater than 2.0 mm) may have a modest negative impact on breast cancer outcomes and are treated as pathologically node-positive breast cancer.

Compared with patients with localized disease (i.e., cancer confined to the breast only), those with regional disease (i.e., spread to the lymph nodes) have a lower rate of survival at 5 years (84% vs. 99%, respectively) [10].

Prognostic and Predictive Assays

Several molecular and immunohistochemical studies of early-stage breast cancer patients have yielded promising results regarding prognostic and predictive value. These assays have led to the determination of different subtypes within breast cancer and subtype-specific treatment planning. Intrinsic breast cancer subtypes and the clinical application of available prognostic and/or predictive assays are explained in the following text.

Intrinsic Subtyping

The indication for chemotherapy has traditionally been based on prognostic factors such as the stage, clinical, and histopathological tumor characteristics described earlier or algorithms defined by different consensus statements. However, risk stratification based on only clinicopathological parameters may be misleading and may cause over- or undertreatment. Most of the international guidelines (ESMO, ASCO, St. Gallen) recommend the additional use of validated protein or gene expression tests that reflect intrinsic tumor characteristics. Progress in gene profiling techniques and hierarchical clustering has confirmed biological heterogeneity at a molecular level. In contrast to classification by immunohistochemistry techniques (IHC), at least six major breast cancer subtypes have been defined: luminal A, luminal B, HER2 enriched, basal-like, normal breast-like, and claudin low or mesenchymal-like [11, 12].

Representing approximately 60% of all breast cancer subtypes, the two molecular luminal subtypes almost entirely comprise tumors expressing a variable degree of ER and/or PR. Luminal A tumors are characterized by the expression of estrogen-regulated genes such as solute-carrier family 39 (zinc transporter); the transcription factors GATA3, FOXA1, and XBP1; and luminal cytokeratins such as CK8 and CK18 [13, 14]. They exhibit relatively low mutation rates and are associated with better outcomes. However, luminal B tumors are characterized by a higher genomic grade, lower ER levels, varying degrees of HER2 gene cluster expression, and poorer outcomes [15, 16]. The luminal B subtype exhibits higher genomic instability and harbors mutations in *TP53* and PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α) [17, 18].

Approximately 20–30% of all malignant breast tumors are of the HER2-enriched subtype. They are associated with high expression of HER2/*neu* proliferation genes and low expression of luminal clusters. These tumors are usually but not always HER2 positive and ER/PR negative and typically exhibit high expression of genes associated with cell cycle progression [14].

The term "basal-like" breast cancer refers to the common gene expression patterns of normal basal/myoepithelial cells. Basal-like tumors are characterized by high expression of basal CK5 and CK17 and other genes typically expressed in basal/myoepithelial cells such as laminin γ1 (LAMC1) and cadherin 3 (CDH3) [13, 19]. These tumors do not express ER or other luminal epithelial genes and are negative for ERBB2. They often overexpress epidermal growth factor receptor (EGFR). This subtype constitutes approximately 15% of all invasive breast cancers.

The normal breast-like subtype was named based on similarities in gene expression patterns with normal epithelial cells, adipose tissue, and other nonepithelial cell types [19]. These tumors do not express proliferation-associated genes and are supposed to have a low tumor cell percentage [14]. They share gene expression features with both the basal-like and luminal subtypes.

Claudin-low tumors are characterized by low expression of genes involved in cell–cell adhesion such as claudins 3, 4, and 7 (CLDN3, CLDN4, and CLDN7) and E-cadherin (CDH1) [20]. These tumors represent a rare type of triple-negative breast cancer with mesenchymal features and high expression of immune system response genes. In contrast to basal-like tumors, they do not exhibit high expression of proliferation-associated genes [11].

Each intrinsic tumor subtype is associated with specific histological, clinical, epidemiological, and therapeutic characteristics [21]. The prognoses of the different intrinsic tumor types differ with respect to both short-term and long-term survival, and adjuvant therapy may affect prognosis in a subtype-specific manner [22]. Thus, future adjuvant treatment modalities should be designed with awareness of these intrinsic subtypes. Because of the limitations of hierarchical clustering for the classification of individual samples, investigators have developed single-sample predictors (SSPs), which enable the subtyping of a single tumor based on microarray gene expression profiling (GEP) [16]. The SSPs have been further refined, and a classifier named prediction analysis of microarray (PAM) was developed using 50 genes to identify the four major intrinsic subtypes, namely, luminal A, luminal B, HER2 enriched, and basal-like [23]. This classifier was subsequently converted to a quantitative real-time PCR (qRT-PCR) assay that can be performed using RNA extracted from formalin-fixed, paraffin-embedded (FFPE) samples, thereby making it applicable to archival material. PAM50 is a standardized gene set based on the NanoString nCounter technology [24]. It was validated for intrinsic subtyping in a clinical trial involving 348 premenopausal women treated with tamoxifen [25]. The test also provides a prognostic score (referred to as the risk of recurrence score [RORS]) for predicting recurrence of cancer over 10 years; this will be discussed in more detail later. PAM50 is considered a robust assay with high concordance between laboratories and was superior to IHC with respect to prognosis and the prediction of endocrine response in the previous study. However, this observation was not confirmed in an independent series of breast carcinomas. Given the similarities of the subtypes defined by gene expression profiling and IHC, surrogate IHC definitions were to be generated. However, the concordance between the two tests was not as expected; 31–59% of cases with HER2 positivity as defined by IHC and/or in situ hybridization (ISH) are classified as an "intrinsic" subtype other than HER2 enriched [26, 27]. Conversely, up to 30% of the HER2-enriched tumors are clinically HER2 negative [17]. The majority of basal-like breast cancers are of the triple-negative phenotype; however, 1–3% of ER-positive tumors display a basal-like phenotype [13, 16].

The other commercial kit available for determining intrinsic breast cancer subtypes is MammaTyper®. It is based on the quantitative measurement of ER, PR, HER2, and Ki67 at the mRNA level instead of IHC. This test was developed based on the inadequacy of IHC for the discrimination of luminal A and luminal B tumors on the basis of Ki67 and tumor grade. MammaTyper® uses a cutoff definition of 75% for HER2 and exhibited high concordance with central IHC assessment in a clinical trial [28]. The HER2 status defined at this cutoff level better predicts OS and DFS compared with the HER2 status determined with IHC. This test also provides continuous values of other parameters such as Ki67 in addition to subtype information. However, the MammaTyper results have not been systematically compared with PAM50 or IHC.

Clinical Application of Protein Markers and Genomic Assays

Recent studies among breast cancer patients have yielded increasing numbers of prognostic and predictive assays that can be routinely used for optimizing diagnosis and orientating treatment choices. Some of these are summarized in the following text.

Urokinase Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor (PAI-1)

Various proteolytic enzymes play a crucial role in tumor invasion and metastasis. The urokinase plasminogen activator (uPA) system involves multiple members that participate in fibrinolysis, cell migration, angiogenesis, tumor cell dissemination, and metastasis in a variety of solid tumors [29]. This system includes urokinase-type plasminogen activator (uPA), the glycolipid-anchored cell membrane receptor for uPA (uPAR), and plasminogen activator inhibitors (PAIs). uPA and uPAR are overexpressed in diverse human malignant

tumors compared to normal tissue. The uPA system transforms inactive plasminogen to active plasmin, leading to the degradation and regeneration of the basement membrane and extracellular matrix (ECM) and thereby facilitating metastasis. The uPA system not only acts through ECM degradation but also promotes tumor metastasis by initiating the activation of matrix metalloproteinases (MMPs) [30]. Moreover, the binding of uPA to uPAR can activate the Ras–Raf–MEK–ERK pathway, resulting in the activation of several cell signaling events [31].

Studies of breast cancer patients have revealed that increased levels of uPA and/or PAI-1 in primary tumor tissues correlate with tumor aggressiveness and poor clinical outcomes. Patients with a high tumor tissue antigen content of uPA and/or PAI-1 have a worse probability of DFS and OS than patients with low levels of both biomarkers (uPA ≤ 3 ng/mg protein, PAI-1 ≤ 14 ng/mg protein) serving as prognostic markers [32]. Moreover, uPA appears to be an important independent variable that is stronger than most traditional prognostic factors, particularly in the node-negative subtype [33]. uPA and PAI-1 can classify approximately half of node-negative breast cancer patients as low risk; low levels indicate a very good prognosis, whereas high levels correlate with shortened DFS and reduced OS [34, 35]. For node-positive patients, the PAI-1 protein has a stronger prognostic impact than uPA [36].

In addition to being clinically useful prognostic factors that allow estimates of the course of disease in early-stage breast cancer, uPA and PAI-1 may also serve as factors that predict the response to systemic therapy. The prospective multicenter Chemo N0 trial included 556 node-negative early-stage breast cancer patients. High-risk patients identified by uPA and PAI-1 tumor tissue levels were randomized to chemotherapy or observation [34]. Initial interim analysis results suggested that high-risk patients in the chemotherapy group benefited with a 43.8% lower estimated probability of disease recurrence at 3 years than high-risk patients in the observation group (relative risk = 0.56; 95% CI 0.25–1.28). Ten-year follow-up results confirmed the prognostic and predictive role of these protein markers. The actuarial 10-year recurrence rate (without any adjuvant systemic therapy) for high-uPA/PAI-1 observation group patients was 23.0% in contrast to the rate of 12.9% for low-uPA/PAI-1 patients. High-risk patients randomized to receive cyclophosphamide–methotrexate–5-fluorouracil (CMF) therapy had a 26.0% lower estimated probability of disease recurrence than those randomized for observation (HR: 0.74, 95% CI 0.44–1.27). Similarly, the ongoing NNBC-3 trial aims to compare risk assessment by traditional clinicopathological factors and by uPA/PAI-1. It is also designed to evaluate the predictive value of these markers for benefit from sequential anthracycline–docetaxel regimen or anthracycline-based chemotherapy in high-risk node-negative breast cancer patients [37].

Data from the Chemo N0 trial has indicated that nearly half of node-negative breast cancer patients (with low concentrations of both proteins) could be spared from the side effects and costs of chemotherapy. Thus, the German Working Group for Gynecological Oncology (AGO) and ASCO [38] have recommended both biomarkers as risk–group–classification markers for routine clinical decision making in node-negative breast cancer, secondary to established clinical and histomorphological factors [www.ago-online.de]. However, probably due to the need for fresh-frozen tissue for analysis, these markers are not extensively used outside Germany.

Immunohistochemistry (IHC) Studies

Immunohistochemistry4 (IHC4)

As a surrogate for assessing RNA-based gene signatures, IHC techniques have been utilized to enable more economical and simplified assays. IHC4 is based on four routine IHC markers: ER, PR, HER2 (with fluorescent or calorimetric in situ hybridization), and Ki67. The retrospective TransATAC (Arimidex, Tamoxifen, Alone or in Combination) study, which included ER-positive chemo-naive breast cancer patients of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, assessed the prognostic impact of IHC4 score. This four-parameter IHC score was initially compared with the 21-gene General Health Recurrence Score (Oncotype DX®) using distant metastasis as the primary endpoint [39]. The results indicated that the IHC score not only provided prognostic information independent of classic clinicopathological variables, but also was similar in strength to Oncotype DX. The prognostic value of the IHC4 score was also validated in a second separate cohort of patients, and the results indicated that the amount of prognostic information provided by the four widely performed IHC assays is similar to that provided by Oncotype DX. By combining the IHC4 score with clinicopathological factors (tumor grade, size, nodal burden, patient age, and aromatase inhibitor treatment), another prognostic tool has been created, known as IHC4+C. This tool was utilized for the reclassification of 101 postmenopausal, hormone receptor-positive, early-stage breast cancer patients defined as intermediate risk by AOL and the Nottingham Prognostic Index (NPI) [40]. The NPI is based on operative pathological findings such as tumor size and nodal status and is calculated postoperatively for each patient. Fifteen of the 26 patients classified as intermediate risk by AoL were reallocated to a low-risk group by application of the IHC4+C score, and no patient was reclassified as high risk. Of the 59 patients classified as intermediate risk by the NPI, 24 were reallocated to a low-risk group and 13 to a high-risk group. The results suggested an improvement in decision making regarding adjuvant chemotherapy. However, there are quality assurance issues with the qualitative

assessment of ER, PR, HER2, and Ki67 IHC due to the potential for interlaboratory variation in values. Although considerably less expensive than gene expression profiling tools, Ki67 in particular has caused apprehension due to variable assessment methods and heterogeneity in interlaboratory results. Recently, the impact of follow-up duration on the prognostic value of IHC4 and another IHC test, Mammostrat, revealed that their efficacy is restricted to the first 5 years after diagnosis [41]. However, this finding needs to be validated in further studies before being accepted as clear evidence.

Mammostrat®

A number of different statistical approaches have been used to identify minimal gene sets for prognostication or to predict response to therapy for early-stage breast cancer patients. The clinical development of gene expression-based assays has made impressive initial progress, but suffers from the inherent limitation that application as a clinical tool will require specialized laboratories for quality assurance. Ring et al. [42] explored the possibility of developing IHC tests utilizing data from several gene studies. The authors investigated gene expression patterns in three patient cohorts and, using a stepwise process, identified a minimal set of five antisera reflecting the expression of five genes: p53, which is involved in cell cycle checkpoint control; SLC7A5, which is involved in nutrient transport; HTF9C, the expression of which oscillates during the cell cycle; NDRG1, a stress- and hypoxia-inducible gene; and CEACAM5, a carcinoembryonic differentiation antigen. These prognosticators were first used to predict outcomes in ER-positive breast cancer patients; however, the first study was underpowered in the node-negative (N0) subsets. Therefore, a second study was performed to further validate this five-antibody IHC test [43]. In the NSABP B-14 trial, a total of 837 patients were evaluated. This study was initiated to determine the benefit of adjuvant tamoxifen. The other patient cohort included 457 patients from the NSABP B-20 trial, which investigated the benefit of adjuvant chemotherapy added to tamoxifen. The test stratified patients into three groups: low, moderate, and high risk. Younger patients in the low-risk group identified by the test had a 20% risk of disease progression that warranted the consideration of aggressive treatment strategies. By contrast, in elderly patients (≥60 years) in whom cytotoxic chemotherapy is currently used much more cautiously, the test identified high-risk patients with a 22% risk of breast cancer-specific death compared with 6% in low-risk patients. In addition, the high-risk patients in the B20 study had a 21% decreased recurrence rate associated with the administration of adjuvant chemotherapy. However, stratification into age groups was not a prespecified analysis in the trial design and therefore must be cautiously interpreted.

Oncotype DX

One of the most widely used gene-based approaches is the 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissues (Oncotype DX). The test was first developed to predict the likelihood of disease recurrence among hormonal receptor-positive, lymph node-negative, stage I or II breast cancer patients who had received tamoxifen for 5 years [44]. Through retrospective analysis of three independent clinical studies involving a total of 447 patients, including the tamoxifen-only group of the NSABP B-20 trial, the relationship between the expression of the 250 candidate genes and the recurrence of breast cancer was initially assessed [45, 46]. Oncotype DX is routinely performed on formalin-fixed, paraffin-embedded (FFPE) tissues. To select a panel of 16 cancer-related genes and five reference genes (Table 8.1), the results of the three studies were utilized to design an algorithm and compute a recurrence score (RS) as a continuous variable between 0 and 100 for each tumor sample. Then, patients were classified into three categories based on their RS: low risk (RS < 18), intermediate risk (RS 18–30), or high risk (RS > 31). Low-risk groups had an estimated risk of recurrence of less than 10% at 10 years according to the NSABP-B20 results. The 16 cancer-related genes involved components of ER pathways (ER, PR, BCL2, and SCUBE2); the HER2 amplicon (HER2 and GRB7); proliferation-related genes (Ki67, STK15, survivin, CCNB1, and MYBL2); invasion-related genes (MMP11 and CTSL2); and GSTM1, BAG1, and CD68 [44]. Higher expression of the estrogen-related genes GSTM1 and BAG1 was associated with improved survival; by contrast, high invasion- or proliferation-related gene expression and HER2 expression were associated with a higher risk of recurrence and poor relapse-free survival.

Oncotype DX has been validated in large retrospective sets of trials. In the first study, tumor blocks were retrieved from the NSABP-B14 study, which was designed to evaluate the benefit of adjuvant tamoxifen among node-negative, ER-positive breast cancer patients. Clinically, a low-risk score (RS < 18) was translated as a 10% risk of distant metastasis at 10 years, and a high score (RS ≥ 31) was

Table 8.1 Genes assessed in the Oncotype DX assay

Cancer-related genes	Reference genes
Estrogen genes	ACTB (β-actin)
ER, PR, BCL 2, SCUBE2	GAPDH
Invasion genes	RPLPO
MMP11 (stromelysin 3), CTSL2 (cathepsin L2)	GUS
Proliferation genes	TFRC
Ki67, STK15, survivin, CCNB1 (cyclin B1), MYBL2	

translated as a 20% risk. The study identified 51% of the patients as low risk, with 93.2% 10-year distant relapse-free survival (DRFS), whereas 27% of the patients were identified as high risk, with 69.5% 10-year DRFS [44]. Subsequently, Oncotype DX was retrospectively evaluated in another trial, the NSABP-B20, which was designed to investigate the benefit of adding adjuvant chemotherapy to tamoxifen for node-negative, ER-positive (potentially including HER2-positive) invasive breast cancer patients. In this trial, patients received either non-anthracycline-based chemotherapy, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or methotrexate and 5-fluorouracil (MF) plus concurrent tamoxifen or tamoxifen alone. Of 2299 patients, 670 patients' FFPE tumor tissues were available for analysis. The NSABP-B20 trial validated Oncotype DX as a prognostic and predictive test. On the basis of the data, 54% of the patients had RS <18, whereas 25% were classified in the high-risk group. The administration of adjuvant CT was associated with 27.6% reduction in the risk of distant metastasis at 10 years in high-risk patients. However, the benefit of adjuvant CT in the low-risk group was quite low (3.78% risk reduction) [47]. Those in the intermediate-risk group did not seem to experience a significant benefit from adjuvant CT, but a clinically significant benefit could not be excluded due to uncertainty in the estimate.

The prognostic and predictive value of the 21-gene RS was also evaluated among node-positive patients in the TransATAC (Arimidex, Tamoxifen, Alone or in Combination) study [48]. RNA was extracted from 1372 tumor blocks from postmenopausal patients with hormonal receptor-positive primary breast cancer in the monotherapy arms of ATAC. RSs were available for 1231 patients, of whom 306 had nodal involvement. Nine-year distant recurrence rates in the low (RS < 18), intermediate (RS: 18–30), and high RS (RS ≥ 31) groups were 4%, 12%, and 25%, respectively, in N0 patients and 17%, 28%, and 49%, respectively, in N+ patients. However, the study failed to demonstrate a predictive effect for differential benefit between tamoxifen and anastrozole.

In clinical practice, physicians usually subjectively combine RS with pathological and clinical measures based on their individual experience. The evidence that RS and traditional measures provide independent prognostic information has encouraged investigators to develop a formal integration of RS and traditional pathological and clinical measures. The RS–pathology–clinical (RSPC) model by Tang et al. [49] included RS, age, tumor size, and grade. Patients in the NSABP B-14 and translational research cohort of the TransATAC studies ($n = 647$ and $n = 1088$, respectively) with assessable clinicopathological factors and ER-positive tumors who received hormonal monotherapy were included. RSPC had significantly more prognostic value for distant recurrence than did RS ($p = 0.001$), with a better discrimination of risk in the study population. Moreover, RSPC classified fewer patients as intermediate risk (17.8% vs. 26.7%, $p = 0.001$) and more patients as lower risk (63.8% vs. 54.2%, $p = 0.001$) than RS. The study indicated that RSPC can provide greater accuracy in the assessment of distant recurrence risk, particularly when RS and clinicopathological measures are discordant.

The 21-gene RS assay was also assessed for the prediction of chemotherapy benefit among node-positive, postmenopausal HR + breast cancer patients within the study population of SWOG 8814 [50]. Because of the inferior efficacy of concurrent tamoxifen and CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) in the parent trial, that arm was excluded. Thus, this analysis compared the sequential CAF-T group to the tamoxifen control group. RS was determined to be a strong predictive factor of CAF benefit for DFS, but the degree of CAF benefit depended on the RS. There was no apparent benefit for scores <18 ($p = 0.97$; HR = 1.02, 95% CI 0.54–1.93) or 18–30 ($p = 0.48$; HR = 0.72, 95% CI 0.39–1.31). However, there was a significant advantage for CAF-T compared with tamoxifen alone for patients with RS ≥ 31 ($p = 0.033$; HR = 0.59, 95% CI 0.35–1.01).

The response to neoadjuvant chemotherapy has been determined to be a valid surrogate marker of survival, with significantly better survival in those patients whose tumors completely regress compared with all other responses. Several gene expression studies of human breast cancer have suggested that gene analyses can discriminate patients who are more likely to benefit from certain therapies such as anthracyclines or taxanes [51, 52]. The first study evaluating RS for predicting the response to neoadjuvant CT was performed by Gianni et al. [53]. They identified a set of genes for which the expression correlated with pathological complete response (pCR) to neoadjuvant doxorubicin and paclitaxel. Of 384 candidate genes tested by RT-PCR analysis, the expression of 86 genes significantly correlated with pCR ($p = 0.05$). The RS strongly correlated with pCR, supporting the previous findings that patients with high RS values, who were thus most likely to experience recurrence, were most likely to receive the greatest clinical benefit from chemotherapy treatment. Similarly, Chang et al. [54] tested the utility of the 21-gene recurrence assay in the neoadjuvant setting to demonstrate that sufficient RNA could be obtained from core biopsies to directly examine the association of RS with the neoadjuvant docetaxel and complete response (CR). CR was associated with lower expression of the ER gene group and higher expression of the proliferation gene group from the 21-gene assay. Moreover, CR was more likely with a high RS ($p = 0.008$).

Although Oncotype DX is a useful and practical tool for prognostic and predictive purposes, like all biomarkers, it has limitations. In particular, the data from RT-PCR and IHC studies for HER2 status conflict. The US Food and Drug Administration (FDA) has approved two immunohistochemical assays and three fluorescent in situ hybridization (FISH)

assays for HER2 assessment in the clinical laboratory. Although test platform preference among pathologists and oncologists remains controversial, both IHC and FISH remain independently validated tests in the clinical laboratory based on outcome data and response to trastuzumab. HER2 gene amplification is closely associated with mRNA overexpression and increased protein levels, and several studies have compared mRNA expression by reverse transcription PCR. The Oncotype DX test depends on mRNA extracted from FFPE tumors. A major study comparing the HER2 FISH assay and qRT-PCR technique indicated an overall 97% concordance rate [55]. However, the results of another analysis that included 843 patients from three high-volume centers contradicted this finding. Of the 784 (93%) patients classified as negative by IHC or FISH, 779 (99%) were also classified as negative by the Oncotype DX RT-PCR assay. However, all 23 equivocal patient cases were reported as negative by Oncotype DX. Of the 36 positive cases, only 10 (28%) were reported as positive, 12 (33%) as equivocal, and 14 (39%) as negative [56]. The results corresponded to >50% false HER2 negativity by Oncotype DX RT-PCR technique. Similarly, another retrospective review evaluating concordance rates between hormonal receptor, HER2 FISH, and Oncotype DX RT-PCR assays revealed a positive percent agreement for HER2 of 0% (0/2) and a negative percent agreement of 100% (245/245). Of the three FISH HER2-amplified cases, two were negative and one was equivocal, and all FISH HER2 equivocal cases ($n = 3$) were negative by Oncotype DX [57]. Although the results demonstrated high concordance between IHC and Oncotype DX for ER and PR, the data indicated poor positive percent agreement for HER2. Patients who were FISH HER2 amplified and Oncotype DX HER2 negative did not receive trastuzumab, and information on the outcome of such patients in the general breast cancer population is lacking. Taken together, these data do not support the use of Oncotype DX as an assay for further clarification, particularly in cases of equivocal IHC and/or FISH results or discordance between FISH and IHC.

The underlying reason for these inconsistencies is unclear. A possible explanation for the discrepancy between IHC/FISH and Oncotype DX is that Oncotype DX utilizes RT-PCR, a molecular technique that disregards tissue morphology. Consequently, tumor mRNA may be contaminated with nonneoplastic tissue or biopsy cavity material [55, 58, 59]. Prior studies have documented that cellular stroma, inflammatory cells, or the presence of a biopsy cavity can influence Oncotype DX results [58, 59]. In addition, the extent of fragmentation of extracted FFPE tissue RNA significantly increases with archive storage time. However, probe and primer sets for RT-PCR assays based on amplicons that are both short and homogeneous in length enable effective reference gene-based data normalization for the cross-comparison of specimens that substantially differ in age. Using RNA extracted from FFPE sections of archived breast cancer specimens, Cronin et al. [60] demonstrated that the RT-PCR and IHC results for ER, PR, and HER2 receptor status were concordant. Similarly, Cobleigh et al. [61] have demonstrated that RNA extraction from paraffin blocks of archived tissues, some more than 20 years old, may yield accurate information regarding the risk of distant recurrence, even among patients with ten or more metastatic lymph nodes.

Despite these limitations, a meta-analysis of 11 published decision-impact studies ($n = 1154$) concluded that the 21-gene RS assay could spare some patients from the high cost of adjuvant chemotherapy. According to the analysis, 404 (49%) of 820 patients were further assigned to a high-risk group with a further recommendation for chemoendocrine therapy. Moreover, 16% ($n = 99$) of the 632 patients initially recommended for endocrine therapy alone were offered chemoendocrine therapy. In total, the recommendations changed for 35% of the patients ($n = 515$). Oncotype DX has consistently resulted in a significant reduction in the number of patients who are prescribed chemotherapy; in addition, this assay can identify a smaller subset of patients who would benefit from chemotherapy among patients who would otherwise receive endocrine therapy alone. Such changes in treatment decisions are cost-effective for the health system [62]. However, long-term follow-up of these patients is lacking, and the effect of the decision-impact studies on survival has not been prospectively evaluated.

Concordantly, one of the major objectives of the TAILORx trial, which uses the Oncotype DX recurrence score to assign ER(+), HER2(−), node-negative patients to receive chemotherapy plus hormonal therapy vs. hormonal therapy alone, is to reduce chemotherapy overtreatment by integrating molecular diagnostic testing into the clinical decision-making process (Table 8.2) [63]. The TAILORx trial has enrolled more than 11,000 patients. Patients with an RS less than 11 are assigned to hormonal therapy only (arm A), those with an RS greater than 25 receive adjuvant chemotherapy plus hormonal therapy (arm D), and patients with an RS of 11 through 25 are randomized to hormonal therapy only (arm B) versus chemotherapy plus hormonal therapy (arm C). In this trial, the RS scores used as cutoffs between these groups differ from those reported in the NSABP studies to minimize the potential undertreatment of high-risk patients. The upper limit of the low-risk score was also reduced from 18 to 11 because RS < 11 is correlated with a recurrence risk of 5–10% for endocrine therapy alone, the minimum threshold for clinical justification of cytotoxic chemotherapy.

For the low-risk population who received endocrine therapy alone, the invasive disease-free survival (IDFS) rate was 93.8%, and the overall survival (OS) rate was 98% at 5 years [64]. Approximately 30% of this group included patients with tumor size ≥2 cm, and 66% had intermediate or high

Table 8.2 Comparison of prospective trials utilizing multigene tests for prognostic and predictive factors

	TAILORx	MINDACT	RxPONDER
Tests	Oncotype DX	MammaPrint and Adjuvant! Online	Oncotype DX (RS ≤ 25)
Receptor status	ER (+), HER2 (−)	ER (+), HER2 (−)	ER (+), HER2 (−)
Lymph node status	Node negative	Node negative or N1	Node positive
Treatment arms	Arm A (RS < 11): HRT	Arm A (clinical and genomic high risk): CT and HRT	Arm A: CT and HRT
	Arm B (RS:11–25): HRT	Arm B (low clinical and genomic risk): HRT	Arm B: HRT
	Arm C (RS:11–25): CT and HRT	Arm C (discordant risk factors): CT and HRT vs. HRT	
	Arm D (RS > 25): CT		
Stratification factor	(For arms B and C: tumor size, menopausal status, planned CT, planned RT	(For arm C: clinicopathological vs. genomic risk	RS < 14 vs. 14–25, menopausal status, axillary dissection vs. SN biopsy

CT chemotherapy, *HRT* hormonal therapy, *RT* radiotherapy, *RS* recurrence score, *SN* sentinel node

histological grades and would otherwise be recommended to receive chemotherapy on the basis of clinicopathological features. The survival outcomes of the intermediate-risk group, which constituted the majority (67%) of the patients in this trial, have been reported recently.

A total of 6711 women with recurrence scores indicating an intermediate risk for recurrence (11–25) were randomly assigned to receive endocrine therapy alone or endocrine therapy plus chemotherapy. The trial was designed to show noninferiority of endocrine therapy alone by not rejecting equality (hazard ratio [HR] margin up to 1.322 for omission of chemotherapy). The final analysis was based on 836 invasive disease-free survival events after a median follow-up of 7.5 years [65]. The study met its primary endpoint and showed noninferiority (HR = 1.08, $P = 0.26$) in the intention-to-treat population. Endocrine therapy was also noninferior for distant recurrence-free interval (HR = 1.10, $P = 0.48$), recurrence-free interval (HR = 1.11, $P = 0.33$), and overall survival (HR = 0.99, $P = 0.89$). The invasive disease-free survival rates at 9 years were 83.3% for endocrine therapy alone versus 84.3% for endocrine therapy plus chemotherapy. Similarly, distant recurrences were observed in 94.5% and 95.0%, and overall survival rates were 93.9% and 93.8%, respectively. Women with recurrence scores of 0–10 had only a 3% rate of distant recurrence with endocrine therapy alone, whereas those with recurrence scores of 26–100 had a 13% risk despite receiving chemotherapy plus endocrine therapy.

In an exploratory analysis of women ≤50 years old, the findings proposed a potential chemotherapy benefit based on recurrence scores for the intermediate-risk group. With chemotherapy, those with RS of 16–20 had 9% fewer invasive disease-free survival events, and those with RS of 21–25 had 6% fewer invasive disease-free survival events. Patients with RS of 11–15 showed no evidence of chemotherapy benefit regardless of age.

Based on recent findings, the 21-gene RS assay system has been validated to quantify the risk of distant recurrence as a continuous variable and to predict responsiveness to both tamoxifen and CMF or MF chemotherapy among ER-positive, stage I or II breast cancer patients of any age (Table 8.3). The test is now included in the ASCO and NCCN guidelines as a predictor of recurrence for ER-positive, lymph node-negative breast cancer patients.

MammaPrint

Several other approaches have been developed to estimate prognosis in breast cancer patients. The MammaPrint assay uses microarray technology to stratify early (T1 and T2) hormonal receptor-negative/receptor-positive breast cancer patients with node-negative (N0) and node-positive (N+) disease into high- and low-risk categories for distant recurrence. The functions of the 70 genes are mainly related to apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative capacity, tissue invasion, metastasis, and angiogenesis. These genes reflect the acquired malignant characteristics of a cancer cell along with tumor progression-related biological activities [66].

Table 8.3 Comparison of Oncotype DX, PAM50, and MammaPrint multigene tests

	Oncotype DX	PAM 50	MammaPrint
Number of genes	21	50 (+5 control genes)	70
Sample	Formalin-fixed, paraffin-embedded tissue	Formalin-fixed, paraffin-embedded tissue	Fresh-frozen tissue
Features	RS predicts the likelihood of recurrence at 10 years	Classifies intrinsic subtypes	Stratifies patients by good or poor prognostic signature
	Identifies low-risk patients to be spared from CT	Predicts DFS and the likelihood of recurrence at 10 years for ER (+) tamoxifen-treated patients	
		Identifies patients who benefit from neoadjuvant endocrine therapy or CT	

Researchers of the Netherlands Cancer Institute (NKI) initially tested MammaPrint in 79 young (<55 years) N0 breast cancer patients [67] and then validated it in a second set of 295 frozen tissue specimens of both N0 and N+ patients [68]. Both of these studies demonstrated that MammaPrint outperformed standard clinical and histological predictors of patient prognosis. In the N0 group of the second study, 10-year distant metastasis-free survival (DMFS) for the low-risk group was 87% versus 44% in the high-risk group. Multivariate analysis revealed that MammaPrint was the strongest prognostic factor, with an HR of 4.6 (95% CI 2.3–9.2). However, both studies included very few chemotherapy-treated patients; thus, the results did not indicate the predictive utility of the test.

The next validation study included 302 patients from the TRANSBIG (Translational working group of Breast International Group) Consortium who had received only locoregional treatment with a median follow-up time of 13.6 years [69]. The 10-year DMFS rates were 88% and 71% for the low-risk and high-risk groups, respectively. Multivariate analysis indicated that MammaPrint provided the most valuable prognostic information for N0 early-stage breast cancer patients compared with other clinicopathological criteria, including age, tumor size and grade, and hormonal receptor status. This study did not present any information about the predictive value of the test because none of the patients received adjuvant chemotherapy or endocrine therapy. Similarly, another trial including patients with pT1-T2N0 disease confirmed the prognostic applicability of MammaPrint [70]. High-risk patients, which constituted 48% of the group, had a median 5-year OS rate of 82%, while low-risk scores corresponded to a median OS of 97%. When compared to the AOL risk scores, the clinical outcomes of discordant cases were most accurately predicted by MammaPrint. Of the high-risk patients classified by AOL, 34% had a low-risk profile according to MammaPrint and thus could have avoided unnecessary chemotherapy. Conversely, 14% of the low-risk group by AOL had a high-risk profile and required adjuvant treatment based on the current outcome data.

Another trial investigating the efficacy of MammaPrint as a prognostic tool for node-positive patients included frozen tumor samples from 241 patients with operable T1–T3 breast cancer and one to three positive axillary lymph nodes [71]. The 10-year DMFS and breast cancer-specific survival (BCSS) probabilities were 91% and 96%, respectively, for the good prognostic signature group and 76% and 76%, respectively, for the poor prognostic signature group. The 70-gene signature was significantly superior to traditional prognostic factors in predicting BCSS, with an HR of 7.17 (95% CI 1.81–28.43; $p = 0.005$), thus accurately identifying patients with favorable disease outcome, even those with node-positive disease, who may be safely spared with adjuvant chemotherapy.

The predictive role of the assay was mainly based on retrospective evidence initially. Knauer et al. [72] evaluated 541 patients in a pooled study series who received either endocrine treatment (ET) or chemotherapy plus endocrine treatment (ET+CT). BCSS and DDFS at 5 years were assessed separately for the 70-gene high- and low-risk groups. The 70-gene signature classified 47% of the patients as low risk and 53% as high risk. In the low-risk group, BCSS was 97% for the ET group and 99% for the ET + CT group at 5 years (HR: 0.58, 95% CI 0.07–4.98; $p = 0.62$). In the high-risk group, BCSS at 5 years was 81% and 94% for the ET and ET + CT groups, respectively (HR: 0.21 95% CI 0.07–0.59; $p = 0.01$). Multivariate analysis yielded similar results and demonstrated that the low-risk group derived no significant survival benefit from CT added to ET. Notably, very few events were observed in this 70-gene low-risk patient group, irrespective of the type of adjuvant treatment, confirming their overall good outcome. One of the clear limitations of this study, in addition to the limited patient numbers and differences in chemotherapy regimens, is its retrospective design.

The first study designed for the prospective evaluation of an adjuvant systemic treatment decision based on the 70-gene signature was the microarRAy-prognoSTics-in-breast-cancER (RASTER) study [73]. RASTER was a prospective, observational, community-based trial in which physicians were encouraged to use chemotherapy based on MammaPrint scores. The 5-year distant recurrence-free-interval (DRFI) probabilities were compared between subgroups based on the 70-gene signature and AOL. Of the 70-gene signature low-risk patients, 15% received adjuvant chemotherapy (CT) versus 81% of the 70-gene signature high-risk patients. The 5-year DRFI probabilities for 70-gene signature low-risk ($n = 219$) and high-risk ($n = 208$) patients were 97.0% and 91.7%, respectively. For 70-gene signature low risk, AOL high-risk patients ($n = 124$), of whom 76% ($n = 94$) had not received CT, the 5-year DRFI was 98.4%. In the AOL high-risk group, 32% (94/295) less patients would be eligible to receive adjuvant CT if the 70-gene signature was used. The omission of adjuvant chemotherapy as judged appropriate by doctors and patients and supported by a low-risk 70-gene signature result appeared not to compromise the outcome.

The predictive role of MammaPrint was also tested in the neoadjuvant setting [74]. To assess chemosensitivity, 167 stage II–III breast cancer patients were classified according to prognostic signatures prior to neoadjuvant therapy. Among 167 patients, none of the good prognostic signature patients ($n = 23$) achieved pCR compared to 20% of the poor prognostic signature patients ($p = 0.015$). Thus, tumors with a poor prognostic signature were assumed to be more sensitive to chemotherapy.

The first prospective, randomized phase III study (MINDACT) utilizing MammaPrint evaluated whether

patients with high-risk clinical features and a low-risk gene-expression profile could be safely spared from chemotherapy [75]. The patients were divided into four main groups according to their clinical and genomic risks: low clinical risk and low genomic risk, which included 2745 patients (41.0%); low clinical risk and high genomic risk, which included 592 patients (8.8%); high clinical risk and low genomic risk, which included 1550 patients (23.2%); and high clinical risk and high genomic risk, which included 1806 patients (27.0%).

Avoidance of chemotherapy on the basis of gene signature results led to a 5-year rate of DMSF (94.7%) that was 1.5 percentage points lower than the rate with chemotherapy (95% confidence interval [CI] 92.5–96.2%) for the high clinical risk and low genomic risk group, thereby achieving the primary objective of the study. The trial included both node-negative and node-positive patients, and similar rates of survival without distant metastasis were reported for both groups. Among patients with node-negative disease, the rate of survival without distant metastasis was 95.7% (95% CI, 93.0–97.4) in the chemotherapy group and 93.2% (95% CI 90.1–95.4) in the no-chemotherapy group; among patients with node-positive disease, the rates were 96.3% (95% CI 93.1–98.1) in the chemotherapy group and 95.6% (95% CI 92.7–97.4) in the no-chemotherapy group. An expert panel reviewed the results of the MINDACT study and recommended the MammaPrint assay for use in patients with one to three positive nodes and a high clinical risk (determined according to Adjuvant! Online) to inform decisions on withholding adjuvant systemic chemotherapy. However, patients with more than one metastatic lymph node should be informed that a benefit from chemotherapy cannot be excluded [76].

Currently, the 70-gene assay is a prognostic test that provides a dichotomous test result for women <62 years of age who are N0 or N+ (one to three lymph nodes), regardless of their ER status. The test uses microarray technology to analyze the gene expression profile from either FFPE or frozen breast tumor tissue. The results are reported as low risk (13% probability of developing distant metastasis at 10 years without adjuvant therapy) or high risk (56% probability of developing distant metastasis at 10 years without adjuvant therapy).

PAM50

The PAM50 test is based on a qRT-PCR assay to classify ER-positive and ER-negative breast cancer patients into subtypes that could predict outcomes [77, 78]. It measures the expression of 50 classifier genes and five control genes, categorizes tumors into the four intrinsic subtypes (luminal A, luminal B, HER2 enriched, and basal-like), and provides a risk of recurrence (ROR) score to estimate the probability of relapse at 5 years [26]. ROR score was utilized to divide node-negative and node-positive tamoxifen-treated patients into low- and intermediate-risk groups and was found to be of greater prognostic value than standard clinicopathological criteria [79]. In the translational research cohort within the ATAC trial (TransATAC), the performance of the ROR score was compared with that of the RS and of IHC4 for distant recurrence in 1007 postmenopausal women. The results demonstrated that the ROR provided more prognostic information for endocrine-treated women with node-negative disease than the RS [80]. Similarly, the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG 8) trial demonstrated that the ROR score predicted the risk of distant recurrence in 1478 postmenopausal women with ER-positive early-stage breast cancer. To determine to what extent the ROR score could help predict late recurrence, Sestak et al. [81] combined the data from the TransATAC and ABCSG 8 trials and investigated the prognostic value of the ROR score for distant recurrence exclusively in 5–10 years after diagnosis. The authors compared the accuracy of the ROR score with the Clinical Treatment Score (CTS), which contains information on nodal status, tumor size, grade, age, and treatment and was developed using the TransATAC data set. A total of 2137 women who did not have recurrence 5 years after diagnosis were included in the analyses. The Clinical Treatment Score (CTS) was the strongest prognostic factor 5 years after diagnosis. The ROR score itself was significantly prognostic in 5–10 years. In the node-negative, HER2-negative subgroup, more prognostic value for late distant recurrence was provided by the ROR score compared with the CTS.

The predictive value of PAM50 was tested using tissue samples from patients involved in the MA.12 trial, which was designed to evaluate the efficacy of tamoxifen versus placebo in premenopausal breast cancer patients [25]. Total RNA from 398 of 672 (59%) patients was available for intrinsic subtyping with PAM50. A tissue microarray was also constructed from 492 of 672 (73%) patients of the study population to assess a panel of six IHC antibodies to define the same intrinsic subtypes. Classification into intrinsic subtypes by the PAM50 assay was prognostic for both DFS and OS ($p = 0.0003$ and 0.0002, respectively), whereas classification by the IHC panel was not. Moreover, intrinsic subtype classification by the PAM50 assay was superior to IHC profiling for both prognosis and the prediction of benefit from adjuvant tamoxifen for both node-negative and node-positive diseases. Cheang et al. [22] classified the patients included in the NCIC.CTG MA.5 trial, which randomized premenopausal women with node-positive breast cancer to adjuvant CMF (cyclophosphamide–methotrexate–5-fluorouracil) versus CEF (cyclophosphamide–epirubicin–fluorouracil) chemotherapy according to PAM50 intrinsic subtypes. The results revealed that intrinsic subtypes were associated with relapse-free survival (RFS) and OS ($p = 0.0005$, $p < 0.0001$,

respectively). The data also demonstrated the predictive value of intrinsic subtyping for anthracycline benefit. The HER2-enriched subtype exhibited the greatest benefit from CEF versus CMF, with a 21% gain in 5-year RFS and 20% gain in 5-year OS. By contrast, no survival advantage for CEF over CMF was observed for basal-like tumors, with a reverse trend of a 10% higher 5-year OS for the CMF arm. The multivariate analysis results suggested that patients with luminal B tumors trended toward better survival when treated with CEF, whereas luminal A tumors had a tendency for better survival when treated with CMF (RFS, $p = 0.25$; OS, $p = 0.11$). The predictive value of PAM50 subtypes was evaluated in 820 patients from the GEICAM/9906 randomized phase III trial comparing adjuvant FEC to FEC followed by weekly paclitaxel (FEC-P) [82]. In GEICAM/9906, the OS of the FEC-P arm was significantly superior compared to the FEC arm (HR = 0.693, $p = 0.013$). The individual PAM50 subtypes were not predictive of weekly paclitaxel efficacy. However, the PAM50 proliferation score signature, which is the average expression value of 11 proliferation-related genes, was predictive for a benefit of weekly paclitaxel in the adjuvant setting. The investigators did not specify a cutoff point for this signature, but the HR for OS in the low quartile group was very significant (unadjusted HR = 0.232, $p = 0.002$). This was an unexpected finding because it is generally assumed that chemotherapy is not effective in tumors with low proliferative activity.

The ongoing RxPONDER (SWOG S1007) trial primarily uses Oncotype DX and PAM50 as a secondary analysis among patients with ER+, HER2 breast cancer with one to three positive nodes [83]. The primary objective is to determine the effect of chemotherapy on patients with node-positive breast cancer who have an RS ≤ 25. The secondary objective of the study is to compare the RS with the PAM50 ROR to provide valuable information regarding the comparison of the two different gene assays.

In conclusion, PAM50 may offer useful information about intrinsic subtype classification, DDFS, and the risk of recurrence at 10 years for ER-positive patients. In addition, PAM50 may help predict the response to tamoxifen for both node-negative and node-positive breast cancer patients. The assay received approval in 2013 and is commercially available in the European Union and Israel.

Genomic Grade Index (MAPQUANT Dx)

The genomic grade index (GGI) is the first microarray-based molecular diagnostic test for measuring tumor grade as an indicator of proliferation, risk of metastasis, and response to chemotherapy. GGI is mainly based on 97 genes related to tumor differentiation and grade. Although histopathological tumor grading has been regarded as one of the most important prognostic indicators, grading currently suffers from the uncertainty of the G2 grade in the context of decision making in particular and from interobserver variability in general. To create more precise and objective grading criteria, the 97-gene signature was identified and validated in a cohort of 597 tumors from different subtypes [84]. The signature was found to be more closely associated with relapse-free survival compared with the histological grade. In addition, the GGI reclassified histological grade 2 tumors into two subgroups: high versus low risk of recurrence (HR: 3.61, $p < 0.001$). The GGI was also shown to be predictor of relapses in postmenopausal patients treated with tamoxifen or letrozole within the BIG 1–98 trial [85]. One of the limitations of this assay was the need for fresh or frozen tissue. A formalin-fixed, paraffin-embedded (FFPE) tissue-based PCR genomic grade was developed to overcome this difficulty. Eight genes (four representative of GGI and four reference genes) were selected from the initial original set of 97 genes and validated in a consecutive series of 212 systemically treated early-stage breast cancer patients [86]. A significant correlation was observed between the microarray-derived GGI and the qRT-PCR assay using frozen (rho = 0.95) and FFPE material (rho = 0.89).

Theros Breast Cancer Gene Expression Ratio Assay

Theros was originally designed by Ma et al. as a qRT-PCR-based gene signature for FFPE tissue to identify the expression of three predictive genes: the homeobox gene HOXB13, interleukin 17B receptor (IL17BR), and EST AI240933 [87]. Ectopic expression of HOXB13 by breast epithelial cells enhances motility and invasion in vitro, and its expression is increased in both preinvasive and invasive primary breast cancers. The initial study involving ER-positive breast cancer patients treated with tamoxifen indicated that the HOXB13:IL17BR (H:I) expression ratio was highly associated with recurrence [87]. The two-gene ratio accurately classified both tamoxifen-treated and untreated patients into high- and low-risk groups [88, 89]. The prognostic value of this ratio was also tested in larger data sets ($n = 1252$) including ER-positive patients. A higher H/I ratio was associated with a more aggressive clinical course and consequently shorter disease-free and overall survival. Furthermore, it was a useful tool for predicting the response to tamoxifen [90]. Currently, the H/I ratio is considered a marker of recurrence in ER-positive and node-negative patients and is used to classify patients into low (10–27%) or high (28% to >60%) breast cancer recurrence risk at 5 years.

EndoPredict

In contrast to Oncotype DX, PAM50, and MammaPrint, the EndoPredict (EP) assay includes eight genes associated with tumor proliferation and hormonal receptor activity and four reference genes but not ER, PR, and HER2 status. An EP score ranging between 0 and 15 stratifies ER-positive,

HER2-negative breast cancer patients to high- and low-risk groups, with a threshold of 5. The qRT-PCR technique allows the assay to be performed in FFPE tissue to estimate distant recurrence in luminal breast cancer patients treated with adjuvant endocrine therapy alone [91]. EPclin, which is a combined score of clinical risk factors (tumor size and nodal status) and the EP score, revealed significant differences in the 10-year recurrence rates for ABCSG 6 and ABCSG 8 patients. Both were randomized trials including only endocrine therapy. According to the analysis, approximately half of the patients were in the high-risk group and further required chemotherapy based on the current data [91]. The EPclin score has been recently compared with purely clinical risk classifications and was found to be strikingly superior to known prognosticators such as St. Gallen, German S3, and NCCN [92].

In light of these studies involving protein markers and genomic assays, future treatment guidelines concerning breast cancer patients will likely be refined based on individual tumor characteristics, probably derived from translational research projects, rather than age, tumor size, or nodal status alone.

Selecting Patients for Adjuvant Chemotherapy

The decision regarding systemic adjuvant treatment should be based on the predicted sensitivity to treatment methods and the individual risk of relapse. The final decision should also consider the possible side effects and the patient's age, general health status, comorbidities, and preferences. Treatment should begin 2–8 weeks after surgery; a retrospective analysis of 2594 breast cancer patients revealed that RFS and OS are significantly compromised by delays of more than 12 weeks after definitive surgery (HR: 1.6, 95% CI 1.2–2.3; $p = 0.005$) [93]. A study by Gagliato et al. [94] evaluated the association between time to initiation of adjuvant chemotherapy and survival according to breast cancer subtype and stage at diagnosis. The initiation of chemotherapy ≥61 days after surgery was associated with adverse outcomes among patients with stage II and stage III diseases. Patients with triple-negative breast cancer (TNBC) tumors and those with HER2-positive tumors treated with trastuzumab who started chemotherapy ≥61 days after surgery had worse survival (HR: 1.54, 95% CI 1.09–2.18 and HR: 3.09, 95% CI 1.49–6.39, respectively) than those whose treatment was initiated in the first 30 days after surgery. Thus, particularly for stage II and III breast cancer, TNBC and HER2-positive tumors, avoiding postponing the initiation of adjuvant chemotherapy, should be prioritized and may lead to an improvement in outcomes for these patient subsets.

The absolute benefit derived from adjuvant chemotherapy varies substantially with the risk of the individual patient, which is determined by the biology and the burden of the disease (e.g., the absolute benefit of adjuvant chemotherapy for a low-burden luminal A-like breast cancer is extremely small and must be balanced against the known short- and long-term side effects). Algorithms, validated computer-based models such as AOL, and the abovementioned genetic assays may help determine the benefits and detrimental effects of a planned treatment schedule.

When multigene assays are readily available, clinical practice has developed to rely on their results to guide decisions about the inclusion of chemotherapy in the treatment of patients with ER-positive, HER2-negative disease. The 70-gene assay returns a dichotomous result, whereas the 21-gene RS is continuous. A subject of debate is the level of RS that should justify cytotoxic therapy: only high RS values (>31) were significantly associated with chemotherapy benefit in prospective/retrospective studies [47, 50], whereas substantially lower values are being investigated in ongoing prospective trials and used in clinical practice. In many regions of the world, the cost of these multigene assays remains prohibitive.

The clinicopathological surrogate definition for luminal A-like disease includes the existence of positive ER and PR, negative HER2, and low Ki-67. The cutoff between "high" and "low" values for Ki-67 varies among laboratories. The 2013 St. Gallen guidelines offered a level of <15% for the best correlation with the gene expression definition of luminal A tumors. This proposal is based particularly on the results of a single reference laboratory [95]. In the St. Gallen 2015 consensus, the minimum level of Ki-67 for luminal B tumors is generally accepted as 20–29 [96]. The value of PR in distinguishing between "luminal A-like" and "luminal B-like" subtypes is derived from the work of Prat et al. [97], who used a PR cutoff of ≥20% to best correspond to the luminal A subtype. "Luminal B-like" disease comprises those cases that lack the abovementioned characteristics typical of "luminal A-like" disease. Thus, either a high Ki-67 value or a low PR value may be used to distinguish between "luminal A-like" and "luminal B-like (HER2 negative)." According to current guidelines, endocrine therapy is the most critical intervention for the "luminal A-like" subtype and is often used alone. However, the panel suggested the addition of cytotoxics in selected patients. Relative indications for the addition of cytotoxics accepted by the majority included the following: (1) high 21-gene RS (i.e., >25); (2) 70-gene high-risk status, if available; (3) grade 3 disease; and (4) involvement of four or more lymph nodes. A minority require the involvement of only one node as an adequate rationale for the addition of chemotherapy. For "luminal B-like" (HER2-negative) disease, cytotoxic therapy was suggested for most patients. The panel could not conclude whether young age (<35 years) per se was an indication for the addition of cytotoxics.

Table 8.4 St. Gallen recommendations for adjuvant treatment of breast cancer depending on intrinsic subtype and clinicopathological surrogate definitions

Intrinsic subtype	Clinicopathological definition	Treatment	Special considerations
Luminal A	*Luminal A-like*		
	ER (+) and PR (+) and HER2 (−) and Kİ 67 ≤ (14–19%)[a] and recurrence risk low with multigene tests	Endocrine therapy	Cytotoxics administered when high gene RS (>25), 70-gene high-risk status, grade 3 disease, ≥4 lymph node metastasis, young age (<35 years)[b]
Luminal B	*Luminal B-like* (*HER2 negative*)		
	ER (+) and HER2 (−) and Ki67 ≥ (20–29%)[a] or PR low/negative or recurrence risk high with multigene tests	Endocrine therapy for all, cytotoxics for most	
	Luminal B-like (*HER2 positive*)		
	HER2 overexpressed or amplified any Ki-67	Cytotoxics and antiHER2 and endocrine therapy	
C-ERB B2 overexpression	*HER2* (+) (*nonluminal*)		
	HER2 overexpressed or amplified and ER and PR absent	Cytotoxics and antiHER2	
Basal-like	*Triple negative*		
	ER and PR absent HER2 negative	Cytotoxics	80% overlap between triple-negative and basal-like subtypes

[a]Panel votes in St. Gallen 2015, the minimum value of Ki67 required for "luminal B-like" is for "14–19%," 14%; for "20–29%," 36%; and for "30% or more%," 7%

[b]The Panel in St. Gallen 2015 was equally divided as to whether young age per se was an indication to add cytotoxics

The St. Gallen 2017 guidelines recommend gene expression assays for guiding the decision on adjuvant chemotherapy mainly for patients with tumors between 1 and 3 cm, with zero to two or three positive lymph nodes, and intermediate proliferative fraction. The Panel has not endorsed a specific multigene assay but has suggested that none of the tests should be the only factor considered in making the decision to proceed with or avoid chemotherapy [98] (Table 8.4).

According to NCCN guidelines, patients with lymph node involvement or with tumors greater than 1 cm in diameter are also appropriate candidates for adjuvant systemic therapy [99]. Patients with invasive ductal or lobular tumors of 0.6–1 cm in diameter and no lymph node involvement are classified as low risk of recurrence; however, those with unfavorable prognostic features may warrant the consideration of adjuvant therapy. Unfavorable prognostic features are defined as intramammary angiolymphatic invasion, high nuclear grade, high histological grade, HER2-positive status, or hormonal receptor-negative status. Adjuvant chemotherapy is not recommended for patients with triple-negative invasive breast cancers less than 0.5 cm (T1aN0M0) in diameter. Patients with T1b and larger tumors should receive adjuvant cytotoxic therapy. An adjuvant chemotherapy regimen for triple-negative tumors should contain anthracyclines and taxanes. Platinum-based chemotherapy regimens are not standard, and data are currently insufficient to recommend these regimens as adjuvant chemotherapy in TNBC patients. The triple-negative phenotype may be an indication for dose-dense chemotherapy with growth factor support.

NCCN member institutions consider performing RT-PCR analysis (e.g., Oncotype DX assay) to further refine risk stratification for adjuvant chemotherapy for patients with node-negative, ER-positive, HER2-negative breast cancers >0.5 cm. The 21-gene RT-PCR assay is presented as an option when evaluating patients with primary tumors 0.6–1.0 cm in size with unfavorable features or in tumors >1 cm in size and node-negative, hormonal receptor-positive, and HER2-negative disease. The results of the EBCTCG overview have demonstrated convincing reductions in both recurrence and death rates in all age groups with the addition of polychemotherapy and endocrine therapy [9]. Thus, the current guidelines recommend adjuvant chemotherapy regardless of patient age. However, the decision to use adjuvant chemotherapy (CT) in elderly patients is challenging, and it requires evaluation of both the benefits and risks, including toxicity and comorbidities. The data remain insufficient to recommend adjuvant CT for those >70 years of age. The Cancer and Leukemia Group B (CALGB) 49,907 trial compared standard adjuvant chemotherapy with CMF or doxorubicin plus cyclophosphamide (AC) with capecitabine alone in fit patients over 65 years of age. AC or CMF was superior to capecitabine, and enrollment was discontinued early [100]. However, age is a known risk factor for the development of myelodysplasia and acute myelogenous leukemia after anthracycline-based adjuvant chemotherapy [101]; thus, life expectancy should be taken into consideration when making a decision. In a retrospective review of four randomized CALGB trials, older patients had

higher chemotherapy-related mortality (1.5% of patients aged ≥65 years), and the incidence of treatment-related mortality increased linearly with age [102]. Recently, the phenomenon of "chemobrain" (long-term chemotherapy-induced cognitive impairment) has been described and associated with altered quality of life and functionality [103]. Moreover, adjuvant chemotherapy has been shown to have a progerontogenic effect, estimated as 10.4 years of chronological aging [104].

The French Group of Geriatric Oncology (GERICO) has developed a trial to evaluate the benefit of adjuvant chemotherapy with regard to OS in patients aged over 70 years with pN0 or pN-positive, HR-positive HER2-negative disease and with a high genomic grade index assessed by reverse transcriptase polymerase chain reaction [105]. This study may help resolve uncertainty regarding the benefit of adjuvant CT in elderly patients.

The most recently updated version of the ESMO guidelines does not offer chemotherapy for most luminal A tumors, except those with the highest risk of relapse (extensive nodal involvement) [106]. Luminal B HER2-negative cancers comprise the population of highest uncertainty regarding chemotherapy indications. ESMO guidelines have defined features associated with lower endocrine responsiveness, such as low steroid receptor expression, lack of PR expression, high tumor grade, and high proliferation marker expression. Moreover, two invasion factors, urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI1), also known as tumor markers, have been suggested as prognostic factors and have been utilized to aid treatment decision making in early breast cancer [107].

Treatment of Rare Histological Subtypes

Invasive breast carcinomas comprise several histological subtypes; the most common types (infiltrating ductal, lobular, or mixed) represent approximately 91% of invasive breast carcinomas, according to Surveillance, Epidemiology, and End Results (SEER) data of the National Cancer Institute from 1992 to 2001 [10]. All other subtypes including mucinous (colloid), tubular, medullary, papillary, and metaplastic breast cancer account for fewer than 10% of cases.

Tubular carcinomas were relatively infrequent in the premammography era, accounting for 2% or less of all invasive breast cancers. However, in some series of mammographically screened populations, the incidence is higher, accounting for 10–20% of invasive cancers. These lesions have a relatively better prognosis than infiltrating ductal carcinomas; their natural history is favorable, and metastases are rare. Mucinous carcinoma lesions are another prognostically favorable variant of invasive breast carcinoma [108]. Some guidelines provide systemic treatment recommendations for histologically favorable invasive breast cancers such as tubular and mucinous cancers based on tumor size and ALN status [109]. The treatment options for endocrine therapy and chemotherapy and the sequencing of treatment with other modalities are similar to those for breast cancers with the usual histology. The vast majority of tubular breast cancers are both ER positive and HER2 negative. Thus, the pathological evaluation and accuracy of the ER and/or HER2 determination should be reviewed if a tubular breast cancer is ER negative and/or HER2 positive. If a breast cancer is histologically identified as a tubular or mucinous breast cancer and is confirmed as ER negative, then the tumor should be treated according to the guideline for tumors with the usual histology, ER-negative breast cancers. Because the prospective data regarding systemic adjuvant therapy of tumors with favorable histology are lacking, decisions regarding treatment should be made on an individual basis.

Medullary carcinomas account for 1–10% of invasive breast cancers. However, there is considerable interobserver variability in the diagnosis of this type of breast cancer depending in part on the classification system employed. Medullary carcinoma is characterized by high nuclear grade, lymphocytic infiltration, and a pushing tumor border. Despite their aggressive histological appearance, the prognosis of pure medullary carcinomas appears to be more favorable than that of infiltrating ductal carcinomas [110]. However, there is also evidence suggesting that the risk of metastases is equal to that of other high-grade carcinomas, even for cases that meet all of the pathological criteria for typical medullary carcinoma. Moreover, many cases classified as medullary carcinoma do not have all of the pathological features upon subsequent pathological review. Patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as a typical medullary carcinoma. Thus, it is often recommended that medullary carcinoma be treated similarly to other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Invasive apocrine carcinoma of the breast is rare, constituting between 0.3% and 4% of all invasive cancer in women. The diagnosis of apocrine carcinoma is made based on the typical cell morphology present in >90% of the tumor population (the same criteria used for all other special histological subtypes) and on the distinctive immunohistochemical profile: ER-negative, PR–negative, and androgen receptor (AR)-positive tumors [111]. Some studies have indicated a poor response to chemotherapy in patients with apocrine carcinomas, although HER-2/neu-enriched apocrine breast carcinomas tend to have the highest rate of complete response to neoadjuvant chemotherapy [112]. Due to its consistent overexpression in apocrine epithelium, AR has been designated as an apocrine differentiation marker.

Briefly, for rare histological subtypes, endocrine therapy alone is recommended for endocrine-responsive subtypes

(cribriform, tubular, and mucinous), and cytotoxics are recommended for endocrine nonresponsive subtypes (apocrine, medullary, adenoid cystic, and metaplastic). However, node-negative adenoid cystic carcinoma can be spared from chemotherapy. For metaplastic carcinoma, the value of histological grading is uncertain; when a specific histological subtype constitutes more than 10% of the tumor, the subtype is considered as an independent prognostic variable.

Type, Dosing, and Scheduling of Chemotherapy

Anthracyclines and Other Alkylating Agents

Adjuvant chemotherapy comprising multiple cycles of chemotherapy is a well-established strategy for lowering the risk of recurrence and death due to breast cancer. Initial studies of adjuvant chemotherapy were conducted among patients with higher risk, lymph node-positive disease. However, subsequent trials with lower risk groups have extended the benefits of adjuvant chemotherapy.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was first established in 1985 to coordinate individual patient-level meta-analyses of all randomized trials of adjuvant treatments. According to the EBCTCG 1998 meta-analysis, for recurrence, polychemotherapy produced substantial and highly significant proportional reductions among both women aged under 50 at randomization (35% reduction; $2p < 0.00001$) and women aged 50–69 (20% reduction; $2p < 0.00001$); few women aged ≥70 had been studied. Reductions in mortality were also significant among both women aged under 50 (27% reduction; $2p < 0.00001$) and women aged 50–69 (11% reduction; $2p = 0.0001$). The recurrence reductions chiefly emerged during the first 5 years of follow-up, whereas the difference in survival increased throughout the first 10 years [113].

Another report on trials that had begun by 1995 reviewed polychemotherapy versus no adjuvant chemotherapy and anthracycline-based chemotherapy (with doxorubicin or epirubicin) versus CMF (cyclophosphamide, methotrexate, and fluorouracil) [9]. The analyses of systemic adjuvant treatment for early-stage breast cancer involved a total of nearly 150,000 women in 200 randomized trials, including many with long-term follow-up. For recurrence, several months of polychemotherapy produced, overall, a highly significant 23.5% reduction in the annual HR ($p < 0.00001$). For mortality, several months of polychemotherapy produced a significant 15.3% reduction in the annual HR ($p < 0.00001$).

In the 2011 EBCTCG meta-analysis, adjuvant chemotherapy using an anthracycline-based regimen was associated with a significant improvement in the risk of recurrence compared to no treatment (RR 0.73, 95% CI 0.68–0.79), which translated into an absolute gain of 8.0% at 10 years, and a significant reduction in overall mortality (RR 0.84, 95% CI 0.78–0.91), which translated into an absolute gain of 5.0% [114]. Compared with no treatment, the use of CMF was associated with significant improvement in the risk of recurrence (RR 0.70, 95% CI 0.63–0.77), which translated into an absolute gain of 10.2% and a significant reduction in breast cancer mortality (RR 0.76, 95% CI 0.68–0.84). The reduction in overall mortality, with an absolute gain of 4.7%, was also significant (RR 0.84, 95% CI 0.76–0.93).

The 2005 EBCTCG analysis included an indirect comparison of adjuvant CMF and anthracycline-based chemotherapy [9]. Approximately half of the available evidence was from trials of CMF-based regimens, and approximately a third was from trials of anthracycline-based regimens. For the CMF-based regimens, 84% of the information was from trials of 6, 9, or 12 months of treatment (with no significant trend toward a greater benefit with longer treatment) and 90% was from trials that involved no cytotoxic drugs other than CMF (the remainder involved these three drugs and vincristine). In the anthracycline-based trials, the mean duration was 6 months, and the anthracycline used was always doxorubicin (66%) or epirubicin (34%). Among both younger and older women, there were no significant differences between the proportional risk reductions (in recurrence or in breast cancer mortality) produced by the CMF-based and anthracycline-based chemotherapy regimens in these particular trials.

Although the indirect comparisons of anthracycline-based and CMF regimens did not suggest any substantial difference in efficacy, the directly randomized comparisons involved smaller standard errors for the comparison between the two treatment effects, particularly at younger ages, favoring anthracyclines [9]. A total of 14,000 women (9000 younger and 5000 older) were included in trials comparing anthracycline-based versus CMF-based regimens. The anthracyclines tested were doxorubicin (60%) or epirubicin (40%), usually administered for approximately 6 months in combination with other cytotoxic drugs (e.g., as FAC or FEC, which were the most widely studied combinations). The CMF-based regimens used in the control groups all involved CMF with no other cytotoxic drugs and were administered for approximately 6 (mean 6.5) months. The overall findings indicated a moderate but highly significant advantage of anthracyclines over CMF (recurrence rate ratio 0.89, $2p = 0.001$; breast cancer death rate ratio 0.84, $2p = 0.00001$). For the probabilities of recurrence, breast cancer mortality, and overall mortality, the absolute difference between anthracycline-based and CMF chemotherapy was approximately 3% at 5 years and 4% at 10 years. The proportional risk reductions among older women and those with ER-positive and node-negative disease had relatively wide confidence intervals.

Two randomized prospective trials of CEF (cyclophosphamide, epirubicin, and fluorouracil) chemotherapy in ALN-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both 10-year RFS (52% vs. 45%; $p = 0.007$) and OS (62% vs. 58%; $p = 0.085$) favored the CEF arm of the trial [115]. The second trial compared CEF given intravenously every 3 weeks at two dose levels of epirubicin (50 mg/m^2 vs. 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year DFS (55% vs. 66%; $p = 0.03$) and OS (65% vs. 76%; $p = 0.007$) both favored the epirubicin 100 mg/m^2 arm [116]. Another trial compared two dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer [117]. This study demonstrated that higher dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free survival and OS. Based on the collective experience, multiple cycles of adjuvant chemotherapy, typically including anthracycline-based regimens, are recommended for the majority of patients with node-positive and higher risk node-negative tumors.

The Story of Taxanes

The introduction of taxanes into early-stage breast cancer treatment was an important development over the historic experience with alkylator and anthracycline-based chemotherapy. The first randomized study of adjuvant taxane therapy was CALGB 9344, which incorporated sequential paclitaxel therapy for women receiving four cycles of cyclophosphamide–doxorubicin (AC) chemotherapy [118]. The study also involved dose escalation for doxorubicin, which did not reveal a benefit of an increase in dose to 75 or 90 mg/m^2. However, sequential paclitaxel therapy (175 mg/m^2 for four cycles) improved both DFS and OS among women with node-positive breast cancer. At 5 years, DFS was 65% and 70%, and OS was 77% and 80% after AC alone and AC plus paclitaxel, respectively. Similarly, the NSABP-B28 trial demonstrated that the addition of paclitaxel to AC significantly reduced the HR for DFS events by 17% (relative risk [RR], 0.83; 95% CI 0.72–0.95; $p = 0.006$). The 5-year DFS was 76% for patients randomly assigned to AC followed by paclitaxel compared with 72% for those randomly assigned to AC [119]. However, the improvement in OS was small and not statistically significant (RR, 0.93; 95% CI 0.78–1.12; $p = 0.46$). The 5-year OS was 85% (±2%) for both groups. In this trial, an unplanned subset analysis suggested that the addition of paclitaxel was more beneficial in women with tumors that had either a negative or unknown ER status, with a hazard ratio for recurrence of 0.72 (0.59–0.86).

Another adjuvant trial reported on 524 women with T1–3, N0–1 invasive breast cancer who were randomized to four cycles of postoperative paclitaxel followed by four cycles of FAC versus a control group who received eight cycles of FAC [120]. Therefore, this trial tested the benefit of substituting a single-agent taxane for some cycles of anthracycline-containing chemotherapy while maintaining the overall number of cycles. A total of 174 patients were treated preoperatively, and 350 were treated postoperatively; the results were presented together. The hazard ratio was 0.70 (95% CI 0.47–1.07, $p = 0.09$) for RFS and was not reported for OS. There was a nonsignificant trend, suggesting that the addition of paclitaxel was more beneficial in women with tumors that were ER negative.

Similarly, another randomized trial (PACS 01) in women with ALN-positive breast cancer compared six cycles of FEC with three cycles of FEC followed by three cycles of docetaxel [121]. The 5-year DFS (78.4% vs. 73.2%; adjusted $p = 0.012$) and OS (90.7% vs. 86.7%; $p = 0.017$) of sequential FEC followed by docetaxel were superior. The GEICAM 9906 study, which compared six cycles of FEC90 with four cycles of FEC90 followed by paclitaxel once a week for 8 weeks, also reported a benefit of paclitaxel for both DFS and OS [122].

The question of the scheduling and dosing of taxanes became more confusing following the results of the Eastern Cooperative Oncology Group (ECOG) E1199 study. The ECOG E1199 study was a four-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-week schedule or a weekly schedule [123]. At a median of 63.8 months of follow-up, no significant differences in DFS or OS were observed when comparing paclitaxel to docetaxel or weekly vs. every-3-week administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-week paclitaxel in DFS (HR 1.27; 95% CI 1.03–1.57; $p = 0.006$) and OS (HR 1.32; 95% CI 1.02–1.72; $p = 0.01$), and every-3-week docetaxel was superior to every-3-week paclitaxel in DFS (HR 1.23; 95% CI 1.00–1.52; $p = 0.02$) but not in OS [124]. Based on these results, as well as on the findings from the CALGB 9741 trial indicating that dose-dense AC followed by paclitaxel every 2 weeks had a survival benefit compared with the regimen of AC followed by every-3-week paclitaxel, the every-3-week paclitaxel regimen has been removed from the guidelines [125].

Breast Cancer International Research Group (BCIRG) 001 was an open-label, phase 3, multicenter trial in which 1491 patients aged 18–70 years with node-positive, early-stage breast cancer were randomly assigned to adjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide (TAC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC) every 3 weeks for six cycles [126]. After 55 months of follow-up, the study demonstrated that a

Table 8.5 Overall and disease-free survival analysis of some of the docetaxel-including trials

Trial	Regimen	Follow-up (years)	DFS (at 5 years)	HR	*p*	OS (at 5 years)	HR	*p*
GEICAM 9805 [133]	FAC ×6 vs. TAC ×6	5	90.1% vs. 85.3%	0.67	0.03	95.2% vs. 93.5%	0.76	0.29
ECOG 2197 [128]	AT ×4 vs. AC ×4	5	85% vs. 85%	1.02	0.78	91.2% vs. 92%	1.3	0.62
USO 9735 [138]	TC ×4 vs. AC ×4	7	81% vs. 75%[a]	0.74	0.033	87% vs. 82%[a]	0.69	0.032
UK TACT [130]	FEC ×3-T ×3 vs. FEC ×8 or E ×4 vs. CMF ×4	5	75.6% vs. 74.3%	0.95	0.44	82.5% vs. 83%	0.99	0.91
BCIRG 001 [126]	TAC ×6 vs. FAC ×6	4.5	75% vs. 68%	0.72	0.001	87% vs. 81%	0.70	0.008
PACS 01 [121]	FEC ×3-T ×3 vs. FEC ×6	5	73% vs. 78%	0.85	0.012	86.7% vs. 90.7%	0.73	0.014

DFS disease-free survival, *OS* overall-survival, *A* adriamycin, *C* cyclophosphamide, *E* epirubicin, *F* 5-fluorouracil, *T* docetaxel, *M* methotrexate
[a]DFS and OS rates at 7 years

Table 8.6 Overall and disease-free survival analysis of some of the paclitaxel-including trials

Trials	Regimen	Follow-up (years)	DFS (at 5 years)	HR	*p*	OS (at 5 years)	HR	*p*
MDACC 2002 [120]	FAC ×8 vs. P ×4-FAC ×4	5	83% vs. 86%	0.83	0.09	NR		
CALGB 9344 [118]	AC ×4 vs. AC ×4-P ×4	5	65% vs. 70%	0.83	0.013	77% vs. 80%	0.82	0.006
GEICAM/2003–02 [134]	FAC ×6 vs. FAC ×3-P (8w)	5	93% vs. 90.3%	0.73	0.04	97% vs. 95%	0.79	0.34
NSABP B28 [119]	AC ×4 vs. AC ×4-P ×4	5	72% vs. 76%	0.83	0.006	85%vs. 85%	0.93	0.46
HeCOG 10/00 [145]	E ×4-CMF ×4 vs. E ×3-P ×3-CMF ×3	5	77% vs. 80%	1.16	0.31	93% vs. 90%	2.42	0.02

DFS disease-free survival, *OS* overall survival, *A* adriamycin, *C* cyclophosphamide, *E* epirubicin, *F* 5-fluorouracil, *P* paclitaxel, *M* methotrexate

regimen incorporating docetaxel reduced the risk of relapse (HR 0.72, 95% CI 0.59–0.88; $p = 0.001$) and death (HR 0.70, 95% CI 0.53–0.91; $p = 0.008$) compared with a standard anthracycline-based regimen. The survival advantage for the TAC regimen was maintained at 10-year follow-up. DFS was 62% (95% CI 58–65) for patients in the TAC group and 55% (51–59) for patients in the FAC group (HR 0.80, 95% CI 0.68–0.93; $p = 0.0043$). Ten-year OS was 76% (95% CI 72–79) for patients in the TAC group and 69% (65–72) for patients in the FAC group (HR 0.74, 95% CI 0.61–0.90; log-rank $p = 0.0020$) [127]. Some of the adjuvant trials of taxanes are summarized in Tables 8.5 and 8.6.

The incorporation of docetaxel with doxorubicin with different schedules has been tested in further trials. One trial that incorporated docetaxel into chemotherapy for high-risk node-negative or node-positive patients did not reveal a significant difference between the two treatment protocols (AT vs. AC) [128]. However, the results from the three-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC → T) demonstrated that AC → T had a significant advantage for DFS (HR: 0.83; $p = 0.006$) but not OS (HR: 0.86; $p = 0.086$) compared with TAC [129]. In addition, both DFS (HR: 0.080; $p = 0.001$) and OS (HR: 0.83; $p = 0.034$) were significantly increased when AC → T was compared with AT, with AT demonstrating non-inferiority compared with TAC.

Not all studies have further supported the use of adjuvant taxanes in early breast cancer. There were no significant differences in DFS in a large ($n = 4162$) randomized study (TACT) comparing adjuvant chemotherapy with four cycles of every-3-week FEC followed by four cycles of every-3-week docetaxel with standard anthracycline chemotherapy regimens (e.g., FEC or epirubicin followed by CMF) in women with node-positive or high-risk node-negative operable breast cancer [130]. In addition, the anthracycline–docetaxel sequential schedule was associated with a higher frequency of adverse events and transiently poorer quality of life than the non-taxane control regimen. Generalizations about taxane benefits are difficult to make because individual trials vary in size, are reported at different times since study initiation, include biologically heterogeneous populations, use one or another taxane with different schedules, and compare different anthracycline control regimens of often unequal duration. Many patients appear to receive benefits of differing magnitude from additional taxanes, particularly in regard to OS. An important role for adjuvant taxanes as a sequential alternative to anthracyclines has been proposed to minimize the overall anthracycline dose and subsequent exposure to associated long-term adverse events (such as the induction of leukemia and cardiotoxicity).

More than a dozen studies have reported improved breast cancer outcomes with the incorporation of the taxanes paclitaxel or docetaxel as substitutes or adjunct treatments to anthracycline-based regimens. A large meta-analysis of 13 studies ($n = 22{,}903$) that incorporated taxanes into anthracycline-based regimens revealed that the pooled HR estimate was 0.83 (95% CI 0.79–0.87; $p = 0.00001$) for DFS and 0.85 (95% CI 0.79–0.91; $p = 0.00001$) for OS. Risk

reduction was not influenced by the type of taxane, ER expression, the number of axillary metastases (1–3 lymph nodes vs. ≥4 lymph nodes), patient age/menopausal status, or administration schedule [131]. Taxane incorporation resulted in an absolute 5-year risk reduction of 5% for DFS and 3% for OS.

Another meta-analysis of nine trials involving more than 15,000 patients also assessed the impact of paclitaxel or docetaxel on survival [132]. Significant differences in favor of taxanes were observed in DFS in the overall (RR: 0.86; 95% CI 0.81–0.90; p = 0.00001) and lymph node-positive populations (RR: 0.84; 95% CI 0.79–0.89; p = 0.0001) and in OS in the overall (RR: 0.87; 95% CI 0.81–0.83; p = 0.0001) and lymph node-positive populations (RR: 0.84; 95% CI 0.77–0.92; p = 0.0001). The absolute benefits in DFS and OS in favor of taxanes ranged from 3.3% to 4.6% and from 2.0% to 2.8%, respectively.

Collectively, these data suggest that the use of taxanes may contribute to modest improvement in outcomes, particularly among women with node-positive breast cancer. Most taxane trials have included node-positive patients, but the effect of the addition of taxanes to adjuvant chemotherapy for node-negative breast cancer patients has been assessed in a few trials. One pure adjuvant study in node-negative patients was the Spanish Breast Cancer Research Group (GEICAM) 9805 trial [133]. The study assigned 1060 women with axillary node-negative breast cancer and at least one high-risk factor for recurrence to treatment with TAC or FAC every 3 weeks for six cycles after surgery. High-risk factors were defined according to the 1998 St. Gallen criteria: tumor size >2 cm, negative for ER and PR expression, histological tumor grade 2 or 3, and age <35 years. The primary endpoint was DFS after at least 5 years of follow-up. In this study, the combination of docetaxel, doxorubicin, and cyclophosphamide (TAC) significantly reduced the risk of recurrence by 32% (p = 0.01) compared with fluorouracil, doxorubicin, and cyclophosphamide (FAC) at the expense of significant toxicity. The benefit of TAC was consistent regardless of hormonal receptor status, menopausal status, or the number of high-risk factors.

Before these results were available, GEICAM/2003–02 began accruing a similar group of high-risk node-negative breast cancer patients to determine the benefits and safety of adding paclitaxel to the standard FAC regimen in this understudied population [134]. Specifically, this trial compared the administration of six cycles of FAC with a regimen of four cycles of FAC followed by eight doses of weekly paclitaxel (FAC-wP). The estimated DFS rates at 5 years were 93% in the FAC-wP arm and 90.3% in the FAC arm (p = 0.04). The difference in DFS between the two arms was mainly due to the greater number of distant breast cancer relapses among those receiving FAC than among those receiving FAC-wP. Subgroup DFS analyses by menopausal status, HR status, tumor grade, and HER2 status suggested that the observed benefit of FAC-wP over FAC in these subpopulations was consistent with that of the overall population. Nonetheless, the 21.4% reduction in the risk of death in the experimental group failed to reach significance (HR, 0.79; 95% CI 0.49–1.26, p = 0.31).

A meta-analysis of 14 studies comparing docetaxel-containing versus non-taxane-containing regimens revealed that the addition of docetaxel significantly reduced the risk of relapse (16% relative reduction) and the risk of death (14% relative reduction) for high-risk early-stage breast cancer [135]. The findings also suggested that the relative benefits for DFS of adding docetaxel were nearly identical in node-negative and node-positive patients [HR 0.86 (0.73–1.00), 4274 patients and HR 0.83 (0.77–0.90), 20,166 patients, respectively]. The authors could not demonstrate a survival advantage with the addition of docetaxel in node-negative patients, but they proposed that this may be due to the lack of statistical power and the short period of follow-up in some of the trials included in the meta-analysis.

Four cycles of AC were demonstrated to be equivalent to 6 months of classic cyclophosphamide, methotrexate, and fluorouracil in two separate National Surgical Adjuvant Breast and Bowel Project (NSABP) studies (NSABP-15 and NSABP-23) [136, 137]. However, whether the benefit of adding a taxane in the adjuvant setting obviates the need for anthracyclines in a subset of patients is not known. While confirmation in larger prospective trials is necessary, one randomized trial supports the use of a non-anthracycline regimen. US Oncology Trial 9735 enrolled 1016 women with stage I–III HER2-negative breast cancer and randomly assigned the women to therapy with AC (doxorubicin and cyclophosphamide) or TC (docetaxel plus cyclophosphamide) [138]. With a median follow-up of 7 years, TC resulted in significantly higher DFS (81% vs. 75%) and OS (87% vs. 82%) [139]. Given the scarcity of prospective randomized data addressing this issue, an anthracycline- and taxane-containing regimen is recommended for most women, particularly those with higher stage tumors and those with triple-negative or HER2-positive cancers. However, for those with contraindications to anthracycline-based therapy, CMF and TC are acceptable alternatives.

Dose-Dense Regimens

Dose escalation studies revealed no benefit, and dose-dense schedules have been evaluated in subsequent trials. Dose density refers to the administration of drugs with a shortened intertreatment interval and is based on the observation that, in experimental models, a given dose always kills a certain fraction, rather than a certain number, of exponentially growing cancer cells [140]. Because human cancers in general and

breast cancers in particular are believed to grow by nonexponential Gompertzian kinetics, this model has been extended to those situations [141]. The regrowth of cancer cells between cycles of cytoreduction is more rapid in volume-reduced Gompertzian cancer models than in exponential models. Hence, it has been hypothesized that the more frequent administration of cytotoxic therapy would minimize the residual tumor burden more effectively than dose escalation. The concept of dose density has been strongly influenced by an alternative model developed by Norton and Simon [142], which hypothesizes that logarithmic cell killing is not constant but is proportional to the relative growth rate. Because smaller tumors are growing relatively more rapidly than larger tumors with the same kinetics, chemotherapy induces greater log killing in smaller tumors. However, due to more rapid regrowth, the eventual outcome is the same.

The CALGB 9741 randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide vs. doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks [125]. No significant difference was observed between the two chemotherapy regimens, but a 26% reduction in the HR of recurrence ($p = 0.01$) and a 31% reduction in the HR of death ($p = 0.013$) were observed for the dose-dense regimens.

In a different approach, ECOG compared weekly and 3-week interval docetaxel or paclitaxel after four cycles of standard doxorubicin and cyclophosphamide in women with node-positive or high-risk node-negative breast cancer [123]. Neither paclitaxel nor docetaxel emerged as superior with respect to DFS. However, subgroup analyses suggested a potential DFS benefit of dose-dense therapy with paclitaxel (HR: 1.20; $p = 0.06$) but not docetaxel. Those results must be interpreted with caution because the planned dose density and cumulative dose were 37% higher for weekly paclitaxel compared with 3-weekly therapy, whereas dose density and cumulative dose were similar for weekly and 3-weekly docetaxel. The schedule for paclitaxel administration was also analyzed by Budd et al. [143] using a 2 × 2 factorial design. The study included 3294 high-risk breast cancer patients with stage I–III diseases. High risk was defined as node positive (pN1-N3), any primary tumor ≥2 cm, or any primary tumor ≥1 cm if it was HR negative or HER2 positive or had a 21-gene RS ≥ 26. Patients were randomized into four arms. Two arms received doxorubicin and cyclophosphamide (AC) every 2 weeks for six cycles, and two arms received AC weekly for 15 cycles. The patients were then randomized to two different paclitaxel regimens. The patients received paclitaxel 175 mg/m^2 every 2 weeks for six cycles or 80 mg/m^2 weekly for 12 cycles. Interim analysis revealed a significant difference in OS but not DFS; all treatments given once every 2 weeks were associated with the highest OS. However, the difference in OS was confined to patients with HR-negative/HER2-negative tumors, although subset analysis by biological type of breast cancer was unplanned. The difference in OS in the absence of a significant difference in DFS is controversial and requires further explanation.

The phase III trial by the European Organization for Research and Treatment of Cancer (EORTC) by Therasse et al. [144] compared six biweekly cycles of epirubicin and cyclophosphamide (EC) with six 4-week-interval cycles of cyclophosphamide, epirubicin, and fluorouracil (CEF) in patients with locally advanced breast cancer. After a median follow-up of 5.5 years, the study failed to show any benefit of dose-dense EC over conventional CEF. Similar efficacy was achieved with both regimens, but duration of treatment was half as long with dose-dense EC without additional significant toxicity.

In contrast to the trials described earlier, the Hellenic Cooperative Oncology Group (He-COG) trial was the first study to directly compare two different dose-dense sequential regimens for node-positive or high-risk node-negative breast cancer [145]. Patients were randomized to sequential dose-dense epirubicin and paclitaxel or concurrent epirubicin and paclitaxel, both followed by three cycles of intensified combination chemotherapy with CMF. The study failed to show any significant difference in DFS or OS between treatment groups but suggested a potential benefit in ER-negative patients treated with paclitaxel.

Concordantly, the published results of the National Surgical Breast and Bowel Project B-38 (NSABP B-38) trial failed to demonstrate a significant difference between dose-dense regimens and conventional strategies [146]. The trial involved nearly 4900 women (65% with pathologically involved nodes and 80% with ER-positive disease) who were randomly assigned to treatment with dose-dense AC-T, dose-dense AC followed by the combination of paclitaxel plus gemcitabine (AC-TG), or TAC. The 5-year DFS rate was similar across treatment groups (82% with dose-dense AC-T vs. 80% with both dose-dense AC-TG and TAC). The 5-year OS rate was also similar (89%, 90%, and 90%, respectively). However, TAC was associated with significantly more serious (grade 3 or 4) toxicity, including febrile neutropenia (9% vs. 3% in both the AC-T and AC-TG arms) and diarrhea (8% vs. 2% with AC-T or AC-TG). In contrast, TAC was associated with significantly less grade 3/4 neurotoxicity (<1% vs. 7% and 6% with AC-T or AC-TG, respectively).

A meta-analysis of dose-dense versus standard dosing that included data from ten trials and over 11,000 women summarized the findings of the trials described earlier [147].

1. In three trials that evaluated similar dosing in the treatment arms, dose-dense treatment was associated with an improvement in DFS (hazard ratio [HR] 0.83, 95% CI 0.73–0.94) and OS (HR 0.84, 95% CI 0.72–0.98).

2. In seven trials in which modified doses or regimens were evaluated, improvements in DFS (HR 0.81, 95% CI 0.73–0.88) and OS (HR = 0.85, 95% CI 0.75–0.96) were also demonstrated.
3. The benefit in DFS was observed in women with ER-negative disease (HR 0.71, 95% CI 0.56–0.98) but not in women with ER-positive disease (HR 0.92, 95% CI 0.75–1.12).

A more recent randomized study including more than 2000 patients evaluated a similar dose-dense strategy comparing 4 cycles of dose-dense adjuvant EC every 2 weeks followed by 4 cycles of tailored dose-dense docetaxel every 2 weeks with standard-interval 3 cycles of FEC every 3 weeks followed by 3 cycles of docetaxel every 3 weeks [148]. The doses in the experimental arm were tailored based on leukocyte-nadir levels. The primary endpoint was breast cancer recurrence-free survival (BCRFS). Although the number of events were numerically higher in the control arm (151 vs. 118), the difference was not statistically significant ($p = 0.06$). OS did not differ among the groups; however, EFS was significantly higher in the dose-dense arm (5-year EFS, 86.7% vs. 82.1%, HR 0.79; 95% CI 0.63–0.99; $p = 0.04$).

Another Italian phase 3 trial randomized node-positive breast cancer patients to four treatment arms, including 5-FU and EC, followed by paclitaxel or EC, further followed by paclitaxel given in 2- or 3-weekly intervals [149]. The study suggested a DFS advantage for dose-dense regimens compared with standard interval chemotherapy protocols. For the dose-density comparison, disease-free survival at 5 years was 81% in patients treated every 2 weeks and 76% in patients treated every 3 weeks (HR 0.77, 95% CI 0.65–0.92; $p = 0.004$). Overall survival rates at 5 years were 94% and 89% (HR 0.65, 0.51–0.84; $p = 0.001$). In addition, there was no DFS or OS benefit of adding fluorouracil to sequential EC and paclitaxel. Moreover, incorporation of 5-FU was associated with increased rates of grade 3–4 neutropenia, nausea, and vomiting.

Dose-dense strategies have been demonstrated to be feasible and safe with G-CSF support and have a modest impact on disease recurrence and OS of unselected patients with early-stage breast cancer. Emerging data are convincing that the benefits of dose-dense therapy will be greater for specific tumor subtypes such as hormonal receptor-negative, highly proliferative, or HER2-overexpressing tumors [150].

Novel Approaches for Adjuvant Chemotherapy

Adjuvant anthracycline- and taxane-based chemotherapy provides substantial benefits for women diagnosed with node-positive, early-stage breast cancer. However, a significant proportion of women treated with adjuvant chemotherapy still develop disease recurrence, necessitating additional studies to evaluate alternative treatment strategies. Unfortunately, attempts to improve outcomes with different regimens by combining additional chemotherapeutic agents with anthracyclines, taxanes, and cyclophosphamide have not yielded promising results.

The randomized, phase III FinXX trial (NCT00114816) investigated whether the integration of capecitabine (X) into a sequential docetaxel (T) → cyclophosphamide + epirubicin +5-FU (CEF) adjuvant regimen might improve clinical outcomes for patients with medium- to high-risk early-stage breast cancer. The primary endpoint of the trial was RFS. The planned interim analysis, after a median follow-up of 3 years, indicated a significant RFS benefit of the X-containing regimen versus the control (HR: 0.66, 95% CI 0.47–0.94; $p = 0.020$) [151]. However, the final results of the FinXX trial after a median follow-up of 59 months demonstrated that the addition of capecitabine did not provide a significant improvement in RFS compared with docetaxel followed by CEF (HR: 0.79; 95% CI 0.60–1.04; $p = 0.087$). Capecitabine administration was frequently discontinued because of adverse effects, such as grade 3–4 diarrhea and hand–foot syndrome [152]. In exploratory analyses, adding capecitabine appeared to improve BCSS and benefit some women with early-stage breast cancer such as those with triple-negative disease and those with more than three metastatic axillary lymph nodes.

Another trial was performed among 2611 high-risk breast cancer patients who were classified as follows: ≥1 positive lymph node, T1–3; node negative with tumors >2 cm; or node negative with tumors >1 cm, both ER and PR negative [153]. The experimental arm comprised four every-3-week cycles of AC (doxorubicin and cyclophosphamide) followed by four cycles of capecitabine and docetaxel (XT) versus AC followed by every-3-week cycles of docetaxel (T) alone. The primary endpoint of the study was DFS. However, the study failed to meet its primary endpoint of DFS (HR 0.84, 95% CI: 0.67–1.05; $p = 0.125$) after a median follow-up of 5 years, although a statistically significant improvement in OS in patients receiving AC → XT was observed.

Recently, the efficacy of adjuvant capecitabine has been investigated in another setting among patients with residual invasive cancer on pathological testing after neoadjuvant chemotherapy containing an anthracycline, taxane, or both [154]. The addition of adjuvant capecitabine therapy was safe and effective in prolonging disease-free survival and overall survival. Disease-free survival at 5 years was 67.6% for the control group and 74.1% for the experimental arm (HR 0.70; 95% CI 0.53–0.92; $p = 0.01$). Overall survival was longer in the capecitabine group than in the control group (89.2% vs. 83.6% of the patients were alive at 5 years (HR 0.59; 95% CI 0.39–0.90; $p = 0.01$). The benefits of capecitabine with regard to disease-free survival and overall survival were consistent across the prespecified subgroups. The rate of disease-free survival for triple-negative disease

was 69.8% in the capecitabine group versus 56.1% in the control group (HR 0.58; 95% CI 0.39–0.87), and the overall survival rate was 78.8% versus 70.3% (HR 0.52; 95% CI 0.30–0.90). Attempts to further incorporate different agents into adjuvant protocols have not been limited to capecitabine. The addition of gemcitabine to paclitaxel has yielded improved outcomes in women with metastatic breast cancer. In light of these findings, the tAnGo trial addressed the addition of gemcitabine in adjuvant treatment protocols. The tAnGo trial was a phase III randomized trial of gemcitabine in paclitaxel-containing, epirubicin-based, adjuvant chemotherapy for ER/PR-poor, early-stage breast cancer, which demonstrated that the addition of gemcitabine to sequential epirubicin and cyclophosphamide followed by paclitaxel conferred no therapeutic benefit [155]. Furthermore, the NSABP B-38 study did not indicate a survival advantage for the addition of gemcitabine to a sequential anthracycline- and taxane-based regimen, confirming the results of the tAnGo study [146]. This trial assigned patients with node-positive early-stage breast cancer to dose-dense AC-T, dose-dense AC followed by paclitaxel plus gemcitabine (AC-TG), or TAC. Primary granulocyte colony-stimulating factor support was required; erythropoiesis-stimulating agents (ESAs) were also used at the investigator's discretion. Exploratory analyses of ESAs revealed no association with DFS events. Adding gemcitabine to dose-dense regimens also did not improve outcomes. Whether the combination of these agents with different schemes will produce a significant benefit is a question of debate. However, it appears unlikely that further changes in dosing schedules will result in appreciable gains.

Recommended Adjuvant Chemotherapy Schedules

There is no single standard adjuvant chemotherapy protocol for the treatment of breast cancer.

Commonly used regimens are described as follows.

Non-taxane Regimens

1. *AC chemotherapy*
   Doxorubicin 60 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   (Cycled every 21 days for four cycles)
   (In dose-dense regimen, every 14 days for four cycles with myeloid growth factor support)
2. *EC chemotherapy*
   Epirubicin 100 mg/m^2 IV day 1
   Cyclophosphamide 830 mg/m^2 IV day 1
   (Cycled every 21 days for eight cycles)
   (With myeloid growth factor support)
3. *CEF chemotherapy*
   Cyclophosphamide 75 mg/m^2 PO days 1–14
   Epirubicin 60 mg/m^2 IV days 1 and 8
   5-Fluorouracil 500 mg/m^2 IV days 1 and 8
   (With cotrimoxazole support)
   (Cycled every 28 days for six cycles)
4. *FAC chemotherapy*
   5-Fluorouracil 500 mg/m^2 IV days 1 and 8 or days 1 and 4
   Doxorubicin 50 mg/m^2 IV day 1
   (Or by 72-h continuous infusion)
   Cyclophosphamide 500 mg/m^2 IV day 1
   (Cycled every 21 days for six cycles)
5. *CMF chemotherapy*
   Cyclophosphamide 100 mg/m^2 (PO) days 1–14
   Methotrexate 40 mg/m^2 IV days 1 and 8
   5-Fluorouracil 600 mg/m^2 IV days 1 and 8
   (Cycled every 28 days for six cycles)
6. *CAF chemotherapy*
   Cyclophosphamide 100 mg/m^2 PO days 1–14
   Doxorubicin 30 mg/m^2 IV days 1 and 8
   5-Fluorouracil 500 mg/m^2 IV days 1 and 8
   (Cycled every 28 days for six cycles)
7. *FEC chemotherapy*
   5-Fluorouracil 500 mg/m^2 IV day 1
   Epirubicin 100 mg/m^2 IV day 1
   Cyclophosphamide 500 mg/m^2 IV day 1
   (Cycled every 21 days for three cycles)
   (With myeloid growth factor support)

Taxane Regimens

1. *Dose-dense AC followed by paclitaxel chemotherapy*
   Doxorubicin 60 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   (Cycled every 14 days for four cycles)
   Followed by paclitaxel 175 mg/m^2 by 3-h IV infusion day 1
   (Cycled every 14 days for four cycles)
   (All cycles with myeloid growth factor support)
2. *Dose-dense AC followed by weekly paclitaxel chemotherapy*
   Doxorubicin 60 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   (Cycled every 14 days for four cycles)
   (All cycles with myeloid growth factor support)
   Followed by paclitaxel 80 mg/m^2 by 1-h IV infusion weekly for 12 weeks
3. *TAC chemotherapy*
   Docetaxel 75 mg/m^2 IV day 1
   Doxorubicin 50 mg/m^2 IV day 1
   Cyclophosphamide 500 mg/m^2 IV day 1
   (Cycled every 21 days for six cycles)
   (All cycles with myeloid growth factor support)

4. *FEC followed by docetaxel chemotherapy*
   5-Fluorouracil 500 mg/m^2 IV day 1
   Epirubicin 100 mg/m^2 IV day 1
   Cyclophosphamide 500 mg m^2 IV day 1
   (Cycled every 21 days for three cycles)
   Followed by docetaxel 100 mg/m^2 IV day 1
   (Cycled every 21 days for three cycles)
   (All cycles with myeloid growth factor support)
5. *FEC followed by weekly paclitaxel*
   5-Fluorouracil 600 mg/m^2 IV day 1
   Epirubicin 90 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   (Cycled every 21 days for four cycles)
   (With myeloid growth factor support)
   Followed by paclitaxel 100 mg/m^2 IV infusion weekly for 8 weeks
6. *FAC followed by weekly paclitaxel*
   5-Fluorouracil 500 mg/m^2 IV days 1 and 8 or days 1 and 4
   Doxorubicin 50 mg/m^2 IV day 1
   (Or by 72-h continuous infusion)
   Cyclophosphamide 500 mg/m^2 IV day 1
   (Cycled every 21 days for six cycles)
   Followed by paclitaxel 80 mg/m^2 by 1-h IV infusion weekly for 12 weeks
7. *AC followed by docetaxel chemotherapy*
   Doxorubicin 60 mg/m^2 IV on day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   Cycled every 21 days for four cycles
   Followed by docetaxel 100 mg/m^2 IV on day 1
   (Cycled every 21 days for four cycles)
   (All docetaxel cycles with myeloid growth factor support)
8. *TC chemotherapy*
   Docetaxel 75 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   (Cycled every 21 days for four cycles)
   (All cycles with myeloid growth factor support)

Special Considerations

Adjuvant Chemotherapy for Triple-Negative Disease

TNBC was identified in the early 2000s as a clinically important subgroup of breast cancer characterized by poor prognosis. The risk of distant recurrence was remarkably higher in patients with TNBC than in those with non-TNBC, peaking 3 years after diagnosis. By definition, triple-negative tumors lack expression of ER, PR, and HER2, the established markers used to select patients for adjuvant endocrine therapy or trastuzumab therapy, respectively. Approximately 80% of TNBCs have a basal-like molecular profile [156]. Beyond the basal-like profile, TNBC encompasses other molecular intrinsic subtypes, particularly normal-like and the recently described claudin-low subtypes. Of basal-like breast cancers, approximately 80% are TNBC [157]. Most germline mutant BRCA1-associated breast cancers are TNBC, but only a minority of TNBC has a BRCA1 mutation. Somatic TNBCs may have BRCA1 functional loss in the absence of a gene mutation due to downregulated BRCA1 transcription and/or translation and may share phenotypic features with BRCA-mutated tumors [158]. As the overlap between TNBC, basal-like breast cancer, and BRCA1 mutation-associated breast cancer is incomplete, these terms cannot be used synonymously.

Thus far, most clinical trials attempting to define optimal adjuvant regimens have included patients based on clinical stage, irrespective of tumor hormonal receptor or HER2 status. Retrospective subset analyses have attempted to characterize outcomes for patients defined by tumor ER and/or HER2 status. However, such analyses have frequently lacked the power to characterize outcomes in TNBC. Most results suggest high sensitivity to chemotherapy in TNBC. However, due to the lack of randomized phase III trials with a conventional control arm, whether this increased sensitivity is agent specific or reflects general chemosensitivity remains to be determined. Due to the phenotypic similarities between TNBC and BRCA-associated tumors, it is tempting to extend promising therapeutic strategies exploiting defective DNA repair in BRCA-associated tumors to the larger subset of sporadic TN tumors. However, much as the terms for TNBC, basal-like breast cancer and BRCA1-associated breast cancer cannot be used synonymously due to incomplete overlap; extrapolation of treatment results between these groups may be inappropriate. Biological heterogeneity within the TNBC cohort prevents such an assumption. In patients with BRCA mutations, platinum combinations may be an option.

Alkylating Agents

Cyclophosphamide is the most commonly used alkylating agent in breast cancer. Classical CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) is reported to be effective in the treatment of TNBC. The International Breast Cancer Study Group (IBCSG) trials VIII and IX compared three or six courses of CMF (with or without endocrine therapy) with endocrine therapy alone. An analysis of these trials showed a benefit for CMF over endocrine therapy only in the subset of women with TNBC (HR: 0.46; 95% CI 0.29–0.73; $p = 0.009$) [159].

Anthracyclines

The effectiveness of anthracycline-containing regimens for TNBC has been reported in the neoadjuvant setting [160]; however, data regarding the benefit of anthracyclines as adjuvant regimens are conflicting. Preclinical evidence also suggests inconsistent results in terms of anthracycline activity in BRCA-deficient breast cancer cells. Cell line studies have revealed differential chemosensitivity based on the BRCA status, with BRCA1/BRCA2 loss associated with increased sensitivity to topoisomerase IIa (topoIIa) inhibitors [161]. In one study, blockade of the topoIIa enzyme prior to exposure to the topoIIa inhibitor markedly reduced cytotoxicity and eliminated any differential BRCA effects, indicating indirect DNA damage through the binding of the cytotoxics to the topoIIa protein rather than direct DNA damage [162]. Conversely, another in vitro work demonstrated greater sensitivity to doxorubicin in BRCA1 wild type compared with BRCA1-mutant breast cancer cells [163]. Clinical studies have revealed concordant results. For instance, the MA5 adjuvant trial, which compared classical CMF with CEF (cyclophosphamide, epirubicin, and 5-fluorouracil) in premenopausal women with node-positive early-stage breast cancer, determined that classical CMF had similar efficacy as CEF regarding RFS and OS rates (HR: 1.1; 95% CI 0.6–2.1 for RFS and HR: 1.3; 95% CI 0.7–2.5 for OS] in a subset of women who had breast cancer of the basal phenotype [22]. However, post hoc analysis of a phase III trial reported that adjuvant CMF was inferior to the combination of epirubicin plus CMF in terms of the 5-year DFS (59% vs. 85%, respectively; $p = 0.002$) and overall survival (73% vs. 91%, respectively; $p = 0.002$) in TNBC patients [164]. According to the available evidence, anthracyclines should still be considered an important component of chemotherapy for TNBC.

Taxanes

The addition of taxanes to adjuvant anthracycline-based therapy has been evaluated several times in populations unselected for biology in the aforementioned early-stage breast cancer trials. The results specifically in TNBC are limited; however, a preferential benefit of microtubule-stabilizing agents has not been clearly demonstrated. Subset analyses of several large trials suggest that taxane combinations (with cyclophosphamide and doxorubicin) are also beneficial in the treatment of TNBC and may be more effective in this subset than chemotherapy combinations that do not include a taxane [165]. Moreover, a retrospective analysis of three adjuvant chemotherapy trials coordinated by CALGB and the US Breast Intergroup revealed that women with ER-negative tumors treated with regimens including higher doses, taxanes, and dose-dense scheduling fared better in terms of the risk of recurrence and OS. ER-negative women who received dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) compared to low-dose cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) experienced a 55% (95% CI 37–68%) relative reduction in the risk of recurrence. Unplanned subset analyses of the subgroups demonstrated that women who were both ER and HER2 negative achieved a statistically significant improvement in DFS with the addition of paclitaxel therapy ($p = 0.002$), whereas ER+ HER2(−) individuals did not experience a similar benefit ($p = 0.71$), thereby supporting the inclusion of taxanes in adjuvant therapy for the treatment of patients with TNBC [166].

The Early Breast Cancer Trialists' Collaborative Group has demonstrated that both anthracyclines and taxanes are effective adjuvant chemotherapeutic agents in hormonal receptor-negative breast cancers, with anthracycline-based regimens conferring modest benefits over non-anthracycline, CMF-type regimens, and taxane-based regimens superior to non-taxane alternatives [113]. A meta-analysis of 12 randomized clinical trials demonstrated that adjuvant docetaxel-based chemotherapy is associated with an improvement in DFS and OS in TNBC compared with regimens without taxanes [165]. Similarly, the PACS 01 trial comparing FEC with FEC followed by docetaxel demonstrated significantly better metastasis-free survival and OS for the incorporation of docetaxel among patients with a basal-like profile, as defined by an immunohistochemical panel [167]. Nonsignificant trends in favor of taxanes in TNBC were observed in the GEICAM 9805 trial, which compared docetaxel, doxorubicin, and cyclophosphamide (TAC) with fluorouracil, doxorubicin, and cyclophosphamide (FAC) in node-negative, high-risk breast cancer and in BCIRG 001, which compared TAC with FAC in node-positive disease [133, 168]. In the BCIRG trial, subgroup analyses addressing 3-year DFS revealed a nonsignificant trend ($p = 0.051$) in the TNBC subgroup in favor of TAC over FAC (74% vs. 60%, respectively; HR 0.50; 95% CI 0.29–1.00).

Using immunohistochemical testing for HER2 positivity in tissue blocks from 1322 women, Hayes et al. [166] investigated whether paclitaxel added after adjuvant AC was equally beneficial to all biological subgroups of CALGB9344 participants. Paclitaxel was associated with improved DFS in the subset of women with HER2-negative, ER-negative tumors.

However, an additional benefit from taxanes has not been consistently observed in this subgroup of patients. The TACT trial observed no significant difference between treatment arms in TNBC when FEC followed by docetaxel was compared to a control of FEC or FEC/CMF [130]. Moreover, in the PACS 04 trial, which compared FEC100 with concurrent epirubicin and docetaxel, no differential effect was observed in TNBC [169].

Platinum Agents

A number of recent preclinical studies examining the activity of platinum agents in the treatment of TNBC- and BRCA1-associated breast cancers have demonstrated increased sensitivity to these agents. Because BRCA1-associated tumors are deficient in the genes encoding proteins that are critical in DNA integrity, genomic stability, and DNA repair, increased susceptibility to DNA-damaging agents is expected. In preclinical models of BRCA1-deficient breast cancers, increased cytotoxicity of platinum agents through the induction of double-strand breaks has been observed [170, 171]. In addition, the p53 family member p63 has been determined to control a survival pathway that directly mediates cisplatin sensitivity in TNBC. In vitro, the co-expression of p63/p73 in TNBC tumors was identified as a predictor of sensitivity to cisplatin but not to other standard chemotherapy agents in TNBC, warranting further investigation of p63/p73 as biomarkers to predict the response to platinum therapy [172].

Clinical data for carboplatin and cisplatin in TNBC are limited, with data predominantly emerging from small studies and retrospective analyses. In a small study, nine of ten women (90%) with TNBC and a BRCA1 mutation had a pCR with single-agent cisplatin treatment [173]. A small neoadjuvant study tested 4 cycles of single-agent cisplatin in 28 patients, 2 of whom had a germline BRCA1 mutation and pCR after chemotherapy [174]. The pCR rate was 22%. A pCR was achieved in 4 of 26 patients with sporadic TNBC (15%). The only randomized phase II data evaluating the effect of cisplatin in TNBC are from the metastatic setting. A single institution trial included 126 TNBC patients pretreated with anthracycline and taxane therapy and then randomized to metronomic oral cyclophosphamide and methotrexate with or without cisplatin as second-line therapy. The cisplatin arm was associated with improvements in the overall response rate (33% vs. 63%), median time to progression (7 months vs. 13 months), and median OS (12 months vs. 16 months).

The issue of cross-sensitivity between carboplatin and cisplatin must also be defined. Currently, there are no randomized phase III data regarding the use of carboplatin instead of cisplatin. Thus, using platinum agents for the adjuvant treatment of TNBC remains under investigation and is not currently recommended in this setting. Given the small numbers of patients in the abovementioned trials, it is difficult to draw conclusions regarding reduction in risk of recurrence and survival. However, these data do suggest the activity of platinum agents in the TNBC subgroup and warrant further study.

Capecitabine

Capecitabine has been investigated in the adjuvant setting for the prevention of breast cancer recurrence. CALGB49907, a prospective trial, evaluated the efficacy of the possibly less toxic single-agent capecitabine among elderly breast cancer patients (65 years or older) in the adjuvant setting. In this trial, both the risk of relapse (HR: 2.09; 95% CI 1.38–3.17; $p < 0.001$) and the risk of death (HR: 1.85; 95% CI 1.11–3.08; $p = 0.02$) were significantly higher with capecitabine compared with standard chemotherapy [175]. Unplanned subgroup analyses demonstrated that patients with hormone receptor-negative cancer benefited more from standard therapy than from capecitabine. In the FINXX adjuvant study, three cycles of docetaxel plus capecitabine (TX) followed by three cycles of CEX (cyclophosphamide, epirubicin, and capecitabine) indicated a trend toward improved 5-year recurrence-free survival (RFS) compared with three cycles of docetaxel (T) followed by three cycles of CEF (T-CEF; 87% vs. 84%, respectively; HR 0.79; 95% CI 0.60–1.04; $p = 0.087$) [151]. In an exploratory analysis of the TNBC subgroup comprising 202 patients, TXCEX was associated with longer RFS compared with T-CEF (HR 0.48; 95% CI 0.26–0.88; $p = 0.018$).

A randomized phase III study of standard adjuvant chemotherapy alone or followed by 1 year of metronomic capecitabine (650 mg/m^2 twice daily) is underway, with DFS as the primary endpoint (NCT01112826). Thus far, capecitabine has not been specifically studied in the triple-negative population. Another multicenter phase III clinical study (NCT01642771) is being conducted among TNBC patients on two adjuvant chemotherapy regimens: sequential docetaxel followed by FEC and sequential docetaxel and capecitabine followed by capecitabine/epirubicin/cyclophosphamide (XEC). The primary outcome measure is 5-year DFS. The results of these trials are awaited to reach further conclusions regarding the efficacy and safety of adjuvant capecitabine among TNBC patients. Other adjuvant trials that are ongoing among TNBC patients are summarized in Table 8.7.

Poly(ADP-Ribose) Polymerase (PARP) Inhibitors

The products of the *BRCA1* and *BRCA2* genes have roles in a highly specialized form of DNA repair, homologous recombination [176, 177]. When the remaining wild-type allele is lost in a tumor precursor cell, this repair mechanism does not function, and the consequent rapid onset of genome instability is sufficient to enable tumor development [178]. Studies of invasive primary breast tumors in individuals with *BRCA1* and *BRCA2* mutations confirm the loss of the remaining wild-type allele [179, 180]. These findings support the clinical usefulness of tumor-specific targeting of the loss of *BRCA1*-associated or *BRCA2*-associated homologous recombination DNA repair in breast cancer patients.

Table 8.7 Ongoing adjuvant phase III–IV clinical trials involving triple-negative breast cancer patients

NCI ID	Status	Primary location	Stage	Regimen
NCT01112826	Completed	Guangzhou, China	T1c-3, N0–2	*Arm A*: standard adjuvant chemotherapy followed by capecitabine 650 mg/m^2 (1 year)
				Arm B: standard adjuvant chemotherapy
NCT01216111	Expanded access	Shanghai, China	Stages I–IIIA	Paclitaxel and cisplatin AUC (2) D1, 8,15 (q28 days)
NCT01642771	Active, not recruiting	China	Node positive or node negative and pT > 1 cm	*Arm A*: 5-FU and epirubicin and cyclophosphamide D1 ×3 (q21 days) followed by docetaxel ×3 (q21 days)
				Arm B: Docetaxel and capecitabine D1 ×3 (q21 days) followed by docetaxel and capecitabine and epirubicin D1 ×3 (q21 days)

Poly(ADP-ribose) polymerase-1 (PARP) is a crucial nuclear enzyme that is involved in the recognition of DNA damage and the facilitation of single-strand DNA repair through the base excision repair (BER) pathway. Following the detection of a DNA strand break, PARP1, as the predominant cellular PARP, catalyzes the synthesis and transfer of ADP-ribose polymers to target proteins to recruit other repair enzymes and facilitate DNA repair and cell survival [181].

The idea of synthetic lethality through the inhibition of PARP has been investigated in preclinical model systems with hereditary mutations in the BRCA1 or BRCA2 genes. The principle hypothesis is based on the assumption that DNA damage by PARP inhibition is irreparable and leads to cell death in homozygote tumor cells but not in normal tissue heterozygote cells, which have one functional BRCA allele. As previously mentioned, preclinical tumor models of BRCA-associated breast cancers have demonstrated increased sensitivity to therapies such as alkylators that induce DNA damage [160, 161]. Farmer et al. [182] demonstrated that BRCA-deficient breast cell lines were highly sensitive to PARP inhibition. Single-agent PARP inhibitors led to impaired single-strand break (SSB) repair, causing double-strand breaks (DSBs) to occur in replicating cells. In BRCA wild-type cells, DSBs are repaired through homologous recombination, but in BRCA-mutant cells, this compensatory repair pathway is impaired, leading to complex rearrangements, repair mechanism loss, and cell death. Concordantly, a phase II study of the PARP inhibitor olaparib verified this strategy in patients with advanced or recurrent BRCA1-/BRCA2-mutated breast cancer [183]. The most frequent causally related adverse events in the cohort receiving 400 mg twice daily were fatigue (grade 1 or 2 in 41%, grade 3 or 4 in 15%), nausea (grade 1 or 2 in 41%, grade 3 or 4 in 15%), vomiting (grade 1 or 2 in 11%, grade 3 or 4 in 11%), and anemia (grade 1 or 2 in 4%, grade 3 or 4 in 11%). The predominance of grade 1–2 adverse events demonstrated the safety profile of these molecules among patients who were heavily treated with a median of three previous chemotherapy regimens. The results of the trial indicated significant objective response rates of 41% (95% CI: 25–59%) among the cohort receiving 400 mg BID and 22% (95% CI 11–41%) among the cohort receiving 100 mg BID. The median PFS was also significantly prolonged in both cohorts (maximal dose cohort 5.7 months (95% CI 4.6–7.4), low-dose cohort 3.8 months (95% CI 4.6–7.4), further supporting the efficacy of PARP inhibitors in BRCA-deficient cells. The results are promising but remain inadequate for PARP inhibitors to be considered as part of an adjuvant treatment modality in TNBC patients.

Ixabepilone

Ixabepilone is a member of the epothilone class of macrolide antibiotics, which possess high microtubule-stabilizing activity and low susceptibility to drug resistance mechanisms, including multidrug-resistant protein and P-glycoprotein [184]. In the United States, ixabepilone is approved for use in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer after failure of an anthracycline and a taxane. It is also approved in the United States as a monotherapy in the same setting after failure of an anthracycline, a taxane, and capecitabine.

The utility of ixabepilone among TNBC patients arises from a subgroup analysis of a phase II study in the neoadjuvant setting that demonstrated a pCR rate of 19% for TNBC [185]. Notably, a retrospective analysis of previous phase II studies (including patients in the neoadjuvant and metastatic setting) showed activity for ixabepilone in TNBC patients, including patients who had previously received or were resistant to anthracyclines, taxanes, and capecitabine [186]. However, a more recent neoadjuvant phase II trial that randomized patients to AC followed by ixabepilone versus AC followed by paclitaxel did not demonstrate a significant difference in pCR rates between the two regimens, 34% versus 41% [187]. In light of this finding, the two adjuvant phase III trials PACS08 (NCT00630032) and TITAN (NCT00789581)) were initiated to compare ixabepilone directly with more commonly used taxanes. Although it is no longer recruiting patients, the PACS08 (NCT00630032) study remains ongoing. The TITAN trial randomized early-stage TNBC patients

to adjuvant doxorubicin/cyclophosphamide (AC) followed by ixabepilone or AC followed by weekly paclitaxel, and the primary outcome measure was defined as DFS [188]. After a median follow-up of 2 years, there was no difference in DFS between the two groups (HR 0.92; ixabepilone 87.1% [95% CI 82.6–90.5] vs. paclitaxel 84.7% [95% CI 79.7–88.6]). The results of the PACS08 trial are being awaited.

Targeted Therapies

Bevacizumab

High levels of vascular endothelial growth factor (VEGF) and VEGF-2 in women with TNBC have led to the emergence of agents that target angiogenesis. Thus, VEGF may be a prognostic tool as well as a putative target for therapeutic intervention [189]. Bevacizumab, a humanized monoclonal antibody to VEGF, has been evaluated in large phase III clinical trials in combination with paclitaxel [190]. E2100, an open-label, randomized, phase III trial conducted by ECOG, demonstrated a significant improvement in PFS and overall response rate (ORR) with paclitaxel plus bevacizumab compared with paclitaxel alone as initial chemotherapy for patients with HER2-negative metastatic breast cancer [191]. The risk of progression was reduced by more than half and the ORR nearly doubled with the addition of bevacizumab to weekly paclitaxel in the analyses, confirming a substantial and robust bevacizumab treatment effect. The PFS was 8.8 months in TNBC patients receiving bevacizumab plus paclitaxel versus 4.6 months in those receiving paclitaxel alone (HR 0.53; 95% CI 0.40–0.70). However, OS was not significantly improved in the whole population.

Bevacizumab has been evaluated in further clinical trials in combination with docetaxel or capecitabine as a first-line and second-line treatment for metastatic breast cancer [192–194]. Subgroup analyses of these studies suggested similar PFS benefits for bevacizumab plus a taxane in patients with TNBC and those with non-TNBC. Adjuvant bevacizumab in combination with taxanes was eventually prospectively investigated in TNBC in the BEATRICE trial [195]. The study included T1b–T3 or T1a tumors with ipsilateral axillary node involvement that were centrally confirmed as HER2 negative by FISH or chromogenic in situ hybridization with either negative or low hormone receptor status. A total of 1290 patients were randomized to receive a minimum of four cycles of chemotherapy either alone or with bevacizumab (equivalent of 5 mg/kg every week for 1 year). The primary endpoint was defined as invasive disease-free survival (IDFS). The median follow-up was approximately 32 months for both groups at the time of IDFS analysis. The 3-year IDFS was 82.7% (95% CI 80.5–85.0) with chemotherapy alone and 83.7% 81.4–86.0) with bevacizumab and chemotherapy. There was no difference in OS between the groups (HR 0.84, 95% CI 0.64–1.12; $p = 0.23$). Nearly half of the study group (49%) consented to the biomarker study, and 1178 (45%) were included in the biomarker-assessable population. Analysis of the baseline plasma VEGF-A concentration showed neither prognostic nor predictive value. By contrast, exploratory biomarker assessment suggested that patients with high pretreatment plasma VEGFR-2 levels might benefit from the addition of bevacizumab (Cox interaction test, $p = 0.029$). However, the use of bevacizumab versus chemotherapy alone was associated with an increased incidence of adverse events such as grade 3 or worse hypertension (12% vs. 1%), severe cardiac events occurring at any point during the 18-month safety reporting period (1% vs. <0.5%), and treatment discontinuation. The data are partially immature due to the low rate of events, although the protocol-specified number of events for the primary analysis was reached. The low rate of recurrence was attributed to the high proportion of patients with node-negative disease (63%) enrolled into BEATRICE; this finding could have important implications for interpretation and follow-up. The investigators concluded that bevacizumab could not be recommended as an adjuvant treatment in otherwise unselected TNBC patients. Final efficacy results with a median follow-up of 56 months also failed to demonstrate a significant difference in OS between the treatment arms. The 5-year OS rates were 88% (95% CI 85.7–89.6%) with CT alone and 88% (95% CI 86.0–89.8%) with chemotherapy plus bevacizumab [196].

Concordantly, another trial investigating the efficacy of adjuvant bevacizumab failed to demonstrate a survival benefit among HER2-expressing high-risk node-negative or node-positive breast cancer patients [197]. The BETH trial included two patient cohorts receiving anthracycline (three cycles of docetaxel+trastuzumab followed by three cycles of FEC followed by 1-year trastuzumab) and non-anthracycline (six cycles of docetaxel+carboplatin+trastuzumab followed by 1-year trastuzumab) regimens. Both of the cohorts were stratified into two arms: bevacizumab combined with chemotherapy and thereafter with trastuzumab and no bevacizumab. High-risk, node-negative early-stage breast cancer was defined as the presence of at least one of the following criteria: age <35 years, ER- and PR-negative disease, pathological tumor size >2 cm, and histological and/or nuclear grade ≥2. The primary objective of the study was comparing invasive disease-free survival (IDFS) for the bevacizumab-included and no bevacizumab arms. The study did not meet its primary endpoint at the median follow-up time of 38 months. The addition of 1-year bevacizumab combined with chemotherapy plus trastuzumab treatment did not prolong IDFS [HR 0.99, 95% CI 0.79–1.25, $p = 0.96$]. In addition, the integration of bevacizumab increased the rate of adverse events such as hypertension (19% vs. 4%), congestive heart failure (2.1% vs. 1%), and bleeding (2% vs. 1%). A similar phase III trial (E5103) comparing doxorubicin and

cyclophosphamide followed by paclitaxel with bevacizumab or placebo also failed to demonstrate a survival benefit [198].

EGFR Inhibitors: Cetuximab

EGFR is frequently overexpressed in TNBC (60%) and is a negative prognostic factor when present [199, 200]. This profile has been suggested as a potential target for EGFR-directed therapies. Clinically, EGFR inhibitors have been studied in the metastatic setting. A randomized, phase II, multicenter trial examined sequential cetuximab followed by carboplatin at the time of progression versus concurrent cetuximab/carboplatin in pretreated TNBC patients [201]. Due to poor response rates for single-agent cetuximab in the sequential arm, this arm of the trial was closed to accrual early. Most patients rapidly progressed, and the overall median PFS was 2.0 months. Preliminary data from another phase II trial suggested improved response rates in the cetuximab and irinotecan/carboplatin arm (39% vs. 19%), thus advocating combination regimens rather than single-agent cetuximab [202]. The triple-therapy regimen achieved a higher overall RR (49% vs. 30%) and longer median survival (15.5 months vs. 12.3 months) than chemotherapy alone, although PFS appeared to be shorter (4.7 months vs. 5.1 months). The overall RR with the triple-therapy regimen was higher in TNBC than in the overall study population (49% vs. 38%, respectively).

An evaluation of the combination of a standard chemotherapy (FEC100 followed by docetaxel) with panitumumab as neoadjuvant therapy for operable TNBC was reported with a pCR rate of 65% [203]. A neoadjuvant phase II open-label study (NCT 01097642) is currently recruiting T1N1-3M0 or T2-4N0-3M0 patients with TNBC who are candidates for preoperative chemotherapy. Patients are being equally randomized between ixabepilone and ixabepilone plus cetuximab. The primary objective of the study is to determine the pCR rate for the breast and axilla. As a result, cetuximab, used in combination with other agents, may have potential for use in TNBC; however, further studies are warranted to investigate the benefit/risk profile of these combinations.

Adjuvant Chemotherapy for Male Breast Cancer

Male breast carcinoma is a rare condition. Few male breast cancer-specific epidemiological or clinical trial data are available; thus, our understanding of male breast cancer comes from studies of female breast cancer, painting an inaccurate picture of contributing factors. In the United States, approximately 2140 new cases of breast cancer in men are diagnosed annually, and 450 deaths occur; this number represents less than 0.5% of all cancer deaths in men annually. Approximately 1% of all breast cancers occur in men, but the male/female ratio is higher among black than among white populations. In areas of Central Africa, breast cancer accounts for up to 6% of cancers in men, and the male/female ratio is much higher compared with the White population (100:1 vs. 70:1) [204]. African populations also have a poorer prognosis, even after adjustment for clinical, demographic, and treatment factors [205].

There is usually no identifiable risk factor that differs from those for female breast cancer; family history, Jewish ancestry, obesity, low physical activity levels, prior chest wall irradiation, and benign breast disease are all believed to play a role [204]. However, specific to male subjects, gynecomastia, Klinefelter syndrome, a history of testicular or liver pathology, and a history of fracture after age 45 are indicated as having a causal relationship with breast cancer in males [206]. For Klinefelter syndrome, high serum concentrations of gonadotropins in response to low serum testosterone levels result in a high estrogen-to-testosterone ratio [207]. Similarly, testicular injury such as orchitis and cryptorchidism is believed to reduce testosterone levels compared with estrogen levels [208]. Several risk factors involving an imbalance between estrogenic and androgenic influences, as is the case for liver disease, may suppress the protective effect of androgens on breast tissue. However, other conditions associated with an increased estrogen-to-testosterone ratio, such as obesity, thyroid disease, marijuana use, and exogenous estrogen use (e.g., transsexuals and patients undergoing prostate cancer treatment), have a less certain relationship with male breast cancer.

Despite differences in the molecular characteristics of breast cancer associated with both age and ethnicity, the most common subtype of breast cancer in men is hormonal receptor-positive disease, as demonstrated in a registry study of male breast cancer patients in which 82% comprised the hormonal receptor positive subgroup [209]. Non-Hispanic Black men were more likely to have TNBC than non-Hispanic White or Hispanic men (9% vs. 3% and 6%, respectively). Cancers of the male breast are significantly more likely to express hormonal receptors than cancers of the female breast, even after adjustment for tumor stage, grade, and patient age [210]. As in female breast cancer, the rates of hormonal receptor positivity increase with increasing patient age. By contrast, the HER2-neu proto-oncogene is less likely to be overexpressed in cancers of the male breast [211].

Tumor size and lymph node involvement are two clear prognostic factors for male patients with breast cancer. Men with tumors measuring 2–5 cm have a 40% higher risk of death than men with tumors with a maximum diameter <2 cm [210]. Similarly, men with lymph node involvement have a 50% higher risk of death than those without lymph node involvement. In general, the prognosis for male and female patients with breast cancer is similar. Overall

survival rates appear to be lower for men; however, this is probably due to older age at diagnosis because the age-adjusted survival rates are comparable between male and female subjects [212].

Local therapy for breast cancer is generally similar in men and women. Most men are treated with modified radical mastectomy with axillary lymph node dissection or sentinel node biopsy. After appropriate surgery, adjuvant systemic therapy is recommended for the majority of men with breast cancer. The same guidelines for adjuvant systemic therapy in women with early-stage breast cancer are generally followed for men with breast cancer [213]. Recommendations for adjuvant chemotherapy are based largely on the benefits that have been observed in clinical trials performed in women [9]. One prospective study of adjuvant chemotherapy in men was published in 1987 [214]. Twenty-four stage II (node-positive) male breast cancer patients were treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The 5-year survival rate projected by actuarial means was in excess of 80% (95% CI 74–100%), higher than that for historical controls of similar stage. The authors concluded that the CMF regimen was feasible and was associated with substantial improvement in DFS and OS. Yildirim et al. [215] published follow-up data for 121 male breast cancer patients, 60% of whom received systemic adjuvant treatment (chemotherapy and hormonal therapy). Adjuvant chemotherapy was associated with a 40% risk reduction for death. Similarly, publications regarding adjuvant chemotherapy for male breast cancer are mainly retrospective and usually reflect institutional experience [216, 217]. A retrospective study from MD Anderson Cancer Center with a median follow-up of 13 years noted a survival benefit from adjuvant chemotherapy, with a 22% risk reduction among node-positive patients, which was not statistically significant [218]. Chemotherapy was administered to 32 men (84% as an adjuvant modality); approximately 81% received anthracycline-based regimens, 9% received additional taxanes, and 16% were treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The 5-year and 10-year OS rates were 86% and 75%, respectively, for men with lymph node-negative disease and 70% and 43%, respectively, for men with lymph node-positive disease. OS was significantly better for men who received adjuvant hormonal therapy (HR = 0.45; $p = 0.01$).

In view of the findings of a clear benefit for adjuvant chemotherapy in women and the positive trends of adjuvant chemotherapy in small series in men, adjuvant chemotherapy should be considered for men with intermediate- or high-risk primary breast cancer, particularly those with hormonal receptor-negative disease. The role of taxanes or dose-dense chemotherapy in male breast cancer has not been adequately established. Well-powered randomized trials for male breast cancer are unlikely. Therefore, given the established benefit of taxanes in women and the suggestive evidence in men, taxanes may be considered when lymph nodes are involved. Because no specific data are available, adjuvant trastuzumab should be considered according to patient and tumor characteristics following female breast cancer guidelines.

Adjuvant Chemotherapy of Pregnancy-Associated Breast Cancer

Gestational or pregnancy-associated breast cancer is defined as breast cancer that is diagnosed during pregnancy, within the first postpartum year, or during lactation. It is a relatively uncommon event. The incidence of pregnancy-associated breast cancer is approximately 15–35 per 100,000 deliveries, with fewer breast cancer cases diagnosed during pregnancy than during the first postpartum year [219, 220]. With the increasing trend for women to delay childbearing, the co-occurrence of cancer and pregnancy, reported to have an average frequency of 1 in 1000 births, is increasing [221]. Breast cancer during pregnancy requires a multidisciplinary approach because the well-being of both the mother and the fetus must be considered in any treatment planning.

The majority of breast cancers in pregnant women are invasive ductal adenocarcinomas, as in nonpregnant women [221–223]. However, pregnancy-associated breast cancers are predominantly poorly differentiated and diagnosed at an advanced stage, particularly in those diagnosed while lactating [220]. In addition, the incidence of inflammatory breast cancer is higher among pregnancy-associated breast cancer than breast cancer in nonpregnant women, but this trend has not been consistently observed. Despite multiple opportunities for clinical breast examinations arising from the increased frequency of physician visits, breast examination during pregnancy is hampered by hypertrophy, engorgement, and indistinct nodularity of the gland. Moreover, densities and nodularities in the breasts of pregnant women are often overlooked or ascribed to benign proliferative changes. The hyperestrogenic state of pregnancy may also contribute to the development and rapid growth of breast carcinoma in these women. In addition, obstetricians frequently direct their attention to the developing fetus and do not perform a comprehensive physical examination. These factors often cause a delay in diagnosis and advanced disease presentation.

The majority of tumors diagnosed during pregnancy are high-grade tumors [223, 224]. Lymphovascular invasion is a frequent finding and also a negative prognostic factor [225, 226]. Most series report a lower frequency of ER and PR expression in pregnancy-associated breast cancer compared with breast cancer in nonpregnant patients (approximately 25% vs. 55–60%) [225, 227, 228]. This immunohistochemical profile does not appear to differ from age-matched,

nonpregnant women [229, 230]. It is believed that the age of the breast carcinoma patient and not the pregnancy itself affects the biological features of the tumor. Therefore, breast carcinomas occurring during pregnancy share many histological and prognostic similarities with breast carcinoma occurring in other young women. Whether there is a higher incidence of HER2 positivity in these patients compared with nonpregnant age-matched controls is unclear [231].

The indications for systemic chemotherapy are the same in pregnant patients as in nonpregnant breast cancer patients; however, chemotherapy should not be administered at any point during the first trimester of pregnancy. The most commonly used treatment in pregnancy has been anthracycline and alkylating agent chemotherapy [232, 233]. Anthracyclines are mutagenic and carcinogenic in vitro and in animals [234]. Because topoisomerase IIα is overexpressed in rapidly growing tissues, targeting topoisomerase II is a potential source of damage to the embryo or the fetus [235]. By contrast, only low concentrations of anthracyclines have been detected in fetal tissues, and their cytotoxic potential remains unknown. A retrospective analysis of 160 patients with breast cancer during pregnancy revealed that following chemotherapy with an anthracycline-containing regimen, progressive maternal disease was the first cause of fetal death (40%) [232]. A total of five malformations (3%) were reported, three in the first trimester (80%), which is the period of organogenesis, and two following chemotherapy during the second trimester, one of which was a case of Down's syndrome unrelated to chemotherapy and the other a case of eye malformation (congenital adherence of the iris to the cornea, without consequence). In contrast to other anticancer agents, which may rapidly cross the placenta and be completely transferred, anthracyclines cross the placenta incompletely for several reasons. First, drugs with molecular weights greater than 500 Da undergo incomplete transfer across the human placenta; the molecular weights of doxorubicin and daunorubicin are 580 and 564 Da, respectively [236]. Second, anthracyclines are substrates of P-glycoprotein, a placental drug-transporting glycoprotein of great importance in vivo in limiting the fetal penetration of potentially harmful compounds [237]. Moreover, the hydrophilic characteristic of doxorubicin likely decelerates its placental transfer [236]. After intravenous injection of anthracyclines, only barely detectable concentrations can be found in the fetus ex vivo. These concentrations are 100- to 1000-fold below those found in adult tissues or in the tumor in similar conditions [238]. Moreover, fetal uptake of anticancer agents can be altered by changes in both uterine and umbilical blood flow [239].

The most commonly used regimens in pregnant women with breast cancer in combination with anthracyclines are cyclophosphamide (AC) or fluorouracil and cyclophosphamide (FAC). Although experience with anthracycline-based regimens in pregnancy suggests their safety and efficacy, there are limited prospective data, particularly on the outcomes of children exposed in utero. In a prospective single-arm study, 57 pregnant breast cancer patients were treated with FAC in the adjuvant (n = 32) or neoadjuvant (n = 25) setting [240]. Parents/guardians were surveyed by mail or telephone regarding outcomes of children exposed to chemotherapy in utero. After a median follow-up of 38.5 months, 40 patients were alive and disease-free, 3 had recurrent breast cancer, and 12 had died from breast cancer. Of the 25 patients who received neoadjuvant FAC, 6 had a pCR, whereas 4 had no tumor response to chemotherapy and eventually died from their disease. All women who delivered had live births. One child had Down's syndrome, and two had congenital anomalies (club foot, congenital bilateral ureteral reflux). The most common neonatal complication was difficulty breathing, with 10% of the neonates requiring supplemental oxygen (likely due to prematurity). One child who was born vaginally at a gestational age of 38 weeks had a subarachnoid hemorrhage on day 2 postpartum. Although this occurred more than 3 weeks after the mother's last course of chemotherapy and although the mother's complete blood count was normal, the child had both neutropenia and thrombocytopenia. No other etiology for the subarachnoid hemorrhage was found. Other smaller retrospective series regarding the effects of chemotherapy on fetal and maternal health have revealed similar results [241, 242]. The evidence suggests that the incidence of congenital malformations is low (approximately 1.3%) if chemotherapy is administered to women in the second or third trimester, which is after the major period of organogenesis. The estimated risk of fetal malformation due to first-trimester exposure to chemotherapeutics is 15–20% [243, 244].

Despite the safety and efficacy of doxorubicin during and after the second trimester, at least four cases of neonatal cardiac effects have been reported after in utero exposure to anthracyclines, and several cases of in utero fetal death after exposure to idarubicin or epirubicin have also been reported [244–247]. Moreover, chemotherapy in the second or third trimester has been associated with intrauterine growth restriction, lower gestational age at birth (prematurity), and low birth weight in about one-half of exposed infants [244–246]. However, patient fears regarding the side effects of treatment should not cause a delay in the initiation of systemic chemotherapy.

A mathematical model using published data was developed to correlate primary breast tumor size with the percentage of pathologically positive axillary lymph nodes [247]. Using this relationship obtained from pathological data and the accepted relationship of tumor growth and time, an equation estimating the increased risk of axillary metastases due to each day of treatment delay was derived. The model suggests that the daily increased risk of axillary metastases due to treatment delay is 0.028% for tumors with moderate

doubling times of 130 days and 0.057% for tumors with rapid doubling times of 65 days. Thus, according to the model, for breast cancer with a 65-day doubling time, a 1-month delay increases the risk of axillary metastases by 1.8%, a 3-month delay by 5.2%, and a 6-month delay by 10.2%. This model emphasizes the importance of initiating treatment as early as possible for pregnant breast cancer patients.

Currently, no data encourage the safety of administering dose-dense AC with or without taxanes; however, G-CSF has been reported to be safe during pregnancy. Moreover, as a general rule, breastfeeding during chemotherapy is contraindicated due to the excretion of cyclophosphamide and doxorubicin into the breast milk [248]. Methotrexate is also avoided during pregnancy due to its abortifacient effect and teratogenic potential [249]. Although no evidence indicates that cisplatin and carboplatin are harmful during pregnancy, higher levels of free drug in the mother and fetus (due to changes in cisplatin protein binding caused by lower albumin levels) may increase the risk of toxicity in both [250].

Data regarding the safety of taxanes during pregnancy are limited. A systematic review of taxane administration during pregnancy identified 23 publications describing a total of 40 women [251]. Twenty-seven patients had breast cancer, ten had ovarian cancer, and three had non-small-cell lung cancer. Docetaxel was administered in the first trimester in two cases, and the rest received taxanes in the second or third trimester. No spontaneous abortions or intrauterine deaths were reported. In two cases exposed to paclitaxel, neonates born at 30 and 32 weeks developed acute respiratory distress possibly related to prematurity, requiring neonatal intensive care [252, 253]. The only malformation possibly related to taxanes was a case of pyloric stenosis in a neonate whose mother had received multiagent chemotherapy (doxorubicin, cyclophosphamide, paclitaxel, and docetaxel). Because the safety of taxanes is less documented than that of anthracyclines, an additional cycle of anthracycline-based chemotherapy during pregnancy and the completion of taxane-based chemotherapy after delivery can be considered in some situations [254]. According to the limited published data, the major cause of undesirable fetal outcomes appears to be derived from premature delivery rather than from any direct effect of the chemotherapy. Follow-up of children with specialized assessments, including detailed physiological and neurological functions, is necessary.

Treatment of Patients with Cardiac Disease

Adjuvant therapy in early-stage breast cancer typically includes anthracycline-containing chemotherapy, sometimes followed by taxanes, the anti-ERBB2 (-HER2) agent trastuzumab, and radiotherapy; each modality contributes to an increased risk of cardiac disease, including atherosclerotic coronary artery disease and left ventricular (LV) systolic and diastolic dysfunction. Thus, cancer patients who are undergoing chemotherapy have an increased risk of developing cardiovascular complications, and the risk is even greater if there is a known history of heart disease. The most common serious clinical cardiac complications reported are arrhythmias, myocardial necrosis causing dilated cardiomyopathy, and vaso-occlusion or vasospasm resulting in angina or myocardial infarction.

Anthracyclines are believed to cause immediate damage to cardiac myocytes by several mechanisms. Activation of calcium channels triggers intracellular calcium overload, and cardiac contractility may be reduced [255]. The generation of reactive oxygen species, which induce sarcomere degeneration, mitochondrial dysfunction, DNA damage, and gene expression alterations, can cause apoptotic and necrotic cell death [256–258]. The incidence of cardiotoxicity increases with the cumulative dose; however, even low doses of epirubicin in adjuvant chemotherapy for breast cancer have been shown to result in mild left ventricular ejection fraction (LVEF) impairment, an increase in brain natriuretic peptide (a marker of increased cardiac filling pressures and heart failure) levels, and an increased QT interval (QTc), all of which may indicate an increased risk of the development of subsequent heart failure (HF) [258] Reported HF rates associated with epirubicin range from 0.6% at a cumulative dose of 550 mg/m^2 to 14.5% at a cumulative dose of 1000 mg/m^2 [259]. A report of 630 patients treated with doxorubicin alone in three controlled trials estimated that as many as 26% of patients receiving a cumulative doxorubicin dose of 550 mg/m^2 would develop heart failure [260]. Based on these observations, it has been generally recommended that cumulative doxorubicin doses be limited to 450–500 mg/m^2 and epirubicin doses to 900 mg/m^2 in adults.

Adjuvant radiotherapy causes additional strain on the heart through the development of both ventricular dysfunction and coronary artery disease [261]. Radiation-induced toxicity is typically a late event and comprises diffuse fibrotic and microvascular damage to the myocardium. Radiotherapy can also promote atherosclerosis, resulting in premature coronary artery events [262]. Highly conformal radiotherapy techniques have helped reduce the heart volume at risk, particularly in patients treated for left-sided breast cancer [263]. However, radiation-induced potentially morbid late effects are long-term side effects and add to the adverse effects of other therapeutic modalities such as chemotherapeutics and targeted agents.

Cardiac dysfunction may occur immediately or, more commonly, months or years after finishing chemotherapy. Acute or subacute cardiotoxicity may present as electrocardiographic abnormalities, arrhythmias (both supraventricular and ventricular), heart block (including Mobitz type II

second-degree AV block, and complete heart block), ventricular dysfunction, increased plasma brain natriuretic peptide (BNP) levels, or pericarditis–myocarditis syndrome (particularly with mitoxantrone) [264, 265]. Acute–subacute toxicity is a relatively rare event. The most common clinical presentation is chronic cardiotoxicity, which is usually overt within 1 year after the completion of chemotherapy in 1.6–5% of patients [266]. However, the onset of symptomatic heart failure can occur more than a decade after the last anthracycline dose. Moreover, the risk of breast cancer treatment-induced cardiotoxicity may be increased in patients with coexisting traditional risk factors for cardiovascular disease, such as hypertension and hyperlipidemia [267]. Both the subacute and chronic forms of anthracycline-mediated cardiotoxicity tend not to be reversible.

Risk factors for anthracycline toxicity include the cumulative dose, intravenous bolus administration; higher single doses; a history of prior irradiation; the use of other concomitant agents known to have cardiotoxic effects, including cyclophosphamide, trastuzumab, and paclitaxel; female sex; underlying cardiovascular disease; age (young and elderly); and an increased length of time since the completion of chemotherapy [268, 269].

In addition to anthracyclines, chemotherapeutics included in adjuvant treatment may also cause cardiac side effects. Left ventricular dysfunction has been associated with cyclophosphamide therapy in 7–28% of patients. Pericardial effusion and myopericarditis have also been reported [270, 271]. The risk of cardiotoxicity appears to be dose related (≥150 mg/kg and 1.5 g/[m^2 days]) and occurs within 1–10 days after administration of the first dose of cyclophosphamide.

According to retrospective analysis, the incidence of HF associated with taxanes is relatively low, ranging from 2.3% to 8% for docetaxel [272]. In the BCIRG 001 trial, the overall incidence of congestive HF (including that during follow-up) was 1.6% among patients treated with docetaxel, doxorubicin, and cyclophosphamide and 0.7% among patients treated with 5-fluorouracil (5-FU), doxorubicin, and cyclophosphamide ($p = 0.09$) [126]. Another study including 46 patients older than 70 years observed five cases of cardiac toxicity related to weekly paclitaxel administration for the treatment of breast cancer [273]. An overview of cardiac toxicity induced by cytotoxic agents utilized in breast cancer treatment is presented in Table 8.8.

Monitoring cardiac function is highly recommended before, during, and after potentially cardiotoxic chemotherapy to detect subclinical cardiac damage, although no clear guidelines are available from any expert group on the frequency or optimal method of LVEF assessment or the best parameters to follow. A baseline cardiovascular examination along with careful cardiovascular management of risk factors such as hypertension or hyperlipidemia is an important and often overlooked component of pretreatment assessment. The most common noninvasive techniques for monitoring LVEF are echocardiography and radionuclide angiography.

Table 8.8 Cardiac side effects of chemotherapeutic agents commonly utilized for breast cancer treatment

Cardiac toxicity	Chemotherapeutic agent	Incidence (%)
Left ventricular dysfunction	Doxorubicin	3–26
	Epirubicin	0.9–3.3
	Cyclophosphamide	7–28
	Docetaxel	2.3–8
	Bevacizumab	1.7–3.9
	Trastuzumab	2–28
Ischemia	Paclitaxel	<1–5
	Capecitabine	3–9
	Docetaxel	1.7
	5-FU	1–68
QT prolongation	Paclitaxel	0.1–31

Two-dimensional (2D) echocardiography is the most widely available method for monitoring LVEF. Its advantages include portability and the capability of assessing other measures of myocardial dysfunction as well as other cardiac lesions such as valvular disease. The limitations of 2D echocardiography include problems with reproducibility and dependence on adequate acoustic windows. Thresholds for normal LVEF should be based on modality- and analysis-specific and population-appropriate normative data. Recent definitions are varied, including a larger change in the LVEF to less than the lower limit of normal or an LVEF less than 50%. As a result, obtaining a clear understanding of the degree of LV dysfunction with different therapies can be problematic [274]. For a borderline depressed LVEF by echocardiography, further evaluation by radionuclide ventriculography may be necessary. Follow-up assessment of systolic dysfunction is also required throughout the treatment course for the normal initial LVEF. The US FDA-approved labeling for doxorubicin indicates that in adults, a 10% decrease in the LVEF to below the lower limit of normal, an absolute LVEF of 45%, or a 20% decrease in the LVEF at any level is indicative of the deterioration of cardiac function [275].

Dexrazoxane, which is an EDTA-like chelator that may prevent anthracycline damage by binding to iron released secondary to lipid peroxidation, can be used for cardioprotection during chemotherapy with anthracyclines [276]. In some trials conducted among women receiving doxorubicin or epirubicin for breast cancer, concerns have been raised about the possibility that dexrazoxane may interfere with cancer therapy or enhance myelosuppression [277, 278]. However, multiple other randomized trials and two pooled analyses have not confirmed these findings [279–281]. The ASCO guidelines for the use of dexrazoxane in conjunction

with doxorubicin include recommendations for cardiac monitoring after a cumulative dose of 400 mg/m^2 is reached; monitoring should be repeated after a 500 mg/m^2 cumulative dose is reached and after every 50 mg/m^2 thereafter [282]. Discontinuing anthracycline and dexrazoxane is recommended in patients who have a decrease in LVEF to below the lower limit of normal or who develop clinical heart failure.

Heart failure is associated with complex neuroendocrine activation, and neuroendocrine blockade with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers has proven efficient in reducing mortality and morbidity in all stages of HF. Moreover, ACEIs prevent or delay the development of symptomatic HF in patients with asymptomatic LV dysfunction [283, 284]. There is evidence that asymptomatic cardiotoxicity may predispose patients to late-onset cardiac events in the presence of additional factors such as hypertension or ischemia [285]. Thus, early intervention with established HF regimens may prove beneficial. Previous studies indicate that the prophylactic use of established HF therapies in the setting of anthracycline-induced cardiotoxicity may prevent or reduce adverse effects. However, the majority of these studies have been performed in heterogeneous patient groups with different types of cancer and treatment regimens [286, 287]. Currently, there are no results from randomized trials concerning the prophylactic effect of beta-blockers, ACEIs, or ARBs in patients receiving standard adjuvant oncological therapy for early-stage breast cancer. The randomized PRADA trial has been designed to evaluate the potential of ARBs, beta-blockers, or both started before chemotherapy to prevent a decline in systolic LV function, as assessed by cardiac magnetic resonance imaging, and diastolic LV function, as assessed by echocardiography [288]. The findings of this trial are expected to contribute to efforts to prevent, detect, and treat the cardiotoxic effects of cancer therapy.

Dose Adjustment for Obese Patients

Obesity is one of the leading environmental causes of cancer in developed countries [289]. A body mass index (BMI) of 30 kg/m^2 or higher has been used to define obesity in most reports. Although it is not a direct causative factor, obesity results in conditions that can lead to carcinogenesis, such as increases in tumor necrosis alpha and other tumor-promoting factors and increased unopposed estrogen from the aromatase conversion of androstenedione in adipose tissues [290]. Studies have addressed a strong association between increased adiposity and breast cancer in postmenopausal women. Obesity has also been associated with poorer survival in women diagnosed with breast cancer [291]. The mechanisms underlying the adverse effects of obesity on breast cancer survival are not clearly identified but are probably multifactorial. Obesity is prognostic in part because of its association with less favorable disease features at diagnosis, such as larger tumors and a greater number of involved lymph nodes [292, 293]. Obesity also interferes with the pharmacokinetic behavior of chemotherapeutic agents, possibly due to previously unmeasured factors such as altered metabolic function in the context of fatty liver, inherited hepatic enzyme phenotypes, or changes in the glomerular filtration rate. Impaired clearance and greater body exposure to a variety of adjuvant agents, including doxorubicin, cyclophosphamide, and fluorouracil, have been demonstrated in different trials [294, 295]. Systemic chemotherapy at less than full weight-based dosing and unnecessary dose reductions may in part explain the significantly higher cancer mortality rates observed in overweight and obese individuals.

Previous analyses have indicated that for a clinical trial population of patients with lymph node-negative, ER-positive breast cancer treated with tamoxifen who have a relatively low risk of cancer recurrence, obesity is associated with an increased rate of contralateral breast cancer, second primary cancers, and other noncancer-related deaths [296, 297].

An analysis of three studies involving 6885 women with stage I–III breast cancer evaluated the relationship between BMI and clinical outcomes [298]. The report included patients enrolled in three National Cancer Institute (NCI)-sponsored clinical trials of adjuvant doxorubicin-containing chemotherapy coordinated by ECOG for whom BMI data were available. The findings of this report were consistent with previous studies. Obese patients, defined as having a BMI of 30 kg/m^2 or higher, exhibited significantly higher risks of recurrence and death. After adjusting for prognostic factors (including age, race, menopausal status, tumor size, number of pathologically involved axillary nodes, and type of surgery), obesity was associated with inferior DFS (HR 1.24, 95% CI 1.06–1.46) and OS (HR 1.37, 95% CI 1.13–1.67) among women with hormone receptor-positive breast cancer but not among women with triple-negative or HER2-positive disease. Concordantly, Sestak et al. [299] reported that in postmenopausal women with ER-positive disease enrolled in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, a high baseline BMI was associated with more distant recurrence. Moreover, better outcomes were observed for adjuvant anastrozole compared with tamoxifen, primarily in women who were not obese.

Drug development and clinical trials in oncology are usually conducted irrespective of patient body weight, and obesity is not usually a stratified covariate in data analysis. Therefore, the differing pharmacokinetic parameters of obese patients are frequently overlooked. Consequently, dosing recommendations are limited regarding chemotherapy dosing in obese patients. This has resulted in the inconsistent use of various body weight estimates in chemotherapy

dosing and, specifically, the calculation of body surface area (BSA). Most often, oncologists have been conservative by either adjusting body weight for obese patients or by assigning a BSA capped at 2 m^2 rather than using the actual body weight to calculate the BSA. Although dosing schemas may vary among practices and institutions, many oncologists tend to remain conservative and empirically dose reduce up to 40% of obese patients despite data suggesting otherwise. The practice of limiting doses in overweight and obese patients may have unfavorable effects on the quality of care and outcomes at a population level when the increasing frequency of obesity is considered. Although dose capping in obese patients is recommended for other drugs, including low-molecular-weight heparins, some anesthetics, and some antibiotics, it may not be ideal in breast cancer chemotherapy [300].

The major target of dosing in chemotherapy is to achieve the maximum tolerated dose, thereby ensuring efficacy. Toxicity is often dose dependent and is commonly the dose-limiting factor in adjuvant chemotherapy. Chemotherapy has been shown to be more effective at higher doses. Thus, to a certain extent, increasing the dose may lead to greater myelotoxicity and greater efficacy [301, 302]. There are no prospective randomized studies comparing full weight-based chemotherapy dose selection and non-full weight-based dose selection. Obese female patients are at risk of suboptimal treatment due to empiric dose reductions. Concordantly, the previously reported increase in cancer mortality may be partly due to inadequate dosing. A recent review regarding the effect of obesity on the toxicity of chemotherapeutic agents identified ten studies investigating fulfilling the criteria [303]. Seven studies found reduced toxicity in obese women compared with nonobese women. Of four studies in which dose capping was precluded or statistically adjusted for, three observed reduced toxicity in obese women. These outcomes included less febrile neutropenia [BMI > 23.6; odds ratio (OR) 4.4; 95% CI 1.65–12.01], fewer hospital admissions (BMI > 35; OR 0.61, 95% CI 0.38–0.97), and fewer neutropenic events (BMI > 25; OR 0.49; 95% CI 0.37–0.66). According to the results of this analysis, obese patients appeared to tolerate chemotherapy better than lean patients. Even after the exclusion of patients with planned dose reductions, a trend toward decreased admission to hospital with febrile neutropenia was observed [304]. Previously, myelosuppression was demonstrated to correlate with the efficacy of treatment and was considered a surrogate [305]. Although the mechanism of low myelosuppression in obese patients has not been elucidated, the tendency to develop less neutropenia suggests a comprised efficacy of chemotherapy. Thus, this tendency is believed to contribute to the poorer prognosis among obese patients compared with lean patients.

Although not confirmed among breast cancer patients, a study involving lung and colorectal cancer patients has reported equal toxicity rates among lean and obese patients with a higher than traditional BSA cap of 2.2 [306]. Currently, there is no evidence for increased short- or long-term toxicity among obese patients receiving full weight-based chemotherapy doses. Most of the data from the aforementioned studies indicate that myelosuppression is the same or is less pronounced among obese patients compared with nonobese patients when full weight-based doses are administered. According to the most recent ASCO guidelines, the actual body weight should be used when selecting cytotoxic chemotherapy doses, regardless of the obesity status [307]. However, the panel acknowledged that data regarding optimal dose selection among the morbidly obese and other special subgroups are extremely limited. The available evidence indicates that morbidly obese patients treated with curative intent and receiving full weight-based doses are no more likely to experience toxicity than lean patients [308]. Moreover, retrospective analyses and observational studies suggest that dose limits in obese patients may compromise DFS and OS rates [309–311]. An analysis of outcomes among obese patients treated in the CALGB 8541 trial demonstrated that obese patients who received less than 95% of the expected chemotherapy (based on full weight-based dosing) had worse failure-free survival rates [312]. The panel did not recommend a different management pattern for dosing in the case of high-grade toxicity. The guideline also emphasized the paucity of information on the influence of obesity on the pharmacokinetics of most anticancer drugs from properly powered trials. Overall, there appear to be insufficient pharmacokinetic data to reject the recommendation to use a full weight-based dosing strategy for chemotherapeutic agents in patients with cancer who are obese, regardless of the route of administration and the infusion time.

Conclusion

In breast cancer, the choice of treatment strategy is based on the features and biology of the tumor as well as on the age, general health status, and personal preferences of the patient. The clinical situations in which molecular tests have the greatest relevance for therapeutic decision making are still being established; however, evidence is also increasing as to the types of breast cancer in which good predictions of prognosis can be obtained. One of the current challenges in treatment is the selection of the subset of patients who might preferentially benefit from therapy. Patients with more than three involved lymph nodes, low hormonal receptor positivity, positive HER2 status, triple-negative status, high 21-gene RS, and high-risk 70-gene scores should receive adjuvant chemotherapy. A high Ki67 proliferation index and histological grade 3 tumors are acceptable indications for adjuvant chemotherapy. For women desiring fertility preservation

and for patients with certain comorbidities such as cardiovascular disease and diabetic neuropathy, specific chemotherapy regimens may be preferred.

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Adjuvant Therapy for HER-2-Positive Early Breast Cancer

9

Gul Basaran and Devrim Cabuk

Introduction

Amplification of the human epidermal growth factor receptor 2 (HER-2/neu) gene was identified as a poor prognostic factor in patients with breast cancer nearly three decades ago, in 1987 [1]. HER-2 gene amplification and/or protein overexpression in breast cancer has subsequently been associated with an aggressive phenotype, increased recurrence, and decreased survival [2]. HER-2 gene amplification and/or protein overexpression has been identified in 10–34% of invasive breast cancers [3]. Trastuzumab, a monoclonal antibody that binds to the extracellular portion of the HER-2 transmembrane receptor, has been widely studied in metastatic breast cancer. Metastatic trials have demonstrated substantial efficacy of trastuzumab and established criteria to select patients who could benefit from this monoclonal antibody [4]. Soon after US FDA approval of trastuzumab use in metastatic breast cancer, a new molecular classification of breast tumors based on gene expression patterns was developed [5]. This molecular classification identified the HER-2-positive group as one of four molecular subgroups with poor prognosis. Subsequent randomized trials provided clear and consistent evidence that the addition of trastuzumab to adjuvant chemotherapy significantly reduces the likelihood of relapse and death among women with HER-2-positive early breast cancer [6–11].

Metastatic breast cancer trials demonstrated that a high level of HER-2 overexpression is a strong predictor of benefit from trastuzumab [2]. Patients who were likely to respond to trastuzumab therapy were identified either by strong (3+) IHC (immunohistochemistry) for the HER-2 protein or by gene amplification (FISH or CISH). Patients with a 2+ IHC score and gene amplification also received benefit from trastuzumab. Based on the data from the metastatic setting, adjuvant trastuzumab trials have considered breast cancer patients with either 3+ IHC or FISH-positive tumors eligible for enrollment. This algorithm for determining tumor HER-2 status was subsequently outlined as a guideline by a joint consensus of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) and was recently updated [12, 13].

Clinical Evidence of Benefit from Adjuvant Trastuzumab

The efficacy and toxicity of trastuzumab in the adjuvant setting have been evaluated by seven large, randomized, multicenter controlled trials that have accrued approximately 17,000 patients [8, 14–24]. These trials had similar eligibility criteria in terms of the assessment of HER-2/neu status (patients with either 3+ IHC or FISH-positive disease were enrolled), but differed in many aspects, including patient population, timing of trastuzumab administration, type of chemotherapy used, duration of trastuzumab use, etc. Table 9.1 provides a summary of pivotal adjuvant trials in HER-2/neu-positive early breast cancer.

The HERA trial, the combined analysis of the NSABP B-31 and NCCTG N9831 trials (joint analysis), and BCIRG 006 trial demonstrated statistically significant improvements in DFS (disease-free survival) as the primary end point. The HERA, joint analysis, and BCIRG 006 trials also reported significant improvements in overall survival (OS).

Herceptin Adjuvant (HERA) Trial

HERA was an international, multicenter, randomized, open-label phase III trial comparing trastuzumab for 1 or 2 years with observation in women with centrally confirmed HER-2/neu-positive early breast cancer. All patients completed

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Table 9.1 Overview of adjuvant trastuzumab trials in patients with HER-2-positive early breast cancer

Study	Treatment regimen	Trastuzumab duration (weeks)	Patients (*n*)	Median follow-up (months)	Disease-free survival			Overall survival		
					HR	95% CI	*P*	HR	95% CI	*P*
HERA	CT	–	1698	96	0.76	0.66–0.87	<0.0001	0.76	0.65–0.88	0.0005
	CT → T	52	1703							
	CT → T	104	1701		0.99	0.85–1.14	0.86	1.05	0.86–1.28	0.63
Joint analysis				100.8	0.60	0.53–0.68	<0.0001	0.63	0.54–0.73	<0.0001
NSABP B-31	AC → P	–	2018							
NCCTG N9831	AC → PT → T	52	2028							
NCCTG N9831	AC → P	–	1087	72	0.67	0.54–0.81	<0.001	0.88	0.67–1.15	0.343
	AC → P → T	52	1097/954							
	AC → PT → T	52	949		0.77	0.53–1.11	0.022	0.78	0.58–1.05	0.102
BCIRG 006	AC → D	–	1073	65	0.64	0.53–0.78	<0.001	0.63	0.48–0.81	<0.001
	AC → DT → T	52	1074							
	DCarboT → T	52	1075		0.75	0.63–0.90	0.04	0.77	0.60–0.99	0.038
PHARE	CT + T	26	1690	42.5	1.28	1.05–1.56	0.29	1.47	1.07–2.02	NR
	CT + T	52	1690							
FinHer	D/V → FEC	–	116	62	0.65	0.38–1.12	0.12	0.55	0.27–1.11	0.094
	(D/V)T → FEC	9	115							
PACS 04	FEC → ED	–	268	47	0.86	0.61–1.22	0.41	1.27	0.68–2.38	NR
	FEC/ED → T	52	260							

NSABP B-31 National Surgical Adjuvant Breast and Bowel Project B-31 trial, *NCCTG N9831* North Central Cancer Treatment Group N9831 trial, *BCIRG 006* Breast Cancer International Research Group trial, *PHARE* Protocol for Herceptin as Adjuvant Therapy with Reduced Exposure trial, *FinHer* Finland Herceptin trial, *PACS 04* Protocol Adjuvant dans le Cancer du Sein trial, *CT* chemotherapy, *T* trastuzumab, *A* doxorubicin, *C* cyclophosphamide, *P* paclitaxel, *D* docetaxel, *Carbo* carboplatin, *V* vinorelbine, *F* 5-fluorouracil, *E* epirubicin

locoregional therapy and received standard neoadjuvant/adjuvant chemotherapy before randomization. Patients were required to have a left ventricular ejection fraction (LVEF) of 55% after primary treatment as measured by multigated acquisition (MUGA) scan or echocardiography prior to randomization. After a median follow-up period of 1 year, the comparison of 1-year treatment versus observation was published in 2005 [6]. There was a statistically significant 36% reduction in disease recurrence (HR 0.64, 3-year DFS of 81% versus 74%) and a significant improvement in overall survival (HR 0.66, 92% versus 90% in the trastuzumab and non-trastuzumab groups, respectively). Efficacy outcomes were similar across subgroups as defined by nodal status or hormone receptor expression. Based on these results, trastuzumab became the standard of care in the treatment of HER-2-positive early breast cancer, and there was a protocol amendment allowing the patients in the observation arm who remained event-free to cross over to the trastuzumab arm. The incidence of grade 3 or 4 adverse and serious cardiac toxicity events was higher in the trastuzumab group than in the observation group. Fatal events (six versus three patients), symptomatic congestive heart failure (CHF) (1.7% versus 0.06%), and LVEF drops (7.1% versus 2.2%) were more frequent in the trastuzumab arm. There was one cardiac death in the observation group, and nine patients (0.54%) in the treatment group had severe CHF.

With a median follow-up of 23.5 months, the early DFS improvement was confirmed, along with the emergence of a statistically significant OS benefit [14]. There were more grade 3 or 4 adverse events (11% versus 6%) and fatal (grade 5) treatment-related toxicities (0.5% versus 0.2%) in the trastuzumab arm compared to the control group. The only death due to cardiac causes was in the control arm. Trastuzumab was discontinued by 72 women (4.3%) because of cardiac problems.

In a subsequent analysis with a median 4-year follow-up, a significant improvement in DFS favoring trastuzumab (4-year DFS 79% versus 72%, HR 0.76, 95% CI 0.66–0.87) remained even though 885 of the 1698 controls had crossed over to trastuzumab; however, the survival advantage was no longer statistically significant (HR for death 0.85, 95% CI 0.70–1.04) [15]. As reported previously in the 2005 publication, there was one cardiac death in the observation group. More patients on 1-year trastuzumab had symptomatic congestive heart failure and a confirmed significant LVEF drop than in the observation group. There were fewer cases of symptomatic congestive heart failure and confirmed significant LVEF drops in the selective crossover cohort associated with delayed trastuzumab treatment compared with 1-year trastuzumab.

The results of the 2-year versus 1-year comparison were published at 8 years of median follow-up in 2013 [16]. There was no benefit of 2-year versus 1-year trastuzumab when administered as sequential treatment following chemotherapy. In addition, patients in the 2-year arm experienced more cardiac toxicity with an increase in secondary cardiac adverse events (LVEF <50% and ≥ 10% below baseline confirmed by repeat assessment) (7.2% versus 4.1%) and no significant difference in CHF New York Heart Association (NYHA) class III or IV events. HERA results at 8 years of follow-up indicated sustained and statistically significant DFS and OS benefit for 1-year trastuzumab versus observation in intention-to-treat analysis despite the selective crossover rate of 52%.

One year of trastuzumab was shown to significantly reduce the risk of a disease-free survival event (HR 0.76, 95% CI 0.68–0.86) and death (0.74, 0.64–0.86) compared with that of observation after a median follow-up of 11 years. In addition, random assignment to 2 years of adjuvant trastuzumab did not improve disease-free survival outcomes compared with those of 1 year of trastuzumab (HR 1.02, 95% CI 0.89–1.17). Ten-year disease-free survival rates were 63% and 69% for the observation and 1 year of trastuzumab arms, respectively. Of note, 52% of patients in the observation group selectively crossed over to receive trastuzumab. Cardiac toxicity remained low in all groups and mostly occurred during the treatment phase. The incidence of secondary cardiac end points was 7.3% in the 2-year trastuzumab group, 4.4% in the 1-year trastuzumab group, and 0.9% in the observation group [25].

Of note, the HERA trial had a different design than North American trials. Patients received adjuvant trastuzumab therapy only after the completion of other local or systemic therapies. The median time from the diagnosis of breast cancer to the initiation of trastuzumab was 8.5 months. This lag time could be particularly important for patients at higher risk of relapse. The relapse rates in the observation arms were higher in patients with hormone receptor-negative disease and those with involvement of more than three axillary lymph nodes. Most women did not receive a taxane as a component of their adjuvant chemotherapy; a larger percentage (approximately one-third) had node-negative disease. Trastuzumab was administered on a triweekly schedule (initial loading dose 8 mg/kg and then 6 mg/kg every 3 weeks for 1 year). CNS (central nervous system) metastases were more frequent numerically than in the observation arm; however, the death rate from CNS metastases was lower in the trastuzumab arm [26]. One year of adjuvant trastuzumab was arbitrarily selected as the study regimen; HERA is the only adjuvant trial that also tested trastuzumab use for longer than 1 year.

NSABP B-31 and NCCTG N9831 Trials

The two North American cooperative group trials, NCCTG N9831 and NSABP B-31, were both multicenter, randomized, open-label phase III trials with a similar parallel design [7].

The National Surgical Adjuvant Breast and Bowel Project 31 (NSABP B-31) trial randomized 1736 women with HER-2-positive (3+ IHC or FISH-positive), node-positive breast cancer either to four cycles of doxorubicin plus cyclophosphamide (AC × 4) followed by four courses of single-agent paclitaxel (175 mg/m^2 over 3 h) (arm 1) or to the same chemotherapy plus weekly trastuzumab (initial loading dose 4 mg/kg and then 2 mg/kg weekly for 1 year) (arm 2), beginning with the first dose of paclitaxel. Weekly paclitaxel was administered after a protocol amendment at 39 months of accrual, and radiation therapy was administered after completion of chemotherapy. Hormonal therapy was initially administered at the start of AC and later following completion of chemotherapy.

In both trials, eligibility required LVEF assessments before entry, after the completion of doxorubicin and cyclophosphamide therapy, and 6, 9, and 18 months after randomization by multigated acquisition scanning or echocardiography. The initiation of trastuzumab required an LVEF that met or exceeded the lower limit of normal and a decrease of less than 16 percentage points from baseline after doxorubicin and cyclophosphamide therapy. Trastuzumab was not permitted in patients with symptomatic left ventricular dysfunction, cardiac ischemia, or arrhythmia while receiving AC. The 6- and 9-month cardiac assessments were used to determine whether trastuzumab should be continued in patients without cardiac symptoms.

The NCCTG N9831 trial randomized 1615 women with HER-2-positive, node-positive, or high-risk node-negative disease (>1 cm ER-negative or >2 cm ER-positive) who received AC × 4 followed by one of three different treatment strategies: weekly paclitaxel (80 mg/m^2) for 12 weeks followed by no further treatment (group A, control arm), the same dose and schedule of paclitaxel followed by sequential trastuzumab for 52 weeks (same schedule and doses as above; group B, sequential arm), or the same dose and schedule of paclitaxel plus concurrent trastuzumab followed by trastuzumab alone for 40 weeks (group C, concurrent arm). Radiation and/or hormonal therapy was administered after the completion of chemotherapy when indicated.

Other than differences in the scheduling of paclitaxel and some aspects of hormonal therapy and radiotherapy, the control groups of the two trials, arm 2 in trial B-31 and the group C concurrent arm in trial N9831, were identical. Therefore, the NCI (National Cancer Institute) and the Food and Drug Administration approved a joint analysis, although this pooled analysis was not part of the original treatment designs. The group B sequential arm of trial N9831 was not included in the combined analysis.

The first joint analysis was published in 2005 and demonstrated a 12% absolute difference in DFS between the trastuzumab group (3-year DFS 75.4% in the control group and 87.1% in the trastuzumab group; HR, 0.48; 95% CI, 0.39–0.59; $P < 0.0001$) and the control group in addition to a 33% reduction in the risk of death (HR, 0.67; 95% CI, 0.48–0.93; $P = 0.015$) at a median follow-up of 2.0 years [7]. The 3-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1% in trial B-31 and 2.9% in trial N9831.

Efficacy results at 3.9 years of median follow-up were published in 2011 [18] and demonstrated that adjuvant trastuzumab concurrent with paclitaxel resulted in a significant 48% reduction in recurrence risk (4-year DFS 86% versus 74%, HR 0.52) and a 39% reduction in the risk of death (4-year OS 93% versus 86%, HR 0.61).

Updated results from the combined analysis at a median follow-up of 8.4 years were presented at the San Antonio Breast Cancer Symposium in 2012 and were consistent with an 11.5% gain in DFS and an 8.8% gain in OS for patients treated with trastuzumab [19]. The relative risk reduction benefit for both DFS and OS was of similar magnitude in virtually all patients, independent of age, nodal status, hormone receptor, tumor size, and histological grade.

After the release of the first joint analysis results at the American Society of Clinical Oncology Annual Meeting in 2005, patients previously randomly assigned to arm A of N9831 and arm 1 of B-31 were allowed to receive trastuzumab based on LVEF measurements. The crossover rate in B-31/N9831 was 20.4%. Cardiac toxicity was similar to the results in the 7-year follow-up of the B-31 trial; there was a 4.0% cardiac event rate for patients receiving trastuzumab versus a 1.3% cardiac event rate in controls [27]. It should be noted that 5% of patients assigned to the trastuzumab treatment arm never received the antibody due to decreases in LVEF or symptomatic heart disease. A combined review of cardiac toxicity data from the NSABP B-31 and NCCTG N9831 trials has also been published [28].

NCCTG N9831 Trial: Concurrent Versus Sequential Administration of Trastuzumab

N9831 was a three-arm trial that was also designed to compare the sequential and concurrent administration of trastuzumab (arms B and C, respectively). The NCCTG trial was initially designed to allow pairwise comparisons of the treatment strategies with three efficacy interim analyses. The original statistical plan was modified due to the temporary closure of arm C in 2002 because of cardiac safety concerns; this arm was resumed after extensive internal review by an independent cardiac safety monitoring committee.

At the time of the first interim combined analysis of the NSABP B-31 and NCCTG N9831 trials, the data monitoring committee overseeing trial N9831 requested an unplanned comparison of groups B and C. That comparison favored concurrent over sequential taxane treatment (HR for DFS

was 0.64, 95% CI 0.46–0.91; $P = 0.00114$), and the HR for OS was 0.74 (95% CI 0.43–1.26; $P = 0.2696$) [29]. Following this preliminary result, the NCCTG Independent Data Monitoring Committee (IDMC) recommended the release of all NCCTG N9831 study data from the preplanned second interim analysis, including the comparison of arm A and arm B and the comparison of arms B and C in 2009, despite low numbers of DFS events. At a 6-year median follow-up, the comparison of arm A and arm B revealed 5-year DFS rates of 71.8% and 80.1%, respectively [30]. DFS was significantly increased by the sequential addition of trastuzumab to paclitaxel treatment (log-rank $P = 0.001$; HR, 0.69; 95% CI, 0.57–0.85). Furthermore, there was an increase in DFS with concurrent trastuzumab and paclitaxel relative to sequential administration (arm C/arm B HR, 0.77; 99.9% CI, 0.53–1.11), but the p value (0.02) did not cross the prespecified O'Brien-Fleming boundary (0.00116) for the interim analysis. The 5-year DFS rates were 80.1% and 84.4% in arms B and C, respectively. There was no statistically significant difference in OS. It was recommended that the decision for concurrent administration of trastuzumab with taxanes should be based on the risk-benefit ratio, given the trend for superior efficacy profiles at the expense of slightly increased congestive heart failure events and asymptomatic LVEF drops in the concurrent arm C [31].

The BCIRG 006 Trial

The efficacy and safety of combining trastuzumab with a non-anthracycline-containing chemotherapy regimen were evaluated in an international, multicenter, open-label phase III trial, the Breast Cancer International Research Group 006 (BCIRG 006) trial. The BCIRG trial enrolled 3222 women with HER-2-positive, node-positive, or high-risk, node-negative disease [8]. Patients with negative lymph nodes (no evidence of involvement in a review of a minimum of six axillary nodes or a negative sentinel node biopsy) were eligible if they had at least one high-risk feature (i.e., age <35 years, tumor >2 cm, ER/PR-negative, or histological and/or nuclear tumor grade 2 or 3). The patients were randomized to four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks followed by four cycles of docetaxel (100 mg/m^2) every 3 weeks (ACT, control arm), the same chemotherapy with the concurrent administration of trastuzumab for 1 year beginning with the first dose of docetaxel (weekly during chemotherapy and then every 3 weeks) (ACTH arm) or a non-anthracycline-containing arm with docetaxel (75 mg/m^2) plus carboplatin (dosed at an area under the concentration × time curve (AUC) 6) every 3 weeks for six cycles concurrent with trastuzumab for 1 year (TCH arm). At a median follow-up of 65 months, the DFS rates were 75% for ACT, 84% for ACTH, and 81% for TCH; the OS rates were 87%, 92%, and 91%, respectively [8]. There were significant improvements in estimated DFS and OS at 5 years for both trastuzumab-containing arms (ACTH or TCH) compared to ACT. The BCIRG investigators concluded that the risk-benefit ratio favored the non-anthracycline TCH regimen over ACT plus trastuzumab even though there were no significant differences in DFS and OS between ACTH and TCH, and the study was not powered to detect equivalence between the ACTH and TCH arms. ACTH demonstrated a trend toward improved DFS and OS compared to TCH that did not reach statistical significance as well as small but significantly greater toxicity compared to TCH (the absolute difference in 5-year DFS between ACTH and TCH was 3%). There were more neutropenia, a significantly lower incidence of congestive heart failure (2% versus 0.4% versus 0.7% in the ACTH, TCH, and ACT arms, respectively), a reduction of mean LVEF (18.6% versus 9.4% versus 11.2% in the ACTH, TCH, and ACT arms, respectively), and less neuropathy, nail changes, and myalgia in the TCH arm compared to ACTH.

At a median follow-up of 10.3 years, a persistent significant DFS benefit was seen in both trastuzumab-containing arms compared to AC-T: AC-TH (HR = 0.70, 95% CI [0.60, 0.83]; $P < 0.001$)) and TCH (HR = 0.76, 95% CI [0.65, 0.90]; $P < 0.001$). At this final analysis, 10-year disease-free survival was 74.6% with AC-TH ($P < 0.0001$), 73.0% with TCH ($P = 0.0011$), and 67.9% with AC-T. An OS benefit was also observed in both AC-TH (HR = 0.64, 95% CI [0.52, 0.79]; $P < 0.001$)) and TCH (HR = 0.76, 95% CI [0.62, 0.93]; $P = 0.0081$). Regarding to cardiotoxicity, the AC-T control arm had 8 (0.8%) symptomatic CHF events, while TCH had significantly lower symptomatic CHF events compared to AC-TH: 21 (2.0%) for AC-TH versus 4 (0.4%) for TCH ($P = 0.0005$). The incidence of patients with a relative LVEF decline >10% was higher in the AC-TH compared to TCH regimens (206 versus 97; $P < 0.0001$) [32].

The BCIRG 006 study also evaluated topoisomerase II alpha (TOP2A) amplification as a predictor of responsiveness to anthracyclines. The TOP2A gene is amplified in 30–40% of patient cases of HER-2-positive breast cancer and has been associated with sensitivity to anthracycline-based chemotherapy in some trials [8, 33]. In 35% of HER-2-positive cancers in which TOP2A was amplified, each of the three treatment arms (ACT, ACTH, and TCH) yielded similar efficacy results, implying no incremental benefit from the addition of trastuzumab to anthracycline-based chemotherapy [34]. Among patients without TOP2A co-amplification, those treated with trastuzumab received more benefit. A similar analysis from NSABP B-31 determined that adding trastuzumab to anthracycline-based chemotherapy significantly reduced recurrence risk, regardless of TOP2A status [35]. Therefore, based on these mixed results, TOP2A should not presently be used to select the adjuvant

chemotherapy regimen or to decide whether to offer trastuzumab.

The data from the BCIRG 006 study suggest that both ACTH and TCH are superior to non-trastuzumab treatment options. The trade-offs between efficacy and adverse effects are important when selecting adjuvant chemotherapy. There appears to be a slightly higher risk of congestive heart failure (2% versus 1%) with ACTH versus TCH. Therefore, TCH represents an effective alternative option for women with contraindications to anthracyclines or patients with lower risk HER-2-positive tumors (small tumors or negative nodes). However, it seems reasonable to use ACTH in women with moderate- to high-risk HER-2-positive tumors without cardiac risk factors.

The FinHer Trial

FinHer was a small sub-study of a national trial conducted in Finland that randomized a total of 1010 women with node-positive and high-risk node-negative disease (defined as tumors greater than 2 cm in diameter and that are progesterone receptor-negative) to three cycles of docetaxel (initially at 100 mg/m^2 but later reduced to 80 mg/m^2 on day 1 every 21 days) or vinorelbine (25 mg/m^2 on days 1, 8, and 15 every 21 days). Both docetaxel and vinorelbine were followed by three cycles of 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2). FEC is administered on day 1 every 21 days [20]. The primary aim of the trial was to compare docetaxel with vinorelbine. The patients with HER-2-positive tumors (n = 232) were further randomized to receive either 9 weeks of docetaxel or vinorelbine with or without trastuzumab given concomitantly followed by three cycles of FEC. At a median follow-up of 3 years, there was a significant reduction in distant recurrence (HR 0.29; 95% CI, 0.13–0.64; P = 0.002), improved 3-year DFS (HR 0.42; 95% CI, 0.21–0.83; P = 0.01), and a trend toward improved OS (HR 0.41; 95% CI, 0.16–1.08; P = 0.07) favoring patients treated with trastuzumab [20]. This impressive efficacy despite the shorter duration of trastuzumab exposure was attributed to the up-front use of trastuzumab and the use of a synergistic chemotherapy regimen. The results at 62 months of median follow-up were published in 2009 and revealed a trend toward improved 5-year DFS (83% versus 73%: HR 0.65, 95% CI, 0.38–1.12) and OS (91% versus 82%: HR 0.55, 95% CI, 0.26–1.60) compared to chemotherapy alone that was not statistically significant [21]. Few patients experienced a decline in LVEF compared to those treated with CT alone (6.8% versus 10.5%), and there was only one symptomatic congestive heart failure in the trastuzumab group.

While the results from this small trial cannot be translated to standard practice until they are compared directly to 1-year therapy in sufficiently powered studies demonstrating non-inferiority, this trial generated intriguing hypotheses for further testing shorter durations of trastuzumab in the adjuvant setting.

The PACS 04 Trial

The PACS 04 study was a multicenter, randomized phase III French trial initially randomizing women with node-positive early breast cancer to two different chemotherapy regimens (six cycles of epirubicin/docetaxel or FEC) and further randomizing patients with HER-2-positive tumors to either trastuzumab (260 patients) for 1 year after completing chemotherapy or observation (268 patients) [24]. Patients who were randomly assigned to receive trastuzumab had a non-significant 14% reduction in the risk of relapse (HR 0.86; 95% CI, 0.61–1.22; P = 0.41), and this finding questioned the value of the sequential administration of trastuzumab. While these results contradict those reported by the herceptin adjuvant (HERA) trial, which also tested a sequential treatment strategy, it should be noted that the HERA trial randomly assigned significantly larger numbers of patients than the PACS 04 study with a larger statistical power. In PACS 04, random assignment occurred before the completion of chemotherapy in contrast to the random assignment after the completion of neoadjuvant or adjuvant chemotherapy in the HERA trial. Therefore, patients with early toxicity and/or relapse were not included in the intention-to-treat analysis in the HERA trial. Of note, only 65% of patients who were randomly assigned to receive trastuzumab fulfilled the cardiac eligibility criteria in the PACS 04 study. In addition, only 75% of the patients who received trastuzumab were able to complete 1 year of trastuzumab therapy. All these facts need to be considered when interpreting the results from the PACS 04 trial. However, although this study was unable to demonstrate a statistically significant advantage for the trastuzumab-containing arm in terms of its primary endpoint, the HR of 0.86 could still be considered favorable.

Optimal Tailoring of Adjuvant Trastuzumab Therapy

Timing of Trastuzumab in Relation to Radiotherapy

While preclinical studies suggest that concomitant trastuzumab and radiotherapy might be more effective, this issue has not been addressed prospectively in clinical trials [36]. Adjuvant radiotherapy was administered concurrently with trastuzumab in all trials except HERA and FinHer. The incidence of radiotherapy-associated adverse events in the

concurrent setting was analyzed in the NCCTG N9831 trial [37]. At a median follow-up of 3.7 years, no significant differences in skin reaction, pneumonitis, dyspnea, cough, esophageal dysphagia, or neutropenia were reported among the treatment arms. A significantly higher incidence of leukopenia was reported in the ACTH arm compared to ACT. Notably, radiotherapy with trastuzumab did not increase the frequency of cardiac events, although a longer follow-up is needed to evaluate the emergence of delayed toxic effects.

Optimal Duration and Timing of Trastuzumab Administration

The results from large randomized phase III trials of adjuvant trastuzumab currently support 1 year of adjuvant trastuzumab as the standard treatment duration. Although trastuzumab is generally well tolerated, it is a prolonged course of treatment, and a shorter duration would be of great benefit to patients by reducing hospital visits for intravenous administration and side effects. In addition, shorter treatment may also reduce the incidence of the major toxicity of concern, cardiac side effects. The cost of trastuzumab is another issue that health-care authorities must consider. Following the initial promising results from the FinHer study, the current recommended duration of 1 year was debated, and several trials were launched to test shorter durations of adjuvant trastuzumab. Table 9.2 describes the trials testing adjuvant trastuzumab duration.

Since 2005, 12 months of adjuvant trastuzumab has been the standard treatment for patients with HER-2-positive early breast cancer. However, there has been great interest in shortening the duration of therapy and reducing both the risk of adverse effects and the cost of therapy because trastuzumab is an expensive drug. Three randomized trials (The Hellenic, PHARE, and Persephone trials) compared 6–12 months of adjuvant trastuzumab and have reported their results.

The PHARE (Protocol for Herceptin as Adjuvant Therapy with Reduced Exposure) trial was designed to address the duration issue in the adjuvant setting. It was a multicenter study, phase III French trial randomizing patients with HER-2 positive early breast cancer who received at least four cycles of chemotherapy (almost 75% received an anthracycline-taxane), and at least 6 months of trastuzumab (initial loading dose 8 mg/kg; 6 mg/kg maintenance every 3 weeks) following breast-axillary surgery. These patients either discontinued trastuzumab at 6 months or continued to receive it for up to 12 months either concomitantly or sequentially to chemotherapy [22, 23]. The primary end point was DFS, and the trial was designed to detect a 2% absolute difference in recurrence and allow a non-inferiority hazard ratio margin of 1.15. After a median follow-up of 42.5 months, 6-month trastuzumab therapy was associated with a hazard ratio of 1.28 versus 12-month therapy (95% CI, 1.05–1.56, $P = 0.29$). Two-year DFS was 93.8% (95% CI, 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group. Subgroup analysis suggested that the overall results were driven by worse outcomes in patients with estrogen receptor-negative tumors who received sequential systemic therapy (HR 1.57). There was a significant difference in cardiac toxicity in favor of the shorter duration of trastuzumab (5.7% versus 1.9% in the 6- versus 12-month trastuzumab arms, respectively; $P < 0.0001$). This trial failed to demonstrate non-inferiority of 6-month trastuzumab compared to 12 months of therapy, and despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab remained the standard of care.

The Hellenic Oncology Research Group trial assigned 481 patients with node-positive or high-risk node-negative HER-2-positive breast cancer to sequential, dose-dense anthracycline and taxane-based chemotherapy [38]. Trastuzumab was started concomitantly with docetaxel and then continued either for 12 or 6 months. The primary end point of the study was to compare the 3-year DFS rates between the two arms of the study. Following a median follow-up of 4 years, the 3-year DFS rates were 95.7% and 93.3% for the 12- and 6-month groups, respectively. Thus, the Hellenic study failed to demonstrate non-inferiority for the 6-months of adjuvant trastuzumab versus the standard 12-month administration. There was no difference in the OS between the two groups ($P = 0.436$). Cardiac toxicity was observed only in two patients. The small number of patients, a large non-inferiority margin (absolute difference in 3-year DFS of 8%), and slow accrual were the main limitations of the study.

The Persephone study is the third phase III randomized controlled trial with a non-inferiority design, evaluating whether treatment with trastuzumab for 6 months is equivalent to the standard 12-month duration in patients with HER-2-positive early breast cancer [39]. Patients were stratified based on estrogen receptor status, chemotherapy type, chemotherapy timing (adjuvant or neoadjuvant), and trastuzumab timing (concurrent or sequential). Eligible patients were then randomized to receive either 6-month or 12-month trastuzumab administered every 3 weeks. In the Persephone

Table 9.2 Adjuvant trastuzumab trials testing duration of therapy

Duration	Trial	Target	Endpoint
1 versus 2 years	*HERA*	*4482*	*DFS*
6 versus 12 months	Persephone	4000	DFS
6 versus 12 months	*PHARE*	*3400*	*DFS*
6 versus 12 months	HORG	478	3 years DFS
9 weeks versus 12 months	Short-HER	2500	DFS, OS
9 weeks versus 12 months	SOLD	3000	DFS

trial, 4088 women from the United Kingdom were randomly assigned to receive 6 or 12 months of trastuzumab. Forty-seven percent of patients received concurrent chemotherapy and 53% received sequential chemotherapy. The chemotherapy was either anthracycline-based, taxane-based, both anthracycline- and taxane-based, or cyclophosphamide/methotrexate/fluorouracil. The primary end point, DFS, at 4 years was 89.4% in the 6-month arm and 89.8% in the 12-month arm, representing an absolute difference of 0.4%. Non-inferiority was defined as no worse than 3% below the 4-year DFS of the 12-month arm. Non-inferiority of the shorter duration was shown with 265 and 247 events in the 6-month and 12-month arms, respectively (HR 1.07, 95% CI [0.93–1.24]; non-inferiority, $P = 0.01$). Overall survival result was similar, 93.8% and 94.8% in the 6-month and 12-month arms, respectively (non-inferiority, $P = 0.0006$). Cardiac function recovered in both groups of patients, but more quickly among those who received shorter duration trastuzumab. In the 12-month arm, 8% stopped treatment because of cardiotoxicity compared with 4% of patients in the 6-month arm.

Among previous non-inferiority trials comparing 6 and 12 months of adjuvant trastuzumab, Persephone is the only one that claimed non-inferiority according to its statistical plan. However, the patient population is less representative of patients today because sequential trastuzumab is much less commonly used than concurrent trastuzumab. The acceptance of 2–3% reduction in DFS with 6 months of trastuzumab therapy by patients is another issue in the routine daily practice.

Two phase III trials, the Synergism or Long Duration (SOLD) and the Short-HER study, compared 9-week trastuzumab administration to 1 year of trastuzumab [40]. In SOLD study, 2176 patients with HER-2-positive early breast cancer were randomly assigned to the 9-week trastuzumab arm or the 12-month trastuzumab arm. Patients in both arms received three cycles of docetaxel (80 or 100 mg/m^2) and trastuzumab three times, followed by three cycles of FEC (600/75/600 sq. m) every 3 weeks. Patients with estrogen receptor–positive cancer received appropriate endocrine treatment and radiation therapy per guidelines. The target population consists of patients with either node-negative or node-positive breast cancer. The primary objective was DFS. SOLD was a non-inferiority trial. In the 12-month arm, the disease-free survival rate was 90.5%, compared with 88% in the 9-week arm after a median follow-up of 5.2 years. There was no substantial difference in distant disease–free survival and overall survival between the two arms: 5-year distant disease–free survival was 93.2% in the 9-week arm and 94.2% in the 12-month arm; 5-year overall survival was 94.7% in the 9-week arm and 95.9% in the 12-month arm. Cardiac failure occurred in 3% and 2% of patients in the 12-month and 9-week arms, respectively. Patients in the 9-week arm had significantly higher cardiac left-ventricular ejection fractions than patients in the 12-month arm, but the absolute differences were small, and ejection fractions mostly returned to the baseline level within 3 years after the date of randomization. Of note, this study had lower statistical power than planned due to a number of factors including not being able to reach the planned number of disease-free survival events within the expected time period.

The Short-HER study randomized 1253 patients with HER-2-positive, node-positive, or high-risk node-negative disease to 1 year of trastuzumab plus chemotherapy or 9 weeks of trastuzumab and chemotherapy [41]. The number of chemotherapy cycles and the sequence of taxanes and anthracyclines differ between the arms as well as the duration of trastuzumab. The 5-year DFS did not achieve non-inferiority in the frequentist analysis (87.5% versus 85.4% in the long and short groups, respectively, HR 1.15, 90% CI 0.91–1.46), as the upper limit of the confidence interval crossed the non-inferiority margin. However, a subset analysis found that patients with stage III disease with multiple positive lymph nodes (representing about 15% of the entire study population) appeared to have greater benefit from the longer duration of trastuzumab (HR 2.30, 90% CI 1.35–3.94; $P < 0.001$ and HR 2.25, 90% CI 1.33–3.83; $P < 0.001$, respectively). The 5-year OS was identical between the two arms (95.1% versus 95.0% in the long and short groups; HR 1.06, 90% CI 0.73–1.55, respectively). There were substantially more cardiac events in the long group compared with the short group (HR 0.32, 95% CI 0.21–0.50; $P < 0.0001$).

As mentioned previously, HERA is the only trial that has tested a longer duration of trastuzumab—2 years versus 1 year—and failed to demonstrate the superiority of 2 years of trastuzumab compared to 1 year of trastuzumab [15].

Regarding the timing of trastuzumab administration, the data from adjuvant trastuzumab trials have clearly demonstrated a benefit of combining trastuzumab with chemotherapy in the adjuvant setting of HER-2/neu-positive early breast cancer, whether given concomitantly with chemotherapy (joint analysis and BCIRG 006) or sequentially after completing chemotherapy (HERA and arm B of N9831) [6–8]. In addition, the concurrent administration of trastuzumab with an anthracycline-free regimen was also effective in the BCIRG 006 study [8]. Collectively, the magnitude of the benefit was greater in the concurrent regimens than in the sequential ones. Notably, the PACS 04 trial did not demonstrate a statistically significant improvement in DFS or OS, although it was a relatively small trial ($n = 528$) [24]. In the NCCTG N9831 study, the comparison of the sequential versus the concomitant arm tended to favor the latter but did not reach statistical significance [31].

Trastuzumab for Small HER-2-Positive Tumors

Adjuvant trastuzumab is an effective therapy regardless of tumor size and nodal status [9–11]. However, the magnitude of benefit in low-risk tumors, i.e., node-negative small tumors, has been questioned. Data from retrospective studies have revealed that small HER-2-positive tumors (T1 a, b) have significantly higher recurrence rates than HER-2-negative tumors [42]. There was a clear benefit of trastuzumab and chemotherapy in the T1 a, b subgroup of patients in the BCIRG data set [43]. The data from five adjuvant trastuzumab trials, HERA, N9831, NSABP B-31, PACS04, and FinHer, were combined to identify a group of patients who could be excluded from trials evaluating additional therapy to avoid unnecessary side effects. This meta-analysis included patients with tumors up to 2 cm and analyzed hormone receptor-positive and receptor-negative cohorts separately. The primary objectives were DFS and OS. Patients with hormone receptor-positive disease with tumors up to 2 cm and involvement of 0–1 axillary lymph nodes had favorable outcomes (5-year DFS of 91% and OS of 97%) with standard chemotherapy plus trastuzumab therapy. These data suggest that patients with small HER-2-positive tumors with limited nodal involvement and hormone receptor-positive disease could receive less chemotherapy.

A phase II prospective trial investigated the role of weekly paclitaxel given concurrently with weekly trastuzumab for 12 weeks followed by continuation of trastuzumab every 3 weeks for 1 year in 400 patients with node-negative (one lymph node micrometastasis was allowed in the presence of a negative axillary dissection) HER-2-positive tumors less than or equal to 3 cm who had an LVEF ≥50% [44]. The primary end point was DFS. Initial results with a median follow-up of 3.6 years were promising; 3-year DFS was 98.7% with few severe events. With a median follow-up of 6.5 years, a total of 23 DFS events were observed: 7-year DFS was 93.3% (95% CI, 90.4–96.2); 7-year DFS was 94.6% (95% CI, 91.8–97.5) for HR+ patients and 90.7% (95% CI, 84.6–97.2) for HR patients [45]. These data suggest that the paclitaxel and trastuzumab combination is a reasonable regimen for patients with stage I HER-2-positive breast cancer that is associated with few recurrences; only four distant recurrences were observed with longer follow-up. Thus, the standard regimens from pivotal trials could be reserved for patients with high-risk features.

Adjuvant Use of the Tyrosine Kinase Inhibitor Lapatinib

Cost is an important issue for patients with HER-2-positive tumors worldwide, and therefore adjuvant trastuzumab may not be available to some women. The TEACH (Tykerb Evaluation After Chemotherapy) study is a randomized multicenter phase III trial designed to evaluate the role of lapatinib in women who previously received adjuvant chemotherapy but not trastuzumab [46]. Patients were assigned (1:1) to receive daily lapatinib (1500 mg) or daily placebo for 12 months and stratified by time since diagnosis, lymph node involvement at diagnosis, and the hormone receptor status of the tumor. The primary end point was DFS. After a median follow-up of 4 years, there was no significant difference in DFS between groups in the intention-to-treat analysis. A marginal DFS benefit from adjuvant lapatinib appeared only in the subgroup of patients who had HER-2-positive disease confirmed by central review (79% of the randomized women). This trial indicated that lapatinib might be an option for women with HER-2-positive breast cancer who did not or could not receive adjuvant trastuzumab. As expected, there were higher incidences of grade 3–4 diarrhea, rash, and hepatobiliary disorders in the lapatinib arm compared to those in the placebo arm.

Escalated Anti-HER-2 Therapy in the Adjuvant Setting

The landscape of adjuvant anti-HER-2 therapy was further shaped by the results of second-generation anti-Her-2 studies testing either dual blockade (ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) and APHINITY) or extension of anti-HER-2 therapy (exteNET) in the adjuvant setting. A recent ASCO clinical practice guideline has reviewed data regarding adjuvant use of pertuzumab and neratinib and provided new recommendations [47]. Based on the available evidence, one-year adjuvant pertuzumab can be added to trastuzumab-based chemotherapy in patients with high-risk, early-stage, HER-2-positive breast cancer. Extended adjuvant therapy with neratinib might be used in patients with HER-2 positive early breast cancer who completed 1 year of adjuvant trastuzumab. Importantly, patients receiving neratinib require diarrhea prophylaxis.

Extended Anti-HER-2 Therapy with Neratinib

Neratinib is an irreversible pan-HER tyrosine kinase inhibitor that shows promising activity in HER-2-positive metastatic breast cancer. ExteNET was a double-blind, placebo-controlled, phase III trial randomizing 2840 women with early HER-2-positive breast cancer who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab to either neratinib (n = 1420) or placebo continuously for 1 year. The primary end point was invasive disease-free survival at 2 years after randomization. The 2-year invasive disease-free survival rate was 93.9% (95% CI, 92.4–952) in

the neratinib group and 91.6% in the placebo group [48]. This significant improvement was confirmed at a median follow-up of 5.2 years. Patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (stratified HR 0.73, 95% CI 0.57–0.92, $P = 0.0083$). The 5-year invasive disease-free survival was 90.2% with neratinib versus 87.7% with placebo [49]. Interestingly, the benefit was confined to patients with hormone receptor-positive tumors (hazard ratio of 0.51 versus 0.93). The incidence of grade 3 diarrhea was nearly 40% in the neratinib arm, but prophylactic strategies have shown substantial improvement of this complication. The FDA approved neratinib for the extended adjuvant treatment of patients with early-stage, HER-2-positive breast cancer following postoperative trastuzumab on July 17, 2017.

Dual Anti-HER-2 Blockade: ALTTO and APHINITY Studies

The ALTTO study randomized 8381 patients into four arms: control group (trastuzumab alone [T]); lapatinib-alone group ([L], closed early); combination group (L + T); and a sequential arm (T → L). Despite promising results from the neo-ALTTO study, the adjuvant study was disappointing. After 5 years of follow-up, with treatment of lapatinib plus trastuzumab, either sequentially or concurrently, the 6-year DFS rates were 85% versus 82% (L + T versus T) and 84% versus 82% (T → L versus T). The 6-year OS rates were 93%, 92%, and 91% for L + T, T → L, and T, respectively [50].

The pertuzumab and trastuzumab combination provided higher pathologic complete response rates in the neoadjuvant setting and longer survival outcomes in the metastatic setting compared to those in the trastuzumab-based treatment strategy. Based on these data, the APHINITY study planned to investigate this combination in the early breast cancer setting [51]. The APHINITY study randomized patients with node-positive or high-risk node-negative HER-2-positive, operable breast cancer to either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. Overall, 63% of patients had cancer with node-positive disease, and 36% had hormone receptor-negative disease. The primary end point was invasive disease-free survival.

At a median follow-up of nearly 4 years, 7.1% and 8.7% of patients developed invasive recurrence in the pertuzumab and placebo groups, respectively (hazard ratio, 0.81; 95% confidence interval (CI), 0.66–1.00; $P = 0.045$). The estimates of the 3-year rates of invasive disease-free survival were 94.1% in the pertuzumab group and 93.2% in the placebo group. The benefit from pertuzumab was slightly greater among patients with node-positive disease; the 3-year invasive disease-free survival rate was 92% with pertuzumab versus 90.2% with placebo (hazard ratio for an invasive-disease event, 0.77; 95% CI, 0.62–0.96; $P = 0.02$). The rates of serious side effects were low and similar in both groups. Heart failure or heart-related death occurred in 0.7% of patients in the pertuzumab group and in 0.3% of patients in the placebo group. Severe diarrhea was more common with pertuzumab and was observed in 9.8% of patients compared to 3.7% in the placebo group. The APHINITY study showed a modest absolute benefit of the addition of pertuzumab to trastuzumab in early-stage HER-2-positive breast cancer. Therefore, currently, pertuzumab should be reserved primarily for women with the highest risk, such as those with node-positive and hormone receptor-negative breast cancer.

Anti-HER-2 Therapy in Patients with Tumors with Low HER-2 Expression: The NSABP B-47 Study

A potential benefit of trastuzumab in low-HER-2 tumors was noted when the reexamination of samples from the NSABP B-31 trial revealed that 9.7% of them were indeed HER-2-negative by central testing (i.e., negative on FISH or IHC <3+); importantly, there was an improvement in 7-year disease-free survival with trastuzumab in these patients with HER-2-negative tumors (7). The NSABP B-47 study was designed to test the possibility that some HER-2-negative patients might benefit from anti-HER-2 therapy [52]. The NSABP B-47 study enrolled 3270 early breast cancer patients with resected node-positive or high-risk, node-negative disease that was IHC 1+, IHC 2+, and/or FISH-negative (ratio < 2.0). The patients were randomized to receive standard adjuvant chemotherapy with or without 1 year of trastuzumab. The primary end point of the study was invasive disease-free survival. After a median follow-up of 46.1 months, the 5-year invasive disease-free survival rate was 89.6% for the trastuzumab arm and 89.2% for the control arm (hazard ratio (HR) = 0.98, $P = 0.90$), and the overall survival rate was 94.8% and 96.2%, respectively (HR = 1.33, $P = 0.14$). Similar findings were observed across subgroups of HER-2 IHC level, extent of lymph node involvement, and hormone receptor status. This study showed that there is no role for trastuzumab in tumors that do not meet the guideline descriptions for HER-2 positivity.

Conclusion and Future Perspectives

Trastuzumab is a rationally designed, molecularly targeted therapy for a specific subgroup of breast cancer, the HER-2-positive group. Consistent evidence of clinical benefit of trastuzumab with tolerable toxicity has been obtained in large multicenter randomized phase III trials and meta-analyses [6–11]. Trastuzumab is the first successful example of the translation of an improved understanding of the molecular

basis of breast cancer to a rational treatment strategy with greater efficacy and reduced toxicity. Thus, trastuzumab represents a milestone in medical oncology as a practice-changing breast cancer therapy. The adoption of trastuzumab into routine clinical practice in the adjuvant setting began with the announcement of the first results from the adjuvant clinical trials in 2005. Some controversial issues regarding the use of trastuzumab, including the timing of administration, the duration of therapy, and the decision to combine with chemotherapy, have been partly resolved by longer follow-up. However, other questions, such as whether trastuzumab can be used with less toxic chemotherapy regimens or with endocrine therapy in small tumors <1 cm, have not been addressed by large phase III trials thus far. The adjuvant use of trastuzumab has been implemented in well-known international guidelines, and it can be considered globally safe in terms of cardiac toxicity due to its reversible nature, but the cost for 1 year of therapy remains an obstacle.

Advances in molecular biology continue, and the efforts to develop and test new anti-HER-2 strategies complement this progress. The translational/clinical search for biomarkers predicting benefit from trastuzumab has not yet identified any markers other than HER-2 expression/amplification despite numerous publications in the literature. Immune system effectors have recently emerged as a new therapeutic approach in HER-2-positive breast cancer even though breast cancer has not been traditionally considered an immunogenic tumor. Indeed, the presence of tumor-infiltrating lymphocytes in breast cancer samples and their association with prognosis have been reported for many years [53]. The retrospective analysis of several trials suggests that the role of the immune system requires further study in specific subgroups of breast cancer, such as triple-negative and HER-2-positive breast cancer [54]. Each 10% increase in stromal lymphocytic infiltration was significantly associated with decreased distant recurrence in patients randomized to the trastuzumab arm in the FinHer trial [55]. Thus, patients with HER-2-positive tumors might benefit from a combination of immunomodulatory agents and anti-HER-2 treatment strategies in the future.

The standard duration of adjuvant therapy is 1 year with intravenous administration. Efforts to develop a more practical, convenient form of administration to reduce demand on health-care resources resulted in the development of a subcutaneous form of trastuzumab. The Hannah trial demonstrated that the pharmacokinetic profile and efficacy of subcutaneous trastuzumab were non-inferior to intravenous administration, with a similar safety profile in the locally advanced breast cancer setting [56]. The PrefHer study included women with early-stage HER-2-positive breast cancer and randomized them to receive four cycles of 600 mg fixed-dose subcutaneous adjuvant trastuzumab followed by four cycles of intravenous trastuzumab or these treatments in reverse order [57]. The primary end point was the proportion of patients indicating an overall preference for subcutaneous or intravenous trastuzumab as assessed by patient interviews in the evaluable intention-to-treat population. Recently reported results indicated that women with HER-2-positive early breast cancer favored subcutaneous over intravenous administration of trastuzumab.

It was recently reported that at a median follow-up of 38 months, there was no DFS benefit from the addition of bevacizumab to chemotherapy plus trastuzumab in a large phase III trial, BETH (bevacizumab and trastuzumab adjuvant therapy in HER-2-positive breast cancer), which enrolled 3509 women with HER-2-positive, node-positive, or high-risk node-negative breast cancer [58].

NSABP B-43 is exploring the role of trastuzumab in ductal carcinoma in situ, and the KAITLIN study is evaluating the role of T-DM1 plus pertuzumab compared to trastuzumab plus pertuzumab in the adjuvant setting. The ATEMPT trial randomized patients either to T-DM1 or paclitaxel in combination with trastuzumab, followed by 1 year of trastuzumab. KATHERINE study is evaluating the use of adjuvant T-DM1 versus trastuzumab in patients who did not achieve a pathologic complete response after neoadjuvant therapy. ATOP study is testing T-DM1 for older patients with stage I–III HER-2-positive breast cancer who decline or are not candidates for standard chemotherapy.

Cost-effectiveness models have justified the use of adjuvant trastuzumab in most countries [59–62]. However, adjuvant trastuzumab therapy remains unaffordable in some countries, and this issue will worsen as the number of other expensive anti-HER-2 therapies increases. This economic dimension will be one of the most important challenges for the future management of HER-2-positive early breast cancer, particularly in developing countries.

The evolution in understanding HER-2-positive breast cancer biology and anti-HER-2 therapies raises future challenges for oncologists. The dissection of heterogeneity within HER-2-positive tumors for developing personalized treatment strategies and identification of specific biomarkers of resistance and biomarkers for improving patient selection are necessary to use new, expensive, and escalated anti-HER-2 strategies only in patients who could benefit from these interventions.

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Post-Mastectomy Adjuvant Radiotherapy (PMRT)

10

Ilknur Bilkay Gorken

Introduction

Post-mastectomy adjuvant radiotherapy (PMRT) is the most controversial topic in radiation oncology. The risk of locoregional recurrence (LRR) after mastectomy is 3–46%, depending on the stage of the disease and prognostic factors [1–7].

In the AJCC 8th edition, patients are clinically staged using the traditional TNM anatomic information modified by the expression of ER, PR, HER-2 Neu and graded to create (*creating*) a Clinical Prognostic Stage Group. Nowadays, this Prognostic Stage Group should be used for all patients whose tumors are evaluated for expression of these markers. In addition, the latest version of AJCC has information of neoadjuvant chemotherapy response and the 21-gene assay Oncotype DX® score. The panel felt strongly supported by literature that this Prognostic Stage Group is the most accurate predictor of outcome [8].

Two different risk groups can be classified according to the radiotherapy (RT) indication:

1. Early-stage breast cancer
2. Locally advanced breast cancer

Early-Stage Breast Cancer

Cases that are assessed as early stage in clinical staging can also be classified into high-risk and low-risk groups depending on the patient and tumor characteristics. We can separate patients into three different groups based on axillary status and the number of involved lymph nodes:

(a) No axillary lymph nodes, tumor >3 cm (T2–T3N0 (stage IIB) or patients with T1–T2 tumor and high-risk features according to Clinical Prognostic Stage Group
(b) One to three positive axillary lymph nodes
(c) ≥4 positive axillary lymph nodes (N2 disease)

In cases with ≥4 positive axillary lymph nodes, the LRRs are 24% and 46%, respectively [2–4, 7]. In these cases, PMRT decreases the local recurrence risk by 14.8% [21]. Patients with one to three positive axillary lymph nodes constitute a gray zone.

T1–T2N0 (Stages I–IIA)

Patients with early stage T1–T2N0 breast cancer with adverse prognostic factors, such as a triple-negative histology, have a high risk for an early relapse and disease progression [10, 11]. Patients with early-stage triple-negative breast cancer (TNBC) can be treated with surgery only, but some microscopic tumor foci might remain in locoregional tissue (e.g., the chest wall or regional lymph nodes), potentially leading to recurrence and distant metastasis [12]. Women with TNBC do not benefit from endocrine therapy or targeted agents and systemic chemotherapy [13].

International consensus and guidelines do not recommend the routine use of PMRT for patients with T1–T2N0–1M0 disease, and there are conflicting data with respect to this inherently heterogeneous subtype. In a retrospective study concluded by Chen et al., patients with clinical T2–T3 tumors and those with clinical N+ disease who underwent PMRT had significantly lower LRR than patients with same pathological features who did not ($p > 0.05$). With respect to pathological features, PMRT reduced LRR in patients with T2 disease and in those with N0 or N2 disease ($p < 0.05$). On multivariate analysis of LRR, PMRT was the most significant factor for LRR, with an HR of 3.97 (95% CI, 1.7–9.3; $p = 0.001$). Fifty-two

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patients in the cohort (50%) developed distant recurrence (DR), and the 5-year cumulative DR rate was 49.6%. Despite their more adverse prognostic features, patients with PMRT had a lower 5-year cumulative DR rate than those who did not receive PMRT (45% vs. 69.1%, respectively, $p = 0.034$) [14]. In another study by Kong and Hong, it was reported that PMRT might be beneficial in a subgroup analysis of T1–T2N1 patients with the TNBC subtype [15]. Gabos et al. reported that PMRT is important in decreasing LRR after modified radical mastectomy, particularly in women with T1–T2N0 TNBC subtype [16]. In a phase III trial from China that included 681 patients with triple-negative stage I–II breast cancer, all patients were treated with mastectomy plus chemotherapy and randomly assigned to receive PMRT or no radiation. Five-year relapse-free survival (RFS) and OS were significantly higher with the addition of PMRT compared to those with no radiation [17]. Jagsi et al. and Tourong et al. also concluded that PMRT decreased the locoregional recurrence rate after MRM in patients with stage I–II TNBC [18, 19]. In an analysis by Abdulkarim et al., who stratified their patients according to locoregional treatment (breast-conserving therapy, MRM without PMRT, and MRM with PMRT), the highest LRR rates were detected in patients who underwent MRM without PMRT. MRM without PMRT was found to be the only independent adverse prognostic factor for increased local recurrence. The results of Abdulkarim et al.'s study were similar to those of Chen and indicated that T and N stage may be insufficient for predicting LRR risk in all patients with TNBC (compared to other molecular subtypes) when considering the benefit of adjuvant radiation therapy after mastectomy. They reported that TNBC might be a powerful prognostic factor when considering the benefit of PMRT in patients with early-stage BC treated with neoadjuvant chemotherapy (NAC) and MRM [20]. Interestingly, Selz et al. and Truong et al., who analyzed molecular subtypes of node-negative breast cancer treated with mastectomy, did not find an association of the triple-negative group with an increased risk of local recurrence [19, 21]. It is notable that these studies included a small volume of TNBC patients, with only 59 and 172 cases, respectively. These results are distinct from those obtained in the randomized controlled study mentioned above.

To identify the best early-stage patients who might benefit from PMRT, additional multicenter studies using contemporary data with modern practices are needed to investigate risk factors for LRR after mastectomy without radiotherapy in T1–T2 breast cancer. In the meantime, we recommend consideration of the risks and potential benefits of adjuvant PMRT in selected women with multiple high-risk factors, such as young age, LVI, positive margin, high-grade, and triple-negative histology.

T2–T3N0 (Stage IIB)

As defined in the American Joint Commission on Cancer (AJCC) Staging Manual, sixth edition, stage IIB breast carcinoma is defined by the following: tumor >5 cm in greatest dimension without direct extension to the chest wall or skin (pT3), no regional lymph node metastasis (N0), and no distant metastasis (M0) [22]. PMRT has been shown to improve locoregional control and survival in T3 and T4 primary breast cancer patients with positive lymph nodes [2–4, 22]. However, axillary-negative patients were not analyzed as a different group in these prospective randomized trials. The British Columbia trial excluded lymph node-negative patients, and we could not define all node-negative patients in the Danish trials as T3. There was no detailed information regarding the pathological involvement of the pectoralis muscle, fascia, and skin in these trials. Therefore, it is very difficult to extract specific information about T2–T3 patients with negative axilla. The median number of axillary lymph nodes evaluated in these trials was 7, less than the number of lymph nodes reported in most mastectomy series. These trials were criticized for possible under-staging and subtherapeutic surgical staging of the axilla.

Tagihan GA et al. reported results from five National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized trials [23]. Of 8878 breast cancer patients enrolled in the NSABP B-13, B-14, B-20, and B-23 node-negative trials, 313 patients had tumors 5 cm or larger in their greatest dimension at pathology report and underwent mastectomy. Of the patients, 34.2% received adjuvant chemotherapy, 21.1% received tamoxifen, and 19.2% received adjuvant chemotherapy plus tamoxifen. Another 25.5% did not receive any systemic therapy. Cumulative incidences for isolated LRR as a first event for patients with tumors of 5 cm or greater than 5 cm were 7.0% and 7.2%, respectively ($p = 0.2$). In patients with stage IIB breast cancer with LN-negative tumors ≥5 cm treated by mastectomy with or without adjuvant systemic therapy and no PMRT, LRR as a first event remained low. The investigator of this trial concluded that PMRT should not be routinely used for these patients.

Using the Surveillance, Epidemiology, and End Results (SEER) database, Yu et al. studied cohorts of pT3N0 tumors treated with mastectomy, of which one-third of patients received PMRT [6]. Women with T3N0 breast disease who met the analysis criteria represented <0.3% of all breast cancer patients in the SEER database. Of the 1844 women analyzed for cause-specific survival (CSS), there was no statistically significant difference in CSS between patients who did or did not receive PMRT. Age <50 years and a grade I tumor were statistically significant independent predictors of increased CSS in multivariate analysis. In this trial, PMRT was associated with increased overall survival (OS). For the whole patient population, the actuarial 10-year OS rate was

70.7% for the PMRT group versus 58.4% for the group without PMRT (HR, 0.65; 95% CI, 0.55–0.80; $p < 0.001$). Age <50 years, grade I tumor, and the number of lymph nodes dissected were associated with increased OS [6]. In a retrospective study of 19,846 nonmetastatic breast cancer patients, Goulart et al. reported the data for 100 node-negative patients with tumors ≥5 cm (0.5%) [24]. Of these 100 patients, 44 (44%) received adjuvant PMRT. The cumulative 10-year LRR was 2.3% in the PMRT group vs. 8.9% in the group that did not receive PMRT ($p = 0.2$). The 10-year breast cancer-specific survival rate was the same between the two groups. In the group that did not receive PMRT, patients with grade III histologic features and those who had not received hormonal therapy had the highest LRRs, 17% (5 of 29) and 15% (5 of 34), respectively. The investigators of this study recommended that PMRT be considered for grade III histological features and for patients not undergoing hormonal therapy.

The South Sweden Breast Cancer Group conducted a randomized trial in which 33% of the 367 patients were lymph node negative. This three-armed phase III randomized trial compared RT with and without chemotherapy (oral cyclophosphamide for 1 year) and chemotherapy alone. The lymph nodes of the supraclavicular and infraclavicular fossae, the axilla, the chest wall, and the ipsilateral parasternal lymph nodes were included as RT target volumes in this trial. Twenty years of follow-up demonstrated that RT reduced the risk of LRR in chemotherapy-treated patients by 75% (13.9% vs. 3.5%). The risk reduction was highly significant in both N0 and N+ patients. No effect on mortality was observed with 20 years of follow-up [25].

In a combined analysis, Floyd et al. reported that the 5-year actuarial cumulative rate of LRR in 70 node-negative patients with tumors ≥5 cm was 7.6%; four of the five failures occurred in the chest wall, and one occurred in the axilla. In a multivariate analysis, lymphatic vessel invasion (LVI) was identified as an independent prognostic factor for LRR, disease-free survival (DFS), and OS [26].

For node-negative patients with tumors ≥5 cm (T3N0), there is no consensus to justify the routine use of PMRT. Unless there is a combination of adverse prognostic factors such as high-grade, young age, positive surgical margin, and infiltration of pectoral fascia and triple-negative histology, the risk of LRR is low. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis does not include the T3N0 group in LRR rates with and without radiation [9]. The last meta-analysis of the same group was reported in March 2014. A group of 1594 women (20%) with pathologically node-negative disease were included in this analysis. Of the 1594 women with node-negative disease, 700 (44%) had axillary dissection. In this group, the locoregional recurrence rate was only 1.4% for women without RT, suggesting that RT has no effect on locoregional recurrence. However, for the 870 women who had only axillary sampling and node-negative disease, the locoregional recurrence rate was 16.3% without RT, and RT reduced LRR ($2p < 0.00001$) and overall recurrence ($2p = 0.0003$), but had no effect on breast cancer mortality ($2p > 0.1$) [27]. In the National Comprehensive Cancer Network (NCCN) (2013–2018) and St. Gallen Breast Cancer Conference 2013, panelists strongly recommended PMRT to the chest wall and regional lymphatic area for patients with negative axillary lymph nodes and when the tumor was >5 cm with positive deep and radial margins [28–31]. However, the panelists concluded that PMRT should not be the standard for patients with adverse pathology (such as HER-2, grade, LVI), regardless of the presence of nodes. In the NCCN guidelines, PMRT was also recommended for patients with negative axillary nodes, patients with tumors ≤5 cm, or patients with margins less than 1 mm.

One to Three Positive Lymph Nodes (pN1) Breast Cancer

Cuzick et al. published a meta-analysis of the results of the effects of PMRT in 1987 [5]. In this study, the survival rates were lower in the PMRT group than the nonirradiated group. In the PMRT group, non-breast cancer-related death rates were high. However, the studies included in this meta-analysis were older, and most of the patients were treated with Co^{60} and orthovoltage devices. The death rate due to cardiac events was high because of the RT techniques. After this paper was released, the use of PMRT dramatically decreased, and the importance of cardiac doses was emphasized.

In 1997, the Danish 82b (premenopausal) and 82c (postmenopausal) trials were published [2, 3]. In these trials, PMRT not only decreased the LRR but also increased OS significantly in high-risk patients in spite of systemic therapy. This effect was particularly prominent in patients with ≥4 axillary lymph nodes. The Danish Breast Cancer Cooperative Group (DBCG) 82b trial randomized 1708 premenopausal women with stage II or III breast cancer to mastectomy followed by nine cycles of chemotherapy or to mastectomy, radiation, and eight cycles of chemotherapy [2]. Irradiation was administered as 50 Gy in 25 fractions to the chest wall and peripheral lymphatics, including the internal mammary lymph nodes. The results demonstrated that patients in the radiation arm had lower 10-year LRR (9% vs. 32%, $p < 0.001$) and an improved 10-year overall survival rate (54% vs. 45%, $p < 0.001$). The British Columbia trial was reported at the same time. In this trial, 318 premenopausal women with high-risk breast cancer were randomized to mastectomy and chemotherapy or chemotherapy plus RT. Patients in the radiation arm exhibited a reduction in

10-year LRR, as in the DBCCG trials. The Danish 82c trial studied the effect of PMRT in high-risk postmenopausal women using a similar design [4]. This trial randomized 1300 patients to mastectomy and tamoxifen or to mastectomy and tamoxifen plus irradiation. In this study, similar to the premenopausal patient group, despite systemic therapy in the RT arm, a significant reduction in LRR (10-year LRR rates of 8% vs. 35%, $p < 0.001$) and an increase in 10-year overall survival (64% vs. 54%, $p = 0.07$) were observed.

These three prospective randomized studies reveal that PMRT reduces the LRR significantly, leading to an increase in OS. In these trials, reducing the rate of LRR from 30–35% to 10% led to a 10% increase in survival rates. The irradiation technique in the DBCG trials minimized radiation exposure to the heart. In these trials, the nodal regions were treated with anterior photon fields, except the internal mammary nodes. The internal mammary nodes were treated with an anterior electron field, and custom blocks were used to shield the heart and lungs. At a median 10-year follow-up, similar proportions in each group died of ischemic heart disease (0.8% in the RT arms vs. 0.9% in the arm without RT). There was no difference in the rate of ischemic heart disease between left-sided and right-sided RT patients (0.7% vs. 0.9%, respectively). Similar rates were observed for death from acute myocardial infarction (MI). When data from patients with local or distant cancer recurrence were censored, deaths from ischemic heart disease were associated with left-sided RT (0.7% vs. 0.3%, HR 2.18) [19]. Decreasing cardiac doses resulted in a decrease in non-breast cancer-related death rates and a significant increase in survival rates.

Since 1995, EBCTCG has gathered all data about breast cancer every 5 years and studied the effect of adjuvant therapies. In the meta-analyses by this group in 2000 and 2005, the effect of RT was studied. In the meta-analysis of 2000, a reduction of approximately two-thirds in local recurrence was observed in all trials during the first decades. The effect was independent of the type of patient or type of RT [33]. Breast cancer mortality was reduced ($2p = 0.0001$), but other mortality, particularly vascular mortality, was increased ($2p = 0.0003$); the overall 20-year survival was 37.1% with RT versus 35.9% in the control arm ($2p = 0.06$) [33].

Van de Steene et al. reanalyzed 36 prospective randomized trials that were included in the EBCTCG-1995 meta-analysis according to objective criteria [34]. In their analysis, a significant survival benefit for the RT arm was observed in trials that were recent (designed after 1980) ($2p < 0.05$), large trials (the number of patients accrued in the trial) ($2p < 0.03$), trials that used standard fractionation ($2p < 0.02$), or trials that had favorable crude survival benefit ($2p < 0.0$). Parameter-effect relationships were obtained for these four parameters.

In a meta-analysis by Whelan et al., the effect of PMRT was analyzed in patients who were treated by mastectomy and systemic therapy in 18 randomized trials [35]. In this analysis, an anthracycline-based regimen was used in only nine trials. Radiation was delivered to the chest wall, supraclavicular, axillary, and internal mammary nodal areas. The most common fractionation schedule was 50 Gy in 25 fractions over 5 weeks. Danish trials were not included in this analysis, and radiation therapy was shown to reduce the risk of any recurrence (OR 0.69, $p = 0.0004$) and LRR with an odds ratio of 0.25 ($p = 0.000001$). A marked difference in LRR resulted in a reduction of BCM with an odds ratio of 0.83 ($p = 0.004$). On multivariate analysis, the timing of radiation therapy ($p = 0.03$) and radiation technique (megavoltage vs. orthovoltage therapy, $p = 0.05$) were independent prognostic factors for a radiation effect.

In the meta-analysis of EBCTCG 2005, treatment data for 42,500 breast cancer patients from 78 randomized trials were studied comparatively. For 23,500 patients (of all 42,500), a comparison of RT vs. non-RT and more surgery vs. less surgery was performed. The patients were grouped according to whether the 5-year LRR exceeded 10% (<10% in 17,000 women, >10% in 25,000 women). These 25,000 women included 8500 who underwent mastectomy and had axillary clearance and node-positive disease in trials of RT. RT was delivered to the chest wall and regional lymphatic in most of the RT trials. At the 5-year follow-up, LRR was 6% versus 23% (absolute reduction 17%), and 15-year breast cancer mortality (BCM) rate was 54.7% versus 60.1% (reduction of 5.4%, SE 1.3, $2p = 0.0002$; overall mortality reduction 4.4%, SE 1.2, $2p = 0.0009$) in the RT group compared to the non-RT group. RT produced similar proportional reductions in local recurrence in all women. This effect was irrespective of age or tumor and radiation therapy treatment characteristics (recent vs. older trials or with vs. without systemic therapy). A 20% reduction in local recurrence risk resulted in a 5% reduction in BCM, which implied that for every four local recurrences prevented by RT, one breast cancer death was avoided [36].

The long-term follow-up results of these three prospective randomized trials indicated a clear effect of PMRT on survival because the LRR risk decreased significantly and the survival rates of the RT arm were significantly higher (Table 10.1) [37, 38]. Other investigators have criticized the Danish trials. One criticism was the inadequacy of axillary surgery because only a median of seven nodes was removed from the axilla. This number is currently defined as inadequate axillary dissection. Most of the patients who had one to three positive nodes in the Overgaard studies would have had ≥4 nodes with a more complete dissection. In response to this issue, Danforth et al. and Saha et al. determined that 64–71% of patients with one to three positive nodes with limited dissection would remain in the same group with more complete dissection [39, 40]. According to DBCG trialists, approximately 50–70% of the patients in the group

Table 10.1 Locoregional control and survival in trials of mastectomy and systemic therapy with or without PMRT

Study	Locoregional recurrence	Overall survival
Danish 82b [2]	@ 10 years	
RT	9%	45% $p \leq 0.0001$
No RT	32%	54%
Danish 82c [3]	@ 10 years	
RT	8%	45% $p \leq 0.003$
No RT	35%	36%
Canada [35]	@ 20 years	
RT	7%	47% $p \leq 0.003$
No RT	18%	37%
Danish 82b and c (1–3 LN+, ≤8 nodes removed) [38]	@ 15 years	
RT	4%	57% $p \leq 0.03$
No RT	27%	48%

Table 10.2 Locoregional recurrence and overall survival at 15 years in patients with 1–3 positive versus ≥4 positive lymph nodes

Endpoint at study and subgroup	PMRT (+)	PMRT (−)	*p*
% LRR @ 15 years			
1–3 LN positive	4	27	0.001
≥4 LN positive	10	51	0.001
% overall survival @ 15 years			
1–3 LN positive	57	48	0.03
≥4 LN positive	21	12	0.03

with one to three positive nodes would likely remain in the same group with a more complete dissection. The evaluation of 1–3 positive nodes together with ≥4 positive nodes raised another objection to the study. In the reanalysis of the Danish trials after 15 years of follow-up, a subgroup of 1152 patients with excision of >8 lymph nodes were evaluated. The 15-year OS of the whole subgroup was 39% for irradiated patients and only 29% for the no PMRT group ($p = 0.015$). Patients with ≥4 involved axillary nodes experienced an absolute increase in OS of 9% (21% vs. 12%, $p = 0.03$) [39]. The subgroup with one to three positive nodes had an absolute survival gain of 9% (57% vs. 48%, $p = 0.03$). PMRT decreased the 15-year LRR for patients with ≥4 positive nodes by 41% and for those with 1–3 positive nodes by 25% (Table 10.2) [38]. The British Columbia trial also evaluated subgroups with ≥4 versus 1–3 positive nodes. In both subgroups, PMRT provided a similar reduction of breast cancer deaths (RR 0.64, 95% CI, 0.42–0.97 and 0.59, 95% CI, 0.38–0.91, respectively). A similar increase in overall survival was observed. As expected, the impact of PMRT on LRR was greater for patients with 1–3 positive nodes (RR 0.46, 95% CI, 0.18–1.13) than for patients with ≥4 positive nodes (RR 0.30, 95% CI 0.10–0.85) [37].

In the Danish 82b trial, the 15-year OS rates in patients with ≥4 positive lymph nodes were very low. This is most likely due to the inefficiency of chemotherapy in this trial. Recently, high-risk patients have been treated with anthracycline- or taxane-based chemotherapy regimens. The LRR rates, in studies in which a more efficient systemic treatment was applied and PMRT was not used, were apparently lower than the rates in these prospective studies and meta-analysis.

LRR rates have been published in studies in which systemic therapy was used after mastectomy, and PMRT was not performed. In the MD Anderson Cancer Center (MDACC), the Eastern Cooperative Oncology Group (ECOG), and the National Surgical Adjuvant Breast and Bowel Project (NSABP) studies, the total LRR rates in T1–T2 patients with one to three positive lymph nodes when PMRT was not applied were 14%, 13%, and 13%, respectively [7, 41, 42]. When patients with distant metastasis were excluded, the reported 10-year LRR rates were 11%, 7–9%, and 4–7%, respectively. In these series, efficient systemic therapy significantly reduced the LRR. When the patients were subdivided into two categories of 1–3 positive nodes and ≥4 positive nodes, the LRR rates were higher in the latter (Table 10.3). The average rate of LRR for patients with one to three positive lymph nodes in these series was approximately 12%, which is almost three times less than the LRR in the no-radiation arm in the Danish trials. When the LRR is significantly low, the efficiency of RT can also be expected to be low. In these three trials, the LRR rates increased for the following patient or tumor parameters: more involved axillary lymph nodes, less excised axillary lymph nodes, larger tumor, estrogen receptor negativity, presence of extracapsular extension, high-grade tumor, presence of lymphovascular invasion, and younger age. The MDACC trial provided additional information about LRR for patients with one to three positive nodes. An analysis of the data from this subgroup found that the presence of extracapsular extension greater than 2 mm, tumor size over 4 cm, positive or close surgical margins (2 mm), presence of lymphovascular space invasion, resection of less than 10 lymph nodes, or invasion of the skin, nipple, or pectoralis muscle were all associated with rates of isolated LRR of ≥25% [41, 43].

Table 10.3 Ten-year LRR rates after mastectomy and systemic therapy in patients with 1–3 positive nodes and ≥4 positive nodes

Study	Number of patients	Systemic therapy	LRR	
			1–3 LN (+)	≥4 LN (+)
MDACC	1031	Doxorubicin based	10%	21%
ECOG	2016	CMF	13%	29%
NSABP	5758	CMF/AC	8.1%	15.5–18.8%[a]

[a]LRR for patients with more than ten positive axillary lymph nodes

Sharma et al. reported their series including 1019 stage II patients who were treated between 1997 and 2002 [44]. With a median follow-up of 7.4 years, the overall 10-year LRR rate was 2.7% in the whole group. This 10-year LRR rate was similar for patients who had node-negative disease (10-year LRR rates 2.1%). The only independent factor for LRR was young age ($p = 0.004$).

LRR risks in node-positive patients after mastectomy and current systemic therapies without RT are no longer as high as those reported by prospective randomized trials and meta-analysis. More complete resection of the axilla combined with more effective systemic therapies such as anthracyclines, taxanes, trastuzumab, and new-generation hormonal therapies with aromatase inhibitors, has permitted substantial reductions in LRR rates [45–54].

In the new era, the response to adjuvant therapies will be predicted using biological factors, including genetic alterations and gene expression profiles in the tumor, biological classification, and molecular features of the tumor. Kyndi et al. reanalyzed the molecular features of tumors in a subgroup analysis of the DBCG 82b and c trials [55]. They included 1000 patients for whom tissue microarray sections were stained for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor (HER-2) and who were randomly assigned to PMRT. The follow-up time for patients who were alive was 17 years. Significantly improved OS after PMRT was observed among patients who had good prognostic markers, such as hormone receptor-positive and HER-2-negative patients. There was no significant improvement in OS after PMRT among patients with a poor prognosis (particularly hormone receptor-negative and HER-2-positive patients). An obvious lack of improvement in survival was observed for the hormone receptor-negative and Her-2 positive subtype. As an extension of this study, the same investigators divided 1000 patients with excision of ≥8 axillary lymph nodes and for whom paraffin blocks were available into three risk groups. The "good-risk group" was defined by at least four of five favorable criteria (≥3 positive nodes, tumor size <2 cm, grade I tumor, ER or PgR positive, HER-2 negative); the "poor-risk group" was defined by at least two of three unfavorable criteria (>3 positive nodes, tumor size >5 cm, grade III tumor); and an intermediate group was defined between these extremes. The lowest LRR at 5 years was observed in patients in the good-risk group. The LRR probability increased from 11% for the good-risk group to 50% for the poor-risk group. PMRT reduced 5-year LRR risk significantly for all three subgroups. The largest absolute reduction in LRR probability with PMRT was observed in the poor-risk group [56]. Kyndi et al. also reported increased overall mortality, distant metastasis, and LRR probability in patients with negative bcl2 expression. In contrast to bcl2-positive patients (HR 0.70 (0.57–0.86), $p = 0.001$), no survival improvement was observed for PMRT in the bcl2-negative subgroup (HR 0.94 (0.75–1.20), $p = 0.4$) [57]. A significant association was observed between p53 accumulation and other poor prognostic markers, such as grade III malignant tumors, hormone receptor-negative tumors, and HER-2-positive/bcl-2-negative tumors. PMRT improved OS probability for both p53-negative and p53-positive patients. Tourong et al. conducted a retrospective analysis of British Columbia Cancer Agency (BCCA) data for 821 patients with T1–T2 breast cancer and one to three positive lymph nodes who were treated with mastectomy and without adjuvant RT [58]. Adjuvant systemic therapy was used in 94% of patients, and approximately 66% of patients received anthracycline-based chemotherapy. The overall 10-year isolated LRR and LRR with or without simultaneous distant recurrence (SDR) rates were 12.7% and 15.9%, respectively. A 10-year LRR risk of >20% was reported in patients with one to three positive nodes plus at least one of the following factors: age <45 years, stage T2, grade III histology, ER-negative disease, medial location of tumor, more than one positive node, or >25% positive lymph nodes. Multivariate analysis revealed that age <45 years, presence of >25% positive lymph nodes, medial tumor location, and ER-negative status were statistically significant predictors of isolated LRR and LRR with or without SDR.

RT standards are also important prognostic factors for the survival effect of PMRT. Gebski et al. reanalyzed the results from 36 prospectively randomized trials, 33 of which were included in the EBCTCG meta-analysis [59]. Patients were separated into three different categories according to biologically equivalent dose (BED) and the appropriateness of target volumes: category I, a BED of 40–60 Gy in 2 Gy fractions with an appropriate target volume; category II, an excessive dose of radiation therapy; and category III, an inappropriate target volume. The absolute increase in survival was 2.9% (OR of death 0.87, $p = 0.006$) in category I patients with 5-year data and 6.4% with 10-year data (OR of death 0.78, $p < 0.001$). No statistically significant change in survival was observed among category II or III patients. Among the 33 EBCTCG trials, the odds of LRR were reduced more among category I trials (80% lower) than category II (70% lower) or III (64% lower) trials. With proper RT techniques, a more precise and effective dose can be delivered to the target volume while preserving normal tissues, i.e., lungs and heart. Demirci et al. analyzed 19 published trials of patients treated between 1968 and 2002 (five randomized controlled trials, five single or multi-institutional trials, and nine national cancer registry database reviews) [60]. All the older trials with a median follow-up time >10 years reported excess cardiac toxicity. By contrast, the majority of RT trials with shorter median follow-up durations (≤10 years) did not report an excess cardiac toxicity risk. For trials that began in or after 1980, the reported relative risk (RR) for cardiac mortality was 0.5–2.1. The recommended optimal follow-up duration for assessing cardiac toxicity is >10–15 years after RT [9, 61, 62]. The follow-up duration in modern studies is shorter than in older RT trials; thus, the long-term safety of modern techniques remains uncertain.

However, several trials have reported reduced cardiac risks in patients treated in the modern era (i.e., since 1980) [63–65].

The American Society of Clinical Oncology (ASCO) and the American Society of Therapeutic Radiology and Oncology (ASTRO) recommended PMRT only for patients with ≥4 positive lymph nodes or advanced primary disease, and both statements highlighted the need for additional prospectively randomized data concerning the use of PMRT for patients with T1–T2 and one to three positive lymph nodes [66, 67]. In the last EBCTCG meta-analysis, among the 1314 women who had one to three axillary positive lymph nodes, RT reduced LRR ($2p < 0.00001$), overall recurrence (RR 0.68, $2p = 0.00006$), and breast cancer mortality (RR 0.80, $2p = 0.01$). No significant difference was detected in the proportional reductions in the rates of overall recurrence or breast cancer mortality with the administration of systemic therapy [27]. Since 2007, the National Comprehensive Cancer Network (NCCN) breast cancer practice guidelines have strongly recommended PMRT in patients with one to three positive lymph nodes [28–30]. In 2009 and 2017, in the consensus reports from St. Gallen, the use of PMRT in patients with one to three lymph nodes positive in the axilla was recommended if the patient was young or had other poor prognostic factors such as high-grade or ER-negative or PgR-negative tumors, high grade features like high Ki-67 score, c-erbB2 positive disease, and extensive lymphovascular invasion [68, 69]. The German Cancer Society reported the first guideline in 2004. PMRT was recommended only in patients with microscopic or macroscopic residual disease with ≥4 positive lymph nodes, pT3 tumors >5 cm, and patients with special risk factors. The risk factors were specified in 2005 by the German Society of Radiation Oncology (Deutsche Gesellschaft für Radioonkologie, DEGRO) [70]: one to three positive lymph nodes plus age <40 years, lymphovascular invasion, tumor >3 cm, grade III histology, multicentric and multifocal tumors, and negative for hormone receptors and recent German guideline also recommend PMRT in this scenario [71]. The American Society of Clinical Oncology, American Society for Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) panel developed recommendations for PMRT. The panel agreed that the available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1–2 breast cancer and one to three positive lymph nodes. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities. These factors include patient characteristics (aged 40–45 years, limited life expectancy because of older age or comorbidities, or coexisting conditions that might increase the risk of complications), pathologic findings associated with a lower tumor burden (e.g., T1 tumor size, absence of lymphovascular invasion, presence of only a single positive node and/or small size of nodal metastases, or substantial response to neoadjuvant systemic therapy), and biologic characteristics of the tumor associated with better outcomes and survival and/or greater effectiveness of systemic therapy (e.g., low tumor grade or strong hormone receptor positivity) [72]. Consequently, PMRT should be in used in the one to three lymph node-positive groups in the presence of additional adverse prognostic factors. These factors are as follows: age <40 years, grade III histology, ER negative, PgR negative, lymphovascular invasion, tumor >3 cm, c-erb B-2-positive tumor, and high Ki-67 index. Recently, investigators from MDACC reported their series including 1027 patients with T1–T2 breast cancer and one to three positive lymph nodes who were treated with modern treatment approaches, such as the use of sentinel lymph node surgery and standard systemic therapy (taxanes and aromatase inhibitors). They evaluated the rate of locoregional recurrence for patients treated in two different time periods: the early era (1978–1998) and the later or modern treatment era (2000–2007). They reported that PMRT reduced the locoregional recurrence rate from 14.5% to 6.1% in the early era cohort ($p = 0.035$). By contrast, PMRT did not reduce the locoregional recurrence rate in patients who were treated in the modern treatment era cohort; the 5-year LRR rates were 2.8% without PMRT and 4.2% with PMRT ($p = 0.48$). It should be kept in mind that this particular trial was a retrospective study and patients treated with PMRT in both eras had worse prognostic factors than patients treated without PMRT. Patients who were treated with PMRT more commonly are younger and have T2 disease, three positive lymph nodes, and gross extracapsular extension of disease [73].

There is a consensus that the use of PMRT should include the chest wall, the supraclavicular region, and the axillary apex, but not the full axilla for patients treated after level I–II axillary dissection (Figs. 10.1 and 10.2). The randomized trial supporting the use of PMRT, which generally treats internal mammary nodes, still remains controversial [2–4].

Recently, three prospectively randomized trials, designed to investigate the effect of nodal irradiation on oncological outcome in terms of survival, were published [74–76]. In

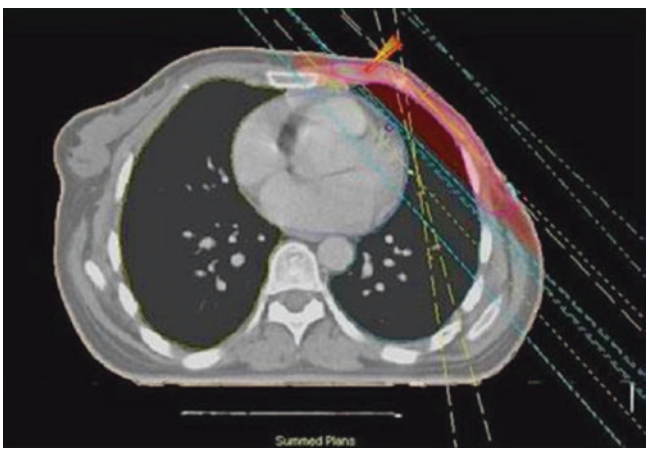

Fig. 10.1 PMRT to chest wall and internal mammary lymph nodes

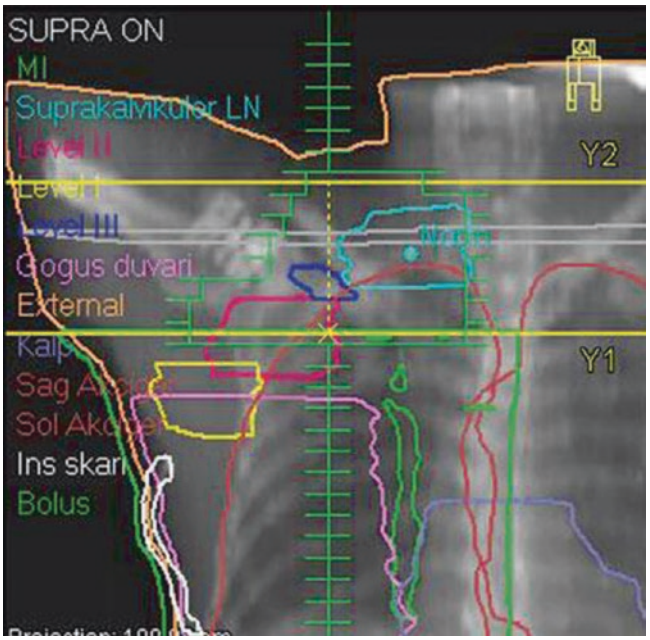

Fig. 10.2 Supraclavicular field encompasses supraclavicular lymph nodes and level III and half of the level II axillary lymph nodes. (Treatment volumes: light blue, supraclavicular lymph nodes; dark blue, level III axillary lymph nodes; pink, level II axillary lymph nodes; yellow, level I axillary lymph nodes)

these trials, irradiation of the regional lymphatics had only a marginal effect on survival (EORTC); however, DFS and distant-free survival rates were improved, and breast cancer mortality was reduced (EORTC and MA-20) [74, 75]. In the EORTC trial, patients in the nodal-irradiation group had higher overall survival rates, at 10 years was 82.3% (95% CI, 80.4–83.9) among patients who underwent regional nodal irradiation and 80.7% (95% CI, 78.8–82.5) [74]. In French trial, there were no benefits with nodal irradiation in terms of 10-year DFS and 10-year OS. There were some limitations in this trial, patients with involved mammaria interna lymph nodes were low (20%) due to this reason benefits of irradiation were could no be detected [76]. Side effects of regional irradiation were modest in all these trials. Patients in the nodal-irradiation group had higher rates of grade II or greater acute pneumonitis (1.2% vs. 0.2%, $p = 0.01$) and lymphedema (8.4% vs. 4.5%, $p = 0.001$) in MA-20 trial. There were no reported significant excess late cardiac events in the IMN-RT group in comparison with IMN-RT(−) group (15 vs. 11, respectively) [76].

A critically important aspect of treatment, particularly for left-sided cancers, is the use of computer-based simulation to ensure that the heart is not included in the treatment field [77, 78] (Fig. 10.3).

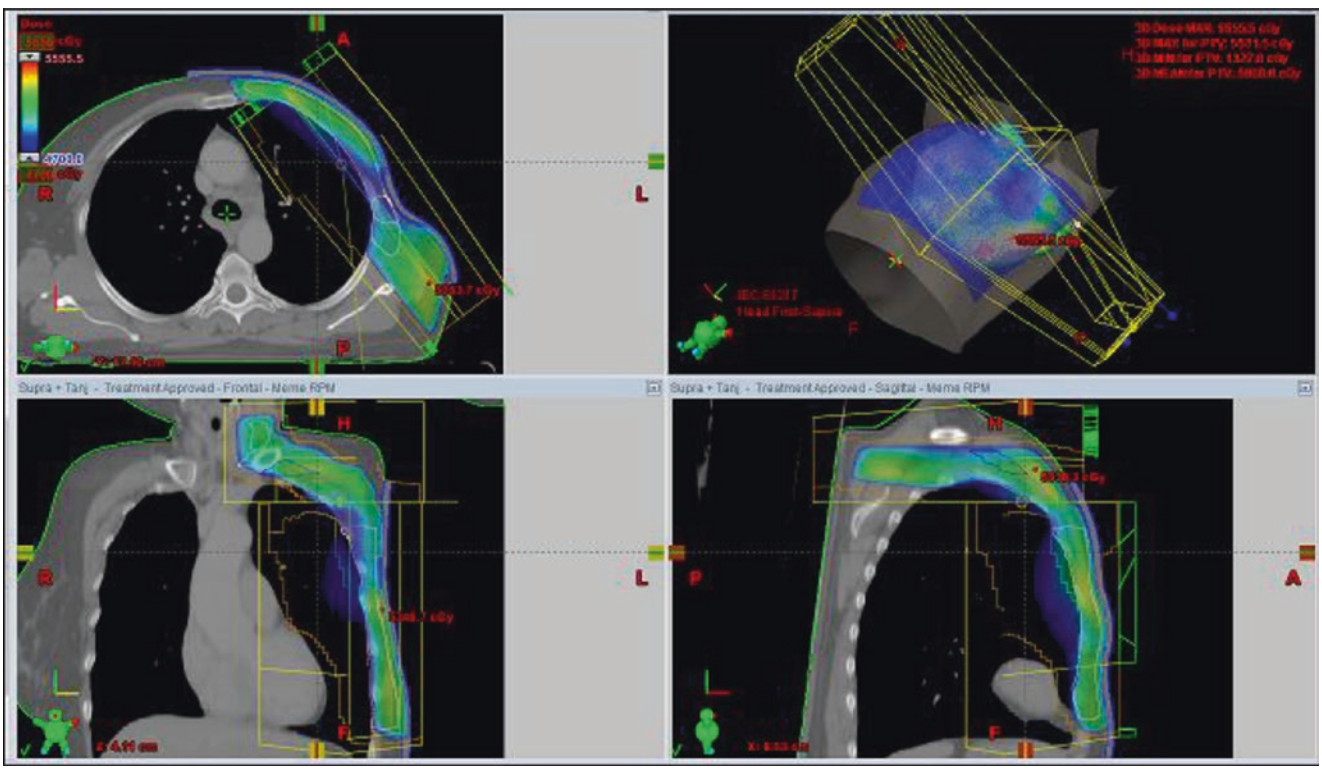

Fig. 10.3 Computer-based simulation for left-sided breast cancer patient for protection of heart

≥4 Positive Axillary Lymph Nodes (N2 Disease)

Patients with ≥4 positive lymph nodes after mastectomy are defined as having N2 disease pathologically in the AJCC manual. As discussed above, the LRR rates are high in these patients, and PMRT is the standard therapy according to all prospective randomized trials, meta-analyses, and guidelines [2–5, 27, 28, 30–32, 34, 52–54, 63–66].

Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) encompasses breast cancer that is inoperable or operable only by mastectomy at initial diagnosis. LABC includes T3 or T4 tumors and any presence of N2 or N3 disease in the axilla (stage IIB, T3N0 to IIIA–C, in AJCC 2002 manual) [22]. Because T3N0 cases were discussed in detail previously, only stage III patients will be discussed in this chapter. LABC constitutes 10–20% of all breast cancers in the United States [79]. Because distant metastases are common, a detailed systemic staging workup is needed. RT plays an important role in the management of LABC. LABC requires multimodal therapy to achieve optimal control of locoregional and distant disease. In the recent past, patients with operable LABC were treated by mastectomy, adjuvant chemotherapy, and PMRT. Currently, neoadjuvant chemotherapy (NAC) has become the preferred treatment method for LABC. The purpose of NAC at LABC is downstaging of the disease and rendering inoperable tumors resectable. After NAC, approximately 80–90% of patients have changes in the pathological extent of the tumor, and 20% of patients exhibit eradication of disease within the lymph nodes [80, 81]. In randomized trials, such as the NSABP B-18, B-27, and the European Organization of Research and Treatment of Cancer (EORTC) 10,902 trials, approximately 10% LRR rates were reported for patients with NAC followed by surgery [82–84].

Trials that study the contribution of PMRT to LABC are usually single-centered non-randomized studies. Piccart et al. used RT followed by mastectomy in patients treated with doxorubicin, vincristine, and cyclophosphamide and reported an LRR rate of 8% [85]. According to Bedwinek et al., in LABC patients treated by mastectomy plus PMRT, the LRR rates were 8%, compared to 61% when treated by RT alone [86]. These results indicate that all these three treatment modalities should be used effectively. In a trial by the Milan Cancer Institute, a total of 133 LABCs were randomized into two arms after doxorubicin and vincristine neoadjuvant chemotherapy. Sixty-seven patients were treated by RT alone, and 65 patients underwent mastectomy. In the RT arm, LRR was 31%, whereas in the surgery arm, LRR was 3% [87]. Kelfström et al. divided patients into three subgroups: LRR was 45% in the mastectomy and postoperative chemotherapy (vincristine, cyclophosphamide, and doxorubicin) group, 8% in the mastectomy and PMRT group, and 5% in the group in which all three treatment modalities were used [88].

A trial from MDACC retrospectively compared 542 patients treated with neoadjuvant chemotherapy, mastectomy, and PMRT with the outcomes of a control group of 134 patients who were treated with neoadjuvant chemotherapy and mastectomy without irradiation. The 10-year LRR rates were significantly lower for irradiated patients, averaging 11% compared to 22% [89]. In cases with a pathological complete response to NAC, when PMRT is not used after mastectomy, the LRR is high. In LABC, RT not only increases local control but also has a positive effect on OS. This positive effect is more significant in cases with a pathological complete response to NAC [89]. McGuire et al. also investigated the role of PMRT in patients with LABC who achieved a pCR to NAC. They reported 10-year LRR rates in PMRT and no PMRT groups after pCR to NAC of 5% and 10%, respectively [90].

The NCCN guidelines provide recommended indications for RT, and the fields of treatment should be based upon the pretreatment tumor characteristics in patients treated with NAC [28–30]. However, the role of the treatment of the regional lymphatic vessels for patients who were treated with NAC is still unclear. In the MDACC retrospective trial, all patients treated with mastectomy received comprehensive regional nodal irradiation consisting of the supraclavicular and internal mammary chain [89]. Hyun Bae et al. reported that there were no differences in LRR in chest wall-irradiated patients regardless of the inclusion of the supraclavicular region (5% and 7%, respectively) [91]. However, this was a retrospective study, and patients in whom the supraclavicular region is treated have higher risk factors.

Two recent randomized trials have shown improved oncological outcomes in terms of DFS for regional nodal irradiation (RNI) for women with high-risk breast cancer [74, 75]. There has been no prospective randomized trial on patients with LABC and who had pathologically complete response to chemotherapy, and therefore, it is difficult to reach a firm conclusion. It is commonly accepted that RT fields should be chosen according to pre-chemotherapy tumor characteristics and should be included regional lymphatic.

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Adjuvant Radiation Therapy After Preoperative Chemotherapy

11

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Introduction

Neoadjuvant systemic chemotherapy has been widely employed for the treatment of locally advanced operable breast cancer, and its use during the early stages of breast cancer has increased [1]. Randomized trials have not observed differences in survival or locoregional control (LRC) between preoperative and postoperative chemotherapy, with hazard ratios (HRs) of 0.98 (95% CI, 0.87–1.09; $p = 0.67$) and 1.12 (95% CI, 0.92–1.37; $p = 0.25$), respectively [2]. pCR to neoadjuvant chemotherapy is associated with better survival rates compared to non-complete responders [2]. The pathological complete nodal response of the axilla was 41% (95% CI, 36.7–45.3%) in a modern neoadjuvant study [3]. This research also indicates that preoperative treatment supports breast-conserving surgery (BCS) due to tumor shrinkage before surgical intervention (HR 0.82; 95% CI, 0.76–0.89) [2]. However, many women who receive neoadjuvant chemotherapy still undergo mastectomy, due to either patient preference or a lack of feasibility of BCS [1]. In this chapter, we attempt to determine whether postmastectomy radiotherapy (PMRT) and regional irradiation in the breast-conserving setting are necessary for all patients undergoing systemic neoadjuvant treatment.

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Postmastectomy Radiotherapy in the Adjuvant Setting

The indication for postmastectomy adjuvant radiotherapy in patients with pT3–pT4 disease and/or four or more positive lymph nodes is well established [4]. Among all node-positive patients with mastectomy and axillary dissection, the absolute effects of radiotherapy on 5-year local recurrence risk are substantial (6.6% vs. 21.3%) [5]. PMRT significantly improves 20-year breast cancer mortality among all node-positive patients (58.3% vs. 66.4%, SE, 2.0, $2p$: 0.001) [5]. Although the routine uses of PMRT in the subset of patients with small tumor disease (pT1–pT2) and one to three involved lymph nodes is controversial, the recent findings of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis could affect this practice. Among women with axillary dissection and only one to three positive nodes, PMRT reduced locoregional recurrence (LRR) ($2p < 0.00001$), overall recurrence (RR 0.68; 95% CI, 0.57–0.82; $2p = 0.00006$), and breast cancer mortality (RR 0.80; 95% CI 0.67–0.95; $2p = 0.01$) [5].

The selective use of PMRT was generally accepted in the St. Gallen 2017 consensus report for patients with pT1–pT2 and one to three involved nodes (omitting of PMRT could be considered for favorable biologic profile) [6]. In the recent ASCO/ASTRO/SSO update, it is indicated that PMRT decreases locoregional failure risk and mortality in pT1–2 N1 patients [7]. Although the balance between potential benefits and complications should be taken into consideration for individual cases, the panel members still couldn't define a population that PMRT could be omitted safely [7]. According to National Comprehensive Cancer Network breast guidelines, PMRT should be strongly considered in this patient population [8]. Most of these studies were designed prior to the use of modern systemic agents such as anthracyclines and trastuzumab. Therefore, the results of modern studies, such as Selective Use of Postoperative Radiotherapy aftEr Mastectomy (SUPREMO), which randomized about 1600

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postmastectomy patients with high-risk node-negative or one to three involved lymph nodes, are awaited to reach firm conclusions on this crucial topic.

Regional Radiotherapy in the Adjuvant Setting

The indications for lymphatic radiotherapy are controversial in both postmastectomy and breast-conserving settings. The lymphatic stations of the breast were routinely irradiated in three randomized trials investigating the role of PMRT [9–11]. Thus, regional radiotherapy contributes to the improvement of the overall survival (OS) obtained with PMRT in patients with node-positive disease [5]. The first results of the MA-20 National Cancer Institute of Canada (NCI-C) trial investigating the role of whole breast radiotherapy ± whole lymphatic radiotherapy (supraclavicular, axillary levels, and mammaria interna) in 1832 randomized patients with pT1–3 N0–1 disease (primarily in one to three node-positive (90% of patients) or node-negative high-risk patients (≥5 cm or ≥2 cm with <10 axillary nodes removed and at least one of the following: grade 3, estrogen-receptor negativity, or lymphovascular invasion)) showed that the 10-year DFS (82.0% vs. 77.0%, $p = 0.01$) were significantly better in nodal radiotherapy arm, whereas OS (82.8% vs. 81.8%, $p = 0.38$) were similar. The incidence of acute pneumonitis (1.2% vs. 0.2%, $p = 0.01$) and lymphedema (8.4% vs. 4.5%, $p = 0.001$) were higher in nodal RT group. The most obvious DFS benefit with nodal RT was found in pN0 patients that hazard ratio was 0.55 (0.28–1.09) and 10-year DFS was 83.7% vs. 72.4% [12].

In the European Organisation for Research and Treatment of Cancer (EORTC) 22922/10925 trial, patients with stage I, II, or III (centrally-medially located tumor irrespective of axillar LN involvement) or axillary LN involvement (externally located tumor) were randomized to whole-breast RT/chest wall RT + nodal RT (including medial supraclavicular and mammaria interna) ($n = 2002$) versus whole-breast RT/chest wall RT without nodal RT ($n = 2002$). Patients underwent BCS or mastectomy and axillary lymph node dissection (ALND) (in case of sentinel LN involvement during last years of studies). Most of tumors were ≤ 5 cm (96% vs. 95.8%), and pN0 ratios were 44.4% vs. 45.4%. pN1a was presented in 42.9% and 43.3%, respectively. Ten-year DFS (72.1% vs. 69.1%, $p = 0.04$) and distant DFS (78.0% vs. 75.0%, $p = 0.02$) were significantly longer in nodal RT arm, while there was a trend in 10-year OS benefit (82.3 vs. 80.7%, $p = 0.06$) in the favor of nodal RT. In addition, nodal irradiation decreased significantly in 10-year breast cancer mortality (12.5 vs. 14.4%, $p = 0.02$) and breast cancer relapse (19.4% vs. 22.9%, $p = 0.02$). The study showed that some patients with no axillary LN involvement may benefit from nodal RT, including medial supraclavicular and mammaria interna fields. On the other hand, there was an increase in pulmonary fibrosis in the nodal RT arm (4.4% vs. 1.7%, $p < 0.001$), whereas there was no difference between groups in terms of cardiac disease (6.5% vs. 5.6%, $p = 0.25$) [13]. Based on these reports, the positive effects of regional radiotherapy on patient outcomes could arguably affect clinical practice. There is no clear consensus on radiotherapy fields and indications for regional irradiation in the adjuvant setting.

Radiotherapy Considerations After Preoperative Chemotherapy

The decision to prescribe radiotherapy after preoperative chemotherapy is still largely based on the initial clinical staging of the patients. Therefore, the initial clinical staging information should be available prior to systemic treatment. History and physical examination, complete blood count, liver function tests, alkaline phosphatase, diagnostic bilateral mammogram (ultrasound as necessary), determination of tumor estrogen (ER)/progesterone receptor (PR), and human epidermal growth factor receptor 2 *neu* (HER-2) status should be routinely performed before the start of neoadjuvant chemotherapy in patients at clinical stages IIA–IIB [8]. Chest computed tomography (CT), abdominal CT, and bone scan can be considered for early-stage patients with symptoms (i.e., pulmonary symptoms, abnormal liver function tests, bone pain, or elevated alkaline phosphatase) or clinical stage IIIA or higher disease. Positron emission tomography and magnetic resonance imaging (MRI) of the breast are not considered part of the standard staging procedure. However, MRI could be helpful in patients with mammographically occult tumors [8]. MRI is also more accurate than mammography in detecting residual tumors after neoadjuvant chemotherapy but requires standardization [14]. Before systemic therapy, a pathological confirmation of the axilla via fine-needle aspiration biopsy is also strongly suggested [8, 15]. Radiopaque marker insertion may be helpful for clarifying the lumpectomy area after systemic treatment, particularly in patients with a complete tumor response [8, 16].

In a recent meta-analysis of 4756 patient individual data from ten randomized trials which compared the long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer, it was found that patients who received neoadjuvant chemotherapy had increased rate of breast-conserving therapy at an expense of increased 15-year local recurrence risk (21.4% vs. 15.9%, $p = 0.0001$), while there was no significant difference in terms of distant recurrence or mortality. It should be noted that none of patients received trastuzumab, while most of the patients did not undergo chemotherapy regimen containing taxane [17].

There is a lack of randomized data to guide decision-making for PMRT after preoperative chemotherapy. Lymphatic irradiation in patients treated with breast-conserving protocols after preoperative chemotherapy and who are staged ypN0 is another area of controversy for which higher-level evidence is urgently needed. In a recent National Cancer Database (NCDB) analysis which included 15,315 patients with cT1–3 N1 disease (3040 postmactectomy-ypN0, 7243 postmastectomy-ypN+, 2070 BCS-ypN0, and 2962 BCS-ypN+) treated with neoadjuvant chemotherapy, PMRT was found to be independently associated with better OS in patients who underwent mastectomy and whose nodal status were ypN0 (HR = 0.729, 95% CI, 0.566–0.939, $p = 0.015$) and ypN+ (HR = 0.772, 95% CI, 0.689–0.866, $p < 0.001$) after neoadjuvant chemotherapy on multivariate analyses adjusted for factors including age, comorbidity score, cT stage, in-breast pathologic complete response, axillary surgery, ypN stage, estrogen receptor status, and hormone therapy. In addition, PMRT provided significant OS benefit in each pathologic nodal subgroup (ypN0, ypN1, and ypN2–3). Interestingly, no improvement was detected when nodal irradiation was added to breast radiotherapy in either BCS-ypN0 or BCS-ypN+ groups [18].

Our current source of information in these controversial areas are the retrospective series, the prospective dataset from a pooled analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 trials, and the results of adjuvant randomized trials. A pooled analysis of the NSABP B18 and B27 trials has recently been published. This analysis included cT1–3 cN0–1 patients who underwent preoperative systemic treatment. The median follow-up time was 11.75 years. PMRT and lymphatic irradiation in a breast-conserving setting were not allowed in this trial [19]. Because the NSABP trials form the only prospective dataset, we will compare the retrospective series and NSABP trial data accordingly.

First, we will review the prognostic factors impacting LRR and then focus on LRR rates separately for each stage.

Prognostic Factors for Locoregional Control After Preoperative Neoadjuvant Systemic Treatment

The literature suggests that the most important factors impacting the risk of LRR are the initial clinical stage, the age at diagnosis, the extent of residual disease after preoperative chemotherapy, and adverse risk factors such as lymphovascular space invasion (LVSI), extracapsular extension (ECE), and a triple-negative (TN) phenotype [20]. In a recent analysis of EORTC 10994/BIG 1–00 study, the significant factors predicting LRR after neoadjuvant chemotherapy were breast cancer subtype and lack of pathologic response [21].

Age

In the previous EBCTCG meta-analysis of adjuvant treatments, there was no correlation between age and the 5-year risk of LRR in patients treated with mastectomy, axillary clearance, and node-positive disease. Hence, the absolute effects of adjuvant PMRT on the risk of local recurrence were also approximately independent of age (local recurrence reductions of 17%, 18%, and 18% for women aged <50, 50–59, and 60–69 years, respectively) [22]. Similarly, age was not a significant predictor of LRR in the multivariate Cox proportional hazards model for patients treated with mastectomy and without PMRT in the NSABP B18 and B27 neoadjuvant trials [19]. In a retrospective trial, age <40 was a significant predictor of LRR in patients with stage II disease treated with preoperative chemotherapy and without PMRT [23]. Although age is not a significant predictor of LRR in patients treated with preoperative systemic chemotherapy and mastectomy, younger patients (<35) with stage IIB or worse disease treated with preoperative chemotherapy and mastectomy should also be treated with PMRT, according to the retrospective data [24].

The effect of age on LRR in patients treated with BCS was also studied in the previous EBCTCG meta-analysis of adjuvant treatments. Most of the local recurrences were in the conserved breast; the 5-year risk of such recurrence in the breast is approximately twofold greater in younger compared to older women. Hence, the absolute effects of post-BCS adjuvant radiotherapy on local recurrence (mainly in the conserved breast) were greater in younger than in older women (5-year risk reductions of 22%, 16%, 12%, and 11% for those aged ≤50, 50–59, 60–69, and ≥70 years, respectively; test for a trend in absolute benefits $2p = 0.00002$) [22]. Similarly, younger age was a significant predictor of LRR in multivariate analyses of patients treated with preoperative chemotherapy and BCS with whole-breast RT in the NSABP B18–B27 neoadjuvant trial (≥50 vs. <50 years HR 0.71; 95% CI, 0.53–0.96; $p = 0.025$) [19].

Clinical Tumor Size

In the previous EBCTCG meta-analysis of adjuvant treatments, there was a correlation between T-stage and the 5-year risk of LRR in patients treated with mastectomy, axillary clearance, and node-positive disease. Hence, the absolute effects of adjuvant PMRT on the risk of local recurrence were also dependent on T-stage (local recurrence reductions of 17%, 24%, and 28% for women staged with T1, T2, and T3/T4 disease, respectively) [22]. Similarly, clinical tumor size was an independent predictor of LRR in patients treated with mastectomy and without PMRT in the NSABP B18–B27 neoadjuvant trial (>5 vs. ≤5 cm HR 1.58; 95% CI, 1.12–2.23; $p = 0.0095$) (Table 11.1) [19].

Table 11.1 Multivariate analysis of independent predictors of 10-year LRR according to type of surgery

Variable	No. of patients	LRR events	HR	95% CI	*p*
Patients treated with mastectomy[a]	1071	131			
Clinical tumor size >5 vs. ≤5 cm[b]			1.58	1.12–2.23	0.0095
Clinical nodal status cN(+) vs. cN(−)[b]			1.53	1.08–2.18	0.017
Nodal/breast pathological status					<0.001
ypN(−)/no breast pCR vs. ypN (−)/breast pCR[b]			2.21	0.77–6.3	
ypN(+) vs. ypN(−)/breast pCR[b]			4.48	1.64–12.21	
Patients treated with lumpectomy plus breast XRT[a]	1890	189			
Age ≥50 vs. <50 years[b]			0.71	0.53–0.96	0.025
Clinical nodal status cN(+) vs. cN(−)[b]			1.70	1.26–2.31	<0.001
Nodal/breast pathological status					<0.001
ypN(−)/no breast pCR vs. ypN (−)/breast pCR[b]			1.44	0.9–2.33	
ypN(+) vs. ypN(−)/breast pCR[b]			2.25	1.41–3.59	

From Mamounas et al. [19], with permission
HR hazard ratio, *LRR* locoregional recurrence, *pCR* pathological complete response, *XRT* external radiation therapy
[a]Includes only patients for whom all covariates are known
[b]Category used as baseline for comparison of risk

Conversely, clinical tumor size was not an independent predictor of LRR in multivariate analyses of patients treated with preoperative chemotherapy and BCS with whole-breast RT in the NSABP B18 and B27 neoadjuvant trials [19].

Lymphovascular Space Invasion (LVSI)

Retrospective studies have indicated that the presence of LVSI increases the risk of LRR [20]. LVSI and the risk of LRR were studied in a large Canadian cohort. Although LVSI had no impact on LRR in the breast-conserving setting, regional relapses were significantly higher in patients treated with mastectomy (HR 1.73; 1.1–2.7; $p = 0.015$) [25]. In a study from MD Anderson Cancer Center (MDACC), the presence of LVSI was associated with worse 5-year LRR (no LVSI 2% vs. LVSI (+)15.4%, $p = 0.006$) in patients with cT1–2 N0–1 disease treated with preoperative chemotherapy and mastectomy without PMRT [26]. In another trial, the effects of LVSI on LRR were studied in clinical stage III patients who achieved pCR to neoadjuvant chemotherapy. The presence or absence of LVSI at the time of initial biopsy exhibited a trend toward an association with LRR in univariate analysis that was not statistically significant (45% ± 24.8% with and 8.6% ± 3.6% without, $p = 0.063$) [27].

Extracapsular Extension (ECE)

ECE has not been studied extensively in neoadjuvant studies; however, it is an accepted risk factor for LRR and is widely used to indicate PMRT [20]. In a retrospective study in India, the presence of ECE had no significant effect on LRR in patients with clinical stage II–III disease receiving neoadjuvant chemotherapy, but 5-year distant DFS was 58% in patients without ECE compared to 10% in patients with ECE ($p = 0.0001$) [28].

Extent of Residual Disease

The presence of residual disease after neoadjuvant chemotherapy was associated with worse outcome in the NSABP B18 and B27 studies for both mastectomy and the breast-conserving setting. Pathological nodal status and pathological breast tumor response (HR, 1.44; 95% CI, 0.90–2.33 for ypN0/no breast pCR vs. ypN0/breast pCR and HR, 2.25; 95% CI, 1.41–3.59 for ypN+ vs. ypN−/breast pCR; $p < 0.001$) were significant independent predictors of LRR in multivariate analyses (Table 11.1) [19].

Receptor Status

In the previous EBCTCG meta-analysis of adjuvant treatments, the 5-year risk of LRR and the contribution of PMRT did not differ according to receptor status in patients treated with mastectomy, axillary clearance, and node-positive disease (ER poor vs. ER positive, 5-year LRR with PMRT 8 vs. 6, and absolute reduction of LRR with PMRT 20 (SE, 2) vs. 18 (SE, 2) [22]. Ten-year local relapse-free survival after mastectomy according to breast cancer subtype was reported in a large Canadian adjuvant trial (10-year LRFS in Luminal A (ER/PR (+), HER-2(−), and Ki-67 ≤ 14%) vs. TN tumors was 92% (95% CI, 89–94) vs. 81% (95% CI, 73–87), respectively) [25]. Unfortunately, the status of the receptors (ER, PR, HER-2 status) was unknown in the NSABP B18 and B27 neoadjuvant trials [19]. In a retrospective study by MDACC, ER negativity and not using tamoxifen were significantly and independently associated with increased LRR (HR, 1.69; 95% CI, 1.04–2.76; $p = 0.033$ and HR, 2.19; 95% CI, 1.19–4.06; $p = 0.012$, respectively) in patients receiving neoadjuvant chemotherapy and mastectomy [29]. Another retrospective neoadjuvant study from Florida demonstrated that TN (negative for ER, PR, and HER-2) status had a significantly higher rate of LRR than non-negative status (12.8% vs. 2.6%) in stage II–III patients treated with

preoperative chemotherapy and mastectomy [30]. In a study from MDACC, patients with TN disease were evaluated. Among the 155 patients treated with neoadjuvant chemotherapy and mastectomy, 27 achieved pCR. All 27 patients had stage I–II disease and were free of LRR. For the entire group of patients treated with neoadjuvant chemotherapy and mastectomy, those who were N0 after chemotherapy had 99% 5-year locoregional control (LRC) with or without PMRT. LRC was poor in those patients with 1–3 N+ residual disease (63%) and was not improved with PMRT ($p = 0.38$). Patients with residual ≥4 N+ also had poor LRC (58%), although there was a trend toward improved LRC with PMRT (61% vs. 43%; $p = 0.07$) [31]. In the multivariate analysis of 1553 patients from EORTC 10994/BIG 1–00 study, breast cancer subtype was a significant predictor of LRR ($p < 0.0001$); HR, 6.44 (95% CI [2.83–14.69]) for TN; 6.26 (95% CI [2.81–13.93]) for HER-2+ without trastuzumab; and 3.37 (95% CI [1.10–10.34]) for HER-2+ with trastuzumab all compared to luminal A cancers [21].

PMRT After Preoperative Systemic Treatment for Initial Clinical Stage I (T1 N0) Disease

There are insufficient data to conclude whether PMRT is necessary for cT1N0 disease treated with neoadjuvant chemotherapy and mastectomy.

PMRT After Preoperative Systemic Treatment for Initial Clinical Stage IIA (T0–1 N1 or T2 N0) Disease

In two retrospective studies, no locoregional failure was observed in cT2N0 patients with complete pathological remission (pCR, no invasive disease in the pathological specimen) [27, 31]. The rates of LRR were 0–7% in patients with cT1N1 that finally staged ypN0 after neoadjuvant chemotherapy, even with the TN phenotype [20, 23, 32]. In studies from MDACC, the LRR was 4–5% in older (>35–40) patients with an initial cT1N1 that finally staged ypN(1–3+) after systemic chemotherapy, unless there were adverse risk factors (LVI, ECE, TN) [23, 33]. In another study from MDACC, patients with cT1–2 N0–1 disease were evaluated. In the total cohort of patients who did not receive RT ($n = 181$), those with ypN(≥4+) had the worst 5-year LRR (ypN0 1%, ypN(1–3+) 5.4%, yp(≥4+) 20%, $p = 0.034$). The presence of LVSI was also associated with worse 5-year LRR (no LVSI 2% vs. LVSI(+) 15.4%, $p = 0.006$) [19, 33]. The 10-year incidences of LRR were 6.5%, 11.2%, and 11.1% without PMRT in patients with cT1–2 N0 disease that finally staged ypN0, ypN(1–3+), or ypN(≥4+), respectively, in the NSABP trial (Fig. 11.1) [19].

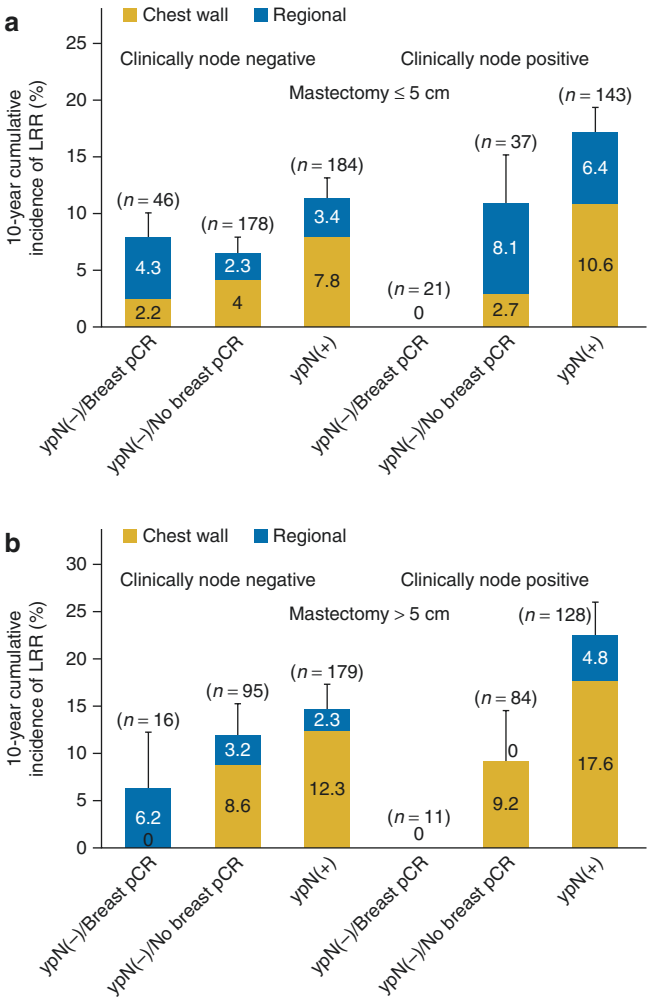

Fig. 11.1 Ten-year cumulative incidence of locoregional recurrence (*LRR*) in patients with (**a**) ≤5-cm tumors treated with mastectomy and (**b**) >5-cm tumors treated with mastectomy. *pCR* pathologic complete response [after neoadjuvant chemotherapy], *ypN* pathologic nodal status [after neoadjuvant chemotherapy]. (From Mamounas et al. [19], with permission)

PMRT After Preoperative Systemic Treatment for Initial Clinical Stage IIB (T2 N1 or T3 N0) Disease

Retrospective data from younger patients (<35) with stage IIB or worse disease treated with preoperative chemotherapy and mastectomy indicate that these patients should also be treated with PMRT [24]. In a study from MDACC, 0% LRR was observed in patients with cT2N1 disease that finally staged pCR after neoadjuvant chemotherapy [27]. Two retrospective studies have investigated whether PMRT is necessary for patients with clinical stage II–III disease that finally staged ypN0. In a French single-center study, PMRT had no effect on LRR-free survival (HR, 0.37; 95% CI, 0.09–1.61; $p = 0.18$) or OS (HR, 2.06; 95% CI, 0.71–6; $p = 0.18$) for

clinical stage II or III disease staged ypN0. A trend was observed toward poorer OS among patients without a pathologically complete in-breast tumor response after neoadjuvant chemotherapy (HR, 6.65; 95% CI, 0.82–54.12; $p = 0.076$) [32]. In a Korean multicenter retrospective study, the addition of PMRT was not correlated with a difference in DFS, LRR-free survival, or OS by multivariate analysis for clinical stage II or III disease that finally staged ypN0. In multivariate analysis, age (≤40 vs. >40 years) and pathological T-stage (0-is vs. 1 vs. 2–4) were significant prognostic factors affecting DFS (HR, 0.35, 95% CI, 0.135–0.928; $p = 0.035$ and HR 2.22, 95% CI, 1.074–4.604; $p = 0.031$, respectively) [34]. The 10-year incidences of LRR were 0%, 10.8%, 14.4%, and 19.5% without PMRT in patients with cT1–2 N1 disease that finally staged pCR, ypN0 (no breast pCR), ypN(1–3+), or ypN(>4+), respectively, in the NSABP trial (Fig. 11.1) [19].

Another study from MDACC evaluated patients with cT3N0 disease treated with neoadjuvant chemotherapy (NAC) and mastectomy. Although all patients were clinically determined to have no nodal disease prior to NAC, 45% had pathologically confirmed disease in the lymph node. The 5-year LRR rate differed significantly between patients who received PMRT and those who did not: 4% (95% CI, 1–9%) with PMRT vs. 24% (95% CI, 10–39%) without PMRT ($p < 0.001$) [35]. Although the LRR rate was 0% in patients with cT3N0 disease that finally staged pCR after preoperative chemotherapy, MDACC suggests PMRT for all patients with cT3N0 disease [1, 23, 27, 33]. The 10-year incidences of LRR were 6.2%, 11.8%, 10.6%, and 17.6% without PMRT in patients with cT3N0 disease that finally staged pCR, ypN0 (no breast pCR), ypN(1–3+), or ypN(>4+), respectively, in the NSABP trial (Fig. 11.1) [19].

PMRT After Preoperative Systemic Treatment for Initial Clinical Stage IIIA (T3 N1 or T0–3 N2) Disease

The role of PMRT in cases of pCR in patients with clinical stage III disease was evaluated at MDACC. The 10-year LRR rate for patients with stage III disease was significantly improved with radiation therapy (7.3% ± 3.5% with vs. 33.3% ± 15.7% without; $p = 0.04$). In this cohort, the 10-year distant metastasis-free survival (DMFS) rate was 87.9% ± 4.6% for irradiated patients and 40.7% ± 15.5% for non-irradiated patients ($p = 0.0006$). The 10-year OS rate was 77.3% ± 6% for irradiated patients and 33.3% ± 14% for non-irradiated patients [27]. The 10-year incidences of LRR were 0%, 9.2%, 14.7%, and 27.2% without PMRT in patients with cT3N1 disease that finally staged pCR, ypN0 (no breast pCR), ypN(1–3+), or ypN(>4+), respectively, in the NSABP trial (Fig. 11.1) [19]. The indications for PMRT in stage III patients achieving pCR varies between institutions. MDACC suggests PMRT for all clinical stage III patients [27]. If pCR is achieved in patients with cT3N1 disease, aged >40 years, and with no TN histology, PMRT is not necessary, according to NSABP data [19, 20]. Clearly, validation is needed for this controversial topic [20].

PMRT After Preoperative Systemic Treatment for Initial Clinical Stage IIIB (T4 N0–2) Disease

The 5-year LRR risk in clinical stage IIIB patients treated with neoadjuvant chemotherapy and without PMRT was 42% in a retrospective study from MDACC [33].

Lymphatic Irradiation After Preoperative Systemic Treatment and Breast-Conserving Surgery

The complete nodal pathological response rate in the axilla was 41% (95% CI, 36.7–45.3) in a modern neoadjuvant study [3]. This encouraging result questions the necessity of axillary lymph node dissection for cN1 patients with good clinical response to neoadjuvant chemotherapy. However, the false-negative rate of sentinel lymph node biopsy after neoadjuvant chemotherapy remains high (12.6%), and studies are needed to decrease axillary surgical interventions, particularly in patients with cN1 disease and a good clinical response to neoadjuvant chemotherapy [36]. The contribution of lymphatic irradiation to DFS and possibly to survival improvement has been demonstrated in modern adjuvant studies such as NCI-C MA20 and EORTC 22922/10925 [12, 13]. How this information will or should be applied in the neoadjuvant setting is not clear. There is no consensus on the optimal management of regional radiotherapy in patients receiving neoadjuvant chemotherapy and axillary dissection.

The role of lymphatic irradiation in clinical stage II–III disease was investigated in a French retrospective study. These researchers compared the outcomes of patients with pN0 status after neoadjuvant chemotherapy and BCS according to whether they received lymphatic irradiation. No improvement in the rates of LRR or survival was observed for nodal irradiation. All patients with initially positive axillary cytology received lymphatic radiotherapy, and 83% of patients in the no-lymphatic-RT arm had cN0 disease in that study [32]. The risk of regional recurrence was less than 10% in the NSABP trial after BCS and breast-only RT (Fig. 11.2). Age and the residual disease burden in

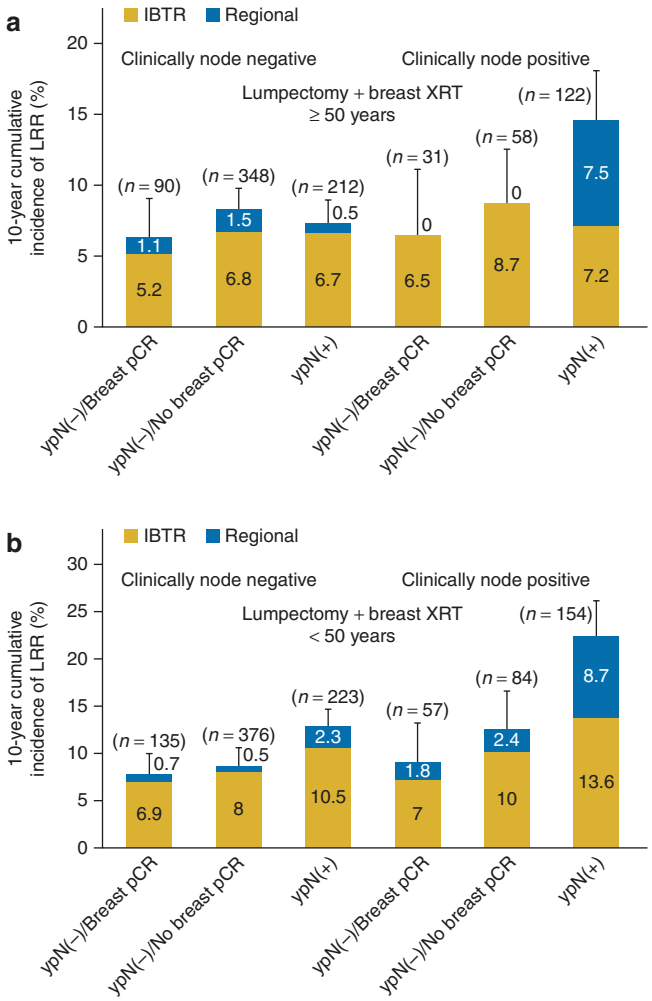

Fig. 11.2 Ten-year cumulative incidence of locoregional recurrence (*LRR*) in patients (**a**) age ≥50 years treated with lumpectomy plus breast external radiotherapy (*XRT*) and (**b**) younger than age 50 years treated with lumpectomy plus breast XRT. *IBTR* ipsilateral breast tumor recurrence, *pCR* pathologic complete response [after neoadjuvant chemotherapy], *ypN* pathologic nodal status [after neoadjuvant chemotherapy]. (From Mamounas et al. [19], with permission)

the axilla had an impact on the 10-year incidence of LRR in the NSABP trial [19]. The 10-year incidences of LRR (<50 years vs. ≥50 years) were 12% vs. 5.9% and 15.6% vs. 11.3% with breast-only RT in patients with cN0 disease that finally staged ypN(1–3+) and ypN(>4+), respectively. The 10-year incidences of LRR (<50 years vs. ≥50 years) were 21.1% vs. 11.4% and 24% vs. 19.6% with breast-only RT in patients with cN+ disease that finally staged ypN(1–3+) and ypN(>4+), respectively (Fig. 11.3) [19].

There are no conclusive data as to whether lymphatic irradiation can be omitted in patients with clinical stage N2 disease that finally staged pCR after neoadjuvant chemotherapy.

Radiotherapy Fields After Preoperative Systemic Chemotherapy

Whole-breast radiotherapy is the standard of practice in patients treated with neoadjuvant chemotherapy and BCS.

If radiotherapy is indicated in the postmastectomy setting, the chest wall should be treated. In most studies from MDACC, full lymphatic irradiation (mammaria interna, supra, level 3, and axillary apex) was also performed [23, 24]. In general, there is no controversy about whether patients with initial clinical stage cN0–1 disease that finally staged ypN(4+) should receive lymphatic radiotherapy including the undissected portion of the axilla (i.e., supraclavicular and level 3). Lymphatic radiotherapy fields may vary between institutions in patients with clinical stage II disease that finally staged ypN(1–3+) [37].

PMRT could be omitted for stage II patients with pCR who are not TN and who are >40 years. All patients with stage II disease but who have had residual disease in the axilla should receive PMRT. One institution is using a supra-level 3 field for stage II patients with no residual axillary cancer but no pCR at the tumor, particularly for younger patients who have no reasonable options for adjuvant systemic therapy (i.e., estrogen receptor (−) and HER-2 Neu(−)). All patients with stage III disease should receive PMRT [37]. The decision to use lymphatic radiotherapy in patients with stage III disease should be based on the pathological status of the axilla, but in a retrospective study from Florida, the omission of the supraclavicular field was significantly associated with LRR by multivariate analysis (HR 3.39; $p = 0.024$) [30]. There are insufficient data examining the omission of radiotherapy in patients with cT4 or cN2 disease. Thus, PMRT with whole lymphatics should be advised for these patients.

Conclusion and Future Directions

Clearly, there is a need for randomized studies to assess the safe omission of PMRT and regional radiotherapy in women with a good response to chemotherapy without compromising breast cancer outcomes. In the NSABP B51/Radiotherapy Oncology Group (RTOG) 1304 study, patients with involved axillary nodes (histologically confirmed) are treated with neoadjuvant chemotherapy. Those who are node negative at subsequent mastectomy are randomly assigned to ± post-mastectomy RT (PMRT) to the chest wall and regional nodes. Similarly, patients who undergo subsequent breast-conserving surgery and whose nodes have become negative after preoperative chemotherapy will be randomly assigned to breast RT ± regional nodal RT [38].

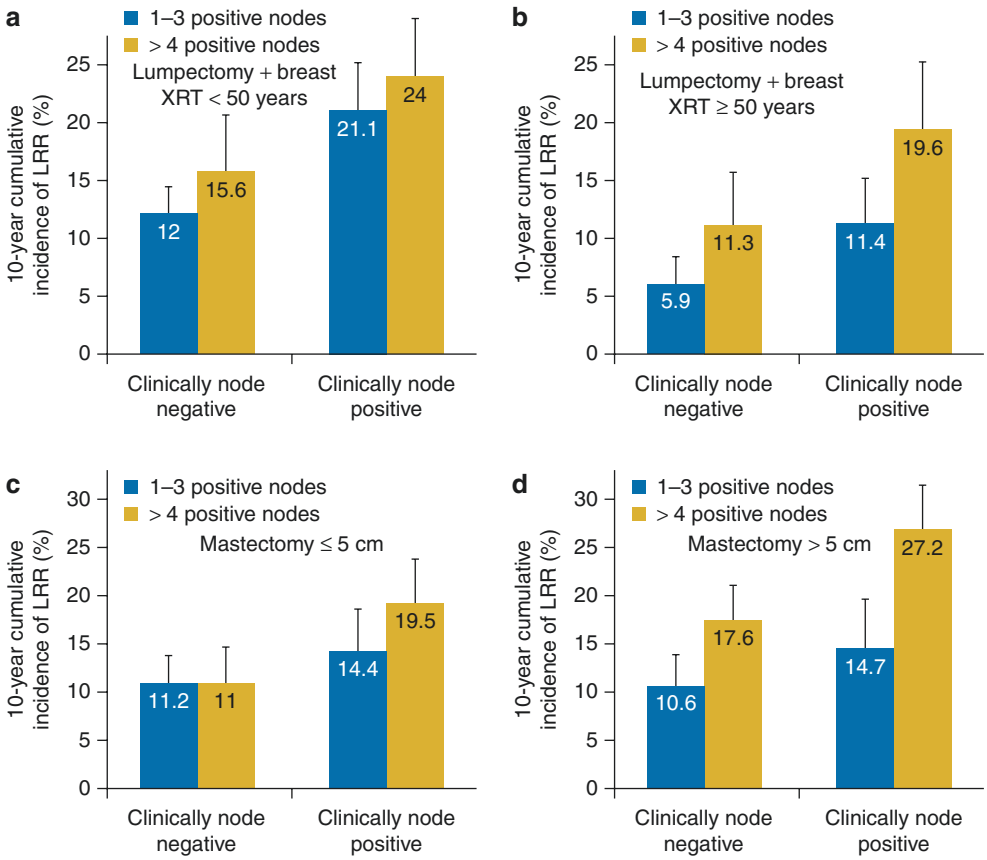

Fig. 11.3 Ten-year cumulative incidence of locoregional recurrence (*LRR*) in pathologically node-positive patients (**a**) age ≤50 years treated with lumpectomy plus breast external radiotherapy (*XRT*) according to number of positive nodes; (**b**) age ≥50 years treated with lumpectomy plus breast XRT according to number of positive nodes; (**c**) with tumors ≤5 cm treated with mastectomy according to number of positive nodes; (**d**) with tumors >5 cm treated with mastectomy according to number of positive nodes. (From Mamounas et al. [19], with permission)

An analysis of sentinel lymph node biopsy (SLNB) after systemic chemotherapy in patients with cN1 disease has recently been published (Z1071 study) [36, 39]. The false-negative rate after the SLNB procedures was 12.6% (90% Bayesian credible interval, 9.85–16.05%) in the entire group. Both the use of dual-agent mapping (blue dye and radiolabeled colloid) and the recovery of more than 2 SLNs were associated with a lower likelihood of false-negative SLN findings (9.1% for ≥3 SLNs). According to the recently presented results of the AMAROS trial, both axillary dissection and lymphatic radiotherapy had the same rates of disease control but fewer side effects with RT in patients with positive SLNB cT1–2 N0 disease [39]. For women who receive neoadjuvant chemotherapy and whose lymph nodes remain pathologically positive after surgery, regional radiotherapy is indicated. However, the ALLIANCE (Alliance for Clinical Trials in Oncology) A011202 phase III clinical trial (NCT01901094) has been designed to answer whether axillary node dissection improves the rate of breast cancer recurrence over that observed with SLNB alone when regional radiotherapy is delivered. If SLNB becomes a standard approach in the neoadjuvant setting, some cN1 patients could be treated with SLNB and axillary radiotherapy without axillary dissection. Clearly, more studies are needed in this area [40].

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12 Breast-Conserving Therapy: Hypofractionated and Conventional Whole-Breast Irradiation and Accelerated Partial-Breast Irradiation

Fusun Tokatlı and Maktav Dincer

Whole-Breast Irradiation

Breast irradiation after breast-conserving surgery (BCS) is an essential component of breast conservation therapy to maximize local control and overall survival. The largest and most recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group has reported the effect of radiotherapy after BCS on 10-year recurrence and 15-year breast cancer death and the absolute magnitudes of these reductions according to various prognostic and other patient characteristics [1]. In this meta-analysis, individual patient data for 10,801 women in 17 randomized trials of radiotherapy versus no radiotherapy after BCS were analyzed to determine whether radiotherapy reduces recurrence and breast cancer death more for some subgroups of patients than for others. Overall, radiotherapy reduced the 10-year risk of any (i.e., locoregional or distant) first recurrence from 35.0% to 19.3% (absolute reduction 15.7%, 2p < 0.00001) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 2p = 0.00005). Of the 10,801 patients analyzed, the vast majority (8337 women) were pathologically confirmed to have node-negative (pN0) cases. In the women with pN0 disease, the absolute reduction in recurrence varied according to age, grade, estrogen receptor status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (≥20%), intermediate (10–19%), or lower (<10%) absolute reductions in the 10-year recurrence risk. The absolute reductions in the 15-year risk of breast cancer death in these three prediction categories were 7.8%, 1.1%, and 0.1%, respectively. In the few women with node-positive disease (n = 1050), radiotherapy reduced the 10-year recurrence risk from 63.7% to 42.5% (absolute reduction 21.2%, 2p < 0.00001) and the 15-year risk of breast cancer death from 51.3% to 42.8% (absolute risk reduction 8.5%, 2p = 0.01). Overall, approximately one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. In summary, after breast-conserving surgery, breast radiotherapy halved the rate at which the disease recurred and reduced the breast cancer death rate by one-sixth. The most widely used fractionation regimen is 1.8- to 2-Gy daily fractions for a total of 45–50 Gy to the whole breast over 5 weeks with or without a boost to the surgical bed [2, 3]. The National Surgical Adjuvant Breast Project group conducted the NSABP B-06 trial in 1851 patients with stage I/II breast cancer smaller than 4 cm locally excised with negative margins [2]. The patients were randomized to three arms: total mastectomy versus lumpectomy alone versus lumpectomy plus 50-Gy whole-breast radiotherapy. Node-positive patients received 5-fluorouracil-based adjuvant chemotherapy. At the 20-year follow-up, overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS) did not differ significantly among the three arms. The addition of breast radiotherapy to breast-conserving surgery reduced the local recurrence rate from 39% to 14%. The Milan group conducted a similar randomized trial in 701 patients with stage I breast cancer [3]. In this trial, randomization was to two arms: radical mastectomy versus quadrantectomy plus 60-Gy breast radiotherapy. Node-positive patients received CMF (cyclophosphamide, methotrexate, and fluorouracil) combination chemotherapy. At the 20-year follow-up, OS (59% and 58%) and cause-specific (76% and 74%) survival rates were nearly identical, whereas local recurrence after radical mastectomy was 2.3% or 8.8% after BCT. However, an optimal dose and fractionation schedule for radiation therapy (RT) after BCS has not yet been

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defined. There is renewed interest in hypofractionation for WBI, and this approach has important practical advantages and biological implications. The convenience of this method may facilitate patient acceptance and compliance with radiation therapy [4].

Biological Rationale for Hypofractionation

The rationale for fractionated RT is that reducing the radiation dose per fraction while increasing the number of fractions and the total dose limits damage to normal tissue because an increased dose per fraction is associated with increased normal tissue damage. Interest in hypofractionation has been revived in the last decade, as the understanding of the radiobiological parameters that affect fractionation in breast cancer has improved [5]. There are two broad categories of target tissues for radiotherapy: acute and late reacting [6]. The linear-quadratic concept is the most commonly used radiobiological model to predict the differential response of these two types of tissues. The α/β ratio (the dose at which cell killing by the linear (α) and quadratic (β) components is equal) is an essential part of this concept and reflects the inherent radiation sensitivity of the relevant tissue. Acute-reacting tissues, such as skin epidermis and the gastrointestinal tract, develop a reaction to radiation within 1–3 weeks of treatment. These tissues generally have a high α/β ratio (range, 10–30). Although sensitive to the total dose of radiation, they are much less sensitive to the fraction size. By contrast, late-reacting tissues, such as soft tissue and neurological structures, do not display reactions to radiation until several years after beginning treatment. These tissues have a lower α/β ratio in the range of 1–5 and are much more sensitive to dose per fraction. Many tumors (e.g., squamous cancers) have high α/β ratios; however, certain cancers, such as prostate cancer and likely breast cancer, have low α/β ratios and are more sensitive to fraction size [7].

A pilot study was designed in 1986 by Yarnold et al. [8] to test the sensitivity of breast tissue to modest increases in fraction size and estimate the α/β ratio for late effects in the breast. In this randomized study, 1410 patients with early-stage breast cancer were randomized to three fractionation schedules: 50 Gy in 25 fractions (2 Gy/fraction), 42.9 Gy in 13 fractions (3.3 Gy/fraction), and 39 Gy in 13 fractions (3 Gy/fraction), which were administered over 5 weeks. Patients were followed up for a median of 8 years. Based on differences in changes to breast appearance and toxicity over time among the fractionation schedules, the α/β ratios were determined. The α/β ratio for late changes in breast appearance was 3.6 Gy (95% confidence interval (CI), 1.8–5.4), and the α/β ratio for breast induration was 3.1 Gy (95% CI, 1.8–4.4). A subsequent analysis estimated the α/β ratio for tumor control to be 4 Gy (95% CI, 1.0–7.8) [9]. These data indicate that hypofractionation with a modest increase in fraction size accompanied by a modest decrease in total dose is likely to result in equivalent outcomes compared with standard fractionation with respect to local control and late radiation morbidity.

Trials of Hypofractionation Versus Conventional WBI

Three randomized trials with long-term follow-up and that investigated the effectiveness and safety of hypofractionation compared to conventional fractionation for WBI have been performed in the last decade and published. Additional trials are ongoing.

Canadian Trial (Ontario Clinical Oncology Group)

Between 1993 and 1996, 1234 women with node-negative breast cancer with clear margins of excision after BCS and axillary dissection were included in the study. Women were randomized to standard WBI of 50 Gy in 25 fractions over 35 days or accelerated hypofractionated WBI of 42.5 Gy in 16 fractions over 22 days. The two groups were similar at baseline: 24.7% of the women were younger than 50 years of age, 31.3% had tumors that were 2 cm or larger in diameter, 26.1% had estrogen-negative disease, and 18.8% had high-grade disease. All patients had invasive carcinoma of the breast and pT1–T2 pN0. Patients with large breasts (>25 cm width of breast tissue) were excluded. Forty-one percent of the patients received adjuvant tamoxifen, and 11% received adjuvant chemotherapy, most commonly cyclophosphamide, methotrexate, and fluorouracil (CMF). Radiation therapy was delivered to the whole breast using two opposing tangential fields. Boost irradiation of the tumor bed and regional irradiation were not used. Ninety-eight (7.9%) patients were lost to follow-up. For the toxicity analysis, 873 patients were evaluated at 5 years, and 455 patients were evaluated at 10 years. The primary outcome was any local recurrence of invasive cancer in the treated breast. Secondary outcomes were distant (including regional) recurrence of breast cancer, second cancers (including contralateral breast cancer), breast cosmesis, late toxic effects of radiation, and death.

The study was first reported in 2002 [10] and has recently been updated with a median follow-up of 12 years [11]. The cumulative incidence of local recurrence was similar in the two groups. The risk of local recurrence at 10 years was 6.7% (42 patients) among the 612 women assigned to standard irradiation compared with 6.2% (41 patients) among the 622 women assigned to the hypofractionated regimen (absolute difference, 0.5%; 95% CI, −2.5 to 3.5). In addition to the 83 invasive recurrences, there were 13 cases of noninvasive local recurrence (i.e., ductal carcinoma in situ): six cases in the control group and seven in the hypofractionated-radiation

group. At 10 years, the cumulative incidence of invasive or noninvasive local recurrence was 7.5% in the control group and 7.4% in the hypofractionated-radiation group (absolute difference, 0.1%; 95% CI, −3.1 to 3.3). Subgroup analysis demonstrated that the treatment effect was similar regardless of patient age, tumor size, estrogen receptor status, or use or nonuse of systemic therapy. The hypofractionated regimen appeared to be less effective in patients with high-grade tumors; in this subgroup, the cumulative incidence of local recurrence at 10 years was 4.7% in the control group and 15.6% in the hypofractionated-radiation group (absolute difference, −10.9%; 95% CI, −19.1 to −2.8; test for interaction, $p = 0.01$).

The probability of survival over time was reported to be similar in the two groups ($p = 0.79$). At 10 years, the probability of survival was 84.4% in the control group and 84.6% in the hypofractionated-radiation group (absolute difference, −0.2%; 95% CI, −4.3 to 4.0). In the control group of 612 patients, 13.4% of deaths were related to cancer, 1.5% were related to cardiac disease, and 5.7% were due to other causes. In the hypofractionated-radiation group of 622 patients, 13.2% of deaths were related to cancer, 1.9% were related to cardiac disease, and 4.5% were due to other causes. No significant differences were observed between groups ($p = 0.56$).

The Canadian trial used the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late scoring schema for skin and subcutaneous tissue toxicity assessment [12]. Moderate and severe toxicity were infrequent and similar between treatment arms at 10 years. Although late toxicity did increase over time, severe toxicity (grade 3) remained less than 4% at 10 years. However, the progression of these effects was not any worse for hypofractionation compared with conventional fractionation. At 10 years, 71.3% of women in the control group and 69.8% of women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5%; 95% CI, −6.9 to 9.8). The repeated-measures logistic regression analysis suggested that the cosmetic outcome was affected by the time from randomization as well as by the patient's age and tumor size, but there was no interaction with treatment.

Rates of pneumonitis, symptomatic lung fibrosis, rib fracture, and ischemic heart disease were also low, and no differences were detected between arms.

START-A Trial

Between 1999 and 2002, 2236 women with early breast cancer (pT1-3a pN0-1 M0) were randomly assigned after primary surgery to receive 50 Gy in 25 fractions versus 41.6 Gy or 39 Gy in 13 fractions over 5 weeks [13]. Most patients underwent BCS, but in contrast to the Canadian trial, 15% of patients underwent mastectomy, and there were no exclusions based on breast size. Demographic and clinical characteristics at randomization were well balanced between treatment groups. The mean age was 57 years (range 25–85 years); 49% had tumors that were 2 cm or larger in diameter, 29% had node-positive disease, and 30% had high-grade disease. No data were available for estrogen receptor status. All patients had invasive carcinoma of the breast. Of the women prescribed chemotherapy (35% of patients), many (70%) received an anthracycline-containing regimen, which was similarly balanced between randomized groups. In this study, 79% of patients received adjuvant tamoxifen. Most patients were treated with 6-MV photons. The planning target volume was the whole breast with a 1-cm margin to palpable breast tissue; where regional radiotherapy was indicated, the planning target volume was supraclavicular nodes with or without axillary nodes with a 1-cm margin. In contrast to the Canadian trial, 14% of patients received regional radiation therapy, and 61% received a boost to the tumor bed. Boost irradiation was used according to local indications, and 10 Gy was delivered in five fractions to the tumor bed prescribed at the 100% isodose using an electron field.

The principal end points specified in the protocol were local-regional relapse and late normal tissue effects. The rates of local-regional relapse at 5 years and 10 years were similar between treatment arms. The rates of relapse at 5 years were 3.6% (95% CI 2.2–5.1) after 50 Gy, 3.5% (95% CI 2.1–4.3) after 41.6 Gy, and 5.2% (95% CI 3.5–6.9) after 39 Gy. The authors have recently updated their results [14]. At a median follow-up of 9.3 years (IQR 8.0–10.0, maximum 12.4 years), 139 local-regional relapses had occurred. The 10-year rates of local-regional relapse did not differ significantly between the 41.6-Gy and 50-Gy regimen groups (6.2%, 95% CI 4.7–8.5 vs. 7.4%, 5.5–10.0; hazard ratio (HR) 0.91, 95% CI 0.59–1.38; $p = 0.65$) or the 39-Gy (8.8%, 95% CI 6.7–11.4) and 50-Gy regimen groups (HR 1.18, 95% CI 0.79–1.76; $p = 0.41$). The upper limits of the one-sided 95% CI for the absolute difference in 10-year local-regional relapse rates indicated an estimated maximum 2.0% excess risk with 41.6 Gy and 4.5% with 39 Gy compared with 50 Gy. The estimated α/β value for local-regional relapse in START-A was 4 Gy (95% CI 0.0–8.9), after adjusting for age, tumor size, primary surgery type, adjuvant chemotherapy use, tamoxifen use, lymphatic radiotherapy, and tumor bed boost radiotherapy.

Rates of distant relapse, disease-free survival, and overall survival were similar among the fractionation schedules, with no evidence of a clinically significant detriment for either of the hypofractionated schedules compared with 50 Gy at 5 and 10 years. At a median follow-up in survivors of 9.3 years, 1700 of 2236 patients (76%) were alive and without relapse, 57 (2.5%) were alive with local-regional relapse (without distant relapse), 78 (3.5%) were alive with distant relapse, 392 (17.4%) had died, and nine (0.4%) had been lost to follow-up. In this trial, 273 of 392 deaths (69.6%) were from breast cancer (92 with 50 Gy, 86 with 41.6 Gy, and 95 with 39 Gy), 26

(6.6%) were related to cardiac disease only (7 with 50 Gy, 13 with 41.6 Gy, and 6 with 39 Gy), 34 (8.7%) were from other cancers (9 with 50 Gy, 10 with 41.6 Gy, and 15 with 39 Gy), 44 (11.2%) were from other noncancer causes (16 with 50 Gy, 16 with 41.6 Gy, and 12 with 39 Gy), and 15 (3.8%) were from unknown cause (6 with 50 Gy, 3 with 41.6 Gy, and 6 with 39 Gy). Fifteen (57.7%) of the 26 deaths from cardiac disease had left-sided primary tumors (4 of 7 with 50 Gy, 10 of 13 with 41.6 Gy, and 1 of 6 with 39 Gy).

Acute toxicity was not reported except for a marked acute reaction observed in the trial, which appeared more common with standard fractionation. Late toxicity was determined from photographs and patient self-assessment questionnaires. Changes in breast appearance and breast hardness were most common. According to patient quality-of-life self-assessments of five key normal tissue effects on the breast or breast area, the rates of moderate or marked breast induration, telangiectasia, and breast edema by 5 years were similar after 41.6 Gy and 50 Gy, but generally lower after 39 Gy than after 50 Gy ($p = 0.004$). At 10 years, this significant difference between the 39-Gy group and the 50-Gy group persisted. The α/β estimates for normal tissue end points in this trial (after adjusting for age, breast size, surgical deficit, lymphatic radiotherapy, and tumor bed boost radiotherapy) were reported to be 3.5 Gy (95% CI 0.7–6.4) for breast shrinkage, 4 Gy (2.3–5.6) for breast induration, 3.8 Gy (1.8–5.7) for telangiectasia, and 4.7 Gy (2.4–7.0) for breast edema. In the 41.6-Gy group, there was one case of brachial plexopathy 2 years after treatment. The incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis was low during follow-up and balanced among the schedules.

START-B Trial

In the START-B trial, between 1999 and 2001, 2215 women with node-negative and node-positive breast cancer (pT1-3a pN0-1 M0) were randomized after BCS or mastectomy to standard WBI of 50 Gy in 25 fractions over 5 weeks or accelerated hypofractionated WBI of 40 Gy in 15 fractions over 3 weeks [15]. Most patients (92%) underwent BCS, but 8% underwent mastectomy, and there were no exclusions based on breast size. Demographic and clinical characteristics at randomization were well balanced between treatment groups. The mean age was 57 years (range 23–86 years); 36% had tumors that were 2 cm or larger in diameter, 23% had node-positive disease, and 25% had high-grade disease. No data were available for estrogen receptor status. All patients had invasive carcinoma of the breast. Of the women prescribed chemotherapy (22% of patients), 59% received an anthracycline-containing regimen, which was similarly balanced between randomized groups. In this study, 87% of patients received adjuvant tamoxifen. Most patients were treated with 6-MV photons. The planning target volume was the whole breast with a 1-cm margin to palpable breast tissue; where regional radiotherapy was indicated, the planning target volume was supraclavicular nodes with or without axillary nodes with a 1-cm margin. In contrast to the Canadian trial, 7% of patients received regional radiation therapy, and 43% received a boost to the tumor bed. Boost irradiation was used according to local indications, and 10 Gy was delivered in five fractions to the tumor bed prescribed at the 100% isodose using an electron field.

The principal end points specified in the protocol were local-regional relapse and late normal tissue effects. The rates of local-regional relapse at 6 years and 10 years were similar between treatment arms. The rates of relapse at 6 years were 3.3% in the 50-Gy group and 2.2% in the 40-Gy group (estimated absolute difference, 0.7%; 95% CI −1.7% to 0.9%). The authors have recently updated their results [14]. At a median follow-up of 9.9 years (IQR 7.5–10.1, maximum 12.5 years), 95 (4.3%) local-regional relapses had occurred. The 10-year rates of local-regional relapse did not differ significantly between the 40-Gy group (4.3%, 95% CI 3.2–5.9) and the 50-Gy regimen group (5.5%, 95% CI 4.2–7.2; HR 0.77, 95% CI 0.51–1.16; $p = 0.21$). The upper limit of the one-sided 95% CI for the absolute difference in 10-year local-regional relapse rates suggested an estimated 0.4% excess risk associated with the 15-fraction schedule.

At a median follow-up in survivors of 9.9 years, 1732 of 2215 (78.2%) patients were alive and without relapse, 50 (2.3%) were alive with local-regional relapse (without distant relapse), 63 (2.8%) were alive with distant relapse, 351 (15.8%) had died, and 19 (0.9%) were lost to follow-up.

In this trial, 236 of 351 deaths (67.2%) were from breast cancer (130 with 50 Gy and 106 with 40 Gy), 17 (4.8%) were related to cardiac disease only (12 with 50 Gy and 5 with 40 Gy), 48 (13.7%) were from other cancers (25 with 50 Gy and 23 with 40 Gy), 40 (11.4%) were from other noncancer causes (21 with 50 Gy and 19 with 40 Gy), and 10 (2.8%) were from unknown causes (4 with 50 Gy and 6 with 40 Gy). Eleven (64.7%) of the 17 deaths from cardiac disease had primary tumors on the left side (8 of 12 with 50 Gy and 3 of 5 with 40 Gy). The 10-year rate of distant relapse was lower in the 40-Gy group (HR 0.74, 95% CI 0.59–0.94), which contributed to the higher rates of disease-free survival and overall survival compared to the 50-Gy group. The reasons for this difference are unclear. There are many factors that affect relapse and survival, including others that were unknown in the trial, such as HER2 status. The authors could not ascribe the survival difference to any biological or treatment-related factor and only concluded that this difference might be due to chance or an imbalance of unknown prognostic factors and could diminish with further follow-up [4].

Acute toxicity was not reported except for marked acute reactions observed in the trial, which appeared more common with standard fractionation (1.2% after 50 Gy/25 fractions

vs. 0.3% after 40 Gy/15 fractions). Late toxicity was determined from photographs and patient self-assessment questionnaires. Changes in breast appearance and breast hardness were the most common. An analysis of patient self-assessments of five key normal tissue effects in the breast or breast area revealed that rates of moderate or marked effects within 5 years tended to be lower after 40 Gy than after 50 Gy, with a significantly lower rate of change in skin appearance after radiotherapy at 40 Gy than at 50 Gy ($p = 0.02$). At 10 years, this significant difference remained between the 40-Gy group and the 50-Gy group. The various assessments of normal tissue effects were consistently better in the 40-Gy group compared with 50-Gy group.

The incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis was low during follow-up and balanced between the schedules. No cases of brachial plexopathy to the supraclavicular fossa and/or axilla were reported in the 82 women who received 40 Gy in 15 fractions or the 79 women who received 50 Gy in 25 fractions.

The authors performed meta-analyses of START-A, START-B, and the START pilot trial by fitting Cox proportional hazards regression models to all individual patient data from the three trials [9, 13–15]. Post-hoc subgroup analyses of the combined hypofractionated regimens versus the control groups for local-regional relapse in these three trials ($n = 5861$) indicated that the treatment effect did not differ significantly regardless of age, type of primary surgery, axillary node status, tumor grade, adjuvant chemotherapy use, or the use of tumor bed boost radiotherapy. In a post-hoc analysis, the incidence of any moderate or marked physician-assessed normal tissue effects in the breast (shrinkage, induration, edema, or telangiectasia) for the 4660 women for whom data were available from these three trials indicated that the treatment effect was similar irrespective of age, breast size, the use of tumor bed boost radiotherapy, adjuvant chemotherapy, or tamoxifen.

UK FAST Trial

The ongoing UK FAST trial is comparing five fractions of 5.7 Gy and 6 Gy at one fraction per week compared with the conventional fractionation of 25 fractions of 2 Gy [16]. Five fractions of 5.7 or 6 Gy are predicted by the linear-quadratic model to be equivalent to 25 fractions of 2.0 Gy, assuming values for α/β of 3.0 and 4.0 Gy, respectively [17]. The aim of this trial was to reduce overall treatment time, not only for patient convenience but also to minimize the potential for rapid tumor growth during radiotherapy. In this trial, women aged ≥50 years with node-negative, early breast cancer were randomly assigned after microscopic complete tumor resection to 50 Gy in 25 fractions versus 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6 Gy, respectively, to the whole breast. Patients with estrogen-positive tumors were eligible for adjuvant endocrine therapy. Exclusion criteria included mastectomy, lymphatic radiotherapy, and tumor bed boost dose as well as neoadjuvant or adjuvant chemotherapy. The primary end point was a 2-year change in photographic breast appearance. In total, 915 women were recruited from 2004 to 2007 (the aim was to recruit 4000 participants), and 2-year photographic assessments were performed on 729 patients. The risk ratios for mild/marked changes were 1.70 (95% CI 1.26–2.29, $p < 0.001$) for 30 Gy and 1.15 (95% CI 0.82–1.60, $p = 0.489$) for 28.5 Gy versus 50 Gy. The 3-year rates of physician-assessed moderate/marked adverse effects in the breast were 17.3% (95% CI 13.3%–22.3%, $p < 0.001$) for 30 Gy and 11.1% (95% CI 7.9%–15.6%, $p = 0.18$) for 28.5 Gy compared with 9.5% (95% CI 6.5–13.7%) for 50 Gy. The rate was significantly higher in the 30-Gy group than in the 50-Gy group (log-rank test $p < 0.001$) or 28.5-Gy group (log-rank test $p < 0.006$), with similar rates in the 28.5- and 50-Gy groups (log-rank test $p = 0.18$).

Thirty-two patients had possible radiotherapy-related adverse effects (10 at 50 Gy, 14 at 30 Gy and 8 at 28.5 Gy), including lymphedema ($n = 25$), rib fracture ($n = 1$), breast pain ($n = 1$), cellulitis ($n = 1$), late-onset asthma ($n = 1$), atrial fibrillation ($n = 1$), irregular heart beat ($n = 1$), and cough ($n = 1$).

At a median of 3 years of follow-up in survivors, there were 2 local relapses (in breast skin or parenchyma), 3 regional relapses (in axilla or supraclavicular fossa), 17 metastases, and 8 patients with a reported second primary cancer. Of 23 patient deaths, 10 were breast cancer related.

In conclusion, the authors suggested that at a median of 3 years of follow-up, 28.5 Gy in five fractions is comparable to 50 Gy in 25 fractions and significantly milder than 30 Gy in 6 fractions in terms of adverse effects in the breast. A five-fraction schedule of WBI delivered in once-weekly fractions has been confirmed to be equivalent to a conventionally fractionated regimen in terms of changes in breast appearance at 2 years and annual clinical assessments of a range of adverse effects in the breast recorded at a median of 3 years. Longer follow-up for a minimum of 5 years is required for reliable estimates of iso-effects.

Use of Hypofractionation in Clinical Practice

The differences in these trials have important implications for the use of hypofractionation in clinical practice. Although most patients had low-risk disease, an important minority had high-risk disease. Subgroup analyses from the Canadian trial did not suggest that hypofractionation was less effective for such patients, except for those with high-grade tumors [4, 11]. The two START trials did not demonstrate any detrimental effect of hypofractionation for high-grade disease [14]. In such instances, additional boost irradiation may be considered, as used in the START trial. However, any biological reasons for a different inherent radiation sensitivity of high-grade tumors or biological subtypes of breast cancer

that are associated with high-grade tumors are speculative. The START trials also included patients with tumors 5 cm or larger in diameter and node-positive disease, again suggesting that hypofractionation may be applied to such patients, although, for the former category, the numbers would be small.

Although the trials did not include patients with ductal carcinoma in situ (DCIS), the Canadian trial included patients with microinvasive disease and patients with an extensive DCIS component as long as DCIS did not involve the margins of excision [11]. Given the demonstrated effectiveness of hypofractionation for invasive disease, it is likely to be effective for earlier stage disease that is widely excised [4]. In a retrospective study from Princess Margaret Hospital [18], 104 patients (39%) were treated with conventional (50 Gy in 25 fractions) and 162 (61%) with hypofractionated (42.4 Gy in 16 fractions or 40 Gy/16 + 12.5 Gy boost) WBI after BCS. Actuarial risk of recurrence at 4 years was 7% with hypofractionated WBI and 6% with the conventional schedule ($p = 0.9$). In this study, univariate analysis revealed an increased risk of relapse for high nuclear grade tumors (11% for grade 3 vs. 4% for grades 1 and 2, $p = 0.029$). Unfortunately, the study had some limitations including its retrospective nature, short follow-up, and imbalance between groups. However, the results of this trial provide further evidence to guide practice.

The type of systemic treatment might influence local tumor control as well as overall survival and side effects due to normal tissue toxicity. In the Canadian trial, only 10.9% of patients received adjuvant chemotherapy (mainly CMF), and 41.8% of patients received adjuvant tamoxifen. Such patients can be at increased risk for an adverse cosmetic outcome with standard radiotherapy, so it is unclear if the outcome of hypofractionation would be worse than that of standard treatment. The Canadian trial reported similar cosmetic appearance after 10 years, which was good or excellent for 69.8% of women treated with the shorter schedule and 71.3% of controls [11]. However, a substantial subset of the patients was treated primarily with adjuvant tamoxifen, and only a minority received chemotherapy. Therefore, the results of this trial may not adequately represent the potential long-term complications of WBI in the presence of chemotherapy. Chemotherapy, primarily anthracycline based, was more commonly used in the START trials. Taxane-based chemotherapy was used infrequently in these trials ($n = 28$). Given the application of conventional fractionation after taxane chemotherapy, it seems reasonable to consider hypofractionation as well, provided it is delivered after chemotherapy with at least a 2- to 3-week break [4].

Although most patients in the trials were treated with BCS, an important minority of more than 500 patients were treated after mastectomy, suggesting that hypofractionation is a reasonable choice for the delivery of chest wall irradiation. The Canadian trial excluded women with large breast size, defined as a >25 cm separation at midbreast, because of an increase in adverse cosmesis observed when such patients are treated with standard fractionation [19, 20]. The START trials, which included such patients, did not report increased adverse cosmesis when adjusted for breast size. If such patients are considered for hypofractionation, the variance across the treatment volume should be less than 5% above the prescribed dose. Boost irradiation was not used in the Canadian trial but was commonly used in the START trials. Despite the use of boost irradiation, no increase in toxicity was observed in patients treated with hypofractionation compared with conventional treatment. In the Canadian trial, the confounding effects of boost irradiation on local recurrence or breast cosmesis have not been examined. Given the acceptable toxicity observed in the START trials, it seems reasonable to consider selective boost irradiation with hypofractionation when delivered as prescribed in these trials.

A major consideration when hypofractionation is used is the treatment of the regional nodes. Previous studies have raised concerns regarding brachial plexopathy in such situations [21–23]. A dose of 40 Gy in 15 fractions at the level of the brachial plexus delivers the equivalent of 46.7 Gy, 47.6 Gy, and 48.9 Gy in 2.0 Gy equivalents, assuming α/β values of 2.0 Gy, 1.5 Gy, and 1.0 Gy, respectively [24]. In other words, 40 Gy in 15 fractions is less damaging to the brachial plexus than 50 Gy in 25 fractions, even under extreme assumptions about the fractionation sensitivity of the nervous system. Regional irradiation was not used in the Canadian study but was used in the two START trials. In the START-A trial, one case of brachial plexopathy was observed when 41.6 Gy was used [13]. No cases were observed with 39 Gy or 40 Gy as used in the START-B trial, but a small number of patients were treated ($n = 278$). Five-year results suggest that the risk of brachial plexopathy is low (1% or less with hypofractionation), but radiation oncologists may want more data and longer follow-up before using hypofractionation for regional therapy. Recently, the START trial results have suggested that appropriately dosed hypofractionated lymphatic irradiation is comparable to the traditional normofractionated schedule in terms of safety at 10 years of follow-up [25]. The percentage of lymphedema and shoulder symptoms (stiffness, pain, and difficulty in raising arm) in START trials did not differ significantly between the treatment groups.

Clinically, even more important is the cardiac toxicity after RT. In the Canadian trial, in the conventional schedule group, 9 deaths were related to cardiac disease (1.5%), compared to 12 deaths (1.9%) in the hypofractionated group. In the START trials, although follow-up was still short for cardiac events, no major difference was reported between the schedules for the number of cases of heart disease in women with left-sided primary tumors. An increase

in long-term risks of cardiac disease (including pericardial, myocardial, and cardiovascular disease) related to RT in patients with early-stage breast cancer is detectable at a follow-up of at least 10 years [26, 27]. Unpublished data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed an increase in fatal cardiac disease 20 years after RT of approximately 4%. The heart is sensitive to radiation regardless of the fractionation used, with no lower dose threshold for adverse effects [28]. Thus, the heart should be protected irrespective of the fractionation dose regimen used, and much longer follow-up of the randomized clinical trials investigating hypofractionated RT schedules is needed.

In the long term, radiation therapy may cause skin telangiectasia and fibrosis of subcutaneous tissue, leading to a loss of volume and retraction of the breast, all of which can adversely affect the cosmetic outcome. In the Canadian trial, the authors reported a worsening of the cosmetic outcome over time that coincided with the increase in toxic effects of irradiation of the skin and subcutaneous tissue [11]. However, there was no increase in toxic effects in women who received accelerated, hypofractionated-radiation therapy compared with those who received the standard regimen. Although older age and large tumor size were associated with a worse cosmetic outcome, the outcomes of the hypofractionated regimen were similar to those of the standard regimen. However, in the START trials, these outcomes were different [14]. In the START-A trial, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common normal tissue effects in the 39-Gy group than in the 50-Gy group. Normal tissue effects did not differ significantly between the 41.6-Gy and 50-Gy groups. In the START-B trial, breast shrinkage, telangiectasia, and breast edema were significantly less common normal tissue effects in the 40-Gy group than in the 50-Gy group. By applying an α/β value of 3.5 Gy for breast shrinkage and assuming no effect of treatment time on late normal tissue effects, 40 Gy in 15 fractions corresponds to 45 Gy in 2-Gy equivalents. The hypofractionated regimens are less harmful to normal tissues, and there are no suggestions that they are less effective in treating the cancer.

Conclusions

In summary, the results of these studies have confirmed that hypofractionation for WBI is safe and effective. The radiotherapy schedule used in the Canadian trial of 42.5 Gy in 16 fractions over 21 days and two of the schedules used in the START trials, 41.6 Gy in 13 fractions over 25 days and 40 Gy in 15 fractions over 21 days, seem to offer local tumor control and rates of late normal tissue effects at least as good as the accepted international standard of 50 Gy in 25 fractions over 5 weeks. The advantages of hypofractionation include patient convenience, fewer treatment visits, less overall treatment time, and fewer costs to the patient and health-care providers.

Considering the published data, hypofractionation was previously considered safe in the following patients [29, 30]:

- Age 50 years or older
- pT1-2, pN0 treated with BCS
- No systemic chemotherapy
- No radiation boost to the tumor bed after BCS
- Feasible acceptable dose homogeneity
- Clinically irrelevant long-term risk of cardiac disease

However, 2018 ASTRO guideline recommends some changes in the following criteria [31]:

- Any age
- Any stage provided that intent is to treat the whole breast without an additional field to cover the regional lymph nodes
- Any chemotherapy
- Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation.

Thus, establishing clinically sufficient selection criteria for patients to identify patients who will benefit from an individualized fractionated WBI remains challenging.

These trials provide results demonstrating that the responsiveness of breast cancer to fraction size is similar to that of the late-responding normal tissues of the breast, as indicated by the α/β estimates. A 13-fraction regimen is unlikely to represent the limits of hypofractionation. This information can be used to model next approaches to hypofractionation. In the NCCN Guidelines, Version 1.2018, it is now proposed a dose of 45–50 Gy in 25–28 fractions or 40–42.5 Gy in 15–16 fractions for the WBI [32]. A boost to the tumor bed is recommended in patients at higher risk for recurrence. The real limits of hypofractionation for breast cancer treatment will likely be better determined from the long-term results of the ongoing UK FAST trial. The use of new radiation technologies, such as three-dimensional conformal therapy and intensity-modulated radiation therapy, can also increase the potential application of hypofractionation.

Accelerated Partial-Breast Irradiation

Background

In the twenty-first century, irradiating only the tumor-bearing quadrant of the breast after BCS instead of the whole breast has gained much popularity. This type of breast radiother-

apy is termed accelerated partial-breast irradiation (APBI). In this technique, the radiotherapy period is considerably shortened, adjacent normal tissue and organs receive a minimal dose, and parts of the breast distant from the tumor bed receive a minimal dose. One disadvantage of this technique, at least in theory, might be that the parts of the breast distant from the tumor bed that harbor occult tumor foci and that do not receive therapeutic doses of radiotherapy may cause higher rates of in-breast recurrence or new primary tumors with longer follow-up. As a result of increasing interest in this technique, many randomized trials have begun to compare APBI with whole-breast radiotherapy. The results of some of these randomized trials have only recently been published with limited follow-up [33, 34]. A large, multi-institutional trial from the USA has completed accrual, and results are pending [35]. Despite a lack of randomized and solid evidence for the safety and efficacy of APBI, the growing popularity of APBI has driven European and American radiotherapy societies to publish guidelines to guide the selection of patients most suitable for APBI application [36–38]. Researchers, such as Holland, Vaidya, Faverly, Frazier, and Rosen, have investigated the presence of tumor foci in surgical specimens from the other quadrants of the breast when a tumor mass has been diagnosed in one site [39–43]. In 60% of the cases, invasive but occult tumor foci were identified in quadrants of the breast other than the quadrant that harbored the index tumor. These findings raised suspicions about the efficacy of APBI. The irradiation period in APBI is shortened to a single fraction to ten fractions in 5 days, which requires very high doses of radiotherapy to be given in very few fractions over a very short time. This type of ultra-hypofractionation raises questions regarding the safety of APBI in terms of late sequelae and cosmesis [44, 45]. In addition, radiobiological considerations regarding the use of a single, very high-dose radiation and relating this to the known mathematical models of radiobiological equivalence have raised questions [44]. At this time, according to the guidelines published by larger radiotherapy societies, it is considered safer to use APBI in women who are postmenopausal, have stage I and hormone receptor-positive disease, and have a single tumor focus that has been removed surgically with clear margins [36–38].

Techniques

Interstitial Brachytherapy

The first technique used for APBI was interstitial brachytherapy. In the first results from the Ochsner Clinic, 50 women were treated with multiplane, multicatheter interstitial brachytherapy applied to the tumor-bearing quadrant between 1992 and 1993; after 6 years of follow-up, only one in-breast recurrence was reported [46]. Vicini et al. reported a larger series of women treated with this technique: 199 cases had implant treatment over 4–5 days using interstitial brachytherapy [47]. After 5 years of follow-up, the in-breast recurrence rate was 1%, and the excellent-good cosmetic result rate was 99%. Their technique involved both low-dose rate (LDR) irradiation, in which a 50-Gy prescribed dose was delivered over 4 days, and high-dose rate (HDR) irradiation, in which 34 Gy in ten fractions was delivered over 5 days with two fractions per day. The implant volume included the lumpectomy cavity plus 1- to 2-cm margins, and multiplanes of implant insertions were performed.

The Radiation Therapy Oncology Group published the results of a phase II trial; in 99 cases treated with interstitial APBI who were followed up for 5 years, the rates of in-breast recurrence were 3% with HDR and 6% with LDR applications, and major toxicity rates were 3% (HDR) and 9% (LDR) [48].

Interstitial APBI using multiplane insertions was compared to WBI in randomized trials reported from Budapest [49, 50]. After 5 years of follow-up, overall survival, disease-free survival, and breast cancer-specific survival rates were identical, and the cosmetic results were equivalent.

Intracavitary Brachytherapy

A catheter to carry the radioactive source for brachytherapy with a balloon on the tip to fill the lumpectomy cavity that was developed and patented in the USA under the name MammoSite was presented for APBI and rather quickly obtained Food and Drug Administration approval in 2002 for off-protocol use [51].

Cuttino et al. reported a very large series of patients treated with MammoSite [52]. From nine institutions, a total of 483 patients were treated with MammoSite as the sole radiotherapy after BCS. Patients had a single tumor less than 3 cm in diameter that was removed with clear surgical margins and no axillary involvement. By 2-year follow-up, the breast recurrence rate was 1.2%, and the excellent-good cosmesis rate was 91%. The American Society of Breast Surgeons conducted a registration trial in patients treated with MammoSite and reported the results in 2009 [53]. Early-stage and good prognosis patients were selected for this treatment. A total of 1440 patients were registered with a median age of 65 years, a median tumor size of 1 cm, a negative axillary rate of 92%, and a negative surgical margin rate of 100%. The prescribed dose was 34 Gy delivered in two fractions per day, with a total of ten fractions in 10 days. In-breast recurrence after 3 years was reported to be 1%.

Despite these good control rates, publications have reported high rates of infection, symptomatic seroma occurrence, fat necrosis, and difficulties in covering the target volume with this applicator [54]. In recent years, newly designed

intracavitary applicators that optimize the dose homogeneity using multiple canals on the tip of the applicator, rather than a single canal as in MammoSite, have been introduced [55].

External Beam, Conformal, or Intensity-Modulated Radiotherapy

Although the first APBI technique was interstitial brachytherapy, this technique has the disadvantages of being invasive, requiring long learning periods before making expert insertions, the limited availability of brachytherapy facilities, and infection and bleeding risks. However, using external beam and three-dimensional conformal techniques for APBI requires a shorter learning period, and radiotherapy machines that are readily available in nearly all radiotherapy centers, is noninvasive, and has better options for obtaining dose homogeneity. Selecting the optimal target volume remains controversial [56]. The technique developed by the William Beaumont Hospital is widely used for defining treatment dose, normal tissue tolerance dose, treatment volume, and fractionation [57]. This clinic reported an in-breast recurrence rate of 1% and a good cosmesis rate of 89% in 94 patients treated with external APBI and followed up for 4 years [58]. Treatment requires 5 days and ten fractions, using two fractions per day to deliver a total prescribed dose of 38.5 Gy. This technique is defined as the external beam APBI technique to be used in the randomized NSABP trial (the largest APBI trial designed, which has been closed to accrual and for which longterm results are pending) [35].

Intraoperative APBI

The intraoperative irradiation of the tumor bed using a single dose with electrons during segmental mastectomy was popularized at the Milan Cancer Institute [59]. After removal of the tumor with clear clinical margins, a special electron generation radiotherapy machine dedicated to the operating theater is used, and the dose is delivered using an appropriately sized conus to the walls of the tumor bed.

A single dose of 21 Gy was tested in phase II trials. The intraoperative radiotherapy versus external radiotherapy for selected (low-risk) early breast cancer (ELIOT) trial was a randomized, controlled equivalence trial conducted at the European Institute of Oncology, Milan, and the results are published [33]. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumor bed during surgery. The patients in the external radiotherapy group received 50 Gy in 25 fractions, followed by a boost of 10 Gy in five fractions, with a total treatment time of 6 weeks. In 1305 patients who were randomized and followed up for a median of 5.8 months, ipsilateral breast tumor recurrence was 4.4% in the intraoperative radiotherapy group and 0.4% in the external radiotherapy group ($p < 0.0001$). The 5-year overall survival was 96.8% in the intraoperative radiotherapy group and 96.9% in the external radiotherapy group. The ipsilateral breast tumor recurrence rate in the intraoperative group was significantly greater than in the external radiotherapy group, and overall survival did not differ between groups. The authors concluded that the improved selection of patients could reduce the rate of ipsilateral breast tumor recurrence with intraoperative radiotherapy with electrons.

One other intraoperative radiotherapy technique involves using a mobile X-ray-generating system adapted for use in the operating theater, with various spherical applicators with diameters ranging from 1.5 to 5 cm to match the size of the surgical cavity. A trial of intraoperative radiotherapy using this machine (50 kV generating orthovoltage X-rays) to deliver a single dose of 20 Gy to the surface of the spherical applicator inserted in the tumor bed during BCS has been named "risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: TARGIT-A randomized trial." Five-year results for this trial are published [34]. In this trial, 1721 patients were randomized to intraoperative radiotherapy and 1730 to external beam radiotherapy. The 5-year risk for local recurrence in the conserved breast was 3.3% for intraoperative radiotherapy versus 1.3% for external beam breast radiotherapy ($p = 0.04$). However, there seemed to be an overall mortality advantage in the intraoperative group. This finding required some speculative explanation.

Both randomized intraoperative trials summarized above reported less skin complications with intraoperative irradiation and claimed better normal tissue protection. One editorial stated that the new data from TARGIT-A and ELIOT reinforce the notion that intraoperative radiotherapy during BCS is a reliable alternative to conventional postoperative fractionated irradiation but only in a carefully selected population at low risk for local recurrence [60]. However, concerns regarding the use of a single dose of radiotherapy intraoperatively for breast-conserving treatment have been raised [45, 61, 62]. Concerns have included the delivery by intraoperative radiotherapy of an inadequate dose for the control of microscopic disease; the lack of image verification of target volume coverage or dose to organs at risk; the agnostic nature of the approach to final pathology findings; the use of a linear-quadratic formalism employing an α/β ratio of 10 for tumor control, which is now known to be incorrect, to determine the prescribed dose; and the financial considerations in terms of technical reimbursement for professional fees arising from the use of a single fraction of radiotherapy.

The review article by Njeh et al. provides a further discussion of all available APBI techniques [63]. APBI is a challenging treatment technique with many advantages as well as disadvantages and concerns. APBI may offer acceptable local control in select patients with low-risk breast cancer

(possibly in very low-risk patients who actually do not need any radiotherapy after conserving surgery). The optimal patient selection criteria, technique, dose and fractionation, and target definition are active areas of research in APBI. While the results of large phase III trials (NSABP B-39/RTOG 0413) are presented with early results it is pending publication.

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Part II

Preoperative Systemic Therapy

Preoperative Therapy for Operable Breast Cancer

13

Yesim Eralp

Introduction

A number of large-scale trials have established the role of neoadjuvant chemotherapy in operable and locally advanced breast cancer [1–4]. The common denominator in these studies is the significant association of pathological complete response (pCR) with not only breast conservation but also a prominent improvement in the odds of survival of 50–67% [5–8]. Therefore, a thorough evaluation of response to neoadjuvant chemotherapy plays a very important role not only to determine the best local treatment strategy for a given patient but also to be able to make prognostic predictions for that specific patient.

The current goal of induction treatment is to improve pCR rates using different combinations administered on variable schedules. Nevertheless, as discussed below in detail, despite use of modern chemotherapy agents in distinct strategies such as dose-dense regimens or as part of combinations, even when used as part of a response-adopted approach, we have unfortunately reached a plateau in outcomes.

Identification of patient groups who are more likely to achieve a pCR is currently the main focus of investigation. This will not only help to select the best chemotherapy regimen for a given patient but would also enable treating physicians to switch to better regimens for nonresponders early in the course of treatment and prevent unnecessary toxicity from an ineffective combination. In other words, a "patient-tailored" approach would hypothetically improve the chance of a pCR, which may ultimately lead to an improvement in survival. To improve generalizability of results, many studies have focused on the role of well-known predictive clinicopathological variables such as lack of hormone receptors and high grade, all of which have already been shown to be associated with an improved response to neoadjuvant chemotherapy. Recently, the advent of genomic tests led to energetic efforts to identify molecular determinants or groups of genetic variables in specific patterns, namely, the "genetic signatures" of response, which are in the early stages of development, and yet there is not a reliable predictor of a pCR.

The main advantage of preoperative systemic treatment is the incorporation of genomic analyses into the clinical setting to identify molecular predictors of response for a given treatment and provide insight into the biology of the tumor. Flipping the coin, residual tumor burden has emerged as a surrogate for poor outcome as shown by many studies reported until now. These data have led to a paradigm shift in the design of modern neoadjuvant trials, which are currently designed with an adoptive approach to investigate the role of additional treatment targeting the potential molecular alterations in patients with residual disease following neoadjuvant chemotherapy. In the near future, preoperative systemic chemotherapy will play an even more important role as a clinical research platform to implement personalized treatment approaches for breast cancer patients.

Basic Concepts

Pathological Complete Response

Substantial evidence from randomized trials has consistently demonstrated a positive correlation between pCR and outcome, as summarized in Table 13.1. Therefore, pCR has been universally accepted as the primary endpoint in nearly all neoadjuvant trials. However, the definition of pCR remains controversial, and the substantial heterogeneity of this definition across different trials complicates the comparison of outcomes. As summarized in Table 13.2, definitions range from no invasive disease in the breast only to no invasive or noninvasive tumor deposits in the breast and lymph nodes (ypT0N0), most of which exhibit a significant association with DFS or OS. A meta-analysis of seven neoadjuvant German trials including data from 6377 patients demonstrated that no invasive or noninvasive residual in both the breast and lymph nodes was the most sensitive definition of pCR predicting a better outcome in terms of OS and DFS [21]. These data con-

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tradict the most recent meta-analysis reporting individual patient data from 12 large randomized trials, which demonstrated that the presence of in situ carcinoma in the breast does not influence the favorable effect of pCR on OS (HR ypT0ypN0 vs. ypT0/isypN0 vs. ypT0/is: 0.36, 0.36 vs. 0.51, respectively). According to this meta-analysis, the definition of pCR should be an absence of invasive tumor in the breast and lymph nodes (ypT0/is ypN0) [22].

Table 13.1 Pathological complete response classification systems and correlations with outcome

Author/group	pCR definition	Outcome correlation
Fisher/NSABP [8]	Breast: no invasive tumor	OS; DFS
Kuerer/MD Anderson CC [7]	Breast and lymph nodes: no invasive tumor	OS; DFS
Pierga/Institut Curie [9]	Breast and lymph nodes: no invasive tumor	OS; DFS
Van der Hage/ EORTC [2]	Breast and lymph nodes: no malignant cells	OS
Ogston/Aberdeen [10]	Breast: no invasive tumor	OS; DFS
Von Minckwitz/ GBCSG [11]	Breast and lymph nodes: no invasive or noninvasive tumor	OS; DFS

pCR pathological complete response, *OS* overall survival, *DFS* disease-free survival

Predictive Biomarkers

With the evolution of molecular and genetic testing in modern oncology, numerous multigene signatures with potential predictive and prognostic roles have been identified. However, correlative validation studies have demonstrated that these classifiers are not only associated with substantially different outcomes but also display a wide variation in response to standard chemotherapy regimens. However, trials evaluating the role of biomarkers have consistently concluded that tumors with a high proliferative capacity, as assessed by a high Ki-67 level or grade, hormone receptor negativity, or HER-2 positivity, display a high probability of response and a higher chance of survival in those patients with a pCR [23–26]. Although molecular tests specifically developed to predict pCR have not demonstrated any predictive superiority over the combination of standard clinicopathological parameters, there are emerging data that some of those molecular tests that have been compared with a survival endpoint may have a role in identifying patients who may or may not benefit from chemotherapy. A retrospective evaluation of gene expression profiling data from eight studies including 996 patients revealed that an immunogenic genomic module added to clinical characteristics significantly increased the accuracy of predicting a pCR in the

Table 13.2 Survival outcome of neoadjuvant chemotherapy and pathological complete response rates

Author	Regimen	pCR (%)	pCR site	*P*	DFS, EFS (%)	*P*	OS (%)	*p*
Aberdeen [12]	CVAP	16	b		77		84	
	CVAP-D	34		0.034	90 (3-year DFS)	0.03	97 (3-year OS)	0.05
AGO [13]	EP	10	bl		50		77	
	E-P	18		0.008	70 (5-year DFS)	0.011	83 (5-year OS)	0.04
SICOG [14]	EP q3 week	6	bl		55		69	
	EPC is q week	16		0.02	73 (5-year DMFS)	0.04	82 (5-year OS)	0.07
NOAH [15]	AP-P-CMF	19	bl		56		79	
	AP-P-CMF + Trastz	38		0.001	71 (3-year EFS)	0.013	87 (3-year OS)	NS
NSABP B-27 [5]	AC-surgery	13	bl		59		74	
	AC-surgery-D	14.5			62		75	
	AC-D-surgery	26		<0.001	62 (8-year DFS)	NS	75 (8-year OS)	NS
ACCOG [16]	AC	16	bl		NA		NA	
	AD	12		NS		NS		NS
MDA [17]	CAF	8	bl		89		NA	
	P	17		NS	94 (2-year DFS)	NS		NS
Baldnini [18]	CED	2.6	bl		48		52	
	dd CEF	4.1		NS	60 (5-year DFS)	NS	54 (5-year OS)	NS
TOPIC [19]	AC	25	bl		63		74	
	ECisF	24		NS	62 (5-year RFS)	NS	82 (5-year OS)	NS
TOPIC 2 [20]	AC	12	bl					
	VE	12		NS	HR: 1.18 (2-year DFS)	NS	HR: 1.41 (2-year OS)	NS

pCR pathologic response rate, *dd* dose-dense, *EFS* event-free survival, *Cis* cisplatin, *AC* doxorubicin-cyclophosphamide, *D* docetaxel, *EC* epirubicin-cyclophosphamide, *CEF* fluorouracil-epirubicin-cyclophosphamide, *ED* epirubicin-docetaxel, *CED* fluorouracil-epirubicin-docetaxel, *AP* doxorubicin-paclitaxel, *D* docetaxel, *CVAP* cyclophosphamide-vincristine-doxorubicin-prednisolone, *VE* vincristine-epirubicin, *wk* week, *b* breast, *bl* breast and lymph nodes, *yr* year, *OS* overall survival, *DFS* disease-free survival, *RFS* relapse-free survival, *DMFS* distant metastasis-free survival

$p < 0.05$

HER-2 subgroup [27]. In the remaining intrinsic subgroups as assessed by the PAM50 assay, there were no specific genomic signatures that would identify patients who would benefit from standard neoadjuvant chemotherapy. Based on translational data from prospective randomized trials showing that increased Her-2 mRNA levels may be associated with improved pCR with trastuzumab-based neoadjuvant chemotherapy [28, 29], some studies have focused their attention to fine-tune the predictive ability by combining these tests. In fact, a recently reported combined analysis of three trials that investigated the role of dual Her-2 targeting by lapatinib and trastuzumab without chemotherapy have shown that a combination of Her-2-enriched genotype by the PAM50 test and increased Her-2 mRNA expression is associated with a higher pCR (45.3% vs. 6.7–19.1%) at an adjusted OR of 6.0 as compared to other groups that have either one or none of these markers [30]. I-SPY 1, another multicenter adaptive design trial, prospectively evaluated the role of multigene classifiers as well as standard pathological biomarkers in 237 patients treated with neoadjuvant anthracycline- and taxane-based chemotherapy [31]. This trial confirmed the general consensus that highly proliferative tumors respond better to chemotherapy because pCR rates ranged from approximately 5–9% for luminal A tumors and those with a low Ki-67 level or low-risk genomic profiles (ROR-S, wound healing signature, PAM-50, 70-gene classifier) to 35% and 54% for high-risk and HER-2-positive tumors, respectively [26, 31]. In terms of outcome, patients with luminal or low-risk tumors had longer survival rates despite lower pCR rates, whereas higher pCR was associated with improved survival in highly proliferative tumors [22, 31–33]. Multivariate analysis demonstrated that most molecular signatures and clinical stage improved the ability to predict RFS, suggesting that molecular classifiers can identify patients with a favorable prognostic profile among the non-pCR hormone receptor-positive subtypes. The wound healing signature was the most accurate classifier for identifying lower-risk patients, consistent with previous studies suggesting that the tumor microenvironment and the inflammatory response may have relevant roles in the pathogenesis of breast cancer [27, 34]. All of these markers need prospective validation before being used in routine clinical practice.

Response-Guided Treatment

Accurate early-response assessment during chemotherapy is an important component of the neoadjuvant treatment strategy to identify patients who are unlikely to benefit from the given regimen. There are substantial data from randomized trials indicating a strong correlation between achieving a pCR and favorable long-term survival, as summarized previously in this chapter. As expected, a poor or minimal response usually suggests a poorer outcome. In fact, a nomogram described by the MD Anderson investigators has clearly shown the prognostic impact of residual cancer burden on survival [35]. An update on this prognostic tool has also shown that the RCB retains its prognostic utility even after 10 years in all molecular subtypes [36]. This index incorporates pathologic findings including invasive cellular fraction, size of the largest metastasis and number of involved lymph nodes, as well the pretreatment tumor size after standard anthracycline and taxane-based chemotherapy in a mathematical formula and gives a continuous estimate of the residual tumor. These estimates are then categorized in four groups ranging between 0 and 4, where RCB-0 is pCR. It has been shown that patients in the RCB-0 and RCB-1 groups have a 10-year RFS of 86% and 81%, respectively, whereas those in the RCB-3 and RCB-4 groups have substantially higher RFS rates, reported as 55% and 23%, respectively [35].

Based on these data and others that validated the prognostic relevance of the RCB [37, 38], numerous neoadjuvant trials with an adoptive design have evaluated the role of an early response to standard chemotherapy regimens in the selection of subsequent non-cross-resistant agents. An earlier study by the MD Anderson group randomized patients with a larger than 1-cm^2 residual tumor burden following five cycles of an anthracycline-based combination to either five additional cycles of the same regimen or five cycles of a different combination including vinblastine, methotrexate, and fluorouracil [39]. Despite the limited sample size, there was a trend for survival advantage for patients treated with the alternative regimen (p: 0.08). Contradicting this data, the TAX 301 Aberdeen Trial showed no advantage in switching to docetaxel in patients who were unresponsive to four cycles of an anthracycline-based combination [12]. However, there was a significant increase in the pCR rate (31% vs. 15%) when responding patients received four additional cycles of docetaxel, which translated to a survival advantage. The recently reported GeparTrio trial included 2090 patients who initially received two cycles of the TAC regimen and randomized nonresponding patients to six more cycles of the same regimen or to two cycles of TAC followed by four cycles of a vinorelbine and capecitabine combination [40]. Although an earlier report failed to show an advantage in terms of pCR in the experimental group, an update analysis suggested a significant survival advantage favoring response-guided treatment that was limited to patients in the luminal A and luminal B subgroups [32]. The results of this study highlight the fact that in patients with hormone receptor-positive tumors, pCR may not be a good surrogate endpoint for survival because these patients receive the most effective regimen in the adjuvant setting.

The search for a predictive biomarker to determine a pCR has traditionally been limited to interval biopsies in transla-

tional studies. Due to limitations based on heterogeneity of tumors, as well as patient-based factors, investigators have focused their attention to less invasive methods to predict responsiveness. Early response assessed by the decline in SUV uptakes by PET scan has been implicated to have a role in the prediction of a pCR by many trials conducted to this date. In fact, a PET sub-study of the randomized neoAltto trial has shown that metabolic responses seen in the 2nd and 6th weeks of treatment are significantly associated with pCR and the level of response is also associated with pCR [41]. Another recently reported adoptive trial design that evaluated the role of PET scan in identifying responders has also confirmed the role of early metabolic response on day 15 in predicting pCR to dual Her-2 blockade with pertuzumab and trastuzumab [42]. In this trial, both the median SUV level decline (1.6 vs. 3.9; for pCR and non-pCR, respectively; $p < 0.001$) and the reduction as percentage estimates (63.8% vs. 33.5% for pCR and non-pCR, respectively; $p < 0.001$) were determined to be significantly associated with pCR; the overall positive predictive value was 55% and 49%, whereas the overall negative predictive value was reported to be higher, 94% and 88% for both endpoints, respectively [42]. These preliminary results have led to the initiation of adoptive trials investigating the role of alternative regimens in nonresponding patients based on early response prediction with PET scans and pathologic correlates.

Strategies to improve the outcome of patients with residual disease are currently a major investigational issue for all subgroups. Molecular analysis of residual tumors has consistently shown persistence of clones with resistant genotypes which portend a poor outcome upon relapse. There are several translational studies showing emergence of basaloid cancer cells following PSC in TNBC and low estrogen-dependent, low-proliferative, and immune-related disease in hormone-responsive BC following AI exposure and luminal A dominant tumors in Her-2-positive disease treated with standard Her-2 blockade and chemotherapy [43–45]. It's obvious that these groups of patients require an innovative approach to prevent recurrence originating from these resistant clones. There are numerous adoptive trials that are investigating the role of targeted therapies against these molecular alterations, including, but not limited to, CDK inhibitors, PARP inhibitors, and immune checkpoint inhibitors, in patients with high-risk residual disease following neoadjuvant chemotherapy.

Systemic Treatment

Chemotherapy Regimens

The significant survival advantage achieved by adjuvant chemotherapy led to trials investigating the role of neoadjuvant chemotherapy toward the end of the last century. In fact, the potential benefit of systemic chemotherapy as a primary treatment was initially reported by De Lena et al. [46], who observed a significant improvement in overall survival for administration of a neoadjuvant doxorubicin and vincristine combination before irradiation compared to radiation alone in locally advanced breast cancer. Pivotal trials investigating the role of PSC compared four to eight cycles of anthracycline-based regimens given as a neoadjuvant versus adjuvant treatment in patients with operable clinical T1-3N0-1 disease [1, 2, 4]. None of these trials reported a difference in outcome between either approach as summarized in Table 13.3.

A recent meta-analysis comparing neoadjuvant to adjuvant chemotherapy from the EBCTCG based on individual patient data from ten trials that started enrolment before 2005 also confirmed that responding patients had lower mortality from breast cancer than nonresponders [47]. This meta-analysis included only one trial that used a modern anthracycline- and taxane-based chemotherapy backbone, accounting for 19% of the study population and showed a higher clinical response than other trials from the pre-taxane

Table 13.3 Earlier neoadjuvant studies comparing neoadjuvant versus adjuvant anthracycline-based regimens

Trial	*n*	Disease status	Regimen	pCR	Local recurrence	*p*	DFS	*P*	OS	*p*
NSABP B18 [1]	1523	T1-3 N0-1	4 AC-surgery	13%[a]	13%		58%		72%	
			Surgery-4 AC	NA	10%	NS	55%[b]	NS	72%[b]	NS
EORTC [2]	689	T1c-T4b N0-1	4 FEC-surgery	4%	10%		65%		82%	
			Surgery-4 FEC	NA	9%	NS	70%[c]	NS	84%[c]	NS
ECTO [4]	1355	T2-3 N0-1	4 AT-4CMF-surgery	23%	4.6%		72%		84%	
			Surgery-4 AT-4CMF	NA	4.1%	NS	76%		85%	
			Surgery-4A-4CMF	NA			69%[d]	NS	82%[d]	NS

pCR pathological complete response, *DFS* disease-free survival, *OS* overall survival, *NA* not applicable, *NS* not significant, *AC* doxorubicin-cyclophosphamide, *FEC* fluorouracil-epirubicin-cyclophosphamide, *AT* doxorubicin-docetaxel, *CMF* cyclophosphamide-methotrexate-fluorouracil

[a]The ratio of patients with pathologically node-positive disease was significantly lower in the neoadjuvant group (59% vs. 43%, $p < 0.001$)

[b]At 8 years

[c]At 4 years

[d]At 7 years

era. As expected, smaller tumor size, higher tumor grade, and hormone receptor negativity were also associated with complete response. Despite a higher local recurrence rate with the neoadjuvant approach, the increase in local recurrence was not associated with any increase in distant metastasis or mortality. The factors related with the higher incidence of local recurrence in this meta-analysis may be the lack of a standard surgical approach, as well as failure to analyze the impact of irradiation, which are the main determinants of local control. The authors concluded that neoadjuvant chemotherapy was as effective as adjuvant treatment in reducing distant recurrence or death from breast cancer, providing reassurance that local recurrence does not have a negative impact on survival if managed successfully [47].

The Quest for a Survival Benefit: Integration of Newer-Generation Agents

Taxanes

Encouraged by the favorable results achieved in the adjuvant setting, taxanes were swiftly incorporated into anthracycline-based combinations in the hope of improving response rates in the neoadjuvant setting. As anticipated, taxanes yielded higher pCR rates compared to non-taxane regimens. The largest of these trials was NSABP B-27, which randomized 2411 patients with operable breast cancer to four cycles of anthracycline (AC) alone, four cycles of AC followed by four cycles of docetaxel before surgery, and four cycles of neoadjuvant AC followed by surgery and four cycles of adjuvant docetaxel [3]. The significantly increased pCR rate (14% vs. 26%, $p > 0.001$) compared to the standard referent regimen and the manageable toxicity profile established the AC followed by docetaxel as the state-of-the-art approach in the neoadjuvant setting. However, despite a nearly twofold increase in the pCR rate, the B-27 trial failed to show a significant difference in overall survival, possibly due to the inadequate sample size, which lacked sufficient power to detect the anticipated small improvement of 3–5% observed in adjuvant taxane trials [5].

The favorable impact of taxanes on response rates is summarized in Table 13.4. Overall, these trials demonstrated that six to eight cycles of anthracycline- and taxane-based combinations, either in sequence or given concomitantly, yield higher pCR rates than non-taxane-based regimens. Furthermore, the response rates attained with dose-dense regimens were not substantially higher than those obtained with the standard dose regimens. Despite the higher pCR rate (21% vs. 14%) in the PREPARE trial, which investigated the effect of a dose-dense regimen, disease-free survival (DFS) (3-year 75.8% vs. 78.8%) or overall survival (OS) (3-year 88.4% vs. 91.8%) did not differ [54]. Although there appears to be an incremental pCR benefit in the hormone receptor-negative subtype, considering the added toxicity, dose-dense regimens incorporating standard 3-weekly doses of paclitaxel or docetaxel should not be used outside of a clinical trial setting.

Capecitabine

Favorable response rates attained by capecitabine in the metastatic setting have led to studies evaluating the role of capecitabine in the neoadjuvant setting. The GeparQuattro trial, which was the largest in sample size, randomized 1495 patients with T1-4N0-3M0 to single-agent docetaxel, sequential docetaxel, and capecitabine or concomitant docetaxel and capecitabine following four cycles of epirubicin/cyclophosphamide (EC) [29]. The study failed to demonstrate a significant improvement in pCR rates, and the combination was associated with a higher rate of serious nonhematological toxicity. Similarly, a phase III trial by the Austrian Breast and Colorectal Study Group (ABCSG-24) revealed no difference between a triple combination of epirubicin, docetaxel, and capecitabine and the doublet regimen consisting of docetaxel and capecitabine [55]. Furthermore, in the NSABP B-40 trial, investigators reported a 29.7% pCR rate for the combination of docetaxel and capecitabine, somewhat lower than that of single-agent docetaxel (32.7%) [56].

Despite discouraging data from single studies and a recent meta-analysis of pooled data [57], a meta-analysis including individual patient data from 966 patients from the German neoadjuvant trials suggested a significantly increased rate of pCR with a hazard ratio of 1.62 by multivariate analysis (p: 0.02) [21].

Until further data from ongoing trials including triple-negative patients are reported, there appears to be no role for incorporating capecitabine in standard anthracycline- and taxane-based neoadjuvant chemotherapy regimens.

Gemcitabine

Gemcitabine has established activity when combined with paclitaxel in patients with advanced breast cancer. The first randomized trial testing the role of this combination in the neoadjuvant setting failed to detect an advantage in terms of pCR compared to single-agent paclitaxel following four cycles of the EC regimen [58]. Likewise, the addition of gemcitabine to docetaxel yielded a lower pCR rate (31.8%) compared to docetaxel (32.7%) in the NSABP B-40 trial [56]. In conclusion, there is no evidence supporting a role for adding gemcitabine in the neoadjuvant setting.

Vinorelbine

Limited data exist on the role of vinorelbine in the neoadjuvant setting. In a considerably resistant patient population, a vinorelbine and capecitabine combination yielded a pCR rate of 6%, which was not different than that of the standard docetaxel-doxorubicin-cyclophosphamide (TAC) combination [32]. In another phase III trial, the epirubicin-vinorelbine

Table 13.4 Benefit of taxanes with respect to clinical and pathological complete response rates

Trial	Regimen	cRR (%)	pCR (%)
EORTC-SAKK Therasse (2003) [11–48]	ddEC × 6	27	14
	CEF × 6	31	10
Romieu (2002) [12–49]	AP × 4	20	17
	AP × 6	32	32[a]
Dieras (2004) [50]	AP × 4	89	16
	AC × 4	70	10
ABCSG-14 Steger (2004) [51]	ED × 3	–	7.7
	ED × 6	–	18.6[a]
Han (2009) [52]	ED × 6	82	24[a]
	ED × 4	72	11
ACCOG Evans (2005) [16]	AD × 6	70	20
	AC × 6	61	17
GeparDuo von Minckwitz (2005) [17–53]	ddAD × 4	75	11
	AC × 4-D × 4	85	22.3[a]
NSABP B-27 Bear (2006) [3]	AC × 4	85	13
	AC × 4-D × 4	91	26[a]
Aberdeen Smith (2002) [12]	CVAP × 8	64	15
	CVAP × 4-D × 4	85	31[a]
GeparTrio von Minckwitz (2008) [40]	TAC × 6	48.2	21.0
	TAC × 8	52.9	23.5

cRR clinical response rate, *pCR* pathological complete response rate, *dd* dose-dense, *AC* doxorubicin-doxorubicin-cyclophosphamide, *EC* epirubicin-cyclophosphamide, *CEF* fluorouracil-epirubicin-cyclophosphamide, *ED* epirubicin-docetaxel, *AP* doxorubicin-doxorubicin-paclitaxel, *D* docetaxel, *CVAP* cyclophosphamide-vincristine-doxorubicin-doxorubicin-prednisolone, *TAC* docetaxel-doxorubicin-doxorubicin-cyclophosphamide
[a] $p < 0.05$

combination resulted in similar pCR rates (12%) and mastectomy rates compared to doxorubicin-cyclophosphamide (AC) [20]. These data do not support a role for vinorelbine in the neoadjuvant setting.

Nano-bound Paclitaxel (nab-Pac)

Following approval of this agent for first-line treatment for those progressing within 6 months of adjuvant chemotherapy or second-line treatment of metastatic breast cancer, numerous phase II studies have investigated the role of nab-Pac for earlier disease. However, nearly all of these studies used this agent in combination with carboplatin and bevacizumab, which yielded encouraging response rates ranging between 53% and 59%, particularly in the triple-negative subgroup [59–61].

The GeparSepto trial, which was a phase III study that evaluated the role of nab-Pac in the neoadjuvant setting, randomized 1204 patients to two arms, including standard paclitaxel weekly at 80 mg/m^2 for 12 weeks or nab-Pac weekly at 150 mg/m^2 for 12 weeks followed by four cycles of EC [62]. Patients with HER-2-positive disease received pertuzumab and trastuzumab throughout the treatment period (*n*: 400). A planned subgroup analysis revealed a significantly improved pCR rate of 48.2% in the triple-negative subgroup (*n*: 275 patients), with a hazard ratio of 2.69. Nevertheless, the 25.7% pCR rate of the standard arm in the triple-negative group was considerably lower than the values of 34.5% in the GeparSixto trial and 41% in the CALGB 40603 trials for similar combinations [63, 64]. Although caution is required to implement subgroup analysis for the whole group, based on the favorable outcome in the advanced setting, it would seem feasible to use this agent in the absence of effective targeted regimens. Nevertheless, it should be noted that further confirmatory data are required to establish the role of nab-Paclitaxel for triple-negative breast cancer.

Platin Compounds

Based on early preclinical data showing higher activity of platin compounds in TNBC and Her-2-positive disease, the role of carboplatin or cisplatin as neoadjuvant treatment was generally evaluated in these subtypes. Since TNBC is a subtype that most frequently harbors BRCA mutations, hence is most likely associated with homologous repair deficiency (HRD), platins may hypothetically have an advantage over other agents due to their DNA-binding effect. Although germline BRCA status has not been consistently linked with response to platin-based chemotherapy, there is clinical evidence suggesting that somatic mutations in the BRCA gene or the homologous repair pathway (HRD) may be potentially associated with platin responsiveness. Nevertheless, due to conflicting results from earlier trials, the use of platins in TNBC has been thoroughly debated until this date. Although a small phase II trial [65] failed to show a benefit with carboplatin added to

docetaxel compared to single-agent docetaxel following four cycles of a standard anthracycline-based combination, two larger randomized trials [63, 64] yielded significantly higher pCR rates, with increments of 13–16% (Table 13.5). Notably, both of these trials also incorporated bevacizumab as part of the combination regimens. Furthermore, a subgroup analysis in the GEPARSIXTO trial revealed that the addition of carboplatin provided benefit, regardless of the germline BRCA mutation status [odds ratio (OR): 2.09 for wild-type patients; $p = 0.005$ vs. OR: 1.6 for germline carriers; $p = 0.41$] [33]. In the triple-negative subgroup of the recently reported German Adapt trial, which incorporates a risk-adapted neoadjuvant strategy, four cycles of a nab-Pac and carboplatin combination yielded a significantly improved pCR rate compared to four cycles of nab-Pac and gemcitabine (45.9% vs. 28.7%, $p < 0$ 0.001) [67]. Translational data from a pooled analysis of three neoadjuvant studies including triple-negative patients suggests that tumors with a high HRD score were more likely to achieve pCR (53% vs. 18%) with a hazard ratio of 4.64 ($p < 0.0001$) irrespective of BRCA status [68]. This has also been confirmed in the recently reported phase III neoadjuvant BrightNess trial, which investigates the role of adding carboplatin and veliparib to the standard AC-T backbone in TNBC [69]. In this trial, carboplatin-containing arms yielded pCR rates of 57.8% and 53.1%, which compared favorably with the standard arm yielding a pCR of 27.9%, while addition of a PARP inhibitor failed to improve on the response by carboplatin (53.1% vs. 57.8%). The translational analysis revealed that HRD, seen in approximately 65–75% of the whole patient group, was indeed associated with improved pCR rates irrespective of the chemotherapy regimens tested, suggesting that HRD is not a predictive factor for either platin or PARP inhibitors but may be a surrogate predictive factor for chemotherapy responsiveness in general. This finding is in line with earlier retrospective studies showing that BRCA mutations are independently associated with improved response (pCR) to standard paclitaxel and anthracycline-based chemotherapy, along with hormone receptor negativity [70].

In light of the data showing significantly improved response rates, it would be reasonable to use platin-based regimens in triple-negative patients, who otherwise lack effective treatment options. The future of triple-negative disease holds promise as results from trials incorporating biomarker-driven strategies, including PARP inhibitors and PD-1 inhibitor-based combinations, are awaited with enthusiasm. Early-phase studies with these agents are discussed below in their corresponding sections.

In Her-2-positive disease, the role of carboplatin as part of a non-anthracycline-based regimen combined with dual blockade (TCH-Lapatinib and TCH-Pertuzumab) was investigated in two phase II trials, which each yielded pCR rates of 52% [28, 71]. Following encouraging response rates, especially in hormone receptor-negative patients, the TCHP regimen was further evaluated in two phase III trials. In the TRAIN-II trial, 27 weeks of this combination was compared to a standard anthracycline- and taxane-based combination with a similar total duration. Overall, the pCR rates were similar in both arms (68% vs. 67%, NS), including in hormone receptor (HR)-positive patients (55% vs. 51%; NS). Nevertheless, the numerically higher pCR rate in HR-negative patients (84% vs. 89%; NS) led to concerns regarding omission of anthracyclines in this subset [72]. Furthermore, in the phase III KRISTINE trial, the standard TCHP arm yielded a 56% pCR rate, in concordance with previous results utilizing the same regimen and confirming the efficacy of this combination [73]. When we put these data in context, non-anthracycline-based combinations incorporating carboplatin with taxanes, in addition to pertuzumab-based dual Her-2 blockade, have shown favorable pCR rates and should be considered in all patients who are eligible for neoadjuvant treatment, especially in those with cardiac comorbidities. In HR-negative patients, who are considered to harbor high-risk disease, omission of anthracyclines remains a matter of debate, and the decision should be individualized. The role of dual Her-2 blockade within the context of neoadjuvant treatment is further discussed in detail below.

Table 13.5 Platin-based neoadjuvant chemotherapy and pathological complete response rates

Author	Regimen	*n*	pCR (%)	*P*	DFS (%)	*P*
Alba [65]	EC-D	46	30		NA	
	EC-DC	48	30	NS	NA	NA
GeparSixto von Minckwitz [33, 63]	LdP-Bev	157	37		76.1%	
	LdPC-Bev	158	53	0.005	85.8% (3-yr DFS)	0.03
Sikov [64, 66]	P-ddAC (±Bev)	218	41		71%	
	PC-ddAC (±Bev)	225	54	0.0029	76% (3-yr DFS)	NS

pCR pathologic response rate, *dd* dose-dense, *AC* adriamycin-cyclophosphamide, *EC* epirubicin-cyclophosphamide, *D* docetaxel, *C* carboplatin, *Ld* liposomal doxorubicin, *P* paclitaxel, *Bev* bevacizumab, *yr* year, *DFS* disease-free survival, *NS* not significant, *NA* not applicable
The difference with $p < 0.05$ is significant

Biological Agents

HER-2-Targeting Agents

Trastuzumab

Trastuzumab-based combinations have initiated a new era in the treatment of early- and advanced-stage HER-2-positive breast cancer. An early study in the neoadjuvant setting, which was a small randomized pilot trial in operable patients, reported a pCR of 65.2% [74]. This unprecedented pCR rate has been confirmed by subsequent larger randomized trials that have evaluated the role of trastuzumab as part of standard anthracycline- and taxane-based regimens. One of these, the NOAH trial, had a unique design that permitted the concomitant use of anthracycline and trastuzumab. In that trial, the combination regimen yielded a pCR rate of 38% and a 5-year EFS of 71%, significantly higher than the pCR rate of 19% (p: 0.001) and EFS rate of 56% (p: 0.013) in the HER-2-positive patient subset of the control arm. The updated data after a median follow-up period of 5.4 years revealed a significant advantage in terms of overall survival, with a hazard ratio of 0.66 (p: 0.05) [15]. In terms of cardiac toxicity, there was no difference with respect to grade 3 and 4 cardiac events; there were only two patients (2%) who developed transient grade 3 left ventricular dysfunction in the trastuzumab arm. In the GeparQuattro trial, which was originally designed to test the efficacy of capecitabine in the neoadjuvant setting, trastuzumab was allowed as part of the treatment in the HER-2-positive subgroup. The pCR rate including residual DCIS was 48.9% among 340 HER-2-positive patients. In patients who were unresponsive to four cycles of EC, the pCR rate in the HER-2-positive group was five times that in the HER-2-negative cohort (16.7% vs. 3.3%), again confirming the role of trastuzumab even in patients with anthracycline-resistant disease [75].

Lapatinib

Lapatinib, a dual EGFR tyrosine kinase inhibitor, has already been established as an active agent in the metastatic setting. In the GeparQuinto trial, lapatinib (L) was tested head-to-head with trastuzumab (H) as part of a standard regimen consisting of four cycles of EC followed by four cycles of docetaxel (T). Of 620 eligible patients, 30.3% in the ECH-TH group had a pCR, significantly higher than the rate in the ECL-TL arm (22.7%) (p: 0.04) [76]. The NeoALTTO trial evaluated the role of lapatinib either as a single agent or in combination with trastuzumab compared to trastuzumab for 6 weeks followed by 12 weeks of paclitaxel added to the three randomized arms before surgery. Despite an amendment for dose reduction in the lapatinib arms due to increased grade 3 and 4 diarrhea and hepatic toxicity, there was a higher pCR rate with the dual blockade (51.3%) compared to single-agent trastuzumab (29.5%) or lapatinib (24.7%) (p: 0.0001) [77]. However, a recently reported subsequent study by the CALGB with a similar design indicated no advantage of dual-targeted therapy in terms of pCR (56% vs. 46%) [78]. The NSABP B41 trial, which differed slightly from the others in design, was a phase III trial that investigated the role of dual blockade following four cycles of an anthracycline-based combination followed by surgery. In this trial, the pCR rate in the combination arm was 60%, which was marginally significant compared to the unexpectedly high pCR rate for the trastuzumab and chemotherapy combination (52.5%; $p = 0.056$) [79]. Although the pCR rate in hormone receptor-negative patients was numerically higher than that in endocrine-responsive patients, the difference was not significant. The high rate of noncardiac adverse effects favored trastuzumab as the single agent of choice. Given these data, there is as yet no evidence supporting the role of lapatinib as a single agent or in the context of dual Her-2 blockade.

Pertuzumab

Pertuzumab is a monoclonal antibody that inhibits ligand-dependent signaling between HER-2 and HER-3 receptors and is thus complementary with trastuzumab. Based on encouraging data in metastatic patients both as first-line and subsequent treatment options, pertuzumab was also evaluated in the neoadjuvant setting. Initially, feasibility and potential cardiotoxicity were evaluated in the phase II TRYPHENA trial, which incorporated dual blockade with pertuzumab and trastuzumab in combination with a standard anthracycline-based and taxane-based regimen, as well as a non-anthracycline-based TCH combination and FEC followed by docetaxel, trastuzumab, and pertuzumab. This trial confirmed the cardiac safety of dual blockade. In addition, the high pCR rate reaching 66% supported the efficacy of non-anthracycline combinations in Her-2-positive disease [28].

In the NeoSphere trial, women with operable or locally advanced or inflammatory breast cancer were randomized to receive four cycles every 3 weeks of docetaxel, trastuzumab, or docetaxel, trastuzumab, and pertuzumab or a doublet of the two monoclonal antibodies, or docetaxel and pertuzumab. After surgery, treatment consisted of adjuvant FEC for three cycles and trastuzumab every 3 weeks for one full year for all cases who had already received docetaxel in the neoadjuvant section of the trial, while in patients who received the doublet of antibodies, postsurgical treatment consisted of docetaxel for four cycles and FEC for three cycles with trastuzumab. The in-breast pCR rate when pertuzumab was added to the conventional trastuzumab and docetaxel combination was 46.8%, significantly higher than the 24% pCR rate for the pertuzumab and docetaxel doublet and 29% pCR rate for the trastuzumab and docetaxel combination. Furthermore, there was a small subset of patients

(16.8%) who had a pCR with the non-chemotherapy-containing doublet antibody regimen, suggesting the possibility that there may be a group of patients who do not require any chemotherapy [80]. There was some concern regarding toxicity because the triplet combination resulted in more neutropenia and febrile neutropenia, and there was one treatment-related death with fulminant hepatitis. Based on the significantly higher pCR rate for the combination, pertuzumab received FDA approval in 2013 for the neoadjuvant treatment of Her-2-amplified breast cancer. An updated survival analysis showed numerically higher 5-year progression-free survival in the dual-blockade group compared with the standard arm of trastuzumab and docetaxel (86% vs. 81%). Although the confidence intervals are large and overlapping, these results suggest a higher efficacy of the pertuzumab, trastuzumab, and chemotherapy combination [81]. In light of accumulating data, further studies are needed to identify predictive markers that would help accurately define patients who would benefit from combined treatment strategies. Despite a lack of profound survival benefit with dual blockade, it seems feasible to utilize pertuzumab and trastuzumab combination in the neoadjuvant setting, based on evidence showing improved outcomes with increased pCR rates.

TDM-1

Trastuzumab emtansine is a new-generation conjugated monoclonal antibody bound with a tubulin inhibitor (maytansine). Based on successful results in trastuzumab-resistant disease as a second-line treatment in the advanced setting, TDM-1 was steadily incorporated in neoadjuvant trials. In the I-SPY trial, which followed an adapted strategy, patients harboring one of the three predictive signatures were more likely to achieve pCR with the TDM-1 and pertuzumab combination than in the standard trastuzumab paclitaxel arm [82]. The KRISTINE trial was a phase III trial comparing six cycles of the TCHP regimen to a non-chemotherapy doublet of the TDM-1 and pertuzumab combination. This trial yielded a lower pCR rate with the investigational regimen compared to the platin-based combination (44% vs. 56%) [73], in line with the recently reported Marianne trial, which showed a lack of benefit of the TDM-1 and pertuzumab regimen in the first-line advanced setting [83].

The data on dual blockade in Her-2-positive disease are summarized in Table 13.6.

Antiangiogenic Agents

Bevacizumab

Bevacizumab, a monoclonal antibody targeting VEGF, has unfortunately been withdrawn by the FDA for indication as a treatment option for metastatic breast cancer patients in light of recent data that failed to show a significant overall survival advantage despite favorable DFS rates. In the neoadjuvant setting, two trials evaluated the role of this antibody in combination with various cytotoxic regimens. In a subset of the GEPARQUINTO trial, HER-2-negative patients were randomized to four cycles of EC with bevacizumab and continued to four cycles of docetaxel plus bevacizumab if responsive to EC and to chemotherapy-only arms. This trial failed to show a benefit in terms of pCR of the addition of bevacizumab in the general population (17.5% vs. 15%), with a subgroup benefit in the receptor-negative subset [86]. To evaluate the role of capecitabine and gemcitabine, a subsequent study by the NSABP Group (NSABP B-40) randomized 1206 patients to docetaxel followed by four cycles of AC and a second randomization with or without bevacizumab. In this trial, the addition of bevacizumab significantly increased the pCR rate, which was the primary endpoint, from 28.2% to 34.5% ($p = 0.02$), with greater benefit observed in the hormone receptor-positive subset [56]. In an update analysis, an overall survival advantage was also reported that was most evident in this subgroup [87]. Nevertheless, it is not clear if the benefit observed in this trial is due to a compensatory effect in the context of a lower dose of docetaxel in the two thirds of patients who received the antibodies. In the CALGB 40603 trial, which included triple-negative patients, addition of bevacizumab resulted in an 8% incremental benefit over the 44% pCR rate achieved with the platin-based combination ($p = 0.057$). However, bevacizumab was associated with an increased incidence of grade 3 hypertension, febrile neutropenia, bleeding, and thromboembolic complications [64]. In the updated survival analysis, use of bevacizumab failed to result in a significant improvement in EFS or OS [66]. In conclusion, considering the conflicting evidence regarding the efficacy of bevacizumab within distinct molecular subgroups and the lack of a valid predictive marker, bevacizumab cannot be considered standard in the neoadjuvant setting at this time.

M-TOR Inhibitors

Everolimus

The mammalian target rapamycin (m-TOR) is a valid target that is frequently disrupted in breast cancer pathogenesis. The accumulation of favorable data in combination with hormonal and cytotoxic agents led to the randomized GeparQuinto trial to evaluate the role of everolimus in combination with paclitaxel as a second randomization in patients who were resistant to neoadjuvant EC with or without bevacizumab. The trial was stopped prematurely after 395 patients were randomized due to completion of the main trial. In terms of pCR, there was no difference between study arms (3.6% vs. 5.6%). Almost half of the patient group had to stop

Table 13.6 Dual Her-2 blockade as neoadjuvant chemotherapy and pathological complete response rates with respect to hormone receptor status

Trial	Phase	*n*	Regimen	pCR (whole population)	pCR (HR positive)	pCR (HR negative)
Lapatinib						
NeoAltto [77]	III	455	TL (6 wk)-TL/Pac (12 wk) T (6 wk)-T/Pac (12 wk) L (6 wk-L/Pac (12 wk)	47%[a] 27% 20%	42%[a] 22% 16%	61%[a] 37% 34%
CALGB 40601 [78]	III	305	TL/Pac (16 wk) T/Pac L/Pac	56% 46% 32%	41% 41% 29%	79%[a] 54% 37%
NSABP B-41 [79]	III	529	AC × 4-TL/Pac (16 wk) AC × 4-T/Pac (16 wk) AC × 4-L/Pac (16 wk)	60% 49% 47%	55% 46% 42%	70% 58% 55%
TRIO-US B07 [71]	II	128	LT (3 wk)-DCTL (18 wk)	52%	40%	67%
CHERLOB [84]	II	121	TL/Pac (12 wk)-FEC × 4 T/Pac (12 wk)-FEC × 4 L/Pac (12 wk)-FEC × 4	47%[a] 25% 26%	29% – –	41% – –
Pertuzumab						
NEOSPHERE [80]	II	417	DTP (12 wk) DT DP TP	39%[a] 23% 18% 11%	26% 20% 17% 6%	63% 37% 30% 29%
TRYPHENA [28]	II	225	FEC/TP (9 wk)-DTP (9 wk) FEC (9 wk)-DTP (9 wk) DCTP (18 wk)	52% 45% 52%	– – –	– – –
KRISTINE [73]	III	432	DCTP (18 wk) TDM-1/P (18 wk)	56%[a] 44%	45% 38%	73% 54%
NSABP FB-7 [85]	II	126	Neratinib/PT (16 wk)-AC × 4	50%	30%	74%
ISPY 2 [65–82]	II	46/52	TP/Pac (12 wk)-AC × 4 TDM-1/P (12 wk)-AC × 4	54% 52%	44% 46%	74% 64%
TRAIN-II [72]	III	438	FEC/TP (9 wk)-TP/Pac (18 wk) TP/Pac (27 wk)	67% 68%	51% 55%	89% 84%

pCR pathologic response rate, *HR* hormone receptor, *AC* adriamycin-cyclophosphamide, *FEC* fluorouracil-epirubicin-cyclophosphamide, *Pac* paclitaxel, *D* docetaxel, *C* carboplatin, *L* lapatinib, *P* pertuzumab, *T* trastuzumab, *wk* week
[a]$p < 0.05$ (vs. standard arm)

the treatment due to side effects in the combination arm, and there were concerns about whether everolimus attenuated the cytotoxic effects of paclitaxel on inhibition of cell cycle progression. In addition, there was no indication that any subgroup may have benefited from the addition of everolimus to paclitaxel in this resistant group of patients [88].

PARP Inhibitors: Veliparib and Talazoparib

Triple-negative breast cancer, which make up for 15% of the whole breast cancer population, comprises 70% of BRCA 1 and 20% of BRCA 2 mutation carriers [89–92]. The identification of PARP enzymes and their role in DNA repair pathways, especially but not exclusively in BRCA mutant patients have led to the development of a new class of agents, called PARP inhibitors in these patient groups. The first-generation PARP inhibitor veliparib has been rapidly moved to phase III-level investigation in combination with carboplatin after being graduated with a high likelihood of response from the biomarker-based adoptive I-SPY 2 trial [93]. The subsequent phase III BrightNess trial unfortunately failed to show a pCR benefit with the addition of veliparib regardless of the chemotherapy regimen used [94]. In this trial 634 patients were randomized to one of three arms comprising of veliparib plus carboplatin and weekly paclitaxel or carboplatin and weekly paclitaxel or single-agent weekly paclitaxel, followed by four cycles of AC and then proceeded to surgery. Patients receiving carboplatin were significantly more likely to achieve a pCR as compared to the standard arm (58% vs. 31%; $p < 0.0001$), whereas the pCR rate in the veliparib arm was slightly inferior than the carboplatin arm (53%; $p = 0.36$). A translational analysis of this study including HRD and gBRCAm, which is discussed above in this chapter, failed to identify a biomarker that would predict for the efficacy of veliparib [69].

Talazoparib, a second-generation PARP inhibitor with a more potent PARP-trapping activity, has been recently evaluated in a single-arm small phase II study in patients with germline BRCA mutations [95]. This trial enrolled 20 patients who were given talazoparib for 6 months before surgery, followed by systemic chemotherapy of physician's choice. Fifteen patients had TNBC; five were hormone responsive.

All but one patient completed all 6 months of therapy and the pCR rate was 53%; the ratio of patients with a RCB 0-1 was reported as 63%. This encouraging pCR rate led to a larger confirmatory phase III trial, which is currently ongoing. Data from this trial and others are awaited with enthusiasm to determine the role of PARP inhibitors in this setting.

Immune Checkpoint Inhibitors

Breast cancer has been considered as a nonimmunogenic tumor for a long time. Nevertheless, the identification of tumor-infiltrating lymphocytes and their association with prognosis, as well as response to anthracyclines, taxanes, and Her-2 blockade in the neoadjuvant setting, generated enthusiasm to explore the role of immunotherapy in breast cancer across all molecular subtypes [96–100]. TCGA analysis of breast cancer subtypes as determined by the PAM 50 assay revealed high stromal TIL infiltrations in the triple-negative and Her-2-enriched groups [101]. Confirmatory data were attained by a collective sensitivity analysis of 8 trials including 5514 patients, which showed a significantly higher pCR rate in lymphocyte-predominant tumors, as well as a robust association with OS in TN and Her-2 subtypes [102]. Based on these data, as well as a clinicopathologic study showing a strong negative prognostic impact of PD 1 (+) TILs in breast cancer [103], the paradigm shift with immune checkpoint inhibitors (ICI) across many cancer types led to the investigation of these agents in breast cancer. Since TILs have been shown to have a strong prognostic and predictive value in TNBC, initial trials with ICI including pembrolizumab, avelumab, and atezolizumab have focused on this subtype. Early phase Ib-II trials with these agents in heavily pretreated metastatic patients have yielded response rates ranging between 19% and 24%, which improved with increased PD-1 expression [104–108]. The higher response rates achieved with chemotherapy combinations in the metastatic setting have led to trials investigating the role of ICI and CT combinations in the neoadjuvant setting [109–111]. These trials are summarized in Table 13.7.

Results from ongoing phase III trials investigating the role of ICI in combination with chemotherapy in the neoadjuvant setting, as well as maintenance treatment in patients with residual tumors following neoadjuvant chemotherapy, will clarify the role of immunotherapy in breast cancer.

Conclusion

Neoadjuvant chemotherapy offers an ideal setting to identify regimens or agents that could be prioritized for adjuvant confirmatory trials and to identify biomarkers or genomic signatures that would predict response or resistance to a given regimen. Numerous trials performed over the last three or four decades have provided valuable information on the biology of breast cancer, as well as efficacy data that helped to improve treatment strategies in earlier stages. There exists substantial evidence from meta-analyses suggesting that pCR is an important surrogate endpoint for outcome in most subgroups, and it is now argued that costly, time-consuming large trials may be spared for agents showing a high pCR rate with survival advantage in the neoadjuvant setting. With the advent of molecular diagnostic techniques and translational medicine, the last decade has proved to be an exciting era for oncology research. Nevertheless, the more we examine the basic mechanisms of oncogenesis, the deeper in the abyss of the cancer enigma we find ourselves. There appears to be much more to be accomplished than ever to develop better treatment options for patients with breast cancer.

Table 13.7 Immune checkpoint inhibitors in the neo-adjuvant setting

Trial	Treatment	BC subtype	*n*	Response
I-SPY 2 [109]	Pembrolizumab 200 mg q3wk + wk Pac 80 mg/m^2 × 12–4 × AC	Her-2 negative	69	TNBC: 60% HR (+): 34%
	wk Pac 80 mg/m^2 × 12–4 × AC	Her-2 negative (control)	180	TNBC: 20% HR (+):13%
KEYNOTE 173 [110]	Pembrolizumab 200 mg q3 + wk nab-Pac 125 mg/m^2 × 12–4 × pembrolizumab AC	TNBC Cohort A	10	pCR: 70%
	Pembrolizumab 200 mg q3 wk + nab-Pac 125 mg/m^2 × 12 + Carboplatin AUC 6 q 3 wk–4 × pembrolizumab AC	TNBC Cohort B	10	pCR: 100%Scmid
GeparNuevo [111]	Durvalumab 1.5 g D1 q28 (+ 2 wk run-in phase) + nab-Pac 125 mg/m2 wk × 12 – durvalumab 1.5 g D1 q28 + 4 × EC	TNBC	88	pCR: 53%[a]
	Placebo + nab-Pac 125 mg/m2 wk × 12 – Placebo +4 × EC	TNBC (control)	86	pCR: 44%

wk weekly, *Pac* paclitaxel, *nab-Pac* nab-paclitaxel, *TNBC* triple-negative breast cancer, *HR (+)* hormone responsive, *pCR* pathological complete response

[a]Preplanned group with a durvalumab run-in phase had a 60% pCR rate (*p*: 0.05 vs. 41% pCR in CT group with placebo run-in)

In conclusion, preoperative systemic chemotherapy is a valuable research tool for identifying predictive molecular biomarkers and a valid treatment option for patients with early-stage breast cancer. However, the decision to treat a patient with neoadjuvant chemotherapy requires careful clinical judgment and multidisciplinary evaluation by an experienced team.

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Neoadjuvant Hormonal Therapy in Breast Cancer

14

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Introduction

Until recently, conventional treatment of estrogen receptor (ER)/progesterone receptor (PgR)-positive breast cancer patients, especially postmenopausal women, consisted of surgery, adjuvant endocrine therapy, radiation therapy, and/or chemotherapy depending on the tumor stage [1]. However, in practice, chemotherapy can lead to additional toxicity in postmenopausal elderly patients. Consequently, different treatment modalities have been developed [2]. One of these is neoadjuvant hormonal therapy (NHT) or neoadjuvant chemotherapy. Neoadjuvant therapy is administered prior to surgery to reduce the size of the tumor as well as to turn an inoperable tumor into an operable one or to allow breast-conserving surgery (BCS) [3]. Tamoxifen, which is a selective estrogen receptor modulator, has been used as an adjuvant therapy for early breast cancer as well as metastatic disease. Recent studies have shown that tamoxifen can also be used for neoadjuvant purposes [3, 4]. Aromatase inhibitors (AI) have since become the main focus as NHT in postmenopausal patients [5].

In the treatment of breast cancer, neoadjuvant treatment approaches remain unclear. The use of NHT was widely accepted at the 13th St. Gallen International Breast Cancer Conference [6]. The general purposes of neoadjuvant treatments in breast cancer include making inoperable large tumors operable, increasing the probability of performing breast-conserving surgery (BCS), obtaining a high antitumoral efficiency benefit, and prolonging general survival as well as the duration until progression. While neoadjuvant treatment may be performed with classic chemotherapy agents, it may also be performed with hormonal therapy in hormone receptor-positive patients. The efficiency of NHT is still under investigation [7]. The aims of neoadjuvant hormonal therapy include reducing the size of breast tumors, maintaining efficient control via early-onset systemic treatment, enabling resection, and increasing the responsiveness of tumor cells to the administered systemic treatment. However, NHT may result in the development of resistance to systemic treatments at an early stage. In addition, NHT is restrictive in terms of delaying surgery while the treatment is administered. Moreover, because the lymph nodes shrink following neoadjuvant treatment, the assessment of the lymph nodes may provide inconclusive data. NHT is administered as tamoxifen, letrozole, anastrozole, exemestane, and other hormonal treatments.

Various studies of NHT have been conducted. In the literature, there are 13 single-arm studies [8], four studies involving AI versus tamoxifen, five studies comparing AIs [3], and four studies of NHT and neoadjuvant chemotherapy. Despite these various studies involving NHT, a comprehensive systematic review has only recently been published [8]. In these studies, the clinical response rate was 13.5–110%, and the duration of treatment varied between 3 and 24 months. NHT studies began in the 1990s. The first administered treatment for this purpose was tamoxifen; however, preliminary studies showed that tamoxifen could not control tumors sufficiently [9]. A subsequent study showed that neoadjuvant tamoxifen treatment reduces the requirement for surgery [10]. In an attempt to assess responsiveness, studies were conducted with tamoxifen+aromatase inhibitors in addition to studies of tamoxifen treatment only. Responsiveness in patients was assessed by breast ultrasonography, mammography, and breast examination.

Postmenopausal hormone receptor-positive patients were included in the Edinburgh study, which included 171 patients. The study was designed to include extended resection ($n = 35$), tamoxifen ($n = 65$), letrozole ($n = 36$), anastrozole ($n = 23$), and exemestane ($n = 12$) [11]. The study revealed that the response rate of patients who received aromatase inhibitors was high, and instead of radical mastectomy, BCS was performed on the patients (Table 14.1). In this study,

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Table 14.1 Neoadjuvant hormonal therapy (Edinburgh study) [11]

Drug	Number of patients	Mastectomy at onset	Surgery after neoadjuvant	Rate of breast conserving (%)
Tamoxifen	65	41	15	63
Letrozole	36	24	2	93
Anastrozole	24	19	2	89
Exemestane	12	10	2	80

patients received treatment with letrozole 2.5 mg and 10 mg and anastrozole 1 mg and 10 mg. Intake of the 10-mg dose in patients who received aromatase inhibitors (AIs) did not provide an additional increase in the response rate. In addition, patients who received AIs exhibited a better response rate than patients who received tamoxifen 20 mg. The response rates were 81% with letrozole, 87% with anastrozole, and 48% with tamoxifen.

Another NHT study was the Bergonie study. In this study, postmenopausal patients who were 50–70 years of age were evaluated, and neoadjuvant tamoxifen treatment was assessed. Ninety-seven of the 199 patients who received neoadjuvant tamoxifen had operable tumors (T2–T3, N0/1), and 102 patients had T4 tumors. During follow-up with a median treatment duration of 5.3 months, T2–T3 (89 patients, 92%), and T4 (93 patients, 91%) were operated. The BCS rates in the T2–T3 and T4 groups were 53.6% and 44%, respectively. General survival was assessed in the 83rd month. Overall, NHT was determined to be administrable [12].

Another NHT trial was the French Exemestane Study. In the Exemestane Study, a phase II study, postmenopausal patients with hormone receptor-positive and T2–T4 tumors (locally advanced) were treated with exemestane 25 mg/day as neoadjuvant therapy for 16 weeks. In cases where patients received neoadjuvant exemestane, the response rate (RR) was 73.3%, whereas the BCS rate was 57.1%. In this study, exemestane reduced Ki-67 expression and PR expression. The significant decrease in PR expression was correlated with the clinical response. No relationship was observed between the generated response and aromatase mRNA or ER-beta expression. As a result, exemestane exhibits efficiency and safety profiles as a neoadjuvant therapy [13]. In the literature, the first phase III clinical study was the study conducted by Eiermann et al. In the PO-24 letrozole efficiency study, letrozole and tamoxifen were compared as NHTs [14]. In this study, the clinical response rate was significant in the letrozole arm based on assessments by palpation ($p < 0.001$), ultrasonography ($p < 0.042$), and mammography ($p < 0.001$). Letrozole had a better outcome in ER-positive and HER-2-positive patients. In the Immediate Preoperative Arimidex Compared with Tamoxifen (IMPACT) study, anastrozole and tamoxifen were compared solely with anastrozole or tamoxifen [15]. A total of 337 patients were enrolled in the study. The drugs were implemented as a preoperative treatment for 12 weeks. In this study, although RRs were the same in all groups, BCS was more performable in the anastrozole group. Again, in this study, the response rate for anastrozole was significant in HER-2-positive patients. This study revealed that anastrozole is applicable as NHT. This trial did not show superiority of the combination. The response rates and breast-conserving surgery rates were 37% and 44%, respectively, in the anastrozole arm but 36% and 21%, respectively, in the tamoxifen arm. There were no differences between the two arms. In addition, there was no difference in response rates or BCS rates according to *HER-2* status.

Table 14.2 Summary of phase III studies where neoadjuvant hormonal therapy was assessed

	Letrozole 024 [14]	IMPACT [15]	PROACT [16]
Number (*n*)	337	330	451
Patient characteristic	BCS not appropriate (14% inoperable)	96 appropriate BCS	Inoperable
Duration	4 months	12 weeks	3 months
Response oRR	55% L vs. 35% T ($p < 0.001$)	37% A vs. 24% AT vs. 31% T $p > 0.05$	43% A vs. 30.8% T $p > 0.05$
BCS	45% L vs. 35% T ($p < 0.022$)	44% A vs. 24% AT vs. 31% T $p > 0.05$	43% A vs. 30.8% T $p > 0.05$

BCS Breast-conserving surgery

In the Preoperative Arimidex Compared to Tamoxifen (PROACT) study, anastrozole was compared with tamoxifen, and the efficiency of anastrozole was shown by assessment with ultrasonography [16]. A summary of phase III studies in which neoadjuvant hormonal therapy was assessed is shown in Table 14.2. In the PROACT study, 451 postmenopausal locally advanced breast cancer patients were enrolled. The patients were randomized to anastrozole and tamoxifen arms for 3 months. The response rates and breast-conserving surgery rates were 39.5% and 38%, respectively, in the anastrozole arm

but 35.4% and 29.9%, respectively, in the tamoxifen arm. There was no significant difference between the two arms.

While no data in the Edinburgh Study were related to the assessment of local relapse after neoadjuvant hormonal therapy, in another study, 112 patients were administered breast-conserving surgery after neoadjuvant hormonal therapy. The median follow-up was 62 months, and during the relapse assessment in the fifth year of follow-up, no difference was observed between tamoxifen and AIs [5]. Moreover, in another study, preoperational and postoperational NHT were assessed; no significant differences were observed between anastrozole and letrozole [17].

In postmenopausal cases, the optimal NHT duration should be >3–4 months [5]. The St. Gallen Consensus Panel advised hormonal therapy alone as neoadjuvant treatment for postmenopausal patients with strongly positive hormone receptors and low-proliferating disease. Moreover, most thought that such a treatment should be continued until the maximal response [6]. Response assessments at 0–3 months, 3–6 months, and 6–12 months of patients who received postmenopausal NHT revealed that the size of the tumor was reduced in each stage. In a phase II study [13], the objective median response was 3.9 months and the maximum response rate was 4.2 months. In these studies, the histological subtype was generally reported to be invasive ductal and lobular breast cancer [18–20].

Studies involving NHT have also been conducted in premenopausal patients [21]. Thirteen estrogen receptor-positive premenopausal patients were administered NHT and goserelin, and a response was obtained in seven of these cases. Thirty-two patients were included in another premenopausal NHT study. Patients were administered LHRH analogues and letrozole treatment. Although pathological complete response was obtained in one patient, clinical partial response was observed in 15 cases. As a result, this treatment modality may be administered in selected clinical cases; however, comprehensive clinical studies are required [22]. In a study by Masuda et al., premenopausal patients were administered ovarian ablation with goserelin and anastrozole versus tamoxifen. A significant clinical response was obtained in patients who received anastrozole [23]. In another study, researchers used exemestane, anastrozole, and letrozole in NHT [24]. In this study, although the RR was 74.8% in the letrozole arm, it was 62.9% and 69.1% in the exemestane and anastrozole arms, respectively. BCS did not differ significantly among these three groups.

In a comprehensive study comparing NHT in and NCT [25], NHT provided an effective response rates at least equivalent to those of NCT. Moreover, the administration rate of BCS was higher in the arm that received NHT. In another study of 95 patients, NHT provided a better response rate compared to that of NCT ($p = 0.075$) [26].

In the ACOSOG Z1031 study, 377 patients were enrolled with clinical stage II/III and strongly ER-positive disease (Allred score 6–8). The patients were randomized to three arms: letrozole, anastrozole, and exemestane. The response rates were 70.9%, 66.7%, and 60.5%, respectively. There were no differences between the arms. Marker panel studies were also performed in this study [24].

A randomized study of postmenopausal hormone receptor-positive breast cancer patients compared NHT to neoadjuvant chemotherapy. In the study, preoperative four-cycle chemotherapy and 12 weeks of anastrozole and exemestane practice were compared [25]. The response rates were 63.4% and 64.5%, respectively, and the BCS rates were 24% and 33%, respectively. There was no difference between the arms. By contrast, the toxicity of chemotherapy was higher than that of NHT.

Finally, the first report of clinicopathological analysis in the neoadjuvant treatment phase of NEOS was noted in a report presented at the 2014 San Antonio Breast Cancer annual meeting as The New primary Endocrine-therapy Origination Study (NEOS: N-SAS BC06 study: UMIN 000001090). The trial was performed as a randomized controlled trail to verify the necessity of adjuvant chemotherapy in node-negative, ER+, and HER-2− postmenopausal breast cancer patients who responded to neoadjuvant endocrine therapy. The trial showed that neoadjuvant letrozole therapy improved breast cancer surgery rates. MRI was useful for predicting the residual pathological invasive tumor size. PR + and a small tumor size at baseline were significant independent predictors of the clinical response.

There are two ongoing clinical trials. The first is Alliance A011106: ALTernate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment ***(ALTERNATE)*** *in postmenopausal women: A phase III study. The second trial, the* ***CYPTAM-BRUT 2*** *trial, is a prospective multicenter study evaluating the effect of impaired tamoxifen metabolization on efficacy in breast cancer patients receiving tamoxifen in the neoadjuvant or metastatic setting. In the near future,* these studies will open up new horizons in neoadjuvant endocrine treatment in breast cancer [26].

Neoadjuvant endocrine therapy is not recommended in premenopausal patients. There are no studies in which NHT

has been administered to premenopausal patients except case reports [27].

The neoadjuvant setting might serve as an attractive model for drug development in ER+ breast cancer. Trials comparing endocrine monotherapy with combination therapy suggest superior radiological response rates. Cyclin-dependent kinase-4 and 6 (CDK4/6) are important in cell proliferation. CDK4/6 inhibitors have shown activity in hormone receptor-positive breast cancer. More recently, a new generation of very specific CDK 4/6 inhibitors have been developed. Three CDK4/6 inhibitors have been tested in clinical BC trials, and three oral agents selectively targeting CDK4/6 are currently in development. These agents are palbociclib, abemaciclib, and ribociclib [28, 41].

The phosphatidylinositide 3-kinase (PI3K) pathway also plays an important role in many cellular processes, including cell proliferation, differentiation, and survival. Taselisib is a potent and selective phosphatidylinositide 3-kinase (PI3K) inhibitor [29]. Several ongoing trials are combining endocrine therapy with selective inhibitors of the PI3K/Akt/mTOR/D-cyclin-CDK4/6 pathways in the neoadjuvant setting, such as letrozole with or without the PI3K inhibitor taselisib (LORELEI) [30] and letrozole with or without the CDK4/6 inhibitor palbociclib (PALLET) [31].

Preliminary analysis of a phase 2 trial examining palbociclib combined with anastrozole as neoadjuvant therapy for stage 2 or 3 ER+ breast cancer showed that the addition of a CDK4/6 inhibitor significantly lowers Ki67 levels, suggesting that the addition of CDK4/6 inhibition can improve the efficacy of NET [32]. Some neoadjuvant studies have focused on cyclin-dependent kinase 4/6 inhibitors. The neoadjuvant trial NeoPalAna evaluated palbociclib in primary breast cancer. Premenopausal and postmenopausal women with clinical stage II/III, estrogen receptor+/HER-2− breast cancer received anastrozole for 4 weeks, followed by the addition of palbociclib until surgery. In this study, the addition of palbociclib to anastrozole enhanced cell cycle control was compared to anastrozole monotherapy and significantly increased the response rate (87% vs. 26%, $p < 0.001$).

The NeoPAL study is an ongoing open-label phase II study that randomizes postmenopausal patients with localized, stage II–IIIA, luminal A, and node-positive or luminal B operable breast cancer, who are candidates for chemotherapy but not candidates or uncertain candidates for breast conservation to receive either sequential standard chemotherapy (3 FEC 100-3 docetaxel 100) or the same duration of the letrozole plus palbociclib combination as the neoadjuvant treatment [33]. The outcomes of this study are expected. There are many studies related to these issues [14–16, 23–27, 34–40]. Details on the selected studies are shown in Table 14.3 [33].

The agents used in combination with NHT in these studies were everolimus, celecoxib, zoledronic acid, gefitinib, dual endocrine therapy with AI plus tamoxifen, and lapatinib. The analysis of monotherapy versus dual therapy showed no difference in terms of clinical response rate (OR, 0.91; 95% CI, 0.70–1.19; $p = 0.50$; $n = 941$) [41]. Many studies have attempted to show an effect of neoadjuvant hormonotherapy. Details on selected studies are shown in Table 14.4 [41].

No markers for the benefit of neoadjuvant hormonal therapy have been identified, and the Ki-67 proliferation index may be used as a marker for this purpose. The recent publication of the ACOSOG Z1031 trial results showed that Ki-67 proliferation marker-based neoadjuvant endocrine therapy response monitoring could be used for tailoring the use of adjuvant chemotherapy in ER+, HER-2− breast cancer patients [24]. Ki-67 cut-points relevant to neoadjuvant endocrine treatment monitoring have been validated, and a Ki-67 clinical trial assay for prospective studies has been developed, validated, and used in the ACOSOG Z1031 trial [36, 42]. The authors developed an efficient and reproducible Ki-67 scoring system that was approved for NCI-supported neoadjuvant endocrine therapy trials. According to the methodology, investigators are able to identify a subgroup of patients with ER+, HER-2− breast cancer that can be safely managed without the need for adjuvant chemotherapy [43].

Table 14.3 Summary of the clinical trials included in the studies [33]

Subtype	CDK4/6 inhibitor	NCT	Phase	Status	Number of patients	Menopausal status	Experimental arm	Control arm
HR+, HER-2–	Palbociclib	NeoPalAna NCT01723774	2	R	87	Premenopausal and postmenopausal	Palbociclib + anastrozole	–
HR+, HER-2–	Palbociclib	NeoPAL, NCT02400567	2	A N/R	125	Postmenopausal	Palbociclib + letrozole	Fluorouracil, epirubicin, cyclophosphamide (FEC 3 cycles) + docetaxel (three cycles)
HR+ (lum A), HER-2–slowly proliferating (Ki67 < 20%)	Palbociclib	PREDIX LumA, NCT02592083	2	R	200	Premenopausal and postmenopausal	ET for 4 weeks, ET + palbociclib for a total of 16 weeks	ET for 16 weeks
HR+ (lum A/B), HER-2–node positive	Palbociclib	PREDIX LumB NCT02603679	2	R	200	Premenopausal and postmenopausal	Palbociclib + ET for 12 weeks, weekly paclitaxel for 12 weeks	Weekly paclitaxel for 12 weeks, palbociclib + ET for 12 weeks
HR+, HER-2–	Palbociclib	NeoRHEA NCT03065621	2	NYR	100	Premenopausal and postmenopausal	Palbociclib + ET	–
HR+, HER-2–	Palbociclib	PALLET NCT02296801	2	R	306	Postmenopausal	A: letrozole for 2 weeks, letrozole + palbociclib for a total of 14 weeks B: palbociclib for 2 weeks, letrozole + palbociclib for a total of 14 weeks C: Palbociclib + letrozole for 14 weeks	Letrozole for 14 weeks
HR+, HER-2–	Palbociclib	NCT02626507	1	R	18	Premenopausal and postmenopausal	Gedatolisib (mTOR inhibitor) + palbociclib fulvestrant	–
HR+, HER-2–	Ribociclib	MONALEESA-1 (NCT01919229)	2	T	14	Postmenopausal	Ribociclib (600 or 400 mg) + letrozole	Letrozole
HR+, HER-2–	Ribociclib	FELINE NCT02712723	2	R	120	Postmenopausal	Ribociclib (600 or 400 mg) + letrozole for 24 weeks	Letrozole for 24 weeks
HR+, HER-2–	Abemaciclib	neoMONARCH NCT02441946	2	C	224	Postmenopausal	Abemaciclib + anastrozolo or abemaciclib monotherapy (14 + 2 weeks)	Anastrozole
HR+, HER-2–	Abemaciclib	ABC-POP NCT02831530	2	R	115	Premenopausal and postmenopausal	Abemaciclib for 14 days before surgery	–
HR+, HER-2+	Palbociclib	NA-PHER2 NCT02530424	2	A N/R	36	Premenopausal and postmenopausal	Trastuzumab (6 cycles) + pertuzumab (6 cycles) + palbociclib (5 cycles) + fulvestrant (5 cycles)	–
HR+, HER-2+	Palbociclib	PALTAN NCT02907918	2	R	48	Premenopausal and postmenopausal	Palbociclib + letrozole + trastuzumab for 16 weeks	–

N/R active but not recruiting, *C* completed, *ET* endocrine therapy, *HR* hormone receptor, *NYR* not yet recruiting, *R* recruiting, *T* terminated

Table 14.4 Summary of the clinical trials included in the meta-analysis [41]

(Trial name) [14–16, 23–27, 34–40]	Experimental arm therapy	Experimental arm therapy duration, weeks	Control arm therapy	Control arm therapy duration, weeks	Total number of participants for comparisons	Primary end point
Alba et al. (2012) (GEICAM/2006–03)	Exemestane, 25 mg/d, plus goserelin, 3.6 mg/mo if premenopausal	24	EC-T: epirubicin, 90 mg/m^2, plus cyclophosphamide, 600 mg/m^2 × 4 cycles q21d Docetaxel, 100 mg/m^2 × 4 cycles q21d plus goserelin, 3.6 mg/mo if premenopausal	24	95	OR by MRI based on RECIST criteria
Palmieri et al. (2014) (NEOCENT)	Letrozole, 2.5 mg/d	18–23	FEC: fluorouracil, 500–600 mg/m^2, plus epirubicin, 75–100 mg/m^2, plus cyclophosphamide, 500–600 mg/m^2 × 6 cycles q21d; switched to docetaxel, 100 mg/m^2 after 3 cycles if SD or PD (n = 11)	18	44	Feasibility of OR (by US or mammography based on RECIST criteria) was a secondary end point
Semiglazov et al. (2007)	Anastrozole, 1 mg/d Exemestane, 25 mg/d	12	Doxorubicin, 60 mg/m^2, plus paclitaxel, 200 mg/m^2 × 4 cycles q21d	12	239	OR by clinical palpation (PR defined as regression >50%) OR by US/mammography was a secondary end point
Eiermann et al. (2001) (PO24)	Letrozole, 2.5 mg/d	16	Tamoxifen, 20 mg/d	16	324	OR by clinical palpation OR by US/mammography was a secondary end point
Smith et al. (2005) (IMPACT)	Letrozole, 2.5 mg/d	12	Tamoxifen, 20 mg/d	12	330	OR by caliper assessment based on WHO criteria OR by US was a secondary end point
Masuda et al. (2012) (STAGE)	Anastrozole, 1 mg/d, plus goserelin, 3.6 mg/mo	24	Tamoxifen, 20 mg/d, plus goserelin, 3.6 mg/mo	24	197	OR by caliper assessment OR by US, MRI, or CT based on RECIST criteria was a secondary end point
Cataliotti et al. (2006) (PROACT)	Anastrozole, 1 mg/d	12	Tamoxifen, 20 mg/d	12	314	OR based on US by RECIST criteria
Ellis et al. (2001)	Letrozole, 2.5 mg/d	16	Tamoxifen, 20 mg/d	16	250	OR by clinical assessment based on WHO criteria OR by US/mammography was a secondary end point
Hojo et al. (2013) (PTEX46)	Exemestane, 25 mg/d	24	Exemestane, 25 mg/d	16	51	OR by caliper assessment based on RECIST criteria

Table 14.4 (continued)

(Trial name) [14–16, 23–27, 34–40]	Experimental arm therapy	Experimental arm therapy duration, weeks	Control arm therapy	Control arm therapy duration, weeks	Total number of participants for comparisons	Primary end point
Kuter et al. (2012) (NEWEST)	Fulvestrant, 500 mg/mo, plus 500 mg on d 14 of mo 1	16	Fulvestrant, 250 mg/mo	16	211	OR by three-dimensional US assessment (PR defined as regression ≥65%)
Ellis et al. (2011) (ACOSOG Z1031)	Exemestane, 25 mg/d	16–18	Letrozole, 2.5 mg/d; anastrozole, 1 mg/d	16–18	374	OR by clinical assessment based on WHO criteria
Polychronis et al. (2005)	Gefitinib, 250 mg/d, plus anastrozole, 1 mg/d	4–6	Gefitinib, 250 mg/d, plus placebo	4–6	56	Change in Ki67 secondary end points included clinical and US assessments
Fasching et al. (2014) (FemZone)	Letrozole, 2.5 mg/d, plus intravenous zoledronic acid, 4 mg q4w	24	Letrozole, 2.5 mg/d	24	131	OR by mammography based on RECIST criteria
Mohammadianpanah et al. (2012)	Letrozole, 2.5 mg/d, plus fluorouracil, 600 mg/m^2, doxorubicin, 60 mg/m^2, and cyclophosphamide, 600 mg/m^2 (FAC), q21d	9–13	Fluorouracil, 600 mg/m^2, doxorubicin, 60 mg/m^2, and cyclophosphamide, 600 mg/m^2 (FAC), q21d	9–13	62 (ER+)	OR by caliper assessment and US based on RECIST criteria pCR

Conclusion

Overall, NHT is safe, and BCS does not increase local relapse. Especially in elderly patients, NHT is a good alternative that can provide high response and BCS rates. A better response is obtained with AI. According to the St. Gallen recommendations [1], NHT may be administered in postmenopausal patients if ER is >50%, and treatment may be continued with AIs until the maximal response is obtained. In addition, new antihormonal agents can be used in these patients.

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Systemic Therapy for Locally Advanced Breast Cancer

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Introduction

Neoadjuvant therapy refers to the systemic treatment of breast cancer prior to definitive surgical therapy (i.e., preoperative therapy). Locally advanced breast cancer (LABC) has always included a heterogeneous group of presentations. According to the American Joint Committee on Cancer (AJCC) staging system, LABC technically can include a patient with a clinically apparent internal mammary or paraclavicular node as well as the more commonly accepted presentations, which include a primary breast cancer larger than 5 cm, disease fixed to the chest wall or involving the skin, or bulky palpable disease in the axilla. Inflammatory breast cancer can also be called LABC. The approach to LABC has evolved considerably over the years. Surgery and radiation therapy were once the only available treatments, but multimodal approaches that emphasize *systemic therapy* have become the standard of treatment [1–3].

Conversely, neoadjuvant therapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except tumor size and wish to undergo breast-conserving therapy. Preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed. In the available data from clinical trials of preoperative systemic therapy, pretreatment biopsies have been limited to core-needle biopsy or fine-needle aspiration (FNA) cytology. Therefore, in patients anticipated to receive preoperative systemic therapy, core biopsy of the breast tumor and placement of image-detectable marker(s) should be considered to demarcate the tumor bed for any future (post-chemotherapy) surgical management. Clinically positive axillary lymph nodes should be sampled by FNA or core biopsy, and positive nodes must be removed following preoperative systemic therapy at the time of definitive surgery. Patients with clinically negative axillary lymph nodes should have axillary ultrasound prior to neoadjuvant treatment. For those with clinically suspicious axillary lymph nodes, positive nodes indicated by core biopsy should be removed following neoadjuvant therapy at the time of definitive surgery [4, 5].

The primary objective of neoadjuvant therapy is to improve surgical outcomes in patients for whom a primary surgical approach is technically not feasible and in patients with operable breast cancer who desire breast conservation but for whom either a mastectomy is required or a partial mastectomy would result in a poor cosmetic outcome [6–8].

Neoadjuvant chemotherapy includes the delivery of systemic therapy early in treatment to attempt to reduce subclinical micrometastatic disease and an evaluation of chemotherapy response, reducing local and regional tumor bulk and increasing the likelihood of successful surgical resection. In addition, the appropriateness of the systemic agents chosen can be assessed by following the patient's locoregional clinical response. Neoadjuvant therapy also enables early evaluation of the effectiveness of systemic therapy.

In addition to these clinical objectives, neoadjuvant therapy gives researchers the opportunity to obtain tumor specimens (both fresh and formalin fixed) and blood samples prior to and during preoperative treatment. This enables research aimed at identifying tumor- or patient-specific biomarkers [9].

Although it was hypothesized that overall survival would be improved with earlier initiation of systemic therapy in patients at risk of distant recurrence, clinical studies have not yet demonstrated a mortality benefit for pre- versus postoperative delivery of systemic therapy.

Neoadjuvant therapy is most appropriate for patients likely to have a good locoregional response, regardless of tumor size at presentation, including those with HER2-positive or triple-negative breast cancers (TNBC)

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[10–12]. By contrast, patients with HER2-negative, ER-positive breast cancers are *less likely* to have a clinical or pathological complete response (pCR) to neoadjuvant therapy [12, 13].

Patients with HER2-positive cancers have a relatively high rate of pCR to neoadjuvant therapy, particularly if treatment includes a HER2-directed agent. This result has been observed in several clinical trials. For patients with HER2-positive disease who receive anti-HER2 treatment as part of their neoadjuvant therapy, pCR is associated with improvements in disease-free and overall survival [13, 14]. For this reason, we recommend the addition of targeted treatment against HER2 to neoadjuvant therapy in these patients.

Rates of pCR to neoadjuvant therapy among TNBC patients range from 27% to 45%, while the pCR rate for HER2-negative, hormone receptor-positive patients is generally less than 10%. However, while TNBC patients who achieve a pCR appear to have a prognosis similar to that of patients with other breast cancer subtypes who achieve a pCR, TNBC patients with more than minimal residual disease at surgery have a much higher risk of early distant disease recurrence [15].

Pretreatment Evaluation

As with all patients presenting with a new diagnosis of breast cancer, histopathological confirmation and an evaluation of receptor status (ER, PR, and HER2) must be obtained before initiating treatment. Patients should undergo an appropriate initial staging workup prior to neoadjuvant systemic therapy. This workup may include imaging studies to rule out detectable metastatic disease depending upon clinical stage and other characteristics. The detection of metastatic disease would likely alter the overall treatment goals and plan.

Tumor Evaluation

In some patients, preoperative systemic therapy results in a sufficient tumor response that enables breast-conserving therapy. Prior to the start of neoadjuvant therapy, radiopaque clips can be placed in the tumor at the time of diagnostic biopsy or at some other time prior to the initiation of neoadjuvant therapy. Because the aim of neoadjuvant therapy is to shrink the primary tumor, the clip facilitates the planning of locoregional treatment (surgery and radiation therapy) and subsequent pathological assessment of the surgical specimen. In addition to the placement of a clip in the tumor bed, the tumor size should be documented prior to treatment. In most cases, an ultrasound of the breast is sufficient to document tumor size. However, breast MRI is often helpful to evaluate disease extent, including assessing the presence of multicentric disease or invasion of the underlying chest wall [16]. MRI is recommended in patients who will undergo breast-conserving surgery (BCS) after neoadjuvant therapy. Clinical examination and radiological imaging modalities (USG, MMG, MRI) are used to evaluate the tissue to be excised (shrinking or patching).

The results of the NSABP B-18 trial demonstrate that breast conservation rates are higher after preoperative systemic therapy [17]. However, preoperative systemic therapy has no demonstrated disease-specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 is a three-arm, randomized, phase III trial of women with invasive breast cancer treated with preoperative systemic therapy with AC (doxorubicin/cyclophosphamide) for four cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for four cycles followed by local therapy, or AC followed by local therapy followed by four cycles of postoperative docetaxel [18]. Results from this study, which involved 2411 women, documented a higher rate of pCR at the time of local therapy in patients treated preoperatively with four cycles of AC followed by four cycles of docetaxel versus four cycles of preoperative AC. There were no differences in DFS and OS between the preoperative and postoperative groups.

An individual patient data meta-analysis was conducted by the Early Breast Cancer Trialists' Collaborative Group based on data from 4756 women in 10 trials that were initiated between 1983 and 2002 [19]. The use of neoadjuvant chemotherapy was associated with an increased frequency of breast-conserving therapy (65 versus 49%). Neoadjuvant chemotherapy was associated with an increased risk of local recurrence (15-year local recurrence rate 21.4 versus 15.9%, rate ratio 1.37, 95% CI 1.17–1.61), which may be attributable to the increased use of breast-conserving surgery. However, there were no significant differences between neoadjuvant chemotherapy versus adjuvant chemotherapy in the risk of distant recurrence (15-year rate 38.2 versus 38.0%) or breast cancer mortality (34.4 versus 33.7%).

Node Evaluation

For patients with palpable axillary adenopathy, physicians can perform ultrasound-guided FNA and/or core needle biopsy of one or more suspicious nodes prior to neoadjuvant treatment to determine whether the axillary nodes are pathologically involved. If FNA is negative, we can suggest a sentinel lymph node biopsy to stage the axilla *prior* to treatment. If FNA is positive, no further evaluation is required. For patients with a clinically negative axillary exam, a sentinel lymph node biopsy can be performed prior to the initiation of neoadjuvant therapy. The results of this procedure may more accurately reflect the status of the axillary nodes if performed

before the initiation of neoadjuvant therapy rather than following completion of treatment, although the status of the lymph nodes after neoadjuvant therapy may have greater prognostic significance. If the sentinel lymph node biopsy is negative, no further evaluation is necessary. If the sentinel lymph node biopsy is positive, further treatment will depend on the outcome following neoadjuvant therapy. At some centers, an axillary ultrasound with FNA of any enlarged or otherwise suspicious lymph node(s) is the initial diagnostic exam of choice, even in patients with a clinically negative axillary exam. This is a reasonable alternative.

According to our view, axillary staging after preoperative systemic therapy may include sentinel node biopsy or level I/II dissection. Level I/II dissection should be performed when patients are confirmed as node positive prior to neoadjuvant therapy. False-negative sentinel lymph node biopsy either pre- or post-pCR following chemotherapy may occur in lymph node metastases previously undetected by clinical exam. A sentinel lymph node excision can be considered before administering preoperative systemic therapy because it provides additional information to guide local and systemic treatment decisions. When sentinel lymph node resection is performed after the administration of preoperative systemic therapy, both the pre-chemotherapy clinical and the post-chemotherapy pathological nodal stages must be used to determine the risk of local recurrence. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative systemic therapy is planned.

Treatment Options

The options for neoadjuvant treatment include chemotherapy, endocrine therapy, and the incorporation of biological therapy in appropriate patients. Much of the information regarding neoadjuvant therapy comes from trials utilizing chemotherapy, with recent studies assessing the role of biologics. There are limited data regarding the use of neoadjuvant endocrine therapy, and clinical studies have predominantly evaluated only postmenopausal women.

A treatment plan is as follows:

- Patients with TNBC should be offered neoadjuvant therapy. These patients have an excellent chance of achieving a clinical and pathological complete response to treatment.
- For women with HER2-negative, estrogen-receptor (ER)- and/or progesterone-receptor (PR)-positive breast cancers who are not candidates for initial resection, we suggest neoadjuvant chemotherapy rather than endocrine therapy [20, 21]. While few of these patients will achieve a clinical or pathological complete response, tumor shrinkage may enable surgery for some unresectable patients and breast conservation for some borderline patients. However, those who are medically unfit for or refuse chemotherapy may be treated with neoadjuvant endocrine therapy.
- Patients with HER2-positive breast cancer should be offered neoadjuvant therapy. We recommend the addition of HER2-tatrgeted agents (trastuzumab plus pertuzumab) to neoadjuvant therapy [22].

Chemotherapy

Several chemotherapy regimens have been studied as preoperative systemic therapy. We believe that the regimens recommended in the adjuvant setting are appropriate for consideration in the preoperative systemic therapy setting [22].

For patients with locally advanced breast cancer, neoadjuvant therapy is associated with high rates of clinical response and a higher likelihood of allowing cosmetically acceptable surgery. However, neoadjuvant therapy does not improve overall survival compared to adjuvant chemotherapy.

The outcomes of neoadjuvant therapy were demonstrated in a 2007 meta-analysis that included data for 5500 women participating in 1 of 14 trials reported between 1991 and 2001 [23]. Compared to adjuvant chemotherapy, neoadjuvant therapy resulted in the following:

- Equivalent overall survival (hazard ratio [HR] 0.98; 95% CI, 0.87–1.09) and disease-free survival (HR 0.97; 95% CI, 0.89–1.07).
- A reduction in the likelihood of modified radical mastectomy (HR 0.71; 95% CI, 0.67–0.75).

Those patients with a documented pCR at surgery had significant improvements in survival compared to patients with residual invasive disease.

The choice of specific chemotherapy drugs and regimens should be based on tumor biology and intrinsic subsets (i.e., triple-negative, estrogen receptor-positive, HER2-positive) [23–25]. There is no reason to assume that regimens administered in the adjuvant setting would be less active when used prior to surgery.

Commonly used regimens for patients with HER2-negative disease include the following:

- AC—neoadjuvant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) (AC) every 2 (dose-dense) or 3 weeks for four cycles.
- AC/weekly T—AC followed by weekly paclitaxel (80 mg/m^2) for 12 weeks.
- AC/taxane—AC followed by docetaxel (100 mg/m^2) every 3 weeks for four cycles.

- TAC—docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) for six cycles.

Because a reduction in tumor size to permit surgery is the primary objective of neoadjuvant therapy, all planned treatment should be administered *prior* to definitive surgery, provided there is no evidence of disease progression during treatment.

Anthracycline-Taxane-Based Regimens

Multiple studies have demonstrated that anthracycline-based regimens incorporating a taxane (either concurrently or in sequence with anthracycline-based regimens) are associated with increased response rates in the neoadjuvant setting compared to the use of non-taxane-containing regimens [26]. As an example, in the NSABP B-27 trial, 2411 patients received four cycles of neoadjuvant AC, after which they were randomly assigned to one of three groups: one group received no further chemotherapy, another group was treated with four cycles of neoadjuvant docetaxel (100 mg/m^2) every 3 weeks, and the third group underwent surgery followed by four cycles of adjuvant docetaxel. Compared to AC alone, the incorporation of docetaxel prior to surgery resulted in the following [18]:

- A higher overall clinical response rate (CRR, 91% versus 86%).
- A higher pCR rate (26% versus 13%).
- No difference in overall survival (74% with neoadjuvant AC only and 75% in the arms containing docetaxel) or disease-free survival at 8 years (disease-free survival, 59% and 62%).

Nonanthracycline-Based Treatment

Based on the results from the adjuvant setting and data from the TRAIN-2 study, we consider taxane-carboplatin-trastuzumab (with or without pertuzumab) regimens to be preferable alternatives to anthracycline-containing regimens as neoadjuvant therapy in patients with HER2-positive cancers due to their lower toxicity and equivalent rates of pCR.

In a phase III trial of 438 patients with stage II–III HER2-positive breast cancer who randomly received anthracycline-containing chemotherapy (three cycles of 5-fluoruoracil, epirubicin, and cyclophosphamide followed by six cycles of paclitaxel and carboplatin) versus nonanthracycline-based chemotherapy (nine cycles of paclitaxel and carboplatin), with trastuzumab and pertuzumab administered every 3 weeks in all chemotherapy cycles, the rates of pCR did not differ between the arms (67% vs. 68%). Patients who received anthracycline experienced higher rates of grade > 3 febrile neutropenia (11% vs. 2%) and grade > 2 declines in left ventricular ejection fraction (29% vs. 18%) [27].

Alternative Regimens

Ongoing clinical research is examining whether the addition of non-cross-resistant agents with demonstrated activity in metastatic breast cancer might improve the clinical and pathologic response rates observed with the use of an anthracycline and/or a taxane. However, there is no evidence that this approach improves survival outcomes or response rates. Thus, we suggest not administering additional agents with standard anthracycline- and taxane-based neoadjuvant therapy.

For patients who have had a previous hypersensitivity reaction to a taxane or a contraindication to the steroids administered with it, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is an acceptable alternative. The results of the GeparSepto trial suggest that nab-paclitaxel improves the pCR rates relative to that of standard paclitaxel but is associated with increased toxicity. In this trial, more than 1200 women were randomly assigned to 12 weeks of neoadjuvant weekly paclitaxel (80 mg/m^2) versus weekly nab-paclitaxel (150 mg/m^2, subsequently reduced to 125 mg/m^2 due to excessive hematologic and neurologic toxicity at the higher dose), both of which were followed by epirubicin plus cyclophosphamide. Those receiving nab-paclitaxel experienced a higher pCR rate than those receiving standard paclitaxel (38% vs. 29%, respectively; odds ratio [OR] 1.53, 95% CI 1.20–1.95). On subtype analysis, an improvement in the pCR rate was primarily observed in patients with TNBC (48% with nab-paclitaxel vs. 26% with standard paclitaxel). The incidence of serious (grade > 3) adverse events was greater among patients receiving nab-paclitaxel (26% vs. 21%), including higher rates of grade 3 peripheral neuropathy, even after a dose reduction [28].

Response-Adjusted Sequential Therapy

Response-adjusted sequential therapy refers to the use of one chemotherapy regimen for a set number of cycles, followed by a clinical assessment of the response and subsequent administration of either the same or a non-cross-resistant chemotherapy regimen based on the observed response to the first regimen. This design allows for an independent evaluation of different drug regimens and the potential to individualize therapy based on the response of a patient's tumor. This approach has been evaluated in a limited number of studies in the neoadjuvant setting and is not recommended outside of a clinical trial.

Endocrine Therapy

At the present time, we restrict the administration of neoadjuvant endocrine therapy to postmenopausal patients who are medically unfit to receive or refuse chemotherapy. However, there is growing interest in studying neoadjuvant endocrine therapy in a broader cohort of postmenopausal patients. However, few studies have evaluated neoadjuvant endocrine therapy in premeno-

pausal women, and none have been performed in the context of a randomized trial. Therefore, a neoadjuvant endocrine therapy approach should be considered investigational as a treatment option for premenopausal women. If a premenopausal woman refuses neoadjuvant therapy, we suggest definitive surgical treatment. Premenopausal women who refuse surgery can also be offered neoadjuvant endocrine therapy, but they should be aware that there is no data regarding the risks and benefits of this approach in this population [29, 30].

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with ER-positive breast cancer. These studies have generally compared the rates of objective response and the rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, or letrozole. These studies have consistently demonstrated that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery. Preoperative endocrine therapy is usually utilized; an aromatase inhibitor is preferred for the treatment of postmenopausal women with hormone receptor-positive disease [2, 31–33].

Endocrine Therapy Versus Chemotherapy

There is a small body of evidence suggesting that the use of endocrine therapy may be equivalent to chemotherapy in postmenopausal women. However, until more data are available, we recommend chemotherapy for most patients in the neoadjuvant setting.

In a phase II trial, 239 postmenopausal women with hormone receptor-positive stage II–III breast cancer were randomly assigned to neoadjuvant treatment with an aromatase inhibitor (AI) (either exemestane or anastrozole) for 3 months or chemotherapy (four cycles of doxorubicin and paclitaxel every 21 days). There were no differences in overall response rates between exemestane, anastrozole, and chemotherapy (67%, 62%, and 63%, respectively). Compared to chemotherapy, neoadjuvant AI resulted in a similar median time to clinical response (57 days vs. 51 days) and a similar rate of pCR (3% vs. 6%). Breast-conserving surgery was performed in 33% of the patients assigned to an AI compared to 24% of the patients assigned to chemotherapy [34].

Duration of Endocrine Therapy

For patients undergoing neoadjuvant endocrine therapy, we continue treatment for at least 3–4 months. If the tumor is amenable to surgery after 3–4 months, we recommend proceeding with definitive surgical treatment. However, if the tumor responds to endocrine therapy, extending treatment to 6 months or longer with clinical monitoring of the response may permit a higher percentage of patients to undergo breast-conserving surgery. If at any time there is evidence of progression or non-response, we recommend surgery. A response to endocrine therapy may not be evident for at least 3–4 months, and a maximal response may not be achieved until much later. Thus, the duration of endocrine treatment prior to surgery must be individualized based on the patient's clinical status and the clinical response.

HER2-Directed Therapy

The benefit of adding trastuzumab to chemotherapy was demonstrated in a pooled analysis of two randomized studies that evaluated neoadjuvant therapy with or without trastuzumab [35]. The addition of trastuzumab to chemotherapy resulted in the following:

- An improvement in the rate of pCR (43% vs. 20%; relative risk for achieving pCR [RR] 2.07; 95% CI, 1.41–3.03)
- A reduction in the relapse rate (26% vs. 39%; RR for relapse 0.67; 95% CI, 0.48–0.94)
- A trend toward a lower mortality rate (13% vs. 20%; RR for mortality 0.67; 95% CI, 0.39–1.15) that did not reach statistical significance

The GeparQuinto phase III trial led by the German Breast Group studied 620 women who were randomized to receive four cycles of epirubicin/cyclophosphamide followed by docetaxel administered concurrently with either trastuzumab or lapatinib [36]. The primary endpoint, pCR, was achieved in 30.3% of patients who received trastuzumab plus chemotherapy compared with 22.7% of patients who received lapatinib plus chemotherapy [37, 38]. In the survival analysis, pCR correlated with long-term outcome. In patients with hormone receptor-positive tumors, prolonged anti-HER2 treatment-neoadjuvant lapatinib for 6 months, followed by adjuvant trastuzumab for 12 months-significantly improved survival compared with anti-HER2 treatment with trastuzumab alone [38].

The NeoALTTO trial randomized 455 patients with HER2-positive primary breast cancer to receive lapatinib plus paclitaxel, trastuzumab plus paclitaxel, or a combination of lapatinib and trastuzumab plus paclitaxel [39]. The pCR rate was 51.3% (95% CI, 43.1–59.5) in the lapatinib plus trastuzumab combination arm, 24.7% (CI, 18.1–32.3) in the lapatinib arm, and 29.5% (CI, 22.4–37.5) in the trastuzumab arm. The difference in pCR rates between the lapatinib plus trastuzumab arm and the trastuzumab arm was statistically significant (difference 21.1%, 9.1–34.2, $p = 0.0001$). The difference in pCR rates between the lapatinib and trastuzumab arms was not statistically significant (difference − 4.8%, −17.6–8.2; $p = 0.34$). Grade 3/4 liver enzyme abnormalities occurred more frequently with trastuzumab plus lapatinib or lapatinib alone compared to trastuzumab alone.

These studies thus confirm that the use of HER2-targeted therapy is important in the preoperative treatment of HER2-positive primary breast cancer. There remains significant uncertainty regarding the optimal regimen of HER2 targeting. The results of the NeoALTTO study confirm the potential of dual HER2-targeted therapy in the neoadjuvant setting.

For patients with HER2-positive breast cancer who are candidates for neoadjuvant therapy, we do not recommend administering lapatinib in place of trastuzumab. Multiple randomized studies have reported similar or inferior pCR rates when lapatinib is substituted for trastuzumab.

Pertuzumab is a recombinant, humanized, monoclonal antibody that inhibits the ligand-dependent dimerization of HER2 and its downstream signaling. Pertuzumab and trastuzumab bind to different epitopes of the HER2 receptor and have complementary mechanisms of action. When administered together in HER2-positive tumor models and in humans, pertuzumab and trastuzumab provide a greater overall antitumor effect than either alone. Because the combination of pertuzumab and trastuzumab exhibited a significant overall survival benefit in a metastatic setting, it has also been examined in the neoadjuvant setting.

The combination of trastuzumab plus pertuzumab was evaluated in the neoadjuvant setting with responses noted even without the use of chemotherapy. These results are fascinating not only because of the higher pCR rate associated with chemotherapy plus trastuzumab and pertuzumab but also because of the frequency of pCR associated with dual HER2-targeted therapy alone, particularly in patients with ER-negative disease.

In the NeoSphere trial, 417 patients were randomized 1:1:1:1 to receive trastuzumab plus docetaxel, pertuzumab and trastuzumab plus docetaxel, pertuzumab and trastuzumab, or pertuzumab plus docetaxel [36]. Of the patients who received pertuzumab plus trastuzumab and docetaxel, 45.8% (95% CI, 36.1–55.7) achieved pCR, compared with only 29% (CI, 20.6–38.5) of patients who received the trastuzumab plus docetaxel regimen ($p = 0.0063$) [40].

TRYPHAENA was a phase II, randomized, multicenter trial designed to evaluate the safety and tolerability of trastuzumab and pertuzumab in combination with anthracycline- or carboplatin-based neoadjuvant chemotherapy [41]. A total of 225 patients with HER2-positive, locally advanced (T2-3, N2-3, M0; T4a-c, any N, M0), inflammatory (T4d, any N, M0), or early-stage breast cancer (tumors >2 cm) were enrolled and randomized 1:1:1 to receive 6 cycles of neoadjuvant therapy with FEC plus trastuzumab and pertuzumab followed by docetaxel, trastuzumab, and pertuzumab; FEC followed by docetaxel, trastuzumab, and pertuzumab; or docetaxel, carboplatin, and trastuzumab along with pertuzumab. Based on pCR assessment, all three regimens appear to be active. The reported pCR ranged from 57.3% to 66.2%. The highest pCR, 66.2%, was observed in patients who received pertuzumab, trastuzumab, docetaxel, and carboplatin chemotherapy.

In the KRISTINE/TRIO-021 study, which compared TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab) to T-DM1 plus pertuzumab without subsequent AC, patients who received TCHP had a higher pCR rate (56% vs. 44%) and a higher rate of breast-conserving surgery (53% vs. 42%) than those assigned to the T-DM1-based regimen [42].

Trastuzumab Biosimilars

A number of pharmaceutical companies are developing trastuzumab biosimilars to compete with the original formulation. The results of a large, phase III equivalence trial that compared one of these agents, designated CT-P6, with trastuzumab among patients receiving neoadjuvant chemotherapy showed equivalent outcomes between the two arms [43]. Similar results have been reported from phase III neoadjuvant trials conducted with two other proposed trastuzumab biosimilars, designated SB3 and ABP 980 [44, 45].

Treatment Evaluation

Patients receiving neoadjuvant systemic therapy should be followed by clinical exam at regular intervals during treatment to ensure that the disease is not progressing. At the end of treatment, an assessment of tumor response is important to help guide the surgical approach.

Clinical Response Assessment During Treatment

Patients undergoing neoadjuvant systemic therapy for breast cancer should undergo periodic clinical evaluations during treatment to assess response and ensure that their tumor is not progressing.

There are no formal guidelines regarding the ideal assessment strategy during neoadjuvant treatment. Our approach is as follows:

- For patients on neoadjuvant therapy, we perform a clinical examination every 2–4 weeks (i.e., prior to each cycle of treatment). This should include evaluation of the affected breast and ipsilateral axilla.
- For patients undergoing neoadjuvant endocrine therapy, we perform clinical evaluations every 4–8 weeks. The response to treatment is expected to take a longer time to become evident.
- Imaging studies (ultrasound [US] or magnetic resonance imaging [MRI]) should only be performed if disease progression is suspected based on clinical exam.
- Limited data suggest that fluoro-2-deoxyglucose positron emission tomography (FDG-PET) may have a sensitivity and specificity as high as 80%, but there are insufficient prospective data to evaluate the ability of FDG-PET to accurately predict the response to neoadjuvant therapy.
- There is no role for repeat biopsy of the index tumor during neoadjuvant treatment unless performed as part of a

clinical trial. Although repeat measurement of biological factors (such as Ki-67) may identify patients who are unlikely to respond to neoadjuvant endocrine therapy, validation of such tests is needed before repeat pathological assessment during treatment is incorporated into clinical practice.

Clinical Response Assessment After Treatment

Once a patient has completed neoadjuvant therapy (typically six–eight cycles of chemotherapy or 3–6 months of endocrine therapy), an assessment of tumor response helps guide the surgical approach. Tumor size is typically assessed using World Health Organization-International Union against Cancer (WHO-UICC) or Response Evaluation Criteria in Solid Tumors (RECIST) criteria. However, the correlation between tumor measurements by physical examination, imaging (mammography, US, or MRI), and tumor size on final pathological analysis is modest at best, as illustrated in the following examples:

- A 2010 meta-analysis of 25 studies involving a total of 1212 patients receiving neoadjuvant therapy concluded that while contrast-enhanced MRI has high specificity (91%), its sensitivity to predict pCR is low (63%) [46].
- In another study involving 189 patients, the reported accuracy (defined as the ability to predict the greatest tumor dimension within 1 cm) of clinical exam, US, and mammography were 66%, 75%, and 70%, respectively, compared with findings at final pathological analysis [47].

The lack of concordance between the clinical and pathologic assessments of response may be due to the variable patterns of tumor response to neoadjuvant treatment, which range from symmetric shrinkage around a central core (that may contain residual cancer or fibrotic tissue) to the complete resolution of a discrete mass despite the persistence of microscopic foci of residual invasive cancer.

Local therapy following a complete or partial response to preoperative systemic therapy is usually a lumpectomy if possible along with surgical axillary staging. After downstaging, resection of the entire area of the original primary tumor is not necessary (if there is shrinkage in the tumor). MRI is recommended in patients who will undergo BCS after neoadjuvant therapy. Clinical examination and radiological imaging modalities (USG, MMG, MRI) are used to evaluate the tissue to be excised (shrinking or patching). However, if the tumor response is patchy, the original tumor area should be removed with clean surgical margins. If diffuse live tumor cells are observed in the excised lumpectomy specimen after neoadjuvant chemotherapy, re-excision should be performed, even if there is no surgical margin involvement. If a lumpectomy is not possible or progressive disease is confirmed, mastectomy is performed along with surgical axillary staging with or without breast reconstruction.

Surgical axillary staging may include sentinel lymph node biopsy or level I/II dissection. If a sentinel lymph node biopsy is performed before administering preoperative systemic therapy and the findings are negative, then further axillary lymph node staging is not necessary. If a sentinel lymph node procedure is performed before administering preoperative systemic therapy and the findings are positive, then a level I/II axillary lymph nodes dissection should be performed.

If an inoperable tumor fails to respond, if the response is minimal after several cycles of preoperative systemic therapy, or if the disease progresses at any point, an alternative chemotherapy regimen and/or preoperative radiation therapy should be considered followed by local therapy, usually a mastectomy plus axillary dissection, with or without breast reconstruction.

Postsurgical adjuvant treatment for these patients consists of the completion of planned chemotherapy if not completed preoperatively followed by endocrine therapy in women with ER- and/or PR-positive tumors. Anti-HER2 therapy should be completed if the tumor is HER2-positive.

Novel Approaches

Combination of Chemotherapy and Endocrine Treatment

The strategy of combined chemotherapy and endocrine therapy in the neoadjuvant setting is feasible but should not be used outside of a clinical trial as the survival benefits are unknown. One study randomly assigned 101 postmenopausal women to neoadjuvant endocrine therapy (letrozole) plus chemotherapy versus neoadjuvant chemotherapy alone [48]. The study observed that the combination therapy had a higher clinical response rate (28% vs. 10%) and pCR rate (26% vs. 10%) compared with those of neoadjuvant chemotherapy alone.

In the NSABP B52 trial, a total of 315 patients were randomly assigned to receive a neoadjuvant therapy consisting of docetaxel, carboplatin, trastuzumab, and pertuzumab with or without estrogen deprivation therapy [49]. Patients with locally advanced, hormone receptor-positive, HER2-positive invasive breast cancer with no evidence of metastatic disease were eligible. Premenopausal women randomized to estrogen deprivation therapy received ovarian function suppression with goserelin (LHRH agonist) or equivalent plus an aromatase inhibitor (AI). Postmenopausal women received an AI. This trial showed that the addition of estrogen deprivation to neoadjuvant chemotherapy is not antagonistic. The addition of estrogen deprivation to neoadjuvant chemotherapy

improved pCR rates numerically (45% vs. 60%), but the improvement was not statistically significant. The combination did not increase toxicity and may be a reasonable approach since all patients will receive endocrine therapy after neoadjuvant therapy. Correlative science studies including an evaluation of the residual cancer burden (RCB) and long-term outcomes will help define the role of estrogen deprivation in the treatment of HER2+ early breast cancer [49].

Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors

Investigational treatment strategies for patients with HR-positive disease include combinations of endocrine therapy with chemotherapy as well as targeted agents. In general, combination therapy is associated with a higher response rate relative to that of single-agent endocrine therapy, but combination therapy cannot be recommended for routine clinical practice at this time given the lack of survival data and concern about its added toxicity. Several ongoing trials are investigating the role of combination therapy, including the combination of AIs with cyclin-dependent kinase (CDK) 4/6 inhibitors (NeoMONARCH), PI3K inhibitors (LORELEI), and dual endocrine therapy (ALTERNATE).

The NeoMONARCH study included 167 postmenopausal women with HR-positive, HER2-negative early breast cancer. Patients were randomized to receive abemaciclib plus anastrozole, abemaciclib alone, or anastrozole alone. At the end of treatment, a radiologic response was evident in 46.4% of all patients, decreased tumor size was observed in 53.6% of all patients, and pathological complete response was achieved in 3.7% of patients assessed following breast cancer surgery.

Incorporation of Angiogenesis Inhibitors

Although studies suggest that the addition of the angiogenesis inhibitor bevacizumab to chemotherapy in patients receiving neoadjuvant treatment can increase pCR rates, it is not clear which patients are most likely to benefit from this approach [50]. Given that the benefits are unclear but the risks can be quite serious, bevacizumab should not be used as part of neoadjuvant therapy outside of a well-designed clinical trial.

The evidence to support this conclusion comes from four trials.

In one German trial (GeparQuinto), the pCR rate with the addition of bevacizumab was significantly higher only in patients with hormone receptor-negative disease [51]. However, in an American trial (NSABP B-40), hormone receptor-positive patients had a significant improvement in pCR with incorporation of bevacizumab [52].

In the TNBC study conducted by CALGB (CALGB 40603), a significant increase in the pCR rate within the breast was observed in women who received bevacizumab; however, if the pCR definition included the axilla, the improvement in the pCR rate was not statistically significant [53].

In all of these studies, bevacizumab resulted in higher rates of serious (grade 3/4) toxicities, including febrile neutropenia, hypertension, and mucositis. Higher rates of bleeding, thromboembolic events, and postsurgical complications (early and late) were also observed with bevacizumab therapy and are all known complications of the drug.

Finally, none of these studies reported whether the pCR rate with bevacizumab improves survival outcomes. Taken together, these data illustrate that the benefits of adding bevacizumab to neoadjuvant therapy are unclear at best and do not justify the risks of toxicity. We therefore do not administer bevacizumab as part of neoadjuvant therapy unless it is within a well-designed clinical trial.

Incorporation of a PARP Inhibitor

Mutations that result in dysfunction of either the BRCA1 or BRCA2 gene predispose patients to the development of breast cancers with deficiencies in DNA repair. This appears to confer sensitivity to chemotherapeutic agents that damage DNA, such as platinum analogs, and to agents that affect alternative mechanisms of DNA repair, such as poly ADP ribose polymerase (PARP) inhibitors. Similarities in tumor characteristics and gene expression patterns between BRCA-associated and sporadic TNBC led to speculation that the addition of these same agents might improve responses in TNBC, including in the neoadjuvant setting.

In the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2) trial, one arm evaluated standard chemotherapy (dose-dense AC/weekly T) with or without the oral PARP inhibitor veliparib. As presented at the 2013 San Antonio Breast Cancer Symposium, patients with TNBC who received carboplatin and veliparib as part of their treatment achieved a higher pCR rate (52% vs. 26% in those who did not receive veliparib) [54]. However, whether the improvement in pCR was due to carboplatin, veliparib, or the combination cannot be determined. Thus, we do not administer this agent or other PARP inhibitors in the neoadjuvant setting outside of a clinical trial. Data from studies investigating the addition of carboplatin to neoadjuvant therapy for TNBC are discussed above.

The BrighTNess trial was designed to assess the addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (n = 634). Although the addition of veliparib and carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide improved the proportion of patients with triple-negative breast cancer who achieved a

pathological complete response, the addition of veliparib to carboplatin and paclitaxel did not. Increased toxicities with the addition of carboplatin (with or without veliparib) to paclitaxel were manageable and did not substantially affect the treatment delivery of paclitaxel followed by doxorubicin and cyclophosphamide. As these results are consistent with those of previous studies, the addition of carboplatin appears to have a favorable risk-to-benefit profile and might be considered to be a potential component of neoadjuvant chemotherapy for patients with high-risk, triple-negative breast cancer [55].

Prognosis

The prognosis of patients with breast cancer who undergo neoadjuvant therapy correlates with the pathological response observed at the time of surgery but is also influenced by presenting clinical stage and tumor characteristics (particularly hormone receptor and HER2 status). As described above, clinical response is not an accurate predictor of pathological response, and achieving a pCR in the breast and axilla is a better predictor of survival than a clinical complete response.

The prognostic significance of pCR on survival endpoints has been evaluated in several meta-analyses [56, 57]. The largest of these was conducted by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) working group and included 12 randomized trials and nearly 12,000 patients [56]. Their major findings were as follows:

- Patients who achieved pCR had significant improvements in event-free survival (hazard ratio [HR] 0.48, $p < 0.001$) and overall survival ([OS] HR 0.36, $p < 0.001$) compared to patients who did not achieve pCR.
- The inclusion of patients with residual ductal carcinoma in situ (DCIS) only (ypT0/is, ypN0) did not diminish the benefit of achieving pCR for event-free survival and overall survival. However, the inclusion of patients with residual axillary nodal involvement in the definition of pCR reduced its prognostic value for both event-free survival and overall survival.

pCR rates and improvement in event-free survival for patients who achieved pCR varied by breast cancer subtype:

- Hormone receptor (HR)-positive, HER2-negative, grade 1–2: 8% (HR for event-free survival 0.63, $p = 0.07$)
- HR-positive, HER2-negative, grade 3: 16% (HR 0.27, $p < 0.001$)
- HR-positive, HER2-positive (treated with a trastuzumab-containing regimen): 31% (HR 0.58, $p = 0.001$)
- HR-negative, HER2-negative (triple-negative): 34% (HR 0.24, $p < 0.001$)
- HR-negative, HER2-positive (treated with a trastuzumab-containing regimen): 50% (HR 0.25, $p < 0.001$)

Despite these results, the threshold of benefit (defined by an increase in the pCR rate) associated with an improvement in event-free survival and/or overall survival is not clear. The investigators hypothesized that the lack of an association may have been due to the heterogeneous patient populations in many of the studies, the relatively low pCR rates (even in the "superior" treatment arm), and/or the lack of effective targeted agents for many of the patient populations studied.

Several models are being developed to better define the prognosis of patients treated with neoadjuvant therapy. Examples of these include calculation of the residual cancer burden (RCB) score, the breast cancer index (BCI), and, for patients treated specifically with neoadjuvant endocrine therapy, the preoperative endocrine prognostic index (PEPI) score [57, 58].

The RCB takes into account residual tumor size, the percentage of the residual tumor composed of invasive cancer cells (as opposed to fibrosis or in situ disease), the number of positive axillary nodes, and the largest nodal metastatic deposit. In the original analysis, the RCB score correlated with prognosis in patients who received anthracycline- and taxane-containing neoadjuvant therapy regimens.

The measurement of the RCB requires the collection of pathological variables, which are not routinely recorded. In addition, the validation of this prognostic index is limited. Therefore, a further evaluation of the RCB is required before it becomes part of routine practice.

Conclusion

Neoadjuvant therapy is administered with the objective of improving surgical outcomes in patients with breast cancer for whom a primary surgical approach is technically not feasible and for patients with operable breast cancer who desire breast conservation but for whom either a mastectomy is required or a partial mastectomy would result in a poor cosmetic outcome. In addition, neoadjuvant chemotherapy is appropriate for patients with HER2-positive or triple-negative breast cancer who are most likely to have a good locoregional response to treatment, regardless of the size of their breast cancer at presentation.

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Systemic Therapy for Inflammatory Breast Cancer

16

Nilüfer Güler

Introduction

Inflammatory breast carcinoma (IBC) is a rare and aggressive subtype of breast carcinoma that is diagnosed clinically [1–5] and was first identified by Lee and Tannenbaum in 1924 [6]. IBC is characterized by skin changes that are suggestive of infection and inflammation, usually with fairly abrupt onset and rapid progression. The duration of symptoms before diagnosis is usually less than 3 months [1–5]. The most common symptoms are a feeling of warmth and heaviness, itching, nipple retraction, and pain in the affected breast. IBC is frequently misdiagnosed as cellulitis or acute mastitis. Acute-phase radiation dermatitis, sarcoma or lymphoma of the breast, inflammatory metastatic melanoma, and Paget's disease of the nipple can also mimic IBC.

The minimum diagnostic criteria for the diagnosis of IBC are the following [7–9]:

- Rapid onset of breast erythema (with a palpable border), edema and/or dermal edema (peau d'orange), and/or warm breast, with or without an underlying palpable mass
- A duration of symptom history of no more than 6 months
- Erythema occupying at least one-third of the breast
- Pathological confirmation of invasive carcinoma

Primary IBC is classified as T4d according to the American Joint Commission for Cancer (AJCC) staging system and is staged as IIIB, IIIC, or IV according to nodal involvement and distant metastases [8, 9]. IBC is not an entity of locally advanced breast carcinoma (LABC) but is completely separate according to epidemiological and molecular evidence. The outcomes of these two diseases are quite different: younger age at diagnosis, higher tumor grade, and the absence of the estrogen receptor (*ER*) in the tumor are more suggestive of primary IBC than LABC [1, 2, 4]. According to the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program records for 828 IBC and 3476 non-IBC LABC patients, 2-year breast cancer-specific survival (BCSS) was 84% in patients with IBC (95% CI: 80–87%) compared with 91% (95% CI: 90–91%) in patients with non-IBC LABC after a median follow-up of 19 months [10]. In a multivariate model, the mortality risk in patients with IBC is 43% higher than that in non-IBC LABC patients (hazard ratio 1.43, 95% CI: 1.10–1.86, $p = 0.008$). In addition, a distinction must also be made between primary and secondary IBC [2]. In primary IBC, skin alterations and carcinoma develop concurrently from the previously healthy breast, whereas in secondary IBC, inflammatory skin alterations appear subsequent to malignancy development [1, 2, 4, 5].

Epidemiology, Etiology, and Risk Factors

The reported incidence of IBC varies due to a lack of consensus regarding the case definition for the disease [11]. In the United States, the incidence of IBC ranges from 1% to 6% [12–14]. Data from the SEER program have demonstrated that the age-adjusted incidence rates for IBC increased significantly between 1988–1990 and 1997–1999 (from 2.0 to 2.5 cases/100,000 woman-years; $p < 0.001$) [15]. The incidence of IBC is significantly higher in African-American women than that in Caucasian women (3.1/100,000 woman-years vs. 2.2/100,000 woman-years, respectively) [15]. The incidence is lowest among Asian Pacific Islander women (0.7 cases/100,000 woman-years) [16]. In Morocco, Egypt, Algeria, and Tunisia, the reported incidence rates are very high, and nearly 10–15% of all breast cancers are stated to present as IBC [17–20]. According to data from two single institutions in Turkey and Spain, however, the incidence of IBC is 5% and 2.9%, respectively [21, 22].

IBC generally has an early onset. Maximal peak age at diagnosis is approximately 50 years. However, maximal peak age at diagnosis is 69 years for non-T4 tumors and 74 years for LABC. According to the SEER database, the

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median age at diagnosis is lower in patients with IBC (58.8 years) than in patients with non-T4 breast cancer (61.7 years, $p < 0.0001$) and LABC (66.2 years, $p < 0.0001$) [15]. In addition, race seems to be an important risk factor, as African-American women are at higher risk for developing the disease. The age of onset also varies according to race and ethnicity [16]. Compared to Caucasians, African-Americans present at a younger age of onset (median age 55.2 vs. 58.1 years) with inferior prognosis. However, Hispanic women present with the youngest average age (median 50.5 years) at the initial diagnosis of IBC. In one study, the epidemiology, biology, and prognosis of IBC in Japanese and US populations were compared [23]. No differences were observed between the two populations regarding age at diagnosis, hormone receptor (HR) status, human epidermal growth factor receptor-2 (*HER2*) overexpression, or overall survival (OS). However, body mass index (BMI) and nuclear grade were lower in Japanese patients than in US patients. For OS, *ER* status and race were prognostic when the two populations were combined.

Possible risk factors for IBC are young age at first birth (<20 years), pregnancy (21–26% of IBC cases develop during or after pregnancy), lactation (longer cumulative duration of breastfeeding history), increased BMI (>26.65; the odds ratio for IBC vs. other types of BC is 2.45), blood group A, and rural residency [1–4, 14, 24–27]. However, it should be recognized that these risk factors are currently based on smaller studies and have not been well established.

Immunological factors have been examined in Tunisian studies. Immunodeficiency was not observed in these studies, but the results suggested that a hyperimmune response may be the cause of this rapidly progressing breast cancer [28, 29].

Because of the rapid onset and clinical characteristics of IBC, the involvement of viral infection was suggested by Pogo et al. [30]. They detected *human mammary tumor virus* (*HMTV*), a provirus structure with 96% homology with *mouse mammary tumor virus* (*MMTV*), in 71% of IBC cases compared with 40% of non-IBC cases in American patients [30]. *HMTV*-positive IBC was significantly higher in breast cancer patients in Tunisia (74%) compared with those in the United States (36%), Italy (38%), Argentina (31%), and Vietnam (0.8%) [31]. Another study from Egypt demonstrated that *human cytomegalovirus* (*HCMV*) infection enhances the expression and activation of transcription factor *NF-κB* (*nuclear factor-κB/p65*, which controls different cytokines) signaling in IBC patients [32]. *HCMV* infection may be associated with the etiology and progression of IBC vs. non-IBC. The relationship between viral etiology and IBC is under investigation in the United States [2].

Although the median age of IBC is younger than that of non-IBC, *BRCA1*, *BRCA2*, and *PTEN* do not play a strong role in IBC. *BRCA* testing is not routinely recommended, except in cases with a strong family history [9]. In one retrospective study by Gutierrez et al., there was no statistically significant difference ($p = 0.169$) in the rate of *BRCA1* and *BRCA2* mutations between IBC (35.9%; total 39 patients) and non-IBC (26.1%; total 992 patients) [33]. In another study, the percentage of patients with a positive family history was 13% in IBC cases and 8% in non-IBC [24]. This difference was not statistically significant. The last study was reported from MD Anderson Cancer Center (MDACC) by the same author, Gutierrez et al., with a higher number of patients. The rates of BRCA pathogenic variants were 27.3% among non-IBC patients (460 of 1684 patients) and 18.1% among IBC cases (19 of 105 patients) ($p = 0.0384$). After propensity score matching, there was no statistically significant difference between the groups ($p = 0.5485$). The ages of the patients with BRCA pathogenic variants with IBC were younger at the time of diagnosis compared with the patients with non-IBC (36.6 ± 8.2 years vs. 41.5 ± 9.4 years respectively; $p = 0.0244$) [34]. They conclude that genetic testing is important for patients with IBC who meet the current clinical criteria for genetic testing in breast cancer. Family history was significantly more common in IBC cases than in non-IBC cases (20% vs. 5%, respectively) in one Pakistani study [35].

Staging Workup

When the patients come to the clinic, after taking their history and physical examination, taking upfront medical photography before starting neoadjuvant chemotherapy (NACT) to document findings and to determine the extent of skin involvement is critical [9, 36]. This step is important for determining follow-up responses to systemic chemotherapy, planning of future radiotherapy fields, and surgery planning. After initiating NACT, patients may have taken these photos themselves, and all of these photos should be filed in the medical record. Whole blood counts and metabolic panels, liver function tests, and alkaline phosphatase assessments are necessary before treatment planning. Genetic counseling to determine if patients are at high risk for hereditary breast cancer and fertility counseling for premenopausal patients are important [9].

Among various diagnostic imaging modalities, mammography is the least sensitive and effective method for the diagnosis of IBC and detects only 43% of breast parenchymal lesions [37]. Therefore, IBC is usually not detected by mammographic scanning. The most common signs of IBC by mammography are skin thickening (84–93%), trabecular thickening (62–81%), trabecular distortion (37%), increased breast density (93%), axillary adenopathy (24%), and calcifications (47–56%); a mass is often visible by ultrasonography (USG) [5, 7, 21, 37, 38]. Both the mammary tissue and local

lymph nodes should be evaluated by USG. Axillary lymph node metastases are detected in 90% of all patients. Parenchymal lesions in the breasts can be identified in nearly 95% of IBC patients by USG, which is also a useful method for obtaining biopsies from lesions. Recently, magnetic resonance imaging (MRI) has become a popular method for visualizing the breast. The reported success rates of MRI, USG, and mammography in detecting parenchymal lesions in patients with proven IBC are 100%, 95%, and 80%, respectively [38]. MRI is also the most sensitive method to diagnose multicentric disease [39]. Finally, MRI best demonstrates the extent of disease, including ipsilateral and contralateral skin involvement, skin thickening, breast and chest wall edema, chest wall and nodal involvement, and contralateral breast assessment. Contralateral breast cancer at 2 years affects as many as 5% of IBC patients compared with 1.1% of non-IBC patients at 2 years [40].

Local-regional disease is present in all patients diagnosed with IBC; however, approximately 30% of patients have metastatic disease at the time of diagnosis. Therefore, a systemic staging workup [computed tomography of the chest-abdomen-pelvis, bone scintigraphy, ^{18}F FDG PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography is optional), etc.] should be performed in every patient [1–5, 7, 9]. In addition, cross-sectional imaging of the neck and an evaluation of infra- and supraclavicular lymph nodes during radiological imaging and planning of radiotherapy are equally important [7]. In recent years, PET/CT has been the main method for detecting distant metastatic disease, assessing the extent of local-regional disease, and aiding radiotherapy and surgical planning. If PET/CT is not available, bone scan and CT scans of the abdomen-chest-pelvis are necessary for disease staging [36]. Routine brain imaging is not necessary in the absence of symptoms.

Tissue Sampling and Pathology

Preoperative systemic chemotherapy (PSC) is the standard therapy for IBC treatment [1–5]. Sufficient tissue sampling from the parenchymal lesion in the affected breast during the pretreatment period is essential for both future treatment planning and subsequent research studies because no cancerous tissue will be available following treatment in patients with pathological complete response (pCR) [1–4, 7]. The presence of an invasive cancer, the identification of the histological type and grade of the tumor, and the expression of the *ER*, progesterone receptor (*PR*), and *HER2* should be clarified with utmost care. If there is doubt about metastasis in the axillary and/or supraclavicular lymph nodes, image-guided core needle biopsies (CNB) and analyses of prognostic and predictive markers are suggested [7]. Specimen tumor cellularity is very important for high-quality tissue collection and must be controlled at the time of CNB [36]. For patients who meet the diagnostic criteria for IBC, obtaining at least two skin punch biopsies to determine dermal lymphatic invasion (DLI) is recommended. Apart from their significance in indicating the presence of DLI, these biopsies are also important for the diagnosis of invasive cancer in patients with no detectable intraparenchymal breast lesions or regional metastases. The best site for sampling is believed to be the region with the most significant color alteration on the breast skin [7]. A 2- to 8-mm biopsy specimen taken from that region is sufficient to demonstrate the presence of DLI. DLI is a frequent feature of IBC and is demonstrated in skin punch biopsies in up to 75% of patients. However, although DLI is responsible for the clinically observed inflammatory alterations in IBC, it is not necessary for diagnosis [7, 9, 41].

All pathological subtypes of invasive adenocarcinoma can be associated with IBC [4, 41, 42]. IBC is also rarely seen in male patients [43]. IBC is often in the form of ductal carcinoma. It is a highly angiogenic and invasive type of cancer characterized by high histological grade and *HER2* positivity with a high rate of *ER* negativity. *p53* mutations are common (70% in IBC and 48% in non-IBC, $p = 0.0238$) [35]. One study from MDACC retrospectively analyzed the histologic subtype distribution of IBC [44]: invasive ductal carcinoma was the most frequent subtype (592 of 659 IBC patients; 89.8%). Invasive lobular histology was seen in 4.5% of the cases (30 of 659 patients), and mixed invasive ductal and lobular histology was seen in 5.6% of the cases. The grade 3 tumor ratios were 78%, 60%, and 61% respectively, and this grade was significantly more common in the ductal group ($p = 0.01$). The 3-year survival rates were 62%, 68%, and 64%, respectively ($p = 0.68$). Histology did not appear to have a significant effect on survival outcomes in IBC patients, unlike in non-IBC patients.

There are three subtypes of IBC: clinicopathologically apparent IBC, clinically apparent IBC, and pathological (occult) IBC [2]. Two population-based studies used this classification for IBC to demonstrate that patients with occult IBC have better disease-free survival (DFS) (5-year DFS 51.6% vs. 25.6%, respectively) and OS than patients with clinically apparent IBC (5-year OS 40% vs. 28.6%, respectively) [22, 45].

The molecular subtypes of IBC are the same as those of non-IBC (luminal, triple negative, and *HER2* positive). Twenty to forty percent are triple negative (TN), whereas 15–20% of non-IBC cases display this molecular subtype [46]. The distribution of the seven subtypes of triple-negative breast cancers (TNBC) (basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem cell-like, luminal androgen receptor, unstable) in patients with TN IBC and TN non-IBC has been investigated by microRNA gene expression profiles [47]. The distribution of molecular subtypes did not differ significantly between the two patient

groups. Moreover, no associations between IBC characteristics and TNBC subtype were observed. Similarly, the influence of the expression of various target genes on prognosis, response to therapy, and classification has been evaluated [48–50]. In one study, the expression of approximately 8000 genes was analyzed in tumor samples from 81 patients with breast carcinoma (37 IBC and 44 non-IBC), and 109 genes were identified as beneficial for the differentiation of IBC and non-IBC [48]. In addition, a set of 85 genes (associated with signal transduction, cell motility, adhesion, and angiogenesis) selected to determine the aggressiveness of IBC were significantly useful in distinguishing two different patient groups with distinct pCR rates (70% vs. 0% pCR) [48]. In another study, gene expression analysis and comparative genomic hybridization were performed in IBC samples using a microdissection technique [49]. No IBC-specific gene signature that distinguishes IBC from non-IBC was identified using this technique. However, these studies must be validated, and further research studies are required [50].

Preoperative Systemic Therapy

Historically, radical mastectomy was the primary modality for the treatment of IBC. Surgery alone resulted in a very poor prognosis and a 5-year survival of less than 5%, with a median survival of 12–32 months [51, 52]. During the past 30 years, the treatment of IBC has significantly evolved. Because of the systemic nature of the disease, adding radiotherapy (RT) after surgery increased only locoregional control without increasing OS [53–55]. The addition of PSC (also referred to as neoadjuvant, preoperative, or induction) before surgery and RT has been associated with significantly increased survival rates of 30–50% for 5-year survival and 24% for 15-year survival [56–61]. SEER data from 7679 stage III IBC patients from 1990 to 2010 were analyzed according to survival [62]. The diagnosed patients were classified over four time periods (1990–1995, 1996–2000, 2001–2005, and 2006–2010), and BCSS during these periods was calculated. Two-year BCSS was 62%, 67%, 72%, and 76%, respectively ($p < 0.0001$). Multivariate analysis revealed that mortality risks decreased with increasing diagnosis year (HR, 0.98; 95% CI 0.97–0.99; $p < 0.0001$).

Historically, preoperative systemic treatment (PST) included only chemotherapy (CT). However, in recent years, some targeted therapies have been used together with CT based on tumor characteristics. Survival was analyzed in IBC cases who were treated before and after October 2006 at MDACC [63]. The date October 2006 was chosen because this date was the beginning of anti-HER2 usage in standard NACT and the opening of a multidisciplinary IBC clinic. Before this date, 3-year OS was 63%; after this date, the ratio increased to 82% ($p = 0.02$). Multivariate analysis demonstrated that anti-*HER2* therapies (HR = 0.38; 95% CI 0.17–0.84; $p = 0.02$) and *ER* positivity (HR = 0.032; 95% CI 0.14–0.74, $p = 0.01$) are important factors for survival.

Breast-conserving surgery is not suggested for IBC because it is a disease that often has a diffuse character [1–4]. When first diagnosed, mastectomy is not suggested; after NACT application, mastectomy can be performed. Mastectomy and axillary lymph node dissection are the optimal surgical procedures. Axillary lymph node metastasis is noted in 55–85% of IBC cases at first diagnosis. A clinical response evaluation by physical examination and imaging techniques may underestimate the extent of residual disease [1–5, 9, 59, 60]. The removal of all gross disease is important because skin lymphatic involvement may extend beyond the area of visible skin changes. Immediate reconstruction is generally not recommended. After mastectomy, postmastectomy RT to the chest wall and axillary, infraclavicular, supraclavicular, and internal mammary lymph nodes (if involved; consider internal mammary nodes if not clinically involved) is part of standard multimodality treatment [1–4, 9, 61].

Randomized clinical trials assessing therapy have not been performed because of the rare occurrence of the disease. Many of the cases are evaluated in protocols in the same way as the LABC study. Data are gathered from one-armed studies and retrospective case series [56–61]. Collaborations between the surgeon, medical oncologist, and radiation oncologist are important in IBC application for optimal therapy [7, 9]. An analysis of 10,197 nonmetastatic IBC patients from the National Cancer Database who underwent surgery and were observed between 1998 and 2010 [64] revealed that trimodality therapy (NACT + surgery + RT) was less common in patients who were old, low paid, and far from health centers and who received therapy during the early period of the study, had other serious health problems, and had insufficient health insurance ($p < 0.05$). The 5- and 10-year survival rates of patients who received all three therapies (55.4% and 37.3%, respectively) were higher than those of the surgery + RT group (40.7% and 23.5%, respectively), the surgery + chemotherapy group (42.9% and 28.5%, respectively), and the surgery-only group (10-year survival 16.5%).

The treatment should begin with NACT. There is no standard primary CT regimen or combination. However, anthracyclines and taxanes are constant members of primary chemotherapy regimens currently. The optimal sequence, dose, duration, and intensity of the CT regimen remain to be defined, and the optimal sequence and type of locoregional therapy have not yet been resolved.

Preoperative Systemic Chemotherapy

In pre-1970 clinical trials, IBC cases were excluded because of the rarity and poor overall prognosis. Most IBC cases

were treated with the same regimens used for the treatment of non-IBC cases. In recent years, specifically designed CT trials for patients with IBC have increased. The response to preoperative systemic chemotherapy (PSC) has prognostic significance. Patients with pCR (complete clearance of the tumor in the breast and axilla; ypT0/Tis ypN0) have a significantly increased DFS rate. Here, I would like to discuss PSC chronologically.

MDACC is the most experienced center for IBC. Since 1974, MDACC has been planning prospective studies on only IBC patients. As of 2010, 242 IBC patients had been enrolled in clinical trials. These studies demonstrated that PSC is necessary for this group of patients. The response to NACT is a surrogate marker for long-term survival. The survival of patients without a response to NACT is shorter than those with a response. In one study, NACT was applied to 175 IBC patients [65]. After NACT and surgery, 61 of 175 patients had residual disease in the breast and axillary lymph nodes. Five-year relapse-free survival (RFS) was 82.5% and OS was 78.6% in patients with pCR after NACT, but in the group with residual disease after NACT, RFS was 37.1% and OS was 25.4%.

First, CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and similar regimens, then anthracycline-containing CT regimens, and, finally, taxanes have been used for NACT in IBC. A total of 527 stage III IBC patients who were observed between January 1989 and January 2011 were retrospectively analyzed in a study at MDACC [66]. The pCR ratio was 15.2% in all groups. The pCR ratio was lowest in the HR-positive/*HER2*-negative group (7.5%) and highest in the HR-negative/*HER2*-positive group (30.6%). The survival of TN-IBC patients was lowest. DFS and OS were related to pCR achievement after therapy, the absence of vascular invasion, non-TNBC type, adjuvant hormonal therapy, and radiotherapy. This study indicated that the predictive and prognostic roles of both HR and *HER2* status are limited and that prognosis is poor in all groups. It is valuable to use new subtype-specific therapies.

Anthracyclines

Active chemotherapy applications for IBC began in 1970. Anthracycline-containing NACT studies involving 15–192 patients have reported improvements in response rates from 20% to 93% and in complete response (CR) rates from 4% to 55% [54]. pCR ratios improved from 3% to 16% [58].

The use of CMF ± VP (vincristine–prednisone) and FAC (fluorouracil–doxorubicin–cyclophosphamide) combinations for NACT in 38 IBC cases was reviewed retrospectively [67] (Table 16.1). The overall response rate (ORR) was 57% in the CMF ± VP group and 100% in the FAC group; the median OS was 18 months in the CMF ± VP group and 30 months in the FAC group. Harris et al. evaluated the long-term follow-up of combined modality therapy in 54 IBC patients [59] (Table 16.1). CMF or CAF (cyclophosphamide–doxorubicin–fluorouracil) was applied as PSC. The clinical CR rate was 52% in patients treated with PSC with or without preoperative radiotherapy. pCR was achieved in 37% (13 patients) of the PSC and RT group and 12% (two patients) of the PSC-only group. Ten-year overall survival was 46% in patients who achieved pCR and 31% in patients with residual disease in the breast and axilla ($p = 0.09$).

A total of 107 stage III breast cancer patients were included in one prospective, randomized NCI study [60] (Table 16.1). Forty-six of the patients had IBC. CAF and methotrexate were applied as NACT until the maximal response was achieved. The median follow-up time was 16.8 years. ORR was 57% within IBC patients.

Two hundred forty-two IBC patients who were enrolled between 1974 and 2001 were examined in five study protocols by MDACC [56, 68–72]. A total of 178 patients received neoadjuvant therapy with four different chemotherapy regimens containing anthracycline [68, 69, 72] (Table 16.1).

1. Protocol A (First Protocol): Patients received FAC neoadjuvant therapy first and then received radiotherapy, followed by FAC or CMF therapies.
2. Protocol B (Second Protocol): Patients received FAC neoadjuvant therapy first and then surgery, followed by adjuvant FAC and radiotherapy.
3. Protocol C (Third Protocol): Patients received FACVP (fluorouracil–doxorubicin–cyclophosphamide–vincristine–prednisone) as induction therapy first and then surgery, followed by FACVP and CMF radiotherapy.
4. Protocol D (Fourth Protocol): Patients received FACVP as induction therapy and then surgery. After surgery, patients with complete responses received adjuvant FACVP. Patients with partial responses (tumors that become decreased in diameter by more than half) received FACVP with MV (methotrexate–vincristine). Patients received MV therapy only when tumors became smaller in diameter by approximately 25–50%.

The response rate for all studies was 72%, and the clinical CR rate was 12% [57, 69, 72] (Table 16.1). There were no differences within the four studies in terms of DFS and OS. The median survival was 37 months. The DFS rates for 5, 10, and 15 years were 32%, 28% and 28%, respectively. The 15-year DFS rates for patients with complete or partial responses who received induction chemotherapy were 44% and 31%, respectively, and the 15-year OS rates were 51% and 31%, respectively. The 15-year DFS and OS of patients whose responses were less than partial with induction chemotherapy decreased to 7%. These results indicate the importance of the response to induction chemotherapy for prognosis.

VP or MV therapy combinations in the third and fourth study protocols had no effect on DFS and OS. Surgery after

Table 16.1 Important neoadjuvant chemotherapy trials in patients with stage III inflammatory breast cancer [56, 59, 60, 68–72]

Study group	Chemotherapy protocol	*n*	ORR (%) (complete+partial)	Median survival (months)	DFS (%)	OS (%)
MDACC Protocol A	FAC-RT-FAC FAC-RT-CMF	40	80	38	–	–
MDACC Protocol B	FAC-surgery FAC-RT	23	57	38	–	–
MDACC Protocol C	FACVP-surgery FACVP-CMF-RT	43	76	64	–	–
MDACC Protocol D	FACVP-surgery-FACVP or FACVP ± MV or MV according to the response to induction CT	72	77	34+	–	–
MDACC-Ueno-whole group [69]	FAC ± VP	178	72	37	32 (5-year) 28 (10-year) 28 (15-year)	40 (5-year) 35 (10-year)
Bauer et al. [67]	CMF ± VP FAC	38	57 100	18 30	–	–
Harris et al. [59]	CMF or CAF	54	54		–	56 (5-year)
Low et al. [60]	CAFM	46	46	–	–	27 (10-year) 20 (15-year)
Cristofanilli et al. [70]	FAC-3 weekly P-surgery-FAC-weekly P-RT	44	77	46	–	74 (2-year OS)
Cristofanilli et al. [71]	FAC	178	72	–	39 (3-year PFS)	53 (3-year)
	FAC-P (weekly or 3-weekly)	62	79		46 (3-year PFS)	71 (3-year)

CAF cyclophosphamide–doxorubicin–fluorouracil, *CMF* cyclophosphamide–methotrexate–fluorouracil, *CMF ± VP* CMF plus/minus vincristine–prednisone, *DFS* disease-free survival, *FAC* fluorouracil–doxorubicin–cyclophosphamide, *FACVP* FAC plus vincristine–prednisone, *FACVP-MV* FACVP plus methotrexate and vinblastine, *MDACC* MD Anderson Cancer Center, *ORR* overall response rate, *OS* overall survival, *P* paclitaxel, *PFS* progression-free survival, *RT* radiotherapy

a poor response to NACT did not alter local relapse risk. Surgery and RT application instead of RT-only as a local therapy did not affect DFS and OS. At the 20-year follow-up, the local relapse rate was 20% [69]. Distant metastasis was observed in 39% of patients, and central nervous system (CNS) metastasis was observed in 9% of patients.

Taxanes

The effect of taxane use in NACT for IBC cases was investigated in 1994 and included 44 patients in an MDACC study (Protocol E) [70] (Table 16.1). FAC chemotherapy was used as NACT and adjuvant therapy in all patients. Paclitaxel (P) was added to the therapy regimen of patients with stable disease or who had a minor response to NACT during the preoperative period, and P was added as an adjuvant therapy in all patients. NACT and then surgery, followed by adjuvant chemotherapy and then radiotherapy, were applied. The objective/clinical response rate was 77% (vs. 72% in regimens containing only anthracycline), and the median survival time was 46 months (vs. 37 months in regimens containing only anthracycline). The results were not statistically significant.

In another study, anthracycline-based and taxane-based NACT protocols were compared in patients with IBC. Group 1 included 178 patients who received anthracycline-containing induction chemotherapy, and group 2 included 62 patients who received taxane-containing chemotherapy (Tables 16.1 and 16.2) [70, 71]. The median follow-up period was 148 months (range: 85–283 months) for group 1 and 45 months (range: 21–99 months) for group 2. The 3-year OS rates were 71% in group 2 and 53% in group 1. In conclusion, P is an important agent in IBC therapy. The 3-year OS rates for patients with *ER*-negative tumors in groups 1 and 2 were 43% and 71%, respectively (32 months and 54 months, respectively ($p = 0.03$)); progression-free survivals (PFS) 31% and 39%, respectively (18 months and 27 months, respectively; $p = 0.04$). Taxanes are clearly more effective, particularly in *ER*-negative tumors. The pCR ratio was 10% in the FAC-only group and 25% in the anthracycline-P group; this difference was statistically significant ($p = 0.012$).

A retrospective analysis substantiated these findings using data from 308 IBC patients who were observed between 1980 and 2000 in a study performed in England [73]. Taxane-containing chemotherapy regimens (AP, cisplatin, P) were better than anthracycline-containing chemotherapy regimens in the 1990s for 10-year BCSS (43.7% and 23.6%, respectively, $p = 0.03$).

Table 16.2 MDACC comparison of neoadjuvant-only anthracycline and anthracycline-taxane-containing chemotherapy protocols in patients with inflammatory breast cancer [69, 71]

Parameter	Group 1	Group 2
N	178 patients	62 patients
Follow-up years	1973–1993	1994–2000
Median follow-up (months)	148 (85–283)	45 (21–99)
Chemotherapy protocol	FAC-based regimens	FAC followed by 3 weekly P or weekly high-dose P
ORR	72%	79%
3-year PFS	39%	46% $p = 0.19$
3-year OS	53%	71% $p = 0.12$
pCR rate	10%	25%
ER-negative tumors	33%	65%
Median PFS (*ER*-negative group)	18 months	27 months $p = 0.042$
Median OS (*ER*-negative group)	32 months	54 months $p = 0.035$
3-year PFS (*ER*-negative group)	31%	39%
3-year OS (*ER*-negative group)	43%	71%

ER estrogen receptor, *FAC* fluorouracil–doxorubicin–cyclophosphamide, *MDACC* MD Anderson Cancer Center, *ORR* overall response rate (complete+partial response), *OS* overall survival, *P* paclitaxel, *pCR* pathological complete response, *PFS* progression-free survival

In the GeparTrio trial, an anthracycline and taxane combination (docetaxel–doxorubicin–cyclophosphamide (TAC)) was used as NACT [74]. Participants were stratified by stage (93 IBC, 194 LABC, and 1777 operable breast cancers) and randomized to arms with six or eight cycles of TAC or two cycles of TAC followed by four cycles of vinorelbine/capecitabine chemotherapy. pCR rates and ORRs were not significantly different between IBC and LABC patients (8.6% vs. 11.3% for pCR, respectively; 71% vs. 69.6% for ORR, respectively) but were significantly lower compared with operable breast cancer (17.7% and 83.4%, respectively; $p = 0.002$ and $p < 0.001$, respectively). In IBC patients, there was a nonsignificant trend toward higher pCR rates with a response at midcourse in patients who received eight cycles of TAC compared with those patients who received only six cycles (17.2% vs. 3.3%; $p = 0.103$).

These studies demonstrate that anthracyclines and taxanes are important and are necessary for primary chemotherapies for IBC. pCR rates are higher with the use of weekly paclitaxel regimens [75, 76]. The optimal dosage and sequence for anthracycline-taxane remain under investigation (taxane first followed anthracycline, anthracycline first followed by taxane, or an anthracycline-taxane combination).

Other Chemotherapies

Dose-dense (Dd) chemotherapy and high-dose chemotherapy with stem cell support may be effective for some selected patient groups. Survival advantages were observed in small, phase II studies (3–4 year DFS of 45–65% and OS of 52–89%), but because there have been no prospective, randomized studies of these protocols, they are not standard and are not suggested except in clinical research trials [1, 2, 58, 77–83].

In one phase III randomized study, a total of 668 primary breast cancer cases (101 IBC and ≥3 cm non-IBC) were randomized to receive preoperative concurrent epirubicin (E)/P every 3 weeks or Dd and dose-escalated sequential E followed by P every 2 weeks. All patients received three cycles of CMF after surgery. In the whole group, pCR rate (18% vs. 10%, $p = 0.008$), DFS (HR: 0.71, $p = 0.011$), and OS (HR: 0.83, $p = 0.041$) were significantly better in the Dd chemotherapy arm compared with the E/P arm. IBC cases had no benefit from Dd treatment. Non-IBC cases significantly benefited from Dd treatment (DFS HR: 0.65, $p = 0.005$; OS HR: 0.77, $p = 0.013$). In multivariate analysis, treatment effects were significant for non-IBC (DFS HR: 0.65, $p = 0.088$; OS HR: 0.82, $p = 0.059$). Dd therapy was associated with significantly more anemia and thrombocytopenia, but the neutropenia and infection rates were similar [84].

High-risk primary breast cancer patients were included in one prospective study at MDACC [82]. Eighteen patients in the study had IBC. High-dose weekly paclitaxel chemotherapy was applied following FAC therapy as NACT. After surgery, cyclophosphamide, etoposide, and cisplatin (CVP) combined therapy was applied, followed by bone marrow mobilization and high-dose cyclophosphamide, carmustine, and thiotepa CT with stem cell support. The clinical CR ratio was 31%, and the mastectomy ratio was 72%. The 5-year OS rate was 36%, and the DFS rate was 28%. The therapy was more effective in young patients and patients with less lymph node metastasis.

The PEGASE 02 study included 95 nonmetastatic IBC patients [80]. After high-dose FAC therapy, blood stem cell support was applied. Mastectomies were performed in 86 patients following PSC. Radiotherapy was performed. The clinical response rate (RR) was 90%, and the pCR rate in the breast was 32%. The 3-year RFS was 44% (95% CI, 33–54%), and the estimated 3-year survival was 70% (95% CI, 60–79%).

One retrospective study from Somlo et al. included 120 IBC patients who received dose-intense CT as NACT [81]. Patients received conventional-dose chemotherapy and surgery and sequentially developed single- or tandem-cycle dose-intense CT. The median observation time was 61 months, the 5-year RFS rate was 44%, and the OS was 64%. Multivariate analysis demonstrated that *ER*/*PR* positivity and <4 positive axillary lymph node metastasis were the best predictors of which patients would benefit from tandem, dose-intense chemotherapy.

The GETIS 02 trial was conducted by the French Adjuvant Study Group [85]. In that study, the efficacy of primary che-

motherapy with four cycles of high-dose FEC (fluorouracil–epirubicin–cyclophosphamide) with or without lenograstim in 120 nonmetastatic IBC patients was evaluated. After preoperative CT, surgery and RT were administered as locoregional therapy, and maintenance CT with four cycles of FEC-75 was then applied. The median DFS was 39 months. After a median of 10 years of follow-up, the DFS and OS rates were 36% and 41%, respectively.

In the CALGB 40603 trial, the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by Dd AC on pCR rates in stage II/III TNBC patients was investigated [86]. A total of 443 patients were included in the study. The percentage of T4 tumors was only 2%. All patients received 12 weeks of P followed by four cycles Dd AC as NACT:

- Arm 1: Only NACT.
- Arm 2: NACT + bevacizumab (with NACT 10 mg/kg, 2-week intervals, nine cycles).
- Arm 3: NACT + carboplatin (with P, four cycles).
- Arm 4: NACT + carboplatin (with P, four cycles) + bevacizumab (with NACT 10 mg/kg, 2-week intervals, nine cycles).

pCR rates were higher with the addition of either carboplatin (60% vs. 44%, $p = 0.0018$) or bevacizumab (59% vs. 48%, $p = 0.0089$). Only carboplatin significantly raised the pCR rate, from 41% to 54% ($p = 0.0029$).

In the GeparSixto GBG 66 trial, 595 stage II/III TNBC and HER2-positive breast cancer included in the study [87]. Patients were treated with 18 weeks P and non-pegylated liposomal doxorubicin (20 mg/m^2, once a week). TNBC patients received simultaneous bevacizumab (15 mg/kg IV every 3 weeks). HER2-positive patients received Tr at 3-week intervals and lapatinib 750 mg/day. Patients were randomized to carboplatin (AUC 1.5 once a week) or no carboplatin arms. The pCR (ypT0 ypN0) rates were 43.7% in the carboplatin arm and 36.9% in the no carboplatin arm. In TNBC patients, these rates were 53.2% and 36.9%, respectively ($p = 0.005$). In HER2-positive patients, the pCR rates were 32.8% vs. 36.8%, respectively ($p = 0.581$). Toxicities were significantly more common in the carboplatin arm. Carboplatin is an effective drug in the treatment of TNBC, but not in HER2-positive patients. After a median of 47.3 months of follow-up, DFS was not different in the whole group [88]. However, in patients with TNBC taking carboplatin, DFS (HR: 0.56, $p = 0.024$) and distant DFS (HR: 0.50, $p = 0.013$) were significantly better than in patients not taking carboplatin. No difference was seen in HER2-positive patients. The multivariable analysis confirmed that pCR (vs. no pCR) was a strong predictor of DFS (HR: 0.23, $p < 0.001$) and OS (HR: 0.29, $p = 0.002$). Neoadjuvant use of carboplatin in TNBC patients was very effective.

The role of platinum-based NACT in TNBC patients is highly controversial, and it is not routinely recommended by current guidelines. One meta-analysis included nine randomized trials with platinum-based NACT in TNBC (2109 patients) [89]. The pCR rate was significantly higher with platinum-based NACT compared with non-platinum NACT protocols (52.1% vs. 37%, $p < 0.001$). Grade 3/4 hematological toxicities were higher in the platinum-based NACT arm, and grade 3/4 neuropathy was not different in the platinum and nonplatinum arms. Castrellon et al. concluded that the addition of carboplatin to standard NACT for TNBC should be individualized [90]. Currently, it is acceptable to use carboplatin in the treatment of IBC, BRCA-associated breast cancer, or LABC.

An international expert panel on IBC recommended a minimum of six cycles of PSC (AC followed by taxane for HER2-negative disease) be administered over a course of 4–6 months before surgery [7]. The recommendation of MDACC involves the use of upfront anthracycline-based therapy according to their findings, including a 10-year OS rate of 35% in IBC patients who received anthracycline-based chemotherapy before locoregional therapy [69] (Table 16.1). The Dana Farber Cancer Institute recommends a dose-dense anthracycline and taxane regimen for these patients [36, 84]. Northwestern University recommends weekly P + Tr followed by four cycles of AC for HER2-positive patients and AC followed by P for HER2-negative patients [36]. However, adding carboplatin to taxane therapy in the PSC of TN-IBC is still controversial, as there is not yet enough data. The last consensus conference did not recommend adding carboplatin to taxane therapy outside of a clinical trial [36].

If the response is insufficient, different CT regimens or RT can be applied [7, 9, 36]. RT is applied after surgery, and if the CT program is not completed before surgery, it should be completed during the postoperative period (Fig. 16.1).

In patients with residual invasive disease after PSC and surgery, according to the CREATE-X study results, the addition of six to eight cycles of capecitabine to standard adjuvant CT (vs. no capecitabine) was associated with increased 5-year DFS (74.1% vs. 67.6%; $p = 0.01$) and 5-year OS (89.2% vs. 83.6%; $p = 0.01$) [91]. Among patients with TNBC, DFS was 69.8% vs. 56.1%, and OS was 78.8% vs. 70.3%. In the last consensus panel, this difference was discussed with the participants. Some participants considered adding capecitabine to the adjuvant treatment of triple-negative IBC patients who do not achieve a pCR [36].

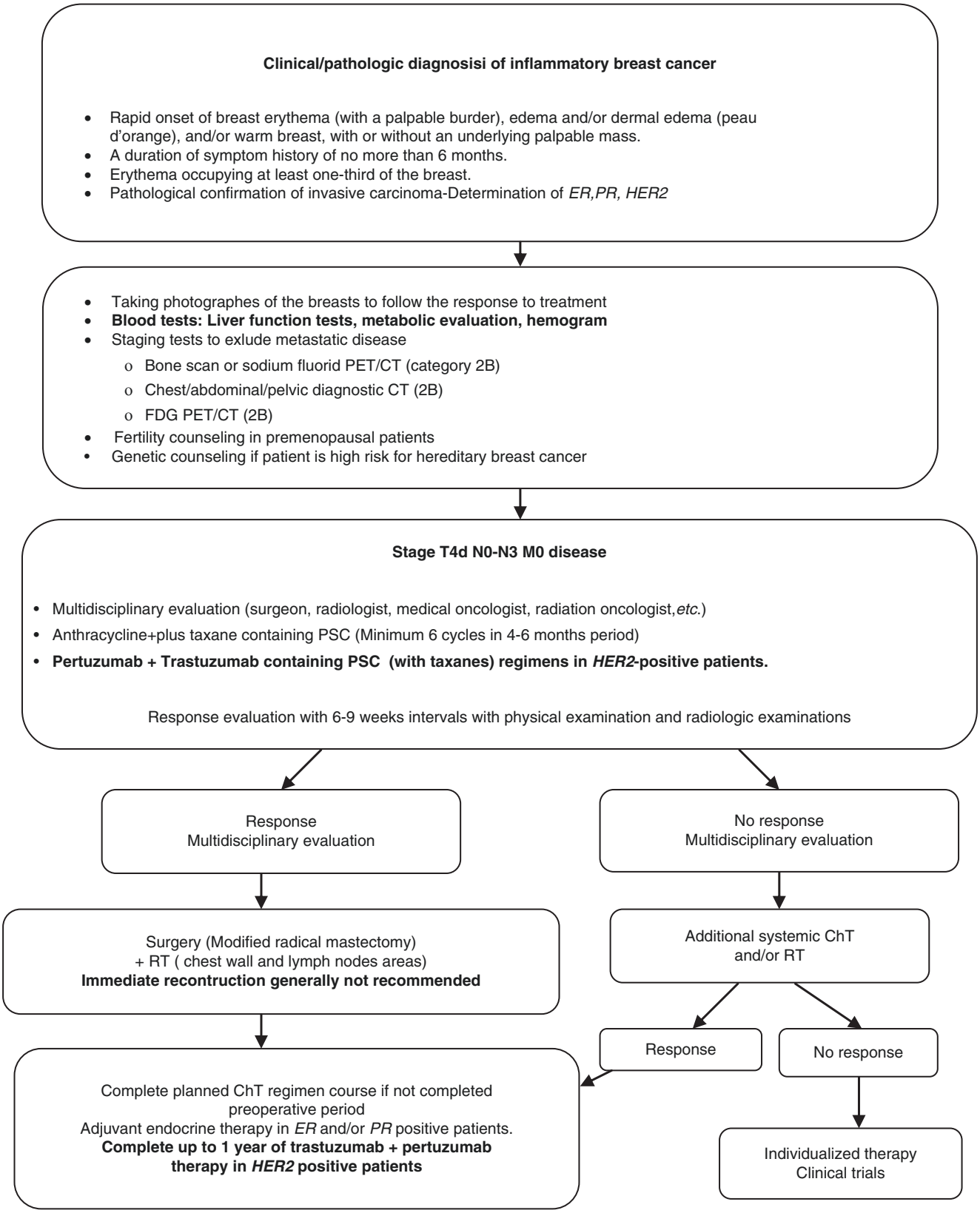

Fig. 16.1 Flowchart for the diagnosis, follow-up, and treatment of inflammatory breast cancer [1–4, 7–9, 36, 57, 153]. *Abbreviations*: *ChT* chemotherapy, *CT* computed tomography, *ER* estrogen receptor, *FDG-PET/CT* fluorodeoxyglucose positron emission tomography/computed tomography, *HER2* human epidermal growth factor receptor 2, *PR* progesterone receptor, *PSC* primary systemic chemotherapy, *RT* radiotherapy

Targeted Therapies

Anti-HER2 Therapies

The HER2 positivity ratio in IBC is very high and varies between 42% and 57% [1–4, 41, 42]. *HER2* positivity is important for the prognosis of non-IBC, but its importance for IBC is not known. A retrospective study that included 179 stage III IBC patients [92] determined that *HER2* positivity or negativity is not related to RFS. Another study of more than 2000 patients conducted in California demonstrated improved BCSS in *HER2*-positive patients compared to *HER2*-negative patients (HR, 0.82; 95% CI 0.68–0.99) [93].

Although the prognostic importance of *HER2* for IBC is not known, *HER2* positivity is important for predicting the response to anti-*HER2* therapies in *HER2*-positive patients. Trastuzumab (Tr) is a monoclonal antibody against *HER2* and the first of the anti-*HER2* agents. The addition of Tr to anthracycline- and taxane-containing PSC regimens yielded a significantly increased response and improved survival compared to non-Tr PSC regimens [5, 83, 93–98]. The increase in the pCR rate from 17% to 62.5% was also statistically significant. Unfortunately, the studies included many LABC and fewer IBC cases. Studies including only IBC cases are very rare.

Dawood et al. reported that the pCR rate was 62.5% in *HER2*-positive IBC cases receiving NACT combined with Tr therapy, and the 2-year PFS was 59.4% [98]. In that study, 3 of 16 IBC patients had metastatic disease at the beginning of treatment. Forty-eight *HER2*-positive, LABC (IBC-containing) patients were enrolled in a study by Hurley et al. [99]. Docetaxel-cisplatin-Tr was applied as induction therapy. After chemotherapy, surgery, adjuvant chemotherapy and radiotherapy were performed consecutively. The OS was 100% in patients with pCR. In patients with residual disease after NACT, the OS ratio ranged from 76% to 83%.

In another study including 9 IBC and 22 LABC patients, docetaxel and Tr were applied as the primary chemotherapy, and the CR rate was 40% [100].

The NOAH (neoadjuvant Herceptin) trial was a prospective, open-label, phase 3, multicenter, randomized study [101]. *HER2*-positive, locally advanced (n = 174) or IBC (n = 61) cases were enrolled in the study. The patients received anthracycline-based and taxane-based NACT alone or with 1 year of Tr (concurrently with NACT and continued after surgery). A parallel group with *HER2*-negative disease was included and received NACT alone. Relapse, progression, and mortality risks were statistically significantly decreased in the Tr group compared with the CT-only group. The pCR ratio was twofold higher in the Tr group than in CT-only group (38% and 19%, respectively). After a median follow-up of 5.4 years, the event-free survival (EFS) benefit of the addition of Tr was maintained in patients with *HER2*-positive disease [102]. The 5-year EFS was 58% in the Tr group and 43% in the CT group (HR, 0.64; 95% CI 0.44–0.93; p = 0.016). Similarly, during that time period, EFS was strongly associated with pCR in patients who received Tr. In that study, 27% of *HER*-positive patients had IBC. The 3-year EFS was 70.1% in the Tr group and 53.3% in the CT-only group (p = 0.0007). The pCR (complete disappearance of the tumors from both the breast and lymph nodes) rate was 48% in the Tr group and only 13% in the CT-only group (p = 0.002) [103].

Tr should be started in the induction chemotherapy period for the treatment of *HER2*-positive LABC or IBC patients. Although there has been no prospective randomized study, Tr therapy should be extended to 1 year. An anthracycline-Tr combination is not suggested because of enhanced cardiotoxicity [5, 7, 9].

Lapatinib is another anti-*HER2* (reversible dual inhibitor of both *HER1* and *HER2*)-targeted drug, and studies with lapatinib or lapatinib with paclitaxel are ongoing [104–106]. The clinical RR was 80% for 21 IBC patients who received a lapatinib-paclitaxel combination [105]. In one multicenter, open-label, phase II study with 49 IBC patients, a lapatinib-paclitaxel combination was used as NACT [106]. Patients were divided into two groups: cohort A was positive for *HER2* 2+ or 3+ by immunohistochemical (IHC) methods or FISH (fluorescence in situ hybridization) ± epidermal growth factor receptor (*EGFR*) expression; cohort B was *HER2* negative/*EGFR* positive. *HER2* 3+ or FISH-positive patients were analyzed separately. First, patients received lapatinib only for 14 days, followed by 12 weeks of lapatinib and paclitaxel weekly. Cohort B was stopped because of slow enrollment and a lack of efficacy in IBC patients with *HER2*-negative/*EGFR*-positive tumors enrolled in a parallel study, EGF103009. Thirty-five patients completed the study and underwent surgery. The pCR rate of cohort A was 18.2%, and the clinical RR was 78.6% for all groups and 78.1% in the *HER2* 3+ group. The clinical RR was 31% in the *HER2*-positive group receiving only lapatinib, and the pCR rate was 17.6% in all patients who underwent surgery after therapy. The most common side effects of lapatinib were diarrhea and skin eruptions. Lapatinib is currently suggested only for clinical research studies and not for routine clinical applications and should only be administered to patients who have *HER2*-positive BC.

In one German randomized, phase III trial (GeparQuinto, GBG 44 trial), lapatinib vs. trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy was compared in the neoadjuvant setting [107]. IBC cases were also included in the study (83 patients had T4d disease). A total of 620 patients were randomly assigned in a 1:1 ratio to receive neoadjuvant therapy with four cycles of EC (epirubicin+cyclophosphamide) every 3 weeks and four

cycles of docetaxel (D) with either Tr (every 3 weeks for eight cycles) or lapatinib (L: 1000–1250 mg/day throughout all cycles) before surgery. Of 620 patients, 309 received ECTr-DTr, and 311 received ECL-DL. The pCR rate was 30.3% in the ECTr-DTr group and 22.7% in the ECL-DL group. The difference was statistically significant ($p = 0.04$). This study demonstrated that the pCR rate was significantly lower in the lapatinib+CT group compared to the Tr + CT group. The investigators concluded that unless long-term outcome data showed different results, lapatinib should not be used outside of clinical trials as a single anti-*HER2* treatment in combination with NACT.

In one prospective randomized study, a lapatinib plus Tr combination was compared to Tr and lapatinib (NeoALTTO trial) [108]. Only early-onset breast cancer patients were enrolled in this study. The NeoALTTO trial demonstrated that dual anti-HER2 inhibition with Tr + lapatinib combined with weekly P significantly increased the proportion of patients achieving pCR (51.3%; 95% CI 43.1–59.5) in the combination group compared with Tr alone (29.5%; 95% CI 22.4–37.5) and lapatinib alone (24.7%; 95% CI 18.1–32.3). The difference was statistically significant ($p = 0.0001$). The EFS and OS did not differ between treatment groups. However, the 3-year EFS and 3-year OS were significantly improved in women who achieved pCR (HR 0.38, $p = 0.0003$, and HR 0.35, $p = 0.005$, respectively) [109]. Findings from this study confirmed that pCR after neoadjuvant anti-*HER2* therapy is an important prognostic factor for survival.

In one meta-analysis, in *HER2*-positive breast cancers, the dual block with trastuzumab and lapatinib plus CT (vs. Tr-CT) was found to be a very active treatment only in HR-negative patients treated with taxane monotherapy (25% absolute difference of the pCR rate) [110]. A total of 1155 patients were included in the analyses. In the whole group, dual block was associated with a 13% absolute increase in the pCR rate as compared with single block with trastuzumab.

The NeoSphere study was a multicenter, open-label, phase II randomized trial. IBC cases (29 of 417 patients) were also enrolled in this study. Tr and another anti-*HER2*-targeted agent, pertuzumab, were used during the preoperative CT period [111]. The pCR ratio was higher in the pertuzumab+Tr + docetaxel combination arm than in the Tr + docetaxel combination arm (39.3% vs. 21.5%; $p = 0.0063$).

The TRYPHANEA study, a phase II cardiac safety study, was a randomized, three-arm study [112]. A total of 225 *HER2*-positive LABC, IBC, and operable breast cancer patients were enrolled in the study. In the first arm, NACT+Tr + pertuzumab was followed by Tr + pertuzumab+ docetaxel. In the second arm, NACT only was followed by docetaxel+Tr + pertuzumab. In the third arm, docetaxel+ carboplatin+Tr + pertuzumab combination was administered. The pCR ratio was the same in all treatment groups but was highest in the third arm (66.2%). Diarrhea was the most common side effect.

After these two studies, the Food and Drug Administration (FDA) approved the use of Tr + pertuzumab+docetaxel combination as NACT for *HER2*-positive LABC, IBC, and early breast cancer (>2 cm tumor or axillary lymph node positive) in September 2013 [113].

WSG-ADAPT (West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy) is a prospective, multicenter, controlled, randomized, investigator-initiated phase II/III German study [114]. This umbrella study ($n = 4936$) aims to establish early predictive markers for treatment response under a short, 3-week induction treatment (using CNB at baseline and after induction therapy). Early response was assessed in a 3-week post-therapeutic core biopsy (proliferation decrease ≥30% Ki-67 or low cellularity <500 invasive tumor cells). In one part of this study, *HER2*-positive and HR-negative patients were included in the study [115]. In that study, 160 *HER2*-positive and HR-negative patients were randomized to 12 weeks of dual blockade with Tr and pertuzumab with or without weekly P. The pCR rate with only dual blockade was 36.3%; with the addition of CT, the pCR rate rose to 90.5%. In the dual blockade arm, the nonresponder pCR rate was only 8.3% compared with 44.7% in responders.

In another German study (GeparSepto study), 1206 breast cancer patients were randomized to four cycles of weekly P or nab-P, followed by four cycles of EC chemotherapy q3 weeks, with concurrent Tr + pertuzumab q3 weeks for those with *HER2*-positive tumors [116]. Including all histologic subtypes, the pCR (ypT0 ypN0) rates were 29% in the P-arm and 38% in the nab-P arm (OR 1.53; $p = 0.00065$). The main additional benefit of nab-P on pCR was shown in TNBC. Overall, 23% patients were noted to have at least one serious adverse event, 26% in the nab-P arm and 21% in the P-arm ($p = 0.057$). In a subgroup analysis of this trial (*HER2*-positive 396 patients vs. *HER*2-negative cohort), the pCR rate was highest in *HER2*-positive/HR-negative tumors (71% in the whole group; 66.7% in the P arm, 74.6% in the nab-P arm) [117]. Grade ¾ toxicities (diarrhea, febrile neutropenia) were significantly more common in *HER2*-positive patients than in *HER2*-negative patients. LVEF (left ventricular ejection fraction) decreases from baseline were uncommon (2% vs. 0.4%, respectively).

In the neoadjuvant setting, according to the international guidelines, the 2017 standard of care of patients with *HER2*-positive breast cancer combines a taxane-containing chemotherapy with a dual anti-*HER2*-directed therapy with pertuzumab and trastuzumab [118, 119]. At that time, after surgery, patients should receive only trastuzumab for 1 year.

Based on the phase III APHINITY trial results, a pertuzumab+Tr-based regimen for adjuvant treatment of *HER2*-positive early breast cancer at high risk of recurrence (lymph node-positive or HR-negative breast cancer), was approved by the FDA in December 2017 [120]. In that trial, after a median 45.4 months of follow-up, in the overall study population, CT + Tr + pertuzumab significantly reduced the risk of invasive breast cancer recurrence or death by 18% compared with Tr + CT alone (HR = 0.82; $p = 0.047$). In the lymph node-positive subgroup, HR = 0.77 and, for the HR-negative subgroup, HR = 0.76.

The pCR rates and survival after anthracycline, anthracycline+taxane, and CT + trastuzumab-containing NACT regimens for the treatment of IBC are outlined in Table 16.3.

In another study, a new anti-*HER2* agent, afatinib (an oral tyrosine kinase inhibitor and irreversible binder of *HER1*, *HER2*, and *HER3*), was compared to Tr and lapatinib in a neoadjuvant setting in patients with *HER2*-positive stage IIIA, B, C, and IBC [121]. A total of 29 patients were randomized to afatinib ($n = 10$), lapatinib ($n = 8$), or trastuzumab ($n = 11$). These drugs were administered for a duration of 6 weeks until the patients underwent surgery. The ORR was determined for eight afatinib-, six lapatinib-, and four trastuzumab-treated patients. Drug-related adverse events were recorded in all afatinib-treated patients and commonly included diarrhea, acneiform dermatitis, and paronychia. Diarrhea and rash were documented in six of eight lapatinib-treated patients. The authors concluded that afatinib demonstrated more favorable clinical activity than lapatinib and trastuzumab for neoadjuvant treatment of *HER2*-positive LABC and IBC.

In the DAFNE trial, *HER2*-positive breast cancer patients were treated with afatinib (20 mg/day) and Tr alone, followed by 12 weeks of weekly P, Tr, afatinib, followed by 12 weeks with EC, and Tr before surgery [122]. The expected pCR rate was 70%, and the study pCR rate was 49.2% in 65 treated patients. The pCR rates of HR-negative and HR-positive patients were 63.2% vs. 43.5%, respectively ($p = 0.153$). pCR rates were not different according to the PIK3CA mutations ($p = 0.363$). Patients with (9 pts) or without (56 pts) lymphocyte predominant breast cancer pCR rates were 100% vs. 41.1%, respectively ($p < 0.001$). Most frequent grade ¾ toxicities were diarrhea (7.7%), increased creatinine (4.6%), and infection (4.6%).

Neratinib is another irreversible oral tyrosine kinase inhibitor of *HER1*, *HER2*, and *HER4*. Neratinib has been used as an NA therapy in an ongoing multicenter, adaptive phase II trial for high-risk stage II/III breast cancer (1-SPY2) [123]. Patients were randomized to standard CT (weekly P for 12 weeks followed by four cycles of AC; for *HER2*-positive patients, weekly Tr with P) ± neratinib arms (240 mg/day with weekly P period). The mean pCR rate was 56% with the addition of neratinib to standard CT vs. 33% without neratinib.

In an NSABP FB-7 phase II trial, 126 *HER2*-positive LABC patients were randomly assigned to neratinib, or Tr, or a neratinib+Tr combination with weekly P followed by standard AC [124]. The pCR rates were 33% for neratinib, 38% for Tr, and 50% in the combination arm. Diarrhea was the most frequent side effect of neratinib.

T-DM1 is a conjugation of Tr and the cytotoxic antimicrotubule agent DM-1 (maytansine derivative). In the open-label phase 3 KRISTINE study, 444 *HER2*-positive stage II–III breast cancer patients were randomly assigned to a T-DM1 + pertuzumab arm ($n = 223$, arm 1) and a docetaxel+carboplatin+Tr + pertuzumab arm ($n = 221$, arm 2) as NACT [125]. The pCR rates were 44.4% in arm 1 and 55.7% in arm 2 ($p = 0.016$). Grade ¾ toxicities (13% vs. 64%) and serious adverse events (5% vs. 29%) were more frequent in arm 2. The most common grade ¾ adverse events were neutropenia, diarrhea, and febrile neutropenia in arm 2.

In another part of the WSG-ADAPT trial, *HER2*-positive/HR-positive early BC patients ($n = 376$) were included in the

Table 16.3 Pathological complete response and survival rates according to neoadjuvant chemotherapy protocol in inflammatory breast cancer

Trial	Type of study / NACT protocol	*n*	pCR rate	Survival
Ueno et al. [69]	Retrospective	178	10%	15-year DFS 28%
	Anthracycline-containing regimens			10-year OS 35%
Cristofanilli et al. [71]	Retrospective	62	25%	3-year PFS 46%
	Anthracycline+paclitaxel			3-year OS 71%
Dawood et al. [98]	Retrospective	16 (3 patients with stage 4 disease)	62.5%	2-year PFS 59.4%
	Anthracycline+paclitaxel+trastuzumab in *HER2*-positive patients			
Baselga et al. [103]	Prospective randomized study (NOAH trial)	61		3-year EFS
	Anthracycline+taxane±trastuzumab in *HER2*-positive patients		48% (+Tr) vs. 13% (−Tr)	70.1% (+Tr) vs. 53.3% (−Tr)

DFS disease-free survival, *EFS* event-free survival, *NACT* neoadjuvant chemotherapy, *NOAH* neoadjuvant Herceptin trial, *pCR* pathological complete response, *PFS* progression-free survival, *OS* overall survival, *Tr* trastuzumab

study [126]. Patients were randomized to 12 weeks of T-DM1 with or without endocrine therapy (ET) and Tr + ET arms. Early response was assessed in a 3-week post-therapeutic core biopsy (proliferation decrease ≥30% Ki-67 or cellularity response). After 12 weeks of treatment, the pCR rates were 41% in the T-DM1 arm, 41.5% in the T-DM1 + ET arm, and 15% in the Tr + ET arm ($p < 0.001$). The pCR rates were 35.7% in early responders and 19.8% in nonresponders (OR: 2.2). The overall toxicity was low.

Antiangiogenic Therapies

Vascular endothelial growth factor (*VEGF*) expression is increased in IBC. Therefore, antiangiogenic drugs have been suggested as therapy targets. The antiangiogenic drug bevacizumab has been used together with chemotherapy in induction therapy, but did not meet the expectations [1–4, 61, 95, 127, 128]. NCI-0173 was a small, phase II study that included 21 patients and assessed the efficacy of doxorubicin and docetaxel combined with bevacizumab in the preoperative treatment of LABC/IBC cases [129]. The clinical RR was 67 %, and the pCR rate was 5 %. The BEVERLY-1 study was a multicenter, one-armed, open-label, phase II study performed in France with HER2-negative nonmetastatic IBC patients [130]. Firstly, four cycles of a FEC100-bevacizumab (15mg/kg) combination were applied, followed by four cycles of docetaxel-bevacizumab combination were given every 21 days as NACT. After 2–4 weeks of surgery, patients received adjuvant RT. Hormonal therapy was started to HR positive patients. Bevacizumab was continued as adjuvant therapy. Total 100 patients were evaluated; pCR rate was 19%. Grade 3-4 neutropenia (89%), febrile neutropenia (37%) and the mucositis (23%) were the most frequent side effects during the NACT period. Grade 3-4 proteinuria (7%) was the most frequent side effect during the adjuvant therapy period. Investigators conclude that, addition of bevacizumab in the NACT and adjuvant treatment period of these patient population was not effective, and had severe toxicity.

The BEVERLY-2 study was a multicenter, one-armed, open-label, phase II study with *HER2*-positive nonmetastatic IBC patients, performed again by a French group [131]. First, four cycles of a FEC100-bevacizumab combination were applied, followed by four cycles of docetaxel-bevacizumab-Tr combination every 21 days. Of 52 patients, 42 (8%) completed eight cycles of therapy, and 49 (94%) underwent surgery. The pCR rate was 63.5%. The 3-year DFS rate was 68%, and the OS was 90%; the 3-year DFS rate for patients who achieved pCR was 80%. Astheny and vomiting were reported as the most common side effects. In the other part of this study, the numbers of circulating tumor cells (CTCs) and circulating endothelial cells (CECs) were counted before the study began, at the fifth cycle, before surgery, during the postoperative period, and during the first year [132]. The 3-year DFS was 95% in patients with pCR, and these patients were CTC-free after treatment. For baseline (before treatment) patient CTC numbers of <1 and ≥1, the 3-year survival was 81% and 43%, respectively; this difference was statistically significant ($p = 0.01$). Prognostic importance was not detected for CEC. This study is important in terms of demonstrating the prognostic effect of CTC.

In 2017, pooled analyses of BEVERLY-1 and BEVERLY-2 were published [133]. The median follow-up period was 43 months. The detection rate of CTC was 39%. The pCR rate was not correlated with CTC or CEC levels. The 3-year DFS (39% vs. 70%; $p < 0.01$; HR 2.80) and the 3-year OS ($p < 0.01$) were shorter in patients with CTC detection (≥1 CTC/7.5 ml) at baseline than in patients without CTC at baseline. A subgroup of IBC patients with pCR after NACT and no detectable CTC at baseline had excellent OS (3-year OS 94%). In multivariate analysis, no pCR, CTC detection at baseline, and negative hormone receptors were independent poor prognostic factors for survival. CEC level had no prognostic significance. In another study, CTCs were determined to be a strong predictor of worse prognosis in patients with newly diagnosed IBC [134]. CTC count could be part of the IBC stratification in prospective trials.

In one phase II trial, 34 patients with IBC were included in the study [135]. Patients received weekly carboplatin and paclitaxel plus bevacizumab every 3 weeks and oral metronomic cyclophosphamide for 6 months. *HER2*-positive patients received Tr, and HR-positive patients received endocrine therapy. The pCR rate was highest (57%) in patients with *HER2*-positive tumors; the rates were 20% in patients with TNBC and 0% in patients with luminal B-like (*HER2*-negative) tumors ($p = 0.019$). The 5-year DFS was 80% vs. 48% for patients who achieved a pCR vs. those who did not ($p = 0.12$). The 5-year OS in patients who achieved pCR was 100%, compared with 61% for patients who did not achieve pCR ($p = 0.029$).

One meta-analysis of randomized controlled trials comparing the effects of NACT with or without bevacizumab in the treatment of breast cancer involved 4526 patients [136]. The overall pCR (breast and axilla) rates were 35% in the bevacizumab arm and 27% in the no bevacizumab arm (RR = 1.26, $p < 0.001$). In TNBC cases, the pCR rate was 30% higher in the bevacizumab arm than in the no bevacizumab arm (RR = 1.30, $p < 0.001$). In addition, in HR-positive cases, there was a 26% increase in pCR rate (RR = 1.26, $p < 0.003$) in patients treated with bevacizumab compared with patients treated without bevacizumab.

In spite of these findings, bevacizumab is not routinely recommended in the neoadjuvant treatment of breast cancer.

Semaxanib (*SU5416*) is an organic small receptor tyrosine kinase inhibitor that inhibits *VEGF*-mediated signaling through *VEGFR2*. The effectiveness of a doxorubicin and semaxanib combination was investigated in 18 stage IIIB and IBC patients in a phase IB study [137]. The median sur-

vival has not yet been provided. After treatment, the density of microvessels and blood flow through the tumor decreased. Neutropenia was reported as a factor in dose-limiting toxicity. Congestive heart failure was monitored in four patients (22%).

Antiangiogenic drug studies continue with pazopanib, a new multitargeted tyrosine kinase inhibitor.

New Targets

There are many ongoing targeted therapy drug studies (*p53* gene therapy, *p53* stabilizer agents, proteasome inhibitors, *Tie-2* kinase inhibitors, *E-cadherin* inhibitors, phosphatidylinositol-3-kinase inhibitors, farnesyltransferase inhibitors, etc.) [1–4, 57, 61, 95, 127, 128].

p53 mutations are associated with decreased responses to CT and decreased survival outcomes. In one study (a total of 24 IBC cases), *p53* gene mutation and nuclear overexpression were associated with an 8.6-fold higher risk of death compared with patients with neither mutation nor overexpression [138]. INGN-201 is an adenoviral vector that carries the normal *p53* gene under the control of the cytomegalovirus promoter. INGN-201-mediated *p53* expression induces apoptosis and inhibition of proliferation in vitro in numerous different tumor cancer cell lines [139]. INGN-201 can be used in future IBC trials.

EGFR overexpression occurs in 30% of IBC cases. Mortality risk is increased with increased expression of *EGFR* and chemokine receptors (*CXCR4* and *CCR7*) in IBC [140]. The 5-year OS was 24.8% in an IHC analysis of *CXCR4*-positive patients and 42.3% in the negative group. The 5-year OS was 20% in an IHC analysis of *CCR7*-positive patients and 41.9% in the negative group. These genes have been announced as new targets for therapy. The effectiveness of the human-*EGFR* antibody panitumumab and chemotherapy (nanoparticle paclitaxel and carboplatin) combination will be investigated in *HER2*-negative IBC cases during the preoperative period.

A deficiency in the Ras signaling pathway member low-affinity insulin-like growth binding protein (*LIBC*/*WINT1*) and overexpression of Ras homolog gene family member C (*RhoC*) guanosine triphosphatase (*GTPase*) have been established in IBC [141]. In situ hybridization analysis of paraffin blocks demonstrated that LIBC deficiency was 80% in IBC cases and 21% in non-IBC cases ($p = 0.0013$). The *RhoC GTPase* overexpression ratio was 90% in IBC cases and 38% in non-IBC cases ($p = 0.0095$). These genes may be a target for the treatment of IBC. Farnesyltransferase inhibitors (*FTI*s) inhibit RhoC and angiogenesis. *FTI*s have been investigated for IBC. The FTI tipifarnib (T) enhances the antitumor effects of chemotherapy in vitro, has activity in metastatic breast cancer, and enhances the pCR rate of neoadjuvant AC chemotherapy. In one phase I–II trial, T plus weekly P and 2-week AC CT were tested as a neoadjuvant treatment for *HER2*-negative *ER* and/or *PR*-positive LABC (stratum A: 33 patients) and IBC (stratum B: 22 patients) irrespective of *ER*/*PR* expression [142]. The breast pCR rate was 18% in stratum A and 4% in stratum B. These results are not sufficient to indicate the use of *FTI*s for the neoadjuvant treatment of IBC.

Anaplastic lymphoma kinase (*ALK*) gene amplification or overexpression may occur in IBC [143, 144]. IBC patients are currently being evaluated for the presence of *ALK* genetic abnormalities and, when eligible, enrolled into clinical trials evaluating *ALK*-targeted therapies (the small-molecule dual tyrosine kinase *cMET*/*ALK* inhibitor crizotinib).

PARP (Poly-ADP-Ribose-Polymerase) inhibitors (olaparib, niraparib, rucaparib, talazoparib, and veliparib) and immune-check-point inhibitors (anti-PD-1 and anti-PD-L1) (pembrolizumab, atezolizumab, avelumab, durvalumab, and nivolumab) are other promising targets, especially for TNBC (with BRCA mutations for PARP inhibitors) [145–148]. PARP inhibitors and platinum compounds have overlapping mechanisms of action. Many NACT trials are planned with the combination of platinum and PARP inhibitors. In addition, PARP-inhibitors and immune-checkpoint inhibitors combinations are being investigated [146]. In the neoadjuvant setting, the preliminary results from very small studies (six to ten patients) are very encouraging, especially after the combination of CT and PD-1 pathway blockade: Reported pCR rates are changing between 60% and 90% [148]. However, these drugs are very expensive and have serious adverse effects. For the future of these treatment modalities, identification of predictive biomarkers is crucial.

Endocrine Therapies

ER and *PR* negativity is higher in IBC than in other types of breast cancer [1–4, 41, 42]. Some studies have reported that up to 83% of IBC tumors are *ER* negative [149, 150]. HR negativity is associated with more aggressive clinical course, shorter survival, and poor prognosis. The median survival for HR-positive IBC is superior to that of HR-negative IBC according to SEER data (4 vs. 2 years; $p = 0.0001$) [15].

There are no studies of neoadjuvant hormonal therapy in primary IBC. Antiestrogen therapy should be applied after induction therapy and adjuvant chemotherapy are completed for all HR-positive patients [7, 10]. Antiestrogen therapy should include either tamoxifen or an aromatase inhibitor depending on the patient's menopausal status. Tamoxifen should be administered for 10 years in pre-or postmenopausal women. Aromatase inhibitors (AI) should be administered for 5 years in postmenopausal women. Ovarian suppression is recommended for HR-positive IBC cases because it is a high risk factor for recurrence [9, 36]. Five years of tamoxifen followed by 5 years of AI is another option for postmenopausal patients.

The anti-inflammatory and cholesterol-lowering effects of statins suggest they may have antitumor effects as well. The effect of statins on IBC was determined in a cohort study conducted by MDACC [151]. PFS was improved in patients who received hydrophobic statins (atorvastatin, pravastatin, rosuvastatin) (HR, 0.49; 95% CI 0.28–0.84; $p < 0.01$). No significant response was observed in patients who received lipophilic statins (fluvastatin, lovastatin, simvastatin). The mechanism of this effect is not known. Double-blind, prospective, randomized studies are needed to explain this effect.

Monitoring the Response to Treatment

The international IBC consensus panel recommends that monitoring of the response to PSC entails a combination of physical examination and imaging techniques [7]. Physical examination of the breast and regional lymph nodes for response may be conducted every 6–9 weeks [152]. The breasts are usually photographed during the examination because the response to treatment can be monitored by the reduction in erythema and edema [153]. After therapy is complete, radiological evaluation should be performed and compared with the initial examination data. If necessary, radiological evaluation can be performed in the middle of the treatment course to confirm or refute the clinical findings. Mammography and USG are recommended for radiological evaluation. MRI may be a better option to evaluate the response to therapy if it is available and affordable [5, 7]. In one trial, FDG-PET/CT was used to evaluate the response to NACT [154]. Thirty-two patients were included in the study. In patients with CR according to the PET/CT imaging, only 26% had pCR. In conclusion, more research is needed to use PET/CT to evaluate the response to therapy.

Follow-Up After Therapy

After the completion of treatment, regular history, physical examination, and mammography are recommended for follow-up by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) [155, 156]. Physical examinations should be performed at 3- to 6-month intervals for the first 3 years, every 6–12 months for years 4 and 5, and annually thereafter. Yearly mammography of the other breast is suggested by ASCO [155]. The examination of local lymph nodes with yearly USG has been suggested, although data are insufficient [7]. Genetic consultations are particularly important for patients with a family history of breast and ovarian cancer [9]. Prophylactic contralateral mastectomy should not be performed unless there are risk factors that make this obligatory. Routine performance of other radiological examinations, blood tests, and tumor markers are not suggested in asymptomatic patients. Distant metastases are common during the follow-up period of the disease. In one study, metastasis was observed in 203 of 478 stage III IBC patients at a median observation time of 29 months [157]. The most common metastasis locations were the bone (28%), lung (21%), liver (21%), and CNS (21%). CNS metastasis was most frequent in *HER2*-positive and triple-negative subtypes, as with non-IBC subtypes ($p = 0.001$). The incidence of CNS metastasis was higher in IBC cases than in non-IBC patients (10-year cumulative incidence rates of 17.4% vs. 12.7%, respectively; $p = 0.0037$), but OS rates following CNS metastasis were similar in both groups (7.6 months vs. 5.6 months, respectively) [158].

Conclusion

Multimodal therapy (PST, surgery, and radiotherapy) is the main treatment method for IBC [1–5, 7, 9, 36, 159] (Fig. 16.1). Underuse of trimodal therapy is associated with decreased survival [59]. Currently, anthracycline- and taxane-containing chemotherapy protocols as PSC are preferred (with the addition of Tr and pertuzumab in *HER2*+ patients). Following PSC, surgical assessment is suggested. A modified radical mastectomy can be performed in patients with recovered skin eruption. Next, adjuvant RT is applied. In patients with no response to PSC, additional systemic CT and/or preoperative RT is planned. Pertuzumab + Tr therapy should be started during the NACT period with taxanes and extended to 1 year for *HER2*-positive patients. Antiestrogen therapy is suggested for 5–10 years for HR-positive patients. New combined CT regimens and new targeted therapies are being investigated to increase the pCR ratio and survival times.

In recent years, an international congress devoted to IBC has been planned [160]. Last year, the Morgan Welch MDACC IBC tenth anniversary conference was held [161]. Opening specific IBC clinics similar to that established by MDACC will improve outcomes and promote well-designed research trials.

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Part III

Surgical Management of Patient with Preoperative Systemic Therapy

Surgical Treatment in Operable Breast Cancer After Neoadjuvant Systemic Therapy

17

Atilla Soran, Ebru Menekse, and Kandace P. McGuire

Introduction

Although routinely used for locally advanced and inflammatory breast cancer, neoadjuvant chemotherapy (NCT) for early-stage breast cancer (defined as stages I and II) should also be considered for appropriate patients [1–3]. As surgery for breast cancer has become less invasive, gradually progressing from Halsted's radical mastectomy in 1894 and toward modern techniques of breast-conserving surgery (BCS) and skin- and nipple-sparing mastectomy, the need to decrease tumor size prior to surgery has increased. Even in the setting of early-stage breast cancer, NCT can decrease tumor size and improve cosmetic results [4]. Randomized trials in early-stage breast cancer demonstrate that NCT can increase the use of breast conservation by decreasing tumor size [5].

Approximately 25% of patients exhibit a pathological complete response (pCR) and greater than 80% exhibit a partial response [6]. Some physicians suggest that decreasing micrometastatic disease and altering tumor kinetics in early-stage breast cancer contribute to improved overall survival [4]. Various trials indicate that neoadjuvant therapy is superior to adjuvant therapy in preventing the spread of micrometastatic disease [4]. However, NCT has not improved overall survival in any large randomized controlled trial [7].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 randomized patients with operable breast cancer to preoperative versus postoperative administration of adjuvant chemotherapy. Patients in the neoadjuvant group demonstrated a statistically significant increase in the use of BCS compared with mastectomy ($p = 0.001$). However, the difference in disease-free survival (DFS) and overall survival was not statistically significant [8, 9].

The primary benefit of NCT for early-stage breast cancer is tumor downstaging, which improves the opportunity for BCS. Furthermore, in early-stage breast cancer, patients with node-positive diseases are suitable candidates for NCT, because nodal downstaging can provide omission of completion axillary lymph node dissection as well as its prognostic value. In addition, NCT provides other advantages, including in vivo evaluation of tumor resistance or sensitivity to therapy, prognostic information based on tumor response, time for the conclusion of suitable genetic testing, and the ability to assess the efficacy of new chemotherapeutic agents in clinical trials. However, potential disadvantages of NCT exist. Tumor downstaging can be inadequate to achieve the preferred surgical therapy. Chemotherapy-resistant tumors can progress, rendering patients inoperable. Knowledge regarding initial lymph node status can be lost, and patients with favorable tumor phenotypes (luminal tumors) could be potentially overtreated [3, 4]. Also, the National Comprehensive Cancer Network (NCCN) alerts about non-suitable patient group for NCT, which is defined as the patients with non-palpable tumor or invasive tumor with uncertain boundaries containing extensive in situ component [3].

Initial Evaluation, Staging, and Diagnosis

The first step in the management of any breast cancer is the establishment of a diagnosis of cancer. Next, prognostic tumor markers (estrogen/progesterone/HER2 receptor positivity, and, when possible, Ki-67%) should be evaluated and staging of the primary tumor performed [3, 10]. A pathological diagnosis is determined by core biopsy in patients receiving neoadjuvant therapy. A post-biopsy localization clip that will be detectable post-chemotherapy should be deployed, and its location should be confirmed prior to initiation of therapy [3]. If appropriate (particularly for patients with stage IIB and greater tumors), staging for distant metastasis should be performed prior to the

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initiation of NCT. Several imaging modalities are available for staging both local and metastatic disease, including diagnostic mammography and tomosynthesis, breast and axillary ultrasound, MRI, molecular breast imaging for local disease, CT, bone scan, and PET/CT [3]. The relative benefits of these modalities are beyond the scope of this chapter.

When planning surgical management, the surgeon and the patient must decide between BCS and mastectomy. If a patient does not have contraindications to BCS (multicentric disease, prior history of radiation or other contraindications to radiation, BRCA mutation, or simply a desire to undergo mastectomy) but has a tumor-to-breast size ratio that is unfavorable for BCS, NCT can be offered [3, 11].

Once the decision for NCT is made, both the medical oncologist and breast surgeon should develop a care plan, including pre-NCT tumor assessment, frequency of tumor response assessment, and final clinical, staging plans. Patients should be prepared that a change in NCT course can be made based on response to therapy. As mentioned previously, initial tumor staging can be performed using a variety of imaging modalities. Consistent imaging modalities are important to accurately assess the response to therapy. Many authors recommend MRI in initial and post-therapy evaluation given its increased sensitivity compared with traditional imaging [12–14]. However, the use of MRI is also associated with increased mastectomy rates. Ongoing tumor assessment during therapy should be routinely performed via physical clinical exam. Mammogram, ultrasound and/or MRI can be performed if progression is a concern [3].

Evaluation of Response to Neoadjuvant Therapy

The evaluation of response to NCT includes clinical and pathological assessments. The clinical response should be determined with physical exam and imaging. Physical exam alone is inaccurate. Mammogram, ultrasound, and MRI are used as adjuncts to increase accuracy. Some clinicians hypothesize that MRI is advantageous for evaluating response to NCT given its ability to detect angiogenic changes, which can be observed before the tumor size is reduced [14, 15]. Multiple studies have reported that MRI is a good predictor of response in all tumor types, particularly triple-negative and HER2+ patients, for which its ability to predict pCR was statistically superior compared to luminal tumors ($p < 0.005$) [16, 17]. Nowadays, the use of PET/CT monitoring has come into question for evaluation of primary tumor response to NCT. MRI is significantly a better predictor than PET/CT for human epidermal growth factor receptor 2 (HER2)-positive patients. However, PET/CT monitoring has comparable results with MRI in patients with triple-negative tumors, so it might be an option in unsuitable patients for MRI [18].

A clinical complete response is defined as complete resolution of all detectable palpation and imaging disease findings. Clinical partial response is defined as a greater than 50% decrease in tumor size. Clinical progressive disease is defined as a greater than 50% increase in tumor mass [8]. Pathological response is determined via surgical pathology. Responses can be measured using a variety of methods, including the Response Evaluation Criteria in Solid Tumors (RECIST). pCR is defined by different organizations in various manners. The strictest definition is that of the German Breast Group and requires the complete absence of invasive or noninvasive disease in breast or axillary lymph nodes. The Austrian Breast and Colorectal Cancer Study Group, Neo-Breast International Group, and MD Anderson define complete response as the lack of invasive tumor in the breast or lymph nodes, whereas residual in situ disease is allowed. The NSABP defines pCR as no residual invasive disease in the breast; however, this criterion allows in situ disease and does not measure residual nodal disease. Using the Sataloff index, various groups actually allow for the persistence of focal invasive tumors [19].

A discrepancy often exists between clinical and pathological tumor responses. Tumor responses to NCT were categorized as a clinical complete response in 36% of patients. However, pCR was observed only in 26% of these patients [9]. This discordance between pathological and radiological responses is attributed to the fact that breast tumors responses exhibit two response patterns to NCT: concentric decrease and patchy regression [4]. These multiple microscopic residual areas cannot be observed via imaging assessments. This discrepancy is also due to intraductal tumors that do not respond to chemotherapy [6].

The NSABP trials B-18 and B-27 established the efficacy of NCT and also evaluated response to therapy as a prognostic indicator [8]. B-18 trial compared pre- and postoperative treatment with doxorubicin and cyclophosphamide in patients with T1-3, N0-1 operable breast cancer. The trial indicated that the degree of response (complete, partial, or none) was strongly related to overall survival, DFS, and recurrence-free survival ($p = 0.0008$, 0.005, and 0.002, respectively). The risk of death decreased by 50% in patients with pCR. However, the death rate increased by 28% in patients with a partial response and 45% in non-responders [20]. Primary tumor response and axillary lymph node response to NCT are separate prognostic factors [4]. In the study, the incidence of pathologically negative axillary lymph nodes was increased in the preoperative group compared with the postoperative group (48% and 42%, respectively; $p < 0.0001$) [6]. However, as a prognostic factor, primary tumor response is more valuable than pathological lymph node status [20].

NSABP B-27 compared three different neoadjuvant/adjuvant regimens: doxorubicin and cyclo-phosphamide followed by surgery, doxorubicin and cyclophosphamide followed by surgery and then paclitaxel and doxorubicin, and cyclophos-

phamide and paclitaxel followed by surgery [6, 8]. The clinical response in the preoperative doxorubicin, cyclophosphamide, and paclitaxel group was increased compared with the other two groups (91% and 86%, respectively; $p < 0.001$). The clinical complete response and pCR rates for the group receiving preoperative taxane were 40% and 26%, respectively, superior to the other groups ($p < 0.001$). pCR was a significant predictor of DFS and overall survival ($p < 0.001$). Post-neoadjuvant nodal status was also a highly significant predictor of DFS and overall survival ($p < 0.001$) [8].

An early response of the primary tumor after two or three cycles of chemotherapy is a predictor of pCR [4]. Factors including age <40, tumor size <2 cm, ductal pathology, high nuclear grade, high rate of cellular proliferation (association with Ki-67), estrogen receptor-negative status, triple-negative status, and HER2-positive status are directly proportional with increased frequency of pCR. On the other hand, patients who have low proliferative subgroups or luminal A subtype are not very suitable candidates for NCT [7, 21]. Similar to the NSABP trials, a number of contemporary studies have demonstrated that pCR after NCT is strongly associated with prolonged DFS and overall survival [22, 23]. Unfortunately, pCR is obtained in only 19.2% of breast cancer patients following NCT. Failure to achieve pCR can lead to delays in surgery and/or hormonal therapy and is potentially detrimental in terms of overall outcome [21].

Higher BCS rates can be acheived by neoadjuvant hormonal therapy (NHT) in postmenopausal women with ER+ breast cancer in clinical stages II or III. The aim of using the Preoperative Endocrine Prognostic Index (PEPI) is to assess response to endocrine therapy and to avoid adjuvant chemotherapy in appropriate pateints by determine the relapse risk of patients after NHT. The lowest risk PEPI group which is called PEPI = 0 criteria is lymph node negative, pathological stage I or IIA, the Ki values ≤2.7 and continued of ER positivity in the pathological tissue after NHT. Furthermore, this approach can identify more resistant tumors during NHT and allow for changing systemic treatment regimens, because the Ki 67 expression after short-term NHT has prognostic value for the predicted PEPI score. Therefore, early repeat core biopsy, after 2–4 weeks from the beginning of NHT is recommended for determining whether the Ki 67 value is over threshold %10 in tissue samples of breast cancer patients with ER+, HER 2− [24].

Surgical Management

Surgical Management of the Breast After Neoadjuvant Chemotherapy

Once the response to NCT has been assessed, a surgical plan can be made by the surgeon and the patient. Generally, surgery is performed approximately 4 weeks after NCT due to the myelosuppressive toxicity of chemotherapeutic agents [25]. Preoperatively, systemic therapy for the purpose of downstaging the tumor to facilitate BCS is recommended for patients with >20 mm tumor [3].

Factors such as tumor size and location as well as breast size can affect the BCS decision. Several algorithms are available to aid decision-making. Some algorithms include the option to continue with additional NCT if the response is inadequate, and second-line therapy may prove effective [3] (Fig. 17.1).

According to NSABP B-18, 68% of patients in the NCT group underwent BCS compared with 60% of patients in the

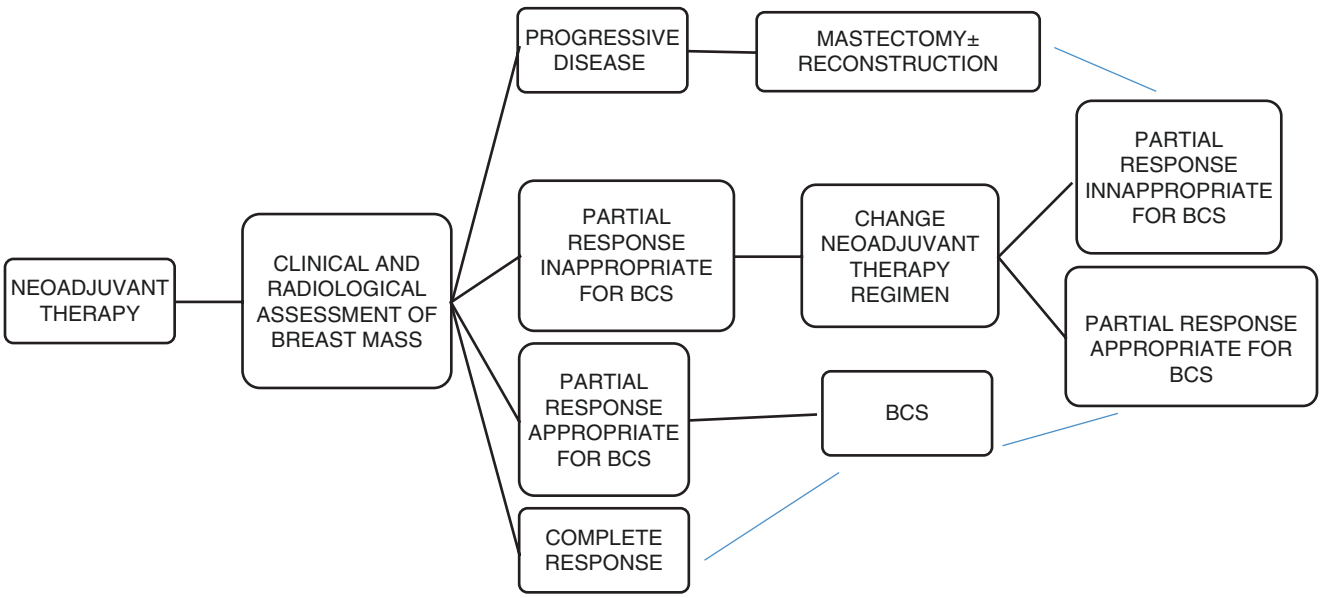


Fig. 17.1 Algorithm for the management of the primary tumor after neoadjuvant therapy. (BCS: Breast Conserving Surgery)

adjuvant chemotherapy group (p = 0.0001) [8]. However, despite modern chemotherapy regimens and targeted therapies that increase the pCR rate, BCS rates after NCT remain stable since NSABP B-18. Long-term outcomes for NCT in early-stage breast cancer were presented by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses. In this cohort, BCS rates were higher in patients who received NCT than adjuvant chemotherapy (65% and 49%, respectively). Age, ER status, and tumor grade were not associated with BCS rates, but patients with poorly differentiated ER− tumors had a higher frequency of BCS. On the other hand, tumor size equal or greater than 20 mm, planned BCS, and chemotherapy regimens with anthracycline and taxane combination significantly increased the rates of BCS [5].

The omission of surgery through imaging with or without vacuum assisted core biopsy in order to predict pCR patients with excellent clinical response to NCT is being discussed in the currently ongoing studies. It is important to note, however, that while these studies are ongoing, removal of the preoperative marked tumor or tumor bed is essential for the present [26]. Due to the limitations of modern imaging, a discrepancy remains between imaging complete response and pCR. Thus, regardless of clinical response, the biopsy clip should be targeted for surgical removal after NCT. If post-treatment imaging suggests residual disease, the surgeon should attempt to remove the area of residual tumor with clear margins as suggested radiographically [16, 25, 27]. However, removal of the entire tumor bed as it existed prior to neoadjuvant treatment is not necessary. It is important to note that the tumor may respond to neoadjuvant treatment as scattered microscopic islands. In this case, negative margins may be difficult to achieve despite response to chemotherapy. Many of these patients will require re-excision or completion mastectomy [21, 25].

In the GEPARDUO trial, a more recent prospective, multicenter study, BCS rates after NCT for operable breast cancer were measured. After neoadjuvant therapy, BCS was attempted in approximately 82% of patients. Re-excision was performed in 12.4% patients. Completion mastectomy was performed in 8.7% of patients. According to the GEPARDUO trial, tumor size ≤40 mm pre-chemotherapy, tumor size ≤20 mm post-chemotherapy, treatment with doxorubicin/cyclophosphamide/taxane vs. doxorubicin/taxane, clinical response, and treatment at a high-volume (>10 enrolled patients) center were correlated with successful BCS after NCT. In addition, non-lobular histopathology and intraoperative evaluation of margins with frozen section analysis decreased the re-excision rate (p = 0.015) [28].

According to results of the NABON Breast Cancer Audit dataset from the Netherlands, the percentage of patients with involved margins, defined as residual invasive tumor in the resection surface over more than 4 mm, was lower for cT3 breast cancer in BCS patients who received NCT than those who did not (28.3%, 31%, respectively). But there was no difference in the invasive margin rates for both groups in patients with cT2 tumor. Also, invasive lobular cancer and hormone receptor positivity were associated with the presence of positive margins regardless of NCT. However, only invasive lobular cancer was associated with mastectomy in patients who planned to undergo BCS before NCT and also had positive margins in their re-excision specimens [29].

When response to NCT is inadequate, no second-line therapy is recommended, and mastectomy is necessary. By contrast, a patient initially motivated for BCS may opt for mastectomy during treatment. If this is the case and the patient desires reconstruction, decisions must be made regarding the potential for postmastectomy radiotherapy and the ability to perform immediate reconstruction. Traditional guidelines for postmastectomy radiotherapy include treatment of positive margins, a tumor that is >5 cm at the time of resection, or lymph node positivity before or after chemotherapy. However, recent trials suggest that a patient who is clinically node positive prior to chemotherapy but is rendered N0 with NCT does not significantly benefit from postmastectomy radiation [30, 31]. Patients with a low likelihood of radiation should be referred for immediate reconstruction barring other contraindications to reconstruction. Patients who absolutely require radiation should be reconstructed in a delayed fashion or in an immediate fashion with caution. In patients for whom the decision for postmastectomy radiotherapy is uncertain, the "delayed-immediate" form of reconstruction can be employed [32, 33]. It is important to note, according to the study, that both delayed and immediate reconstruction with nipple-areola complex sparing mastectomy can be achieved in suitable patients after NCT with safe LRR ratios when compared with total mastectomy after NCT [34].

Surgical Management of the Axilla After Neoadjuvant Chemotherapy

The evolutionary process for management of axilla is ongoing in patients undergoing NCT. Therefore, a standard axillary approach is not clear for these patient groups. The expectation of reduction in surgical morbidity was accompanied by new axillary approaches instead of standard axillary lymph node dissection following NCT [35, 36].

Based on current approaches, there are two main challenges for axillary management in patients who undergo planned NCT. The first is the timing of sentinel lymph node biopsy (SLNB) in patients with clinically node-negative axilla prior to NCT. The second is choosing the method of axillary lymph node sampling after NCT for patients who are node-positive prior to NCT.

SLNB is widely accepted in the setting of primary surgery for breast cancer. Landmark trials, such as NSABP

B-32 and ACOSOG Z0010, have demonstrated sentinel node detection rates of 95–99% and a false-negative rate (FNR) of 9.8% [37, 38].

However, the management of the axilla and the timing of SLNB in relation to NCT are controversial. Varying reports have described SLNB in the clinically node-negative patient both before and/or after NCT, and each option possesses inherent advantages and disadvantages [25, 39–41] (Table 17.1).

Proponents of pre-NCT SLNB note that valuable staging information is lost if nodal staging is performed after chemotherapy and that SLNB has a higher detection rate and lower FNR if performed prior to NCT. In addition, for borderline candidates, axillary status may aid the decision for preoperative systemic therapy. Concerns also exist regarding whether chemotherapy may cause scarring that could affect lymphatic drainage, thus making SN identification more difficult and/or less accurate. Single institution studies typically describe identification rates of approximately 96% for pre-NCT SLNB and 90% after NCT. FNRs are approximately 7% pre-NCT and 12% after NCT [42]. Large multicenter trials, such as NSABP B-18 and B-27, have demonstrated slightly reduced FNRs of 11% [43]. Pecha et al. have also demonstrated that the success of finding SLNs increased in breast cancer patients administered with NCT and <50 years of age, clinically lymph node negative at the time of diagnosis, harbored ER (+) primary tumors, exhibited a Ki 67 proliferation index of ≤15%, and without lymphatic and/or vascular space invasion. The absence of lymphovascular space invasion was also predictive of a lower FNR in this study [44]. A multicentric prospective GANEA French group study typically describes post-NCT SLN identification rate and FNR as, respectively, 94.6% and 9.4% for operable patients with initially cN0 patients [45]. GANEA 2, a large multicenter trial, demonstrated 7 locoregional and 1 axillary recurrence at 36-month follow up in 419 patients who had clinically negative axillary nodes at the time of diagnosis and were treated with SLN alone [46]. Despite these arguments, outcomes for patients undergoing SLN either before or after NCT do not vary significantly.

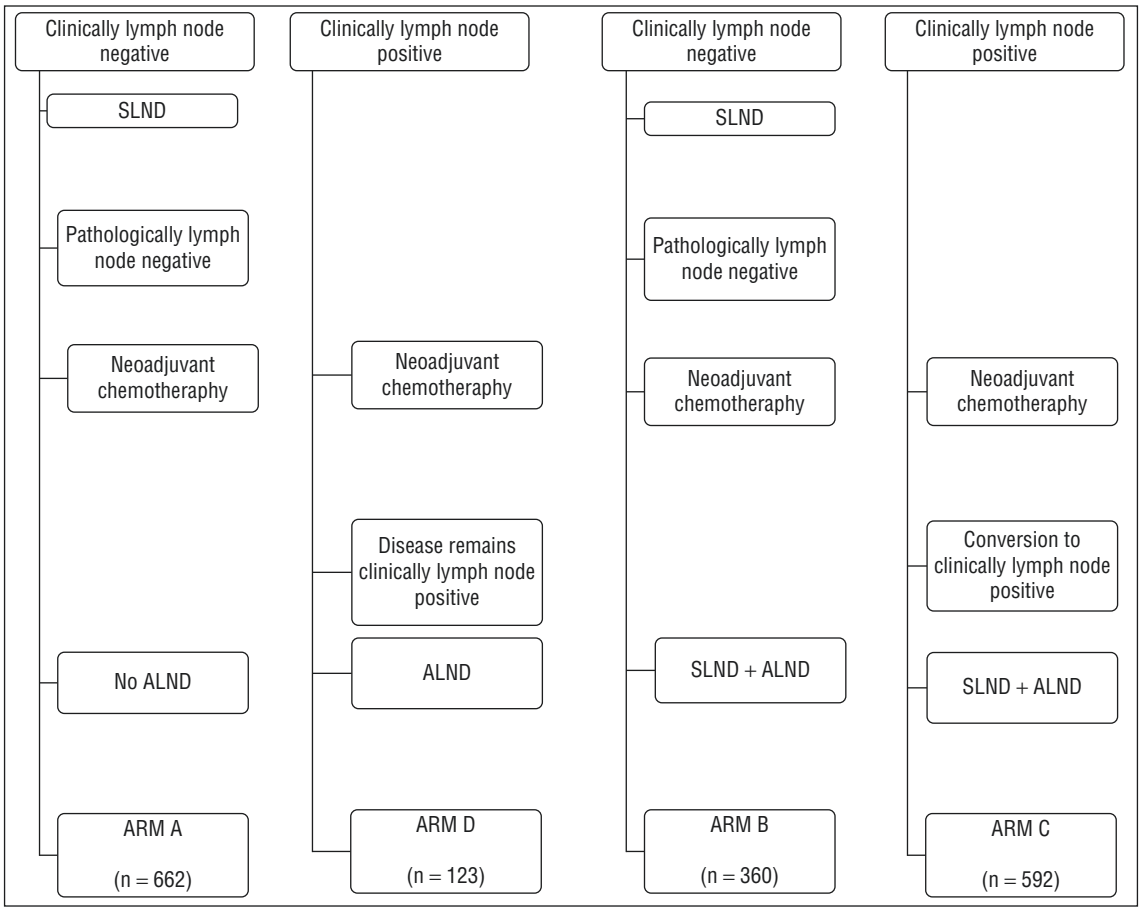
Table 17.1 Comparison of SLND before and after neoadjuvant treatment

SLND before neoadjuvant treatment		SLND after neoadjuvant treatment	
Advantage	Disadvantage	Advantage	Disadvantage
Higher detection rate	Increased ALND rate and increased morbidity	Lower ALND rate and reduced morbidity	Lower detection rate
Lower FNR	Lack of information regarding response	Proven to predict differences in DFS/OS	Higher FNR
Guides decision regarding type of NCT	Makes subsequent SLNB attempts less successful	Decreases the time between diagnosis and systemic therapy	Questionable alteration of lymphatic drainage
	Increases # of surgical procedures	Decreases # of surgical procedures	

SLNB Sentinel lymph node biopsy, *ALND* Axillary lymph node dissection, *FNR* False-negative rate, *DFS* Disease-free survival, *OS* Overall survival, *NCT* Neoadjuvant chemotherapy

There is also a strong argument on performing SLNB after NCT for node-positive patients before NCT. pCR can be achieved 40–70% within cN+ patients at first evaluation by NCT. This efficacy enables a single surgery and decreases the morbidity of patients undergoing axillary dissection for what has been rendered a negative axilla. Additionally, post-NCT axillary assessment provides the care team with important prognostic information. In NSABP B-18 and B-27 protocols, patients who presented with clinically node-positive diseases and were node negative by SLNB after chemotherapy exhibited improved DFS and overall survival. In these patients, staging options for axilla include either axillary lymph node dissection (ALND) or SLNB, but the trend of axilla protective approach is increasing for suitable patients [8, 47].

Two recent prospective trials have examined the issue of SLNB either before or after NCT, particularly in patients who were clinically node positive at presentation. The SENTINA (SENTinel Neo Adjuvant) trial primarily aimed to investigate the accuracy of SLNB by defining its FNR in patients converted to clinically N0 from N+ before NCT. As a secondary aim, this study investigated detection rates of SLNB before and after NAC in patients with N+ clinically before NCT. This study included 1737 patients undergoing NCT into 2 groups based on the clinical nodal status at presentation. The clinically node-negative patients underwent SLNB prior to NCT. If these patients were confirmed as SLN−, no further axillary staging was performed. If the patients were SLN+, they underwent SLNB followed by ALND post-NCT. Clinically node-positive patients were randomized to SLNB followed by ALND after NCT or ALND only after NCT (Fig. 17.2). Patients who underwent SLNB before NCT exhibited an overall detection rate of 99.1% (Arm A and B) compared with 80.1% after NCT (Arm C). Those undergoing repeat SLNB after NCT exhibited the lowest detection rate (60.8%) (Arm B). The detection rate was significantly higher in a patient (Arm B and Arm C) who used combined mapping (blue dye and radiotracer) than radiotracer alone (76.2% vs. 52.9% in Arm B, 87.8% vs 77.4% in Arm C, respectively) as the detection technique. FNR values in Arm B were greater than 50%. SLNB after NCT in patients who were clinically node positive at presentation was associated with an FNR of 14.2% (Arm C). The FNR was lower in Arm C using combined mapping than radiotracer alone (8.6% vs. 16%, respec-



SLND: Sentinel lymph node dissection

ALND: axillary lymph node dissection

Fig. 17.2 Modified SENTINA trial schema. (SLND: Sentinel lymph node dissection. ALND: axillary lymph node dissection)

tively). Furthermore, the increased of number of SLNs removed significantly decreased FNRs in Arm C on multivariate analysis. FNRs, who (Arm C) had one, two, or three SLNs removed was 24.3%, 18.5% and 7.3%, respectively. The FNR was <10% in the subset of patients who had three or more SLNs removed [48].

The second recent trial, ACOSOG Z1071, identified 603 patients who were clinically staged as N+ at presentation either by a clinical exam or axillary ultrasound/biopsy. Residual nodal disease after ALND post-NCT was detected in 310 of 525 patients who had two or more SLNs removed. residual nodal disease after ALND post-NCT was detected. In 39 patients SLN was negative despite axillary lymph node involvement. The overall FNR was 12.6%. However, FNR was 10.8% when a dual tracer was used. Furthermore, the FNR was 9.1% in patients who had three or more SLNs removed, whereas the FNR was 21.1% for two SLNs [41].

Targeted axillary dissection (TAD) involves removal of pathological confirmed lymph nodes which were marked before NCT in addition to SLN following NCT. A recent prospective series of 208 patients reported false negative rates of SLN when the originally positive node prior to NCT was clipped. Clipped lymph nodes were removed after NCT with or without the SLNs, and a complementary ALND was performed. In this series, FNRs for SLN alone, tagged lymph nodes—irrespective of SLN—and tagged lymph nodes with SLNs were 10.1%, 4.2%, and 1.4%, respectively [49].

These studies have taken their places in practice patterns for suitable cases (Fig. 17.3) [3].

The use of IHC for evaluation of SLN is another auxiliary method to reduce FNR in evaluation of axillary lymph node involvement with SLNB. In the prospective multicentric SN-FNAC study, which included patients who were pathologically lymph node positive before NCT, immunohisto-

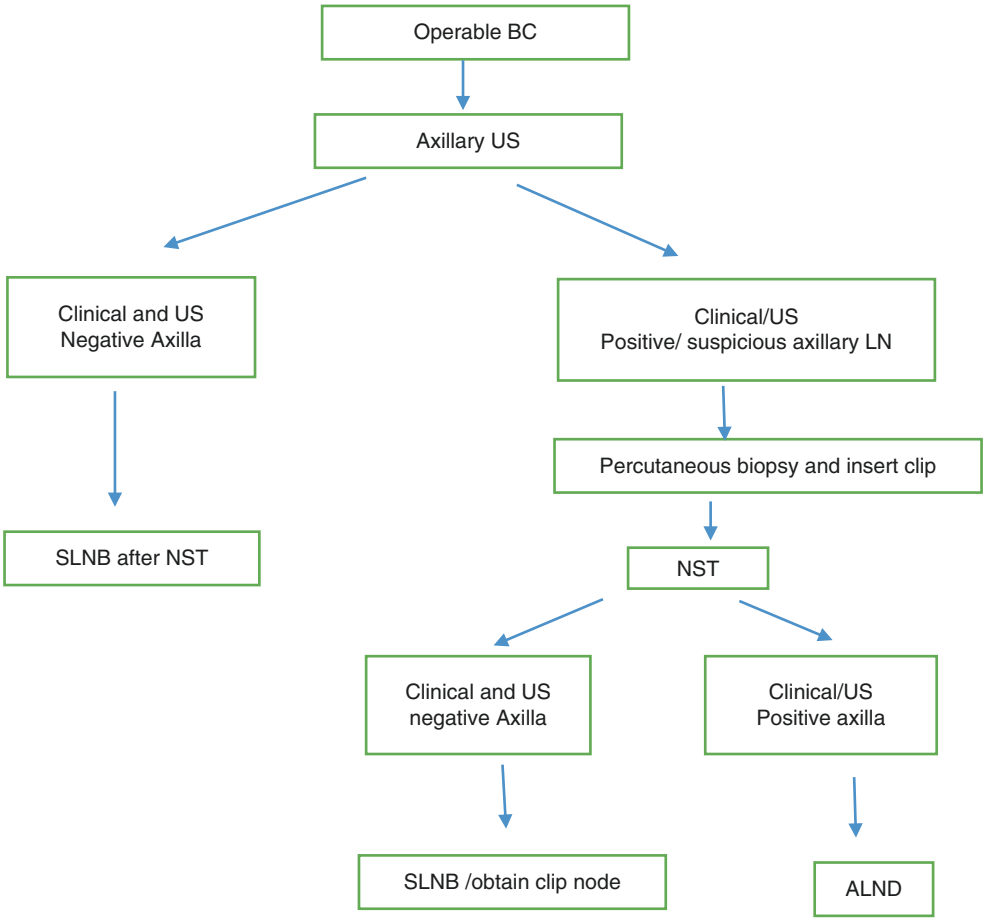


Fig. 17.3 Algorithm for the management of axilla after neoadjuvant therapy

chemistry (IHC) was mandatory for evaluation of SLNs, and isolated tumor cells (≤ 0.2 mm) were considered positive. FNRs were 8.4% in this condition. If the hematoxylin and eosin (HE) stain was used and negative results were accepted as no lymph node involvement, FNR was 13.3% [50].

The prediction of nodal negativity after NCT with noninvasive methods could be important for predicting nonsentinel lymph node involvement, resulting in avoidance of axillary surgery or in guiding reconstruction decisions after mastectomy for patients who may require adjuvant radiotherapy depending on whether axillary involvement exists.

The SENTINA study group analyzed data from 715 patients within Arm C and Arm D regarding the predictive value of axillary ultrasound and palpation in predicting cN status after NCT. Their results represent that the accuracy of palpation, ultrasound, and combined evaluation in predicting cN0 status are under the negative effect of NCT [51]. As a result, imaging techniques reduce the FNR of SNB following NCT, but various prospective and retrospective studies demonstrate that noninvasive imaging methods are not suitable for restaging the axillary lymph node status post-NCT [51–54].

The nomogram developed using the SENTINA C Arm includes parameters such as estrogen receptor status, multifocality, lymphovascular invasion, and sonographic tumor diameter with AUC 0.81. Estrogen receptor positivity, multifocality, lymphovascular invasion, and increased tumor size were determined to be independent risk factors for maintaining positive axillary status [55].

The previously mentioned study, GENEA 2, demonstrated that residual breast tumor diameter ≥5 mm and lymphovascular invasion (LVI) were independent risk factors for axillary lymph node positivity regardless of the number of SLNs removed [46].

Although the pursuits for prediction of axillary involvement with noninvasive methods as clinical, molecular, or imaging procedures have continued, the standard method is still SLNB.

Adjuvant therapy in patients who present with clinically positive axilla is another fertile area of debate and study. Two current trials are examining the role of radiotherapy in the management of these patients. NSABP B-51 randomizes patients with positive axilla at presentation (cT1-3, N1), who converted to node negative on SLNB, to axillary radiation versus no axillary radiation. Alliance A011202 randomizes patients with persistently positive axillary nodes to axillary dissection plus comprehensive breast/chest wall/regional

nodal irradiation or axillary radiation plus comprehensive breast/chest wall/regional nodal irradiation. The primary end point for both studies is recurrence-free survival [56, 57].

As a result, firstly, there is also a strong support for performing SLNB after NCT. This efficacy enables a single surgery and decreases the morbidity of patients undergoing axillary dissection for what has been rendered a negative axilla. Secondly, instead of ALND, SLND for the evaluation of axillary lymph node involvement in patients with cN0 after NCT, initially cN+, seems to be safe under certain conditions. In these patients, FNR should be attempted to be minimized by removing at least three SLNs, using the dual localization method, showing lymph node negativity with US and TAD, and maybe using IHC to evaluate in negative SLNs in HE staining.

Surgical Management After Neoadjuvant Hormonal Therapy

NHT can be considered to decrease tumor size to facilitate BCS in postmenopausal women with hormone receptor-positive breast cancer. Studies comparing NHT and NCT in patients with HR-positive disease indicate that NHT is as effective as NCT in downstaging tumors and promoting BCS in postmenopausal women [58–60]. In studies comparing NHT regimens, aromatase inhibitors are superior to tamoxifen in regard to tumor response and BCS [61]. ACOSOG Z1031 revealed that in patients with a tumor-to-breast size ratio considered marginal for breast conservation, exemestane, letrozole, and anastrozole made BCS possible in 45.2%, 40.0%, and 48.7% of patients, respectively, with an overall BCS rate of 83.1% for the study. Moreover, this study revealed that for patients who were candidates for mastectomy only, BCS could be performed following NHT with exemestane, letrozole, and anastrozole in 21.7%, 20.0%, and 27.4% of patients, respectively. However, clinical response and BCS rates did not significantly differ for exemestane, anastrozole, and letrozole [62].

Another candidate group for NCT is patients with HER2+ breast cancer. Traditionally, trastuzumab at least for 9 weeks is combined with chemotherapy. NCCN represents that dual anti-HER2 regimen which is combined trastuzumab plus pertuzumab with chemotherapy can be used in early-stage breast cancer patients with ≥T2 or ≥N1 tumor and HER2+ (3). Dual anti-HER2 treatment has higher pCR ratios (57–66%) than single agent anti-HER2 treatment when either are combined with cytotoxic chemotherapy [63, 64].

Locoregional Recurrence

NSABP B-18 and NSABP B-27 described locoregional recurrence rates (LRRs) in early-stage breast cancer patients who underwent NCT (14.3% and 12.2%, respectively, at 10 years). Patients undergoing NCT exhibited higher overall recurrence rates compared with those who underwent adjuvant therapy. Mamounas et al. reported LRR of 12.3% (8.9% local; 3.4% regional) for patients who underwent mastectomy and 10.3% for patients (8.1% local; 2.2% regional) treated with BCS followed by radiotherapy after NCT at a median follow-up of 10 years. Table 17.2 presents independent predictors for LRRs based on NSABP B-18 and NSABP B-27. LRRs were higher in patients who did not achieve pCR in both the breast and axilla. This effect was particularly pronounced in young patients [65]. Similarly, results for LRR were shown in Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses. The data of 4756 women with early-stage breast cancer in 10 trials were investigated to compare LRRs in patients who received NCT or adjuvant chemotherapy. LRRs at 15 years during follow-up were 21.4% for the NCT group versus 15.9% for the adjuvant chemotherapy group ($p = 0.0001$). Patients undergoing NCT exhibited higher overall recurrence rates compared with those who underwent adjuvant therapy [5].

Von Minckwitz et al. evaluated tumor response at surgery and its association with long-term outcomes in 6377 patients with primary breast cancer receiving NCT in seven randomized trials. DFS was significantly superior in patients with no invasive and no in situ residuals in the breast or nodes [19]. In the NSABP B-18 and NSABP B-27 trials, patients who received systemic therapy before and after surgery were compared. No differences between groups were noted for cancer-related death, disease progression, or distant recurrence [66]. A significant relationship between treatment age and overall survival ($p = 0.01$) was observed. In patients younger than 50 years, overall survival and DFS rates were 55% and 38%, respectively, in the adjuvant chemotherapy group compared with 61% and 44%, respectively, in the neoadjuvant group ($p = 0.06$ and 0.09, respectively) [8].

According to the studies noted above, LRR differs significantly based on intrinsic tumor subtype (luminal, HER2, and

Table 17.2 Independent predictors of locoregional recurrence rate according to type of surgery in patients receiving neoadjuvant chemotherapy

Patients undergoing mastectomy	Patients undergoing breast-conserving surgery
Clinical tumor size >5 cm	Age <50 years
Clinically lymph node + disease	Clinically lymph node + disease
Pathologically lymph node + disease	Pathologically lymph node + disease
	M.D. Anderson Prognostic Index
	1. Clinically N2,3 lymph node
	2. pT >2 cm
	3. Multifocal tumor pattern
	4. Lymphovascular invasion

triple negative). In the seven German Breast Group trials, pCR was associated with improved DFS in luminal B/HER2− ($p = 0.005$), HER2+ ($p < 0.001$), and triple-negative ($p < 0.001$) tumors but not in luminal A ($p = 0.39$) or luminal B/HER2+ ($p = 0.45$) tumors. pCR in HER2-positive (non-luminal) and triple-negative tumors was associated with excellent prognosis [19]. On the other hand, the hormone receptor-positive subtypes have lower LRR rates independent of pCR, but LRRs in patients with Her 2+ and triple-negative subtypes were associated with pCR [66, 67].

MD Anderson has developed a prognostic index that stratifies risk of LRR in patients who undergo BCS following NCT. This index includes four predictors of an increased risk of LRR: clinical N2-3 disease, residual pathological tumor size >2 cm, multifocal pattern of residual disease, and lymphovascular space (Table 17.2) [68].

A study by Valachies et al. supports a predictive scoring system for local recurrence, defined as only ipsilateral breast and LRR, in patients who received NCT with any stage breast cancer. According to this study, the factors associated with increased local recurrence risk were ER negativity, clinical N1 disease, failure to achieve pCR in axilla, and pN2-3 disease. In addition, cT3-4 breast cancer and failure to acheive pCR in the breast were associated with an increased risk of LRR [69].

In order to reduce LRR in patients who undergo planned BCS after NCT, proper management includes tumor localization, pathological assessment, and radiotherapy [5].

Postoperative Complications

One of the concerns regarding NCT is the rate of surgical complications after therapy. However, these concerns are not supported by the literature. Numerous studies have reported postoperative complication rates in this situation, and the rates are statistically equivalent. Broadwater et al. compared patients undergoing mastectomy after NCT and patients undergoing mastectomy followed by adjuvant chemotherapy. No differences were noted between the two groups regarding wound infection and wound necrosis rates. Interestingly, seroma formation was significantly decreased in the preoperative chemotherapy group compared with the postoperative chemotherapy group ($p = 0.04$) [70]. A more recent study by Unalp and Onal found no correlation between seroma formation and the use of NCT [71].

Several studies have described outcomes in mastectomy and immediate reconstruction after NCT. Recent studies have evaluated outcomes after both autologous tissue reconstruction and tissue expander/implant-based reconstruction following NCT. Both studies reported no difference in overall complication rates in patients who received preoperative chemotherapy [72, 73]. The only statistically significant difference observed was the rate of skin necrosis in patients receiving tissue expander or implant-based reconstruction. However, this difference did not result in an increased rate of implant loss [73].

Certainly, one of the greatest concerns after surgery of the breast and axilla is lymphedema. A commonly stated reason for NCT is the opportunity to downstage the axilla and reduce the extent of axillary surgery. The major advantage of SLNB compared with ALND is reduced lymphedema rates. NSABP B-32 reported lymphedema rates of 12.5% in patients after ALND, whereas the rate was 0% in patients who had SLNB only. Z0010 and Z0011 reported lymphedema in 7% of patients at 6 months [74]. SLNB may be particularly important in this population as recent data suggests that patients who receive ALND after NCT exhibit significantly higher rates of lymphedema at 5 years compared with those receiving adjuvant therapy (41.6% vs. 21.7%, respectively) ($p < 0.001$) [75]. Studies such as NSABP B-51 and A011202 will provide an opportunity to study the long-term rates of lymphedema after SLNB in the setting of NCT as the data mature.

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Surgical Management of Locally Advanced Breast Cancer

18

Abdullah Igci and Enver Özkurt

Introduction

Patients with locally advanced breast cancer (LABC) have been historically considered inoperable cases. However, in light of recent research and studies, even metastatic breast cancers have been downstaged to operable cases using new treatment modalities. The incidence of LABC is less than 5% [1–3]. Annually, 300,000–450,000 new cases of LABC are diagnosed worldwide.

According to the American Joint Committee on Cancer (AJCC) staging system, LABC is classified as follows: T3, large tumors; T4, tumors with skin or chest wall involvement; N2, nodal disease with fixed or matted axillary lymph nodes; and N3, nodal disease with involvement of the ipsilateral subclavicular and supraclavicular lymph nodes [4]. However, tumors that do not clinically match the criteria for LABC according to the AJCC staging system, such as tumors 3–5 cm in size located in a low-volume breast, behave similarly to LABC; thus, these tumors are optimally treated with combined modality approaches.

The administration of preoperative systemic therapy (PST) as the first modality of treatment is favored by most expert groups for the management of stage III and most large stage II breast cancers [5–11]. This treatment may result in downstaging for approximately 70–95% of patients [5, 10–13]. Several studies have compared preoperative systemic therapy with postoperative (adjuvant) systemic therapy and demonstrated that these new treatment modalities prolong disease-free and overall survival [14–16].

Patients treated with PST were significantly more likely to undergo breast-conserving surgery (BCS) without significant increase in local recurrence (LR) compared with patients treated with surgery first [14–16]. In addition, PST enabled downstaging of the axillary lymph nodes in up to 40% of patients [14, 15, 17, 18]. Downstaging the axilla can reduce morbidity due to decreased rates of axillary dissection. Several randomized and non-randomized studies have demonstrated a significant achievement of pathologic complete response (pCR) in the breast and axillary nodes and improved outcome. According to these studies, clinical and pathological response to PST can be used as an intermediate marker of chemotherapy efficacy, thus enabling a decision as to which chemotherapy regimen should be used following surgery. Furthermore, the efficacy of chemotherapy is slightly enhanced prior to surgery based on robust vascular and lymphatic drainage of the breast and the tumor itself. Based on the findings above, multidisciplinary collective and coordinated work between surgical and oncological teams as well as other clinicians is crucial when evaluating patients with LABC.

Evaluation of Primary Tumor Between Diagnosis and Surgery in Patients Who Will Receive Preoperative Systemic Therapy

Patients who are candidates for PST should be assessed before, during, and after chemotherapy. One of the most important benefits of PST is the potential for converting patients who require mastectomy to patients who can undergo BCS. Therefore, assessment of patients before, during, and after chemotherapy clinically via physical examination and radiologically is crucial before deciding on a surgical strategy.

Chagpar et al. reported that physical examination appears to be at least as accurate as mammography or ultrasound in estimating residual tumor size [19]. However, the false-negative rate (FNR) is approximately 60%; thus, many small tumors may be missed with this approach.

Before starting the treatment, a pathologic assessment of the tumor is needed via fine-needle aspiration (FNA) or core biopsy (CB). Additionally, defining prognostic and predictive factors, such as estrogen/progesterone receptors (ER/

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PR) and human epidermal growth factor receptor 2 (HER2), before chemotherapy is particularly important in cases of pCR in the breast and axillary nodes. In addition, in patients who plan to undergo BCS, the tumor bed should be marked during CB. Thus, if pCR is determined at the end of PST, the surgeon can resect exact tumor location.

Although the rate of a false-positive FNA is very low in patients with newly diagnosed breast cancer [20], this technique cannot readily differentiate invasive from noninvasive carcinoma. By contrast, CB results in minimal tumor perturbation while providing important diagnostic information, including the identification of tumors that are predominantly or completely in situ [21]. Furthermore, CB can provide sufficient material to evaluate prognostic and predictive tumor biomarkers, such as ER/PR, HER2, Ki-67, etc. [22, 23].

Clinical and Radiological Assessment

Mammography

When estimating the extent of the primary tumor and to eliminate the presence of diffuse malignant microcalcifications potentially indicative of an extensive intraductal component, careful physical examination and a pre-chemotherapy mammogram are important [24]. The extent of the mass and the presence of microcalcifications in the breasts must be determined before and after PST, particularly in patients who are candidates for BCS (Fig. 18.1).

Ultrasound and Elastography (Sonoelastography)

Although primary tumor assessments are potentially laborious in patients with dense breasts, ultrasound can be useful to determine the extent of the tumor and monitor the tumor during PST [25] (Fig. 18.2). Ultrasound elastography (sonoelastography or elastography) is a novel ultrasound method that provides a representation of tissues and organs and evaluation of their elasticity and stiffness. In this procedure, slight repeated pressure is placed on the examined organ with the ultrasound transducer. Elasticity and deformations are processed and presented in real time as color-coded maps called elastograms. Masses are typically coded from blue to red (blue for rigid masses and red for soft masses) (Fig. 18.3). This method is based on the fact that pathological changes in tissues generally also affect their stiffness [26–29].

Ianculescu et al. reported Virtual Touch IQ (VITQ) shear wave elastography results for 110 breast lesions [30]. Of these lesions, 48 were benign, and 62 were malignant. Breast imaging-reporting and data system (BIRADS)-based B-mode evaluation of the 48 benign and 62 malignant lesions achieved 92% sensitivity and 62.5% specificity. Elastography was performed using visual interpretation of the color overlay, displaying relative shear wave velocities with similar stand-alone diagnostic performance with 92% sensitivity and 64.6% specificity. Lesion and surrounding tissue shear wave speed values were calculated, and a significant difference was observed between the benign and malignant popu-

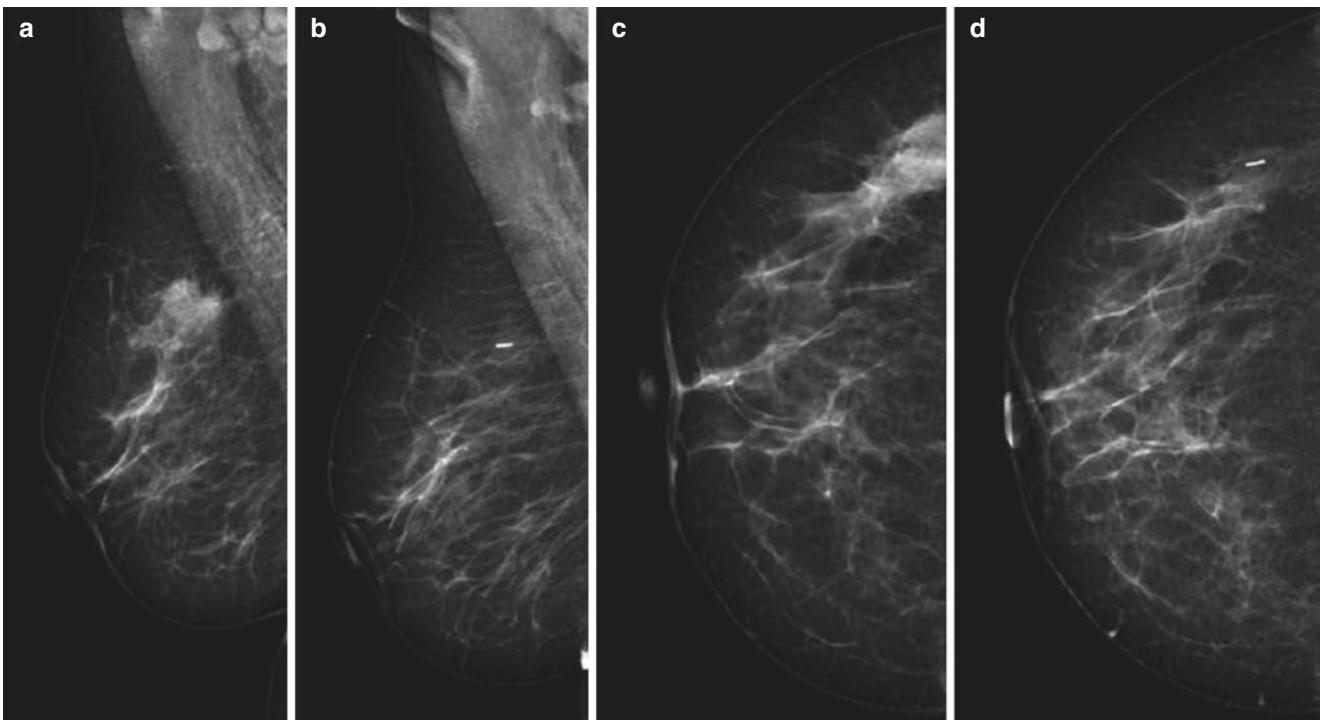

Fig. 18.1 Mammography imaging of the patient before (**a**, **c**) and after (**b**, **d**) PST with complete pathological response. Titanium clip for tumor bed localization is also seen in mammograms

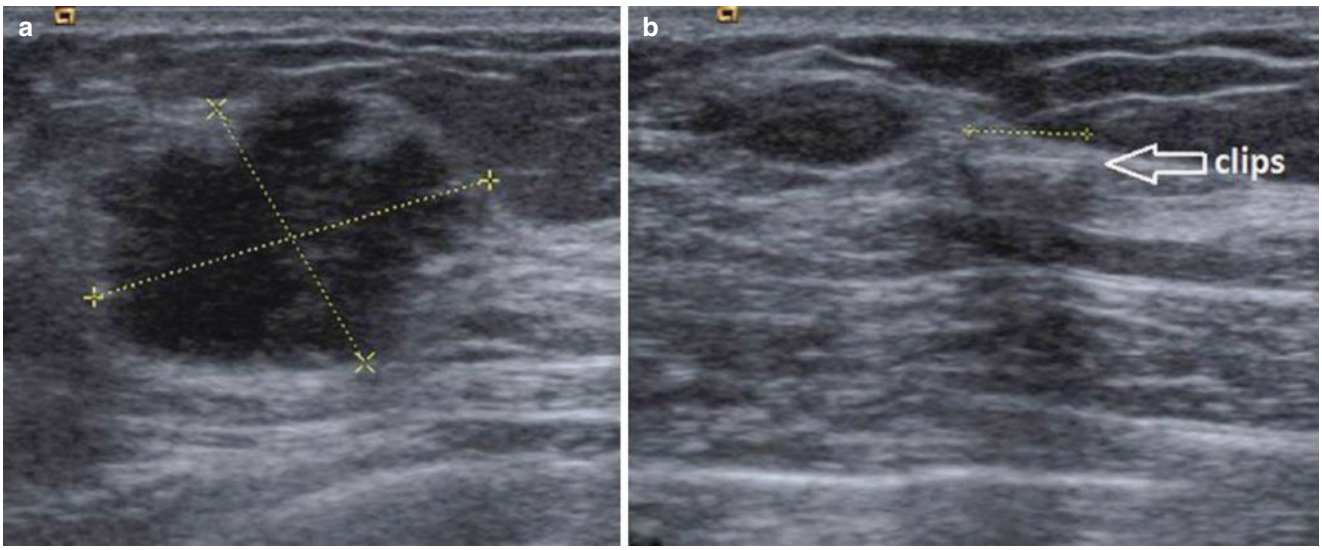

Fig. 18.2 Ultrasonographic imaging of the patient before (**a**) and after (**b**) PST with complete pathological response. Titanium clip for tumor bed localization is also seen in ultrasound

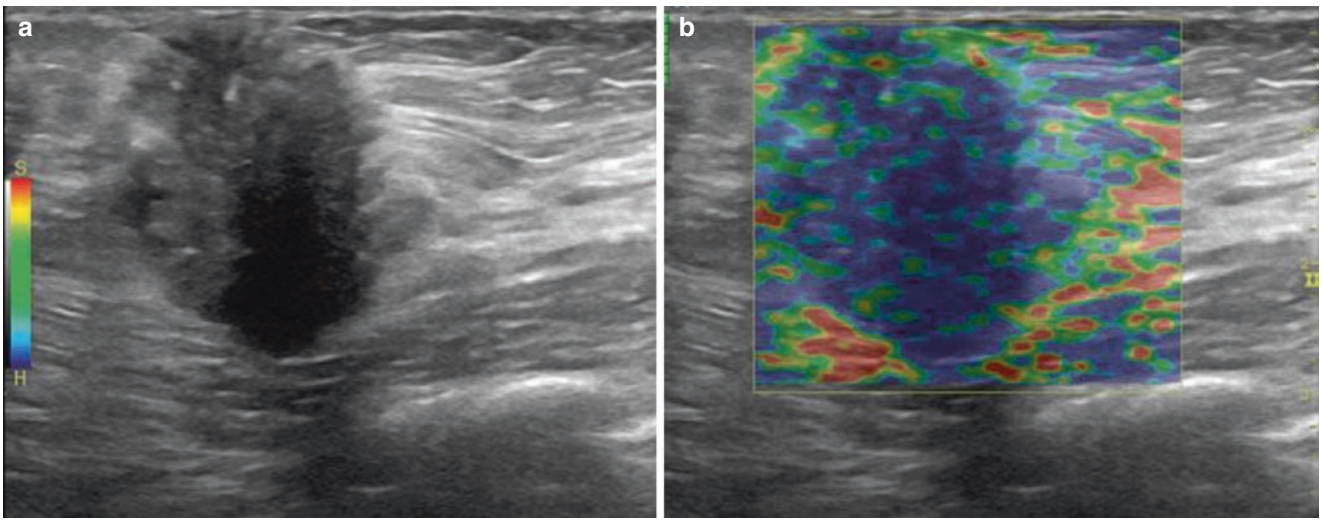

Fig. 18.3 (**a**) A malignant characterized mass in the left upper quadrant with irregular margins (**b**) The mass is showing a rigid color (blue) in elastography (This image is used with the permission of Dr. Ravza Yilmaz from Istanbul University, Istanbul School of Medicine, Department of Radiology)

lations (Mann-Whitney U test, $p < 0.0001$). Using a lesion cut-off value of 3.31 m/s, 80.4% sensitivity and 73% specificity were achieved. Exclusively applying this threshold to BIRADS 4a masses, overall levels of 92% sensitivity and 72.9% specificity were achieved. VTIQ qualitative and quantitative elastography has the potential to further characterize B-mode-detected breast lesions, increasing specificity and reducing the number of unnecessary biopsies.

Although recent studies suggest that elastography reduces unnecessary biopsy numbers [30–32], additional prospective randomized trials with a large number of patients are required to evaluate the clinical use of this novel technique.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has emerged as a very useful tool for defining the extent and patterns of primary breast tumor growth [33], particularly in high-risk patients [34, 35] and patients with increased mammographic density [36]. MRI is also valuable in assessing tumor response to PST [37, 38] and demonstrates superior accuracy compared with mammography [33]. MRI also provides valuable information regarding the extent of surgical margins in patients who are candidates for BCS as well as the response of the axillary lymph nodes to PST (Figs. 18.4 and 18.5). MRI before and after PST can identify distinct patterns of tumor growth and

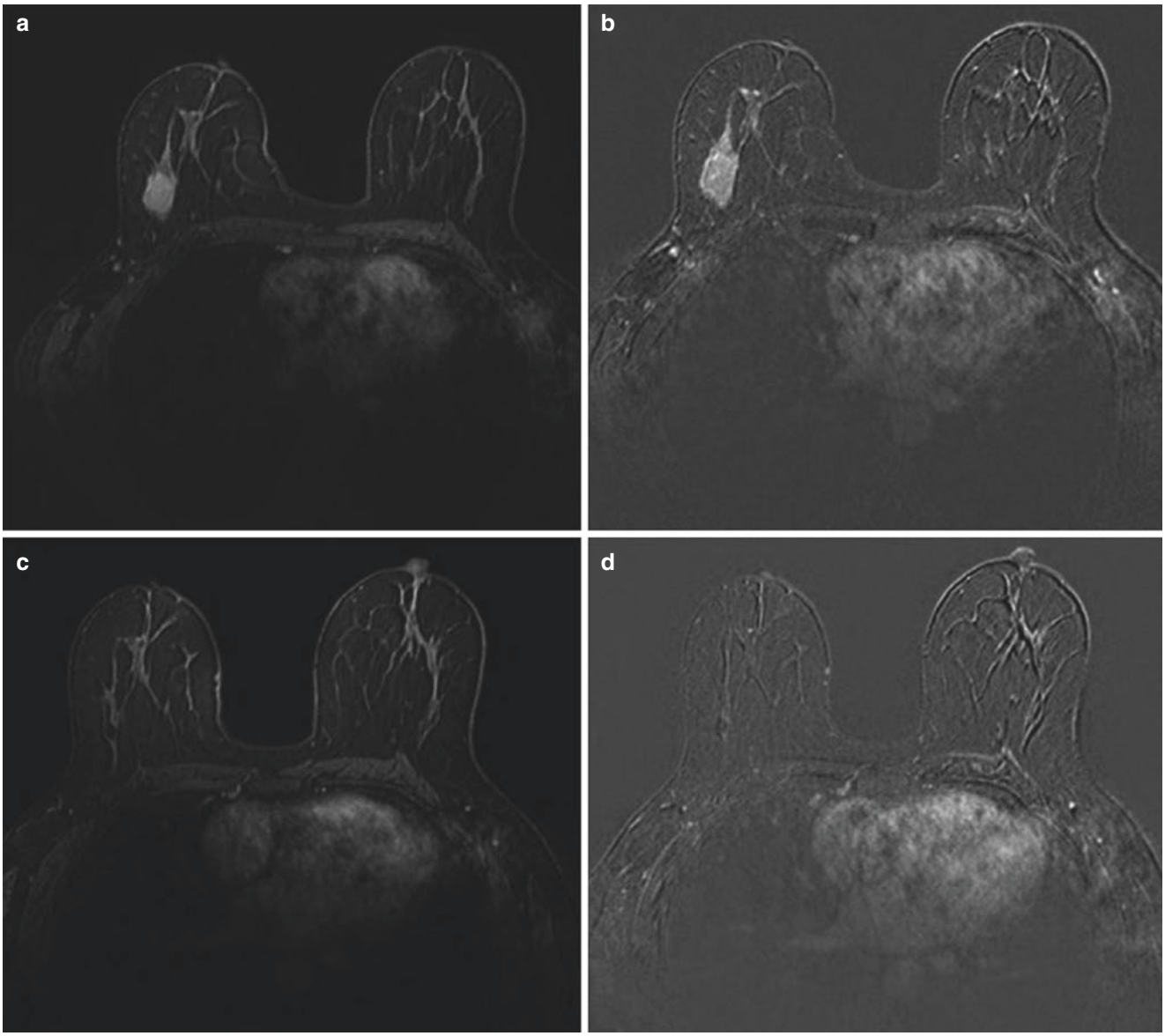

Fig. 18.4 Magnetic resonance imaging of the patient with a mass in her right breast. (**a**, **b**) Before PST. (**c**, **d**) After PST with complete pathological response

shrinkage (concentric versus dendritic) [39] and thus can be useful in identifying appropriate candidates for BCS after PST [40]. Although MRI is less predictive of the true residual tumor size when a substantial clinical response is noted [41, 42], the residual tumor size based on MRI correlates well with microscopic findings on pathologic examination [43, 44]. However, the use of MRI has raised concerns regarding the potential of decreasing the pool of BCS candidates regardless of whether patients receive PST or not [45]. Thus, for patients who are not good candidates for BCS based on the presence of multicentric lesions on the original or post-chemotherapy MRI, consideration should be given to obtaining histological confirmation of these additional MRI abnormalities before the decision to proceed with mastectomy [45].

In a meta-analysis of MRI detection of residual breast cancer after neoadjuvant therapy, 44 studies including 2050 patients were reviewed [46]. MRI exhibited increased accuracy compared with mammography ($p = 0.02$); the evidence only weakly indicated that MRI exhibited increased accuracy compared with clinical examination ($p = 0.10$). No difference in MRI and ultrasound accuracy was observed ($p = 0.15$).

Contrast-Enhanced Computed Tomography

When determining tumor extent in the breast and identifying appropriate candidates for BCS, contrast-enhanced computed tomography (CE-CT) also exhibits increased sensitivity and specificity before and after PST [47]. Similar to MRI, CE-CT classifies breast tumors into localized and diffuse

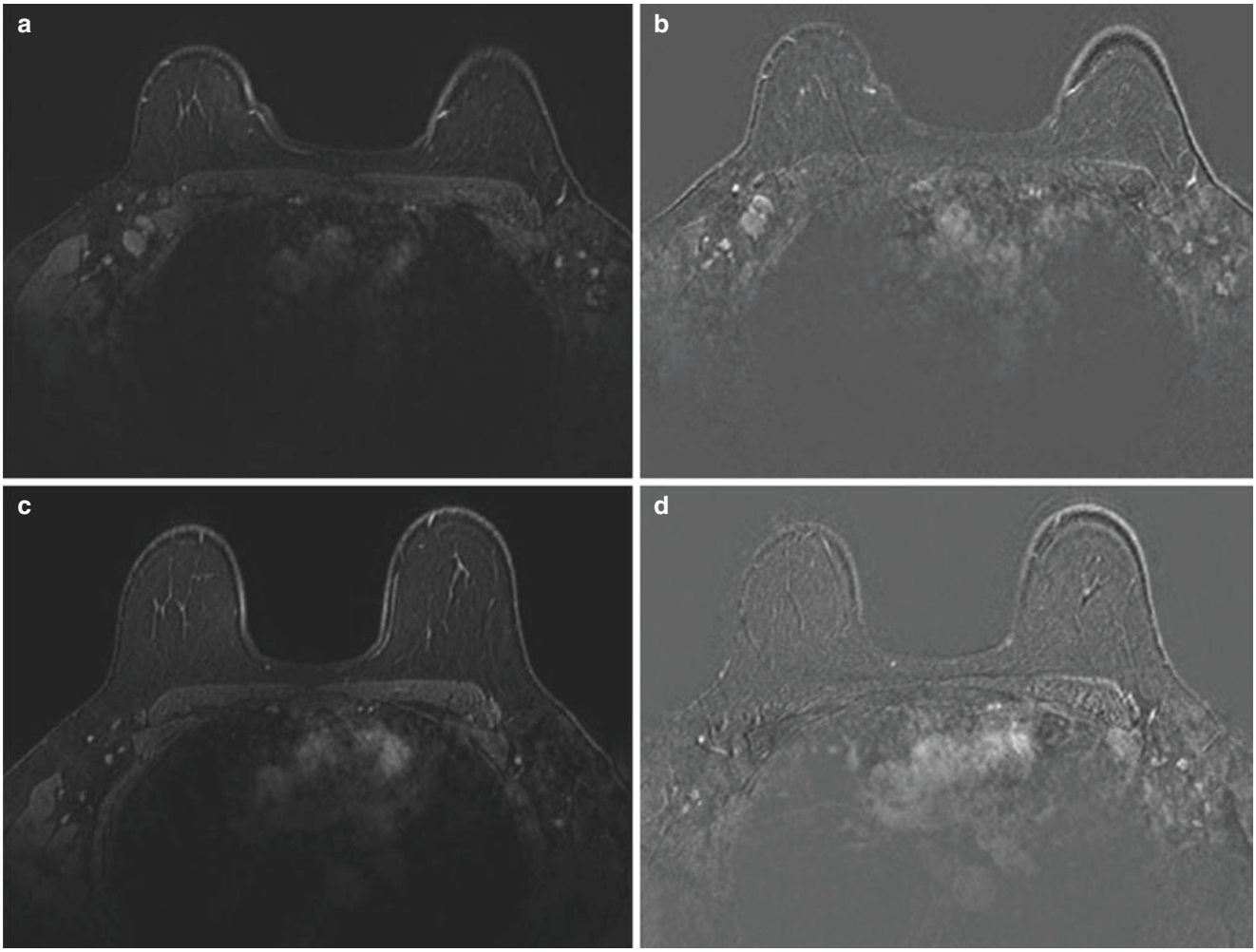

Fig. 18.5 Magnetic resonance imaging of positive lymph nodes before (**a**, **b**) and after (**c**, **d**) PST with complete pathological response

patterns of growth [48]. Tumors exhibiting a diffuse growth type shrink in a mosaic pattern, exhibit reduced rates of pCR, and are not generally suitable for BCS. By contrast, tumors exhibiting a localized growth pattern generally shrink concentrically, exhibit increased rates of pCR, and are often appropriate candidates for BCS [48]. CE-CT can be a less expensive and readily attainable alternative to MRI, but studies comparing these two imaging modalities are needed.

Positron Emission Tomography

Recent studies of technetium-99 sestamibi scintimammography and 18-fluoro-deoxy-glucose positron emission tomography (^{18}FDG-PET) indicate that these imaging modalities are useful when assessing patients undergoing PST before, during, and after chemotherapy. Alterations in ^{18}FDG uptake exhibit a strong correlation with clinical response [48–51] (Fig. 18.6). However, the value of this technique in identifying pathologic complete responders among clinical complete responders is variable [48, 50]. Intraductal cancer is typically not affected by cytotoxic chemotherapy and will persist during treatment [52]. Thus, the discrepancy between a radiographic and pathological response can be attributed to the persistence of intraductal cancer.

Mghanga et al. reviewed 15 FDG-PET studies with 745 patients who underwent PST with the diagnosis of breast cancer [53]. In their meta-analysis, the pooled sensitivity and specificity of FDG-PET or PET/CT were 80.5% (95% CI, 75.9–84.5%) and 78.8% (95% CI, 74.1–83.0%), respectively; the positive predictive and negative predictive values were 79.8% and 79.5%, respectively. After one and two courses of chemotherapy, the pooled sensitivity and false-positive rate were 78.2% (95% CI, 73.8–82.5%) and 11.2% and 82.4% (95% CI, 77.4–86.1%) and 19.3%, respectively. Analysis of the findings suggests that FDG-PET exhibits moderately increased sensitivity and specificity in the early detection of responders compared with nonresponders. In addition, this technique can be applied in the evaluation of breast cancer response to neoadjuvant chemotherapy in breast cancer patients.

In another meta-analysis of 17 studies and a total of 781 patients, FDG-PET/FDG-CT and PET exhibited reasonable

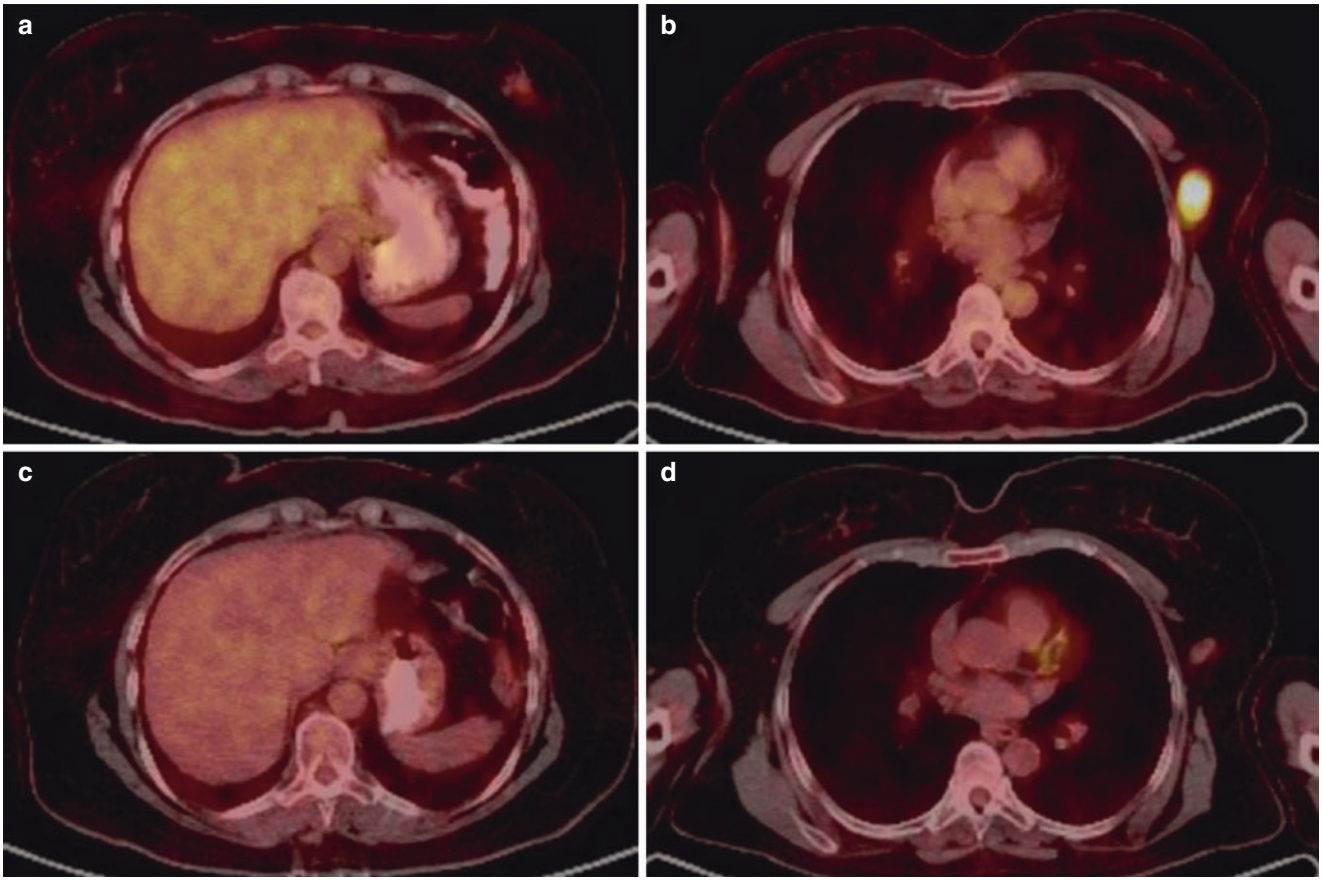

Fig. 18.6 Positron emission tomography imaging of the invasive ductal carcinoma in the left breast and positive axillary lymph nodes before (**a**, **b**) and after (**c**, **d**) PST

sensitivity in evaluating the response to neoadjuvant chemotherapy in breast cancer; however, the specificity was relatively low. The authors of this analysis recommended combining other imaging methods with FDG-PET/FDG-CT or PET [54].

Determining the Tumor Bed Location in Patients with Clinical or Pathologic Complete Response

Determining the exact tumor bed location in patients, especially those with clinical complete response or pCR who receive PST, is crucial before and during chemotherapy. When complete response is assessed, there is no evidence of the tumor after PST using imaging modalities. Thus, care should be taken, and all patients who undergo PST should be assessed promptly [55, 56]. Approximately 30% of these patients (and up to 60% of those treated with trastuzumab) will achieve a clinical complete response, making it difficult to locate the tumor site during surgery [57].

The exact tumor location must be marked with a radiopaque marker (embolization coils, titanium clips, and metallic harpoon) under mammographic or sonographic guidance before administering chemotherapy or early during chemotherapy when there is evidence of response [55, 56]. Studies have indicated that the identification of the tumor site is difficult or impossible in as many as half of the patients receiving NACT without the placement of such a marker [58, 59]. Marker placement is crucial for both the surgeon and pathologist before and after surgery. The surgeon will decide where to operate and how much volume to remove in patients who are candidates for BCS, and the pathologist will focus on that particular area in search of a residual tumor [55, 56]. Nearly two-thirds of patients with a clinical complete response will have residual tumor on final pathology, and thus it is critically important to precisely localize and remove the original tumor site and ensure that the surgical specimen has clean margins [57].

Determining the Axillary Nodal Status Before Preoperative Systemic Therapy

Radiological Assessment

Although considerable advances in imaging modalities, such as CE-CT, MRI, and PET-CT, have been made, none of these

techniques are as accurate as FNA of the axillary lymph nodes. The sensitivity of these imaging modalities ranges from 70% to 90% [47, 49, 60]. However, in the presence of micrometastases or small macrometastases, the sensitivity is considerably reduced [49]. Consequently, the recent approach to identify pathologically enlarged lymph nodes in the axillary region involves the use of ultrasound and subsequent biopsy of these lymph nodes by FNA [61, 62]. This method can also provide important information for decision-making before starting PST. Common causes of decreased sensitivity of this approach include failure to visualize all lymph nodes by ultrasound and small size of axillary metastases in some patients [62]. In addition, the radiologist may occasionally sample from a nonmetastatic portion of the lymph node, and the biopsy result will therefore mislead the clinician.

Sentinel Node Biopsy

Sentinel node biopsy (SNB) can also be used to assess axillary nodal status before PST [63–65]. SNB may provide valuable information regarding the nodal status of the axilla, allowing the clinician to choose an appropriate regimen and estimate the effects of PST. The feasibility and accuracy of SNB in patients who are the typical candidates for PST has been demonstrated in several studies [63–67]. Moreover, patients with large operable breast cancer have been included in several multicenter and randomized trials. None of these trials has demonstrated reduced feasibility or accuracy of SNB according to tumor size [68–71].

A considerable number of studies have suggested that SNB can be performed either before or after PST [72–75]. The appropriate timing of SNB is an important and controversial locoregional therapy issue for patients who are candidates for neoadjuvant chemotherapy. However, the current trend is SNB after PST [72, 75]. A detailed review of this topic is presented in the section on the surgical management of the axilla.

Surgical Management of the Primary Breast Tumor After Preoperative Systemic Therapy

The most important advantage of PST in women with large primary tumors or those with moderate-sized tumors but large tumor size to breast size ratio is the potential for tumor shrinkage to facilitate breast-conserving surgery [76–78].

Vlastos et al. [78] reported that at MD Anderson Cancer Center, 129 patients treated with preoperative chemotherapy (either paclitaxel or FAC [fluorouracil, doxorubicin, and cyclophosphamide]) exhibited significant tumor downsizing. Although the number of patients eligible for breast conservation was not defined preoperatively, 26% of tumors initially categorized as T2 were downstaged to less than 1.0 cm, and 11% of patients experienced pCR in the breast. In addition, of those tumors clinically larger than 5 cm, 29% decreased to less than 1.0 cm, and 9% exhibited no residual disease at surgery [78].

Bonadonna et al. [77] reported the 8-year results of two prospective trials from the Milan Cancer Institute in women with primary tumors larger than 2.5 cm. Following a variety of preoperative chemotherapy regimens, 85% of the patients were able to undergo breast-conserving surgery. In addition, breast conservation was possible in 62% of patients who presented with primary tumors larger than 5.0 cm [77]. Overall, 34% underwent breast-conserving surgery. By contrast, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial [79], in which patients were randomized to preoperative versus adjuvant chemotherapy and surgeons were required to state beforehand whether a patient was a candidate for breast conservation, breast conservation rates were significantly improved but only increased from 60% to 67%. Similarly, in the Royal Marsden randomized trial of preoperative plus adjuvant chemotherapy (mitoxantrone/methotrexate with or without mitomycin) versus the same chemotherapy administered in the adjuvant setting, breast conservation was increased from 13% to 28% [80]. In addition, 23% of patients in the European Organization for Research and Treatment of Cancer (EORTC) randomized trial of preoperative fluorouracil, epirubicin, and cyclophosphamide (FEC) underwent breast conservation instead of planned mastectomy [15].

Another important issue is the quantity of breast tissue removed from patients who are candidates for BCS. This issue is particularly important for patients with pCR. The surgeon should consider the original tumor configuration, the pattern of tumor shrinkage, and the presence or absence of suspicious microcalcifications. Accordingly, the surgeon must identify the extent of the tumor before and after chemotherapy via clinical and imaging assessments. The surgeon must consider additional removal of tissue instead of removing the center of tumor bed if the lumpectomy margins are found to be compromised on pathologic evaluation or if there is evidence of “honeycomb” tumor regression.

Invasive lobular carcinoma is often multicentric, can extensively involve the breast without significant clinical or imaging findings of a defined mass [45, 81, 82], and is associated with reduced clinical response rates compared with invasive ductal carcinoma [83, 84]. Thus, particular attention is needed when planning the extent of lumpectomy in patients who present with invasive lobular carcinoma. Among patients with lobular invasive histology, the rate of pCR is low [84–86]. In one series, lobular histology was identified as one of the independent predictors of ineligibility for BCS after preoperative chemotherapy [87]. Thus, it is unlikely that preoperative chemotherapy will convert patients who present with extensive lobular invasive carcinoma requiring mastectomy to lumpectomy candidates.

Breast-Conserving Surgery After Preoperative Systemic Therapy

For selected patients (i.e., complete resolution of skin edema [*peau d'orange*], adequate reduction in tumor size, no extensive intramammary lymphatic invasion, absence of extensive suspicious microcalcifications, and no evidence of multicentricity), BCS can be an appropriate local treatment option. In patients meeting these criteria, the LR rate and 10-year overall survival after BCS are equivalent to those observed in early-stage breast cancer patients [88].

Second-generation randomized phase III trials incorporating paclitaxel and docetaxel into neoadjuvant regimens as well as those evaluating preoperative targeted therapies, such as trastuzumab, continue to demonstrate improved BCS rates and, importantly, increased pCR rates: 10–28% for trials incorporating paclitaxel and docetaxel and 36–78% for trials incorporating trastuzumab [89]. Achievement of pCR is associated with improved overall survival and disease-free survival. At this point, a question emerges. What will be the margins of resection and the extent of the lumpectomy? Surgical excision does not attempt to remove the pre-chemotherapy volume of tumor. The goal is to remove any residual lesion with 1 cm of clear margins. Alternatively, if no detectable residual lesion is evident, a 2-cm specimen with the metal coil in the center is removed. While the patient is still in surgery, the specimen is then sectioned by a pathologist. If there is any indication of a positive margin, the surgeon must remove additional tissue from the positive site to obtain a negative margin.

Radiation therapy plays a crucial role in successful BCS and reduces LR risk by approximately 50% [90]. The 5-year LR risk is significantly reduced from 26% after lumpectomy alone to 7% after lumpectomy with radiation therapy, with an absolute reduction of 19% [90].

Ipsilateral Breast Tumor Recurrence Following Preoperative Systemic Therapy and Lumpectomy

LR after BCS can be described as follows:

1. True recurrence, one within the primary tumor bed.
2. Marginal miss, one within the same quadrant just outside of the tumor bed.
3. Recurrence elsewhere, one in a separate quadrant of the breast.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that greater than 75% of all recurrences occur within 5 years [90].

Studies in patients with operable breast cancer and in those with locally advanced disease have demonstrated that BCT can be safely performed in patients who respond to preoperative chemotherapy without compromising local control [14, 15, 18, 91]. The evidence is stronger in patients with operable breast cancer, for whom large randomized trials have demonstrated no statistically significant increase in LR between the preoperative and adjuvant chemotherapy arms of the trials [14, 15, 18]. In the European Organization for Research and Treatment of Cancer (EORTC) trial, which compared preoperative versus postoperative 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy in 689 patients, no significant difference in locoregional recurrence (LRR) was observed [15]. Similarly, in the NSABP B-18 trial, in which 1523 women were randomized to preoperative versus postoperative doxorubicin and cyclophosphamide chemotherapy, a small difference in LRR favoring the adjuvant chemotherapy arm was observed but was not statistically significant.

Kümmel S. et al. reported LR rates in a recently published review [92]. Long-term follow-up results of the NSABP B-18 and B-27 trials have recently been published [93]. These two studies included a total of 3088 patients undergoing PST or adjuvant chemotherapy. All underwent surgery in the course of treatment. RT was limited to whole-breast irradiation following BCS. The 10-year cumulative LRR rate after NACT was 12.3% for patients who underwent mastectomy and 10.3% for those treated with BCS and consecutive whole-breast irradiation. Clinical tumor sizes larger than 5 cm in patients who underwent mastectomy and age < 50 years in the BCS group had a significant impact on the risk of LR by 10 years. Clinically node-positive (cN+) disease before PST and pathological nodal involvement after PST were independent predictors of LR, regardless of the type of surgical therapy. Patients who failed to achieve downstaging of the axilla (cN+ to ypN0) and breast pCR were at higher risk of LR. In addition, data concerning hormone receptor and HER2 status were not available; thus, it could not be determined whether certain subgroups may benefit more or may be at increased risk of LR after PST. Moreover, a direct comparison of LR rates between the two groups in NSABP B-18 that received the same type of chemotherapy (one group before and one after surgery) was not reported.

LR may occur in both mastectomy and BCS patients. The slightly increased rates of LR in patients with BCS are due to regression of tumors in a "honeycomb" pattern rather than a "concentric" pattern after PST.

Breast Reconstruction After Preoperative Chemotherapy and Mastectomy

Several studies have demonstrated that immediate breast reconstruction with autologous tissue is safe [94–96], does not delay further adjuvant therapy [94, 97], and is not associated with an increase in LR [94, 98] or a delay in detecting such a recurrence in patients who have received prior PST [99]. However, evidence suggests that immediate reconstruction

can compromise the quality of RT, which can lead to more radiation to the heart and lung [100]. The optimal type of reconstruction remains the subject of debate because the effect of RT on breast implants or autologous tissue is unpredictable and may lead to increases in capsular contraction or flap contraction, respectively [96, 98, 101]. Given this concern, some investigators have recently adopted the so-called immediate-delayed or delayed-delayed reconstruction approach in patients who are likely to require postmastectomy RT [102]. With reference to this approach, a submuscular expander is placed and partially inflated during the skin-sparing mastectomy procedure. After the final pathology report, if RT is not required, expansion continues until sufficient space is obtained for the replacement of the expander by the permanent implant. However, if adjuvant RT is required, the expander is deflated for adequate skin or chest wall and ipsilateral regional lymph node irradiation. After completion of radiotherapy, reconstruction is performed at the appropriate time.

Surgical Complications After Preoperative Systemic Therapy

The effect of preoperative systemic therapy on surgical complications has not been investigated widely. The influence of new agents on postoperative wound healing, wound infection, and other complications regarding the need for reoperation remains unknown. In a current retrospective analysis [103], data were collected from 44,533 patients after breast surgery. To identify predictors of postoperative wound complications, a multivariable regression analysis was performed; 2006 patients received PST prior to surgery. Wound complication rates were generally low and comparable in the neoadjuvant treatment and primary surgery groups (3.4% versus 3.1%). In the study, PST did not influence postoperative wound healing, although a trend toward a higher rate of wound complications (4.0%) was noted among patients who underwent mastectomy and immediate reconstruction after PST. Postoperative complication rates were higher for mastectomies with immediate or delayed reconstruction compared with BCS [104]. In smaller series [105–107] of immediate breast reconstruction following PST, complication rates after mastectomy and immediate autologous or expander/implant reconstruction with or without preceding PST were similar. In light of this information, PST does not appear to affect postoperative complication rates.

Surgical Management of the Axillary Nodes After Preoperative Systemic Therapy

SNB for detecting axillary nodal status is crucial for breast cancer patients regardless of whether they receive PST or undergo surgery. As previously mentioned, the nodal status of the patient at the time of admission guides the clinician in the selection of the treatment modality. The use of PST for LABC patients has increased continuously since its introduction in clinical practice. Preoperative chemotherapy downstages axillary lymph nodes in a considerable proportion of patients (up to 40% with anthracycline- and taxane-containing regimens). Thus, if SNB is accurate following preoperative chemotherapy, patients who present with involved axillary nodes at the time of diagnosis may potentially be spared from axillary dissection if the sentinel node is found to be negative following preoperative chemotherapy. At this point, relevant questions include whether axillary dissection is feasible, the false-negative and false-positive rates of SNB, the potential for PST to affect the results of SNB and mislead the surgeon, and the LR rate after SNB without axillary dissection.

Newman et al. [108] reported 54 consecutive breast cancer patients with biopsy-proven axillary nodal metastases at initial diagnosis who underwent SNB and axillary lymph node dissection after receiving PST. The sentinel node identification rate was 98%, and the FNR was consistent with the literature. Based on their results, the authors concluded that SNB after PST in patients with documented nodal disease at presentation accurately identified cases that were downstaged and commented that this approach can potentially spare this subset of patients (32%) from the morbidity of an axillary dissection.

Lee et al. [109] reported on 238 patients with positive axillary nodes at presentation and underwent SNB and axillary dissection following PST. The identification rate was 77.6% in patients who received PST, and the FNR was 5.6%. Based on these results, the authors concluded that for patients who present with involved axillary nodes and who achieve complete clinical axillary response with PST, SNB could replace axillary node dissection.

Shen et al. [110] reported on 69 patients with clinical T1–4, N1–3 disease in whom axillary metastases were identified by ultrasound-guided FNA and who then underwent SNB following PST using prospective, institutional protocols. The sentinel node identification rate was 92.8%, and the FNR was 25%. Based on these results, the authors concluded that SNB is feasible after PST.

Larger single-institution studies have been reported, including various studies in which the axillary nodes were documented to be involved prior to PST [108–113]. When these studies are examined collectively [114, 115] or when larger, multicenter data sets are analyzed [116, 117], the performance characteristics of SNB after PST appear to be similar to those of SNB prior to systemic therapy [68, 69, 71, 117, 118].

The largest report to date comes from the NSABP B-27 trial [116], in which 428 of the 2411 patients treated with PST underwent lymphatic mapping and attempted SNB prior to the required axillary node dissection. The identifica-

tion rate was 85%, which was significantly increased when radiocolloid (with or without Lymphazurin (isosulfan blue: Tyco Healthcare Group, North Haven, Connecticut)) was used for lymphatic mapping (88–89%) compared with Lymphazurin alone (78%). The FNR was 11%, and this result was also lower when radiocolloid (with or without Lymphazurin) was used for lymphatic mapping (8%) compared with Lymphazurin alone (14%). By contrast, no significant differences in the FNRs were observed for patients who presented with clinically negative versus clinically positive axillary nodes (12.4% versus 7.0%, respectively; $p = 0.51$).

Xing et al. [114] published a meta-analysis of 21 studies of SNB after PST. Studies were eligible for inclusion if they evaluated patients with operable breast cancer who underwent SNB after PST followed by axillary dissection. A total of 1273 patients were included in the 21 studies. The reported identification rates ranged from 72% to 100% with a pooled estimate of 90%. The sensitivity of SNB ranged from 67% to 100% with a pooled estimate of 88% (95% CI, 85–90%). Thus the FNR ranged from 0% to 33% with a pooled estimate of 12%. Based on their results, the authors concluded that SNB is a reliable tool for planning treatment after PST.

The identification rates are slightly lower for SNB after PST in multicenter studies and in the meta-analysis compared with those from other multicenter and randomized trials of SNB before systemic therapy, but the FNRs are similar [68, 69, 71, 118].

In the NSABP B-27 [17] as well as other large PST trials [18, 79, 119], patients achieving pCR in the breast had the lowest rate of involved axillary nodes (13–15%). However, in the NSABP B-27 SNB, no significant differences were noted in the sentinel node FNRs according to clinical or pathological breast tumor response. Thus, as expected, in the NSABP B-27 trial, the rate of remaining positive non-sentinel nodes was the lowest among patients with pCR (1.7%) compared with those with clinical complete response but residual invasive cancer in the breast (4.0%) and those with any other type of clinical response (5.5%). However, these differences did not reach statistical significance.

The accuracy and utility of SLNB in patients who present with axillary node involvement and undergo PST remain controversial but feasible. Two prospective clinical trials regarding the characteristics of SLNB after PST in patients with documented axillary nodal involvement were recently published [120, 121]. The German SENTINA (SENTInel NeoAdjuvant) trial [120, 122] is a four-arm prospective multicenter cohort study designed to (1) evaluate a specific algorithm for the timing of SLNB in patients who undergo PST and (2) provide reliable data regarding the detection rate and FNR in different settings. Patients were categorized into four treatment arms according to the clinical axillary staging before and after PST. Patients with cN0 status underwent SLNB prior to PST (arms A and B). If the SLN was histologically negative, no further axillary surgery was performed after PST (arm A). However, if the SLN was positive, a second SLNB and axillary dissection were performed after PST (arm B). Patients with cN1 status before PST did not undergo axillary surgery prior to PST and were stratified as arms C and D. If patients converted to cN0 after PST, SLNB plus axillary dissection were performed (arm C), but patients who remained cN1 after PST underwent axillary dissection (arm D). A total of 1737 eligible patients were accrued. The detection rate for SLN was 99.1% before PST (arms A and B), 80.1% in arm C (after PST), and 60.8% in arm D (after PST and prior SLNB) ($p < 0.001$). In arm C, the FNR was 14.2%. However, in the multivariate regression analysis, the number of removed SLNs was a significant predictor of the FNR (OR for >1 SLN versus 1 SLN removed = 0.505, $p = 0.008$). Thus, the FNR was 24.3% when one SLN was removed, 18.5% when two SLNs were removed, and only 5% when more than two SLNs were removed. The SLNB FNR was 51.6% in arm B, indicating that SLNB prior to PST significantly impairs the detection rate and accuracy of SLNB after PST. Based on these findings, the authors concluded that the SLNB detection rate is significantly reduced compared with primary SLNB in patients who convert from a positive to a negative clinical nodal stage during PST. The FNR was less favorable after PST compared with primary SLNB, but the FNR improved with removal of more than one SLN in this setting.

The second recently reported prospective trial is the ACOSOG Z1071 [121] trial, a single-arm prospective trial of women with clinical T0–4/N1–2/M0 breast cancer receiving PST. At the time of surgery, all patients underwent SLNB followed by axillary lymph node dissection. The primary endpoint was FNR in women with cN1 disease with two or more SLNs reviewed. The protocol encouraged use of the dual-tracer technique. A total of 756 patients were enrolled from July 2009 to July 2011. In patients with SLNB and ALND, the SLN identification rate was 92.5% (92.7% in cN1, 90% in cN2). For patients with cN1 disease and > 2 SLNs identified, the FNR was 12.8%. In patients subjected to the dual-tracer technique, the FNR was 11.1%. Based on these results, the authors concluded that SLN surgery after NAC in node-positive breast cancer patients correctly identified nodal status in 84% of all patients and was associated with a FNR of 12.8%. This FNR was higher than the prespecified study endpoint of 10%; Boughey and colleagues demonstrated in their multivariate logistic regression model analysis that when dual mapping was used in the Z1071 cohort, a significantly higher identification rate and lower FNR were achieved [123]. Finally, the SN FNAC study assessed the reliability of SLNB after NAC in biopsy-proven node-positive breast cancer patients [124]. The authors reported an identification rate of 87.6% and FNR of 8.4%. The 2017 St. Gallen International

Expert Consensus Panel considers SLNB for clinically node-positive patients converted to node-negative after NAC feasible if at least three or more lymph nodes are removed and the dual SLN mapping technique is used to achieve low FNR and high identification rates.

Ultimately, the surgeon must decide on whether to perform an axillary dissection. Preoperative imaging studies as well as traditional frozen section can be used for preoperative and intraoperative assessment of pCR in the breast, respectively. Touch imprint cytology is reliable for intraoperative detection of nodal metastases after PST [125]. Patients achieving a clinical complete response or, more importantly, pCR are the best candidates for preserving the axilla and reducing morbidity due to axillary dissection if the sentinel node is negative.

Conclusion

Patients treated with PST were significantly more likely to undergo BCS without a significant increase in LR compared with patients treated with surgery first. Downstaging the axilla can reduce morbidity due to decreased rates of axillary dissection. Several randomized and non-randomized studies have demonstrated a significant achievement of pCR in the breast and axillary nodes and improved outcomes. According to these studies, clinical and pathological response to PST can be used as an intermediate marker of chemotherapy efficacy, thus prompting the decision as to which chemotherapy regimen should be used following surgery. Furthermore, the efficacy of chemotherapy is slightly enhanced prior to surgery based on robust vascular and lymphatic drainage of the breast and the tumor itself. Based on the findings above, multidisciplinary collective and coordinated work between surgical and oncological teams as well as other clinicians is crucial when evaluating patients with LABC.

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Surgical Management of Inflammatory Breast Cancer

19

Atilla Soran, Bulent Unal, and Tara Grahovac

Introduction

Inflammatory breast cancer (IBC) has been characterized by rapid progression and poor outcome since its first description by Sir Charles Bell in 1814. Patients present with the clinical signs of edema (peau d'orange) and erythema of the skin overlying the breasts. Upon histopathological examination, plugging of the dermal lymphatics of the breast is noted, but this finding is not mandatory for diagnosis. Bryant first noted this "lymphatic absorption" of cancer cells, which leads to edema, in 1887. He also acknowledged how easily IBC could be confused with a benign etiology, given that IBC is often not associated with a palpable mass, as well as the magnitude of this misdiagnosis. The diagnosis of IBC equates to a T4d classification according to the American Joint Committee on Cancer (AJCC) staging system and has significant prognostic implications. Early distant metastasis is present in approximately 30% of patients at diagnosis, and disease-related death occurs twice as often compared with noninflammatory breast cancers [1–5]. Recognizing IBC as a distinct entity, an international expert panel gathered in 2008 to develop guidelines for diagnosis and management. In addition, international IBC registries have been developed, and several clinical trials have been initiated in the last decade to address the unmet need for therapeutic advancements specific to this deadly form of breast cancer.

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Epidemiology and Risk Factors

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program registry database, diagnosis of IBC represents 1% and 0.59% of all newly diagnosed breast cancer cases among women and men, respectively [6, 7]. IBC remains a rare disease, but the incidence is increasing worldwide [3, 4]. The true incidence is difficult to determine due to regional differences in diagnostic criteria as well as a lack of attention to clinical symptoms. The percentage of IBC among breast cancers varies geographically, with lower proportions in the United States (1–2%) than other parts of the world (i.e., Turkey, Morocco, Tunisia, Egypt, Nigeria, 10–17%) [8, 9]. The results of large population-based studies indicate that the incidence of IBC is higher in black women (3.1/100,000) than white women (2.2/100,000). IBC is also diagnosed at earlier ages than non-IBC (median age 57 vs. 62 years, respectively). Patients with IBC are more likely to have had their first pregnancy at younger ages compared with non-IBC patients. Other reproductive parameters, such as menarche at an early age, premenopausal status, and older age at first live birth, are not associated with IBC. Some authors report that higher BMI and a family history of IBC are associated with IBC in both premenopausal and postmenopausal women [2, 7, 10].

IBC was defined to be lethal before 1974 with a median survival time period of 1.2 years and a 5-year survival rate of 5% [10, 11]. The SEER program noted an overall increase in survival for IBC patients throughout the 1990s; however, survival remains poor compared with non-IBC patients. Among microscopically confirmed malignancies of the breast diagnosed in the SEER 9 registries database between 1988 and 2000, median survival times differed significantly among women with non-T4 breast cancer, non-IBC T4 breast cancer, and IBC (10 vs. 6.4 vs. 2.9 years, respectively) [1].

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Diagnosis

Clinical Characteristics

The American Joint Committee on Cancer (AJCC) defines IBC as "a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass." These clinical findings should involve the majority of the skin of the breast (Figs. 19.1 and 19.2) [4, 12, 13]. Less than 50% of IBC patients present with a discretely palpable mass. Peau d'orange refers to the unique appearance of the breast skin, which may have ridges or pits resembling the surface of an orange. Other symptoms of inflammatory breast cancer include a rapid increase in breast size, sensations of heaviness, burning or tenderness in the breast, or a retracted nipple [14]. Metastatic axillary lymph nodes are present at diagnosis in over half of IBC patients. Distant metastases are also noted in approximately 30% of IBC patients at diagnosis [15]. The term "primary IBC" or "de novo IBC" is defined as the new development of IBC in a previously normal breast, whereas the term "secondary IBC" describes the inflammatory recurrence of non-IBC breast cancer [10]. "Occult IBC" has also been described and refers to cases in which dermal lymphatic invasion is present in the absence of clinical criteria.

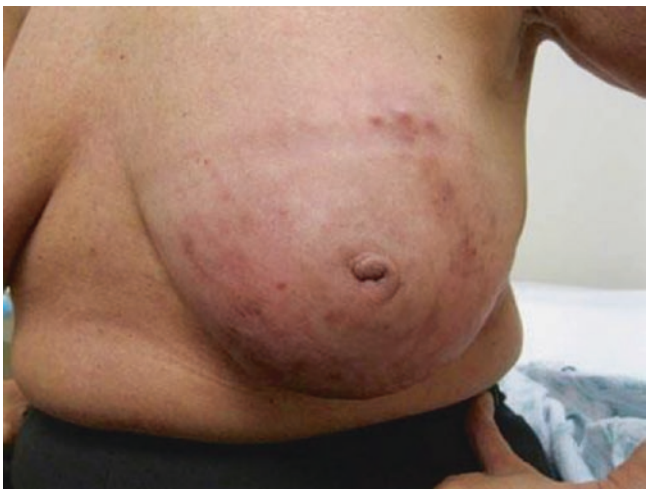

Fig. 19.1 Clinical findings in patients with IBC

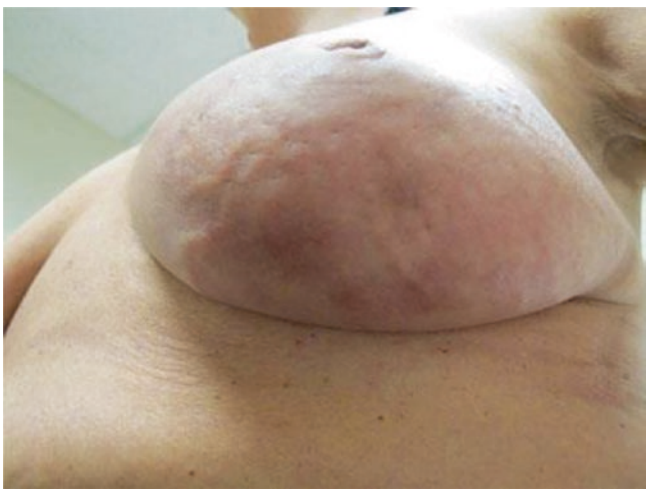

Fig. 19.2 Clinical findings in patients with IBC

The differential diagnosis for IBC primarily includes mastitis and locally advanced breast cancer. The distinction among these entities is important because the treatment algorithm and prognostic information differ drastically. Recognizing the nonspecificity of the traditionally used diagnostic criteria, the expert panel of the First International Conference on Inflammatory Breast Cancer developed the following guidelines for a more standardized diagnosis of IBC [16].

The following minimum clinical diagnostic criteria are required for the diagnosis of IBC:

- Rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast with or without an underlying palpable mass.
- History of flattening, crusting, or retraction of the nipple may be present.
- Patients may have a history of being diagnosed with mastitis not responding to at least 1 week of antibiotic administration.
- Duration of no longer than 6 months.
- Clinical examination revealing erythema occupying at least one-third of the breast.
- Clinical examination may reveal underlying palpable mass with or without palpable locoregional lymph nodes with or without nipple abnormalities.
- Pathological confirmation of invasive carcinoma from a core biopsy of the breast.
- Recommendation to obtain adequate skin punch biopsy to possibly document dermal lymphovascular tumor emboli.

Pathological and Molecular Criteria

No pathological diagnostic criteria are available for IBC, although dermal lymphatic involvement is pathognomonic. Patients with IBC typically have ductal tumors with high histological grades. Skin punch biopsies should be a standard requirement in the diagnostic work-up of all clinically suspected cases of IBC [16, 17]. Histopathologically, IBC is characterized by the presence of cancer cells involving and plugging dermal lymphatic vessels of the involved skin, but dermal lymphatic involvement is not a prerequisite for diagnosis (Fig. 19.3). Dermal lymphatic invasion is evident in up to 75% of IBC patients. There is no correla-

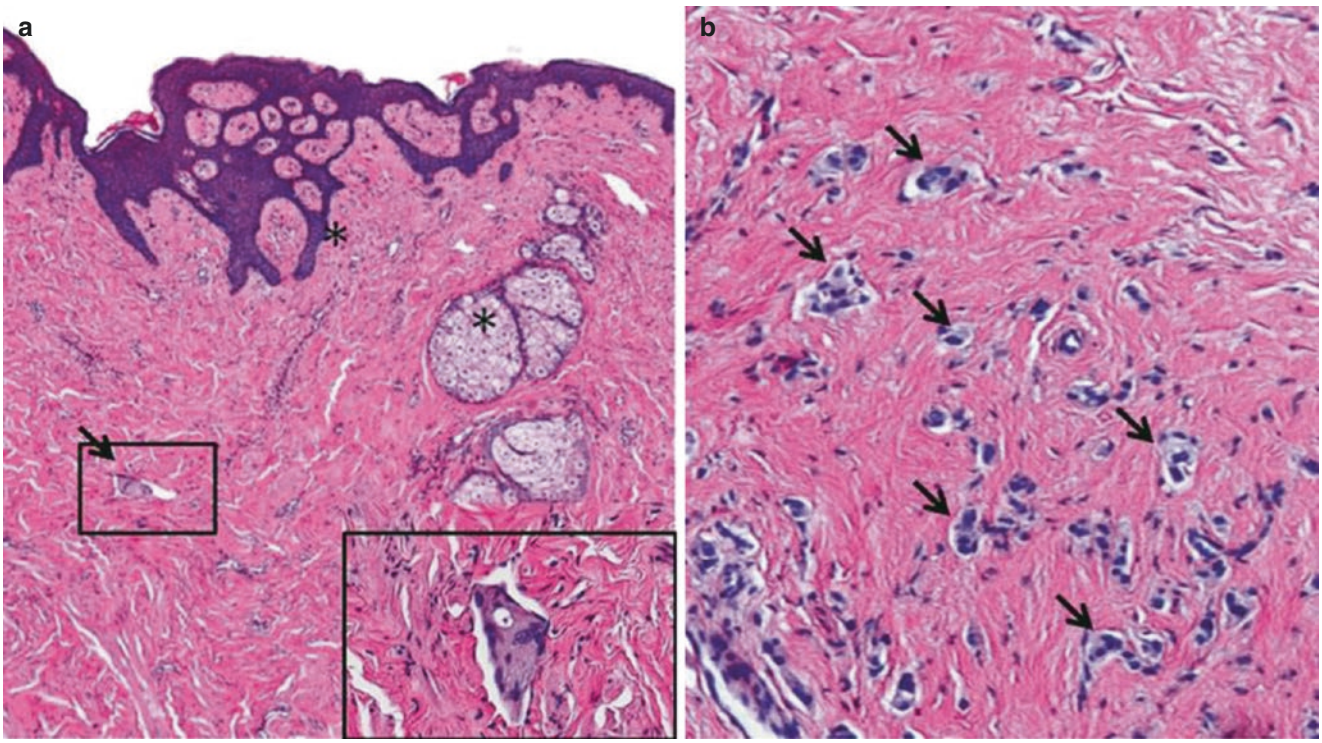

Fig. 19.3 Inflammatory mammary carcinoma, involving dermal lymphatics. (**a**) H&E, 4×: skin surface and adnexa (*epidermis, rete, sebaceous glands) with a tumor embolus within superficial dermal lymphatics. (*Arrow* and *box/inset*, H&E 20×). (**b**) H&E, 10×: numerous tumor emboli were present within lymphatics of deep dermis

tion between the extent of this invasion and the severity and distribution of the cutaneous manifestations of the disease [10, 18].

No established molecular criteria are available for distinguishing IBC from non-IBC. Molecular subtypes of IBC are similar to molecular subtypes of non-IBC. Compared to other forms of breast cancer, IBC typically exhibits negative ER and PR status and is associated with poor prognosis. Moreover, IBC exhibits increased HER2 overexpression compared with non-IBC cases. Molecular studies demonstrate increased angiogenesis and lymphangiogenesis in IBC based on endothelial cell proliferation fraction assessment. Several markers have been studied, but limited evidence is available regarding the prognostic or predictive role of these markers in IBC. However, p53 mutations and elevated CXCR4/CCR7 receptor expression have been demonstrated in IBC and may reduce the chemotherapeutic response and patient survival [16, 18]. Notch-1, E-cadherin, MUC1, RhoC guanosine triphosphatase (GTPase), and vascular endothelial growth factor (e.g., VEGF-C, VEGF-D, VEGFR-3, Prox-1, and lymphatic vessel endothelial receptor1) expressions are also increased in IBC tumors compared with non-IBC tumors and have been associated with high histological grade, advanced stage, and poor prognostic outcome [16, 19–23].

Imaging Modalities

Use of suitable imaging methods is important in IBC for the following reasons [10]:

- Identifying a primary breast tumor and facilitating image-guided diagnostic biopsy to enable optimal biomarker evaluation.
- Staging locoregional disease (most authors recommend the use of the AJCC tumor-node-metastasis (TNM) system for staging; IBC is defined as T4d according to the TNM system).
- Diagnosing distant metastases and recurrent diseases.
- Evaluating tumor response to neoadjuvant therapy.

Standard breast-imaging techniques, such as mammography and ultrasound, are still frequently used for diagnosis, clinical staging, and therapeutic monitoring of breast cancer. In recent years, magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET/CT) have also been used frequently. No specific radiological diagnostic criteria are available.

Mammographic breast abnormalities associated with IBC include masses, global skin thickening, and trabecular distortion [24]. Both skin thickening and trabecular distor-

tion are observed in 80% of IBC patients. These abnormalities are also associated with mastitis or locally advanced breast cancer. Calcification and focal mass lesions are less commonly observed in IBC compared with non-IBC. Calcification rates vary from 41% to 47% in different series [24–26].

Ultrasonography is a practical and useful imaging modality in IBC patients. Ultrasound imaging is an important localizing tool for biopsy of underlying masses and nodal involvement. Some authors argue that breast ultrasound imaging is useful in determining the presence of breast parenchymal lesions, which are detected in approximately 95% of breasts affected with IBC [27]. Common sonographic findings include a singular mass or masses (50% of patients with a clinical diagnosis of IBC), skin thickening, heterogeneous infiltration of the breast parenchyma, lymphatic dilatation, lymphadenopathy, architectural distortions, and skin and subcutaneous edema [28]. In addition, ultrasonography may affect locoregional therapeutic planning based on initial disease involvement and is useful for evaluating responses to induction chemotherapy.

More advanced imaging techniques, such as MRI and PET/CT, have an evolving role in IBC. MRI T2-weighted images are particularly promising; this technique is more reliable and accurate in distinguishing between IBC, non-IBC, and acute mastitis [29]. In a study of IBC patients at the University of Texas MD Anderson Cancer Center, breast MRI detected 100% of breast parenchymal lesions, whereas mammography and ultrasound exhibited detection rates of 80% and 95%, respectively [24]. MRI is currently recommended for patients with suspected IBC when a breast parenchymal lesion is not identified on mammography or ultrasonography (Fig. 19.4).

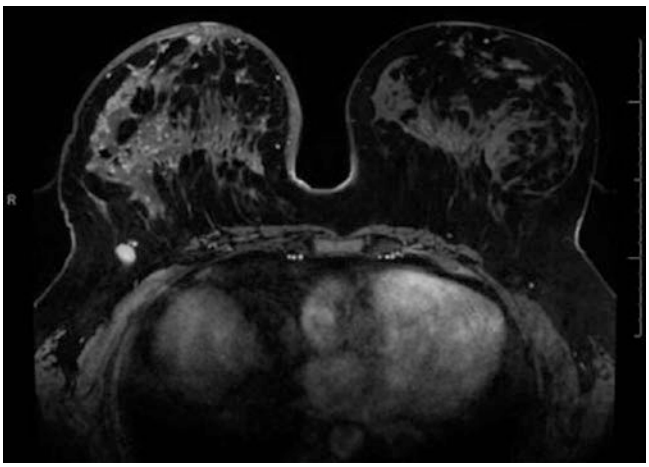

Fig. 19.4 Breast MRI of a patient with right inflammatory breast cancer. Note the large mass-like enhancement and skin thickening on right compared to left. This patient had no palpable breast mass. (*Arrow* denotes an abnormal axillary lymph node)

All IBC patients should be staged at the time of diagnosis because early distant metastasis is detected in approximately 30% of patients at diagnosis. CT of the chest, abdomen, and pelvis along with a bone scan is standard. F18-FDG PET is used as an alternative staging imaging modality in women with locally advanced breast cancer and can be considered in IBC as well [30, 31]. However, the role of PET/CT in IBC diagnoses remains underinvestigated and does not have a defined role [32].

In summary, most authors recommend diagnostic mammogram accompanying ultrasound of the breast and regional lymph nodes as the initial imaging steps for patients with suspected IBC. All patients should be imaged to evaluate distant metastases. MRI and PET/CT have evolving roles in mapping locoregional diseases and documenting distant metastases, but routine use of diagnostic MRI and PET is not recommended [4].

Management of IBC

The management of IBC has changed significantly in recent years, and no standard regimen has been defined for IBC. However, IBC treatment should be multimodal, including systemic therapy, surgery, and radiation. ER/PR status is commonly negative in IBC, and chemotherapy is considered the mainstay systemic treatment [33]. Algorithms for IBC management are summarized in Fig. 19.5.

Primary Systemic Treatment

The widely accepted consensus for the treatment of IBC patients without evidence of distant metastases at the time of diagnosis is systemic chemotherapy followed by surgery and subsequent radiation. An early report from MD Anderson investigators indicated that taxane-based combination chemotherapy was effective as neoadjuvant therapy for IBC [9, 34]. The same group of researchers studied the beneficial effects of adding paclitaxel to fluorouracil, doxorubicin, and cyclophosphamide in a group of 178 IBC patients. The benefits were more obvious in patients with ER-negative disease. Following the combination of these components, taxane-based neoadjuvant chemotherapy has improved the prognosis for IBC when combined with an anthracycline. Twenty years of experience (1974–1993) with anthracycline-based chemotherapy in patients with IBC at MD Anderson resulted in an increase in overall survival rates at 5 years to 40% and at 10 years to 33%. The researchers of this extended study reported the effect of four different multimodal anthracycline-containing protocols for the prognosis of and survival in IBC. Overall clinical response and complete response rates were 72% and 12%, respectively. For patients

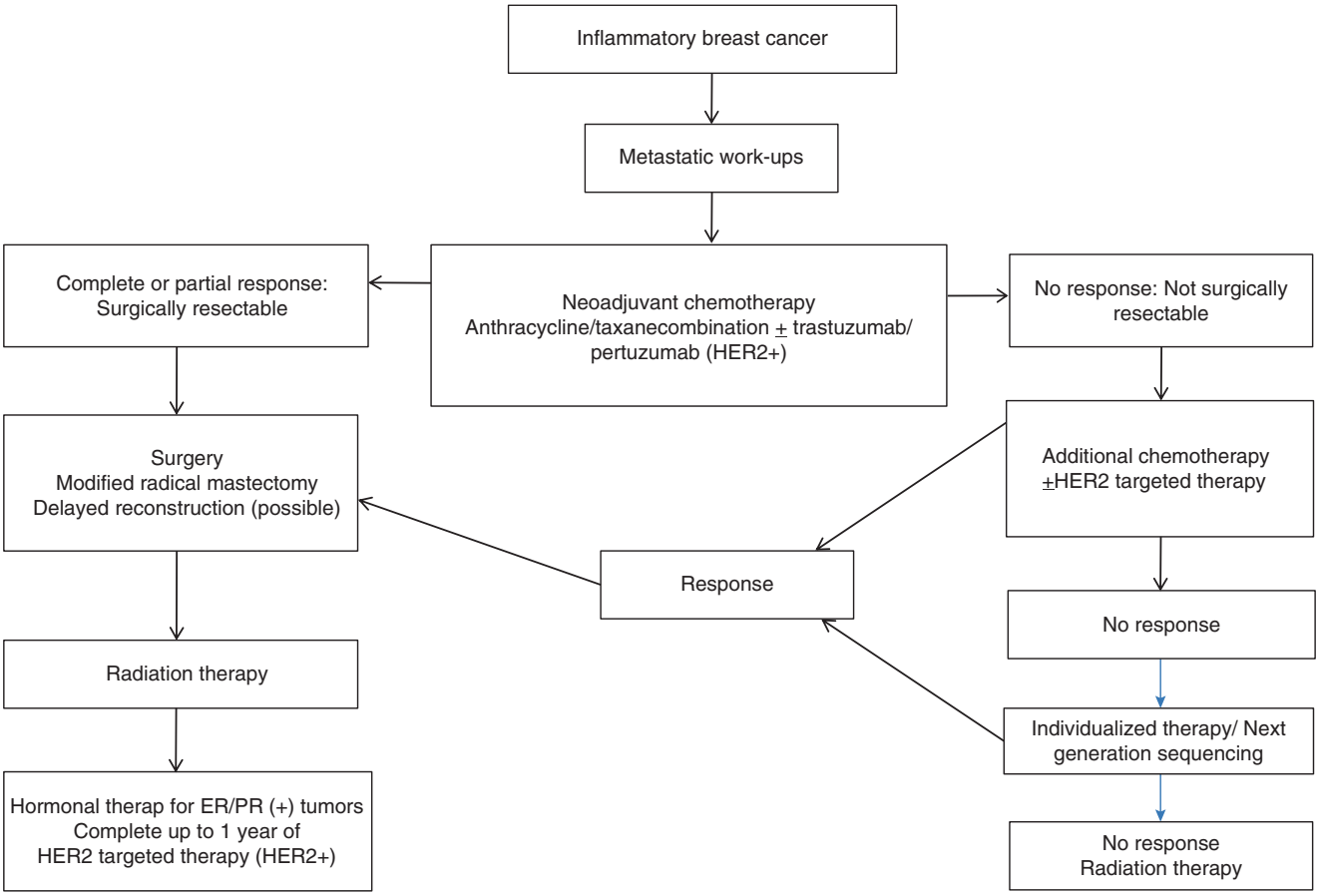

Fig. 19.5 Algorithm for management of IBC. (Adapted from Iniesta et al. [33]. If ER (+) and/or PgR (+) tumor)

on all four protocols, the median survival was 37 months [35–37]. Two prospective randomized trials involving IBC patients treated with three cycles of either cyclophosphamide, doxorubicin, and 5-fluorouracil or cyclophosphamide, epirubicin, and 5-fluorouracil followed by surgical operation, adjuvant therapy, and radiation therapy reported overall survival rates of 44% at 5 years and 32% at 10 years [38].

Several studies have reported a higher incidence of epidermal growth factor receptor 2 (HER2) overexpression in patients with IBC. For patients with HER2-positive disease, trastuzumab and lapatinib therapy (an antibody targeting HER2) may be an option. Anti-HER2 therapy can be administered as a part of neoadjuvant therapy and adjuvant therapy. Women with IBC who receive trastuzumab in addition to chemotherapy exhibit better responses to treatment and survival rates. Several anthracycline-based, anthracycline+taxane-based, trastuzumab-based, lapatinib, and high-dose regimens are preoperatively used in IBC, and their effects on survival are reported in the literature [39–45]. Other targeted therapies, such as those targeting vasculolymphatic pathways (angiogenesis, lymphangiogenesis, and vasculogenesis), RhoC GTPase overexpression, or loss of WISP3, as well as high-dose chemotherapy may be considered for the treatment of IBC in the near future. In the case of hormone receptor-positive patients, tamoxifen or aromatase inhibitor therapy should be started as components of a long-term therapeutic regimen [10, 46].

Locoregional Therapy

Following neoadjuvant chemotherapy (NAC), modified radical mastectomy (MRM) and subsequent radiotherapy are the widely accepted approaches to achieve maximum local control in patients with IBC [47, 48]. A systematic review of studies prior to 1980 of mastectomy alone revealed dismal survival rates of 12% at 5 years, with a mean survival of 19.8 months and local recurrence rates of approximately 50% [49]. A review of more recent studies utilizing multimodality therapy indicated improved locoregional recurrence rates of 20% on average. Other studies of the role of chemotherapy and radiation without mastectomy have reported similar outcomes [35]. However, these studies are small and challenged by other retrospective

studies that demonstrate a benefit to adding MRM. The MD Anderson group reported OS and LRR rates of 48% and 41%, respectively, for complete multimodal treatment compared with 37% and 35%, respectively, for chemotherapy/RT without mastectomy [36]. In the absence of prospective, randomized data, multimodal treatment including MRM should be considered the standard of care. Combined RT and surgery can also provide information regarding the pathological response to NAC. This combination has prognostic significance for both IBC and non-IBC [39]. The aim of the surgery should be to achieve complete resection of residual gross disease with negative margins. The degree of the clinical response of the skin to NAC often underestimates the amount of pathological residual disease, and skin-sparing mastectomy is contraindicated [16]. Axillary lymph node involvement rates are 55–85% in patients with IBC at the time of presentation [5]. Therefore, complete axillary lymph node dissection is a standard approach for IBC patients. Historically, there have been concerns for the accuracy of sentinel lymph node biopsy (SLNB) following neoadjuvant chemotherapy. Although recent data suggests that NAC is not a contraindication to SLNB, this has not been evaluated specifically in IBC patients. In fact, the small numbers of IBC cases included in these studies appear to have higher false-negative rates and higher rates of failed SLNB [49]. SLNB should remain contraindicated in IBC patients. The timing of reconstruction is controversial. Therefore, delayed breast reconstruction is preferred for IBC patients who request reconstructive surgery.

RT is a crucial component of multimodal therapy approaches. All IBC patients undergoing MRM are recommended for postmastectomy RT. RT fields are planned to target the chest wall and possible undissected axillary lymphatics, including supraclavicular-infraclavicular regions and internal mammary lymph nodes. Different approaches for preoperative and postoperative and/or radical RT series in IBC are presented in the literature [35, 36, 39, 48, 50–56]. Pretreatment imaging, including PET/CT, is extremely useful for correlated pretreatment-posttreatment status. Postmastectomy radiation therapy should be provided to all IBC patients, but questions concerning accelerated hyperfractionated radiation therapy, the role of preoperative radiation therapy, and the effect of concurrent chemoradiation remain to be answered.

Metastatic IBC

Up to 30% of women with newly diagnosed IBC have metastatic disease at diagnosis compared with 4% of women with newly diagnosed non-IBC. Metastatic IBC currently follows the same treatment as metastatic non-IBC. At this point, clinical trials should be considered, including phase I trials, if appropriate. Currently, no standard systemic treatment is available for metastatic IBC. No standard approaches are available for locoregional therapy in metastatic IBC patients. Locoregional treatment is challenging, and its effect is limited. It is generally suggested that patients with metastatic IBC should first undergo systemic CT followed by radiation and/or surgery for palliation. No prospective randomized studies have assessed the biological behavior of metastatic IBC. Moreover, the differences in the characteristics of metastatic non-IBC and metastatic IBC are unknown [10, 16].

Follow-Up and Outcome

Following multimodal treatment, physical examinations should be conducted every 3–6 months in combination with yearly mammograms of the contralateral breast. Despite the limited data offered by this procedure, ultrasound of the locoregional lymph nodes may also be considered. However, additional imaging methods and laboratory examinations are not recommended [57].

Again, despite trimodal therapy, IBC remains a fatal and aggressive disease. The expected median survival time for patients with IBC is less than 15 months, with a local recurrence rate of approximately 50% with surgery and/or RT before the introduction of comprehensive multimodality treatment for IBC. In cases of recurrence, suggested management algorithms for these patient scan can be considered for more RT and CT. Currently, overall survival among women with IBC is less than 48 months [40]. Survival analyses of patients with IBC have yielded conflicting results depending on subtypes, such as “clinical-only,” “pathological-only,” or clinical-pathological IBC. Localization, disease stage, patient age, and response to therapy may influence prognosis. IBC survival is 48.5% for ER-positive cases and 25.3% for ER-negative cases according to SEER’s comprehensive data from 1988 to 2002 [5]. Given appropriate treatment, disease-free survival in IBC patients ranges from 24 to 49% at 5 years [1, 6].

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Part IV

Special Therapeutic Problems

Occult Primary Breast Cancer with Axillary Metastases

20

Lejla Hadzikadic Gusic and Ronald Johnson

Introduction

In 2011, an estimated 31,000 cases of occult primary tumors were diagnosed in the United States, comprising 2% of all cancers diagnosed in the United States. Deaths from cancer of unknown primary were estimated to be 45,900 in 2012. Occult primary cancer is defined as the presence of metastatic cancer with an undetectable primary at the time of presentation. This chapter focuses specifically on occult primary breast cancer presenting with axillary metastases, a rare form of breast cancer with an incidence of 0.3–1% across the literature [1–8]. A positive family history has been observed in 20–30% of patients with an axillary presentation of occult breast cancer [2, 9]. First described by Halsted in 1907, this disease process continues to be described in the literature [2, 9]. In 1909, Cameron recommended ipsilateral mastectomy for occult breast carcinoma presenting with axillary metastases, and this remained the standard of care for some time [2, 10]. However, treatment has changed drastically over time in parallel with advancements in the management of primary breast cancer. This chapter examines the clinical presentation, evaluation, and management of occult primary breast cancer with axillary metastases.

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Clinical Presentation

The peak incidence of occult breast cancer is in postmenopausal females (age 50–55), as observed in multiple retrospective studies [1–16]. A patient will typically present to a primary care physician with isolated axillary lymphadenopathy without other physical complaints. Although cancer is in the differential diagnosis, all sources of possible axillary lymphadenopathy must be considered. The differential diagnosis includes disease processes of benign and malignant etiology, including inflammatory processes, hidradenitis, lymphoma, metastatic melanoma, or metastases from the thyroid, pancreas, stomach, colon/rectum, and lung (all references). Another source to consider in the axilla is cancer in the axillary tail or in ectopic breast tissue within a lymph node [2]. An astute primary care physician is critical in the diagnosis of this disease. If the initial workup is not complete, the diagnosis can easily be missed, thus allowing the disease process to continue silently until a more classic or ominous presentation presents, with a timeline from months to years.

Many breast surgeons contribute to the education of their local communities about breast cancer by providing various presentations to both the medical community and the general public. Particularly in presentations to the medical community, it is important to include the rare presentation of occult breast cancer presenting as axillary metastases and to thoroughly review the workup required to ensure that this diagnosis has been considered and investigated.

Initial Evaluation

When a patient presents with isolated axillary lymphadenopathy, a complete history should be obtained that includes a thorough review of risk factors for breast cancer by inquiring about the patient's history of childbearing, start and end of menses, and any past use of hormone therapy. Past breast biopsies should be reviewed, as should any pathology,

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inquiries about any nipple discharge or eversion, or masses palpated by the patient. Perhaps most importantly, a thorough family history of cancer should be evaluated, focusing on breast and gynecological malignancies. It is important to ask if there is a paucity of women in the family on either the maternal or paternal side, as this may complicate the discernment of a familial pattern and should not be overlooked. Once the history has been completed, a complete physical exam should be performed, focusing on a thorough breast exam with the patient in sitting and supine positions and with arms placed at the side as well as overhead. The head and neck nodes and both axillae should be carefully examined. Once a complete history and physical exam have been conducted, a search for the primary disease should begin after a differential diagnosis has been formulated. Once other disease processes have been ruled out and breast cancer has become a concern, the search for a breast primary cancer must proceed in a logical manner. National Comprehensive Cancer Network (NCCN) guidelines suggest starting with a mammogram and/or breast ultrasound for women and/or a CT of the neck, chest, abdomen, and pelvis for either men or women. Mammograms can detect a primary lesion in 7–29% of clinically false-negative cases [9, 14]. If these examinations are negative, proceeding with an MRI is the next step in the current NCCN guidelines. If presented with imaging from an outside institution, the physician and the physician's radiology department should thoroughly review the images to confirm the findings and determine if the imaging is adequate in quality and extent. Pathology from an outside institution should also be reviewed thoroughly. When available, fine needle aspiration (FNA) or core needle biopsy (CNBx) of the isolated axillary lymph node must be reviewed to confirm the diagnosis. Specifically, the sampled material should be evaluated for cytokeratins, specifically CK7 + 20− (90% of breast cancers have this cytokeratin/keratin distribution), and immunohistochemical markers such as GCDFP-15 and mammaglobin, ER/PR, and MABm4G3 [11]. However, only 50–60% of breast cancers are ER/PR positive; thus, a negative result does not rule out breast cancer [3, 9, 15]. Generic assessments such as CBC, liver function tests, and alkaline phosphatase, with inclusion of cancer markers such as CEA, should also be performed [11].

Imaging

As stated above, diagnostic mammography should be the first attempt to identify the location of a primary breast tumor. There can be significant variation between the quality of mammography and additional views; thus, the clinician must ensure that high-quality diagnostic mammography is performed. Ultrasound should be used as an adjunct to mammography to search for masses. If these modalities fail to find a primary lesion, the NCCN guidelines suggest that a bilateral MRI be performed. MRI is able to identify the primary tumor in 75–86% of mammographically negative patients [7, 8, 14, 15]. MRI has a reported sensitivity of 88–100% for detecting breast masses. The specificity, however, is much lower, with some reports indicating values as low as 35% [14]. In one study, among patients with a negative MRI, tumors were identified in pathology specimens from mastectomy in two of eight patients (25%) [15]. Additional studies are indicated only if signs or symptoms suggest additional disease. For example, a bone scan is indicated if a patient describes localized bone pain or if alkaline phosphatase levels are elevated. Abdominal and pelvic CT scans are indicated if there are elevated liver function test values, if the patient exhibits abdominal symptoms, or if the physical exam of the abdomen or pelvis is abnormal. Chest CT is indicated if the patient presents with pulmonary symptoms. PET has been used experimentally to detect breast disease but has not yet been endorsed for routine use in this scenario [2, 11].

NCCN Guidelines for the Treatment of Occult Primary Breast Cancer

Due to the low incidence of this disease presentation, only a few small retrospective studies are available for review. Regardless of when these studies were conducted, they present a similar picture of how a patient may present and how the management has changed over time. There are no prospective trials on this topic, and a prospective trial will likely never be conducted given the low incidence of occult primary breast cancer. We thus rely on these retrospective studies, which were taken into account when establishing the NCCN guidelines, to provide options for the treatment of this disease.

According to the NCCN guidelines, after a comprehensive workup has been performed and a primary breast cancer has been identified, treatment should be performed according to the clinical stage of the breast cancer. However, if the workup determines no primary breast cancer, there are specific guidelines for men and for women. A patient without an identified primary breast cancer but with an isolated axillary lymph node proven to be of breast origin is designated as T0N1M0–T0N2M0 or stage II/III [13]. Therefore, the NCCN guidelines for stage II/III breast cancer are followed for locoregional treatment. For men, the guidelines state that an axillary lymph node dissection (ALND) should be performed; following this, radiotherapy and chemotherapy should be administered if clinically indicated. For women, the guidelines state that for those with MRI-negative disease, treatment should be based on nodal status. For patients with T0N1M0 disease, the options include traditional mastectomy and ALND with or without postmastectomy radiation or axillary nodal dissection followed by whole-breast irradi-

ation with or without nodal irradiation. Systemic chemotherapy, endocrine therapy, or anti-HER2 therapy should be administered according to the pathological status of the disease. Patients who present with T0N2M0–T0N3M0 disease should be considered for neoadjuvant chemotherapy and/or neoadjuvant anti-HER2 therapy and endocrine therapy, followed by axillary nodal dissection and mastectomy [11].

Literature Review

As mentioned above, the standard treatment of occult breast disease presenting as axillary metastases has historically been total mastectomy and ALND. This technique has traditionally yielded occult cancer in approximately two-thirds of patients. However, pathological evaluation of the removed breast fails to show carcinoma in one-third of these patients, suggesting that the surgery was unnecessary [9]. If locoregional treatment of the axilla and breast are separated, several options exist. Here, we examine select retrospective studies to review the data. For the axilla, we can consider radiation vs. ALND, although most retrospective series included ALND unless the patients refused surgical treatment [1, 2, 7–10, 12–16].

For locoregional treatment of the breast, we consider mastectomy vs. whole-breast radiotherapy vs. segmental mastectomy vs. observation. The Memorial Sloan-Kettering Cancer Center series demonstrated that 45% of the identified occult cancers were multifocal, suggesting that partial mastectomy of suspicious areas on mammogram or MRI might miss additional disease [9]. When the ipsilateral breast is left untreated in occult breast cancer following ALND, clinical disease in the ipsilateral breast develops in approximately 40% of patients [12]. Therefore, it is prudent to consider some form of treatment to the ipsilateral breast, despite the absence of a definite primary. Baron et al. observed no 5-year survival benefit of mastectomy vs. breast preservation. They suggested that omitting mastectomy in the treatment of occult breast cancer is a valid option and that salvage mastectomy should be reserved for recurrences if the breast received prior whole-breast radiation [9]. To evaluate the role of ipsilateral breast radiotherapy, Barton et al. and Masinghe et al. compared outcome data for patients with occult primary breast cancer presenting with axillary metastases treated with breast preservation and radiotherapy vs. observation. Patients who had radiotherapy to the preserved breast exhibited superior 5-year local recurrence-free survival (84% vs. 34%, $p < 0.001$) and relapse-free survival (64% vs. 34%, $p = 0.05$). Barton et al. also observed no difference in overall survival [12]. Barton et al. did not observe a difference in 5-year local recurrence-free survival between the traditional dose of 50 Gy in 25 fractions and doses >60 Gy, suggesting that additional doses are not necessary [12].

In a series at MD Anderson, no difference in survival was observed between patients whose breast was preserved compared to those who underwent mastectomy, indicating that local therapy to the breast in occult breast cancer need not necessarily include removal of the breast [1]. This sentiment was echoed by Galimberti et al. [2]. Merson et al. actually observed no difference in survival between whole-breast radiation or breast surgery compared to observation only and agree that less treatment to the breast is better than more [4]. They also noted that the primary tumor distribution observed no pathological sectioning and was no different from the distribution in common cases of primary breast cancer, with ductal invasive histology as the predominant type.

Wang et al. demonstrated that patients who underwent mastectomy had better disease-free survival and overall survival compared with those who had no local therapy to the breast. Their series, however, did not include a group with other local therapies to the breast [16].

Another MD Anderson series used SEER data from 1983 to 2006 to perform a population-based analysis of T0N1M0 breast cancer. This study included four groups: observation (i.e., no treatment), ALND only, TM + ALND plus or minus postmastectomy radiotherapy (PMRT), and breast conservation therapy with ALND and XRT. Patients who underwent definitive locoregional treatment with either mastectomy or breast conservation therapy with ALND and XRT to the breast had significantly increased 10-year overall survival compared with patients who underwent ALND only or observation (65% compared with 59% and 48%, respectively). There was no difference in the 10-year cause-specific survival for breast conservation therapy with ALND and XRT compared to mastectomy. Multivariate analysis revealed that ER-negative tumors, >10 positive lymph nodes, and <10 resected lymph nodes were correlated with an unfavorable outcome. This population-based SEER analysis included 750 patients, making it the largest study to date, and supports the conclusions of smaller retrospective studies that locoregional treatment of occult breast disease does not necessarily include mastectomy. This series, published in 2010, also confirmed that in recent years the trend for treatment has favored whole-breast radiation without mastectomy [15].

Khandelwal and Garguilo conducted a survey of the American Society of Breast Surgeons (ASBS) of surgeons' preferences for management of the breast in occult primary breast cancer presenting with axillary metastasis. With a response rate of 42%, they observed that despite recent literature supporting the use of whole-breast radiation, 43% of responders preferred mastectomy, whereas 37% opted for whole-breast radiation [14]. This suggests that the correct treatment of this rare form of breast cancer remains controversial in the surgical community.

Even more disputed is modern breast conservation therapy, i.e., partial mastectomy or quadrantectomy, in the setting of occult primary breast cancer, suggesting that resection may be performed based on an abnormality deemed suspicious on imaging despite negative pathological analysis by biopsy. Several of these retrospective studies have included patients who received a partial mastectomy or quadrantectomy as their surgical treatment, although these patients and those who received mastectomy were not compared directly [2, 4, 9].

Although mostly comprised of small retrospective studies, the data available to us suggest no survival benefit or locoregional control benefit of mastectomy compared to whole-breast irradiation with breast preservation. Due to the low incidence of this disease, there will not likely be any future prospective study on this topic; thus, we are left to interpret the currently available data. Given this information and the cosmetic advantage of breast preservation, whole-breast irradiation has become the treatment of choice [9, 12, 14].

Adjuvant Systemic Therapy

In their series, Baron et al. demonstrated that there was no statistically significant survival benefit for those patients who received adjuvant chemotherapy compared to those who did not, with 5-year survival rates of 79% vs. 77%. They note, however, that this result suggests a benefit of adjuvant therapy because patients with positive nodes should have had decreased survival [9]. Ellerbroek et al. also reported no survival benefit of chemotherapy but did note a trend in favor of chemotherapy, concluding that all patients should be treated according to the same guidelines matched stage for stage as patients with a known breast primary [1]. Most other studies, as well as NCCN guidelines, recommend adjuvant chemotherapy and hormone therapy when appropriate, similar to the guidelines for staged disease of a known primary breast cancer. The current NCCN guidelines also endorse neoadjuvant chemotherapy for N2 disease [11].

Survival Data and Prognosis

As noted in the above series, no difference in survival has been demonstrated for mastectomy vs. whole-breast radiotherapy for definitive locoregional treatment of the breast in occult primary breast cancer. Less radical treatment appears to correlate well with the reported better prognosis of this presentation of breast cancer compared to matched stage II/III cancer with a breast primary [2, 4]. Some studies have also reported worse and equivalent survival among matched groups, but the overall trend is toward an improved prognosis. However, there has been some evidence of improved disease-free and overall survival in certain circumstances and treatment options. This section examines these data.

Baron et al. reported that patients who underwent an ALND following a positive lymph node biopsy had the same 5- and 10-year survival rates, both 80%, if all subsequent nodes were negative, compared with rates of 72% and 43%, respectively, if at least one other node was positive on the final pathological examination [9]. Ellerbroek et al. also noted that local control and survival were improved at 5 years for N1 compared with N2 disease [1, 4, 5, 14, 16]. Baron et al. also noted that 5- and 10-year survival did not significantly differ for patients in whom the primary breast cancer was found on final pathological examination compared to those in whom it was not discovered. They also demonstrated decreased 5- and 10-year survival for patients who were ER negative compared with those who were ER positive [9].

Montagna et al. specifically compared 80 patients with occult primary breast cancer to 80 patients with early-stage breast cancer. The groups were matched for age, nodal status, and biological features, and immunohistochemical differences, and outcomes were compared. No significant differences in disease-free survival (DFS, 66% vs. 68%) and overall survival (OS, 80% and 86%) were observed between the two groups; however, the findings did add to the existing literature indicating a worse prognosis for occult breast cancer with more than four involved lymph nodes and triple-negative tumors [5].

Ductal Carcinoma In Situ (DCIS)

Interestingly, the reported rate of axillary lymph node metastases among patients with DCIS is 1–2% in the literature. By definition, DCIS is an in situ disease and cannot metastasize, but there have been reports of its metastasis in the literature [2, 16]. The significance of these findings remains unclear; however, this phenomenon is another indication that we do not yet fully understand the mechanism of this disease and the tumor/host relationship.

Looking Forward: What Does the Future Hold?

This rare occurrence of breast cancer remains controversial. The low incidence of this cancer precludes prospective trials; thus, we must rely on retrospective data to make evidence-based conclusions.

The treatment of occult breast cancer with axillary presentation is a particularly interesting topic in light of the recent trend of less invasive axillary treatment. The recent findings of ACOSOG Z11 suggested that complete axillary dissection is not necessary in postmenopausal women with

hormone receptor-positive disease treated with breast conservation therapy, including lumpectomy and whole-breast irradiation, with findings of limited disease in the axilla after a sentinel lymph node biopsy [17]. In the specific population of women studied, who had limited nodal disease and were treated with breast conservation therapy, a completion axillary nodal dissection did not improve survival. With careful patient selection, this has greatly affected current therapy and will likely continue to do so.

Similarly, the findings of ACOSOG Z1071 suggest that in women with biopsy-proven node-positive disease, a negative sentinel lymph node biopsy may be sufficient axillary treatment after neoadjuvant chemotherapy [18]. The examination of two or more sentinel nodes had a false-negative rate of 12.6% among women with residual N1 nodal disease, based on the completion of ALND. The false-negative rate decreased to 9.0% when at least three sentinel lymph nodes were removed, which has significant implications for women presenting with nodal disease who will undergo neoadjuvant therapy. The literature suggests that 34–40% of node-positive women convert to node-negative status following systemic therapy. Recent data suggest that in this cohort of women, ALND is not indicated, which would prevent a significant number of women from experiencing complications such as lymphedema.

As treatments for the staging and treatment of the axilla in breast cancer develop, it will be interesting to observe how these developments affect the treatment of occult primary breast cancer presenting with axillary metastases.

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Breast Cancer in Older Women

21

Soley Bayraktar and Adnan Aydiner

Introduction

Breast cancer (BC) remains principally a disease of old age, and 35–50% of cases occur in women older than 65 years. For the period 2004–2008, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) reported that approximately 40% of BCs were diagnosed in elderly women: 19.7% in women aged between 65 and 74 years, 15.5% in women between 75 and 84 years, and 5.65% in those aged 85 years and older [1].

BC of the elderly most often displays favorable biological characteristics, i.e., luminal molecular subtype, presence of hormone receptors (HR), low mitotic rate and nuclear grade, absence of p53 mutations, and no overexpression of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2) [2, 3]. However, these features have not historically translated into better outcomes in older vs. younger patients [1]. The improvement in 5-year survival observed in recent decades in developed countries in all classes of ages is less evident for older women [4]. Mortality for BC in the United States has decreased by 24% between 1990 and 2000, mostly in younger women (3.3% per year) and less for older women (2% per year) [1]. Various reasons have been proposed to explain this paradox, such as the competing risks of death from other diseases or the possibility that tumors exhibiting the same markers but arising at young vs. old age behave differently. It has also been argued that adherence to treatment guidelines is poor and, in particular, that systemic chemotherapy is frequently not delivered in advanced age because of the concern of toxicity [5]. The fact that elderly subjects have been underrepresented in clinical trials, resulting in a lack of evidence-based data, has probably strengthened the tendency to omit chemotherapy in this population. In this chapter, the role of screening, diagnosis, and treatment of breast cancer in older women and some of the special considerations relevant to this population of patients will be reviewed.

Screening

Several randomized trials have demonstrated mortality reduction from regular screening mammograms [6, 7]. Only some of these studies included older women, and the available information from women aged 70 or older is therefore limited [8]. Therefore, it is not surprising that countries around the world have developed guidelines regarding the age at which to start mammographic screening and the frequency of screening; however, the age at which screening by mammography may lose its benefit is unknown.

The Swedish Two-County Trial included women aged 40–74 and revealed a significant reduction in breast cancer mortality in women who underwent a screening mammography [9]. The Malmo trial included women aged 45–69 years at the start of the trial and concluded that women older than 55 had a 20% reduction in mortality from breast cancer [10]. Another study reported by Van Dijck et al. evaluated breast cancer mortality in women aged 68–83 years. The control group included women from the same birth cohort in a neighboring city without a screening program. The women were enrolled from 1977 to 1978 and were followed until 1990. The cumulative mortality rate ratio was 0.80 (95% CI = 0.53–1.22). The cumulative mortality rate ratio decreased to 0.53% (95% CI = 0.27–1.04) 9–13 years after screening. Based on the follow-up data, the authors concluded that mammographic screening in women over 65 years of age yielded a 40% reduction in breast cancer mortality after 10 years [11].

Another interesting finding is that early-stage BC is detected less frequently in elderly women than in younger patients [12]. For example, T1 tumors are observed in 70% of patients between 45 and 64 years of age but only 47% of

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women over 75 years [13]. This difference further highlights the fact that elderly women undergo mammography less frequently.

Given the anxiety, false positives, additional tests, and procedures that may result from a mammogram, screening in this group may not always be beneficial. However, it has been demonstrated that the false-positive rate decreases slightly with older age [14]. Currently, women who are in good or moderately good health with a reasonable life expectancy are considered appropriate for screening mammograms. The patient and the clinician should each consider the potential benefit and harm of the test as well as whether the patient would be amenable to undergoing diagnostic tests and therapeutic treatment should an abnormal finding be discovered.

Breast Cancer Treatment in Elderly Women

Surgical Treatment Options

Many studies have shown that older breast cancer patients in good health can obtain the same benefit from adequate treatment as [15, 16] younger patients. Livi et al., in a study of 15,500 women over 65, found that the type of surgery, histotype, pN status, and pT status were the only independent prognostic factors, whereas age was not a prognostic factor for disease-specific survival or disease-free survival. It is important to offer older women the same treatments offered to younger women unless unworthy due to limited life expectancy. Otherwise, age becomes not only a risk factor for BC but also a poor prognostic factor [17].

Most elderly women can tolerate breast-conserving operations and mastectomies; the mortality during surgery ranges from 1% to 2% according to previous studies that applied old anesthesia techniques. However, after advances in anesthesiology, the rate of surgical mortality in elderly patients without other health problems has decreased [18]. Despite the documented safety and efficacy of breast operations in the elderly, common clinical practice is substantially different. For example, in some countries, up to 50% of elderly patients do not undergo surgery [19]. Moreover, according to a multinational study, the vast majority of patients (92%) over 80 receive hormonal therapy without any surgery [20].

The surgical management of the axilla in older women should be similar to that in younger women. In older women with no palpable lymph nodes, forgoing lymph node dissection in early BC has almost no effect on OS, as shown by the low frequency of recurrence in the axillary lymph nodes [21, 22]. The practice-changing American College of Surgeons Oncology Group trial (Z0011) showed that patients with positive sentinel lymph nodes who did not undergo axillary dissection did not have worse 5-year survival [23]. In the European Organisation for Research and Treatment of Cancer (EORTC) AMAROS trial (310 of 1425 sentinel lymph node-positive patients were over 65 years of age), axillary irradiation was evaluated as an alternative to axillary dissection. The results indicated that the axillary node status did not influence the administration of adjuvant radiotherapy, suggesting that axillary radiotherapy is an acceptable option [24].

Furthermore, elderly patients generally undergo less aggressive local operations, without any postoperative radiation therapy or chemotherapy [25]. Yood et al., in a cohort study of 1837 women aged 65 or older treated for stage I or II breast cancer, observed a significative difference between those treated with standard surgery [mastectomy or breast-conserving surgery (BCS) + radiotherapy] and those who received BCS alone. At 10 years follow-up, the risk of death for those who underwent BCS alone was double that for those who had undergone standard surgery, even after adjustment for demographics and tumor characteristics [17].

Moreover, age often becomes a reason to overlook aesthetics and psychophysical aspects. Wang, in a survey of 31,298 patients with early BC from Australia and New Zealand between 1999 and 2006, observed that women older than 70 years were more likely to receive mastectomy in place of breast-conserving surgery or no surgery at all (3.5%) than their younger counterparts [26]. Research has also shown that postmastectomy reconstruction is associated with improved patient quality of life; however, overall reconstruction rates continue to be low in the United States and decrease with increasing patient age [27].

Systemic Chemotherapy

Delivery of chemotherapy is a more complicated decision in elderly patients because the patients' wishes, estimated life expectancy, presence of comorbid conditions, and estimated benefit from treatment should be considered before any type of adjuvant therapy. According to a systematic review [28], there are age-related differences in the pharmacokinetics of breast cancer treatments containing anthracyclines (reduced clearance) and platinum agents (reduced creatinine clearance), as in all neoadjuvant chemotherapy protocols. However, the clinical relevance of these differences is questionable. Nevertheless, in recent years, there has been a reappraisal of the balance between the benefits and side effects of chemotherapy for older patients with BC.

With the exception of high-risk patients, who receive clear benefits, the efficacy of adjuvant chemotherapy in elderly BC patients with hormone receptor-positive status is debated. Paik et al. observed that only patients with a high risk of developing metastases within 10 years benefit from chemotherapy administration [29]. In addition, the CALGB

and United States Breast Cancer Intergroup have shown that chemotherapy mostly benefits patients with negative hormone receptor status [30]. Likewise, the Early Breast Cancer Trial Group demonstrated that adjuvant chemotherapy was beneficial for patients up to 70 years of age, although the efficacy decreased with age [31]. Similarly, a retrospective study that compared tamoxifen adjuvant monotherapy against a combination of tamoxifen and anthracycline-based chemotherapy in BC patients (29.4% of patients over 65 years) with positive ER status and infiltrated lymph nodes found that survival was not improved as long as the recurrence score was low [32].

Adjuvant chemotherapy has historically included four cycles of doxorubicin and cyclophosphamide (AC) or six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). These regimens have been shown to notably improve BC survival [33]. In addition, regimens such as cyclophosphamide/doxorubicin/5-fluorouracil, cyclophosphamide/epirubicin/5-fluorouracil, or AC plus four cycles of taxanes have recently been shown to be somewhat more effective than standard CMF or 4 AC therapies [34]. In a recent trial with women aged 65 years or older, both AC and CMF were found to be superior to capecitabine monotherapy in terms of both relapse-free survival (85% vs. 68%, respectively) and OS (91% vs. 86%, respectively) after 3 years of follow-up [35]. In addition, four cycles of docetaxel/cyclophosphamide were found to be superior with regard to DFS and OS compared to standard 4 AC, not only in younger patients but also in older women [36]. Hence, third-generation regimens such as dose-dense AC and paclitaxel, AC followed by docetaxel, or the combination of docetaxel/doxorubicin/cyclophosphamide are recommended for patients without major health problems but with a very high risk of recurrence [33]. It is now recommended not to consider age as an exclusion criterion for cancer treatment as long as survival for a significant period of time is likely and the burden of comorbidity is low [37]. However, the toxicity of chemotherapy is enhanced at older ages [15].

In patients with triple-negative breast cancer, the majority of relapses occur less than 5 years after diagnosis [35], and chemotherapy is not likely to be of value to patients with short life expectancy. We suggest calculating the benefits of chemotherapy using the PREDICT model [38], which provides 5- and 10-year survival estimates of the benefits of chemotherapy based on patient age and clinical factors (although this model is less accurate in older women and in women with hormone receptor-negative tumors) [29]. Chemotherapy should be discussed with women who have a projected overall survival benefit of 3–5% at 10 years, and chemotherapy should be considered when its 10-year survival benefit exceeds 5%. The author suggests using a nonanthracycline regimen, such as four to six cycles of TC, rather than an anthracycline and taxane regimen unless the latter regimen improves the patient's estimated 5-year survival by more than 2% in the PREDICT model. This approach represents a trade-off between less toxicity and a questionably shorter survival for the nonanthracycline regimen.

The neoadjuvant use of chemotherapy is not usually offered, partly because it is less investigated in this population [39]. For some physicians, neoadjuvant chemotherapy is only an option for elderly patients with inflammatory breast cancer or with locally advanced inoperable breast cancer. A recent analysis [40] of eight GBG trials showed the high and independent impact of age on pathologic complete response (pCR) as well as the association of age with prognosis for patients undergoing NACT. Some other studies have reported that women >65 years have a lower pCR rate and detrimental prognosis as well as higher toxicity compared to those of younger women [41, 42]. Likewise, a recent analysis found that pCR was dependent on age, with the lowest values for elderly patients >65 years of age (11.7%) and increasing with decreasing age. The highest pCR rate was observed in the group of women <40 years of age (20.9%) [43]. In the same study, multivariate analyses of molecular subgroups also showed that age >65 years is a predictor of significantly lower pCR in TNBC, HR+/HER2−, G3, and N+ breast cancers. By contrast, the pCR rates in our analysis were not different between elderly and younger patients in the histological subgroups HR+/HER2+ and HR−/HER2+. As HER2+-specific therapies, such as trastuzumab, are routinely added to chemotherapy, this effect may dominate the age-dependent absolute effect of chemotherapy. For overall survival, we observed a significantly worse outcome for patients >65 years compared to women 51–65 years of age and women 40–50 years of age.

Metastatic breast cancer remains incurable regardless of patient age, and all treatment is palliative. The median survival time for patients with metastatic triple-negative breast cancer is approximately 14 months [44]; in general, older age is a risk factor for early death (within 1 month of diagnosis) in those who present with de novo metastatic breast cancer [45]. Several single agents are recommended as preferred single agents. Capecitabine, weekly paclitaxel, nab-paclitaxel, eribulin (as second- and third-line treatment), liposomal doxorubicin, vinorelbine, and gemcitabine have been studied in older populations, and the choice should be based on toxicity profile. As first-line treatment, response rates vary greatly according to patient characteristics and average approximately 30–50%, whereas progression-free survival averages approximately 3–6 months. Second- and third-line therapies are less effective. Several new agents show promise. Olaparib, a poly(ADP-ribose) polymerase inhibitor, was associated with a significant improvement in progression-free survival compared with that of the treating physician's choice of therapy (7 months vs. 4.2 months) in a phase III trial of patients with BRCA germline mutations;

however, as with most trials of newer agents, only a small number of patients (n = 15) were 65 years of age and older [46]. Modulating the immune system using checkpoint inhibitors also shows promise, but almost no data are available in older breast cancer patients [47]. While frail older patients may occasionally benefit from chemotherapy, for most, the value of chemotherapy will be modest at best; these patients should all be considered for palliative and hospice care.

Targeted Therapy

As aforementioned, HER2 positivity is relatively uncommon in BC of the elderly. Nonetheless, there is already extensive experience with the use of the HER2-targeting antibody trastuzumab in the geriatric population with HER2-expressing tumors [48, 49]. Registry-based retrospective analyses have reported an incidence of congestive heart failure (CHF) of approximately 25% in elderly women receiving trastuzumab compared with 10–15% in those not given any therapy for BC, and the risk of CHF has been estimated to be twofold higher in >60–65-year-old trastuzumab users vs. non-users [50–52]. Extremely advanced age and preexisting cardiac disease have been shown to predispose trastuzumab cardiotoxicity. By contrast, the HERA trial did not demonstrate a significant difference in cardiac adverse events between patients older or younger than 60 years [53].

The combination of weekly paclitaxel and trastuzumab has also been studied in 406 patients with small (<3 cm), node-negative Her2-positive disease. Although this was a single-arm phase II study with no specific focus on the elderly population, the relapse rate was encouragingly low (3-year DFS: 98.7%), and the combination was relatively non-toxic (0.5% incidence of symptomatic heart failure) [54]. Weekly paclitaxel plus trastuzumab is therefore a potential treatment alternative for elderly patients with stage I disease or who are not suitable for standard polychemotherapy.

RESPECT (N-SAS BC07) is a prospective phase III multicenter trial aiming to compare the efficacy and safety of trastuzumab monotherapy vs. standard trastuzumab in combination with chemotherapy [55]. The results are awaited and may be particularly useful for elderly patients with contraindications to or unable to tolerate chemotherapy. For now, there are no clinical data available for treatment with trastuzumab alone in patients who are not candidates for chemotherapy; however, the 2013 St. Gallen consensus supports that if chemotherapy cannot be given in certain situations, then it might be reasonable to give trastuzumab without chemotherapy [56].

Lapatinib is another targeted drug that interrupts the HER2 and epidermal growth factor receptor pathways. A multicenter, randomized phase III trial recently documented lapatinib as an accepted treatment option for trastuzumab-naïve HER2-positive early-stage BC women who do not or cannot receive adjuvant trastuzumab [57]. However, more data are needed to elucidate the role of lapatinib in early-stage BC in elderly patients. To minimize the risk of cardiac toxicity, we suggest that the selection of older patients for treatment with trastuzumab should be primarily based on their general status and the presence of comorbidities; previous chemotherapy, especially with anthracyclines, should also be taken into account. Once therapy has started, efforts should be made to ensure regular cardiac surveillance. The role of selected biomarkers, such as cardiac troponin, or new imaging techniques (three-dimensional, tissue Doppler echocardiography, magnetic resonance imaging), is promising but must be further investigated, especially in the elderly [58].

Systemic treatment options for recurrent or metastatic HER2-overexpressing breast cancer are shown in Fig. 21.1.

Endocrine Therapy

Regarding endocrine therapies, the use of tamoxifen in women with receptor-positive tumors is a relatively simple decision in light of its favorable toxicity profile [16]. Tamoxifen has been proven to significantly reduce the chance of developing distant metastasis in node-negative elderly patients with invasive tumors [59]. Muss observed that older women can expect the same improvement in survival from endocrine therapies as younger women when HR positive [31]. According to the Early Breast Cancer Trialists' Collaborative Group overview, 5-year adjuvant therapy with tamoxifen in women of all ages with positive ER and PR status reduces the frequency of yearly BC relapse by more than 39% and mortality by more than 31% regardless of age [60]. Yood, in the cited paper, reports significantly longer survival in patients assuming tamoxifen for 5 years or more than in those who had HT for 1 year or less [17] (Fig. 21.2).

Several large-scale randomized trials have demonstrated that adjuvant treatment with aromatase inhibitors (AIs) provides additional benefits compared to tamoxifen treatment, but only a small proportion of the participants in these studies were elderly [61–63]. The Breast International Group 1–98 study, which compared letrozole treatment to tamoxifen therapy in a cohort of 8010 patients (36% aged 65 or over) with a median follow-up time of 5 years, demonstrated

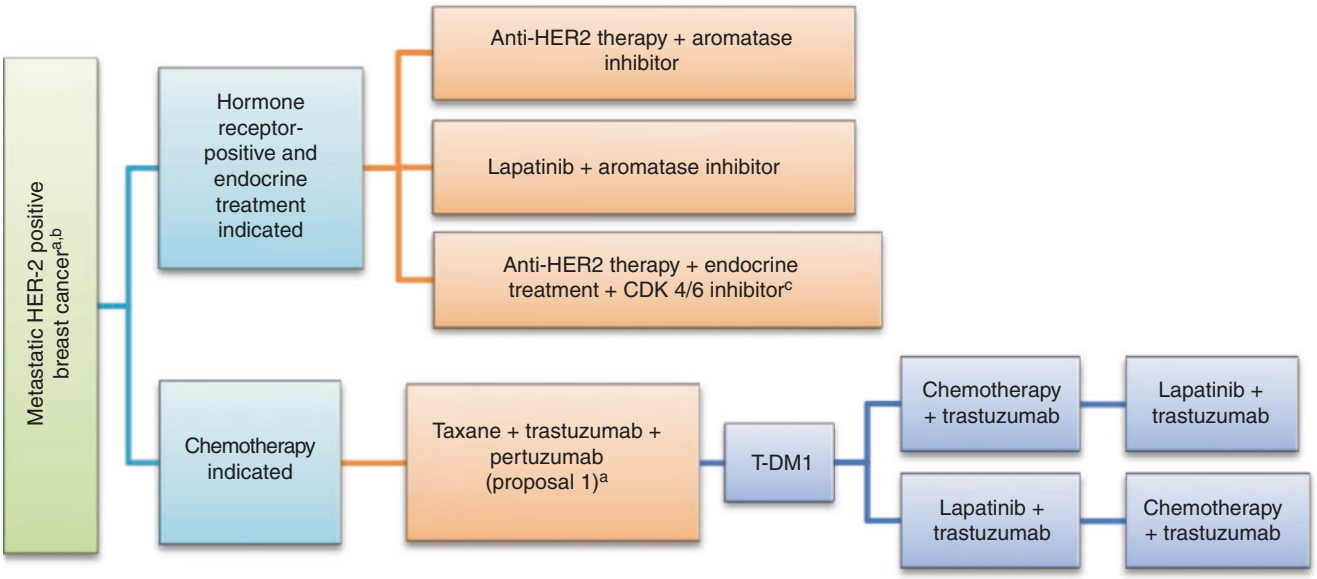

Fig. 21.1 Systemic treatment of recurrent or metastatic HER2-overexpressing breast cancer. [a]Administration of ado-trastuzumab emtansine and pertuzumab was not superior to treatment with chemotherapy + trastuzumab or ado-trastuzumab alone as the first choice treatment in HER2-positive disease. According to the PERTAIN trial, addition of pertuzumab to trastuzumab and endocrine treatment in the first choice prolonged progression-free survival. The addition of pertuzumab in the second choice in patients who did not receive pertuzumab in the first choice provided a minor clinical benefit. [b]T-DM1 may be used as the frontline therapy if the patient develops metastasis within 6 months of finishing adjuvant therapy with anti-HER2 treatment. [c]Clinical trials are ongoing for anti-HER2 therapy + endocrine treatment + CDK 4/6 inhibitor

that letrozole was superior in terms of local and distant metastasis reduction, decreased contralateral BC development, and improvement of DFS irrespective of age [64, 65]. Furthermore, treatment with tamoxifen can result in a range of adverse effects, and their co-evaluation is significant, particularly for the elderly. More specifically, tamoxifen treatment in women aged 70–79 years increases the absolute risk of endometrial carcinoma (2.2%), strokes (2%), thromboembolic episodes (0.5%), and cataracts (3.8%). By contrast, administration of AIs poses a lower risk of developing endometrial cancer, thromboembolism, vaginal hemorrhage, and hot flushes compared to administration of tamoxifen in any age group. However, arthralgia, myalgia, bone loss, and synovial pain occur more frequently with AIs [66, 67].

According to the St. Gallen 2015 consensus, some postmenopausal patients could be treated with tamoxifen. However, it was strongly suggested that women at high risk (involvement of four or more nodes, grade 3, high Ki-67, or HER2 positivity) should be treated with AIs upfront and then switched to tamoxifen treatment. AIs can also be administered beyond the first 5 years in node-positive patients treated initially with tamoxifen or for less than 5 years with AIs. No consensus has been reached on AI administration after the first 5 years of AI treatment [56, 68].

One may consider omitting endocrine therapy in patients with very small tumors (≤5 mm) or those with multiple comorbidities. Data from a population-based cohort study suggest that omitting adjuvant systemic therapy produces similar OS compared to that of the general population for women aged 60–74 years with ≤10-mm, node-negative, hormone-sensitive, and grade 1 ductal carcinoma or grade 1 or 2 lobular carcinoma [69]. Despite the benefits of endocrine therapy, it is true that many patients 80 years of age or older show poor compliance or are unable to correctly receive medications, which can result in a higher risk of side effects or even be fatal [70].

In patients with a short life expectancy in whom surgery may not be feasible, primary endocrine therapy can effectively control tumor growth for approximately 18–24 months [71]. Although the time to onset of a response may take several months, endocrine therapy alone may provide continuous disease control in those who are not surgical candidates, have limited life expectancy, or do not want surgery. The trial of Fennessy et al. [72] included 455 women aged 70 years or older. Their primary outcome was time to treatment failure (TTF). TTF was significantly shorter in the tamoxifen-alone group. In addition, they showed that both overall survival and mortality

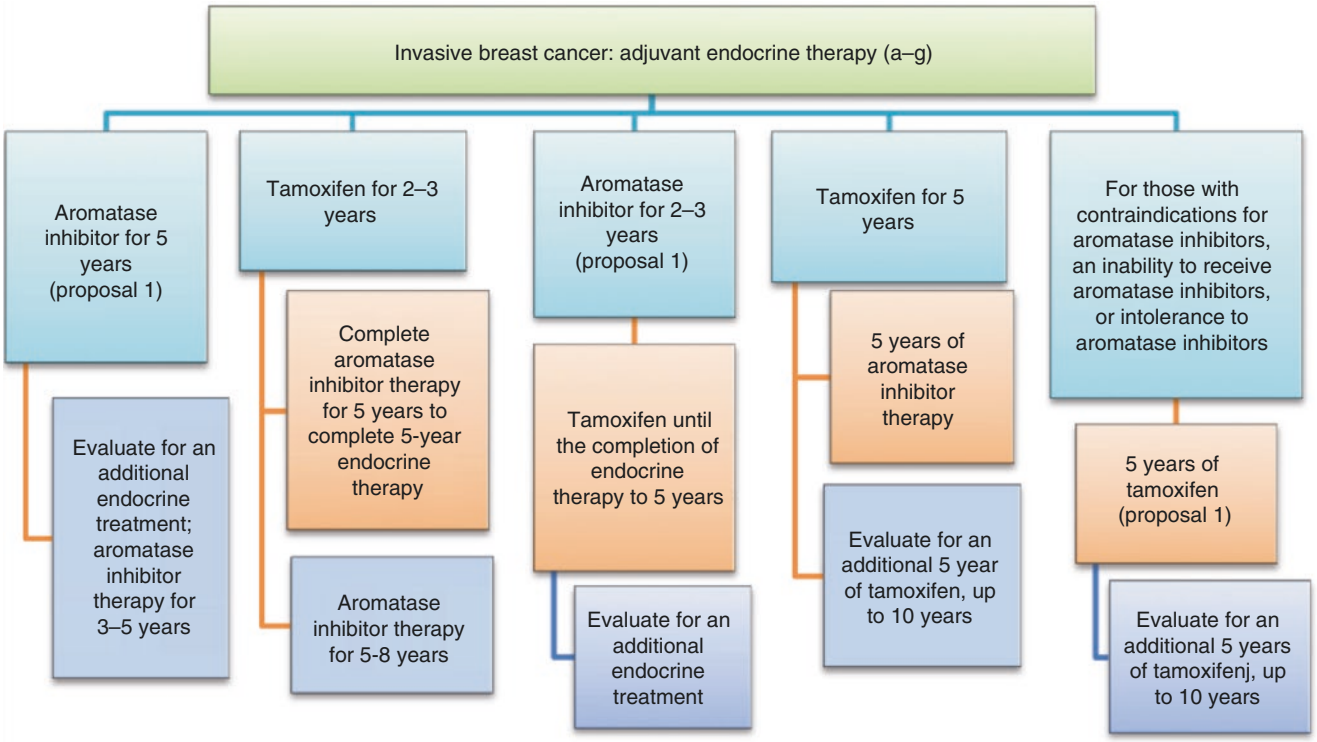

Fig. 21.2 Adjuvant endocrine therapy for postmenopausal patients. [a]In patients with luminal A-like tumors and 1–3 positive lymph nodes (with the evaluation of other factors such as grade, age, or multigene signature test results), "adjuvant endocrine therapy alone" may be an option. [b]Some patients may be adequately treated with tamoxifen alone. In high-risk postmenopausal patients, aromatase inhibitors (AIs) may be preferred over tamoxifen. The following factors argue for the inclusion of an AI at some point: lymph node involvement, grade 3 disease, high Ki-67 proliferation index, or HER2 positivity. If an AI is used, it should be started upfront in patients at higher risk. The upfront AI can be switched to tamoxifen after 2 years in selected patients (e.g., those experiencing side effects of the AI). [c]After 5 years of adjuvant tamoxifen, continued AI or tamoxifen (for patients with intolerance to AI therapy) for up to 10 years should be recommended to patients with node-positive disease, grade 3 disease, or high Ki-67. [d]After 5 years of adjuvant therapy involving a switch from tamoxifen to an AI (therefore assuming postmenopausal status at the 5-year time point and reasonable tolerance to endocrine therapy), patients may continue AI therapy for a cumulative total of 5 years. This subject requires clarification. [e]After 5 years of continuous AI adjuvant therapy, extension of treatment with an aromatase inhibitor may be recommended for 3–5 years. In patients with moderate to high risk, adjuvant endocrine treatment should be increased to 10 years (in patients with stage II and III disease); this increase is not recommended for stage I patients. [f]By multigene signature tests: Chemotherapy may be omitted for patients with luminal B-like (HER2-negative) disease with a low Oncotype Dx® score, MammaPrint® low-risk status, low PAM50 ROR score, or EndoPredict® low-risk status. [g]Consider adjuvant bisphosphonate therapy in patients receiving adjuvant therapy

from breast cancer were significantly increased in this group.

More recently, Johnston et al. [73] reported on 20 years of follow-up of a randomized controlled trial of primary tamoxifen compared to mastectomy and adjuvant tamoxifen. They randomized 153 women 70 years and older with breast cancer stage T1/2, N0/1, and M0 who were fit to undergo surgery. They found no statistically significant difference in breast cancer-specific or overall survival. In addition, there were no differences in the rates of locoregional recurrence and metastasis.

In summary, primary endocrine therapy compared to surgery with adjuvant endocrine therapy was shown to be an inferior treatment alternative, mostly because of the significantly improved progression-free survival and local control with dual therapy (HR: 0.65, 95% CI 0.53–0.81, $P = 0.0001$). There was no significant difference in overall survival; however, the P value was 0.06 (HR 0.86, 95% CI 0.73–1.00) in the meta-analysis of Hind et al. [74]. Hence, combined therapy might be a better treatment option in terms of overall survival outcomes.

Combination Regimens Targeting Multiple Signaling Pathways

Although elderly patients with HR+ breast cancer derive benefits from treatment with endocrine monotherapies, the development of endocrine resistance remains a problem in this patient population. Combination regimens targeting

Table 21.1 Endocrine therapy in hormone receptor-positive HER2-negative advanced breast cancer

Endocrine treatment naïve		Previous endocrine treatment	
No contraindication to CDK inhibitors	Contraindication to CDK inhibitors	Under endocrine treatment or within 12 months after the end of adjuvant endocrine treatment	Disease recurrence at least 1 year after the end of adjuvant endocrine treatment
CDK inhibitor[a] and aromatase inhibitors	Fulvestrant	CDK inhibitor and fulvestrant	Treat as patients who are endocrine treatment naïve
CDK inhibitor and fulvestrant	Aromatase inhibitors	CDK inhibitor and aromatase inhibitors	
Fulvestrant	Tamoxifen	Everolimus and exemestane	
		Abemaciclib and tamoxifen if not used previously	
		Abemaciclib	
		Fulvestrant if not used previously	
		If an aromatase inhibitor was used previously, switch to other (steroidal to nonsteroidal or vice versa)	
		Tamoxifen	
		Progestins	
		Estrogens or androgens	

[a]Pablociclib, ribociclib, abemaciclib

multiple signaling pathways, such as everolimus plus exemestane, have shown efficacy in elderly patients with disease previously resistant to endocrine monotherapies [75, 76], suggesting that combined targeted therapies may represent a valid treatment option in elderly patients (Table 21.1).

Dysregulation of the cyclin D–CDK4/6 inhibitor of the CDK4 (INK4)–retinoblastoma (Rb) pathway in breast cancer cells has been associated with endocrine therapy resistance [77], and preclinical studies in HR+ breast cancer models have demonstrated improved efficacy when CDK4/6 inhibitors are combined with endocrine therapy. The phase III MONALEESA-2 study (clinicaltrials.gov, NCT01958021) reported that the addition of the cyclin-dependent kinase (CDK)4/6 inhibitor ribociclib to letrozole was well-tolerated and significantly improved progression-free survival (PFS) compared with that of letrozole alone as a first-line therapy for HR+, HER2− advanced breast cancer [78]. In the recent pre-specified analysis of the MONALEESA-2 trial, ribociclib plus letrozole demonstrated clinical efficacy and manageable tolerability in elderly patients with HR+, HER2− advanced breast cancer. The PFS benefit of ribociclib was maintained in both elderly and younger patients, with no significant difference observed in ribociclib treatment benefit between the two subgroups, as demonstrated by an interaction test ($P = 0.589$). In both age groups, patients derived early clinical benefits from ribociclib plus letrozole, with separation of the PFS curves occurring from 8 weeks onward. The overall response rates were numerically higher with ribociclib plus letrozole compared with those of placebo plus letrozole, regardless of patient age (37% vs. 31% for patients aged ≥65 years and 44% vs. 25% in patients aged <65 years) [79]. Ribociclib plus letrozole was well-tolerated in elderly patients, with no new safety concerns raised and a safety profile comparable to that observed in the overall MONALEESA-2 patient population [78]. The safety profile in elderly patients was similar to that observed in younger patients, despite an increased proportion of elderly patients in the ribociclib plus letrozole arm presenting with an ECOG performance status of 1. Other CDK4/6 inhibitor-based regimens have also demonstrated efficacy in elderly patients [80, 81], further supporting CDK4/6 inhibitors as a valuable treatment option in elderly patients with HR+ advanced breast cancer.

Radiotherapy

Adjuvant radiation therapy significantly reduces the risk of local recurrence after conservative surgical resection [82]. Furthermore, according to a meta-analysis of 17 trials of BCS, radiotherapy after surgery not only halves the risk of local or distant 10-year recurrence but also reduces the BC annual death rate in early BC patients (T1–T2) by a sixth (rate ratio, 0.82) [83]. However, there are also some data indicating that it may be safe to omit radiation therapy in women over 70 years of age. Hughes et al. reported data from the CALGB 9343 study, in which women with estrogen receptor-positive stage I breast cancer treated with lumpectomy were randomized to tamoxifen plus radiation or tamoxifen alone. In this study, there were no significant differences in time to subsequent mastectomy, time to

distant metastasis, breast cancer-specific survival, or overall survival [84]. Subsequently, the population-based pattern of practice was studied by Nichol et al. [85]. The 10-year locoregional recurrence-free survival rate was 98% with HT and radiation therapy (HT-RT) and 90% with hormone therapy (HT) alone ($P = 0.01$), whereas the 10-year breast cancer-specific survival rate was 96% with HT-RT and 95% with HT alone ($P = 0.2$). Patients with grade 3 histology or lymphovascular invasion were more likely to have low event-free survival. On multivariate analysis, treatment type did not predict overall survival ($P = 0.3$). Chesney et al. evaluated the effect of adjuvant radiotherapy on recurrence and survival for elderly women (≥70) with early-stage hormone receptor-positive breast cancer treated with breast-conserving surgery (BCS) and tamoxifen [86]. For elderly women (≥70 age), radiotherapy reduced the risk of breast and axillary recurrence but did not impact distant recurrence or overall survival in early-stage breast cancer treated with BCS and tamoxifen.

The National Comprehensive Cancer Network Guidelines allow for lumpectomy with negative margins plus endocrine therapy in women aged 70 years or older with T1, node-negative, ER-positive breast cancer to omit breast radiation [87]. Notably, despite the fact that the omission of radiotherapy is not widely performed and warrants further study, post-mastectomy chest wall irradiation improves the survival of elderly patients (70 years or older) with advanced disease (T3–T4, N2–N3) [88].

Currently, the most common radiotherapy regimen in the United States takes approximately 6 weeks to complete. However, shorter regimens of higher doses over fewer weeks (resulting in lower total doses) have recently been demonstrated to be as effective as traditional radiotherapy regimen [89, 90]. Whelan et al. studied women with invasive cancer who had undergone lumpectomy with negative lymph nodes and were randomized to 50 Gy in 25 fractions over 35 days or 42.5 Gy in 16 fractions over 22 days. The risks of local recurrence were 6.7% and 6.2% (95% CI = −2.5 to 3.5), respectively [89]. Haviland et al. compared 50 Gy in 25 fractions over 5 weeks to 40 Gy in 15 fractions over 3 weeks and also demonstrated no significant difference in local-regional recurrence in the two groups (4.3%, 95% CI = 3.2–5.9 and 5.5%, 95% CI = 4.2–7.2) [90].

Another development in the quest to shorten the duration of radiotherapy after lumpectomy is intraoperative radiation (TARGIT). The 5-year risk of local recurrence was reported to be 3.3% (95% CI = 2.1–5.1) for women in the TARGIT group compared with 1.3% (95% CI = 0.7–2.5) for external beam radiation. Notably, there were also fewer non-breast cancer deaths in the TARGIT group [91]. Therefore, shorter radiation regimens and intraoperative radiation provide alternatives to the widespread use of longer duration radiotherapy.

Alternative Treatments

Clinicians and researchers are exploring other modalities to treat breast cancer. For instance, ultrasound-guided percutaneous radiofrequency ablation with endocrine therapy in a small group of patients was reported as well-tolerated but is not recommended for lobular carcinoma [92]. Other studies have investigated cryotherapy for breast cancer treatment and reported minimal patient discomfort with no short-term recurrences detected [93]. Further research regarding recurrence and disease-free survival relative to those of the conventional treatment is needed.

Conclusion

Breast cancer in the elderly is not definitely a less-aggressive disease compared with cancer arising in younger women. The predictive factors are the same and must be assessed with the same attention reserved for younger women, although many patients should be considered for less-invasive treatments. Socioeconomic factors and general health status are thus effective factors affecting prognosis and modifying life expectancy and compliance with therapies.

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Male Breast Cancer

22

Abdullah Igci, Mustafa Tukenmez, and Enver Özkurt

Introduction

Breast cancer is observed in men 100-fold less often than in women [1, 2]. The risk of breast cancer for men is approximately 1 in 1000 throughout life. The American Association of Cancer predicts that 2360 men will be diagnosed with breast cancer in 2014 and 430 male patients with breast cancer will die [3]. Estimated new cases and deaths from breast cancer (men only) in the USA in 2018 are 2550 and 480 [4]. Breast cancer is responsible for 0.1% of cancer-dependent deaths in men [5, 6]. Similar to women, breast cancer is observed more frequently in the left breast in men [7]. The bilateral case rate is 1.4% [8]. The incidence is lower in Japan, Colombia, Singapore, Finland, and Hungary, whereas the incidence is higher in North America and England and very high in some African countries [9, 10].

Anderson et al. reported on male breast cancer (MBC) from the Surveillance, Epidemiology, and End Result (SEER) database during the period 1973–2005 and found an annual increase in incidence of 1.19%, with a peak in 2000 of 1.24 cases per 100,000 men [11].

There is no difference in the frequency of deaths from MBC between Europe and the USA [3]. The frequency is 0.1 deaths per 100,000 cases at 35 years of age and reaches up to 11.1 deaths per 100,000 cases after 85 years. One percent of MBC is observed in males younger than 30, and 6% of cases are detected below the age of 40 [12]. The mean age of diagnosis of MBC is 67.7, which is 5–10 years older than for female breast cancer (FBC) patients in the USA, but in other parts of the world, such as the Middle East and South Asia, the age gap is smaller [3, 13–17].

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In a study based on an international population [17], the world-standardized incidence rates of breast cancer were 66.7 per 10^5 person-years in women and 0.40 per 10^5 person-years in men. Women were diagnosed at a younger median age (61.7 years) than men (69.6 years).

Previous studies have shown that MBC cases are significantly different from female cases, but new studies have reported that breast cancer has similar characteristics at the same stages in both genders [12].

Epidemiology and Risk Factors

The majority of cases are sporadic. Only 5–10% of all male breast cancer cases are considered to be related to a genetic predisposition [18–21]. In a study investigating the familial characteristics of men with breast cancer, FBC or ovarian cancer cases were reported by 30% of the families that included men with breast cancer [22, 23]. The risk of breast cancer in the sister or daughter of a patient with breast cancer is increased by two- to threefold [10]. Breast cancer was reported in two brothers, one of whom also had prostate cancer [24]. BRCA1 is a suppressor gene that has been isolated and located on chromosome 17q. The risk of breast cancer increases in the presence of this germline mutation, and the disease appears at early ages in patients with mutations in BRCA1. BRCA2, which has been localized to chromosome 13, has been reported to be responsible for 70% of hereditary breast cancer cases [25]. The genetic presence of the BRCA2 germline mutation is a risk factor for early-age MBC. A mutation in BRCA2 is not likely to exist in MBC cases without a family history of breast cancer [16, 22, 26]. BRCA2 and BRCA1 were detected by 77% and 19% of cases with familial MBC, respectively [27]. Breast cancer eventually develops in 5–10% of men with BRCA2 mutations (and in a smaller proportion of those with BRCA1 mutations) [28].

In a study conducted in Iceland, mutations in BRCA2 were found at rates of 0.6% in the community, 7.7% in patients with FBC, and 40% in the patients with MBC [20].

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Breast cancer cases with the BRCA2 mutation generally have similar prognostic characteristics as the cases without the mutation; however, the nuclear grade tends to be higher in those with the mutation, and the frequency of p53 mutation is increased [22]. In another collaborative multicenter study from Italy [29], BRCA2 mutations were associated with a family history of breast/ovarian cancer ($p = 0.0001$), a personal history of other cancers ($p = 0.044$), and contralateral breast cancer (BC) ($p = 0.001$). BRCA2-associated MBCs presented with high tumor grade ($p = 0.001$), PR− ($p = 0.026$), and HER-2+ ($p = 0.001$) status. Ding et al. reported from the USA that the difference in BRCA2 mutation frequencies between cases with and without a family history of breast cancer was not statistically significant ($p = 0.145$), suggesting that, in males, family history is not a strong predictor of carrying a mutation [30]. They observed that carrying a pathogenic BRCA2 mutation showed a highly significant association with a high tumor grade ($p = 0.001$) and a weak association with positive lymph nodes ($p = 0.02$). Of the 97 BRCA2-negative MBC cases, they identified one PALB2 mutation with confirmed pathogenicity and one mutation predicted to be pathogenic, corresponding to a prevalence of pathogenic PALB2 mutations of 1–2%. Based on their results and previous studies, they recommend genetic testing for BRCA2 for any diagnosed MBC case, regardless of the family history of breast cancer.

Data are mixed regarding the relevance of other germline mutations such as those in PALB2, the androgen receptor (AR), CYP17, and CHEK2 [31–34]. Other mutations that increase the risk of FBC (e.g., BRIP1 and RAD51C) have not been found to increase the risk of MBC [35, 36], and one study reports that polymorphisms in the vitamin D receptor do not appear to be associated with risk [37]. The main risk factors for male breast cancer are listed in Table 22.1.

In the studies conducted on the BRCA1 and BRCA2 genes, MBC was shown to have a greater association with the BRCA2 gene [18]. BRCA2 is considered a useful marker for identifying men with higher risk of breast cancer [18].

Mutations in p53, a tumor suppressor gene, result in Li-Fraumeni syndrome. It is reported that the incidence of breast cancer and many other tumor types increases when suppression disappears upon p53 mutation [15]. There is no convincing evidence for the association of MBC with gynecomastia, which is considered to be related to common hormonal risk factors [38].

Klinefelter's syndrome (genotype XXY) is a syndrome including characteristics such as less developed sex organs, gynecomastia, small testicles, aspermatogenesis, and increased FSH. It is the strongest risk factor for MBC, and the risk increases by 50-fold compared to a male with a normal genotype [39–43]. Hypertrophy in the breasts of such men is secondary to gynecomastia and the development of acini and lobules [44]. Patients with Klinefelter's syndrome have significant hyperestrogenemia in their blood, and the incidence of breast cancer in such male patients reaches 6% [25]. Whether the causes of gynecomastia other than Klinefelter's syndrome increase the risk for MBC remains unknown. However, when slides from Klinefelter's syndrome patients with MBC are examined histologically, microscopic findings of gynecomastia are observed in 40% of cases [45]. The most common side effect of finasteride, which is used for the treatment of prostate hyperplasia, is gynecomastia; additionally, breast cancer was reported in three patients who used finasteride [46].

Table 22.1 Main risk factors for male breast cancer

Genetics	**Endocrine**
Klinefelter's syndrome	Liver disease
Family history of breast cancer	Exogenous estrogens
BRCA2 mutations	Androgen deficiency (prolactinoma)
BRCA1 mutations	
Ashkenazi Jewish men	
Cowden syndrome	
Environmental, occupational, and other factors	
Chest wall radiation	
Testicular disorders	
Undescended testes, congenital	
Inguinal hernia, orchiectomy	
Orchitis, infertility	
Lifestyle	
Obesity, alcohol, diet	
Occupational and environmental exposures	
Occupational exposure to heat	
High ambient temperature	
Exhaust emissions	
Electromagnetic field radiation	

In the MBC pooling project [47] involving a consortium of 11 case-control and 10 cohort investigations involving 2405 case patients ($n = 1190$ from case-control and $n = 1215$ from cohort studies) and 52,013 control subjects, individual participant data were harmonized and pooled. The risk of MBC was significantly associated with weight (highest/lowest tertile: OR = 1.36; 95% CI = 1.18–1.57), height (OR = 1.18; 95% CI = 1.01–1.38), and body mass index (BMI; OR = 1.30; 95% CI = 1.12–1.51), with evidence that recent rather than distant BMI was the strongest predictor. Klinefelter's syndrome (OR = 24.7; 95% CI = 8.94–68.4) and gynecomastia (OR = 9.78; 95% CI = 7.52–12.7) were also significantly associated with the risk, independent of BMI, and diabetes emerged as another independent risk factor (OR = 1.19; 95% CI = 1.04–1.37). Additionally, there were trends indicating relationships with cryptorchidism (OR = 2.18; 95% CI = 0.96–4.94) and orchitis (OR = 1.43; 95% CI = 1.02–1.99). Although age at the onset of puberty and histories of infertility were unrelated to risk, never having had children was statistically significantly related (OR = 1.29; 95% CI = 1.01–1.66). Among individuals diagnosed at older ages, a history of fractures was statistically significantly related (OR = 1.41; 95% CI = 1.07–1.86).

In men, obesity is associated with high levels of estrogen and low levels of testosterone and sex-hormone-binding globulin [48], leading to greater estrogen bioavailability. Thyroid diseases, marijuana use, and external estrogen cause gynecomastia, but their associations with MBC are much weaker. Only 2 of more than 17,000 patients who were treated with estrogen because of prostate cancer developed breast cancer [20]. Increases in estrogen circulation and hepatic metabolism may explain the increased incidence for MBC as follows: hepatic dysfunction because of cirrhosis and chronic malnutrition is common in some territories of Africa and is connected with increased rates of MBC [49]. The incidence of MBC is increased in regions where schistosomiasis is common. This parasitic infestation causes hepatic failure and hyperestrogenemia. In Egypt, where schistosomiasis is endemic, MBC was reported more frequently than prostate cancer [25].

Chronic liver diseases with other etiologies have also theoretically increased the risk for the development of MBC; however, severe hepatic dysfunction has a high mortality rate; thus, the increased risk may become significant [38]. MBC accompanying liver disease is observed in younger ages (40–50) and more frequently (15%) in Zambia [10].

In testicular abnormalities that cause androgen deficiency, an increase in the incidence of MBC was reported in men with orchitis, undescended testicles, and testicle injuries [50, 51]. Radiation is also a risk factor for men and women. Cancer develops 12–36 years after contact with radiation [52]. Exposure to radiation of over 50–100 cGy during childhood or adolescence increases the risk of cancer similarly in both sexes [44, 49]. Unlike in women, white race does not appear to be a risk factor in men [11].

Work and environmental factors may also play an increasing role in MBC. Based on a multicenter case-control study that was conducted in eight European countries and included 104 cases and 1901 controls, it was concluded that some environmental chemicals are possible mammary carcinogens [53]. Petrol, organic petroleum solvents, or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of MBC observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer. The prevalence is increased in those who work in high-temperature ovens and steel factories because of cancer potentialization; in other words, testicular failure appeared as a result of heat [12, 18]. Vapors of gasoline and other flammable substances were shown to play a role in the appearance of breast cancer in men [53, 54].

Long-term therapy with the drugs which are commonly used today and cause hyperestrogenemia such as digital agents, cimetidine, methyldopa, and spironolactone has higher risk of breast cancer [55]. Obesity of which the frequency gradually increases in economically developed countries has become a social problem. Especially, obesity under age of 30 is a risk factor for breast cancer in women as well as men. The suggested mechanism of appearance is the increase in conversion of androgens into estrogen in increased fat tissue. Other risk factors include being unmarried, being Jewish, the presence of previous benign breast disease history, late puberty, and hypercholesterolemia [55].

Clinical Progress

Patients with MBC generally refer with a hard and painless mass located centrally under the nipple. The mass gradually settles in the upper outer quadrant [56]. Nipple ulceration is commonly observed, but first referral with an efflux from the nipple is rare [25]. However, if serous-hemorrhagic efflux comes out of the nipple, the underlying disease is cancer in general (75%). If metastasis exists, patients may complain about cough and bone pain [10]. It is more common in the left breast [57]. Bilateral masses are very rare (0–1.9%). The period between onset of the disease and diagnosis is 18 weeks to 6 months [10]. Moreover, in MBCs, easy invasion of the dermal tissue because of its superficial and central location allows the diagnosis of the disease during advanced stages [58].

Diagnosis

Breast cancer biology is distinct in men, but diagnostic approaches and treatments for men are generally extrapolated from those in women due to inadequate research in men [59]. Perhaps due to poor awareness of the disease and diagnostic delays, most (but not all) studies suggest that men are diagnosed with higher stage tumors and have a poorer prognosis overall [60, 61]. It often presents as a painless subareolar lump [62].

MBC is diagnosed with biopsy. Fine-needle aspiration biopsy (FNAB) may be performed in medical centers where experienced cytopathologists are employed. If FNAB is not appropriate, Tru-Cut biopsy should be performed. Removal of sufficient tissue is important for both diagnosis and determination of hormone receptors [12, 49]. Two studies that compared FNA with core and/or excision biopsies demonstrated that the former had sensitivity and specificity that approached 100% [63]. Chest X-ray, bone scintigraphy, and liver enzymes should be assessed to determine invasion of the disease before the treatment [41]. Clinical examination is invaluable, although it must be noted that concurrent gynecomastia, the most common breast-related diagnosis in men, may mask an underlying tumor [64].

Gynecomastia which is generally confused with MBC in mammography is observed as a nodular lesion with three edges and small extensions in subareolar area. Edges are irregular in general. It should be noted that cancers may be

hidden well in such benign density increases and nodularities. Although microcalcifications are not cancer specific, they are the most important traces for malignancy in mammography. Evaluation with mammography alone is difficult for men [16, 64] (Fig. 22.1). Calcifications are not in spot or stick form like observed in women; they are generally wider and round. The mass is solid, spiculated, and located eccentrically associated with the nipple (Fig. 22.2) in general [64]. The mass in gynecomastia is symmetrically associated with the nipple. Breast skin retraction may exist in malignancies. Enlargements on axillary lymph nodes may be observed via mammography [65, 66]. Male patients with cancer on one breast may be followed by mammography to search a secondary tumor on the other breast. Cases with non-palpable breast cancer were reported by mammography in the normal breast which seems clinically normal.

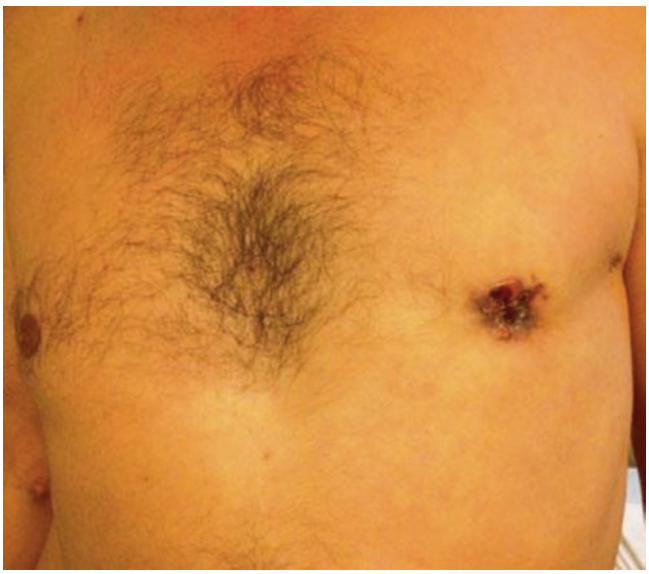

Fig. 22.1 Physical examination finding of a 45-year-old male showing ulceration around his nipple

Subareolar triangular, anechoic, and hyperechoic fibroglandular appearances exist in gynecomastia by ultrasound. Ultrasonographic microcalcifications in MBC are not detected in the ultrasound. Structural distortion, asymmetric appearance in nipple shadows, and shadowing around the nipple may be detected by the ultrasound (Fig. 22.3). Ultrasonography generally visualizes a mass with hypoechogenicity and indistinct or irregular margins [64]. The use of ultrasound alone is deemed insufficient for male breast growths. However, much attention should be paid during diagnosis when suspicious changes are found by either ultrasound or mammography. In some cases, the combination of both techniques may be required for the final diagnosis [65, 66]. Clinical examination, ultrasound, and mammography

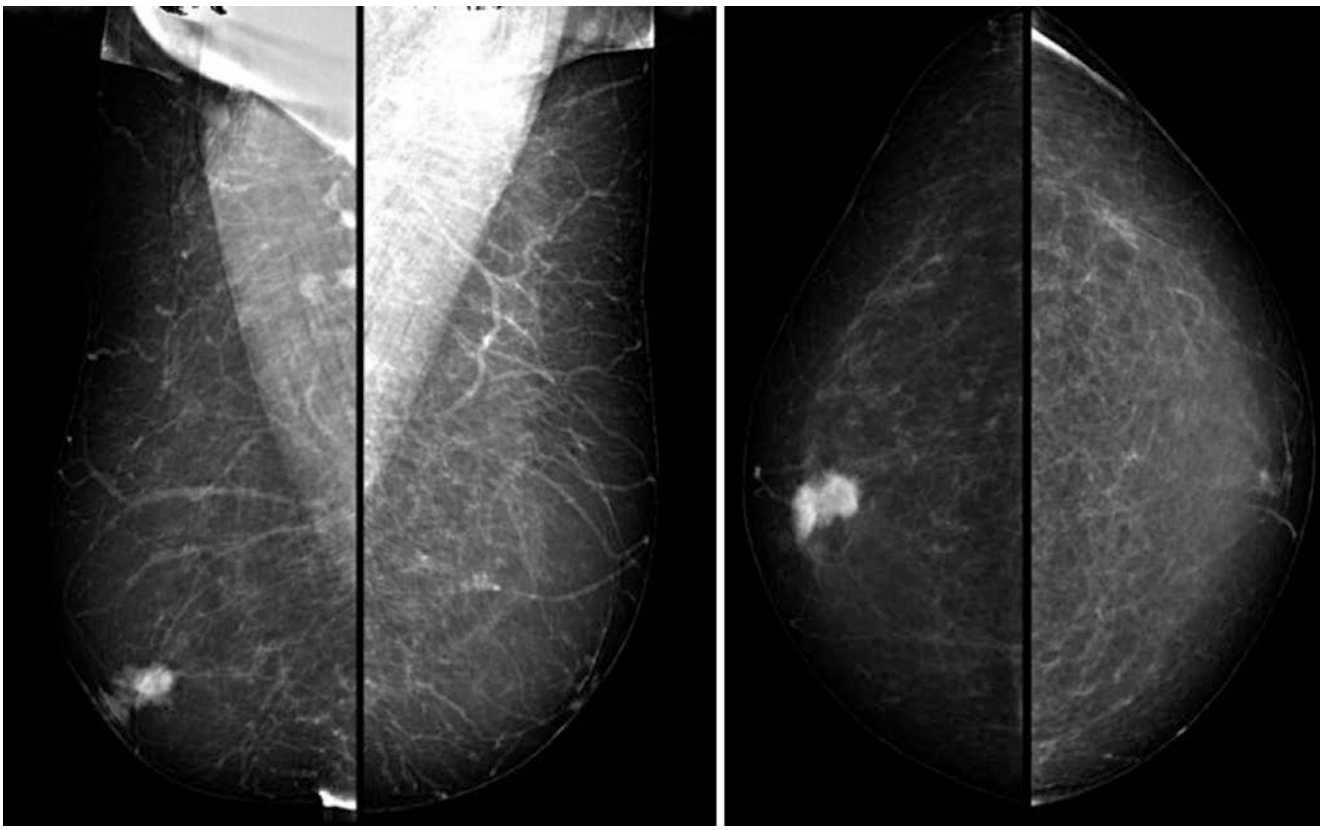

Fig. 22.2 Mammography imaging of a 65-year-old male patient with a malignant mass on his right breast

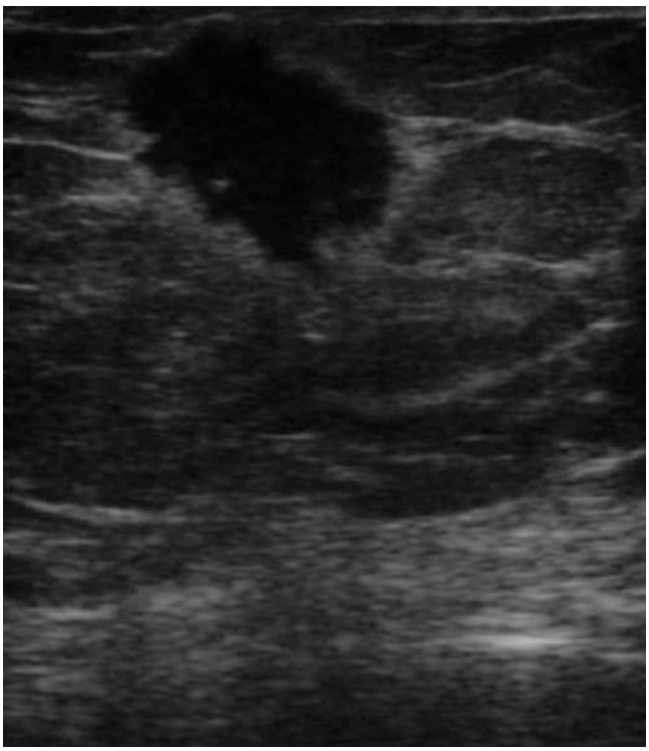

Fig. 22.3 Ultrasonographic imaging of a 65-year-old male patient with a malignant mass on his right breast

may reduce the need for biopsy in patients who are considered to have a benign disease [67].

Smear examination is required for patients with nipple efflux. When a mass is detected on the breast of a man, a procedure should be run for histological diagnosis to definitively differentiate between benign and malignant disease. This may be performed by fine-needle aspiration, core needle biopsy, or open biopsy. A cytological examination performed by fine-needle aspiration biopsy depends on the experience of the clinician and cytopathologist. In fact, the use of such a technique is safer with increased experience; however, fine-needle aspiration biopsy is not commonly used for differentiation of the lesion on the male breast. The gold standard is open biopsy [49]. Cellularity, dyshesion, and morphism are important criteria for the diagnosis of cancer, which is also assisted by nuclear changes. A mild cellularity or cellular failure exists in gynecomastia. Although anisonucleosis may exist in gynecomastia, a smooth surface of the membrane indicates a benign case. Honeycomb pattern, macronucleus, and mixed cell groups support malignancy [68].

Differential Diagnosis

The differential diagnosis should be made between gynecomastia and cancer for male breast masses. The most common unilateral or bilateral benign mass is gynecomastia [69]. It is generally detected by physical examination. Gynecomastia is characteristically a symmetrical, bilateral discoid under the nipple and areola. Carcinomas have an eccentric settlement and a hard mass; no sensitivity exists. Breast skin adjacencies may be observed in both gynecomastia and carcinoma. However, adjacency to the pectoral fascia, nipple efflux, nipple inversion, and ulceration are only detected in breast cancer. These characteristics are difficult to determine in adults, and a biopsy should be performed in any suspicious case [12]. Benign neoplasms are extremely rare in a male breast. Cystosarcoma phyllodes, phylloid papillomatosis, ductal papillomas, lipomas, and other tumor types that are not associated with the breast may be detected on the breast [49].

Pathology

The distribution of breast cancer in male and female patients differs because of the lack of lobule development in the male breast. Because a normal male breast does not contain any lobular elements, the most frequent cancer type detected in men is invasive ductal carcinoma (85–90%) [70]. Invasive lobular cancer or lobular carcinoma in situ has been reported in several cases with a normal genetic profile and without any history of hormone use [8]. All histological types of breast cancer observed in women (ductal carcinoma in situ, medullary, papillary, and colloid) can also be observed in men (Table 22.2). Inflammatory breast cancer and Paget's disease were also reported in men. Granular cell tumor, adenoid cystic carcinoma, myofibroblastoma, carcinoid tumor, and metastatic tumors (generally originating from the lungs and prostate) are other possible tumor types [38].

The vast majority of MBCs are hormone sensitive [71, 72]. MBC shows higher estrogen (75–94%) and progesterone (67–96%) hormone receptor positivity than does breast cancer in women. In the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) database, between 1973 and 2005, 92% of the 5494 MBCs but only 78% of the 838,805 FBCs were estrogen receptor (ER) positive [11]. Receptor positivity was not reported to be

Table 22.2 Frequency of histological types observed

Histology	Incidence (%)
Invasive ductal carcinoma	90
Ductal carcinoma in situ	10
Invasive papillary carcinoma	2
Medullary carcinoma	2
Mucinous carcinoma	1
Paget's disease	1
Lobular carcinoma	1

associated with age, histological grade, stage, and axillary lymph node involvement [8].

Information with other molecular and genetic markers is limited for MBC [73]. The Mayo Clinic assessed 111 cases and reported positive estrogen receptors in 91% of cases; positive progesterone receptors in 96% of cases; positive androgen receptors in 95% of cases; the expression of bcl-2, which is a determinant for apoptosis, in 94% of cases; p53, which is one of the proto-oncogenes, in 21% of cases; HER-2 in 29% of cases; and cyclin D1, which is one of the cell cycle regulatory proteins, in 58% of cases [74]. The overexpression of cyclin D1 and c-myc may correlate with better outcomes [75]. In addition, studies have reported higher rates of HER-2 in 40% of cases and p52 in 54% of cases [10, 71, 76].

Cordoso et al. reported the results of a retrospective joint analysis of cases diagnosed during a 20-year period. The analysis included patients with follow-up and tumor samples who were treated between 1990 and 2010 in 93 centers/9 countries. Samples were centrally analyzed in three laboratories (the UK, the Netherlands, and the USA). A total of 1483 patients were analyzed; 57 (5.1%) had metastatic disease (M1). The median age at diagnosis was 68.4 years. Of 1054 M0 cases, 56.2% were node negative (N0), and 48.5% had T1 tumors; 4% underwent breast-conserving surgery (BCS), and 18% underwent sentinel lymph-node biopsy; half received adjuvant radiotherapy; 29.8% received (neo)adjuvant chemotherapy; and 76.8% adjuvant endocrine therapy (ET), mostly tamoxifen (88.4%). According to the central pathology of M0 tumors, using immunohistochemistry (IHC) surrogates, 41.9% were Luminal-A-like, 48.6% were Luminal-B like/HER-2 negative, 8.7% were HER-2 positive, and 0.3% were triple negative. BC-specific mortality was higher for men younger than 50 years. Better overall survival (OS) and recurrence-free survival (RFS) were observed for highly ER+ (p = 0.001), highly PR+ (p = 0.002), and highly AR + disease (p = 0.019). There were no associations between OS/RFS and HER-2 status, Ki-67, IHC subtypes, or grade. Of note, 56% patients had T1 tumors, but only 4% had BCS. ER was highly positive in >90% of cases but only 77% received adjuvant ET [77].

Treatment

Treatment for Early-Stage Male Breast Cancer

Treatment in early-stage MBC patients is surgery followed by adjuvant endocrine therapy, chemotherapy, or radiotherapy according to the prognostic factors. A large population-based study conducted in Europe and Asia demonstrated that males with BC were significantly less likely to receive surgery and radiation therapy (RT) than females with BC. However, the rates of the use of chemotherapy and hormonal therapy were similar [17].

Surgical Treatment

Surgical options for men with early-stage breast cancer include breast-conserving therapy and mastectomy [78]. Standard treatment is mastectomy and sentinel node biopsy or axillary lymph node dissection [23, 79]. Radical mastectomy has been performed throughout the history of MBC. Today, this method is applied for wide chest wall invasions only. Currently, most patients undergo modified radical mastectomy [78]. The rarity of breast-protective therapy may be because men have less breast tissue than women and have tumors located more centrally; in addition, male patients do not request breast-protective therapy [18].

In a study conducted in the USA, the Surveillance, Epidemiology, and End Result (SEER) database was used to identify all MBC patients who underwent either mastectomy or less than mastectomy between 1983 and 2009 [80]. A total of 4707 (86.8%) men underwent mastectomy and 718 (13.2%) underwent lumpectomy. They mentioned that lumpectomy was performed in a small but growing proportion of MBC patients. These patients were not only older and more likely to have advanced disease at the time of diagnosis but were also less likely to receive standard therapies such as lymph node sampling and adjuvant radiotherapy. Despite those observations, breast cancer-specific survival was unaffected by the type of surgery. A recent report found a considerable desire by men to preserve their breast to maintain a positive self-image [81].

A retrospective cohort analysis was conducted between 2007 and 2016 using the American College of Surgeons National Surgical Quality Improvement Program database (NSQIP) to examine MBC treatment patterns and postoperative complication rates. All men undergoing surgery for the treatment of invasive or in situ carcinoma of the breast were identified. A total of 1773 MBC patients with a median age of 65 years (IQR 56–74 years) were included in this analysis. In this study population, 10.0% had a diagnosis of in situ breast cancer, whereas the remaining 90.0% had invasive disease. While most men underwent a mastectomy, 15.9% underwent breast-conserving surgery. There were 74 (4.2%) patients who underwent immediate breast reconstruction. In addition, 6.7% of patients elected to have a contralateral prophylactic mastectomy. Overall, the rate of morbidity was 4.6%, comprising mostly wound complications (3.2%). Analysis of this large, prospective multi-institutional cohort revealed that the complication rates are low and comparable to the reported rates in the female breast cancer population. Significantly, this cohort demonstrates the importance of cosmetic considerations in MBC patients, as some men decide to undergo breast-conserving surgery or immediate breast reconstruction. Contralateral prophylactic mastec-

tomy in the treatment of MBC is also performed [82]. These data suggest that breast conservation therapy may be considered a reasonable local treatment option for male patients presenting with breast cancer because it may offer functional advantages over mastectomy with comparable rates of local control and disease-free survival and overall survival.

In the guidelines of the American Society for Clinical Oncology, sentinel lymph node biopsy is reported as acceptable in MBC [16, 83]. More radical surgical procedures do not improve survival. Preoperative chemotherapy may be useful for cases with a critical tumor load. Simple mastectomy or localized tumor excision can be performed for patients who have a metastatic disease or non-suitable overall status; this may be combined with postoperative radiotherapy [9].

Adjuvant Chemotherapy

The benefit of systemic adjuvant treatment for MBC was not assessed in randomized clinical surveys; however, progress and response to the therapy in patients with metastatic MBC is similar to that in female patients. Therefore, patients with early-stage MBC are considered to benefit from adjuvant therapy [4]. There is not yet sufficient information about various prognostic factors for selecting specific adjuvant chemotherapy. Generally, the prognostic factors used for women are also valid for men. Deciding on the treatment is difficult, particularly for lymph node-negative cases or cases with one to three positive lymph nodes and strongly positive for estrogen receptor. Chemotherapy is applied to lymph node-negative patients according to the indications in FBC. There is an indication for chemotherapy in those with positive lymph nodes [84]. The same chemotherapeutic drugs are used for both male and female patients. The agents generally used are CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and FAC (5-fluorouracil, doxorubicin, cyclophosphamide) regimes. However, treatment regimens including doxorubicin are superior to classical CMF [9]. Bagley [85] and Patel [86] reported in two small-scaled retrospective studies that survival was increased by adjuvant systemic therapy. Bagley reported a 5-year survey in which patients with stage II MBC who received 12 courses of CMF therapy showed a survival rate of 80% and a mean overall survival of 98 months; he also suggested adjuvant therapy for its benefits. The precision of such data should be supported by prospective studies; however, because MBC is rare, it is difficult to perform large randomized studies.

Adjuvant Endocrine Therapy

Based on the positive clinical study results of adjuvant endocrine therapy alone or in combination with chemotherapy in female patients with early-stage breast cancer, adjuvant endocrine therapy is also recommended for male patients [87]. Likewise, in a Chinese retrospective single-institution study of 72 male patients over 40 years old, a multivariate regression found that the receipt of endocrine therapy was associated with better survival [88]. Tamoxifen or another hormone treatment is recommended for male patients with estrogen receptor-positive cancer, based on the prognostic factors for female patients [84]. Adjuvant therapy combined with radiotherapy was applied after surgery in 39 patients with Stage II and Stage III MBC with positive axillary nodes; the 5-year disease-free survival rate was reported as 55% and the overall survival as 61%. For former patients who were not treated systemically, the 5-year disease-free survival and overall survival were reported as 28% and 44%, respectively. Based on these indirect comparisons, tamoxifen increases both 5-year disease-free survival and overall survival. The long-term use of tamoxifen is suggested because it does not cause severe bone marrow toxicity or drug-induced death. However, tamoxifen may not be tolerated well in male patients. Men often experience bothersome symptoms from endocrine therapy, and approximately one in four discontinue treatment early because of hot flashes or sexual dysfunction [89, 90].

A limiting factor in the duration of tamoxifen therapy in men is the high incidence of adverse effects, with 20% of participants in one study discontinuing therapy as a result. Common adverse effects include weight gain, sexual dysfunction, hot flashes, neurocognitive deficits, and thromboembolic events [90]. One study reported few adverse effects of tamoxifen [15]. However, further studies reported high rates of treatment-limiting side effects upon tamoxifen treatment in male patients, including a decrease in libido (29.2%), weight gain (25%), hot flashes (20.8%), mental disorders (20.8%), depression (16.6%), sleeping disorders (12.5%), and deep vein thrombosis (4.1%). The rate of those who discontinued the treatment because of side effects was reported to be as high as 20.8% within 1 year, compared with approximately 4% for women who received tamoxifen [91]. Eggeman et al. [92] studied adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 hormone receptor-positive MBC patients. They found that the overall survival with MBC was significantly better after adjuvant treatment with tamoxifen compared to adjuvant treatment with an aromatase inhibitor. In conclusion, tamoxifen should be considered the treatment of choice for hormone receptor-positive MBC.

Adjuvant Radiotherapy

Postsurgical radiation criteria are generally extrapolated from data in women [93]. There are no prospective randomized studies evaluating the clinical effects of postoperative adjuvant radiotherapy in MBC. In a population analysis using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, a total of 1933 patients were included in the unmatched cohort. There

was no difference in 5-year OS between those who received PMRT and those who did not (78% vs. 77%, respectively, $p = 0.371$); however, in the case-matched analysis, PMRT was associated with improved OS at 5 years (83% vs. 54%, $p < 0.001$). On subset analysis of the unmatched cohort, PMRT was associated with improved OS in men with 1–3 positive nodes (5-year OS 79% vs. 72%, $p = 0.05$) and those with 4+ positive nodes (5-year OS 73% vs. 53%, $p < 0.001$). On multivariate analysis of the unmatched cohort, independent predictors for improved OS were the use of PMRT, HR = 0.551 (0.412–0.737), and estrogen receptor-positive disease, HR = 0.577 (0.339–0.983). The authors concluded that there may be a survival benefit in the addition of PMRT for male breast cancer with node-positive disease [94].

Such studies have different technical characteristics, making clinical assessments difficult. Radiotherapy decreases local and regional relapse after mastectomy; however, it is not significantly effective for survival [41]. Radiotherapy should be considered based on similar criteria as for female cancer patients, and the indications are related to local findings. Tumors invading the skin and the chest wall require radiotherapy. Skin and nipple invasion occurs more frequently in men than in women. This may be associated with breast size and the distance of the tumor to these formations. Radiotherapy is imperative for patients who choose breast-protective surgery [10]. Consistent with the results of two studies on the benefits of radiotherapy after mastectomy on overall survival for patients with FBC, radiotherapy was considered a requirement after mastectomy for male patients with positive axillary lymph nodes [95]. Raguse et al. [96] showed that radiotherapy reduced the first 2-year local relapse (from 60% to 20%) for the patients with positive nodes. However, a decrease in local relapse does not reflect overall survival. Postoperative radiotherapy is a basic component of the treatment plan for localized advanced tumors [9, 97].

Treatment in Advanced-Stage Male Breast Cancer

Metastasis and the relapse pattern in MBC are similar to that in women. Metastasis is detected in 4–17% of patients during diagnosis. Metastasis will develop in 18–54% of the patients who do not have metastasis at the beginning. Distant metastases are commonly observed on the bones, lungs, and brain [86]. Isolated metastases are best treated by excision or radiotherapy. Systemic treatment options include ablative hormone treatment, additive hormone treatment, and chemotherapy; however, ablative hormone treatment is no longer commonly used. Ablative hormonal treatments include orchiectomy, adrenalectomy, and hypophysectomy. In 1942, bilateral orchiectomy was shown to be effective as hormone therapy in the treatment of patients with metastatic MBC [85]. Orchiectomy has a low morbidity rate. The remission rate was reported as 55% in a study including 271 cases between 1959 and 1987 [12]. Some researchers have reported a remission rate of 60–83% by this treatment [98]. The basis for performing adrenalectomy was not clearly explained. The treatment response in an adrenalectomy series including 38 patients was shown to be 7.4% [12]. In another study, the effect of adrenalectomy followed by orchiectomy was reported as 80% [98]; however, when chemotherapy and hormone treatment options are available, adrenalectomy followed by orchiectomy is not preferred because of the low achievement rate and the presence of morbidity.

Tamoxifen and other antiestrogen substances used as additive hormonal treatments, such as clomiphene and nafoxidine, bind to estrogen receptors and reduce the hormone intake of the target tissue. Tamoxifen has fewer side effects and is more commonly used for FBC than are other drugs. A response rate of 48% was obtained in 73 male patients with metastatic breast cancer who received tamoxifen treatment. All the patients responded to tamoxifen treatment, regardless of whether they responded to orchiectomy. Tamoxifen and orchiectomy are two individual treatment methods that do not show cross-resistance [12, 41, 99]. Second-generation hormone therapy is currently used for FBC by inhibiting estrogen production through aromatase inhibitors, and good outcomes have been obtained. The role of aromatase inhibitors in male patients is limited. A case series including five patients who were treated with aromatase inhibitors was published [100]: three of the five patients had a stable period; however, those patients showed slow disease progress before adding aromatase inhibitors, and no objective response could be obtained from the patients. In another study, anastrozole was tested on healthy male volunteers [101]. Unlike in women, men treated with anastrozole did not show complete estrogen suppression; instead, a decrease of 50% was observed in the estradiol concentration. Furthermore, testosterone levels were increased by 58%. Two case studies reported responses to letrozole [102, 103]. Additional studies are required for evaluating both the adjuvant and metastatic efficiency of aromatase inhibitors on MBC. Luteinizing hormone-releasing hormone (LH-RH) agonists were reported as effective for the treatment of MBC with or without antiandrogens [104–106]. An LH-RH analogue drug called buserelin was introduced for use in advanced MBC. This drug first causes stimulation and then causes a paradoxical decrease in LH and FSH release; it presents an effect that can be called medical orchiectomy. Partial remission was obtained for 12 months in one of five patients who were treated with buserelin only. This period was extended to 24 months by the addition of flutamide, which is a nonsteroidal antiandrogenic agent. A partial response for 15 months was observed in four of five patients who were treated with a combination of buserelin and flutamide [12]. Treatments including progesterone (megestrol

acetate and medroxyprogesterone acetate) may be used for metastatic MBC; however, these studies included fewer patients. A 7-month partial remission was observed in five of six patients treated with a high dose of medroxyprogesterone acetate [12, 41, 99].

Prognosis

Men with breast cancer reportedly have poorer outcomes than matched women patients, even at the same disease stages, which might be because of variations in tumor biology between male and female patients [107]. Mortality in MBC has continued to improve over the past 30 years, despite its late presentation [12, 23]. The most important prognostic factor in MBC, similar to FBC, is positive axillary lymph nodes [45, 56, 71, 88, 97, 108]. The poorer progress in male patients was explained by the anatomic location of the tumor. It has been reported that nipple invasion occurs very early because of such placement, and increased lymphovascular invasion and higher axillary lymph node invasion were observed compared to FBC, despite the small tumor size; those characteristics and the referral of the patient at advanced stages result in poor prognosis [109, 110]. When matched by stage and age, men appear to have a similar or better prognosis compared to women [17, 111].

In an international population-based study including 459,846 women and 2665 men diagnosed with breast cancer in Denmark, Finland, Geneva, Norway, Singapore, and Sweden over the past 40 years, male patients had a poorer 5-year relative survival ratio than women (0.72 [95% CI, 0.70–0.75] vs. 0.78 [95% CI, 0.78–0.78], respectively), corresponding to a relative excess risk (RER) of 1.27 (95% CI, 1.13–1.42). However, after adjustment for age and the year of diagnosis, stage, and treatment, male patients had a significantly better relative survival from breast cancer than female patients (RER: 0.78; 95% CI, 0.62–0.97) [13].

In a multivariate analysis of the prognostic factors performed on patients with MBC, tumor size and nodal invasion were presented as significant prognostic factors [71]. Published data also indicate that advanced age is a predictor of lower overall survival [112]. Guinee et al. [113] showed that both axillary lymph node involvement and clinical tumor size play important roles in prognosis in 335 patients. Patients with palpable axillary lymph nodes have a twofold greater risk for disease-related death, and a tumor diameter larger than 3 cm increases the risk of treatment failure. Fixation of the tumor to the skin or chest wall and tumor ulceration were reported more often in men than in women, but these factors were not shown to affect prognosis in multivariate analyses [49].

In a retrospective analysis of Egyptian patients, the collective 5-year survival in this cohort was 46.4% [114]. Kiluk et al. reported that the 5-year survival estimates for node-positive and node-negative diseases were 68.5% and 87.5%, respectively (p = 0.3) [79]. Ethnic differences might also affect the prognosis of MBC [115]. In a Turkish cohort of 86 male patients treated over 37 years, Selcukbiricik and his coworkers reported a 65.8% 5-year overall survival rate [116]. Similar in an Iranian cohort of 64 patients, the 5-year overall survival rate was 66% [13].

The most significant protective factor is ER and PR receptor positivity. The significance of HER-2 status in MBC remains unclear because there are few studies that have assessed its significance in terms of treatment options and prognosis [23]. There is no demonstrable correlation between Ki-67 expression and MBC prognosis [117]. To identify risk factors, the period between the appearance of the symptoms and diagnosis and less differentiated tumor must indicate a bad prognosis [12]. The prognosis of ductal-type carcinoma is worse than that of the medullary, colloidal, and papillary types [41]. In another study, no connection could be found between C-erbB2 and c-myc oncogenes, p53 suppressor genes, and survival [118]. The overexpression of cyclin D1 and c-myc may correlate with better outcomes [75]. One recent study identified more high-grade, progesterone receptor-negative, HER-2-positive disease male patients who carried BRCA2 mutations [29], and earlier research found a poorer prognosis in men with BRCA2-associated tumors.

Survivorship issues in men may include sexual and hormonal side effects of endocrine therapies and unique psychosocial effects of the disease [59]. In a quality of life and symptom survey over MBC survivors, patients experience substantial sexual and hormonal symptoms [119].

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Breast Cancer in Pregnancy

23

Maurício Magalhães Costa and Paula Saldanha

Introduction

Breast cancer is the most frequent malignant pathology in developed countries. In the USA, it is the second most common cause of death from cancer after lung cancer. The American Cancer Society (ACS) estimates that 63,410 cases of female carcinoma in situ of the breast and 255,180 cases of invasive breast cancer will be diagnosed in the USA. About 41,070 deaths were estimated for 2017 [1]. On the other hand, mortality rate from breast cancer has dropped 38% from 1989 through 2014, part of this attributed to mammographic screening. Approximately 28% of cases worldwide are observed in the European region. Between 1950 and 1980, mortality from breast cancer increased in all European countries, with the exception of Norway and Sweden. Since 1990, a drop in this growth was noted, eventually leading to a reduction of cases of deaths. A progressive increase has been observed in the incidence of breast cancer, even in Latin America. In 2020, 70% of new cases are estimated to occur in emerging countries [1, 2].

In the 1960s and 1970s, the World Health Organization recorded a tenfold increase in the incidence of female breast cancer adjusted by age on the various continents. In relation to most frequent type of cancer worldwide, breast cancer is the most common among women. Breast cancer comprises 22% of new cancer cases each year. This observation is mainly attributed to the increased longevity of the population during this period [2].

The majority of the increases in the incidence rates have occurred in women over 50 years of age, but the rates also increased among younger patients. These changes in incidence are not only attributed to sociocultural factors because the incidence has also increased in women who migrate from low-risk areas to high-risk areas. These studies suggest that environmental factors have a substantial effect on the risk of breast cancer [2, 3].

Pregnancy-associated breast cancer (PABC) is defined as breast cancer that is diagnosed during gestation, lactation, or the first postpartum year [4, 5]. PABC is rare, but it is extremely serious. The disease puts the lives of both mother and fetus at risk. PABC typically causes clinical, ethical, and psychological problems as well as doubts related to diagnosis and treatment. PABC was formerly characterized by a poor prognosis and minimally efficacious treatment options due to the worsening promoted by gestation. Today, it is evaluated with less pessimism and is studied more clearly given less alarming data.

History

Klotz made the first citation regarding PABC in 1869. Following this landmark, a series of authors committed themselves to studying the disease, persistently emphasizing the very poor prognoses of these patients. In 1929, Kilgore was the first to attribute little importance to the gestational and lactation periods, opposing the idea that the disease's behavior is invariably hopeless. In 1943, Haagensen and Stout studied 29 cases of breast cancer diagnosed during gestation and the postpartum period, and 20 of these cases underwent radical mastectomies. Because a cure was not available and long-term survival was not possible, PABC was considered inoperable [6]. In 1946, Westberg evaluated 224 cases diagnosed as

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PABC in Sweden and concluded that although gestation did not influence the prognosis, it did delay the diagnosis. In the same study, he observed that interrupting the gestation did not improve the possibility of a cure [7]. In 1967, Haagensen reviewed his initial position in relation to the inoperability attributed to these cases. Since then, most authors have indicated that disease progression depends more on its stage and the compromising of the axilla at the time of diagnosis than on the association with gestation or lactation [8].

Epidemiology

In developing or underdeveloped countries, the incidence of breast cancer varies from low to moderate (20–40 per 100,000 women), with a tendency to increase over time. The incidence has increased yearly, and the International Agency for Research on Cancer (IARC) estimates an incidence of 120,000 new cases per year in Latin America. The incidence of breast cancer has increased yearly, and the International Agency for Research on Cancer (IARC) predicts 297,500 new cases for 2020 in women less than 65 years of age in Europe [9]. Breast cancer is one of the most common cancers in nonpregnant and pregnant women. Up to 20% of breast cancers in women under 30 are pregnancy-associated, but fewer than 5% of breast cancers diagnosed in women under age 50 are detected during pregnancy or in the postpartum period. Fortunately, PABC is rare. Reviewing the international literature over a period of approximately 100 years, White (1954) noted a PABC rate of 2.8% among 45,000 cases evaluated [10]. In 1983, Wallack reviewed 32 series of reports of breast cancer and reported PABC rates varying between 0.2% and 3.8% [11]. He also mentioned the incidence of 10–39 cases per 100,000 births. The incidence estimated varies from 1:3000 to 1:10,000 gestations, with a greater number of cases diagnosed during gestation compared with the postpartum period [5]. This incidence appears to be increasing because women currently delay pregnancy. The case of the youngest patient (16 years old) was reported by Birks in 1973 [12]. In 1984, Richards mentioned an 18-year-old patient with metastases [13]. In principle, one should initially suspect a primary site located in the breast in any pregnant woman who presents with metastatic adenocarcinoma.

Diagnosis

The diagnosis of PABC is always difficult and delayed. The turgidity and the irregularities in the mammary parenchyma during this period make the clinical examination difficult, delaying the indication for a biopsy and consequently the final diagnosis. Max (1983) observed that the mean delay in the detection of the disease during pregnancy ranges from 5 to 15 months compared with patients who are not pregnant [14]. This delay is serious because a delay of 1 month can increase the risk of lymph node metastasis from 1% to 2% [15]. These findings could be minimized by prenatal consultations, wherein it is possible to proceed to a more accurate clinical examination as well as self-examination.

A breast mass that persists for more than 2 weeks should be investigated. The differential diagnosis of a breast mass in pregnant or lactating women includes epithelial breast cancer, a lactating adenoma, fibroadenoma, cystic disease, lobular hyperplasia, milk retention cyst, abscess, lipoma, and, rarely, leukemia, lymphoma, phyllodes tumors, sarcoma, neuroma, or tuberculosis [16].

Ultrasound is the preferred examination for breast cancer evaluation in pregnancy and allows for ultrasound-guided biopsy if necessary. Ultrasound has been reported to have 100% sensitivity and negative predictive values in the detection of breast malignancy in pregnant women, although in some studies, sensitivity as low as 70% has been reported. In addition to assisting enhanced characterization of the mammary tumor, ultrasound may be useful in the investigation of abdominal metastases.

Mammography does not appear to reduce the delay in diagnosis. In young, nonpregnant patients (less than 35 years old), mammography may produce false-negative results in up to 50% of cases. These data appear to be increased in pregnant patients. Tests involving radiation used to track lesions at a distance, such as radiography and scintigraphy, are contraindicated in most occasions. Nevertheless, the doses associated with these techniques are below the level of danger and appear to be reasonably safe in pregnant women. If scintigraphy is essential, it may be used; however, appropriate hydration and the use of a Foley urinary catheter are important to prevent radiation retention.

Magnetic resonance imaging has been used during pregnancy and may be indicated in cases in which ultrasound is inconclusive. Although no harmful effect has been reported, the National Radiological Protection Board advises that this technique should not be used in the first trimester because insufficient evidence is available for its safe use during the period of organogenesis [17]. In animals, gadolinium has exhibited teratogenic effects, but no reports have been published regarding humans [18]. In Europe, the novel MRI contrast agents gadobenate dimeglumine and gadoterate meglumine are both currently approved for use in pregnant women, although further study regarding their efficacy and safety is necessary [19].

Tests involving radiation, such as radiography and scintigraphy, that are used to track lesions at a distance are contraindicated on most occasions. Nevertheless, it is believed that their doses are below the level of danger and reasonably

safe in pregnant women. Radiographic examinations should be performed only when the results will change clinical management. Metastatic investigations for breast cancer during pregnancy include chest radiograph, liver ultrasonography, and non-contrast skeletal MRI. Radionuclide bone scans can be used with adequate hydration and an indwelling catheter to prevent retention of radioactive agents.

Fine-needle biopsy is valuable in diagnosis. Although the specificity of mammary cytology is reduced during gestation and lactation due to the hyperplastic and inflammatory phenomena that are characteristic of the period, the increased sensitivity of this technique alerts us to the indication of surgical biopsy. A definitive diagnosis is exclusively obtained through histopathological examination. Surgical biopsy can be safely performed during pregnancy. The procedure occurs under local or general anesthesia via core biopsy or mammotomy.

With respect to the pathological aspects, most are invasive ductal carcinomas, as they are in women who are not pregnant, are predominantly poorly differentiated, and are diagnosed in more advanced stages. The pathological aspects are also associated with aggressive behavior (high incidence of grade 3 tumors, lymphovascular invasion, and a high rate of estrogen receptor negativity). Negative hormonal receptors and an increased incidence of overexpression of HER2 (human epidermal growth factor receptor 2) are also frequently found [20]. It has been reported that 80% of PABCs are infiltrating ductal carcinoma, 49–84% are estrogen receptor/progesterone receptor negative, and 28–58% are HER2/neu overexpressed. Approximately 67% present with positive lymph nodes [20, 21]. The pathological features of breast cancer do not appear to be changed by pregnancy but are determined by age.

Women with a family history or those who carry the BRCA1 and BRCA2 genetic mutations are at greater risk of developing breast cancer at a younger age, a period in which pregnancy is common. Various studies have revealed differential behavior of these mutations in relation to pregnancy. Antoniou et al. compared 457 carriers who developed cancer with 332 carriers who did not develop cancer. The protective effect of gestation was exclusively observed in those women over 40 years of age, and the occurrence of the first gestation at a more advanced age was associated with increased risk of breast cancer in women with the BRCA2 mutation and not in women with the BRCA1 mutation [22]. Cullinane et al. evaluated 1260 multiparous women who carried BRCA1 and BRCA2 mutations compared with multiparous women lacking these mutations. Women with BRCA1 exhibited a reduced risk of breast cancer, whereas those with the BRCA2 mutation exhibited an increased risk. In addition, this study also observed that BRCA2 carriers exhibit an increased risk in the first 2 years postpartum [23].

Treatment

The diagnosis of breast cancer during pregnancy has a strong emotional impact on all those involved because it affects young patients in a special period of their lives. Multidisciplinary evaluation is necessary from the beginning. Psychological assistance should be emphasized with various issues addressed: the maternal prognosis, first and foremost, followed by the effects of the therapy on the fetus, and the risk of continuing with the pregnancy. In its early stages, breast cancer does not interfere with the course of the pregnancy. However, advanced-stage breast cancer can lead to cachexia, which causes delayed intrauterine growth and preterm birth.

The course of breast cancer treatment during pregnancy must consider the gestational age and the stage of the disease. In general, the treatment follows the same advice given to cases outside the gestational cycle because no evidence is available suggesting that breast cancer in pregnant women biologically differs from that found in premenopausal women who are not pregnant. Interruption of the pregnancy does not improve survival. Additionally, the possible teratogenic risks of the therapy in isolation do not justify an interruption.

Pregnancy-associated breast cancer should be treated as aggressively as and according to the standards applicable in nonpregnant women; pregnancy after breast cancer does not jeopardize outcome. The guidelines addressing risks connected to pregnancy and breast cancer lack a high level of evidence for better counseling young women about pregnancy considerations and preventing unnecessary abortions. Ideally, evidence from large prospective randomized trials would set better guidelines, and yet the complexity of such studies limits their feasibility [24].

Surgical Treatment

In 1943, Haagensen asserted that “carcinoma of the breast developing during pregnancy or lactation is so malignant that surgery can not cure it often enough to justify this method of treatment” [6]. At that time, he defended palliative radiotherapy as the only therapy despite the fetal risk. Subsequently, Haagensen modified his criteria and began to surgically treat PABC [8].

The general anesthesia used in surgery is relatively safe for the mother and fetus. Numerous studies have indicated that there is no increase in mortality and that the risk of premature labor in extra-abdominal surgical procedures is minimal. Breast and axillary surgery can be performed during any trimester of pregnancy; however, there is an increased risk of miscarriage associated with surgery in the first trimester [25].

The choices of breast cancer surgery follow the same guidelines as for nonpregnant women. Modified radical mastectomy (MRM) is the technique stipulated most [25] and is generally recommended in the first and second trimesters to avoid radiotherapy (RT), which should be delayed until after delivery. Even for women with clinical anatomic stage I or II disease, mastectomy can be chosen, especially if the diagnosis is made early, systemic therapy is not warranted, and there would be a significant delay in performing RT. Therefore, mastectomy is not mandatory.

Breast-conserving surgery (BCS) can be used effectively because RT can be delayed after administration of adjuvant or neoadjuvant chemotherapy. BCS has no adverse impact on locoregional recurrence rates or complication rates and is considered a feasible and safe procedure during pregnancy. Survival is similar to that for mastectomy for stage I and II cancer.

Currently, the use of the sentinel lymph node technique with a radiotracer in initial tumors with clinically negative axilla is possible [26]. The procedure's radioactivity and the changes in the lymphatic drainage patterns of the breast during the pregnancy must be evaluated. The use of dyes for researching the sentinel lymph node has not been tested in animals and humans to date and must therefore be avoided. This technique is not indicated in patients with fewer than 30 weeks gestation, and lactation is contraindicated for some days following the procedure due to the excretion of the radioactive substance in the breast milk [27].

Patients whose disease is initially systemic may undergo tumor resection with the palliative objective of cytoreduction. Locally advanced and inflammatory tumors are treated with a combination of chemotherapy, radiotherapy, and surgery. In these cases, the surgery has a hygienic purpose [5].

Radiotherapy

Radiotherapy must be discouraged unless delayed until after the birth because the standard radiation technique for the breast field subjects the fetus to unacceptably high risks. A complete treatment would expose the fetus to doses between 20 and 100 cGy, depending on the field and the fundal height. The risk of malformations increases when the dose of radiation is greater than 10 cGy [28]. Maximum fetal sensitivity occurs during the period of organogenesis and up to the 20th week of gestation. However, in the last trimester, a considerable risk of adverse effects is noted due to the proximity of the fetus to the radiotherapy fields. The sequelae of radiotherapy include loss of pregnancy, malformation, growth and development disorders, and mutagenic and carcinogenic effects in the fetus [21, 29].

Chemotherapy

The primary mechanisms of action of antineoplastic chemotherapies are related to cell growth. Thus, tissues with dividing cells are very sensitive. The cells in the embryo are constantly dividing, making the fetus extremely vulnerable. The risk of teratogenesis depends on the stage of the pregnancy, during which the chemotherapy is administered, and the type of drug. The most frequent malformations occur in patients who are exposed to alkylating and antimetabolic agents in the first trimester of gestation. For example, 5-fluorouracil (5-FU), methotrexate, and 6-mercaptopurine are the most teratogenic chemotherapeutic agents.

The risks posed by the association of chemotherapy with pregnancy are not yet clear. Many of the studies have been undertaken using laboratory animals, and research in humans has been restricted to the immediate effects. Thus, information is unavailable regarding the future risk of neoplasias and the risks posed to cognitive development and fertility.

Chemotherapy is indicated in the cases of locally advanced/inflammatory/systemic disease and is neoadjuvant to the primary treatment. In all situations, one must evaluate the risk/benefit of administering chemotherapeutic agents. In the locally advanced and inflammatory disease, chemotherapy is mandatory, generally preoperative. There is urgent need to initiate the therapy, and any delay can result in increased morbidity. A 3–6-month delay can increase the risk of metastasis by 5–10% [15]. Care for the mother takes priority, and the fetal risk is secondary because the mother's life is threatened. In this situation, interruption of the pregnancy may be considered.

Adjuvant chemotherapy is indicated in patients who are treated surgically and those who have a greater risk of developing metastases. The decision to institute treatment must be discussed with the patient, and all the risks of malformations must be explained.

The chemotherapy protocols used in most breast cancer cases include cyclophosphamide/methotrexate/5-FU (CMF) and 5-FU/adriamycin/cyclophosphamide (FAC). Regarding the administration of chemotherapy, methotrexate must be excluded. A study has reported that the weekly administration of doxorubicin in the second and third trimesters resulted in satisfactory results without additional fetal risks of suffering or malformations [30].

The use of any chemotherapeutic agent during the first trimester of pregnancy must be discouraged. FAC or AC may be given with relative safety during the second and third trimesters of pregnancy [31]. Ondansetron, lorazepam, and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen. Although the use of chemotherapy in the second and third trimesters probably induces few abnormali-

ties, further studies that monitor long-term effects must be performed. Chemotherapy should ideally be postponed until after birth.

In 2010, a review of the literature evaluated 40 cases involving the administration of taxanes during gestation. The taxanes are a group of antineoplastic medications with antimitotic action that improve the prognosis of women with breast cancer, particularly those with affected lymph nodes. Docetaxel and paclitaxel are the most commonly used taxanes. Further studies are needed to evaluate the pharmacokinetics and transplacental passage [32]. If used, the National Comprehensive Cancer Network (NCCN) Panel recommends weekly administration of paclitaxel after the first trimester if clinically indicated by disease status [31].

Trastuzumab (Herceptin) is a human monoclonal antibody that is indicated in tumors that exhibit amplification or overexpression of the HER2 oncogene. Reports have indicated an association between trastuzumab and gestation, namely, that oligohydramnios is reversible upon suspension during use [33, 34]. The use of trastuzumab is contraindicated during gestation because it can lead to pulmonary hypoplasia and neonatal death. In addition, this drug must not be used by those who are breastfeeding, and breastfeeding is contraindicated up to 6 months after the last dose [34].

Lapatinib, a tyrosine kinase inhibitor that affects both HER2/neu (erbB-2) and the epithelial growth factor receptor (erbB-1), was approved for use in tumors exhibiting HER2 overexpression and in patients who do not obtain a satisfactory response through the use of trastuzumab. No studies are available regarding its safe use during pregnancy and lactation. A single case report of 11 weeks of exposure to lapatinib in the first and second trimesters during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate [35].

Methotrexate is contraindicated in all phases of pregnancy because of its abortive and teratogenic effect [31].

Hormone Therapy

Pregnancy can reduce hormonal receptor levels in the cytoplasm of breast cancer cells, culminating in false-negative results. The high levels of circulating estrogen in pregnant women cause the receptor to translocate to the nucleus. In addition, the circulating estrogen occupies all the cytoplasmic receptors.

The difficulty of defining whether the tumor is hormone receptor positive or negative is an additional obstacle to hormone therapy because it is unknown whether the tumor will respond to hormonal manipulation. In young patients regardless of pregnancy, the tumors are generally undifferentiated and hormonal receptor negative.

The relative increased incidence of malformations, miscarriages, and fetal losses suggests that tamoxifen should not be administered during pregnancy. The principal malformations observed include ambiguous genitalia, hypertrophy of the clitoris, and cleft palate [36]. Aromatase inhibitors (AI) are not used in premenopausal women but may be used with ovarian suppression via luteinizing hormone-releasing hormone (LHRH) agonists following term delivery.

Summary of the Recommendations for the Treatment of Breast Cancer During Pregnancy (Fig. 23.1)

Stages I and II

These tumors are operable. Modified radical mastectomy is the treatment of choice. Segmental resection with axillary dissection and radiotherapy is restricted to those tumors that are up to 4 cm and diagnosed close to term. A sentinel lymph node study may be indicated when the axilla is clinically negative [26]. Sentinel node biopsy should not be offered to pregnant women under 30 weeks gestation. Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is discouraged during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the nonpregnant patient. Adjuvant chemotherapy may be administered in patients with poor prognosis but only in the second and third trimesters. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3–4 weeks of planned delivery in order to avoid complications during delivery.

Stages III and IV

These stages include locally advanced tumors or systemic disease. The initial treatment is clinical via chemotherapy. The surgery indicated (i.e., hygienic mastectomy or tumorectomy) depends on the response to the treatment.

Prognosis

A review of the older literature on breast cancer in pregnancy demonstrates a worse prognosis compared with nonpregnant women [37]. Subsequent studies have revealed similar results when comparing groups with the same stage (Table 23.1). The divergence results from the fact that the

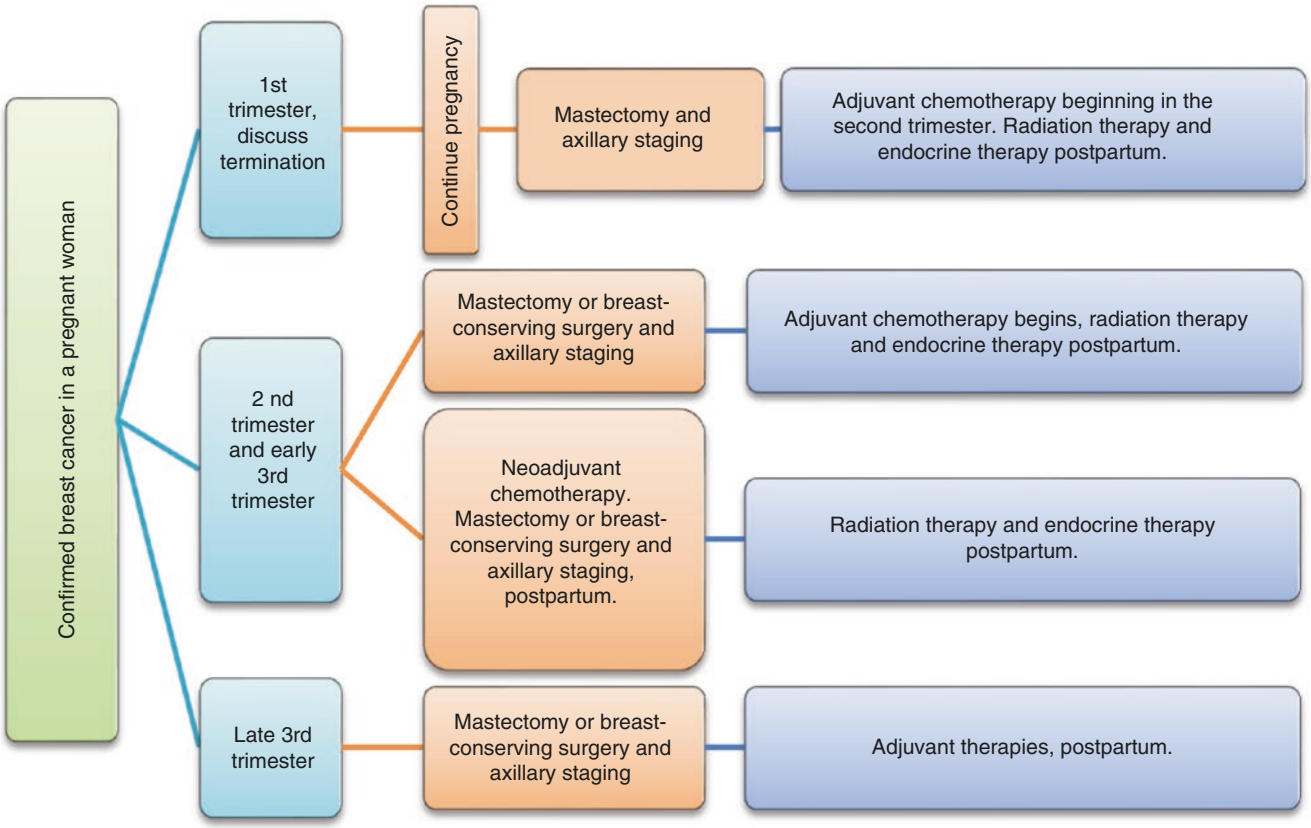

Fig. 23.1 Management of breast cancer during pregnancy

Table 23.1 Survival rate of pregnant and nonpregnant women below 40 years of age with breast cancer [38]

Survival (%)			
Stage	Pregnant	Nonpregnant	*P*
I	4/4 (100)	59/84 (70)	0.57
II	7/14 (50)	27/57 (48)	1.0
III	0/1 (0)	1/14 (7)	1.0
General	11/19 (57)	87/155 (56)	1.0

diagnosis of breast cancer in pregnant women generally occurs later and at more advanced stages.

Petrek (1994) undertook a retrospective study comparing age and stage in pregnant women with breast cancer and a control group [25]. Nugent (1985) was also associated with this study and compared groups of patients greater and less than 40 years of age [38]. The results demonstrated that age, not pregnancy, is the main predictive factor of a poor prognosis.

Effects on the Fetus and Gestation

The embryonic period lasts up to the ninth week of gestation, when the embryo is 4 cm in size and most of the organs are forming. From the tenth week onward, the fetal period begins, which is characterized by the growth and maturation of the newly formed structures. Harm during the embryonic period results in spontaneous miscarriage or significant malformations, whereas deficiencies of growth and development predominate in the fetal period. The susceptibility to teratogenic drugs and radiation decreases as the pregnancy progresses, and this susceptibility becomes minimal after organogenesis (20 weeks) [39, 40].

Children who had prenatal exposure to cancer and the associated stress, imaging studies, and treatments have normal development during testing at 18 months, 36 months, or both. Chemotherapy has no clear adverse effects on postnatal growth or on cognitive or cardiac function. The diagnosis of cancer during pregnancy is not an indication to terminate the pregnancy. Treatment of the maternal cancer in the second trimester or later may not be harmful to the fetus. Pregnant women may be informed that the likelihood of prematurity is higher than that in the general population, but among preterm babies, the child is unlikely to have unique problems more serious than those of preterm babies born of women without cancer during pregnancy [19].

Although no guidelines have been issued for obstetricians to monitor pregnant patients treated for breast cancer, some

important care should be taken. Before staging examinations or oncological treatment, fetal structural development should be assessed to exclude preexisting anomalies. Preterm labor and growth restriction are increased, and thus perinatologists should pay special attention. When anthracyclines are used, special consideration should be given when maternal conditions involving the cardiovascular system are apparent. When breast cancer is diagnosed in the third trimester and when only one cycle of chemotherapy is needed before fetal maturity, delivery at 35 weeks and postnatal start of treatment can be considered. A 3-week interval should be left between the last cycle of chemotherapy and delivery to avoid problems associated with hemopoietic suppression (bleeding, infection, anemia) in the mother and baby and to avoid drug accumulation in the fetus. The examination of the placenta is advised [20].

Metastases of any kind to the fetus and placenta are rare. 52 cases are reported in the literature (different sites), including 45 for the placenta and 7 for the fetus. Although no case of breast cancer metastasis to the fetus has been reported, four studies have reported breast cancer metastasis to the placenta [41].

Stages I and II do not interfere with the progression of the pregnancy. In advanced and metastatic cases, the general state of the pregnancy may be compromised due to cachexia and consequently delayed intrauterine growth.

The type of birth does not interfere in the progression of the disease. The criteria must be rigorously obstetric.

Lactation

There is no evidence that the suppression of lactation improves the prognosis of patients experiencing breast cancer during the pregnancy-postpartum cycle. Lactation appears to be safe and possible. Breastfeeding from the contralateral breast is not affected.

In patients who receive conservative surgery and subsequent radiotherapy, the production of milk may be affected in the treated breast. Breastfeeding is not recommended from the irradiated breast due to the increased risk of developing mastitis.

The majority of the drugs used to treat breast cancer (mainly the alkylating agents) are excreted in human breast milk. Lactation must be avoided during chemotherapy with trastuzumab and lapatinib and during endocrine therapy [42, 43].

Fertility and Subsequent Pregnancy

The development of modern treatments for malignant tumors allows long survival and preservation of gonadal function. Pregnancies after successful treatment of breast cancer do not worsen prognosis.

The risk of infertility is a difficult topic to study because few studies have focused on and collected outcomes and due to the difficulty in determining the right metric for fertility. Although it is easiest to assess for the presence or absence of menses, data in the postchemotherapy population demonstrate that ovarian reserve may be diminished despite the resumption of regular menses; however, it should be noted that menstruation does not necessarily connote fertility. Given that the risk of chemotherapy-related amenorrhea (CRA) increases by an order of magnitude over only a 5–10-year interval, considering average CRA rates for all premenopausal women is of limited value for an individual patient; age-stratified data and the discovery of biomarkers predictive of fertility after treatment are needed and are the focus of ongoing research efforts.

Despite these limitations, a general understanding and estimation of a woman's infertility risk with a specific treatment regimen are necessary components of effective fertility preservation counseling. The risk of CRA directly correlates with cyclophosphamide dose because alkylating agents are particularly gonadotoxic. Hence, cyclophosphamide/methotrexate/5-fluorouracil (CMF) causes significantly higher rates of CRA than doxorubicin/cyclophosphamide (AC). The gonadotoxic effect of docetaxel is also unclear. Further investigation of docetaxel-based regimens is warranted. Gathering data on the clinical gonadotoxicity of platinum agents should also be a priority, given recent evidence that platinum compounds are particularly effective in BRCA1/2-mutated patients.

Recently, pretreatment levels of anti-Müllerian hormone (AMH) have consistently appeared to predict chances of postchemotherapy recovery of ovarian reserve and menstruation. In one multivariable model, baseline body mass index (BMI) in the overweight or obese range (compared with the normal range) also predicted menstrual resumption, in addition to age and AMH levels, although data regarding BMI have been inconsistent [44].

The best-established method for preserving fertility is embryo cryopreservation, followed by in vitro fertilization (IVF) and embryo freezing. Oocyte cryopreservation, which was adopted as a standard treatment for infertility in 2012 by the American Society for Reproductive Medicine when success rates were improved, is similar to embryo cryopreservation except that oocytes are frozen before fertilization. A concern associated with both methods is the need to delay cancer treatment. The second major issue associated with standard ovarian stimulation methods is the use of exogenous hormones that increase (approximately ten times normal) estrogen levels, a concern in patients with hormone-sensitive malignancy.

Additional fertility-preserving methods are in development. Cryopreservation of ovarian tissue involves surgical oophorectomy and cryopreservation of ovarian cortical strips before chemotherapy. Subsequently, the ovarian tissue is thawed and transplanted back into the host in an autologous fashion.

The first report of a successful pregnancy resulting from this method, documented in a young woman who became infertile after receiving high-dose chemotherapy for non-Hodgkin's lymphoma, was published in 2005. As of 2013, at least 42 live births had been achieved via auto transplantation of ovarian tissue [44].

A final strategy and a topic of much debate is the use of gonadotropin-releasing hormone (GnRH) agonists concurrent with chemotherapy. The use of GnRH agonists has been posited to improve the chances of ovarian recovery. Two large breast cancer-specific randomized controlled trials, the Prevention of Early Menopause Study (POEMS) and the PROMISE trial (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients), demonstrated a significantly lower rate of postchemotherapy ovarian failure in patients receiving a GnRH agonist plus chemotherapy versus chemotherapy alone [44]. Although increasing data support the use of GnRH agonists for ovarian protection, it is important to note that the overall body of evidence remains inconsistent.

The effect of chemotherapy on ovarian function is similar to that of radiotherapy, and the probability of ovarian insufficiency is proportional to the cumulative dose and the patient's age. Young patients are less prone to present permanent ovarian insufficiency.

Many women treated for breast cancer wish to become pregnant in the future. It was formerly believed that gestations could favor tumor relapses due to the high hormonal levels; however, studies by Hoover (1990) and Vange (1991) [45, 46] demonstrated that a further pregnancy does not influence prognosis. Petrek et al. (1991) demonstrated greater survival in a group of patients who became pregnant than in a control group [47].

Although a subsequent gestation does not alter the prognosis, it is recommended that patients should avoid a further pregnancy for at least 2 years following diagnosis. The highest risk of relapse occurs in the first 2 years, and the recurrence of the cancer in a pregnant woman would complicate treatment. The POSITIVE trial (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer; ClinicalTrials.gov identifier: NCT02308085) is a currently enrolling single-arm study that will prospectively evaluate the safety of interrupting hormonal therapy to attempt pregnancy for women with hormone receptor-positive breast cancer, including disease, reproductive, and psychosocial outcomes. These data will help address several outstanding questions in this area [44].

Interruption of the Pregnancy

Formerly, interruption of the pregnancy was routinely indicated as part of the treatment for breast cancer because it was believed that placental hormones stimulated tumor cell growth. Furthermore, in the pregnancy, immunological alterations cause reduced cellular immunity.

Studies by Max [14], Ribeiro [48], and Hoover [45] demonstrated that interruption of the pregnancy does not influence the prognosis; currently, this practice is exclusively indicated in cases wherein there is risk to the mother's life.

Conclusion

Various factors have been implicated in the poor prognosis of PABC, including high hormonal levels, lymphatic and blood vessel vasodilation, and pregnancy-associated immunodeficiency. However, this prognosis does not depend to such an extent on the pregnancy; it is mainly associated with the clinical stage of the disease and these patients' young age.

If there is clinical suspicion of a mammary tumor during pregnancy and lactation, we must never delay the diagnosis. Fine-needle biopsy and ultrasound can be useful; however, negative results do not exclude the need for surgical biopsy. Once the disease is diagnosed, its stage must be established quickly, always bearing in mind the difficulties caused by the gestation.

The treatment frequently encounters clinical and ethical obstacles. The gestational age is fundamental in our therapeutic options, resulting in persistent modifications and procedural delays. Surgical treatment can be undertaken in any phase of the pregnancy. Chemotherapy may possibly be administered in the second or third trimesters. Endocrine therapy and radiation therapy are contraindicated during pregnancy, and these treatments are reserved for the postpartum period.

Interruption of the gestation does not affect the treatment; however, it undoubtedly facilitates therapeutic conduct. The indication of this course of action must be undertaken with great consideration and discussed openly with the patient and her family.

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Paget's Disease of the Breast

24

Abdullah Igci, Nihat Aksakal, and Enver Özkurt

Introduction

Paget's disease of the breast is a rare breast tumor that was first identified by Sir James Paget in 1874 [1]. Paget's disease of the breast is characterized by eczema-form changes accompanied by erosion and ulceration of the nipple and areolar epidermis and is mostly correlated with ductal carcinoma in situ (DCIS). Additionally, Paget's disease of the breast can be accompanied by invasive ductal carcinoma (IDC). The diagnosis of Paget's disease of the breast is determined upon microscopically observing Paget cells in a skin biopsy. The width of the lesion is evaluated via mammography and magnetic resonance imaging (MRI) in patients for whom breast-preserving surgery is planned. Based on the extent of the lesion, sentinel lymph node biopsy and axillary curettage for those with axillary metastases are the treatment alternatives to breast-preserving surgery or mastectomy.

Epidemiology

Paget's disease is a less frequent malignant breast tumor than other breast cancers, constituting 0.5–3% of all breast cancers [2–4]. The incidence of Paget's disease is reported to be 1% clinically, but histologically, the incidence of Paget's disease has been reported to be approximately 5% in some mastectomy series. Paget's disease is observed in all decades of life in adult women; however, it is most frequently observed in postmenopausal women in the sixth and seventh decades of life [5, 6]. Paget's disease develops on the ground of a ductal carcinoma, most frequently on DCIS ground. Rarely, Paget's disease is observed in men, and its clinical course is similar to that of other breast cancers.

Pathogenesis

The transformation theory and epidermotropic theory have been suggested for the pathogenesis of Paget's disease. The transformation theory suggests that Paget's disease develops as a result of malign changes of the epidermal keratinocytes on the nipple skin independently from ductal epithelial malignancy. In some cases, Paget's disease is accompanied by parenchymal breast disease; however, it is suggested that these two tumors are independent from one another because Paget's disease has peripheral localization [7–9]. According to the epidermotropic theory, Paget's disease originates from an underlying breast disease. Paget cells develop via the migration of neoplastic ductal epithelial cells toward the epidermis of the nipple through ductal canals. The fact that DCIS and IDC accompany Paget's disease to a great extent supports the accuracy of this theory. Other evidence confirming the accuracy of this theory includes molecular markers, such as HER2, that show similarity to Paget's disease and underlying ductal epithelial breast tumors; additionally, Paget cells and ductal epithelial cells show similarity in immunohistochemical (IHC) staining. Furthermore, epidermal keratinocytes are not similar to Paget cells [10–12].

Clinic

Paget's disease begins with itching, redness, crusting, and ulceration of the nipple and areola (Fig. 24.1). Erosions and ulcerations imitating eczematous lesions appear around the nipple [13, 14]. At times, hemorrhagic nipple discharge can occur as well. When symptoms such as pain, itching, and burning occur, Paget's disease can easily be confused with benign skin diseases of the nipple. Application of medical treatment is thus the most significant cause of delay in

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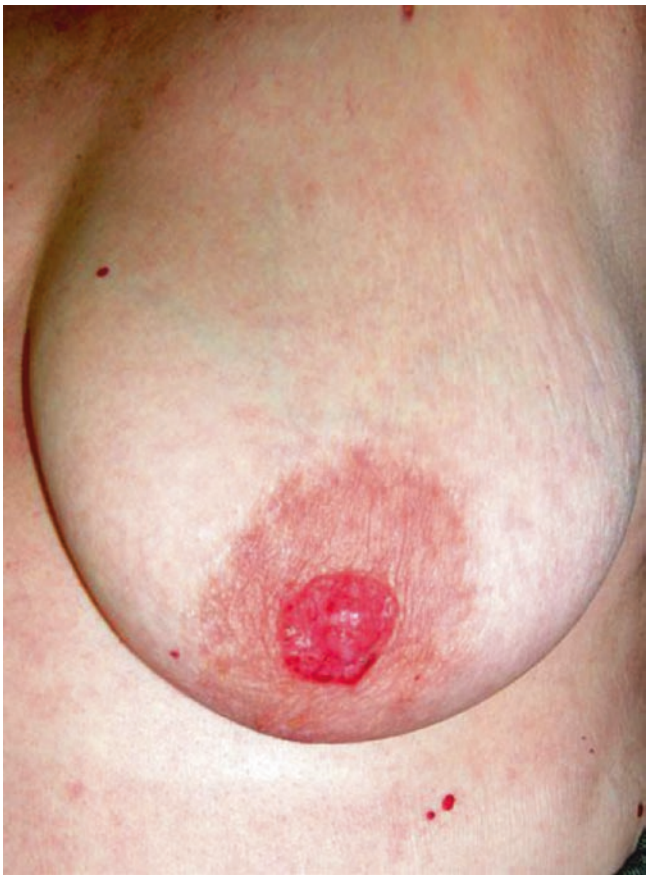

Fig. 24.1 Redness, crusting, and ulcer of the nipple and areola

diagnosis. The disease is mostly unilateral, but bilateral cases have been reported. The involvement of the entire nipple and areola in cutaneous Paget's disease is a less frequent malignant breast tumor than other breast cancers, constituting 0.5–3% of all breast cancers [2–4]. The incidence of Paget's disease is reported to be 1% clinically, but histologically, the incidence of Paget's disease has been reported to be approximately 5% in some mastectomy series. Paget's disease is observed in all decades of life in adult women; however, it is most frequently observed in postmenopausal women in the sixth and seventh decades of life [5, 6]. Paget's disease develops on the ground of a ductal carcinoma, most frequently on DCIS ground. Rarely, it is observed in men, and its clinical course is similar to that of other breast cancers.

Differential Diagnosis

Benign skin diseases such as contact dermatitis and psoriasis, which resemble eczematous lesions, should generally be considered first. When these lesions are considered in differential diagnosis, short-term steroid treatment can be accepted. However, in unilateral and chronic-coursing lesions, Paget's disease should definitely be considered in differential diagnosis. Additionally, some malignant skin lesions, such as basal cell carcinoma, superficial spreading malignant melanoma, and Bowen's disease, should be considered in differential diagnosis [7, 15].

Detailed anamnesis is very significant, and whether symptoms such as pain, burning, itching, nipple discharge, and hemorrhage are accompanied by the initiation process of the lesions should be determined. Risk factors should be taken into consideration in terms of individual and familial breast cancer. The breasts should be examined bilaterally, and suspected nipple lesions should be evaluated via biopsy.

Diagnosis

Mammography

In approximately half of Paget patients, mammographic abnormalities, such as microcalcifications, masses, and parenchymal distortions, are detected. The sensitivity is extremely high in palpable lesions but low in nonpalpable lesions. Accompanying parenchymal tumors and extensive microcalcifications may alter surgical treatment alternatives in patients, particularly in those for whom breast-preserving surgery is planned. The presence of multicentric tumors and synchronous tumors in the other breast should be investigated. Thus, patients should be evaluated via bilateral mammography in Paget's disease [16, 17].

Ultrasound (US)

Ultrasound (US) is a very beneficial complementary imaging method, particularly in patients who are negative mammographically. US is more sensitive in showing a mass or parenchymal distortion, and it is also a good alternative for evaluation of the axilla [18, 19].

Magnetic Resonance Imaging (MRI)

Although MRI has low sensitivity in terms of DCIS, it is a very sensitive method for the evaluation of IDC. MRI can show the difference between normal tissue and a nipple-areola complex (NAC) with a tumor. In nonpalpable and preoperative evaluations, it is a very beneficial method for occult lesions for which mammography and US are negative. However, negative MRI findings do not exclude the presence of occult lesions [20, 21].

Biopsy

The definitive diagnosis of Paget's disease is revealed via histopathological examination. A diagnosis can be made with a nipple swab; however, obtaining a tissue sample from the lesion via a full-thickness wedge or punch biopsy is generally required. In microscopic evaluation, Paget cells not invading the basal membrane are observed. These cells

consist of hyperchromatic cells with a wide, clear cytoplasm and a prominent nucleolus (Figs. 24.2 and 24.3). They are present in the nipple epidermis as single cells or in groups. Histologically, these cells can be confused with malignant melanoma because of the presence of epidermal cells containing melanin. The presence of cytoplasmic mucin vacuoles may be helpful in the diagnosis. Immunohistochemical tests may be helpful in differential diagnosis. In immunohistochemical tests, positive staining for CEA and negative staining for S100 are differentiating characteristics of malignant melanoma. Positivity for estrogen and progesterone (which is negative in half of cases) is very beneficial. Hormone receptor negativity is mostly accompanied by high grades of invasive ductal carcinoma. Cytokeratin positivity with low molecular dominance is a helpful characteristic for differentiating Bowen's disease, which displays cytokeratin positivity with high molecular dominance.

In the absence of typical histopathological findings, CK7 is a very beneficial marker [22, 23].

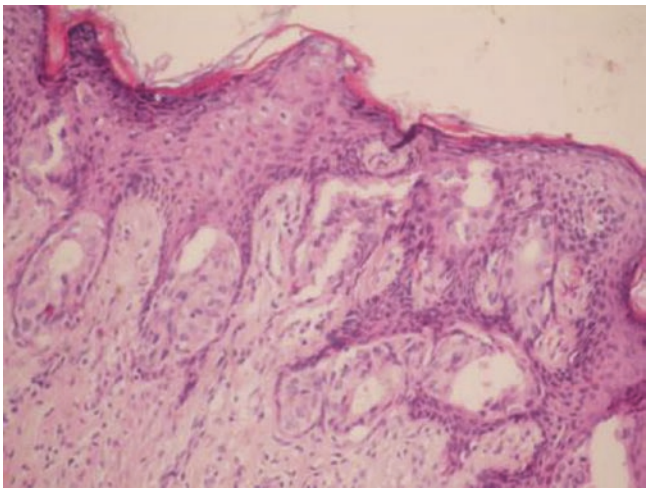

Fig. 24.2 A case of Paget's disease of the nipple: neo-plastic glandular cells inside the nipple epidermis (hematoxylin-eosin × 20 original magnification)

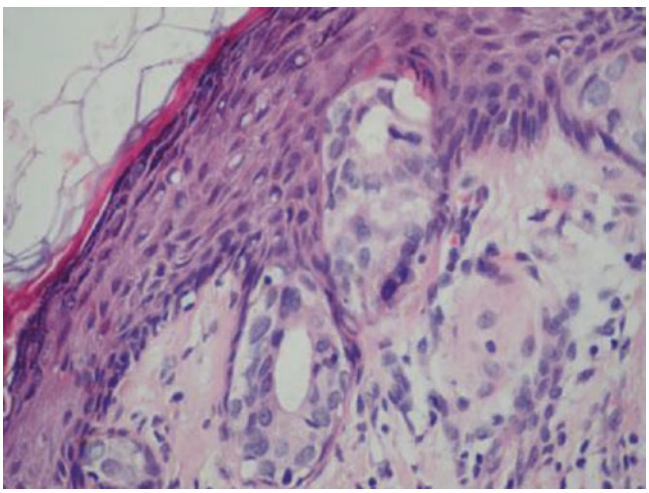

Fig. 24.3 Detailed appearance of neoplastic glandular cells of Paget's disease of the nipple. Note the neoplastic cells are forming apparent glandular structures inside the epidermis (hematoxylin-eosin × 40 original magnification)

Staging

Staging is conducted in accordance with the TNM classification of the accompanying breast tumors. The presence of Paget's disease does not change the stage of the tumor. Paget's disease is classified as Tis (Paget) in isolated disease.

Treatment

Determining the treatment of Paget's disease is based on whether an accompanying parenchymal pathology exists in the same side. The main factors that determine the treatment approach are the size, invasive characteristics of the accompanying tumor, and whether it is an axillary lymph node or not. Simple mastectomy was a preferred method in the past, but recently, breast-preserving surgery has gained favor. Paget's disease is more likely to be diagnosed at an advanced stage than conditions not accompanied by a mass [24]. In this condition, mastectomy is required in many patients. In the presence of a palpable mass or mammographic abnormality, breast-preserving surgery involving the nipple-areola complex with negative surgical margins and acceptable cosmesis can be performed. In this situation, administering radiotherapy to the entire breast is required. In addition, breast-preserving surgery performed with negative surgical margins and reduction of the other breast to provide symmetry and cosmesis can be performed for large breasts (Fig. 24.4).

Simple mastectomy should be preferred in cases with extensive microcalcification, multicentric cancer, or positive histological margins despite re-excision. Despite achieving negative surgical margins, simple mastectomy may be preferred in conditions with poor cosmesis.

In most Paget cases not accompanied by a palpable mass or microcalcification, an underlying carcinoma is the subject. Most of these cases are DCIS; a few are invasive cancers. In this situation, simple mastectomy or breast-preserving surgery involving the nipple-areola complex (central resection) and radiotherapy may be preferred. Local recurrence, disease-free survival, and life expectancy are similar in these two methods [25]. The risk of axillary lymph node metastasis is higher in Paget patients with invasive cancer and a

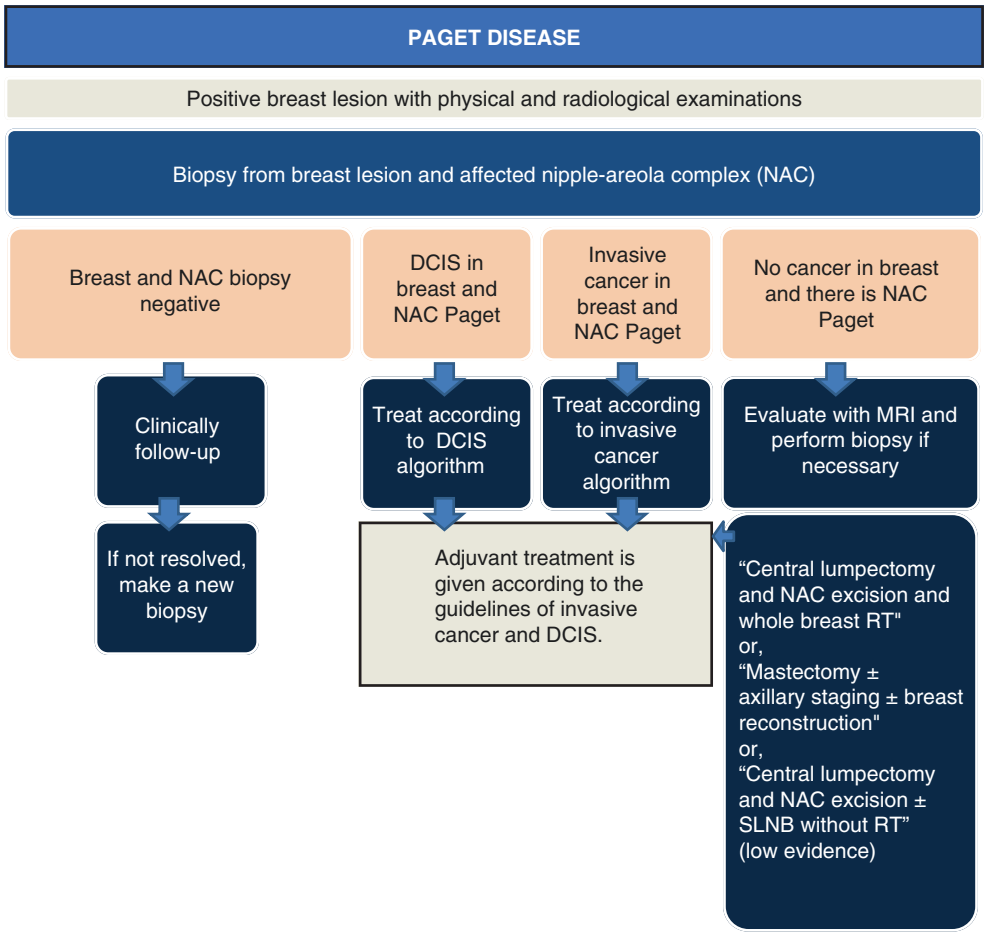

Fig. 24.4 Management of Paget disease

palpable mass. The evaluation of axillary lymph node metastasis and the treatment algorithm are similar to those for other cancers of the breast [26, 27].

Adjuvant Systemic Therapy

Systemic chemotherapy in Paget carcinoma is necessary in cases of invasive cancer and axillary involvement. Endocrine treatment is preferred, as with DCIS.

Prognosis

Tumor stage is the most significant marker affecting the prognosis of Paget's disease. Accompanying invasive ductal cancer and the presence of axillary lymph node metastasis are factors affecting the prognosis. Because the presence of a palpable mass is accompanied by advanced-stage disease, the prognosis is worse than in patients without a mass [28, 29]. Survival in cases without invasive cancer is similar to that in DCIS cases. Additionally, the survival of patients who undergo mastectomy is similar to that of patients treated with breast-conserving surgery and adjuvant radiotherapy.

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Phyllodes Tumors of the Breast

25

Fatih Aydoğan, Yunus Taşçı, and Yasuaki Sagara

Introduction

Phyllodes tumors are rare fibroepithelial neoplasms of the breast that comprise <1% of all breast malignancies and 2–3% of fibroepithelial neoplasms [1, 2]. Müller first described phyllodes tumors in 1838 as a mass with leaflike projections and cysts [3]. The clinical course for phyllodes tumors can be unpredictable, but these neoplasms are typically benign, unlike their namesake. In the past, these neoplasms have had various names; however, the World Health Organization (WHO) has designated "phyllodes tumors" as the standard nomenclature, with its histological types classified as benign, borderline, and malignant [4]. The malignant form of phyllodes tumors can have an aggressive clinical course with local recurrence and metastatic spread, whereas the benign form is clinically nearly indistinguishable from a benign breast lump. It is important to differentiate a phyllodes tumor from fibroadenomas, which are treated differently. Diagnostic evaluations remain challenging because these tumors have few characteristic findings on most imaging modalities. The surgical management of phyllodes tumors typically consists of wide excisions with adequate surgical margins or simple mastectomies.

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Epidemiology and Risk Factors

Because of the rarity of these tumors, well-defined risk factors have not been identified. There is some evidence suggesting that there is increased risk for East Asians and for Latina women born in Central or South America but living in the United States [5–7]. For women in the United States, the incidence rate for malignant phyllodes tumors is 2.1 cases per million [5]. In addition, these tumors are clearly more frequent in women, with only a few cases reported in men, which have invariably been associated with gynecomastia [8, 9].

Clinical Presentation and Diagnosis

According to the current literature, the median age of patients diagnosed with phyllodes tumors is 45 years, with an age range of 9–93 years [2, 5, 10, 11]. Although phyllodes tumors can be observed in all ages, the majority of patients are over 40 years old [1, 2, 5]. The most common symptom leading to diagnosis is a rapidly growing mass in the breast (Fig. 25.1). Dilated veins and a blue discoloration can also be observed with large tumors (Fig. 25.2); however, nipple retraction and skin ulcerations are uncommon. Bilateral cases are very rare, with an occurrence rate of 1.6% [8]. The mean tumor size ranges between 5.2 and 7.3 cm [8, 12, 13]. Tumors up to 50 cm in size have been reported in the literature [14, 15]; however, tumor size and growth rates are not often associated with histopathology. Clinical, radiological, and histopathological evaluations of suspected breast lumps are mandatory. Ultrasound imaging typically shows a smooth, lobulated border, a radiolucent halo, and coarse microcalcification, but malignant calcifications are rare. Intramural cysts and an absence of posterior acoustic enhancement can be present. On mammographic imaging, phyllodes tumors typically appear as nonspecific, large, round, or oval masses with well-circumscribed lesions (Fig. 25.3). There is no indicator of malignancy or any characteristic findings on ultrasounds

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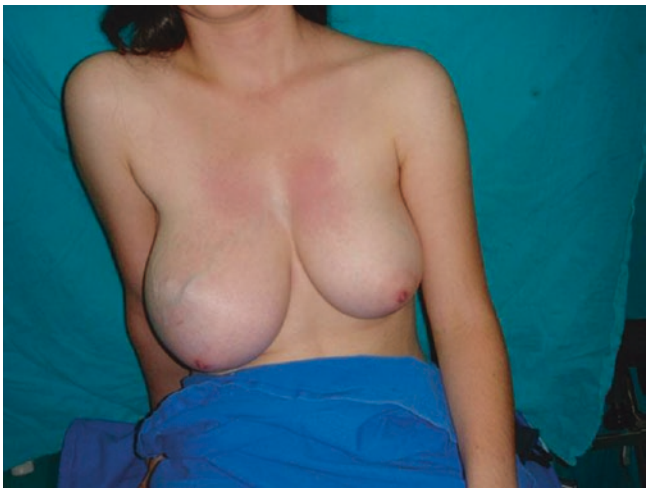

Fig. 25.1 Presentation of a giant primary phyllodes tumor

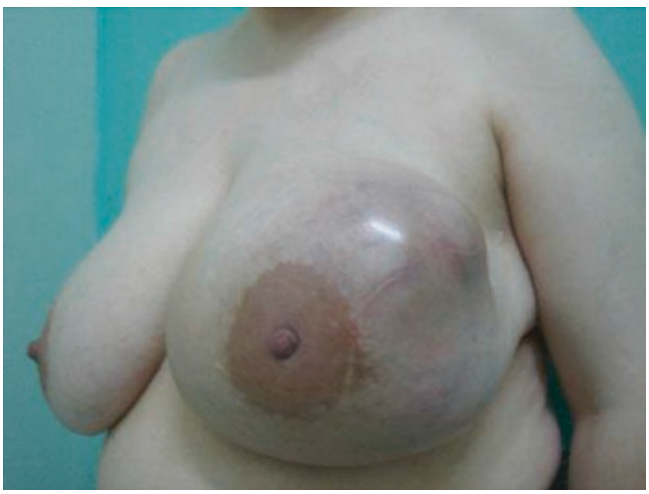

Fig. 25.2 Presentation of a giant recurrent malign phyllodes tumor

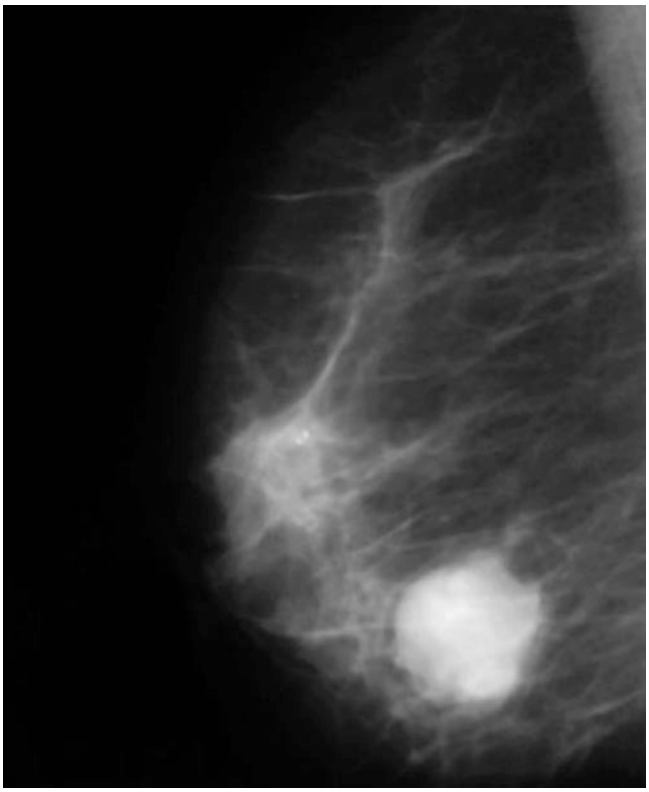

Fig. 25.3 Mediolateral oblique mammography view demonstrating a circumscribed round mass

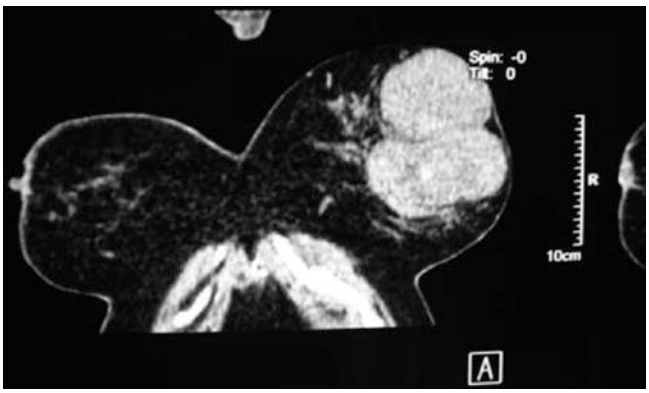

Fig. 25.4 Magnetic resonance imaging of a phyllodes tumor

or mammography. Phyllodes tumors have higher signal intensities than normal breast parenchyma on T1-weighted images and lower or equal signal intensity on T2-weighted images (Fig. 25.4). The role of magnetic resonance imaging (MRI) in this setting remains under debate, but some authors have found evidence suggesting that MRIs may correlate with histopathology [2, 16]. A fine-needle aspiration (FNA) biopsy is often inadequate for a clear, differential diagnosis. Ultrasound-guided Tru-Cut biopsies can be a useful method but can be insufficient in some cases. Differentiating between fibroadenomas and benign phyllodes tumors is more difficult than differentiating between benign and malignant phyllodes tumors. The accuracy of clinical, radiological, and histopathological diagnoses is poor; all three have low specificity. Both epithelioid and stromal components must be visible to confirm a pathological diagnosis, but only the stromal component determines the biological behavior [17] of phyllodes tumors. Generally, there are no masses in the axillary region. Axillary palpable nodes, which are observed in 20% of patients, are often reactive in nature [13, 18]. Phyllodes tumors metastasize hematogenously rather than through the lymphatic system; therefore, routine axillary dissection is not recommended [2, 8, 13].

Pathology

Fibroepithelial neoplasms mostly originate from the stroma in the terminal ducto-lobular unit. Phyllodes tumors are evaluated in fibroepithelial neoplasms, and their microscopic appearance is widely variable, often mimicking fibroade-

noma or sarcoma (Fig. 25.5). The established histological types—benign, borderline, and malignant—are determined by the tumor margin, stromal cellularity, stromal overgrowth, tumor necrosis, cellular atypia, and number of mitoses per 10 high-power fields (hpf), as defined by Azzopardi and Salvadori [10, 19] (Table 25.1). A phyllodes tumor is not a pure sarcomatoid lesion. If there are no epithelial components observed during a histological examination, tissue sarcomas [20] should be considered. The clinical appearances of malignant and benign phyllodes tumors are more alike than different; however, tumors of the malignant type often show a more aggressive course. Today, it is widely accepted that fibroadenomas should be treated conservatively; therefore, it is critical to differentiate between benign phyllodes tumors and fibroadenomas, which display similar clinical, radiological, and cytological findings. Benign phyllodes tumors constitute between 35% and 64% of known cases, whereas the malignant form constitutes approximately 25% of cases [13, 15]. Fibroadenomas and phyllodes tumors can appear synchronously or metasynchronously. Noguchi et al. showed that phyllodes tumors can arise from monoclonal proliferation caused by somatic mutations in a portion of a fibroadenoma [21]. Because of the rarity of this phenomenon, there are no well-described risk factors; however, the expression levels of some genetic factors, such as Ki-67, p53, c-myc, c-kit, CD117, and actin, may be helpful in distinguishing between the malignant and benign forms [22–24].

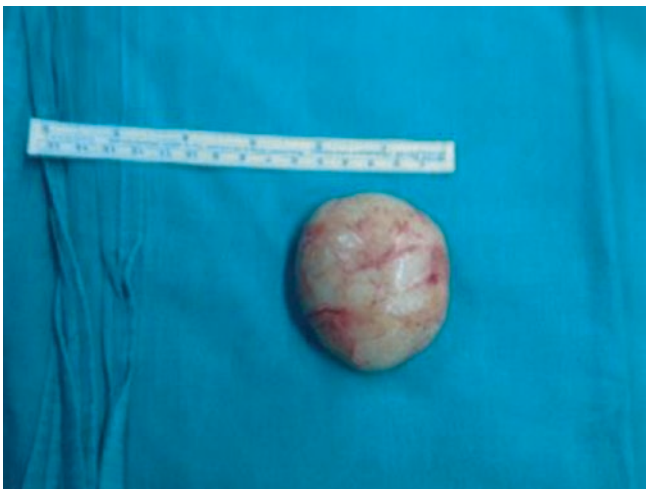

Fig. 25.5 Gross specimen of a phyllodes tumor

Table 25.1 Histological features used in the classification of phyllodes tumor subtypes

Histological features	Benign	Borderline	Malignant
Tumor margins	Pushing	↔	Infiltrative
Stromal cellular atypia	Mild	Marked	Marked
Mitotic activity	<4 per 10 high-power fields	4–9 per 10 high-power fields	≧10 per 10 high-power fields
Stromal overgrowth	Absent	Absent	Present

Treatment

Surgery is the mainstay treatment of phyllodes tumors [25]. Wide excision with at least 10 mm tumor-free margins should be performed for recurrent and malignant forms of the tumor [26]. However, due to the lack of an accurate preoperative diagnosis, these tumors are treated as fibroadenomas with enucleation [27]. Wide excision tends to be preferred for all phyllodes tumors, but recent data have revealed that there is no direct relationship between the margin status or width of negative margins and recurrence [26, 28]. Additionally, re-excision may cause poor cosmetic results. A consensus review for phyllodes tumors of the breast recommended that the conservative approach be used for benign phyllodes tumors that have been initially enucleated without margins [26]. Mastectomy is preferred for patients with a giant lesion. The management for phyllodes tumors is shown in the algorithm presented in Fig. 25.6. Axillary lymphadenopathy is clinically positive in 10% of patients, but metastases occur in <1% of patients [2, 29]. Adjuvant radiotherapy after breast-conserving surgery should be considered for malignant phyllodes tumors larger than 2 cm in diameter [30–32]. There are no prospective randomized data supporting the use of radiation treatment with phyllodes tumors. However, in settings in which additional recurrences would create significant morbidity (e.g., chest wall recurrence following mastectomy), radiation therapy may be considered following the same principles that are applied for the treatment of soft tissue sarcoma. Adesoye et al. noted increasing utilization of adjuvant radiotherapy in patients diagnosed with phyllodes tumors of the breast based on the Surveillance, Epidemiology, and End Results Program (SEER) database [33].

The use of adjuvant chemotherapy is more controversial and is generally not recommended. There is no evidence that adjuvant cytotoxic chemotherapy provides benefits in reducing recurrences or death. Although the epithelial component of most phyllodes tumors contains estrogen receptor (58%) and/or progesterone receptor (75%), endocrine therapy has no proven role in the treatment of phyllodes tumors [34].

Twenty percent of phyllodes tumors lead to metastases in distant organs. In most of these cases, the affected organs are the lungs and pleura. Chemotherapy, radiotherapy, and hormonal therapies are all used to treat metastatic disease, but their role and efficacy are unclear.

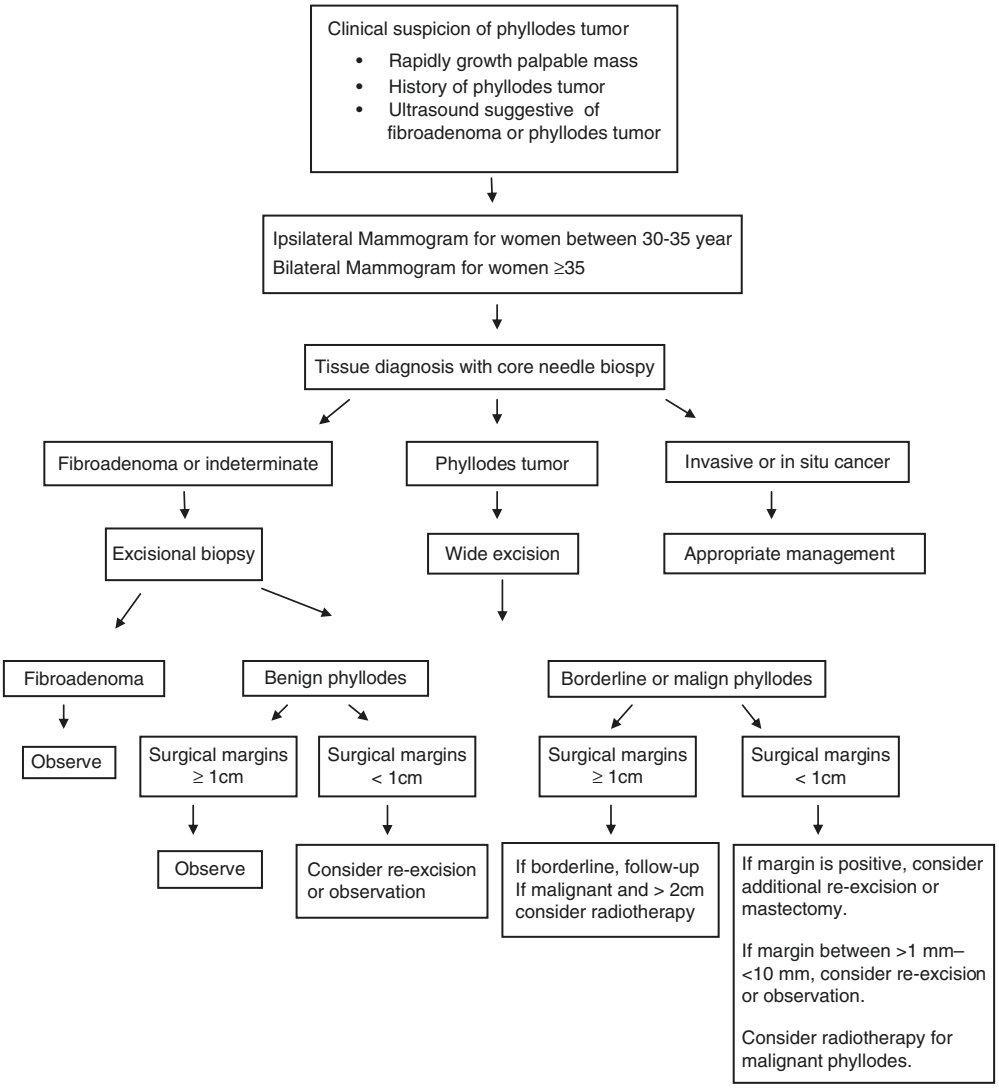

Fig. 25.6 Management algorithm for a phyllodes tumor

Local Recurrence and Metastatic Disease

Local recurrence rates ranging between 0% and 60% have been previously reported [26, 31]. Local recurrence usually occurs within the first 2 years [35]. For patients with positive surgical margins, the local recurrence rates are as high as 32% [8]. Distant metastases are very unusual in the benign form, but it has been reported that borderline tumors can metastasize to distant organs [13].

Follow-Up

The most important mode for detecting recurrent disease is clinical evaluation. After treatment for a phyllodes tumor, a clinical assessment should be performed every 6 months. In the vast majority of recurrences, breast phyllodes tumors develop in the excision bed. The 5-year survival rates are approximately 96%, 74%, and 66% for benign, borderline, and malignant types, respectively [2, 35].

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Nonepithelial Malignancies of the Breast

26

Gursel Remzi Soybir

Sarcomas

Epidemiology

Breast sarcomas comprise a heterogeneous group of malignant tumors arising from nonepithelial elements of the breast. They are quite rare neoplasms, constituting less than 1% of breast cancers and less than 5% of all sarcomas. The increased use of radiotherapy has led to increased breast sarcoma incidence. Breast sarcomas resemble other soft tissue sarcomas of the body. It is very important to differentiate breast sarcomas from other breast cancers because they have substantial biological differences. The phenomenal and predominantly retrospective literature makes it difficult to understand the nature of the disease and to direct disease management. Breast sarcomas are a disease of advanced age, with the median age of breast sarcoma patients between 50 and 60. The disease is more common in women for all subgroups except leiomyosarcomas, for which the incidences are equal in both genders [1–5].

Etiology

The large majority of breast sarcomas have no familiar etiologic factors. While previous radiotherapy and chronic lymphedema are the main etiologic factors, exposure to vinyl chloride, arsenic compounds, and alkylators and exposure to artificial implants are also risk factors. An incidence of 0.3% in 15 years has been reported for breast sarcoma. Radiation-induced sarcomas usually present with more advanced disease than primary sarcomas because of the delay in diagnosis due to changes after radiotherapy. Angiosarcomas appear to be the most common type of radiation-induced sarcoma, while undifferentiated pleomorphic sarcoma, leiomyosarcoma, and liposarcoma are the other common subtypes. Ultimately, breast sarcomas may be part of the spectrum of tumor syndromes such as Li-Fraumeni syndrome or Cowden disease that result from genetic mutations [1, 5–10].

Subgroups

Breast sarcomas are generally divided into three distinct groups. The first group is malignant phyllodes tumors, in which the tumor cells originate from epithelial cells. The second and third groups are primary breast sarcomas and postirradiation breast sarcomas, respectively [3]. However, malign phyllodes tumors are usually excluded from soft tissue sarcomas of the breast as a distinct clinicopathologic entity [4]. Breast sarcomas are histologically similar to soft tissue sarcomas and include all subtypes. Although all of the subtypes have been reported to occur in breast, the most common subtypes are angiosarcoma, malignant fibrous histiocytoma, fibrosarcoma, and spindle cell sarcoma. The other rare subtypes are leiomyosarcoma, liposarcoma, rhabdomyosarcoma, hemangiopericytoma, malignant schwannoma, osteogenic sarcoma, chondrosarcoma, and stromal sarcoma [11–16].

Symptoms

Primary sarcomas often present as large, well-defined, firm, painless, and rapidly growing masses, whereas secondary angiosarcomas typically present as skin rashes. Blue or purple discoloration of the skin may reflect hemorrhage or vascularity in angiosarcomas. Advanced breast cancer symptoms such as skin ulcers, discharge, and nipple and skin retractions are unusual manifestations. Axillary lymphatic involvement by the tumor is uncommon [2, 3, 16–19].

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Diagnosis

Diagnosis is based on a triple assessment comprising clinical examination, radiologic imaging, and histological evaluation. Core biopsies, which yield more material, are preferred over fine needle aspiration (FNA) biopsies for histological examination [1, 3, 20].

Radiologic Imagination

Three methods—mammography, ultrasonography, and magnetic resonance imaging (MRI)—are used for radiologic diagnosis and staging. No distinguishing characteristics are found in all three imaging methods in breast sarcomas, except calcification in osteogenic sarcoma. Mammographic appearance may mimic a benign condition such as fibroadenoma. A non-spiculated dense mass with indistinct borders may be the only sign found in mammography. Calcifications or spiculated lesions are uncommon. Architectural distortion without a discrete mass may be seen in 30% of the mammograms. Sometimes, mammogram may be normal even in the palpable breast sarcoma. The findings in ultrasonography are usually heterogeneous and oval, lobulated, solid, hypervascular, and hypoechoic mass with posterior acoustic enhancement. MRI may aid in differentiating malignant tumors from benign tumors based on the washout characteristics of the tumor, which will display rapid enhancement [2, 3, 21–24].

Histological Diagnosis

A biopsy provides a definitive diagnosis. Although there are reports indicating 83% positive diagnosis by FNA biopsy, breast sarcomas are easily confused with fibroadenomas on cytological analysis. Furthermore, one report indicated that FNA biopsy was benign for all 28 nonepithelial breast malignancies on which it was performed [25]. FNA cytology is inadequate for determining the subtype or grade. A core biopsy should be the definitive diagnostic method of choice in all cases. An open incisional or excisional biopsy may be an alternative method if a core biopsy is not possible. All of the needle pathways should be included in the subsequent wide local excision area in cases diagnosed with breast sarcoma. Postoperative hematomas may disseminate malignant cells throughout the biopsy cavity, so hemostasis is very important. Sarcomas are graded according to their cellularity, degree of differentiation, nuclear atypia, and mitotic activity. Immunohistochemistry is essential to distinguish sarcomas from other breast tumors as well as to classify into histological subtypes [2, 3, 5, 16, 26].

Staging

To screen for possible remote metastases in patients diagnosed with breast sarcomas, the thorax, abdomen, and pelvis should be scanned by tomography or MRI. Imaging of the central nervous system is essential in patients with angiosarcoma. Positron emission tomography (PET) scan may be helpful in staging, distinguishing benign and malign lesions, screening for recurrence, and evaluating response to therapy. The staging of breast sarcomas is different from that of breast carcinomas. Tumor grade is one of the decisive factors in staging. Well-differentiated grade I sarcomas are classified as stage I, grade II sarcomas are classified as stage II, and grade III tumors and tumors of any grade with regional lymph node involvement are classified as stage III in the American Joint Commission on Cancer (AJCC) classification system [1, 2, 5, 26–28].

Treatment

The management approach to breast sarcomas should be multidisciplinary in nature. The treatment paradigm is the same as for general sarcomas. The mainstay of treatment is surgery.

Surgery

Complete surgical resection of tumor with wide margin is the mainstay of treatment for breast sarcomas. The skin around the biopsy site should be included to the excised specimen to preclude seeding of malign cells along the biopsy tract [28]. When presumably benign lesion is excised and the histopathology result is sarcoma, the excision should be regarded as inadequate even if the lesion has been completely removed, and reexcision with wide margin is necessary [26]. Wide local excision with clear margins is the preferred method for small, localized sarcomas. Mastectomy with reconstruction is the best choice for larger sarcomas for which tumor resection with safe margins or good cosmetic results is not technically feasible [20]. Wide local excision produced the same survival as mastectomy in retrospective trials [29]. However, retrospective trials reported local recurrence rates between 8% and 53% [30] with wide local excision or mastectomy, and a more radical surgery provided no additional survival and local control advantage [5, 31]. These trials highlight the importance of negative surgical margins and the tumor biology rather than the type of surgery [32]. Although there is a lack of guidelines for surgical margins in the literature, most surgeons agree that 1-cm margins are generally sufficient for breast sarcomas except for angiosarcomas [1, 3, 33]. It has been suggested that a 3-cm negative margin is necessary for angiosarcomas because multicentric and infiltrative character of the tumors causes to extend beyond grossly or radiographically assessed boundaries [32].

Sarcoma surgery usually results in complex wounds, and the native tissues may not be in adequate redundancy

to close the incision. Postoperative radiotherapy will further compromise the wound healing. So, oncoplastic breast surgery with skilled reconstructive techniques plays a critical role in the surgical management of breast sarcomas [34].

Axillary Approach

Sarcomas exhibit predominantly hematogenous spreading. Metastatic spreading through the lymphatic route is unusual. Although up to 25% patients may have palpable nodes, these nodes tend to be reactive. The rate of nodal metastasis is less than 5% [1, 11, 16, 29, 35]. All patients were reported as node negative in a retrospective trial comprising 34 sarcomas [36]. The rarity of lymph node involvement by a tumor and the considerable additional morbidity discourage the routine performance of lymphatic dissection. Axillary dissection is associated with no survival benefits [25, 29, 30]. Furthermore, the radiotherapy field should be extended up to the axillary dissection area resulting with increased morbidity such as lymphedema [37].

However, nodal metastases may be observed most commonly in patients with significant disseminated end-stage disease and in angiosarcomas. Sentinel lymph node (SLN) application should be considered in cases with suspicious or palpable lymph nodes [1]. Axillary dissection should only be performed in cases with histologically proven nodal involvement [1–3, 16].

Surgical Outcome

Surgical outcome is affected both by the size and excision margins of the tumor [38, 39]. Tumors larger than 5 cm have a worse prognosis [3]. Higher-grade sarcomas tend to exhibit a worse prognosis, but no consensus has been reached regarding the significance of tumor grade on the surgical outcome, likely due to the low number of patients studied. Patients with tumor enucleation without clear surgical margins experience higher local recurrence rates of up to 85% [40]. Five-year disease-free survival rates range from 44% to 74% in patients with adequate surgery.

Neoadjuvant Therapy

The role of chemotherapy or radiotherapy as a neoadjuvant treatment for breast sarcomas is debatable [5]. In cases of locally advanced disease, neoadjuvant chemotherapy and radiotherapy can be useful to decrease the tumor size, which leads to excision with negative margins and the avoidance of mastectomy [1, 26, 41]. However, limited data indicate that locally advanced unresectable breast sarcomas are not likely to become surgical candidates after neoadjuvant chemotherapy [42]. Furthermore, soft tissue sarcomas are relatively insensitive to chemotherapy, and there is a constant concern of tumor progression on chemotherapy [43].

Adjuvant Therapy

Chemotherapy and radiotherapy both have roles in the management of breast sarcomas. Usually, they are provided sequentially in adjuvant therapy protocols; however, concomitant application can also be used [1–3].

A significant survival advantage has been shown with combined regimens, but the role of chemotherapy alone is less clear. However, the combined regimen improved survival without resulting in a complete response in the MD Anderson trial. Several combined regimens have been reported in the literature to produce complete or partial responses [25, 30, 35, 44]; however, none of the reports indicated statistically significant improvements.

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in breast sarcoma management remains undefined. There are no prospective clinical trials yet, evaluating the benefit of adjuvant chemotherapy for breast sarcomas. Therefore, indications and protocols for soft tissue sarcomas are used in breast sarcomas [36]. Adjuvant chemotherapy is considered on an individual basis depending on patient age, comorbidity, tumor grade, and size [26]. Patients with small, low-grade tumors and negative excisional margins do not require adjuvant chemotherapy. The absolute indications for adjuvant chemotherapy are as follows: higher-grade tumors (grades II and III), a larger tumor size (>5 cm), and resections with positive margins that cannot be re-excised.

The choice of chemotherapeutic agent is dependent on experiences treating soft tissue sarcomas [45]. Classical sarcoma regimens, including anthracyclines, are initially preferred [1, 2].

Adjuvant Radiotherapy

There is no clear evidence for the benefit of adjuvant radiotherapy in the treatment of breast sarcomas [5]. The majority of studies in the literature show a trend toward improved survival by radiotherapy [3]. A course of 48 Gy radiotherapy was reported to improve the survival from 50% to 91%. However, this difference did not reach statistical significance [5, 12]. In a retrospective trial, local failure was decreased from 34% to 13% by radiotherapy, but the change was not statistically significant again [36]. Adjuvant radiotherapy indications are similar to chemotherapy indications. In general, it is recommended for tumors with high grade, larger size (>5 cm), and close/positive margins regardless of the extent of surgery [26, 46]. Additionally, patients with clear margins of less than 2 cm have been reported by some authors to be candidates for adjuvant radiotherapy [2]. At least a 60-Gy dose to the tumor bed was recommended together with tumoricidal dose to the whole breast to achieve significant local control [5].

Hyperthermia

Hyperthermia is reported to be an effective complementary treatment in breast sarcomas acting as a sensitizer of chemotherapy and radiotherapy. Besides direct cytotoxic effect on sarcoma cells, it enhances the effect of chemotherapy by increasing chemical reaction and intratumoral drug absorption. Adjuvant radiotherapy with hyperthermia is also announced to improve local control in radiation-induced angiosarcomas of the breast and chest wall. Hyperthermia is performed through selective heating of the tumor area to 40–43 °C temperatures by an electromagnetic heating device [5, 47].

Targeted Therapy

Studies have been conducted on therapies targeted at specific genetic mutations in breast sarcomas [5]. Ten percent of angiosarcomas have vascular endothelial growth factor (VEGF) receptor-2 gene mutation, and receptor-targeted therapy is found to be effective for these patients. Bevacizumab is reported as an effective agent in phase II studies in angiosarcoma and epithelioid hemangioendothelioma [5, 48].

Survival and Prognosis

In general, breast sarcomas have a poorer prognosis than breast carcinomas. As for the other soft tissue sarcomas, tumor size, grade, subtype, and surgical margins are predictors of the prognosis [11, 15, 42]. The depth of the tumor, which is a predictor of prognosis for sarcomas in other locations, is irrelevant in breast sarcomas because they are usually superficial. Angiosarcomas or postirradiation sarcomas have the worst prognosis [13, 42, 49]. Extending the depth of surgery does not affect survival [12, 14]. The lung is the most commonly reported metastatic site, and the liver, brain, and bones are the next most common sites [2].

Five- and 10-year disease-free survival rates have been reported as 47% and 42%, respectively [12]. The 5-year overall survival rates reported in the literature range between 61% and 91% and are thus better than the disease-free survival rates [30, 35, 44, 50, 51]. The average 10-year overall survival rate is 62% [42].

Prognosis According to Molecular Pathogenesis

It is not difficult to observe different prognoses in cases within the same histological subtypes. Distinct specific molecular lesions may lead to different prognoses for sarcomas. There are a few studies in the literature discussing the specific molecular features of breast sarcomas [1]. However, the molecular pathogenesis of a sarcoma is dependent on the histological subtype and is independent of the primary tumor location.

Based on the currently defined specific molecular lesions of sarcomas, alveolar sarcoma, which is associated with a worse prognosis, is characterized by translocations that fuse the PAX3 or PAX7 gene with the transcription factor POX01. Nevertheless, the same alveolar rhabdomyosarcoma has a much better prognosis, such as that of embryonal rhabdomyosarcoma, when lacking this fusion. Synovial sarcomas, which have been reported to arise in the breast in rare cases, have also been defined by specific translocation-fused genes [52, 53].

Thus, the molecular characterization of sarcomas together with the search for translocations will be helpful to better define the biology of the disease and to develop specific therapies in the future [1].

Novel Treatments

Novel scientific approaches are encouraging for the treatment of sarcomas [3]. Palifosfamide and Eribulin are promising new chemotherapeutic agents that are associated with higher percentage responses in metastatic disease and liposarcomas, respectively. Targeted treatment with new tyrosine kinase inhibitors has been successfully used in sarcomas, but no specific data have been reported in breast sarcomas [54, 55].

VEGF is a well-known predictor of angiogenesis and is highly expressed in soft tissue sarcomas and angiosarcomas [56]. VEGF may also be a strong predictor of disease prognosis [57]. Mutant VEGF receptors, which were detected in angiosarcomas, were inhibited by the VEGF receptor inhibitors sorafenib and sunitinib [56].

Angiosarcomas

Epidemiology

Angiosarcomas are rare with the incidence rate of less than 0.05% of all reported breast cancers [58, 59]. Angiosarcomas are the most common nonepithelial sarcomas of the breast, and they account for 15–34% of all breast sarcomas and 5% of soft tissue sarcomas [30, 60]. Angiosarcomas occur most often in women in their 60s and 70s [19, 61].

Etiology, Incidence, and Classification

Angiosarcomas are classified according to their occurrence de novo, post irradiation, or in association with lymphedema [16]. Primary angiosarcomas of the breast account for 8% of breast sarcomas, predominantly affecting premenopausal women (mean age of 35), and 13% occur in pregnancy [58, 61–63].

Secondary angiosarcomas may arise in breast or on thoracic wall of patients after mastectomy or breast-conserving surgery (BCS) and radiotherapy. Radiation-induced angiosarcomas are genetically different from primary breast angiosarcomas and are often associated with high MYC and FLT4 gene amplification [60, 64, 65].

More than 50% of angiosarcomas arise from the irradiated breast, and 20% arise from the contralateral breast [8, 16, 30, 50, 66]. The criteria for radiation-induced sarcoma are histological diagnosis of sarcoma near to or within previously irradiated field with 3–4 years (or more) latency period [5, 26, 67]. The risk of post irradiation malignancy following BCS and radiotherapy was reported as 16% at 10 years [68]. Breast cancer patients treated with radiotherapy had a 15.9 times higher risk of developing angiosarcoma in comparison with controls who received no radiation [5, 69]. In a large series, the 15-year cumulative incidence of sarcoma was 3.2 per 1000 irradiated patients. The time between irradiation and the development of sarcoma ranges between 65 months and 17 years with an average of 10 years after radiation [19, 70, 71].

Symptoms

Angiosarcomas are usually dermal or subcutaneous tumors, typically present as a large (average 4–5 cm), painless, sometimes rapidly growing mass and have a hemorrhagic, spongy cut surface. A rash, cutaneous violaceous nonpigmented nodule, plaque, vesicula, or macula is frequently the initial lesion [72]. Atypical vascular skin lesions are rare smaller lesions but may be the precursors to angiosarcomas. Radiation-associated angiosarcoma typically presents with skin discoloration and thickening in cutaneous tissues [26, 67].

Diagnosis

Mammography and ultrasonography have high false-negative rates for breast angiosarcomas [73, 74]. MRI is a better imaging method in diagnosis which reveals blood lakes and a rapidly enhancing heterogeneous mass [74]. Diagnostic confirmation is made by an incisional biopsy at more than one site. All of the detected small atypical lesions should be excised with wide margins [75].

Cytology

Specific diagnostic cytological findings include hyperchromatic nuclei, a connecting dense vascular network, and vascular elements in the parenchyma.

The histological grading is similar for primary and secondary angiosarcomas. The histological grade is one predictor of prognosis. High-grade tumors are most common in younger patients and have a low survival rate (5 years, 14%) [60, 61]. Low-grade tumors are usually misdiagnosed as hemangioma and have better survival rates (5 years, 91%).

Radiation-induced angiosarcoma expresses endothelial markers such as VEGF, von Willebrand factor, CD-34, CD-31, *Ulex europaeus* agglutinin 1, and anti-Fli-1 protein antibody [73, 76]. Ovoid laminated organelle-like (Weibel-Palade) bodies may be seen on electronic microscopy [73].

Management

Surgery is the primary treatment, and wide local excision is the recommended procedure. Due to the presence of infiltrative margins, angiosarcomas require larger margins compared with other sarcomas. Some authors recommend up to 3-cm negative margins together with oncoplastic surgery [33]. Wide negative margins are essential for long-term cures in previously irradiated breast because further adjuvant radiotherapy cannot be administered [3]. All detected hemangiomatous lesions around the tumor or in the breast should be included in the excised specimen. Mastectomy is the treatment of choice for tumors that cannot be excised with safe margins [2].

Angiosarcomas can metastasize to regional lymph nodes in 7% of cases [35]; thus, SLN biopsy should be considered, particularly in patients with high-risk factors such as high grade, large tumor, or advanced disease [77].

The adjuvant therapeutic indications for angiosarcomas are similar to those for sarcomas. In addition to conventional chemotherapeutics, angiosarcomas are also sensitive to taxanes and liposomal doxorubicin [78]. Ongoing debate exists regarding whether post irradiation breast sarcomas can be treated similarly by localized radiotherapy. Although most clinicians are reluctant to use more radiotherapy, it has been reported in a retrospective trial that hyper-fractionated accelerated radiotherapy is well tolerated and provides local control in 60% of patients [1, 7].

Recently, molecular targeted therapies have been investigated for angiosarcomas. Antiangiogenic therapies, such as tyrosine kinase inhibitor (sorafenib) and monoclonal antibody against VEGF (bevacizumab), have shown some activity in angiosarcoma [79, 80].

Outcome

Angiosarcomas, especially high-grade ones, are highly aggressive tumors. They have high local recurrence rates (50–60%) and high distant metastatic potential [71, 72]. Bone, lung, ovary, and liver are common sites of metastasis. The 5-year survival rates are 80% and 20% for well-

differentiated and poorly differentiated tumors, respectively [2, 81].

Fibrosarcoma (Pleomorphic Sarcoma: Malignant Fibrous Histiocytoma)

Fibrosarcoma is one of the rare histological variants of the nonepithelial tumors accounting for only 16% of all the breast stromal sarcomas [4, 82]. The definitive diagnosis is confirmed by Tru-Cut biopsy and immunohistochemical (IHC) staining [82]. By definition, it is negative at the IHC stains for epithelial myogenous and neural markers and for CD34, CD99, bcl-2, and nuclear beta-catenin [86]. Malignant phyllodes tumors and sarcoma with mesenchymal differentiation should be excluded in the differential diagnosis.

Fibrosarcomas may occur at any age, but they are commonly seen in women between 40 and 50 years [82, 83]. Ultrasonography shows nodular, well-circumscribed hypoechoic, heterogeneous, and hypervascular lesion. Cystic echo due to hemorrhage, necrosis, and mucoid degeneration can be seen in tumor [82]. MRI is more useful than computed tomography in evaluating tumor borders and surrounding tissue. High-grade types are vulnerable to metastasis, whereas low-grade types are not [84, 85]. Metastases are common to the lung but may occur in the brain, kidney, and the bone via hematogenous route; lymphatic spread is rare [82, 83]. Surgical approach is the main therapeutic procedure, and negative margins as a major factor effecting survival should be achieved [12, 82]. Axillary lymph node dissection is not recommended in the absence of clinically palpable nodes [12, 36, 82]. Radiotherapy and chemotherapy may be the options in high-grade fibrosarcomas, positive surgical margins, or in recurrence [82].

Liposarcoma

Liposarcoma are rare, slow-growing, firm, occasionally painful, and nonepithelial breast tumors that do not have any specific clinical features. Tru-Cut biopsy is necessary for the diagnosis of liposarcoma. Malignant phyllodes tumors should be considered in the differential diagnosis. Well-differentiated, atypical, myxoid/round cell, poorly differentiated, and pleomorphic types comprise the histological subgroups. Well-differentiated types are less aggressive.

Atypical lipomatous tumors may arise in breast parenchyma or as an intramuscular mass in pectoralis muscle and show a high rate of local recurrence [86, 87]. The presentation of myxoid liposarcoma as a primary breast tumor is unusual, and metastatic mass should be considered in differential diagnosis [86]. Pleomorphic liposarcoma of the breast is the least common subtype. It may be a component of malignant phyllodes tumor [86, 88, 89].

Wide local excision or mastectomy is the standard treatment for liposarcoma of the breast. Axillary lymph node sampling is not recommended [86, 88, 90, 91]. All of the histological types of liposarcomas tend to recur with metastasis [1, 61, 91, 92] but more common in high-grade and pleomorphic histology. Recurrences or metastasis usually occur within 2 years of diagnosis [6, 86].

Leiomyosarcoma

Leiomyosarcoma is a rare type of breast sarcoma. Straight muscle cells in the nipple-areola complex can be the origin. Immunohistochemistry is necessary for the differential diagnosis. Recurrence and metastasis frequently occur [61, 93, 94].

Rhabdomyosarcoma

Rhabdomyosarcoma is a rare tumor that occurs more often in adolescent women between the ages of 15 and 24. Rhabdomyosarcoma is most commonly found as a metastasis from another origin [60]. Rhabdomyosarcomatous differentiation can also be detected in malignant phyllodes tumors and in metaplastic carcinoma of the breast. Alveolar rhabdomyosarcoma is the most frequent histological subtype [95], whereas solid and classic types are the others. Immunohistochemistry is essential for definitive diagnosis. Five-year survival rates have been reported as 90% in stage I and 30% in stage IV [61, 96]. Alveolar subtype metastasis in 20% of cases with bone, lungs, lymph nodes, and bone morrow being the most common sites of involvement [97, 98].

Specific Syndromes

Li-Fraumeni Syndrome

Lynch et al. described in detail a complex syndrome with multiple tumors in different anatomical sites of the body, including sarcomas, breast cancer, brain tumors, lung cancer, laryngeal cancer, leukemia, lymphoma, and adrenal cortical carcinoma, which was first described by Li and Fraumeni [99–101]. A P53 gene mutation is characteristic for this syndrome. Breast tumors occur at an early age and tend to recur in this syndrome [102].

Cowden Disease

This syndrome occurs as a result of a PTEN gene mutation, which leads to multiple tumors of the body, including breast cancer, thyroid cancer, female genitourinary tract cancer, and mucocutaneous hamartomas and trichilemmomas [103, 104]. Lesions frequently occur on the face and dorsal and ventral aspects of the hands, feet, and forearms. Breast cancer is observed in 30% of patients with Cowden disease and is sometimes bilateral. Bilateral prophylactic mastectomy or close surveillance, including monthly breast self-examination, biannual physician examination, biannual mammography, and/or MRI, is usually offered to patients with a PTEN mutation [105, 106]. Virgin hypertrophy, hamartomas, ductal hyperplasia, intraductal papillomatosis, adenosis, fibroadenomas, and fibrocystic mastopathy are not rare. Thyroid lesions such as goiter, adenomas, follicular lesions, and thyroid dysfunction are common. Uterine leiomyomas, brain tumors, gastrointestinal tract hamartomas, and colon cancer have also been reported [99, 100].

Primary Breast Lymphoma

Epidemiology

Lymphoma is the malignant disease of the lymph nodes. Primary extranodal lymphoma is a rare entity that usually originates from B-cells and is of non-Hodgkin's type. The skin, brain, gastrointestinal system, thyroid, testis, and breast are the sites of disease occurrence that have been reported. Diffuse large B-cell lymphoma is the most common type [107]. There are many retrospective studies [108–111] but only one prospective study [112] of primary breast lymphoma in the literature. Breast involvement in Hodgkin's lymphoma has also been reported [113].

Lymphoma in the breast is defined as primary when the breast is the first major site of manifestations without any evidence of a concurrent systemic disease. The disease is considered secondary in the case of breast involvement in addition to a systemic disease. Sometimes, it is difficult to determine which the primary disease is when there are both breast involvement and systemic disease, because there is no morphological difference between primary and secondary lymphoma [107].

Primary breast lymphoma arises from the periductal and perilobular lymphatic tissue and intramammary lymph nodes [2]. It accounts for 2.2% of extranodal lymphomas [114] and 0.1% of all breast tumors [115–122]. Although it can be observed at all ages, in both genders, and on both sides, it is more frequent in women (95%) between 50 and 60 years and more frequently occurs in the right breast and the upper outer quadrant [117–121]. It tends to be bilateral and exhibits features of Burkitt's lymphoma in young and pregnant women [121, 122].

There are also case reports of primary breast lymphoma induced by implant capsules in the literature [123]. Six cases of anaplastic cell lymphoma in association with silicone breast implants have been reported [124].

Symptoms

A painless, mobile, large, and rapidly enlarging mass is characteristic [107]. Sometimes, the entire breast grows, or pathological lymph nodes in the axilla become palpable as the initial symptom [2]. The tumor is multicentric in 20–30% of the cases. Locally advanced tumor signs such as skin changes are rare. The tumor is usually misdiagnosed as breast cancer or a benign lesion [125].

Radiology

A mass with clear margins without calcification is the most common sign in radiographic images. However, multiple amorphous masses with diffuse, increased parenchymal density or a spiculated mass may also represent the abnormal findings. Patients may also have normal mammograms.

Ultrasonographic findings are also not specific and cover a wide spectrum, including hypoechogenicity with well-defined borders and without acoustic shadowing.

Enlarged intramammary lymph nodes identified by mammography with increased density, a lack of well-defined borders, and fatty hilum are considered pathological. Lymph nodes are hypoechoic by ultrasonography.

PET has an 89% sensitivity and 100% specificity in the differential diagnosis for non-Hodgkin's lymphoma [122].

Diagnosis

The diagnostic criteria for primary breast lymphoma have been defined by an international extranodal lymphoma study group as an extranodal lesion as the main symptom with or without lymph node involvement or a tumor limited to a unilateral breast or bilateral breasts with or without lymph node involvement [116, 126, 127]. There are also some specific criteria, such as a primary tumor in the breast, lack of previous lymphoma history, lack of widespread disease, and close histopathological associations with breast tissue. Ipsilateral lymph nodes that develop simultaneously with the primary tumor are not considered exclusion criteria [122]. All other lymphomas that do not meet these criteria are considered

secondary breast lymphomas. Clinical and imaging findings are not enough by themselves for the definitive diagnosis. Tru-Cut biopsy and IHC staining are necessary [122].

Staging

The Arbor classification [128] is used for the staging, in which stage I indicates disease limited to the breast, stage II indicates disease limited to the breast and ipsilateral axilla, stage III indicates disease limited to the breast but involves both axillae, and stage IV indicates disease limited to the breast with metastasis to the extra-nodular tissue [122].

To accurately stage the disease, chest, abdominal, and pelvic tomography, bone morrow biopsy, and blood tests are mandatory in addition to the assessment of both breasts and axillae [129].

Histopathology

A definitive diagnosis is based on cytological and histopathological features. Primary breast lymphoma histologically resembles other lymphomas of the body, as well as other breast carcinomas. It is often difficult to distinguish it from poorly differentiated carcinomas. A specific feature of primary breast lymphoma is the infiltration of mammary lobules by uniform malignant lymphoid cells. Adequate tissue sampling is the mainstay for diagnosis; however, IHC may also be essential. BOB1 and OCT2 overexpression can be used as IHC markers [130].

Macroscopically, the mass has a smooth, round shape, and a clear surface and does not have a membrane, and the cut surface is pink or gray in color. Most primary breast lymphomas comprise B-cells, and nearly 70% of cases are diffuse large B-cell lymphoma [131].

Management

Lymphomas are sensitive to chemotherapy and radiotherapy; thus, surgery is limited to Tru-Cut or excisional biopsy [116]. Axillary lymph node excision may be required for the diagnosis, staging, or palliation of palpable large nodes. Mastectomy is not recommended.

The treatment varies widely and depends on the subtype and stage of disease. Systemic chemotherapy, including anthracycline regimens, is usually the standard treatment of choice. Combined rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) therapy is the most commonly used regimen in diffuse large B-cell lymphoma. Systemic medical treatment should be combined with radiotherapy. Three cycles of CHOP followed by radiotherapy have been found to be superior to eight cycles of CHOP [122]. Although the optimal treatment for diffuse large B-cell lymphoma has not been defined, several reports have suggested improved survival and local control with radiotherapy following an extensive course of chemotherapy. Radiotherapy can be used as the sole treatment for stage I indolent lymphoma that is limited to the breast [107].

Prognosis

Spontaneous regression of primary breast lymphoma has been reported in the literature [132].

The clinical stage and histological subtypes are the main prognostic factors [107]. The 5- and 10-year survival rates have been reported to be 43–74% and 51%, respectively [16].

Synchronous or metachronous contralateral breast involvement should be monitored for up to 10 years. The common relapse sites of primary breast lymphoma have been reported to be the contralateral breast (15%) and the central nervous system (3%) [122].

Metastases to the Breast

Epidemiology

Any malignancy may metastasize [133] to the breast; however, metastatic lesions to the breast are rare. Since the first report in 1907, which described ovarian tumors metastasizing to the breast [134], nearly 500 cases have been reported in the literature [135].

The frequency of metastatic involvement of the breast is between 0.4% and 1.3% [135, 136]. Most breast metastases originate from the contralateral site [12]. Non-mammary metastatic breast neoplasms account for 0.5–6% of all breast carcinomas [137].

The most common malignancy that metastasizes to the breast is malignant melanoma [138–140]. Both the isolated metastases to the breast [138, 140, 141] and metastases to both the breast and other sites [142] from extramammary cutaneous malignant melanoma have been reported. The detection of bilateral breast metastases from melanoma is highly suggestive of metastatic multiorgan disease and could be useful to address the therapeutic approach [139]. Hematological malignancies such as leukemia and lymphomas [137, 143] are also common. Other malignancies that may metastasize to the breast include oropharynx tumors, ovarian carcinomas, thyroid carcinomas, small bowel carcinoids [143–146], gastrointestinal system malignancies such as esophageal/stomach and colorectal cancers, sarcomas,

and, rarely, pulmonary carcinomas [11, 133, 143, 147, 148]. Nineteen colorectal carcinomas that have metastasized to the breast have been reported in the literature [143, 149]. Twenty-five gastric cancer cases with metastases to the breast have been reported in the literature [6–8, 13, 15], whereas the incidence of metastatic gastric tumors to the breast has been reported as 1–2% in clinical series [149, 150].

Metastases to the breast usually occur several months after the discovery of the primary tumor; however, in 25–40% of cases, the metastases are the first sign of the primary tumor [7, 137, 150].

Metastases to the breast are frequently observed in reproductive-aged groups (30–45 years) [150]. The tumors are usually in the upper outer quadrant of the breast and are superficially located, solitary, discrete lesions. Unlike primary breast cancers, skin or nipple retraction is rare [136, 143, 151]. Metastases are bilateral in 25% of cases, and concomitant axillary lymph node involvement can be detected in 15% of cases [11–13].

Clinical and Radiologic Signs

Clinical and radiologic signs are quite polymorphic and vary widely. Furthermore, metastatic lesions can mimic primary breast cancers or even benign lesions [137]. Thus, distinguishing metastatic tumors in the breast from the primary lesion by clinical and radiologic evaluation is extremely difficult [13, 136, 143, 146]. The occurrence of multiple tumor nodules in the breast is rare. Diffuse involvement of the breast is unusual, with the exception of metastases from malignancies of hematological origin [152]. The most common mammographic evidence is often single but sometimes multiple well-circumscribed lesions with smooth margins. Spiculated irregular density can also be observed [6]. Microcalcification is unusual, except for metastases of ovarian papillary carcinomas [143, 145, 146, 150, 153].

Diagnosis

Accurate diagnosis is important because the treatment and outcome for primary breast tumors and metastases to the breast are quite different. There are some specific histopathological features of metastases to the breast. The absence of in situ carcinoma and the presence of sharply circumscribed lesions from the surrounding tissue and elastosis strongly support the diagnosis of metastatic carcinoma [136, 143, 148, 154]. IHC helps to diagnose the majority of cases. Estrogen and progesterone receptors and c-erbB2 are usually negative in metastatic tumors to the breast [1, 135].

Management and Prognosis

Comprehensive screening is necessary to identify the origin of the primary tumor, and treatment is modified according to the primary tumor. In most cases, systemic treatment or palliative care is more appropriate than extensive surgery [148]. Most metastases to the breast are correlated with extensive disease and a poor prognosis [148, 150, 155]. Patients usually die within a year of diagnosis [155, 156]. However, considerably improved survival rates have been reported in some patients who were administered effective systemic treatment [155].

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Part V

Evaluation After Primary Therapy and Management of Recurrent Breast Cancer

Surveillance of Patients Following Primary Therapy

27

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Introduction

Regular and appropriate follow-up of patients after treatment for breast cancer is an important aspect of comprehensive care. Breast cancer survival has increased due to improvements of treatment, leading to a much higher long-term survival of women diagnosed with breast cancer. Recent data suggest that women have a 5-year survival of 78–91% according to Surveillance, Epidemiology, and End Results (SEER) database [1].

The primary purpose of follow-up is often regarded as the early detection of recurrence as well as the detection of second primary tumors along with long-term sequelae of breast cancer treatment. The other goals are to assess and treat the complications of the therapy, evaluate the symptoms that may or may not be related to the disease, encourage compliance with ongoing therapy, provide psychosocial support, and give advice about health decisions like pregnancy that may be influenced by a history of breast cancer.

Follow-up care is provided by specialist oncologists in many countries. There is evidence that follow-up care provided by primary care physician or survivorship programs is equivalent to hospital-based outpatient care in detection of cancer recurrences [2]. This brings a high level of patient satisfaction and greater cost-effectiveness [3, 4].

Although local recurrence is generally seen in the first 3–5 years, it may manifest in 5–10 years and even later in patients with estrogen receptor-positive tumors and who receive adjuvant tamoxifen and/or chemotherapy [5–9]. Recurrences tend to occur more often after breast-conservative surgery compared to mastectomy [10, 11]. The recurrence incidence starts to decline after 5 years [12]. Women with a history of breast cancer are at risk of developing ipsilateral breast recurrence (IBR) or a new cancer in the treated breast and/or collateral breast cancer (CBC). Breast cancer distant metastasis is mostly seen in the bones, lungs, liver, and brain. Site of metastasis can show differences according to the subtypes of the breast cancer [13].

Recommendations for Breast Cancer Follow-Up

History

A careful history should be taken. New symptoms or changes in the symptoms should be noted. Persistent pain, fatigue, sexual dysfunction, hot flushes, weight loss, cough, shortness of breath, abdominal pain, lymphedema, and swelling of the arm are some of the most common symptoms. Forty percent of isolated locoregional relapses are detected in asymptomatic patients during routine controls, whereas the remaining 60% are detected in self-examination (SE) [14, 15]. Early detection of recurrence in asymptomatic breast cancer patients may decrease the mortality rate by 0.5–0.8% [16].

Survivors on tamoxifen therapy have two to three times the risk of developing endometrial cancer compared to age-matched women who are not taking tamoxifen [17]. Women receiving tamoxifen should be advised to report any abnormal

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vaginal bleeding. Annual gynecologic examination is recommended in all women, but specific screening for endometrial cancer in survivors is not recommended. Transvaginal ultrasound in asymptomatic women taking tamoxifen may be associated with false-positive results due to tamoxifen-induced endometrial proliferation, so it is not advised [18]. Women using tamoxifen should be referred to ophthalmologic examination for symptoms suggestive of retinopathy. The incidence of thromboembolic events such as deep vein thrombosis and pulmonary embolism is also increased by tamoxifen [19]. Patients on chemotherapy and aromatase inhibitors should undergo bone densitometry to detect osteopenia and osteoporosis. Vitamin D, calcium, and bisphosphonates can be recommended. Breast cancer tumor markers such as CEA or CA 15–3 should not be used in screening for breast cancer or as a routine follow-up test. Routine blood tests like complete blood count are not recommended for controls.

Physical Examination

Physical examination should be performed every 3–6 months for the first 3 years, then every 6–12 months for the next 2 years, and then annually. In the physical examination of breasts and lymph nodes, axillary, cervical, and supraclavicular regions next to the chest wall must be checked bilaterally. Examination findings must be noted in the patient's file because some tissue changes, such as tissue necrosis due to injected methylene blue for sentinel lymph node biopsy, may be felt as a new mass causing confusion. Both extremities must be controlled for lymph edema. Physicians should counsel patients about the symptoms of recurrence, including new lumps, bone pain, chest pain, dyspnea, and abdominal pain.

Referral for Genetic Counseling

Women at high risk for familial breast cancer syndromes should be referred for genetic counseling. Five to ten percent of familial breast cancers originate from inherited gene mutations [20]. Among these genes, BRCA1 and BRCA2 are responsible for many hereditary breast and ovarian cancers. Patients with mutations in BRCA1 and BRCA2 have a lifetime risk of breast cancer of 35–87% and ovarian cancer of 16–60%, depending on the type of mutation [21–23]. Genetic testing by The American Society of Breast Surgeons is recommended to patients who meet the following criteria: 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 the age of 50; 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 [24].

Breast Self-Examination

All women must be encouraged to perform breast self-examination (SE) monthly. The most convenient time is within 5–7 days after the menstrual period in reproductive ages. Breast self-examination (SE) in women diagnosed with breast cancer is important for early detection of recurrences. Tumors that are detected by SE are often smaller than those detected by screening [25, 26]. However, in a wide study including more than 260,000 Chinese women, SE was shown not to be effective on surveillance. No difference was detected between trained and untrained groups in terms of tumor diameter, TNM staging, and cumulative mortality rates. However, no randomized data have been assessed for the cumulative effects of SE as well as mammography in women who were treated for breast cancer.

Mammography

The incidence of contralateral breast cancer is higher in patients diagnosed with breast cancer, so annual mammographic screening should be performed for the healthy breast. Mammography is the first radiological choice of follow-up after a breast-conserving surgery. A routine screening mammography should be performed bilaterally. Mammographic follow-up protocols may differ between patients with quadrantectomy and lumpectomy. Mammography is performed after 6 months of operation and then every year for both breasts. In breasts that have a cosmetic implant, the mammographic screening technique is different [27]. Mammography screening reduces the mortality of breast cancer patients by about 15% [28, 29]. Women treated with breast-conserving surgery should have their first mammogram 6 months later. Subsequent mammograms should be performed every 6–12 months for surveillance of abnormalities.

Breast Ultrasonography

Breast ultrasonography can be used as an adjunct to mammography for dense breasts and in young patients to obtain additional information. Internal structures and the borders of the lump can better be evaluated in ultrasonography than mammography because in ultrasonography there is no superposition of tissues. Ultrasonography is a modality that is user dependent and challenging in detecting microcalcifications,

so it cannot be used alone for screening of breast cancer [30–32]. Ultrasonography is the first radiological modality for evaluation of the chest wall in patients with mastectomy. It is also used for differentiation of cystic-solid masses, evaluation of axilla, and biopsies of non-palpable masses. Ultrasonography is used for evaluation of implant integrity. Short performance time and low cost are some of its advantages. The handicap of ultrasonography is its user dependency.

Breast Magnetic Resonance Imaging

Breast magnetic resonance imaging (MRI) gives us useful information for the evaluation of the chest wall in patients who have undergone mastectomy and lesion status assessment [33]. Breast MRI is used in implant patients to distinguish recurrence and scarring after breast-conserving surgery, and it may be used in genetically high-risk patients. The best-known indication of breast MRI is its usage for evaluation of breast parenchyma and the integrity of implants in patients with breast-conserving surgery and silicone implants. Breasts with prostheses can be shown in any axes by MRI, while there is no need to use contrast material to identify the integrity of implants in breasts with prostheses. It is mandatory to use contrast with dynamic MRI in routine follow-up and malignancy detections. In MRI, low-intensity linear lines (collapsed membranes swimming in silicone) are defined as the "linguine sign" and reveal an intracapsular rupture. Silicone, which can seep out of the capsule, is another sign of capsular rupture.

Other Imaging Studies

Chest X-rays, bone scans, ultrasonography of the liver, CT scanning, fluorodeoxyglucose positron emission-computed tomography (FDG-PET/CT) scanning, and breast MRI are not recommended for routine breast cancer surveillance [34–41]. Recommendations for breast cancer follow-up are shown in Table 27.1.

Most of the patients with axillary lymph node involvement have bone metastases within 10 years after the mastectomy. This incidence increases with time: for the first 3 years, this rate is 8.9%, 11.2% for 5 years, and 14.4% for 10 years. In advanced stages of the disease, 70% of the patients may develop bone metastases [42]. In large studies, bone scintigraphy was shown to be very sensitive and specific. In a 10-year study conducted by Crippa et al., bone scintigraphy had 98.2% sensitivity, 95.2% specificity, and 95.5% accuracy [43].

FDG-PET scanning is more sensitive in recurrences of breast cancer [44–46]. One study included 60 breast cancer patients with suspicion of relapse. Forty of them had relapse, and the efficiency of PET scan in detecting locoregional and distant metastases was assessed. PET scan and CA 15–3 were compared for detection of the relapses, and PET scan was more sensitive. In a meta-analysis discussing 16 patient-based studies and 8 lesion-based studies, the mean sensitivity and specificity of PET scan were 92.7% and 81.6%, respectively [47].

Follow-up can be coordinated by primary care physicians, and further oncology assessment may be considered if needed, especially for patients receiving adjuvant endocrine therapy [34]. Long-term management of breast cancer survivors requires a multidisciplinary approach including psychological health and other health issues [48–50].

Table 27.1 Recommendations for breast cancer follow-up and management in the adjuvant setting

Surveillance	History/physical examination	Regular visits every 3–4 months in the first 2 years, every 6 months from years 3 to 5, and annually thereafter are recommended
	Breast self-examination	Monthly
Imaging	Mammography	Screening mammogram annually
	Breast ultrasound	Annual ipsilateral (after BCT) and/or contralateral mammography with ultrasound is recommended. Ultrasound can also be considered in the follow-up of lobular invasive carcinomas
	Breast MRI	In women with familial breast cancer, with or without proven BRCA mutations, annual screening with MRI of the breast, in combination with mammography, is recommended
	Other imaging studies	Chest X-ray, bone scan, liver ultrasound, CT scanning, and FDG-PET scanning are not recommended for routine breast cancer surveillance
Blood tests	CBC, automated biochemistry, and tumor markers	Not recommended for routine surveillance of patients with breast cancer after primary therapy
Monitoring for late effects	Bone health	Yearly
	Pelvic examination	Yearly
	Lymphedema assessment	Personalized
	Sexual health/ fertility	Personalized
Risk reduction	Genetic counseling	Women at high risk for familial breast cancer syndromes

BCT breast-conserving therapy, *CBC* complete blood count, *MRI* magnetic resonance imaging, *FDG-PET* [^{18}F] fluorodeoxyglucose positron emission tomography

Pregnancy

Loss of fertility as a result of treatment is a stressful aspect of breast cancer diagnosis [51–53]. Chemotherapy, tamoxifen, and ovarian ablation can affect fertility. Tamoxifen itself is not a direct cause of infertility, but women are instructed not to get pregnant while taking it. The risk of chemotherapy depends on the therapy regimen, the patient's age, and the ovarian history. Even if menstruation continues during chemotherapy, the patient is likely to experience a premature menopause. Regarding future pregnancy following breast cancer treatment, patients are advised to wait for at least 2 years. According to most of the retrospective studies, there is no significant risk of recurrence due to pregnancy [54–58].

Psychosocial Problems

Younger women are at a greater risk of depression and anxiety because they have a fear about their body image, hair loss, and sexuality. If they have children, they may worry about not seeing them grow up [59–61]. They may have fatigue, which can affect their job. In follow-up, doctors should be careful about signs of depression and refer the patients to psychiatry or a support group if needed.

Conclusion

Breast cancer survivors face potentially significant impacts of cancer and its treatment and deserve high-quality, comprehensive, coordinated clinical follow-up care [62]. Primary care clinicians must consider each patient's individual risk profile and preferences of care to address physical and psychosocial impacts. More information is available at asco.org/guidelines/breastsurvivorship and asco.org/guidelineswiki.

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Surgery for the Primary Tumor in Patients with De Novo Stage IV Breast Cancer

28

Atilla Soran and Serdar Ozbas

Introduction

Breast cancer (BC) is the most common cancer in women worldwide and the second most common cancer overall. The incidence of synchronized distant metastatic disease in newly diagnosed BC patients is as high as 10% [1–3]. BC is also the most frequently diagnosed cancer among women in 140 of 184 countries worldwide and represents one in four cancer cases in women [4]. In general, BC with distant metastasis is considered incurable, and the traditional goal of primary tumor surgery is to palliate symptoms to improve quality of life. Currently, the role of surgery to remove the primary tumor and its impact on distant metastatic disease and patient survival are controversial. Therefore, surgical treatment of the intact primary tumor is indicated only if it is symptomatic, i.e., it is bleeding or fungating or is associated with ulceration, pain, or hygienic disturbances. These are among the palliative indications for locoregional surgery. Systemic therapy (ST) is the primary treatment for stage IV BC [5]. However, with advances in adjuvant therapies and a better understanding of tumor biology, the survival of stage IV BC patients appears to be improving [6, 7]. Furthermore, with advances in sensitive imaging modalities, low-volume metastatic BC is being diagnosed more often; patients with a single metastatic deposit may represent a very different cohort of patients than those with multiple solid organ metastases. By contrast, there is no evidence that local control in the metastatic setting worsens prognosis. The surgical treatment indications of the intact primary tumor are:

(a) Prolonged overall survival
(b) Prolonged progression-free survival
(c) For locoregional control
(d) Palliative

Earlier disease detection with improved adjuvant treatments may enable improved survival [8]. Removing the primary tumor improves survival in other settings, such as metastatic melanoma, renal cell carcinoma, colorectal cancer, and gastric cancer [9–12]. Removal of the primary tumor may have an immunomodulatory effect, decrease the overall tumor burden, remove a "seed source" of new metastases, or decrease the likelihood of the development of potentially resistant cell lines [13, 14]. It is also possible that enhanced survival in BC patients treated with surgery may be explained by selection bias [15]. Patients who are offered surgery may be younger, may be healthier, or may have a lower burden of disease, metastases in more favorable locations, or a more favorable tumor profile than those for whom surgery was not considered (Table 28.1).

Although retrospective studies do not support the hypothesis that the surgical resection of the primary tumor increases the risk of relapse, in animal models, removing the primary tumor can stimulate metastatic growth [16, 17]. Two underlying mechanisms have been proposed: angiogenic and proliferative. The angiogenic surge is due either to the removal of inhibitors or the appearance of stimulators or growth factors in response to surgery [18, 19]. This activation temporarily causes inactive distant micrometastases to vascularize and consequently enter a rapid growth phase. The data suggest that such stimulated angiogenesis may occur in approximately 20% of premenopausal patients with node-positive disease. The proliferative mechanism for early relapse, which is also the result of surgery, is the stimulated division of single dormant cells or even changes in the dynamics maintaining the steady state of dormant or indolent micrometastases, ultimately resulting in angiogenesis and growth [20]. For primary breast tumors smaller than 2 cm, 50% of all relapses belong to this first wave of relapses, and for

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Table 28.1 Does local surgery increase survival in stage IV BC? Hypotheses based on retrospective and animal studies

Removal of the primary tumor eradicates one of the sources of further metastatic spread.
A reduction in the number of cancer cells may lead to increased ST efficacy by decreasing the risk of the emergence of chemoresistant cells and by removing necrotic, avascular tumor tissue that is poorly accessible to drugs.
Immunocompetence may be restored because surgery suppresses the growth of metastases by removing primary cancer-associated inflammatory products (hormonal, angiogenic) from circulation.
Tumor-induced immunosuppression may be another mechanism of interaction between the primary tumor and metastases.
The number of metastatic sites increases as the size and duration of the tumor increase.
Endocrine or cytokine-mediated effects may modify the behavior of tumor cells at the metastatic sites.
Debulking surgery is clinically effective in other common solid tumors (ovarian, colorectal, gastric, renal cancers, and malignant melanoma (not generalizable)).
A single metastatic deposit may be deemed "stage IV" using modern (PET/CT) imaging; thus, "low burden" stage IV disease can be identified.
Selection bias may be responsible for the surgery-mediated increase in survival.

larger tumors, 75–83% of relapses fall in this category. Early relapses among patients receiving no adjuvant treatment due to stimulated angiogenesis occur in the first 10 months after surgery, whereas the adverse events stimulated by rapid changes occur in the first 4 years after surgery, with a peak at 18 months. There is overlap between these two distributions of outcomes. Together, these distributions create an early peak in relapses that occurs sooner than observed otherwise due to a stimulation of growth by surgery.

Retrospective Studies on Survival

Several retrospective studies and meta-analyses have indicated that surgery to remove the primary tumor in de novo stage IV BC not only controls locoregional progression but also prolongs overall and disease-free survival (Table 28.2). A retrospective analysis of the American National Cancer Database (NCDB) indicated that the resection of the primary breast tumor in patients with stage IV BC was associated with a significant survival advantage [21]. Women in whom the primary breast tumor was removed with tumor-free margins had a superior overall prognosis with a hazard ratio of 0.61 compared to women who did not undergo surgery. In a small retrospective study, Carmichael et al. reported a single-institution case series (n = 20) of patients who underwent primary tumor resection for stage IV BC at presentation or were diagnosed with metastases within 1 month of surgery [1]. They found that median survival after surgery was 23 months and that half of the patients were alive with no

Table 28.2 Selected retrospective studies of overall survival for surgery or no surgery of the primary tumor

Author	Surgery survival	No-surgery survival	HR
Bafford [32]	3.52 years	2.36 years	0.47
Blanchard [3]	27.1 mths	16.8 mths	0.71
Cady [31]	24 mths	24 mths	n/a
Fields [24]	31.9 mths	15.4 mths	0.53
Gnerlich [2]	36 mths	21 mths	0.63
Hazard [26]	26.3 mths	29.2 mths	0.79
Khan [21]	31.9 mths	19.3 mths	0.61
Rapiti [23] [5 year]	27%	12%	0.6
Ruiterkamp [33]	31 mths	14 mths	0.62
Shien [36]	27 mths	22 mths	0.049
Leung [43]	25 mths	13 mths	0.004
McGuire [Median 37 mths] [44]	33%	20%	0.0012

HR Hazard ratio, *mths* months

local disease at 20 months. Because there was no control group to compare these results, no evident conclusion about the superiority of local control could be drawn in this study.

Gnerlich et al. reviewed SEER data for stage IV BC patients between 1988 and 2003 and found that patients who underwent surgical removal of the primary tumor had better survival than women who did not undergo surgery [2]. This study demonstrated that patients who underwent primary surgery were 37% less likely to die than those who did not undergo surgery. In 2006, Barbiera et al. reported their institutional findings for a retrospective cohort of 224 patients with stage IV BC and intact primary tumors [22]. They observed that removal of the primary tumor significantly improved progression-free survival in BC patients with distant organ metastases. However, overall survival did not differ between groups. Rapiti et al. reported another retrospective study of 300 stage IV BC patients from the Geneva Cancer Registry [23]. They reported that women who underwent complete excision of the primary breast tumor with negative surgical margins had a 40% reduced risk of death compared with women who did not undergo surgery. In another similar study, Blanchard et al. reported a retrospective series of 427 patients with stage IV BC from their institutional registry [3]. Their results revealed that the interval from diagnosis to death was 27 months for patients who underwent surgical resection of the primary tumor but 17 months for the no-surgery group. This difference between groups was significant. Fields et al. reported a retrospective analysis of their institutional cohort of 409 patients with stage IV BC [24]. This study provided additional evidence that BC patients with distant metastases at diagnosis benefit from surgical excision of the primary lesion in terms of improved survival. After controlling for age, comorbidity, tumor grade, histology, and sites of metastasis, patients who underwent surgical resection were 47% less likely to die than patients who did

not undergo surgery for the primary tumor. The median overall survival was significantly longer in patients who had resection (26.8 months versus 12.6 months). Thus, not only does patient selection contribute to improved survival, but patients do better with a more complete oncological resection. However, the timing of locoregional tumor resection is controversial and varies in all studies. The literature reports from registry data provide limited information about the timing of surgery because patients underwent locoregional resection of the primary tumor at various times after diagnosis. In an evaluation of chest wall disease and its influence on outcome, Arriagada et al. found that the development of distant metastases was related to local failure as a time-dependent covariate [25]. A similar conclusion was reached by Hazard and colleagues, who reported that uncontrolled chest wall disease was associated with decreased overall survival, independent of surgical intervention [26]. Hazard et al. observed that 36% of women not initially offered surgery required some form of locoregional therapy, either surgical or radiotherapeutic, to control chest wall disease. Only 17% of the nonsurgical group was maintained with asymptomatic, intact tumors in the breast throughout their course. This result supports the theory of reduced seeding or a reduction of potentially resistant cell lines. The number of metastatic sites negatively influences survival, and it can be argued that the primary tumor constitutes an additional metastatic site. This hypothesis is supported by studies indicating improved survival in patients with limited metastatic BC when a single metastatic site is treated aggressively [27]. However, concerns have been raised that surgery to the primary tumor can actually adversely affect survival [28–30]. Cady et al. studied the impact of the sequence of systemic and surgical treatments in stage IV patients. They observed 2-year survival of 90% in patients receiving chemotherapy first, which was higher than the rate for patients who received chemotherapy simultaneously with or after surgery, suggesting that delaying surgery after an excellent response to initial chemotherapy may be beneficial. The 2-year survival advantage occurred with pre-surgery chemotherapy for bone metastases, but no difference in survival with or without surgery occurred when these treatments were simultaneous. Among 5-year survivors, the frequency of primary site surgery after an excellent response to ST, breast surgery in stage III patients incorrectly classified as stage IV, and the frequency of oligo-metastases all indicated selection bias [31]. A review of a prospectively maintained database of patients who presented with stage IV BC between 1998 and 2005 was reported by Bafford et al. [32]. Of the 147 women who presented with stage IV BC, 61 (41%) underwent mastectomy or lumpectomy, and the median unadjusted overall survival was 3.52 years for surgery versus 2.36 years for no surgery ($p = 0.093$). The ER and HER2neu status and central nervous system and liver metastases were predictors of survival, and multivariate analysis revealed that survival was significantly superior in the surgery group (HR: 0.47 $p = 0.003$, mean 4.13 years versus 2.36 years). In women undergoing surgery, 36 were diagnosed with metastatic disease postoperatively, and 25 were diagnosed preoperatively. These groups had median survival durations of 4.0 years and 2.4 years, respectively, comparable to the median survival of the no surgery group (2.36 years, $p = 0.18$). They concluded that breast surgery is associated with improved survival in stage IV BC. However, this benefit is only realized among patients operated on before the diagnosis of metastatic disease and is likely a consequence of stage migration bias [32]. Ruiterkamp et al. obtained similar results, and in their study, removing the primary tumor in patients with primary distant metastatic disease was associated with an approximately 40% reduction of mortality risk [33]. The association was independent of age, the presence of comorbidities, and other potential confounders. The median survival of patients who underwent surgery for their primary tumor was significantly longer than that for patients who did not have surgery (31 vs. 14 months), and the 5-year survival rates were 24.5% and 13.1%, respectively ($p < 0.0001$). In a multivariate Cox regression analysis, adjusting for age, period of diagnosis, T-classification, number of metastatic sites, comorbidity, use of LRT, and use of ST, surgery appeared to be an independent prognostic factor for overall survival [33].

These studies were all subject to selection biases due to their retrospective nature. It was evident that surgeons were inclined to use surgery in patients with more favorable features (i.e., younger age, smaller tumor size, less evident axillary involvement, fewer sites of metastasis). Therefore, these studies should be interpreted with caution. Further limitations of these trials, such as a lack of information regarding radiation/ST, histopathological features, and the timing of surgery to remove the intact primary tumor, were obvious. To eliminate selection biases, randomized clinical trials should be designed to compare locoregional treatment for the primary tumor with no intervention to the primary tumor; two trials with such a design and other ongoing studies will be discussed later in this chapter.

Regarding axillary disease control in stage IV BC patients, in the NCDB study, although the extent of nodal disease was not significantly associated with survival, women undergoing total mastectomy were expected to have nodal dissection to some extent. Nodal dissection may have contributed to the survival advantage observed in the total mastectomy group [6]. In the Geneva study, a trend toward improved survival was observed for women who had both a tumor-free surgical margin and axillary clearance [23]. Previous studies have lacked regional radiotherapy (RT) data. In the Geneva registry study, administration of whole-breast RT to patients who underwent breast-conserving surgery (BCS) increased the hazard of death independently [23].

Harris et al. published a meta-analysis of nine retrospective cohort studies and one case-control study in 2013 [34] (Table 28.1). Seven studies covered the period 1988–2005; three of the smaller studies included results dating to the 1970s, and all were multicenter studies. This meta-analysis suggested that appropriately selected patients may derive a survival benefit from resection of the primary tumor. Collated data from 28,693 patients demonstrated that patients undergoing surgery on the primary tumor had improved 3-year survival times (40%) compared with those treated with ST alone (22%). However, there are some limitations to this meta-analysis and its conclusions; the data presented are limited to retrospective studies, and surgical patients had a more favorable profile before operative intervention. Selection biases, lack of intervention at metastatic sites, and stage migration are limiting factors that could contribute to the better outcome in retrospective studies. However, even if the published meta-analysis failed to demonstrate any survival benefit of neoadjuvant versus adjuvant chemotherapy, it is unclear from these studies whether patients received chemotherapy in a neoadjuvant setting rather than an adjuvant setting [35]. HER2 data are also limited in many of the studies, and therefore, it is difficult to achieve any meaningful conclusions regarding the role of primary excision in the setting of HER2-positive stage IV disease. Ongoing randomized clinical trials will determine the optimal timing, most favorable tumor biology, and indications for surgery to remove the primary tumor.

A retrospective study from Japan evaluating the prognostic impact of local surgery and other clinicopathological features in patients with de novo stage IV BC found that overall survival was prolonged with local surgery, younger age, and bone or soft tissue metastases ($p < 0.05$). Furthermore, they found that local surgery did not improve overall survival in older patients (>51 years old) or patients with visceral or bone/soft tissue-only metastases ($p > 0.05$). The authors concluded that local surgery should be considered for younger and fewer patients [36].

Randomized Clinical Trials

There are eight randomized, controlled trials in progress that will address and hopefully clarify the role of primary tumor excision in the setting of stage IV BC, but unfortunately two of them have been terminated because of poor recruitment (Table 28.3, Fig. 28.1). Two randomized clinical trials (RCTs) were presented at the San Antonio Breast Cancer Conference in 2013 and published later [37–39]. A group in India conducted a prospective randomized trial to assess the impact of locoregional treatment on outcome in women with metastatic BC at initial diagnosis [37]. In this RCT, anthracyclines±taxane-based chemotherapy was initially administered to all de novo stage IV BC patients, and patients who exhibited regression of the primary tumor were randomized to receive surgery or no surgery. The mean ages were 47 years and 48 years, respectively, and 74% of the patients had three or more metastases in both groups. There is a drawback of the Indian study; although 26% ($n = 45$) of LRT group patients and 35% ($n = 62$) of no-LRT group patients had HER2/neu (+), no HER2/neu (+) patients received HER2-targeted therapy in the LRT group, and 15% received such therapy in the no-LRT group. The overall survival hazard ratio for surgery was 1.04 (95% CI; 0.80–1.34; $p = 0.79$); however, the local progression-free survival hazard ratio was 0.16 (95% CI; 0.10–1.26; $p = 0.00$), which is additional evidence that locoregional intervention in the metastatic setting provides a reduction of progression of the primary tumor of >80%. According to the data presented from India, locoregional treatment of the primary tumor did not result in any benefit in overall survival. In fact, surgical removal of the primary tumor may even encourage the growth of distant metastases, lending support to the argument that less is more. This unexpected result should be evaluated in other studies and will remain controversial in the absence of appropriate ST and good patient selection.

The Turkish trial (MF07-01) is a phase III, multicentric, randomized controlled clinical trial comparing locoregional

Table 28.3 Randomized clinical trials evaluating the importance of surgery of the primary tumor in de novo stage IV breast cancer

Country	ClinicalTrials.gov Identifier	Initial therapy	Study period	Sample size	Status
India	NCT00193778	CAF ± T	2005–2012	350	Published
Japan	JCOG	ST	2011–2016	410/5000	Recruiting
ECOG 2108	NCT01242800	ST	2010–2016	368/258	Recruiting
Thailand	NCT01906112	ST	2013–2019	476	No record
Turkey (MF07-01)	NCT00557986	Surgery	2008–2012	278	Published
Turkey (BOMET): registry	NCT02125630	Surgery	2014–2017	288	Ongoing
Netherlands	NCT01392586	Surgery	2011–2016	516	Terminated
Austria	NCT01015625	Surgery	2010–2019	254	Closed

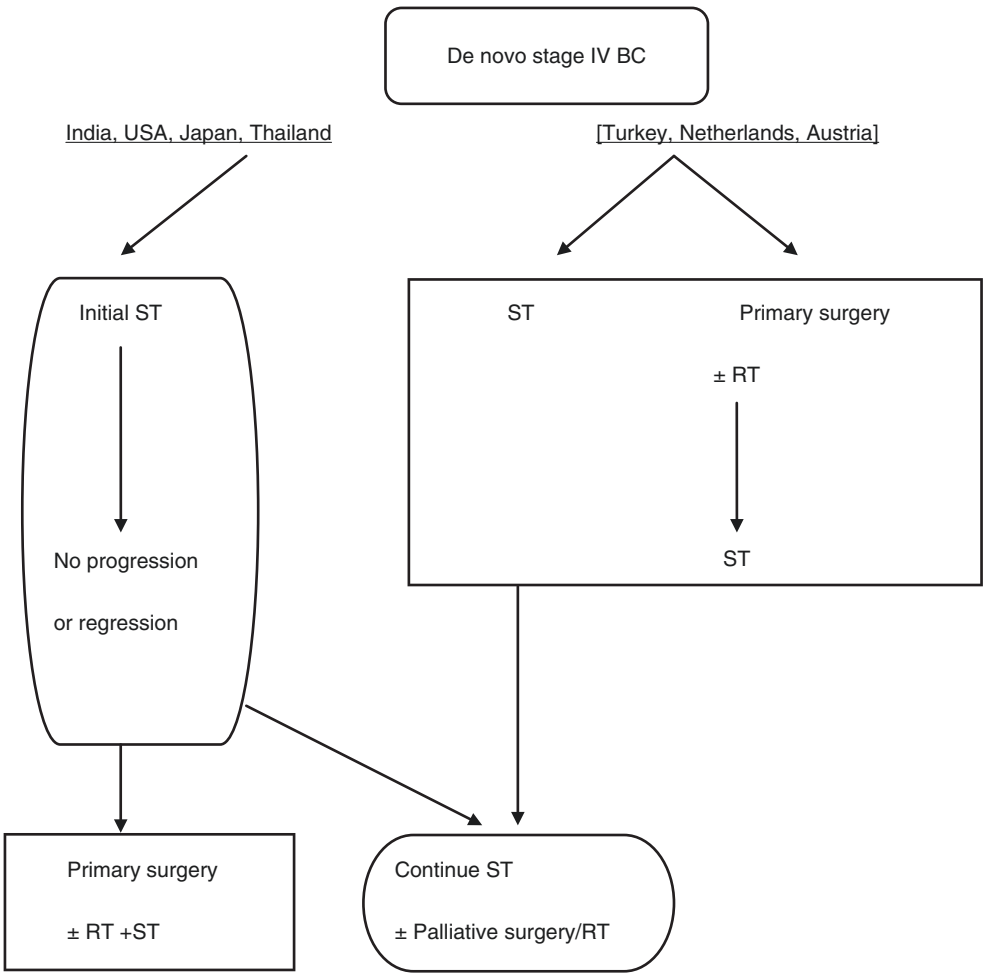

Fig. 28.1 Hypothesis testing of the importance of surgery of the primary tumor in de novo stage IV breast cancer in randomized studies. ST Systemic therapy, RT Radiation therapy

treatment (complete resection of the primary tumor and, when necessary, axillary clearance and RT to the whole breast, thoracic wall and/or regional lymph basins) with no locoregional treatment in stage IV BC patients [38, 39]. The protocol differed from the previous trial in that locoregional therapy is performed before initiating ST. All patients receive ST regardless of their study assignment. In the locoregional treatment arm, ST is administered after surgical extirpation of the intact primary tumor, whereas in the no locoregional treatment arm, ST is given immediately after randomization. The hypothesis of this trial is that adequate locoregional treatment of the primary tumor as described earlier prolongs overall survival compared with no locoregional treatment in stage IV BC patients. Locoregional treatment consists of complete resection of the primary tumor (either as mastectomy or breast-conserving surgery (BCS)) and level I–II axillary clearance if axillary nodes are involved and RT to the whole breast is done after BCS. All patients who are clinically node positive undergo standard level I–II axillary clearance. However, in clinically node-negative patients, SLN biopsy is used to assess axillary involvement. Axillary clearance is not required in patients with negative SLN. These patients remain N0. In SLN-positive patients, level I–II axillary clearance is required. All patients who undergo BCS receive RT to the whole breast as indicated for early-stage BC. In the no-locoregional treatment group, primary tumor resection is only allowed when the tumor requires palliation (in conditions such as bleeding, ulceration, and pain). Patients who are assigned to the no-locoregional treatment arm receive ST immediately after randomization, whereas patients who are randomized to the locoregional treatment arm receive ST after their primary tumor is resected. No statistical difference in overall survival was observed at early follow-up [38]. LR progression was 11 times higher in the ST group (n = 15; 11%) than in the surgery group (n = 2; 1%). During the 40-month follow-up, 55% (176/38) and 74% (101/136) patients died in the LRT and ST groups, respectively. Hazard of death was 34% lower in the LRT

group as compared to the ST group (HR: 0.66, 95% CI 0.49–0.88, $p = 0.005$). By the fifth year of follow-up, 41.6% (95% CI 32.5–50.4) of patients were alive in the LRT group and only 24.4% (95% CI 16.9–32.6) were alive in the ST group ($p = 0.005$). With unplanned subgroup analyses, patients ER (+) or HER2/neu (−), those with solitary bone metastasis, and patients <55 years old had a significant survival benefit with initial surgery. Patients with triple negative phenotypes appear to derive less benefit from early surgical intervention, and patients with multiple liver and/or pulmonary metastases had a significantly worse prognosis with initial surgery. The overall 30-day mortality rate did not differ between the surgery and ST groups ($p = 0.98$). This is the first randomized study to show statistically significant improvement in median survival with surgery (46 vs. 37 months; HR: 0.66, $p < 0.005$) at 5-year follow-up. Median survival was almost 10 months longer in the LRT group compared with the ST group in solitary bone only metastasis with HR 0.47.

The Translational Breast Cancer Research Consortium (TBCRC) presented registry study, similarly designed to Indian Study, at the 2016 American Society of Clinical Oncology meeting [40]. This prospective observational study concluded that most patients (85%) responded to ST and no non-responders underwent primary tumor surgery. Despite a very limited number of patients in this study, survival benefit with primary tumor surgery was not shown in responders. This concluded that HER2 status and patient age were strong prognostic factors influencing survival.

Surgery Versus Radiotherapy

Similar to surgery, the use of radical locoregional therapy (LRT) with surgery or radiation therapy (RT) alone is controversial. To examine the effect of LRT on survival in patients with stage IV BC at diagnosis, Nguyen et al. searched the database to identify women with clinical or pathological M1 BC at diagnosis [41]. They included women in whom the M1 disease was identified at the same time as or within 4 months of the initial diagnosis of primary BC ($n = 733$). Women with supraclavicular metastasis but no evidence of distant disease were also excluded from the study. The median follow-up time was 1.9 years, and LRT consisted of surgery alone in 67% of patients, RT alone in 22%, and both surgery and RT in 11%. ST was administered to 92% of patients who underwent LRT and 85% of patients who did not. The 5-year OS rates were 21% for patients treated with LRT and 14% for patients treated without LRT ($p < 0.001$), and the rates of locoregional progression-free survival were 72% and 46%, respectively ($p < 0.001$). Multivariable analysis indicated that treatment-related variables associated with improved overall survival were LRT (hazard ratio [HR] 0.78; 95% confidence interval [CI], 0.64e0.94; $p = 0.009$), clear resection margins (HR 0.63; 95% CI, 0.49 0.81; $p < 0.001$), chemotherapy (HR 0.82; 95% CI, 0.69e0.97; $p = 0.02$), and hormone therapy (HR 0.66; 95% CI, 0.53e0.82; $p < 0.001$). The authors concluded that locoregional treatment of primary disease is associated with improved survival in some women with stage IV BC at diagnosis. Among those treated with LRT, the most favorable rates of survival were observed in the subsets with young age and good performance.

In another retrospective study of 581 eligible patients by Le Scodan et al., 320 received LRT, and 261 received no LRT. LRT consisted of exclusive LRR in 249 patients (78%), surgery of the primary tumor with adjuvant LRR in 41 patients (13%), and surgery alone in 30 patients (9%) [42]. At a median follow-up time of 39 months, the 3-year OS rates were 43.4% and 26.7% with LRT and without LRT ($p < 0.001$), respectively. The association between LRT and improved survival was particularly marked in women with visceral metastases. LRT was an independent prognostic factor in multivariate analysis (hazard ratio [HR] = 0.70; 95% CI, 0.58 to 0.85; $p < 0.001$). The adjusted HR for late death (>1 year) was 0.76 (95% CI, 0.61 to 0.96; $p = 0.02$). The authors concluded that LRT was associated with improved survival in de novo stage IV BC patients and that exclusive LRR may consequently represent an active alternative to surgery.

Although no randomized clinical trial has evaluated the role of LRT in de novo stage IV BC patients, LRT would be a reasonable alternative approach, particularly in patients with comorbidities for whom surgery may not be indicated.

Uncertainties

Survival prolongs with an effective ST and locoregional treatment, but it is unclear how physicians should address issues such as:

- Surgery or RT to primary tumor and axilla.
- Risk and morbidities of surgery and RT.
- Reconstruction.
- Optimal timing of surgery for the patient who received ST.
- What is the optimal ST regimen?
- Delay of ST.
- Contralateral mastectomy.
- Complete response of metastases to ST; what is next?
- Intervention for metastases.
- Surgery to non-responders after ST.
- Quality of life.
- Cost.
- Is solitary bone only metastasis different than other de novo stage IV BC?

One randomized study alone cannot answer all the questions and we need more well-designed studies covering these uncertainties, but we have now more solid evidence that LRT has a role in de novo stage IV BC. Not all metastatic BC are the same, and there is a subgroup of patients who live longer. Newly diagnosed stage IV BC deserves comprehensive discussion, but survival benefit depends on resection completeness and locoregional RT. De novo stage IV BC patients should be discussed in the tumor board for the possibility of LRT to prolong the survival and for the locoregional control which affects the quality of life of the patient.

Conclusion

BC outcomes are progressively improving such that BC is beginning to be viewed as a chronic ailment to manage rather than a terminal event and indicating a continually changing role of surgery in the future. Even though the survival advantage of surgery to remove the primary tumor in patients with de novo stage IV BC is still in debate, patients with de novo stage IV BC should be informed about study results and ongoing clinical trials. There is enough evidence to prove that primary surgery to remove the tumor provides a local control advantage. If the aim is to control locoregional progression with surgery in this cohort of patients, the patient should have well-controlled distant metastasis and receive ST. In conclusion, there is a need to constantly reevaluate the standards of care to ensure that optimum treatment of BC in all stages is provided.

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29 Local-Regional Recurrence After Breast-Conservation Treatment or Mastectomy

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Introduction

Tumor recurrence can occur in local or regional lymph node areas after the definitive local treatment of breast cancer following either breast-conservation treatment or mastectomy with or without definitive radiation treatment. Local recurrence after breast-conservation treatment may occur in the ipsilateral treated breast, parenchyma, or breast skin. Local recurrence after mastectomy is observed in the ipsilateral chest wall, including the skin. Regional recurrence is defined as the reappearance of cancer involving the locoregional lymph nodes, including mostly ipsilateral axillary or supraclavicular lymph nodes or less frequently infraclavicular or internal mammary lymph nodes [1]. Local recurrence can be the first manifestation of disease as isolated or solitary recurrence or can occur simultaneously with regional and/or distant metastases.

Local Recurrence After Breast-Conservation Treatment

Contemporary management of early-stage breast cancer decreases the local recurrence rates from 1% per year to less than 0.5% per year [2–4]. National Surgical Adjuvant Breast and Bowel Project (NSABP) protocols demonstrated that 37% of local recurrences were detected in the first 5 years following breast-conservation treatment, whereas the remaining majority of recurrences occurred as late recurrence after a 5-year follow-up period [3].

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Local recurrences are primarily classified as a true recurrence (TR), which is defined as regrowth of the disease at the tumor bed, and new primary (NP), which is distinct from the index lesion based on histology and location [5–8]. This distinction is commonly made by comparing the characteristics, such as location, pathologic features, and interval to local recurrence, of the initial tumor versus the local recurrence [5–8]. Patients with NP have better clinical outcomes compared with those with TR [5–8]. Distinguishing NP breast carcinomas from TR may be important for therapeutic management strategies.

Diagnosis

The clinical and radiologic characteristics of recurrent lesions are similar to the initial tumors. Both surgery and radiation treatment may cause some changes, such as a mass-like fibrosis that may be difficult to distinguish clinically or occasionally radiologically from a local recurrence. Any changes noted via physical examination that occur after more than 1–2 years following the completion of radiation treatment must be considered as suspicious. A thorough history along with physical examinations appears to be the most effective method to detect local recurrences [9, 10]. In routine practice, mammography with ultrasound is commonly used for surveillance of the affected breast and to screen the contralateral breast after radiotherapy (Figure 29.1). A post-treatment mammogram should be obtained 1 year after the initial diagnostic mammogram or 6–12 months after the completion of radiation therapy to establish a new baseline. Post-treatment changes, such as edema, trabecular thickening, and architectural distortion, may remain stable but typically decrease on subsequent annual mammograms. However, any new findings on mammography, such as calcifications, mass, or increasing architectural distortion, should be evaluated carefully for ipsilateral breast tumor recurrence. In the study by Günhan-Bilgen et al., recurrent tumors were similar in mammographic appearance to primary tumors in

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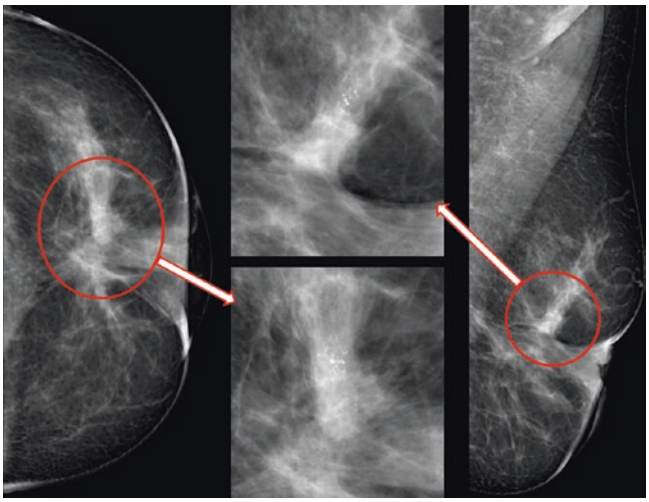

Fig. 29.1 Mammography imaging of a 39-year-old premenopausal patient with a local recurrence 3 years after breast-conserving surgery. A parenchymal distortion, together with pleomorphic microcalcifications, is noted in the upper-outer quadrant of the left breast. Her biopsy revealed invasive ductal carcinoma that was estrogen receptor- and progesterone receptor-negative and -HER2 positive, which was almost the same as the initial pathology. She received adjuvant chemotherapy, radiotherapy, and trastuzumab for one year after her first operation

27 (66%) of 41 cases [11]. Of the 27 primary tumors that initially presented as masses, 19 (70%) recurred as a mass. Of the six isolated calcifications, five (83%) recurred as calcifications. Ten (53%) of the 19 recurrent masses and all 5 recurrent calcifications (100%) exhibited morphologic features that were similar to those of the primary tumor. In addition, 92% (11/12) of the recurrences with microcalcifications (isolated or associated with a mass) also contained microcalcifications in the corresponding primary tumor. Seventy-six percent (31/41) of recurrences were located within the lumpectomy quadrant. Furthermore, histologic findings from the primary tumor and the recurrence were identical in 25 (61%) cases. The majority of recurrent tumors appear to be mammographically similar to primary tumors. Therefore, the researchers concluded that it is important to review preoperative mammograms during the follow-up of these patients. In contrast, Weinstein et al. [12] reported that the mammographic appearance of the local recurrence often varied from the appearance of the original breast among 95 patients who developed a recurrence after breast-conservative therapy. The mammographic appearance of the local recurrence often varied from the appearance of the original breast cancer.

Breast sonography is an essential imaging technique that is complementary to mammography in our routine practice to characterize suspicious mammographic findings and identify palpable masses as cystic or solid. Screening sonography has been used to detect mammographically and clinically occult cancers with a higher sensitivity in dense breasts [13]. The role of sonography in addition to mammography in screening has been investigated in the American College of Radiology Imaging Network (ACRIN) trial (protocol 6666) [14]. The study included high-risk patients with dense breast tissue on mammography and sought to determine the detection rate of nonpalpable, mammographically occult breast cancers identified solely by sonography. From April 2004 to February 2006, 2809 women, with heterogeneously dense breast tissue, were recruited to undergo mammographic and ultrasonographic examinations. Forty patients (41 breasts) were diagnosed with breast cancer: 8 suspicious on both ultrasound and mammography, 12 on ultrasound alone, 12 on mammography alone, and 8 patients (9 breasts) on neither. The diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound. The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67–0.87), whereas adding a single screening ultrasound to mammography increased the accuracy to 0.91 (95% CI, 0.84–0.96). Of the 12 cancers detected by ultrasound alone, 11 (92%) were invasive cancers with a median size of 10 mm (range, 5–40 mm). The authors concluded that adding a single screening ultrasound to mammography will yield additional 1.1–7.2 cancers per 1000 high-risk women.As another imaging modality, magnetic resonance imaging (MRI) dynamically evaluates the morphology and vascularity of breast lesions after intravenous contrast enhancement. The enhancement pattern on contrast-enhanced MRI is effective in distinguishing post-treatment scars from recurrent cancer in patients with breast-conserving therapy [15]. However, according to the American Cancer Society guidelines, data are insufficient to recommend routine MRI screening for women after breast-conserving treatment [16].

In the last decade, digital mammography has replaced conventional mammography in many centers due to its enhanced accuracy in dense breasts. Digital breast tomosynthesis (DBT) is also a novel breast imaging tool that is used in three-dimensional planes. Finally, contrast-enhanced spectral mammography (CESM) has been recently introduced as a new breast imaging technique [16, 17]. This technique has been compared with MRI regarding the detection and size estimation of histologically proven breast cancers. Recent studies have demonstrated the enhanced sensitivity of CESM and MRI in breast cancer detection compared with conventional mammography. In addition, contrast-enhanced spectral mammography has promise because it offers comparable results to MRI in the detection of malignant breast lesions [17, 18]. Future studies are needed to determine the role of these new technologies in improving the sensitivity of mammography in distinguishing post-treatment changes from recurrent cancers in patients after breast-conservation treatment.

Management

Various previous studies have demonstrated concurrent distant metastases and/or locally extensive recurrences or regional nodal recurrences (RNRs) in 5–10% of patients presenting with local recurrences [19–23]. Therefore, staging should be performed, preferably by positron emission tomography-computed tomography (PET-CT, for patients diagnosed with locally recurrent disease to exclude patients with distant metastases before making decisions regarding the management of these patients. Other studies have demonstrated that local recurrences and distant metastases are independent events that occur at different times [24]. Veronesi et al. evaluated the incidence and associated factors related to local and distant recurrences in patients with breast-conservative therapy (BCT) (n = 2233) at the Milan Cancer Institute from 1970 to 1987. In total, 119 local recurrences, 32 new ipsilateral carcinomas, and 414 distant metastases were detected as first events. The annual probability for local failures was approximately 1% up to the tenth year. For distant metastases, the annual probability was 5% in the second year and decreased progressively until the eighth year. In local failure patients, the 5-year overall survival (OS) rate was 69%. Patients with local recurrences exhibited an increased risk of distant metastases. In particular, women 35 years old or younger at first diagnosis who had initial peritumoral lymphatic invasion and local recurrence within 2 years are at high risk for distant spread and should be considered candidates for aggressive systemic treatment.

In the study of Shen et al., 120 women who developed isolated IBTR after BCT for Stage 0–III breast carcinoma between 1971 and 1996 at the MD Anderson Cancer Center were investigated to identify factors associated with systemic recurrence [25]. At a median follow-up of 80 months after IBTR, 45 patients (37.5%) exhibited systemic recurrence. Initial lymph node status (P = 0.001), lymphovascular invasion (LVI) in the primary tumor, time to IBTR ≤48 months, clinical and pathologic IBTR tumor size >1 cm, LVI in the recurrent tumor, and skin involvement at IBTR were identified as significant predictors of systemic recurrence. In a multivariate logistic regression analysis, initial positive lymph node status (relative risk [RR], 5.3; 95% confidence interval [95% CI], 1.4–20.1; P = 0.015) and skin involvement at IBTR (RR, 15.1; 95% CI, 1.5–153.8; P = 0.022) remained independent predictors of systemic recurrence. Patients who initially had lymph node-positive disease, skin involvement, or LVI at IBTR represented especially high-risk groups that warranted consideration for aggressive, systemic treatment and novel, targeted therapies after IBTR. In their multicentric study in Japan, Komoike et al. also reported that IBTR significantly correlated with subsequent distant metastases (hazard ratio [HR], 3.93; 95% CI, 2.676–5.771; P < 0.0001) [26]. Among the patients who developed IBTR, initial lymph node metastases and a short interval to IBTR were significant risk factors for subsequent distant metastasis. Similar findings were obtained in the study of Doyle et al., which included 93 patients with an invasive local recurrence after BCT. In addition, the interval from diagnosis to local recurrence was predictive of overall survival (OS) at 5 years (≤2 years, 65% vs. 2.1–5 years, 84% vs. >5 years, 89%; P = 0.03) [27]. However, whether IBTR is an indicator or a cause of subsequent distant metastases remains unclear.

Furthermore, uncontrolled local disease (ULD) following breast conservation is defined as the appearance of clinically manifested invasive cancer in the remaining breast or on the ipsilateral chest wall that could not be eradicated within 3 months of detection [28]. In a cohort of 5502 patients treated for Stage I–II invasive breast cancer with breast-conserving surgery (BCS) from 1976 to 1998 in Stockholm, 307 patients with subsequent IBTR were identified. At a median follow-up time of 11 years, 50 of 307 patients developed ULD, whereas the 5-year cumulative incidence of ULD following IBTR was 13%. In multivariate logistic regression analyses, nonsurgical treatment of IBTR, the presence of concurrent distant metastasis with IBTR, initial axillary lymph node metastases, <3 years between breast conservation and IBTR, and no adjuvant endocrine therapy were significant predictors of ULD. Moreover, 88% of the patients were treated with salvage mastectomy (SM) (n = 207) or re-excision (n = 62). The 5-year cumulative incidence of ULD following salvage mastectomy and salvage re-excision were 10% and 16%, respectively, compared with 32% among patients who were treated nonsurgically. Following IBTR, the 5-year overall survival among patients with local control was 78% in contrast with 21% among patients with ULD. Therefore, the authors concluded that patients with IBTR independent of concurrent distant metastases should be recommended for salvage surgery when feasible because it provides superior local control compared with salvage systemic therapy alone.

The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial [29] investigated the efficacy of chemotherapy for ER− and ER+ isolated locoregional recurrence (ILRR) of breast cancer. This report examining the prognosis of second locoregional recurrences in the trial's cohort demonstrated that second ILRR and distant recurrences as a second event were associated with poor prognosis, and almost half of the patients died. Predictive factors for survival were chemotherapy for primary cancer (HR, 3.55; 95% CI, 1.15–10.9; P = 0.03) and time interval from primary surgery (HR, 0.87, 95% CI, 0.75–1.00; P = 0.05).

A recent review by Wadasadawala et al. [30] highlighted that a multidisciplinary approach to individualized treatment based on the expected risk-benefit ratio of retreatment is important for all patients with locoregional recurrence. For all patients with locoregional recurrence, a systemic scan

should be performed to rule out systemic involvement. A second breast-conserving surgery is an option for selected patients followed by radiation therapy, with a 5-year overall survival rate of 76–100%. For isolated chest wall recurrences after mastectomy, hyperthermia and photodynamic therapy in combination with conventional treatment provide better outcomes. Furthermore, the addition of systemic therapies (chemotherapy and/or hormonal therapy) to local therapies improves survival. This approach also improves outcomes for isolated regional recurrences, with an average 5-year survival rate of 50%.

Mastectomy

The standard treatment for ipsilateral breast tumor recurrence after breast-conserving therapy is mastectomy with/without axillary staging depending on the initial axillary staging procedure [19–23]. Local recurrences have been detected in 3–22% in patients treated with mastectomy after IBTR [28, 31, 32]. Beard et al. investigated the clinical outcome after mastectomy in patients with IBTR ($n = 59$) using a database of 2101 breast cancer patient with BCT, including Tis (24%) [33]. IBTR lesions were classified as Tis (20%), T1 (46%), T2 (25%), or T3 (9%). At a median follow-up of 4.6 years, 13 patients (22%) developed postmastectomy recurrence (PMR) associated with decreased OS ($P = 0.002$). PMR was more common with larger IBTR tumors ($P = 0.03$), specifically IBTR ≥T2 ($P = 0.003$). In addition, 85% of PMR occurred within 2 years of mastectomy. Therefore, patients with IBTR tumors >2 cm should be considered for adjuvant local and systemic therapies, especially during the first 24 months.

After salvage surgery, the 5- and 10-year disease-specific survival rates after IBTR were 78% and 67–68%, respectively, and the 5- and 10-year overall survival rates were 69–89% and 39–64%, respectively (Table 29.1) [24, 25, 32–35]. Furthermore, the 5- and 10-year systemic recurrence-free survival rates after IBTR were 61% and 36–55%, respectively [25]. Voogd et al. reported the long-term prognosis of 266 patients with isolated IBTR at a median follow-up of 11.2 years [35]. The 10-year OS rate for the 226 patients with invasive local recurrence was 39% (95% CI, 32–46). The distant recurrence-free survival rate was 36% (95% CI, 29–42), and the local control rate (i.e., survival without subsequent local recurrence or local progression) was 68% (95% CI, 62–75). Patients with a local recurrence measuring 1 cm or less exhibited enhanced distant disease-free survival (DFS) compared with those with larger recurrences, suggesting that early detection of local recurrence can improve the clinical outcome of these patients. Finally, Botteri et al. from the European Institute of Oncology reviewed 282 patients presented with an operable invasive IBTR after BCS between 1997 and 2004 [36]. Of these patients, 161 (57%) underwent a second conservative surgery (CS), whereas 121 patients (43%) underwent mastectomy. Recurrences of the mastectomy group were T2–T4 and/or multifocal in 83 cases (68.6%). With a median follow-up of 5 years after the mastectomy, 5-year OS and disease-free survival (DFS) were 73.3% (95% CI, 65.0–81.6%) and 50.4% (95% CI, 40.9–59.8%), respectively. Based on multivariate analyses, early onset of IBTR, the presence of vascular invasion and Ki67 ≥20 of the recurrent tumor significantly affected both DFS and OS as poor prognostic factors.

Limited data are available for patients with BRCA1/2 mutations who develop local recurrence after BCT. In the study of Turner et al., 8 (15%) of 52 breast cancer patients with deleterious BRCA mutations had IBTR [37]. The median time to IBTR for patients with BRCA1/2 mutations was 7.8 years compared with 4.7 years for patients without BRCA1/2 mutations ($P = 0.03$). All patients with BRCA1/2 mutations and IBTR underwent successful surgical salvage mastectomy at the time of IBTR and remain alive without evidence of local or systemic progression of the disease.

Table 29.1 Outcome of patients detected with IBTR after BCT who were treated by salvage mastectomy or a second breast-conservative surgery

Study	Median follow-up	*N*	5-year DFS	5-year OS	10-year OS	5-year DSS	10-year DSS
Veronesi et al. [24]	nr	119	nr	69%	nr	nr	nr
Shen et al. [25]	80 months (range, 0.3–331 months)	120	nr	nr	nr	78%	68%
Kurtz et al. [30]	nr	178	nr	89%[a]	nr	nr	nr
Le et al. [31]	138 months ±66 months	105	nr	76%	56%	nr	nr
Galpar et al. [32]	85 months	341	nr	81%	nr	nr	nr
Voogd et al. [33]	134 months (11.2 years)	226	nr	nr	39%	nr	nr
Botteri et al. [34]	60 months	121	50.4%	73.3%	nr	nr	nr
Fodor et al. [36]	165 months (range, 75–240 months)	16[b]	nr	nr	81%	nr	nr
Albert et al. [38]	166 months (13.8 years)	116	nr	nr	66.7%	nr	nr

IBTR ipsilateral breast tumor recurrence, *BCT* breast-conservative therapy, *DFS* disease-free survival, *OS* overall survival, *DSS* disease-specific survival

[a]Including patients with wide local excision; *nr* not reported

[b]Patients with ≤2 cm in-breast recurrence

However, more studies with larger patient populations are needed to conclude whether local recurrence is not associated with poor prognosis in these patients. Furthermore, in patients with an IBTR in an irradiated breast, mastectomy with a myocutaneous flap reconstruction (i.e., latissimus dorsi flap, transverse rectus abdominis muscle) is the preferred method of reconstruction with improved cosmetic results and lower complication rates compared with implant reconstructions. Lee et al. [38] reported a series of 75 patients with chest wall reconstruction using an external oblique myocutaneous flap to cover the defects of advanced or recurrent breast tumors. All patients were Stage III or Stage IV cases. In their series, there were no major complications, and among 59 Stage III patients, locoregional relapse occurred in 5 patients (8.5%).

Breast-Conservative Therapy

As an alternative to salvage mastectomy, a second conservative treatment has been proposed, namely either lumpectomy alone or associated with re-irradiation of the tumor bed. Between 1983 and 1987, 56 patients developed an isolated local recurrence (ILR) in the chest wall after primary surgery for mastectomy (n = 894), and 68 developed an ILR after primary surgery for BCT (n = 415) [39]. The 10-year actuarial rate of cause-specific survival after treatment for ILR is 52%. On multivariate analysis, operability of recurrence (operable vs. inoperable, relative risk [RR]: 5.9), age at initial diagnosis (>40 vs. ≤40 years; RR, 2.2), and time to ILR (>24 vs. ≤24 months, RR, 2) were identified as independent prognostic factors for OS after ILR. In the conservative surgery (CS) group, the type of salvage surgery (mastectomy vs. repeat complete excision) had no significant impact on survival (P = 0.2). The majority (n = 44) of CS patients developed ≤2 cm in-breast recurrence, and the 10-year cause-specific survival was 81% after both salvage excision (n = 28) and mastectomy (n = 16), suggesting that patients with ≤2 cm in-breast recurrence potentially may undergo a second BCS.

Similarly, Gentilini et al. from the European Institute of Oncology studied 161 patients with invasive IBTR who underwent a second BCS to identify the subset of patients with the best local control [40]. The median follow-up after IBTR was 81 months. The 5-year overall survival after IBTR was 84% (95% CI, 78–89). The 5-year cumulative incidence of a second local event after IBTR was 29% (95% CI, 22–37). In the multivariate analysis, IBTR size >2 cm and time to relapse ≤48 months significantly increased the risk of local reappearance (hazard ratio [HR] 3.3, 95% CI 1.6–7.0; HR 1.9, 95% CI 1.1–3.5). The 5-year cumulative incidence of a further local reappearance of the tumor after repeating BCS was 15.2% in patients with IBTR ≤2 cm. In addition, patients with time to IBTR >48 months were identified as the best candidates for a second BCS, whereas patients with IBTR >2 cm and time to relapse ≤48 months exhibited a 71.2% 5-year local recurrence rate (P < 0.001), indicating that these patients should be considered for a mastectomy after IBTR.

Furthermore, Albert et al. at Yale-New Haven Hospital compared outcomes of salvage mastectomy (SM) and salvage breast-conserving surgery (SBCS) to determine the feasibility of SBCS [41]. Of 2038 patients treated with BCT, 166 developed IBTR. Patients were considered for SBCS if the recurrence was localized on mammogram and physical examination, was <3 cm pathologic tumor size, was confined to the biopsy site, did not exhibit skin or lymphovascular invasion, and was associated with ≤3 positive nodes. Of the 146 patients who were definitively managed by IBTR, surgery involved SM (n = 116) or SBCS (n = 30). At a median follow-up time of 13.8 years after IBTR, OS after IBTR was 64.5% at 10 years, with no significant difference noted between SM (65.7%) and SBCS (58.0%). Only two patients in the SBCS cohort subsequently had a second IBTR and were salvaged with mastectomy. Although mastectomy is considered the standard surgical salvage of IBTR, SBCS is feasible, and the prognostic factors are related to favorable tumor biology and early detection (Table 29.2).

Ishitobi et al. further investigated the risk factors associated with local control in patients (n = 78) who were treated with repeat lumpectomy after IBTR [42]. At a median follow-up period of 40 months, the 5-year second IBTR-free survival rate was 78.8%. Multivariate analysis revealed that the ER status of IBTR was a significant independent predictive factor for second IBTR-free survival (P = 0.0177).

Table 29.2 Outcome of patients detected with IBTR after BCT who were treated by a second breast-conservative surgery

Study	Median follow-up (months)	*N*	5-year DFS	10-year DFS	5-year OS	10-year OS
Fodor et al. [36]	165 months (range, 75–240 months)	28[a]	nr	nr	nr	81%
Gentilini et al. [37]	81 months	161	nr	nr	84%	nr
Albert et al. [38]	166 months (13.8 years)	30	nr	nr	nr	58%
Hannoun-Levy et al. [43]	47 months (range, 13–124 months)	217[b]	84.6%	77.2%	88.7	76.4

IBTR ipsilateral breast tumor recurrence, *BCT* breast-conservative therapy, *DFS* disease-free survival, *OS* overall survival, *DSS* disease-specific survival

[a]Patients with ≤2 cm in-breast recurrence; *nr* not reported

[b]Patients received partial breast irradiation for IBTR by multicatheter brachytherapy after a repeat breast-conserving surgery

Ishitobi et al. investigated the impact of breast cancer subtype on prognosis after IBTR in 185 patients in another study [43]. A significant difference in distant disease-free survival (DDFS) after IBTR was noted according to breast cancer subtype defined by a Ki67 index cutoff of 20% ($P = 0.0074$, log-rank test). The 5-year DDFS rates for patients with luminal A, luminal B, triple-negative, and HER2 types were 86.3%, 57.1%, 56.6%, and 65.9%, respectively.

A PubMed literature review was performed by Hannoun-Levi et al. to assess four different strategies of local treatment options: (a) salvage mastectomy alone, (b) salvage mastectomy with postoperative re-irradiation, (c) a second CT with surgery alone, and (d) a second CT with re-irradiation [44]. Although the 5-year OS rates after salvage mastectomy and the second CT appeared to be equivalent (≈75%), the rate of second local recurrence was approximately 10% (3–32%), approximately 25% (7–36%), and approximately 10% (2–26%) after salvage mastectomy, salvage lumpectomy alone, or salvage lumpectomy in combination with a re-irradiation of the tumor bed, respectively. Sedlmayer et al. similarly evaluated the outcome after partial breast re-irradiation for IBTR following the second BCT by surveying the literature between 2002 and 2012 (PubMed) [45]. Local treatment modalities included partial breast radiotherapy by external beam radiotherapy (EBRT); interstitial brachytherapy (BT) in a low-, high-, and pulse-dose rate technique; combined EBRT/BT; and intraoperative radiotherapy (IORT). The majority of the 310 patients (82%) were treated by brachytherapy. The selection criteria for a second breast-conservation procedure included T0–2 recurrent lesions, late onset after primary treatment, and no evidence of metastatic disease before undergoing gross tumor resection with free surgical margins. Treatment doses were similar to those for brachytherapy (LDR, 30–55 Gy; HDR, 30–34 Gy; PDR, 40–50 Gy) and biologically comparable to the only series that exclusively used EBRT (50 Gy). At a follow-up time of 49 months, the oncologic results were similar among the different methods, with local control rates ranging between 76% and 100%, and the disease-free and overall survival rates were comparable to the mastectomy series. The GEC-ESTRO working group presented a collaborative analysis on 217 patients at the 35th San Antonio Breast Cancer Meeting treated between 2000 and 2009 in 8 European institutions by brachytherapy (LDR, PDR, and/or HDR) [46]. With a median follow-up of 3.9 years (1.1–10.3) after IBTR retreatment, 5- and 10-year actuarial second local recurrence rates were 5.6% and 7.2%, respectively. In comparison to those series with salvage mastectomy series, the outcome of patients with a repeat breast-conservative surgery treated by brachytherapy was found to be similar with 5- and 10-year-actuarial rates for metastatic recurrence of 9.6% and 19.1%, DFS of 84.6% and 77.2%, and OS of 88.7% and 76.4%, respectively. Acute toxicity was low in all studies, and major late effects included fibrosis in re-irradiated parenchyma as a function of dose and volume, asymmetry (primarily due to double surgery), and breast pain. The cosmetic outcome was satisfactory, with scoring results from excellent to good in 60–80% of patients. In a highly selected group of patients with IBTR, partial breast irradiation with brachytherapy after second BCS could be safely performed as an alternative to mastectomy to potentially increase breast-conservation rates. Although published data about brachytherapy are more extensive [47–55], there is relatively little information about the oncological safety of other modalities, including PBI via EBRT or novel strategies, such as IORT [56]. All of these studies suggest that repeat BCS may represent a safe and feasible treatment method for isolated ipsilateral breast tumor recurrence in selected patients (Table 29.2).

Limited data are available about the efficacy of intraoperative radiotherapy in the treatment of IBTR in the previously irradiated breast. In their pooled analysis, Thangarajah et al. [57] included patients with IBTR who were previously irradiated by EBRT to the breast for any indication. They identified 41 patients and performed IORT with the Intrabeam™ device using low kV X-rays with a median follow-up of 58 (4–170) months. They reported 5-year local recurrence-free survival and overall survival rates of 89.9% and 82.7%, respectively, with no grade 3 or 4 acute toxicity. They emphasized that BCS in combination with IORT in IBTR is feasible in pre-irradiated patients. Furthermore, Trombetta et al. reported their long-term experience with balloon brachytherapy for retreatment of the breast after IBTR [56]. Between 2004 and 2012, 18 patients who had been previously treated with external beam radiotherapy were retreated with the MammoSite (Hologic Corporation, Marlborough, MA), MammoSite ML (Hologic Corporation), or the Contura (Bard Peripheral Vascular, Inc., Tempe, AZ) brachytherapy devices. Sixteen patients were treated for an ipsilateral breast tumor recurrence after breast-conservation surgery and postoperative irradiation (11 of these patients had infiltrating ductal carcinoma [IDC]). The recurrent histology of seven patients was IDC, whereas seven additional patients recurred as DCIS, three recurred as a combination of IDC/DCIS, and one recurred as infiltrating lobular carcinoma. All patients received a twice-daily tumor dose of 3400 cGy at 340 cGy per fraction. With a mean follow-up of 39.6 months, only two patients developed local recurrence. Both patients were treated locally by salvage mastectomy. The use of balloon brachytherapy devices in the treatment of the previously irradiated breast is feasible and may provide adequate local control in carefully selected patients.

Houvenaeghel et al. [58] compared the survival outcomes after mastectomy and lumpectomy plus interstitial brachytherapy for the treatment of breast cancer local recurrence. In their cohort of 348 patients, 66.7% of patients underwent

mastectomy, 17.8% underwent lumpectomy plus interstitial brachytherapy, and 15.5% underwent lumpectomy alone. There was no significant difference between the two modalities regarding overall and metastasis-free survival rates, suggesting that a second breast-conserving surgery and interstitial brachytherapy are feasible for selected patients.

There is an ongoing phase 2 NRG Oncology-Radiation Therapy Oncology Group study to determine the safety, associated toxicity, and tolerance of repeat breast-preserving surgery and three-dimensional conformal partial-breast re-irradiation for in-breast recurrence [59]. They included patients with unifocal in-breast recurrence occurring >1 year after whole-breast irradiation of <3 cm and resection with negative margins. Using a dose of 45 Gy in 1.5-Gy fractions twice daily for 30 treatments, they targeted the partial-breast re-irradiation to the surgical cavity plus 1.5 cm. The primary objective was to evaluate the rate of grade ≥3 treatment-related skin, fibrosis, and/or breast pain adverse events, and a rate of ≥13% was determined to be unacceptable (86% power, one-sided $\alpha = 0.07$). They analyzed and presented the 1-year follow-up results for 55 patients between 2010 and 2013. In the cohort, all patients were clinically node negative, 33 had invasive disease, and 22 patients had ductal carcinoma in situ. Nearly half of the patients received systemic therapy. They recorded grade 1 adverse events in 64%, grade 2 in 7%, and grade ≥3 in <2% of the patients. In their 1-year toxicity report, they concluded that partial-breast re-irradiation with three-dimensional conformal radiation therapy after the second lumpectomy for in-breast failures after whole-breast irradiation is safe with acceptable adverse events. However, further studies with larger patient populations are needed for more definitive results. Furthermore, other novel techniques, including radiofrequency (RF) ablation, to treat the local recurrence of breast cancer were investigated in various pilot trials; the results indicated insufficient efficacy for recommendations of routine use [60].

Surgical Management of the Axilla

Limited information regarding regional lymphatic recurrence (RLR) after salvage mastectomy or re-excision for IBTR without axillary surgery is available. Therefore, 102 patients who underwent salvage breast surgery without local treatment for the regional lymphatic basin (surgery or radiotherapy) for IBTR after BCT for primary breast cancer were studied [61]. Of these patients, 9 (8.8%) had RLR with a median follow-up period of 3.7 years after breast surgery for IBTR. ER negativity and the presence of lymphovascular invasion of the recurrent breast tumor were significant predictive factors of RLR ($P = 0.04$ and 0.02, respectively). These results suggest that axillary surgery should be performed to determine nodal involvement during salvage surgery for IBTR and provide locoregional control, especially in patients with aggressive ER (−) recurrent cancers or cancers with lymphovascular invasion. Therefore, the feasibility and the clinical impact of performing a second sentinel lymph node biopsy (SLNB) in patients with locally recurrent breast cancer were investigated in two European studies: the "Sentinel Node and Recurrent Breast Cancer (SNARB)" study and a study by Intra et al. from the European Institute of Oncology [62, 63]. A total of 150 patients with locally recurrent breast cancer were subject to lymphatic mapping with SLNB using a dual technique with blue dye and ^{99m}Tc-colloidal albumin. For validation, the surgeons were advised to perform axillary lymph node dissection (ALND) in cases with an intact axillary nodal basin. A total of 41 patients previously underwent BCT with SLNB. In addition, 82 patients underwent BCT with ALND and 9 patients were subject to mastectomy with SLNB. Twelve patients underwent mastectomy with ALND. Of these patients, 50 (33%) had a previous SLNB, 94 (63%) had a previous ALND, and 6 (4%) had no axillary surgery. A sentinel lymph node was detected in 95 patients (63.3%) by preoperative lymphoscintigraphy, and an SLNB was successfully performed in 78 patients (52%). As expected, extra-axillary lymphatic drainage was observed in 58.9% of the patients; an increased likelihood of this condition was noted after a previous ALND (79.3%) compared with a previous SNB (25.0%) ($P < 0.0001$) by lymphoscintigraphy. In a pathologic examination, 18 patients (22.8%) exhibited a (micro)metastasis, whereas additional 18 patients had no axillary lymph node metastases. Overall, performing a second SLNB altered the adjuvant treatment plan in 16.5% of the patients with a successful second SNB. These results suggest that although the detection rates are not satisfactorily high, an SLNB is feasible in approximately half of the patients with a previous axillary surgery as an axillary staging procedure and provides useful information for adjuvant treatment in one of six patients.

A similar study was conducted by Intra et al. in 212 patients with IBTR who were previously treated with BCT, had a negative SLNB, and subsequently underwent salvage breast surgery and a second SLNB from 2001 to 2011 [63]. Preoperative lymphoscintigraphy demonstrated at least one new axillary sentinel lymph node in 207 patients (97.7%), whereas no drainage was observed in five patients (2.3%). An SLNB by removal of 1 or more lymph nodes was accomplished in 196 of 207 patients (95%). Extra-axillary drainage pathways were identified via lymphoscintigraphy in 17 patients (8%). At a median follow-up period of 48 months, the 5-year axillary recurrence rate was 3.9%. All these studies demonstrated that a second SLNB is feasible, accurate, and oncologically safe for selected patients with IBTR who previously underwent a BCT with a negative SLNB finding.

Chest Wall Recurrence After Mastectomy

Chest wall recurrence (CWR) after mastectomy has been noted in up to one-third of cases [64]. In a pooled analysis of randomized trials, Jatoi et al. found that BCS was associated with a greater odds of local-regional recurrence (LRR) than mastectomy (pooled odds ratio [OR], 1.56; 95% CI, 1.29–1.89). Moreover, LRR still occurred in 8.5% of mastectomy patients [65]. LRR after mastectomy tends to occur earlier than in-breast recurrences after breast-conservation treatment [66]. Local recurrences appear in up to 90% of patients 5 years after the mastectomy, with a median interval to LRR of approximately 3 years [67, 68]. However, local recurrences have been reported even decades after the primary surgery. These late recurrences may be NP tumors rather than TRs of the prior cancer. CWR rates of up to 40% have been reported, depending on the initial treatment and primary tumor characteristics [69]. Even with the addition of adjuvant systemic therapy, CWR remains a significant issue in a considerable proportion of patients.

Prevention

The addition of postmastectomy radiation therapy (PMRT) may reduce the rate of CWR by up to 70% [40]. Although the British Columbia [71] and Denmark studies [72, 73] were criticized for a variety of reasons, the American Society of Clinical Oncology [74] and the American Society of Therapeutic Radiology and Oncology [75] have both issued guidelines recommending PMRT in patients with four or more positive lymph nodes or with tumors larger than 5 cm. PMRT is not recommended for node-negative patients with tumors smaller than 5 cm, and it remains controversial in the one to three positive-node group. A study of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed that a 20% reduction in 5-year local recurrence risk resulted in a 5% absolute reduction in 15-year breast cancer mortality, thus prompting more widespread use of PMRT in these patients [70].

In a recent meta-analysis by EBCTCG to determine the efficacy of postmastectomy radiotherapy, 8135 women randomly were assigned to treatment groups from 1964 to 1986 in 22 trials of radiotherapy to the chest wall and regional lymph nodes after mastectomy and axillary surgery versus the same surgery without radiotherapy [76]. Radiotherapy included the chest wall, supraclavicular or axillary fossa (or both), and internal mammary chain. At a follow-up of 10 years for patients with a negative axilla ($n = 700$), radiotherapy showed no significant effect on locoregional recurrence (two-sided significance level [$2P$] > 0.1), overall recurrence (RR, irradiated vs. not, 1.06; 95% CI, 0.76–1.48; $2P > 0.1$), or breast cancer mortality (RR, 1.18; 95% CI, 0.89–1.55; $2P > 0.1$). However, in patients with one to three positive nodes and ALND ($n = 1314$), radiotherapy reduced locoregional recurrence ($2P < 0.00001$), overall recurrence (RR, 0.68; 95% CI, 0.57–0.82; $2P = 0.00006$), and breast cancer mortality (RR, 0.80; 95% CI, 0.67–0.95; $2P = 0.01$). As expected, for patients with four or more positive nodes and ALND ($n = 1772$), radiotherapy also reduced locoregional recurrence ($2P < 0.00001$), overall recurrence (RR, 0.79; 95% CI, 0.69–0.90; $2P = 0.0003$), and breast cancer mortality (RR, 0.87; 95% CI, 0.77–0.99, $2P = 0.04$). The ongoing Medical Research Council (MRC) Selective Use of Postoperative Radiotherapy After Mastectomy (SUPREMO) trial will also provide important information about this important question, and biological markers of tumor aggressiveness and radiosensitivity may be identified that can then help tailor future therapy [77].

Diagnosis

CWR is defined as a breast cancer recurrence in the skin, subcutaneous tissue, nipple-areola complex, muscle, or underlying bone after mastectomy, and this condition requires a high index of suspicion upon physical examination (Fig. 29.2). Regional recurrences occur in the nodal tissue draining the primary tumor, including the supra- and infraclavicular (55%), axillary (28%), internal mammary (2%), and multiple (15%) lymph node basins [78]. Numerous CWRs occur within 2–3 years after mastectomy. CWRs have been identified more than 10 years later in a significant number of cases. Therefore, careful surveillance of the chest wall is required after mastectomy. Patients presenting with LRR after mastectomy typically exhibit aggressive progression.

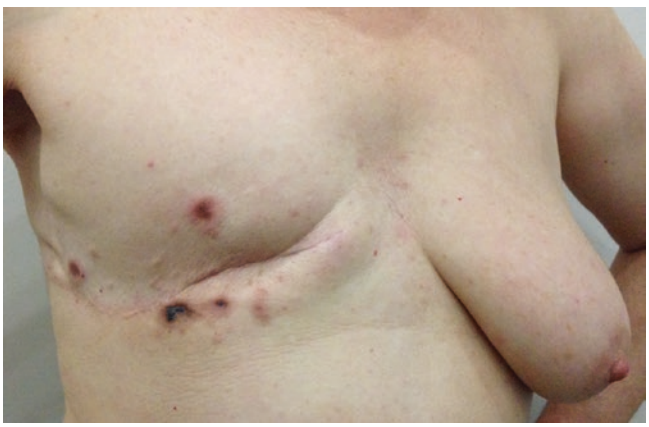

Fig. 29.2 A 58-year-old postmenopausal patient presents with multiple local chest wall recurrences 8 years after modified radical mastectomy. The patient did not receive systemic chemotherapy and chest wall irradiation after her primary surgery. She did not exhibit any nodal involvement or distant metastasis in any of the imaging modalities at the time of chest wall recurrence

Metastatic Stage IV disease occurs in almost 33% of these patients at the time of LRR. Some CWRs present as large fungating masses, whereas most are subtle, often presenting with an asymptomatic nodule in the skin or a slight erythematous rash. Over 50% of all CWR present as a solitary nodule in the skin; the remainder presents as multiple nodules or diffuse disease on the chest wall [79]. Therefore, a physical examination is the most important step for early detection of CWR.

Radiologic imaging after the initial treatment using mastectomy rarely demonstrates recurrences that were not suspected clinically. Therefore, routine imaging of the mastectomy site is not recommended. In a group of 827 postmastectomy patients with or without reconstruction, Fajardo et al. [80] found that mammography demonstrated recurrences that were previously clinically suspected based on physical examination findings. Similarly, Propeck and Scanlan [81] studied a group of 185 postmastectomy patients and concluded that routine imaging of this population was not helpful in detecting recurrent disease. However, the contralateral breast should be imaged in the routine fashion. Further work-up of the patient, including MRI, thorax CT, bone scintigraphy, PET-CT, and other modalities, may be needed if metastases are suspected (Fig. 29.3) .

In 23–70% of cases, the recurrence appears on the previous mastectomy scar [82–84] (Fig. 29.2a), and CWRs may be mistaken for fat necrosis, radiation-induced injury, or foreign body granuloma [85]. In these cases, histological confirmation is required and can be obtained with a punch biopsy. The estrogen-receptor status of the primary tumor and that of the subsequent recurrence are the same in approximately 75–85% of patients.

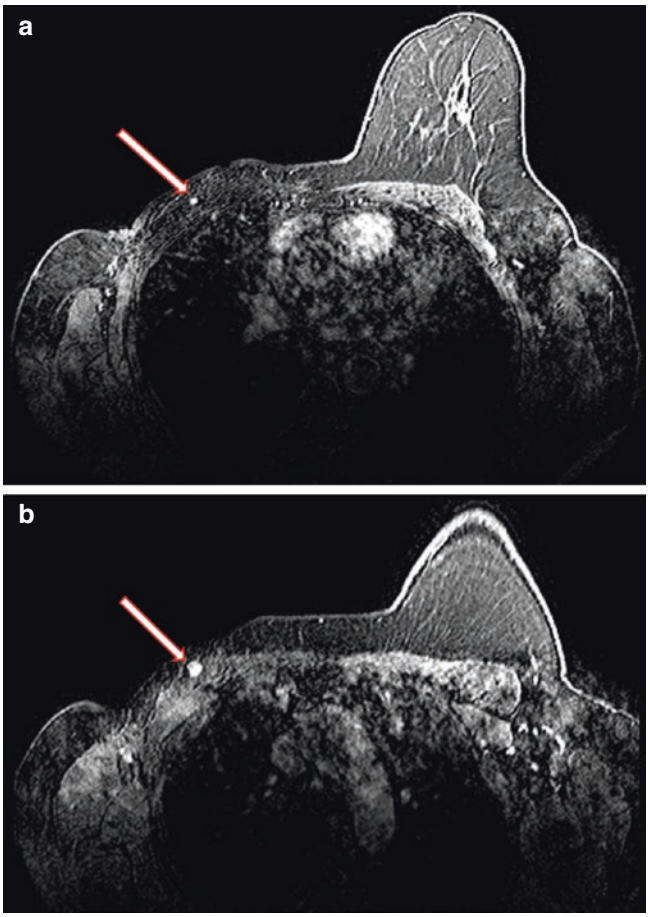

Fig. 29.3 MRI images showing recurrences within the pectoralis major muscle in two different foci (**a**, **b**) of a 51-year-old postmenopausal patient who underwent MRM one year ago with a diagnosis of triple-negative, T4-invasive ductal carcinoma

Prognostic Factors

CWR may be accompanied by the presence of distant metastases in up to 30% of patients [85]. Numerous factors are associated with improved prognosis in these patients, and a variety of prognostic tools are available to assist clinicians in predicting survival in these patients [82, 86, 87] The MD Anderson Cancer Center reported that initial node-negative status, time to CWR greater than 24 months, and treatment with radiation therapy for the isolated CWR are independent predictors of improved disease-free and overall survival [88]. Patients with all three favorable features have a median overall survival of 141 months (10-year actuarial survival: 75.4%). Those with one or two favorable features exhibited a median overall survival of 54 months (10-year actuarial survival: 25.1%), and those without any favorable features had a median overall survival of 16 months (10-year actuarial survival: 0%) [87]. These data suggest that patients presenting with CWR are a heterogeneous population, and aggressive management using a multidisciplinary approach is needed for patients anticipating a good prognosis. Haffty et al. [88] reported that positive HER-2/neu status was associated with an increased rate of local-regional disease progression compared with negative HER-2/neu (41% vs. 8%, respectively; $P = 0.007$) [88].

Fodor et al. found that patients who developed a CWR greater than 24 months from their initial mastectomy and who were initially node negative exhibited enhanced 10-year disease-specific survival [89]. They also found that the prognosis was improved if the recurrence was a single operable lesion in the scar. Subsequent local or regional recurrence after salvage treatment occurs in 25–35% of treated patients, typically within 5 years of salvage treatment [66].

Surgical Therapy

Surgical resection of CWR is an important issue in the management of patients with CWR because it provides excellent

local control in patients with resectable disease. Surgery is particularly useful in patients who have previously undergone radiation therapy or those in whom radiation therapy is inadvisable.

Resection of the CWR is often straightforward for patients with isolated recurrences involving only the skin or the surgical scar. Resection with primary closure is generally favorable and provides excellent local control. Although high response rates are noted with the use of radiation therapy alone for CWR, 60–70% of patients experience a second failure; thus, surgical resection must be considered for any patient with localized, recurrent disease [89–93]. With more extensive disease, reconstructive procedures, such as coverage with either a skin graft or autologous flap, may be needed [89–93]. The goal of resection should be maintaining a clear margin. Although there is no consensus on what constitutes a "clear margin," wide resection is generally recommended.

Dahlstrom et al. [89] reported 69 patients who underwent wide local excision for local recurrences, and the 5-year actuarial local control rate was 50% with a 5-year overall survival of 62%. Pameijer et al. reviewed their experience with full-thickness chest wall resection for CWR of breast cancer ($n = 22$) and conducted a meta-analysis to determine patient characteristics and outcomes between 1970 and 2000 [90]. The 5-year DFS was 67% at City of Hope National Medical Center (COH) and 45% for the entire group of 400 patients. The 5-year OS was 71% for the COH group and 45% for the entire group. Patients with a disease-free interval longer than 24 months exhibited the best prognosis in most studies. In another study by Friedel et al., chest wall resection with a myocutaneous flap was performed in 63 women (mean age, 58 years) with CWR between 1985 and 2006 [91]. The cumulative 5-, 10-, and 15-year OS rates were 46%, 29%, and 22%, respectively, with a median survival of 56 months, whereas mortality was 1.6% and morbidity was 25%.

Locoregional chest wall recurrences with the involvement of the ribs and/or sternum after primary breast cancer surgery are associated with a poor outcome. The oncological benefit of extensive CWR, including the ribs and sternum, remains controversial regarding its morbidity. However, various studies have demonstrated good long-term prognosis with full-thickness resections in selected patients. Of 76 patients with isolated sternal or full-thickness chest wall (SCW) recurrences, 44 were treated surgically, and 32 were treated nonsurgically between 1992 and 2011 [92]. No difference in 5-year OS was observed between patients treated with surgery and those who were not (30.6% and 49.6%, respectively; $P = 0.52$). Patients who were selected for surgery had more advanced and biologically aggressive disease and were more likely to have triple-negative breast cancer at recurrence (52% vs. 17%; $P = 0.006$). Complications related to radical surgical resection occurred in 25% of patients. For hormone receptor (HR)-positive recurrence, the 5-year progression-free survival was significantly increased among surgical patients (46.3% vs. 14.5%; $P = 0.01$). Similarly, prognostic factors predicting survival after chest wall resection and reconstruction (CWRR) were investigated in 28 patients at the H. Lee Moffitt Cancer Center between 1999 and 2007 [93]. The postoperative morbidity and mortality rates were 21% and 0%, respectively, and the 5-year OS rate was 18%. The 1-, 2-, and 5-year OS rates for the triple-negative phenotype were 38%, 23%, and 0%, respectively. In contrast, the 1-, 2-, and 5-year OS rates for the non-triple-negative phenotype were 100%, 70%, and 39%, respectively. These findings suggest that patients with isolated SCW recurrence and hormone receptor-positive recurrence are associated with improved survival, whereas the clinical outcome is poor in patients with triple-negative recurrent cancers.

With the increased use of skin-sparing mastectomy and nipple-sparing mastectomy (total skin-sparing mastectomy) with immediate reconstruction, various concerns regarding the incidence, detection, and management of CWR have been noted. Evidence does not suggest any difference in local recurrence rates following skin-sparing or nipple-sparing versus conventional mastectomy in terms of the incidence of CWR [94–100]. Furthermore, the incidence of CWR does not vary with the type of reconstruction [94]. Langstein et al. demonstrated that most CWRs following skin-sparing mastectomy with reconstruction occur under the skin (72%) and are easily palpable on clinical examination [88]. Although the length of time between mastectomy and identifying CWR may be slightly longer in patients with reconstruction, the prognosis between these patients and those who develop a CWR after a conventional mastectomy does not significantly differ [101]. The management of CWR in patients with a reconstructed breast does not necessarily mandate a take-down of the reconstruction [101, 102].

In patients experiencing recurrence at the reconstruction site, such as latissimus flap reconstruction or transverse rectus abdominis musculocutaneous (TRAM), the CWR can often be resected with local flap rearrangement to preserve the breast mound. In patients with implant-based reconstruction, however, removal of the implant is often warranted to facilitate subsequent radiation therapy.

Little information regarding the feasibility and potential clinical benefit of lymph node evaluation in CWR patients is available. Axillary surgery is often required to obtain local control. Sentinel node biopsy is feasible in the setting of recurrent breast cancer [62, 63], and some researchers are also investigating the feasibility of sentinel node biopsy following mastectomy [103].

Radiation Therapy

When treating CWR, radiation therapy is an independent factor leading to improved prognosis [87]. In general, large field radiotherapy encompassing the entire chest wall is preferable to less extensive radiation. Approximately 93% of recurrences are controlled within 2 months of the completion of radiotherapy [104]. In a study of 224 patients with CWR, Halverson et al. found that the 5- and 10-year disease-free survival rates of patients treated with large field radiation were 75% and 63%, respectively, compared with 36% and 18%, respectively, when smaller fields were used [105]. Subsequent supraclavicular metastases were also significantly reduced with the use of radiation therapy (16% vs. 6% without radiation therapy). For recurrences that were completely excised, good local control could be achieved with doses ranging from 4500 to 7000 cGy [105]. Recurrences 1–3 cm in diameter were best controlled with a dose of at least 6000 cGy. However, larger tumors exhibited worse local control (50%) despite the use of 7000-cGy doses.

Hastings et al. studied risk factors for LRR after mastectomy in over 1259 T1 N0 breast cancer patients and identified a small subgroup of patients with grade 3 disease and a close or positive margin (≤3 mm) who exhibit an increased risk of LRR. These authors concluded that these patients may benefit from the administration of PMRT [106].

In terms of the value of re-irradiation, data were previously limited for patients who had previously been treated with radiation therapy to the chest wall. A recent multi-institutional study of re-irradiation in the setting of CWR reviewed 81 patients who presented with a local recurrence after a median dose of 60 Gy [107]. Thirty-one of these patients originally had a mastectomy with PMRT and subsequently presented with a CWR. This study found that the second course of radiation at the time of the local recurrence (median: 48 Gy) was not associated with significant grade 3–4 toxicity and was associated with a 57% overall complete response rate. Factors correlating with an improved 1-year disease-free survival included a greater dose of radiation therapy at the time of recurrence, a longer interval from initial radiation therapy, and the use of concurrent chemotherapy. Janssen et al. [108] reported the outcomes of 83 breast cancer patients with local recurrence who underwent partial external beam re-irradiation with second breast-conserving therapy (n = 42) or following mastectomy (n = 41). The re-irradiation schedules were 45 Gy (1.8 Gy per fraction). In univariate and multivariate analyses, younger age (P = 0.045), lower T-category (P = 0.019), and N0 category (P = 0.005) were prognostic factors for favorable overall survival rates. Outfield recurrences occurred more in node-positive patients (P = <0.001), and breast cancer-specific survival was significantly better for node-negative patients (P = 0.025). There were few adverse events. They concluded that re-irradiation after the second surgery resulted in high local control rates and tolerable skin toxicity.

Other Treatment Modalities

Hyperthermia involves heating the tumor bed to a temperature of 40–45 °C along with the delivery of radiation. Hyperthermia in conjunction with radiation therapy has been evaluated by a number of studies. Although no significant difference was noted in terms of complete response rates between radiation therapy alone and radiation combined with hyperthermia in four studies, two other trials reported a benefit regarding the addition of hyperthermia [85]. A meta-analysis revealed a benefit for hyperthermia with a complete response rate of 59% versus 41% in patients treated with radiation therapy alone (OR, 2.3; 95% CI 1.4–3.8; P = 0.007) [109]. This benefit was particularly noted in those who had undergone previous radiation therapy and was maintained in follow-up. In another prospective randomized controlled trial of hyperthermia and radiation therapy for superficial tumors in 99 of 109 patients, 70 of whom had CWRs, the complete response rate for hyperthermia and radiation was 66% versus 42% for radiation therapy alone. Again, previously irradiated patients exhibited the greatest benefit (68.2% vs. 23.5%, respectively).

Other modalities used in the treatment of CWR include photodynamic therapy and intra-arterial chemotherapy [79]. However, both of these modalities result in transient responses. A few studies demonstrated that injection of interferon into the recurrent tumor (with or without concomitant radiation therapy) yields reasonable results [85]. When surgical excision of CWR is not possible, topical chemotherapy and electrochemotherapy might also provide a safe, efficient, and non-invasive locoregional treatment approach for CWRs [110, 111]. Electrochemotherapy can be performed either with cisplatin injected intratumorally or via the intratumorally or intravenously administration of bleomycin [110]. Furthermore, novel modalities, including cryotherapy, radiofrequency ablation, laser, and microwave therapy, might be investigated in future studies regarding the management of CWR.

Regional Lymph Node Recurrence

Regional nodal recurrence (RNR) or regional events are defined as breast cancer in ipsilateral lymph nodes based on Maastricht Delphi consensus on event definitions for the

classification of recurrence in breast cancer research [112]. The incidence of isolated RNR is generally low (<4%) [2, 113]. This condition generally presents as an asymptomatic mass, but specific symptoms are occasionally evident in a minority of patients [114]. MRI may be helpful in this setting [115].

With the increasing use of PET-CT imaging, many RNRs are nonpalpable axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes (Fig. 29.4). Although nodal recurrence generally exhibits a poorer prognosis than local recurrence, it remains curable if adequately resected. Nonpalpable masses must be localized either preoperatively with a radioactive seed or a wire guide. These masses can also be localized intraoperatively with ultrasound.

RNRs generally have a poor prognosis, and the risk of distant metastasis is high (>50%). Supraclavicular, internal mammary, or multiple sites of nodal disease are correlated with a worse overall prognosis than isolated axillary recurrences [116].

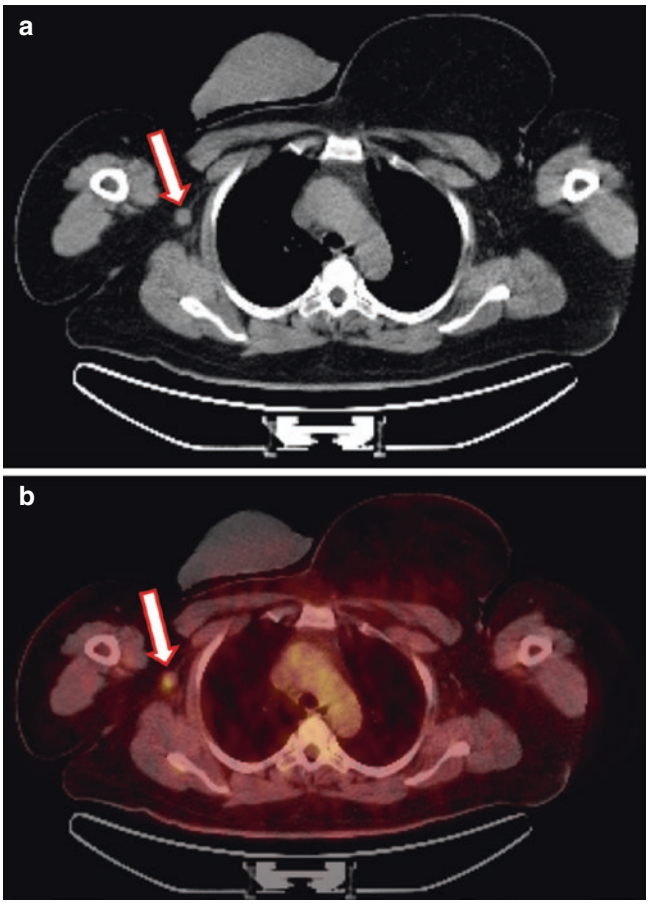

Fig. 29.4 CT and PET fusion imaging (**a**, **b**) of a 45-year-old woman with an isolated axillary nodal recurrence 3 years after mastectomy with a negative SLNB. PET-CT modality revealed an increased uptake value of F-18 fluorodeoxyglucose (SUVmax: 16.2)

Axillary Nodal Recurrences

In one study, axillary recurrence was observed in 1.2% (2/162) of positive-sentinel node patients and 0.8% (5/625) of negative-sentinel node patients [117]. The management of axillary recurrences is typically limited by the extent of disease and the previous therapies that the patient received. Complete level I–II axillary dissection is warranted if a patient had an axillary regional recurrence after SLNB. In patients who undergo ALND with or without axillary radiation, re-dissection is generally not a technically viable option, but axillary exploration and resection of gross disease may be considered for small, mobile, isolated recurrences. The sentinel node can be identified in approximately 87% of cases when 10 or less lymph nodes were removed during the original surgery in the preoperative setting [118]. Repeat surgical assessment of the axilla may provide prognostic information that is useful in guiding management decisions for recurrences. Given the altered drainage patterns in these patients, particularly in those patients with 10 or more lymph nodes removed, clinicians should utilize a preoperative lymphoscintigram when considering repeat surgical axillary assessment [119]. In a recent study, repeat sentinel node biopsy was performed in greater than 150 patients with locally recurrent breast cancer. Aberrant drainage pathways were visualized in 58.9% of the patients, and this result was significantly more frequently observed after a previous ALND (79.3%) compared with a previous SNB (25.0%) ($P < 0.0001$). Overall, the result of their repeat SNB led to a change in the adjuvant treatment plan in 16.5% of the patients with a successful repeat SNB. These authors concluded that repeat SNB is technically feasible and provides reliable results in patients with locally recurrent breast cancer, leading to a change in management in one of six patients [120].

Technological advancements in the delivery of radiation, such as the use of intraoperative electron beam therapy, have facilitated promising preliminary investigations of re-irradiation of the axilla [121]. Nevertheless, this technique warrants further investigation prior to its routine use in patients with RNR.

Supraclavicular Nodal Recurrences

The majority of supraclavicular nodal recurrences are associated with a poor prognosis. In addition, the overall survival and outcomes of regional relapses in the supraclavicular fossa are worse compared with those in the axilla [122]. In a large series of supraclavicular recurrences involving 305 patients with an isolated supraclavicular recurrence with or without other local-regional metastases but no distant metastases, additional sites of synchronous local-regional disease were present in 38% of the patients. In addition, 19%

underwent excisional biopsy of the tumor, 33% had curative radiation, 26% had combined local-regional treatment and systemic therapy, and only 10% underwent surgery plus radiation. Combined local-regional and systemic therapy resulted in the highest rate of initial remission (67%) compared with either local-regional therapy alone (64%) or systemic therapy alone (40%), but the 5-year progression-free and overall survival rates were only 15% and 24%, respectively. In addition, the only significant predictor of favorable outcomes on multivariate analysis was the receipt of combined local-regional and systemic therapy [123]. In some retrospective series, patients with isolated supraclavicular recurrences have long-term disease-free survival rates ranging from 15% to 30% with the utilization of multimodality therapies [124]. Another more recent study by Kong M and Hong SEinvolving N1 breast cancer patients (n = 113) reported 5- and 10-year actuarial supraclavicular lymph node recurrence rates of 9.3% and 11.2%, respectively [125]. Factors associated with supraclavicular lymph node recurrence based on multivariate analysis revealed that the patient group with grade 3 and extracapsular extension exhibited a significantly increased rate of supraclavicular lymph node recurrence compared with the remainders (5-year SCLR rate; 71.4% vs. 4.0%, respectively, $P < 0.001$). Thus, the researchers mentioned that supraclavicular nodal RT is necessary in N1 breast cancer patients featuring histologic grade 3 and extracapsular extension [125]. Therefore, patients with isolated supraclavicular recurrences without distant metastases should be considered for curative multimodality therapy whenever possible.

Regional re-irradiation with therapeutic doses is generally not considered safe if a patient had an isolated nodal recurrence in a previously irradiated field. In this case, limited field re-irradiation may be considered as a salvage option in patients who are unresponsive to systemic treatment or those with unresectable disease. Particularly for supraclavicular and axillary recurrences, the utilization of standard external beam techniques results in doses to the normal structures that are well beyond the threshold (i.e., brachial plexus).

Internal Mammary Nodal Recurrences

The increased proportion of screening-detected cancers, improved imaging and techniques (i.e., lymphoscintigraphy for radio-guided SLNB) make it possible to visualize lymphatic drainage to the internal mammary nodes (IMNs). IMN drainage is noted in approximately 18–30% of breast cancer patients [126, 127]. Although IMN acts as a secondary lymph node drainage basin for breast cancer, nodal recurrence in the IMN chain is rare. This condition is typically not intentionally treated after definitive surgery in most breast cancer patients. In a PET-CT study by Oh et al., 3561 PET-CT scans were performed in 1906 postoperative breast cancer patients. Fifty-seven patients (2.99%) demonstrated isolated extra-axillary nodal recurrences (n = 85) on PET-CT (28 IMN recurrences, 24 supraclavicular, 4 infraclavicular, 8 interpectoral, 12 cervical, and 9 mediastinal) [128]. With IMN recurrence rates <2% after definitive treatment [129], data regarding the effects of surgical resection, systemic therapy, and/or radiation therapy in this setting are limited. One of the largest series of IMN recurrences in breast cancer describes 133 patients with IMN failure after definitive treatment. The 5-year overall survival rate of patients with IMN recurrences was approximately 30%, whereas the rate for those with isolated IMN recurrence was generally increased (approximately 45%) [130]. Endocrine therapy for ER/PR+ patients (HR, 0.2; 95% CI, 0.1–0.5; $P = 0.001$), radiotherapy delivered to the IMN area after recurrence (HR, 0.3; 95% CI, 0.1–0.9; $P = 0.026$), and no concurrent distant metastases (HR, 0.7; 95% CI, 0.4–0.9; $P = 0.031$) were significantly correlated with improved disease-free survival rates after IMN recurrence on multivariate analysis. Although surgical resection of an isolated IMN recurrence has been described utilizing various techniques and appears to be associated with a low mortality rate, the surgery itself is typically very extensive in some cases, requiring en bloc resection of the recurrence, surrounding chest wall, ribs, sternum, and previously radiated areas, and often requires reconstruction of the chest wall defect [131]. Recently, a less invasive technique for treating IMN recurrence using a thoracoscopic approaches was described [132]. For patients who have not previously received radiation to the IMN region, the mainstay of treatment for recurrences is radiation therapy, typically with doses of 40–60 Gy.

Systemic Therapy for Locoregional Recurrence

Local recurrences after mastectomy or BCT or locoregional recurrences are frequently accompanied by distant metastases; so, systemic therapy is generally part of the multidisciplinary management of these patients. Although local control is generally the aim of surgery and radiation therapy, various studies have reported a trend toward improved survival using systemic chemotherapy after adequate resection of local recurrence after mastectomy and radiation therapy [83]. The use of hormonal therapy is also associated with an improved prognosis in patients with an estrogen-receptor positive CWR [103]. Borner et al. reported a significant reduction in second local failures at 5 years in a multicenter trial in which estrogen-receptor positive patients with isolated CWR were randomized to tamoxifen or placebo after complete local excision and radiation therapy [133]. Overall survival,

however, was not significantly altered [133]. Given the potential usefulness of hormonal therapy and because the estrogen-receptor status is the same as the original tumor in only 75–85% of cases, the hormone receptor status of the CWR should be ascertained.

The final analysis of the Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial, a randomized trial that investigated the efficacy of adjuvant chemotherapy in patients with completely excised isolated locoregional recurrences (ILRR) with negative margins after a mastectomy or lumpectomy for primary breast cancer, was recently published [134]. The type of chemotherapy used was determined by the investigator to be a multidrug regimen for at least four courses. Between August 2003 and January 2010, 85 patients were randomly assigned to receive chemotherapy, whereas 77 were assigned to receive no chemotherapy. Patients with ER-positive ILRR received adjuvant endocrine therapy. Of the 162 patients, 58 were diagnosed with ER-negative ILRR, whereas 104 had ER-positive ILRR. At a median follow-up of 9 years, 27 DFS events were determined in the ER-negative group (hazard ratio, 0.29 [95% CI, 0.13–0.67; 10-year DFS, chemotherapy, 70% vs. no chemotherapy, 34%]) and 40 in the ER-positive group (hazard ratio, 1.07 [95% CI, 0.57–2.00; 10-year DFS, 50% vs. 59%, respectively; $P = 0.013$]). Furthermore, the HRs were 0.29 (95% CI, 0.13–0.67) and 0.94 (95% CI, 0.47–1.85), respectively, for the breast cancer-free interval ($P = 0.034$) and 0.48 (95% CI, 0.19–1.20) and 0.70 (95% CI, 0.32–1.55), respectively, for overall survival ($P = 0.53$). In conclusion, the final analysis of CALOR demonstrated that patients with resected ER-negative ILRR benefit from CT, whereas no survival advantage of adjuvant CT could be shown for patients with ER-positive ILRR.

The ongoing Breast International Group (BIG) 1–02, the International Breast Cancer Study Group (IBCSG) 27–02, and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-37 Study (BIG 1–02/IBCSG 27–02/NSABP B-37) are investigating whether cytotoxic chemotherapy is needed in patients with a resected CWR [135]. In this trial, 977 patients with locally recurrent breast cancer will be randomized to receive chemotherapy or no chemotherapy along with radiation therapy, trastuzumab, and hormonal therapy. This study will also hopefully answer the question of whether these patients will benefit from cytotoxic chemotherapy.

In HR-positive patients, endocrine therapy should be changed or started following surgery, whereas chemotherapy with or without anti-HER2-neu therapy (e.g., trastuzumab and pertuzumab, lapatinib, TDM-1) should be considered in HER2-neu-positive or triple-negative patients followed by surgery. Therefore, systemic therapies should be personalized to the individual patient.

Conclusion

Locoregional recurrences following BCT or mastectomy are challenging clinical problems that require a multidisciplinary approach. Although LRRs are considered as a poor prognostic factor and some of these patients will be diagnosed with concurrent systemic disease, patients with LRRs constitute a heterogeneous population. Patients who develop their LRRs more than 2 years from their previous surgery for mastectomy or BCT and were originally node negative exhibit long-term survival, particularly if they can be treated aggressively with surgery, radiation, and systemic therapy. By understanding the molecular biology of LRRs and developing personalized tailored approaches to systemic therapies along with emerging newer biological agents, systemic therapies for LRRs will also evolve. Finally, the potential utility of genomic expression tests in estimating the benefit of chemotherapeutic agents might also provide useful information for tailoring both local and systemic therapies [136]. Further study is needed to delineate the optimal management of these patients.

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Treatment of Metastatic Breast Cancer: Endocrine Therapy

30

Fatma Sen and Adnan Aydiner

Introduction

Breast cancer is the most frequently diagnosed malignancy in women and one of the leading causes of cancer-related deaths worldwide. Breast cancer death rates changed little between 1930 and 1989, but decreased to 39% from 1989 to 2015. Early diagnosis via mammographic screening and implementation of postsurgical systemic adjuvant therapy are responsible for this significant decrease in breast cancer mortalities in developed countries. However, breast cancer remains the second leading cause of cancer death in females according to the 2018 WHO Cancer Statistics, with ~90% of these mortalities due to metastasis of tumor cells to other organs. The 5-year survival rate of females with metastatic disease is approximately 22% [1].

Efforts aimed at curing patients with early-stage breast cancer have increased during the last five decades, but approximately 6% of breast cancer patients present with distant metastasis, and more than one-fifth of patients with initial early-stage disease will develop distant metastases that require immediate and appropriate management [1–3]. The main purposes of systemic treatment, including endocrine therapies, for patients with advanced disease are prolonging survival and improving patient symptoms. Therefore, less toxic treatment approaches should be chosen. Endocrine therapies for hormone receptor-positive (HR+) tumors have a lower toxicity potential than that of other systemic treatment options, including many cytotoxic agents or some targeted drugs. Furthermore, treating metastatic HR+ breast cancer with endocrine therapy is at least as efficacious as chemotherapy, if not more so [4].

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In this chapter, initial, second-, and third-line therapies for HR+ metastatic breast cancer (MBC) in premenopausal and postmenopausal women and novel agents for endocrine-resistant HR+ breast cancers will be discussed with a review of the literature.

Estrogens and Estrogen Receptors

The responsiveness of a cell to estrogen depends mainly on estrogen receptor (ER) positivity. Estradiol has a high affinity and specificity for the ER. After estradiol binding to the ER, heat shock proteins dissociate from the ER, enabling receptor-receptor dimerization. Dimerized ERs preferentially translocate to the nucleus and bind to estrogen response elements, discrete DNA sequences located in the regulatory parts of target genes. AF1 and AF2 are activation functions (AFs) and activate transcription [5]. Gene activity is regulated by ligand-bound receptors via AFs by recruiting other proteins to the general transcription complex. These proteins act as coactivators or corepressors of estrogen-regulated transcription [6]. The activity of the amino-terminal AF1 is regulated by growth factors acting through the mitogen-activated protein (MAP) kinase signal transduction pathway and is cell type specific. However, the carboxy-terminal AF2 is located in the ligand-binding region of the ER and is activated by estradiol. Full agonist activity requires both AF1 and AF2 to be active [7, 8].

Receptor Status Determination at Metastatic or Recurrent Sites

The HR and human epidermal growth factor receptor 2 (HER2) status of the primary tumor must be determined to determine breast cancer subtypes, prognosis, and the treatment choice. Approximately 80% of breast cancers are HR+ and are eventually sensitive to endocrine treatments. However, HR positivity varies with patient age; series have

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demonstrated that the positivity rate is 10% in patients younger than 19 years and 90% in patients older than 70 years [9]. HR positivity is inversely correlated with tumor grade: it is very high in grade 1 tumors (90%) but decreases to nearly 40% in grade 3 tumors [9].

Substantial discordance in receptor positivity between the primary and metastatic site or the recurrence site of breast cancer has been reported [10]. Differences in receptor status in different sites of the tumor may affect the selection of treatment type and thus alter patient prognosis. In a retrospective study, HER2 and HR status were compared in primary and MBCs using immunohistochemistry and/or in situ hybridization [10]. Conversion from HR+ in the primary site to HR negative (HR−) in the metastatic site was detected in 21% of patients, and HR− to HR+ conversion occurred in 3.6% of patients. HER2 status was discordant between primary and metastatic sites in 12% of patients [10]. In another recently published retrospective study, the rates of discordance between primary and recurrent/metastatic lesions were 19%, 34%, and 7% for ER, progesterone receptor (PR), and HER2, respectively. ER, PR, and HER2 discordance were observed in 20%, 38%, and 6.7% of patients with distant metastasis and in 14%, 18%, and 7% of patients with locoregional recurrence, respectively [11]. Among patients with distant metastasis, ER discordance, ER loss, HER2 discordance, and HER2 loss resulted in worse overall survival (OS) and PRS compared to the respective concordant cases ($p < 0.05$ for all). Unstable ER or HER2 status in breast cancer appears to be clinically significant and correlates with worse prognosis.

Discordance in the HER2 and HR status between primary and metastatic tumors may change the treatment decisions of patients. In a recently published review by Criscitiello C et al., biopsy of recurrent or metastatic sites led to changes in therapy in approximately 15% of patients [2]. Therefore, although biopsy of all metastatic or recurrent sites is not required before the initiation of treatment, the evaluation of HER2 and HR in metastatic or recurrent tumors should be considered in patients with breast cancer. Although interventional radiology techniques and the ability of minimally invasive techniques to access metastatic sites have improved, performing biopsy from metastatic lesions can be difficult. When the receptor status of the metastatic or recurrent site cannot be determined, treatment should be planned according to the features of the primary tumor.

International oncology guidelines recommend that metastatic disease at presentation or the first recurrence of breast cancer should be biopsied as part of the initial workup for breast cancer patients with disease recurrence or distant metastasis [12]. For recurrent disease, if the receptor status is previously unknown, originally negative, or not overexpressed, the receptor status should be determined. In the case of the previously known HR positivity and/or a clinical course consistent with HR+ breast cancer, endocrine therapy can be started without retesting the receptor status.

Definition of Menopause

Before selecting and/or starting endocrine therapy, particularly aromatase inhibitors (AIs), clinicians should obtain a detailed menstruation history of the patient. Menopause should be defined carefully because the type of endocrine therapy depends on menopausal status. The discontinuation of menstrual cycles with previously administered chemotherapies does not definitively indicate menopause. Menstrual cycles may return in subsequent months or years. Thus, clinicians should not accept chemotherapy-induced amenorrhea as menopause before serial determination of plasma follicle-stimulating hormone (FSH) and estradiol levels.

Although clinical trials have not featured a clear consensus on the definition of menopause, menopause is defined by NCCN guidelines as a history of bilateral oophorectomy or age older than 60 years. For younger patients (<60 years), women must be amenorrheic for at least 1 year or more without a history of past or ongoing chemotherapy, ovarian function suppression, toremifene, and tamoxifen in addition to having plasma estradiol and FSH levels in the postmenopausal range [12]. Menopausal status cannot be determined accurately according to amenorrhea or based on FSH or plasma estradiol in patients being treated with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist.

Candidates for Initial Endocrine Treatment in the Metastatic Setting

Chemotherapy alone, endocrine therapy alone, and the concomitant use of chemotherapy or new targeted agents, mainly CDK4/6 inhibitors, and endocrine therapy combinations are all initial treatment options for patients with metastatic HR+ tumors. The management of these patients depends on the patient's general health, age, presence of comorbidities, extent of disease, course of disease, previous anticancer drug history, and patient choice. HER2 positivity should also be considered during the decision to provided targeted therapy.

Patients without disease-related or severe symptoms and with a long disease-free interval, a limited number of metastatic sites or metastasis, and only soft tissue or bone metastasis are good candidates for initial endocrine therapies without cytotoxic agents. These characteristics, in addition to HR positivity, indicate a favorable prognosis. By contrast, when a patient has symptomatic and/or disseminated bone or

visceral metastases and there is high probability of rapid progression carrying the risk of vital organ failure or other catastrophic complications, chemotherapy should be the first choice of treatment. However, the exact symptom criteria as the cutoff to begin chemotherapy rather than endocrine therapy remain controversial.

A prior systematic review performed by the National Collaborating Centre for Cancer compared the activity of endocrine therapy with chemotherapy in treatment-naive patients with advanced hormone-sensitive breast cancer [13]. Wilcken et al. also subsequently performed a systematic review to compare chemotherapy with endocrine treatments. Ten randomized controlled trials were identified as appropriate for the analysis [14]. OS was similar between the two treatment types. Furthermore, chemotherapy resulted in greater toxicity, particularly emesis, and alopecia. Thus, endocrine therapy was recommended as the first-line treatment option in the absence of severe symptomatic disease in which an immediate tumor response is necessary [15, 16].

Recently, the American Society of Clinical Oncology published a guideline to determine the optimal systemic treatment approach for HER2-negative breast cancer patients with advanced-stage disease [15]. A systematic review of randomized studies, previous meta-analyses, and systematic reviews published since 1993 was performed. In total, 20 meta-analyses and/or systematic reviews, 30 first-line treatment trials, and 29 second-line and further lines of treatment trials were identified as appropriate for analysis. Progression-free survival (PFS), survival, toxicity, tumor response, and quality of life were investigated as outcomes to establish recommendations. The expert panel reported that in patients with hormone-sensitive MBC, endocrine therapy is the preferred first-line treatment option instead of chemotherapy in the absence of a life-threatening disease that requires sudden improvement with cytotoxics. When chemotherapy is indicated, a single agent should be chosen instead of a combination. The optimal chemotherapeutic agent as the first line and subsequent treatment lines could not be determined, but the number of agents and type of agent depend on the characteristics of the patient and tumor, including previous types of therapy, severity of adverse reactions, performance status, medical comorbidities, and patient choice. A single agent may be administered for long durations; however, toxicity should be balanced with effectiveness. No consensus has been reached on bevacizumab, and the present evidence is insufficient to support the use of other targeted agents in combination with other chemotherapeutic agents in breast cancer patients with HER2-negative disease [15]. However, the expert panel explained the limitations of the review and emphasized that more data about these important issues from randomized trials would be valuable [15].

Endocrine Treatment History for Local or Locally Advanced Breast Cancer

A patient who develops metastasis after or during adjuvant treatment should be evaluated for previous endocrine treatment, including type and duration of treatment and time since cessation of treatment. If progression occurred more than 1 year after the termination of adjuvant therapy, the patient should be accepted and treated as an endocrine treatment-naive patient. However, if the disease progresses or reoccurs under adjuvant endocrine treatment, under first-line endocrine treatment in a metastatic setting, or within 1 year after adjuvant endocrine treatment ended, eligible patients should be evaluated for subsequent endocrine treatment.

HER2-Negative Hormone Receptor-Positive Metastatic Breast Cancer

Premenopausal: Ovarian Ablation/Suppression, Tamoxifen, Selective Estrogen Receptor Modulators, AIs, Tamoxifen Plus Ovarian Suppression, and Tamoxifen Versus Ovarian Suppression

Ovarian Ablation/Suppression

The role of hormones in the growth of some tumors was first discovered when tumor regression was observed after ovariectomy in a patient with metastatic breast carcinoma more than a century ago [17]. Estradiol has subsequently been identified as the most powerful hormone stimulator of breast cancer. Thus, medical or surgical deprivation and/or antagonism of estradiol is important in HR+ breast cancer.

In premenopausal patients with advanced breast cancer, bilateral oophorectomy has long been performed as a classical endocrine manipulation. Bilateral adrenalectomy in the 1950s and hypophysectomy in the 1960s were important advances in endocrine therapy for breast cancer patients aimed at the depletion of estrogen biosynthesis.

In addition to oophorectomy, ovarian ablation can be accomplished by irradiation. During the 1970s, based on the positive results of a clinical trial, the practice in Europe was to recommend ovarian irradiation to all premenopausal women and to women within 3 years of menopause at the time of the initial diagnosis of breast cancer [18]. Patients received endocrine therapy when they were not suitable for ovarian irradiation. Patients within 5 years of menopause were administered androgens with or without a chemotherapeutic agent; however, patients who were 5 years or more past menopause were treated with estrogens. The patients in whom breast cancer occurred during perimenopause had the worst response rate to endocrine therapy [18].

The development of HR measurements has allowed clinicians to identify patients who will most likely to respond to endocrine therapy [19]. This development was followed by many preclinical and clinical trials examining antiestrogens, progestins, LHRH agonists, LHRH antagonists, and inhibitors of estrogen synthesis.

Ovarian function suppression with an LHRH agonist subsequently became a noninvasive alternative to bilateral oophorectomy. In premenopausal women, pulses of LHRH stimulate the pituitary gland, resulting in pulsatile secretion of gonadotropins and establishing menstrual cycles. Treatment with a long-term depot formulation of an LHRH agonist initially stimulates gonadotropin release and subsequently leads to a reduction in gonadotropin secretion and circulating estrogen to postmenopausal ranges [20]. Despite in vitro studies demonstrating direct antitumor effects of LHRH agonists and evidence of specific binding sites for LHRH in primary breast cancer tissue, the key role of LHRH agonists remains medical castration [21, 22]. In an intergroup trial, 138 premenopausal patients with HR+ MBC were randomized to 3.6 mg of goserelin administered every 4 weeks ($n = 69$) vs. surgical oophorectomy ($n = 67$). Failure-free survival and OS were similar between the two treatment arms. The death hazard ratio for goserelin/oophorectomy was 0.80 (95% confidence interval [CI], 0.53–1.20). Serum estradiol levels were reduced to postmenopausal levels by goserelin treatment. The tumor flare rate (16 vs. 3%) and rate of hot flashes (75 vs. 46%) were higher in patients treated with goserelin than in those treated with surgical oophorectomy, but neither of the treatment arms was associated with severe toxicities [23].

Tamoxifen

Development of Tamoxifen

Tamoxifen (Nolvadex, Imperial Chemical Industries, DE 46,474), a nonsteroidal antiestrogenic compound synthesized in 1966 in Great Britain, was initially developed for antifertility. However, it was later demonstrated to stimulate ovulation in infertile women [24–26] and suppress carcinogen-induced rat mammary tumors [27]. Cole et al. were the first to report the clinical efficacy of tamoxifen for metastatic breast cancer in 1971 at Christ Hospital [28]. Following a pharmacological and clinical evaluation of tamoxifen in Great Britain and the United States, the Committee on the Safety of Medicine approved it for the treatment of MBC in postmenopausal women in 1973, and in 1977, the Food and Drug Administration also approved it for the same indication. Tamoxifen was also approved in premenopausal women and in men with HR+ advanced breast cancer as a first-line endocrine therapy. Tamoxifen has also become an important form of systemic adjuvant therapy for early breast cancer [24].

Mechanisms of Action of Tamoxifen

In vitro studies suggest that the main antiproliferative effects of tamoxifen are mediated by competition with estrogen to bind cytoplasmic ER. After the formation of a complex with the ER, tamoxifen subsequently inhibits many actions of endogenous estrogen within tumor cells [29]. The inhibition of tumor growth by tamoxifen and its active metabolite correlates with the potency with which they bind to the ER [24]. The tamoxifen/ER complex prevents estrogen/ER-mediated gene transcription, DNA synthesis, and tumor cell growth and increases autocrine polypeptides, such as transforming growth factor-alpha, epidermal growth factor, insulin-like growth factor-II, and other growth factors that may be involved in cell proliferation [30, 31]. By contrast, estrogen stimulates the production of the PR and plasminogen activator and decreases the level of transforming growth factor-beta, an inhibitory factor of epithelial cells, including breast carcinoma [32]. In vitro studies of the effects of tamoxifen on cell cycle kinetics demonstrated that tamoxifen prevents the transition of cells from the early **GI** phase to the mid-G1 phase and leads to the accumulation of cells in the early **GI** phase of the cell cycle and to the reduction of cells in the **S** and G2 plus M phases [33]. These shifts have cytostatic effects. Thus, tamoxifen has been considered a chemosuppressive agent [33]. The continuous administration of tamoxifen to animals inoculated with breast tumor cells prevents tumor growth, whereas the discontinuation of therapy results in the appearance of tumors [34]. Although some studies suggest that tamoxifen has cytocidal activity, the lethal effect of tamoxifen on breast tumor growth in addition to its cytostatic effects is controversial [35].

In tissue culture, the inhibitory effect of tamoxifen on hormone-sensitive breast cancer cell growth is dose dependent. At low concentrations, the cytostatic effect of tamoxifen mediated through ERs can be completely blocked by estradiol [36]. At higher concentrations of tamoxifen, the cytostatic effect is not reversible by estrogens [37]. Tamoxifen may also inhibit cell replication by mechanisms other than the events mediated by ERs. Tamoxifen binds to the antiestrogen-binding site, a microsomal protein, with high affinity [38]. The functional importance of this protein in mediating the clinical effects of tamoxifen is unknown. In addition, tamoxifen inhibits protein kinase C and blocks the activation of calmodulin, a protein that may play a role in tumor promotion [39, 40]. Tamoxifen also induces antibody formation, enhances natural killer cell activity, and inhibits suppressor T-cell lymphocytes [41]. These non-ER-mediated actions of tamoxifen, heterogeneity of ER content within a tumor, or variability of receptor assay methodology may explain the inhibition of tumor growth by tamoxifen in 10–15% of ER-negative tumors. Tamoxifen also inhibits angiogenesis; this inhibition is not altered in the presence of excess estrogen, suggesting that the antiangiogenic activity

of the drug is mediated through a mechanism other than inhibition of estrogen action [24]. Further studies are necessary to characterize the antiangiogenic activity of tamoxifen.

Finally, tamoxifen may also increase serum high-density lipoprotein cholesterol, reduce antithrombin III activity, and inhibit prostaglandins D, F, and E, which may be involved in bone resorption [45]. Whether these effects are crucial to antitumor action remains unknown. Tamoxifen does not appear to have unwanted effects on bone mineral content [42].

The mechanism of action of tamoxifen, particularly its antiproliferative activity, may differ in ER-negative and ER+ cell lines. Unfortunately, data about treatment of ER-negative tumor cell lines with tamoxifen are limited and indicate a reduction in the proportion of cells in GO to G1 phases and an increased percentage of cells in S and G2 plus M phases [43].

Tamoxifen is currently the most widely prescribed agent for the treatment of breast cancer patients in the United States and Great Britain. However, it has several frequently observed side effects, including mild nausea, vaginal bleeding or discharge, menstrual irregularity, fluid retention, and hot flashes, particularly in premenopausal women. Nonspecific central nervous system symptoms such as depression, irritability, headache, dizziness, nervousness, inability to concentrate, sleep disturbance, lethargy, and fatigue have been observed rarely in women receiving tamoxifen [44, 45].

Tamoxifen Versus Ovarian Suppression

The National Cancer Institute of Canada Clinical Trials Group performed a randomized crossover trial named MA.1 that compared 40 mg of tamoxifen daily with ovarian ablation in premenopausal breast cancer patients with advanced disease. They reported objective responses in 25% of the patients treated with tamoxifen and 16% of the patients treated with ovarian ablation ($p = 0.69$). The overall response, including stable disease, was 60% in the tamoxifen arm and 42% in the ovarian ablation arm ($p = 0.34$). The median time to progression was 184 days in the tamoxifen arm and 126 days in the ovarian ablation arm ($p = 0.40$, odds ratio (OR) for progression, 0.71). OS was also similar in the two groups (median: 2.35 years in the tamoxifen group vs. 2.46 in the ovarian ablation group; $p = 0.98$, OR for death, 1.07). The most frequent side effects of tamoxifen were hot flashes and menstrual abnormalities. These side effects did not result in a dose reduction except in one patient. Although it was a small study, tamoxifen was associated with response rates, response durations, and survival times similar to those observed with ovarian ablation [46].

In 1997, Crump et al. [47] performed an individual patient-based meta-analysis to compare tamoxifen with ovarian ablation as a first-line endocrine therapy in premenopausal women with MBC. Ovarian ablation was performed by either bilateral oophorectomy or ovarian irradiation. Four randomized trials were eligible for analysis, and the individual patient data for eligible patients ($n = 220$) were updated to June 1992. The patients were required to have ER+ or unknown breast cancer. No difference in the overall response rate was observed between the tamoxifen arm and the oophorectomy arm among the four trials ($p = 0.94$). The odds reductions for progression ($p = 0.32$) and the odds reductions for mortality ($p = 0.72$) did not significantly favor tamoxifen treatment. Although the patients were allowed to cross over to the other treatment arm in all four trials, only 54/111 patients initially treated with ovarian ablation and 34/109 patients receiving tamoxifen as their primary therapy actually crossed over to the other arm at the time of disease progression. The response to the initial treatment type was predictive of the response to subsequent treatment arms ($p < 0.05$). The authors concluded that the activity of tamoxifen is similar to that of ovarian ablation obtained by either surgery or radiation in premenopausal ER+ MBC as first-line therapy and was unlikely to be substantially inferior.

Tamoxifen Plus Ovarian Suppression

The purpose of combining an LHRH agonist with tamoxifen in premenopausal women is to inhibit tamoxifen-induced stimulation of pituitary-ovarian function. LHRH agonists are as effective as surgical castration. In 2001, Klijn et al. performed a meta-analysis that combined the findings of four randomized trials and compared OS, PFS, and the objective response for combination therapy or an LHRH agonist alone in premenopausal women with advanced-stage breast cancer [48]. A total of 506 women were randomized in those trials. The overall response rate was significantly higher for combination therapy with a median follow-up of 6.8 years; a significant survival benefit ($p = 0.02$; hazard ratio, 0.78) and PFS benefit ($p = 0.0003$; hazard ratio, 0.70) favoring combination therapy ($p = 0.03$; OR, 0.67) were demonstrated.

Based on the findings of this meta-analysis, the combined administration of an LHRH agonist with tamoxifen has been recommended as the new standard treatment option; however, tamoxifen alone was not compared with combination treatment in the analysis. The Adjuvant Breast Cancer Trials Collaborative Group performed an international study in an adjuvant setting. Pre- and perimenopausal patients who had been treated with prolonged (5 years) tamoxifen with or without chemotherapy were randomized to ovarian ablation or suppression vs. no ovarian ablation or suppression [49]. Ovarian ablation or functional suppression was achieved by bilateral oophorectomy, irradiation of the ovaries, or administration of an LHRH agonist. The authors did not observe any additive activity of ovarian ablation or functional suppression on relapse-free survival or OS. However, further study is required to demonstrate the role of ovarian ablation

or suppression in premenopausal women younger than 40 years with HR+ breast cancer, particularly those without previous chemotherapy administration. SOFT is the largest trial of ovarian suppression in premenopausal women with early-stage breast cancer. A total of 3066 premenopausal women were randomized to 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. Women who were randomly assigned to ovarian suppression in either arm had the choice of monthly injections of triptorelin, surgical removal of the ovaries, or radiation. Women who had undergone chemotherapy entered the trial 8 months post chemotherapy, whereas those who did not undergo chemotherapy entered the trial soon after surgery. The estimated disease-free survival rate at 5 years was reported to be found as 84.7% in the tamoxifen alone group and 86.6% in the tamoxifen plus ovarian suppression group with a median 67 months follow-up (hazard ratio for disease recurrence, second invasive cancer, or death, 0.83; 95% CI, 0.66–1.04; $p = 0.10$). A multivariable allowance for prognostic factors indicated that tamoxifen plus ovarian suppression has a higher treatment effect than with that for tamoxifen alone (hazard ratio, 0.78; 95% CI, 0.62–0.98). Most recurrences occurred in patients with prior chemotherapy history, among whom the rate of freedom from breast cancer at 5 years was 82.5% in the tamoxifen-ovarian suppression group and 78.0% in the tamoxifen group (hazard ratio for recurrence, 0.78; 95% CI, 0.60–1.02). The rate of freedom from breast cancer at 5 years was found to be 85.7% in the exemestane plus ovarian suppression group (hazard ratio for recurrence vs. tamoxifen, 0.65; 95% CI, 0.49–0.87). Authors concluded that for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, disease outcomes were improved with the addition of ovarian suppression [50]. Unfortunately, whether combination therapy with LHRH agonists and tamoxifen is superior to single-agent tamoxifen in a metastatic setting remains unknown.

Endocrine therapy for patients with advanced breast cancer should be planned as the sequential administration of single agents. However, combination therapy with an LHRH agonist and tamoxifen was observed to be superior to single-agent therapy in clinical trials [51]. Jonat et al. investigated the activity of goserelin with or without tamoxifen in 318 pre- and perimenopausal women with advanced breast cancer in a randomized multicenter trial [51]. Statistically similar objective responses were obtained in the goserelin treatment arm (31%) and in combination arm (38%) ($p = 0.24$). A modest benefit in time to progression (median: 23 weeks in the goserelin alone arm vs. 127 weeks in the combination arm, $p = 0.03$) favoring the combination treatment was reported, but no survival benefit favoring any arm was observed (median survival: 28 weeks in the goserelin alone group vs. 140 weeks in the combination group; $p = 0.25$). The response rate, time to progression, and survival were significantly different in favor of the combination group in patients with skeletal metastases only ($n = 115$). The tolerability and safety of both treatment arms were similar. Therefore, tamoxifen in combination with ovarian function suppression or ablation was deemed superior to tamoxifen monotherapy as a first-line treatment for metastatic or recurrent HR+ disease [51].

Other Selective Estrogen Receptor Modulators

The role of selective estrogen receptor modulators (SERMs) in breast cancer treatment is now well established. The antiestrogen MER 25 was first introduced more than five decades ago [52], and 10 years after MER25, tamoxifen, and several antiestrogens with diverse chemical structures were reported [53, 54]. The first SERM to be introduced, tamoxifen, provided a revolutionary new treatment strategy for HR+ breast cancer patients. Currently, tamoxifen is one of the most widely used endocrine therapy drugs in both metastatic and adjuvant settings. Tamoxifen was subsequently shown to decrease breast cancer incidence in healthy women at high risk of developing breast cancer, and raloxifene has been demonstrated to prevent osteoporosis [55, 56]. The therapeutic success of tamoxifen has motivated considerable efforts to synthesize and investigate new-generation antiestrogens for breast cancer therapy.

Although many analogs of tamoxifen, including chlorotamoxifen, idoxifene, and droloxifene, have been described, only a few have been marketed for patients with breast cancer [57–59]. The chemical and pharmacological properties of these agents are similar and include partial agonist activity, a triphenylethylene backbone, and a nonsteroidal structure. Compared to tamoxifen, droloxifene (3-OH-tamoxifen citrate) has higher affinity for ER, a lower estrogenic to antiestrogenic activity ratio, and faster pharmacokinetics. In a double-blind randomized multicenter dose-finding phase II trial, droloxifene was administered in doses of 20, 40, or 100 mg once daily to 369 postmenopausal women with HR+ or HR unknown locally advanced or advanced breast cancer. Sixty women were ineligible because of violation of entry criteria, 20 were inevaluable, and 15 still await a definitive response evaluation. Thus, 234 patients have been evaluated for response. The overall complete plus partial response rate was 39.3%: 31% (23/74) for 20 mg, 44.6% (33/74) for 40 mg, and 42% (36/86) for 100 mg (not significantly different within this dose range). The time to progression was similar between the three doses, and toxicity was mild at all doses. The preliminary results of this study demonstrated that droloxifene is active against advanced breast cancer. The outstanding preclinical characteristics of this drug support a large-scale clinical investigation [59].

Several nonsteroidal agents with antiestrogenic effects have been developed, such as substituted

tetrahydronaphthalenes (e.g., nafoxidine and trioxifene), indole derivatives (e.g., zindoxifene and ZK 119010), benzothiophenes (e.g., LY117018 and keoxifene), and benzopyrans [60]. These nonsteroidal agents have partial agonist activity with pharmacological characteristics similar to those of tamoxifen. Therefore, although they inhibit the trophic action of estrogens, their activities are incomplete because of their intrinsic agonist activity in vivo. The effects of drug treatment depend on the balance between agonist and antagonist activities.

Toremifene is another SERM that has been widely administered to HR+ breast cancer patients for decades. The structure of toremifene differs from that of tamoxifen by the replacement of one of the hydrogen atoms in the ethyl side chain with a chlorine atom. This difference may modify the metabolism of toremifene by preventing or reducing DNA adduct formation. Several prospective randomized phase III trials comparing toremifene with tamoxifen have established the efficacy of toremifene [61]. Although many studies have demonstrated therapeutic equivalence of tamoxifen and toremifene in terms of response rate (24 vs. 25%), time to treatment failure (4.9 vs. 5.3 months), and survival (31.0 vs. 33.1 months), some studies reported an advantage for toremifene. Furthermore, toremifene has been associated with less serious vascular events and uterine neoplasms and a better effect on serum lipids than tamoxifen. The safety and tolerability of the initially registered dose (60 mg per day) has been greatly increased to 240 mg per day [61, 62]. NCCN breast cancer guidelines recommends toremifene as one of the subsequent endocrine treatment options for both premenopausal and postmenopausal HR+ recurrent or metastatic breast cancer. However, toremifene is cross-resistant with tamoxifen and is therefore ineffective as sequential therapy in patients who are refractory to tamoxifen.

Fulvestrant

The development and mode of action of fulvestrant will be discussed in detail in the section about endocrine therapy in postmenopausal women. Although it has an attractive mode of action, studies of fulvestrant that include premenopausal women have been limited. Currently, a randomized phase II study is investigating the activity of fulvestrant + goserelin in premenopausal women with HR+ recurrent or metastatic breast cancer compared with anastrozole + goserelin and goserelin alone (ClinicalTrials.gov identifier NCT01266213).

Aromatase Inhibitors

During the last five decades, tamoxifen has been widely used for the treatment of patients with breast cancer; it reduces or delays recurrences and incidence of contralateral breast cancer. Because it has both estrogen agonist and antagonist action in different tissue types, the prolonged use of tamoxifen may cause adverse reactions or events. Patients are at an increased risk of stroke and endometrial cancer. In the early 1970s, many alternate agents were studied to prevent the agonist effects of antiestrogens and increase their efficacy and safety [63, 64]. The main purpose of treatment with estrogen biosynthesis inhibitors is to reduce circulating estrogen levels, and studies of these inhibitors highlighted the importance of the enzyme aromatase as an important endocrine agent for the effective and selective treatment of hormone-sensitive breast cancer [65, 66].

Aromatase, a member of the cytochrome P450 enzyme system, catalyzes the final enzymatic step of estrogen biosynthesis and converts androstenedione to estrone and testosterone to estradiol, thereby increasing estrogen levels both in pre- and postmenopausal women. A xenograft tumor model named MCF-7Ca was developed using human ER+ breast cancer cells stably transfected with the human aromatase gene. MCF-7Ca cells were grown as neoplasms in ovariectomized, immunosuppressed mice [67, 68]. These tumors act as autocrine sources of estrogen produced by aromatization. Because these mice did not have the ability to produce adrenal androgens, androstenedione was administered throughout the experiment. The xenografts were not only sensitive to the antiproliferative effects of aromatase inhibitors (AIs) but were also sensitive to the antiproliferative effects of antiestrogens [67, 68]. AIs block the conversion of androgens to estrogens but lack partial agonist effects, supporting aromatase as an attractive therapeutic target.

According to chronological order of development, AIs are grouped into three classes: first, second, and third generation. Testolactone and aminoglutethimide are pioneer drugs of this type, that is, first-generation AIs. Testolactone has been administered to postmenopausal breast cancer women with a modest response rate for 20 years and was later shown to inhibit aromatase irreversibly with very low potency [69]. Aminoglutethimide is a nonsteroidal, reversible, nonspecific, and competitive AI. The clinical use of aminoglutethimide as an anticonvulsant serendipitously revealed its endocrine characteristics [70]. Because of the limited efficacy or tolerability of these agents in postmenopausal breast cancer, many studies were conducted in the 1980s to identify more potent, specific, and safer AIs. Fadrozole, formestane, and rogletimide were developed as second-generation AIs, and letrozole, anastrozole, and exemestane were subsequently produced as third-generation AIs [71, 72].

In premenopausal women, the ovaries are the primary source of estrogen, and the primary type of estrogen is estradiol. By contrast, in postmenopausal women, estrogen in circulation is mainly produced by the aromatization of androgens (androstenedione and testosterone) in the adrenals and ovaries to estrogens (estrone and estradiol) and by aromatase, which is located in peripheral tissues comprising muscle and body fat. Aromatase inhibition alone is not recommended in premenopausal women because inhibition of

the hypothalamus pituitary aromatase increases gonadotropin, which in turn stimulates ovarian follicular growth, producing high levels of circulating estrogen, which can thereby induce mammary tumor proliferation [73]. AIs have therefore been studied in phase II trials in combination with ovarian suppression with promising results.

Carlson et al. [74] investigated the antitumor activity of anastrozole in the treatment of premenopausal women with HR+ MBC whose ovaries were functionally suppressed by goserelin, an LHRH agonist, in a prospective, multicenter, single-arm phase II trial. Goserelin was administered subcutaneously in a dose of 3.6 mg every month, and 21 days after the first injection of goserelin, the patients were allowed to receive 1 mg of anastrozole peroral daily. The treatment was terminated if disease progressed or any unacceptable toxicity developed. Of the 35 patients who were initially enrolled in the study, 32 were available for response and toxicity. Estradiol suppression was assessed at 3 and 6 months (mean estradiol levels = 18.7 pg/mL and 14.8 pg/mL, respectively). Three percent of the patients experienced a complete response, 34% experienced a partial response, and the remaining 34% had stable disease for 6 months or longer, resulting in a clinical benefit rate of 72%. The median time to progression was 8.3 months (2–63 months), and at the time of analysis, the median survival was not reached (11–63 months). The commonly observed toxicities were hot flashes (59%), arthralgias (53%), and fatigue (50%). No grade 4–5 toxicity was reported.

In another phase II trial, 73 patients with HR+ MBC (35 premenopausal and 38 postmenopausal) were treated with letrozole (2.5 mg orally daily) as first-line endocrine therapy [75]. Premenopausal women were rendered postmenopausal by administration of goserelin (3.6 mg every 28 days). The baseline characteristics of the premenopausal and postmenopausal women were similar, with the exception of older age (median, 41 vs. 53 years; $p < 0.001$) and a longer disease-free interval (median, 1.8 vs. 3.3 years; $p = 0.03$) in the postmenopausal patients. The clinical benefit rates of the two groups were similar (77 vs. 74%). The median time to progression was not different between the premenopausal and postmenopausal patients at the median follow-up of 27.4 months (9.5 months vs. 8.9 months). Letrozole (±goserelin) resulted in a greater loss of bone mineral density at 6 months in patients who did not receive bisphosphonate compared to patients who received bisphosphonate (at the lumbar spine: premenopausal patients, −16.7 vs. 53.9%; $p = 0.002$, and postmenopausal patients, −13.3 vs. 17.4%; $p = 0.04$). The clinical efficacies of combination therapy with letrozole and goserelin in premenopausal MBC women were comparable to single-agent letrozole in postmenopausal patients. Although letrozole (± goserelin) was shown to modestly increase bone resorption, concurrent administration of bisphosphonate with endocrine therapy prevented bone resorption at 6 months.

Postmenopausal Women: Progestins and Tamoxifen, AIs, Switching Between Third-Generation AIs, Fulvestrant, and CD

For postmenopausal patients with HR+ MBC who have not previously received endocrine therapy, who present with disease progression after 12 months from the end of adjuvant therapy, or who present with de novo MBC, the options for endocrine therapy include an AI, SERM, or fulvestrant [76].

Although sequencing of ET was the recommended approach until recently, few randomized trials directly compared the effects of the order in which different agents are used. Thus, definitive recommendations regarding the optimal ET sequencing in patients with HR+ metastatic breast cancer were difficult to provide due to a lack of sufficient scientific data on ET sequencing. However, based on data about ET plus other targeted agents from recently published phase II/III randomized trials, some ET options can be used sequentially or preferentially as the first line or second line.

Progestins and Tamoxifen

The progestins used for breast cancer therapy are megestrol acetate and medroxyprogesterone. The response rate for megestrol acetate is approximately 30%, and activity similar to that of tamoxifen was obtained in patients treated with megestrol acetate [77]. Unfortunately, megestrol acetate is associated with important adverse effects such as weight gain at the standard dose of 160 mg daily [78]. Dose escalation did not improve the outcome of megestrol acetate [78]. With the development of new agents such as the AIs and fulvestrant, progestins are now usually administered in later lines of endocrine therapy.

Tamoxifen was initially evaluated in postmenopausal women with MBC [28] at doses of 20–40 mg daily. Tamoxifen was subsequently used in the adjuvant setting, and the current standard recommended dose for early-stage breast cancer is 20 mg daily.

Tamoxifen has also been compared to other endocrine therapies, such as diethylstilbestrol and progestins, including megestrol acetate and medroxyprogesterone, for this indication. Petru and Schmähl [79] evaluated the findings of clinical trials reported between 1971 and 1986 that studied the therapeutic efficacy of endocrine monotherapy with tamoxifen, aminoglutethimide, and medroxyprogesterone acetate in MBC. A total of 7000 patients were enrolled in those studies. The overall response rates obtained with these endocrine single agents at various dose levels were 31–42%. When only ER+ patients were evaluated, the response rates of tamoxifen or aminoglutethimide were approximately

41–54%. The duration of response was 12 months in patients treated with tamoxifen and aminoglutethimide and 6–16 months in patients treated with medroxyprogesterone acetate. The overall mean survival, which was defined as the time from the initiation of the endocrine agent to death from any cause, was 20 months in tamoxifen- and aminoglutethimide-treated patients, whereas information concerning overall survival was obtained only in a minority of patients treated with medroxyprogesterone acetate. When the response was evaluated based on the site of metastatic lesions, all three drugs resulted in a higher degree of remission in the soft tissue than in visceral disease. Although the response rates and OS rates were similar among these endocrine agents, tamoxifen was most tolerable [24, 80].

Because the sequential administration of various endocrine therapies can produce repeated tumor regressions, efforts have been made to increase the antitumor activity of tamoxifen by simultaneous administration with endocrine agents such as DES, MPA, aminoglutethimide, and corticosteroids. However, the objective response rate is not significantly higher, and the durations of response and OS are not improved compared to tamoxifen monotherapy. In a collaborative double-blind randomized trial designed by the North Central Cancer Treatment Group and the Mayo Clinic, the superiority of tamoxifen + prednisolone to tamoxifen alone was investigated in postmenopausal MBC patients [81]. The objective response rates, median time to disease progression, and median survival time were statistically similar between the treatment arms. There was no association between treatment and outcome in the covariate analyses. Tamoxifen + prednisolone was associated with a significantly higher rate of weight gain and edema. Combining prednisolone with tamoxifen did not provide any advantage over tamoxifen alone in postmenopausal patients with MBC.

Limited data suggest a higher response rate and/or a longer time to progression without a survival advantage in postmenopausal women with MBC treated with fluoxymesterone in combination with tamoxifen compared to tamoxifen alone [82, 83].

In conclusion, the routine clinical use of tamoxifen concurrently with other endocrine agents is not justified given the lack of improvement in survival and the significant toxicity associated with multiple endocrine agents.

Simultaneous Administration of Tamoxifen with Cytotoxics

Because all breast tumors are heterogeneous (i.e., composed of hormone-dependent and hormone-independent cells), trials of tamoxifen with chemotherapy have been performed with the aim of killing the ER+ component of the tumor plus the rapidly dividing ER-negative cells. Tamoxifen administered as single-agent therapy has been compared to tamoxifen plus combination chemotherapy administered sequentially or simultaneously in postmenopausal women with disseminated breast cancer. In some of these studies, an increase in the initial response rate was demonstrated when tamoxifen was added to chemotherapy compared to tamoxifen alone [24, 84, 85] However, the median durations of response and overall survival were similar between the two treatment strategies [84, 86, 87]. Cavalli et al. randomized postmenopausal women with advanced breast cancer into two groups to be treated with either tamoxifen alone followed by chemotherapy after disease progression or concurrent administration of tamoxifen with chemotherapy initially [84]. No difference in survival was observed between the two treatment arms. However, in the subgroup of low-risk postmenopausal patients, the survival rate was significantly higher in the tamoxifen arm than the tamoxifen and chemotherapy arm. The Australian and New Zealand Breast Cancer Trials Group demonstrated that tamoxifen followed by chemotherapy on disease progression is as effective as chemotherapy and tamoxifen administered simultaneously in postmenopausal women in terms of overall response rate and survival [85]. Moreover, tamoxifen administered simultaneously or sequentially with chemotherapy produces a higher response rate, although without significant differences in survival, compared to chemotherapy alone [88–90].

It is appropriate to use tamoxifen alone instead of tamoxifen plus chemotherapy as the initial treatment in postmenopausal patients with advanced breast cancer who are candidates for hormonal manipulation. Chemotherapy should be reserved for patients who have failed to respond to endocrine therapy or whose disease is severely symptomatic and requires an immediate response. To improve the effectiveness of phase-specific cytotoxic agents, attempts have been made to exploit cell cycle arrest using tamoxifen to synchronize tumor cells and then estrogen to prime the cells in S phase.

Estrogens and Androgens

Estrogenic compounds can be used for patients with MBC, although there are no clinically significant data on the impact on treatment outcomes compared to placebo. Prior to the introduction of tamoxifen, high-dose estrogen resulted in a secondary response defined as the “withdrawal response” in 25–35% of patients after estrogen was ceased at disease progression. This withdrawal response provided palliation over 12 months [76]. Patients treated with other endocrine therapies (AIs, tamoxifen, and megestrol acetate) may occasionally respond to estrogen therapy as well [76]. If estrogen therapy is used, estradiol should be the preferred estrogen option. Although high doses of estrogen (30 mg of estradiol daily in divided doses) have been typically administered, lower doses, such as 6 mg of estradiol daily in divided doses, may be just as effective with less toxicity.

As with progestins, estrogen is contraindicated if the patient has a thromboembolic disorder or other risk factors for thromboembolic events. Progestins should be given to patients who have vaginal bleeding because of estrogen. In addition, patients should be treated with bisphosphonates before the administration of estradiol to prevent hypercalcemia.

Androgens are inferior to high-dose estrogen and are rarely used for MBC. Testosterone, fluoxymesterone, and danazol are the most frequently prescribed agents for this indication. The major side effects of androgens are virilization, edema, and jaundice.

Aromatase Inhibitors

Postmenopausal women continue to have low circulating estrogen concentrations even though the ovaries fail to synthesize estrogen during menopause. Circulating estrogen in postmenopausal women was previously believed to derive from adrenal glandular synthesis, but it has since been well established that the adrenals only contribute plasma androgens. Estrogens are produced by conversion from androgens in various body compartments such as the liver, muscle, skin, and connective tissue in postmenopausal women [91]. As emphasized previously, estrogen ablation in postmenopausal women via adrenalectomy and hypophysectomy became an attractive approach in the 1950s [92–95]. Because adrenalectomy and hypophysectomy are associated with high morbidity, trials of "medical adrenalectomy" led to the evaluation of glucocorticoids and inhibitors of adrenal enzymes such as ketoconazole [96–99]. Although the tumor response obtained with these drugs is inferior to surgical adrenalectomy and hypophysectomy, these efforts have opened the way for aminoglutethimide followed by aromatase inhibition for breast cancer therapy.

Although there is a single aromatase gene, at least ten different promoters are present in the gene [100]. In different tissue types, different promoters and ligands regulate estrogen synthesis [101, 102]. These promoters have different key roles in benign and malignant breast tissue. The main activator is the 1.4 promoter in normal breast tissue, whereas promoters II, 1.3, and 1.7, in addition to 1.4, play a role in breast cancer tissue [100]. However, the different promoters encode similar proteins. Aromatase can convert testosterone into estradiol and androstenedione into estrone. Although plasma androstenedione and testosterone are derived from the adrenals in postmenopausal women, the ovary is reported to contribute circulating testosterone at minor, albeit significant, levels [103, 104]. These plasma androgens are taken up by various body compartments for subsequent aromatization.

The benefits of tamoxifen are mainly attributed to ER blockade, which eliminates the stimulus to continue proliferation, resulting in tumor regression. However, tamoxifen therapy does not result in the maximal inhibition of the effects of estrogen because it has a weak or partial agonist effect on ER. For nearly three decades, tamoxifen has been the mainstay of endocrine therapy in breast cancer, but now third-generation AIs are emerging as potential alternatives with higher clinical efficacy and a better overall safety profile than tamoxifen [105].

Two classes of third-generation AIs, steroidal (e.g., formestane and exemestane) and nonsteroidal (e.g., fadrozole, anastrozole, and letrozole), are currently available. The pharmacokinetic properties, selectivity, and potency of these agents differ, although all third-generation AIs are more selective than aminoglutethimide [51]. Steroidal AIs (SAIs) are analogs of androstenedione, which is the substrate of natural aromatase and irreversibly inactivates the enzyme by binding covalently to the substrate-binding site of aromatase. Nonsteroidal AIs (NSAIs) such as letrozole and anastrozole, however, inhibit aromatase in a reversible manner by binding to the heme moiety of the enzyme. In this way, nonsteroidal AIs prevent androgens from binding to the catalytic site [106]. Therefore, the steroidal nonreversible AIs are also known as aromatase inactivators, whereas nonsteroidal AIs are reversible inhibitors of aromatase. For third-generation AIs, 98% inhibition of total body aromatization has been reported, whereas for first- and second-generation AIs, only inhibition <90% has been achieved [107].

Folkerd et al. suggested that the level of estradiol and estrone sulfate suppression depends on body mass index in postmenopausal women with early-stage ER+ breast cancer who were previously treated with AIs [108]. These data provide a basis for the improved outcome of AIs compared to tamoxifen in lean patients but not obese patients, which may enable individualized treatment with AIs by regulation of the AI dose depending on the circulating estradiol and estrone sulfate concentrations. Although the measurement of AIs is not difficult using mass spectrometry, the measurement of estrogens, particularly estradiol, is quite challenging.

AIs are associated with less frequent vaginal bleeding and thromboembolic events compared to tamoxifen, although they are known to affect bone turnover and possibly lipid metabolism. The adverse effects profiles between and within these two AI classes may also differ. Because available AIs have similar efficacy, it is likely that their safety and tolerability profiles will affect agent selection in clinical practice. Therefore, the elucidation of the differences in the safety profiles of third-generation AIs is critical.

Nonsteroidal AIs

Third-generation AIs were initially compared to megestrol acetate as a second-line therapy. Two randomized, multicenter trials were designed identically to compare the tolerability and efficacy of anastrozole and megestrol acetate for the treatment of postmenopausal women with advanced breast carcinoma after progression with tamoxifen [49].

Anastrozole was used at doses of 1 or 10 mg once daily, and megestrol acetate was administered in doses of 40 mg four times daily. Both studies were double blind for anastrozole and open label for megestrol acetate. Buzdar et al. performed a combined analysis of the two studies, which enrolled a total of 764 patients. At a median follow-up of 31 months for survival, 1 mg of anastrozole daily exhibited a statistically significant survival benefit over megestrol acetate (HR, 0.78, $p < 0.025$) and longer median survival (27 months) compared to the megestrol acetate group (22 months). A dose of 10 mg of anastrozole also resulted in a survival advantage over the megestrol acetate group (HR, 0.8, $p = 0.09$). Both doses of anastrozole (56.1 and 54.6%) were associated with higher 2-year survival rates than megestrol acetate therapy (46.3%) [109]. This combined analysis clearly demonstrates that anastrozole treatment at a dose of 1 mg once daily results in a statistically and clinically significant benefit over megestrol acetate after disease progression with tamoxifen. In addition to the good tolerability profile of anastrozole, this clinical benefit supports the administration of anastrozole as a valuable new treatment option for this patient population.

Two doses of letrozole (0.5 and 2.5 mg) were compared to megestrol acetate (40 mg qid) in postmenopausal women with advanced breast cancer who had previously received antiestrogens in a double-blind, randomized, multicenter, multinational study [110]. Patients with breast cancer whose disease had progressed during adjuvant antiestrogen therapy, within 12 months of the end of adjuvant antiestrogen therapy received for at least 6 months, or while receiving antiestrogen therapy for advanced disease were enrolled in the study. Their breast cancers had to have ER and/or PR positivity or unknown status. The primary efficacy variable was confirmed with an objective response rate. The performance status according to Karnofsky and quality-of-life assessments according to the European Organization for Research and Treatment of Cancer were evaluated for 1 year. The median duration of treatment was longer in the 0.5 mg letrozole treatment arm (171 days) than the 2.5 mg letrozole (120 days) and megestrol acetate arms (136 days). However, the overall objective tumor response was similar among the three treatment groups. Patients who received 0.5 mg of letrozole had a longer median time to progression compared to the other treatment arms (6 months vs. 3 months). The patients who received 0.5 mg of letrozole had a lower risk of disease progression than the patients who received megestrol acetate (HR, 0.80; $p = 0.044$). Administration of 0.5 mg of letrozole improved disease progression ($p = 0.044$) and decreased the risk of treatment failure ($p = 0.018$) compared to megestrol acetate. The time to progression between the three treatment groups was not statistically significant. Administration of 0.5 mg of letrozole produced a trend ($p = 0.053$) for survival advantage compared to megestrol acetate. Megestrol acetate resulted in a higher incidence of weight gain, vaginal bleeding, and dyspnea, and letrozole at both doses was more likely to cause headache, hair thinning, and diarrhea. Thus, letrozole is equivalent to megestrol acetate based on its favorable tolerability profile, once-daily dosing, and evidence of a clinically relevant benefit. Similar to anastrozole, letrozole should be considered for use as an alternative endocrine therapy in postmenopausal women with advanced breast cancer after treatment failure with antiestrogens.

AIs were subsequently studied as a first-line therapy compared to tamoxifen based on the positive findings obtained in the second-line setting [111–114] (Table 30.1). Bonneterre et al. [111] performed a randomized, double-blind, multicenter study in which the efficacy and tolerability of 1 mg of anastrozole once daily was compared to 20 mg of tamoxifen once daily in postmenopausal patients with advanced breast cancer as a first-line therapy. The tumors were required to be HR+ or of unknown receptor status. The time to progression, overall response rate, and tolerability were planned as primary end points. In total, 668 patients were randomized to the anastrozole arm (340 patients) and the tamoxifen arm (328 patients) and were followed up for a median of 19 months. Both treatment arms resulted in a similar median time to progression (8.2 months in the anastrozole arm and

Table 30.1 Comparison of various aromatase inhibitors with tamoxifen as first-line hormonal therapy in hormone receptor-positive advanced breast cancer

	Treatment arms		Overall response rate		Clinical benefit rate[a]		Time to progression/ progression-free survival	
	Agent	No. of patients	%	*p* value	%	*p* value	%	*p* value
Bonneterre et al. (2000) [111] (TARGET study)	Anastrozole	340	33	0.787	56		8.2	0.941
	Tamoxifen	328	33		55		8.3	
Nabholtz et al. (2000) [112] (The North American trial)	Anastrozole	171	21		59	0.0098	11.1	0.005
	Tamoxifen	182	17		46		5.6	
Mouridsen et al. (2003) [113] Phase III trial	Letrozole	453	32	0.0002	50	0.0004	9.4	<0.0001
	Tamoxifen	453	21		38		6	
Paridaens et al. (2008) [114] (EORTC-BCCG)	Exemestane	182	46	0.005	Unknown		9.9	0.121
	Tamoxifen	189	31		Unknown		5.8	

[a]Clinical benefit rate: complete response + partial response + stable disease for at least 6 months

8.3 months in the tamoxifen arm, hazard ratio for tamoxifen; anastrozole, 0.99). Anastrozole also produced a similar overall response rate compared to tamoxifen (32.9 vs. 32.6%). The clinical benefit (complete response (CR) + partial response (PR) + disease stabilization ≥24 weeks) rates were 56.2% in the anastrozole arm and 55.5% in the tamoxifen arm. These findings support the equivalent efficacy of anastrozole and tamoxifen. Although both treatments were well tolerated, fewer thromboembolic events and vaginal bleeding were reported in patients treated with anastrozole compared to those treated with tamoxifen (4.8 vs. 7.3% [thromboembolic events] and 1.2% vs. 2.4% [vaginal bleeding], respectively). Because the predefined criteria were satisfied, anastrozole was accepted to have at least equivalent efficacy with tamoxifen. Furthermore, based on the lower incidence of certain side effects such as thromboembolic events and vaginal bleeding, anastrozole has been considered as first-line therapy for postmenopausal women with advanced breast cancer [111].

In the same time period, another randomized, double-blind, multicenter trial was conducted by Nabholtz et al. in North America with a similar design as the study conducted by Bonneterre et al. [112]. Again, anastrozole was demonstrated to be as effective as tamoxifen in terms of OR (21% vs. 17%, respectively), with a clinical benefit in 59% of anastrozole-treated patients and 46% of tamoxifen-treated patients (two-sided $p = 0.0098$, retrospective analysis). The median time to progression was significantly longer in the anastrozole arm than the tamoxifen arm (11 vs. 5.6 months, respectively; two-sided $p = 0.005$, tamoxifen/anastrozole hazard ratio, 1.44). The safety profiles were also similar to those observed by Bonneterre et al. In this study, anastrozole also satisfied the predefined criteria for equivalence to tamoxifen [112].

Overall, the efficacy of AIs is at least equivalent to that of tamoxifen; thus, they are currently one of the standard first-line treatment options for postmenopausal women with HR+ MBC.

Steroidal AIs

Exemestane is the only third-generation steroidal AI. Its efficacy has been demonstrated as a first-line treatment option in MBC. Therefore, exemestane could be considered a valid first-line therapeutic option or for use in second-line or further situations. This AI has been studied in the neoadjuvant setting as a presurgical treatment option and even as a means of chemoprevention in high-risk healthy postmenopausal women. Exemestane may reverse the side effects of tamoxifen, such as endometrial changes and thromboembolic disease, but may also cause inconvenient side effects. In addition, exemestane and nonsteroidal AIs do not exhibit total cross-resistance with respect to antitumoral efficacy; moreover, the two classes of AIs display a nontotal overlapping toxicity profile. Therefore, exemestane is a useful treatment option at all stages of breast cancer.

Clinical studies have found that 25 mg/day of exemestane administered orally is the minimum effective dose to produce maximum estrogen suppression [115, 116]. The mean maximum suppression of aromatase by exemestane is 97.9% [117]. Third-generation AIs achieve 98% inhibition of total body aromatization, whereas first- and second-generation AIs achieve only 90% inhibition [107]. Exemestane, similar to other AIs, is associated with increased bone turnover, loss of bone mineral density, and an increased incidence of fractures, thus requiring close observation and treatment if necessary.

The Exemestane Study Group evaluated the efficacy, pharmacodynamics, and safety of exemestane vs. megestrol acetate in 769 postmenopausal women with advanced breast cancer whose disease progressed after tamoxifen in a phase III, double-blind, randomized, multicenter trial [118]. A total of 366 postmenopausal women received 25 mg/day of exemestane, and 403 patients received 40 mg of megestrol acetate four times daily. The overall objective response rates were higher in the exemestane arm than the megestrol acetate arm (15 vs. 12.4%); similar results were observed in patients with visceral metastases (13.5 vs. 10.5%). Median survival was longer in the exemestane arm (median not reached) than the megestrol acetate arm (123 weeks; $p = 0.039$). In addition, the median duration of the overall response (60 vs. 49 weeks; $p = 0.025$), time to tumor progression (20.3 vs. 16.6 weeks; $p = 0.037$), and time to treatment failure (16.3 vs. 15.7 weeks; $p = 0.042$) were also superior in the exemestane arm. Pain, tumor-related signs and symptoms, and quality of life were similar in the two arms or were improved with exemestane compared to megestrol acetate. Both drugs were well tolerated, but grade 3 or 4 weight changes were more common with megestrol acetate (17.1 vs. 7.6%; $p = 0.001$). Based on these findings, including the prolongation of survival, time to progression, and time to treatment failure by exemestane compared to megestrol, exemestane offers a well-tolerated treatment option for postmenopausal women with advanced breast cancer who experienced disease progression under or after tamoxifen treatment.

Although exemestane is often used as a second-line treatment, its efficacy as a first-line treatment has also been demonstrated in clinical trials [114]. The European Organization for the Research and Treatment of Cancer Breast Cancer Cooperative Group undertook a phase III randomized open-label clinical trial to investigate the efficacy and tolerability of exemestane compared to tamoxifen in 371 postmenopausal patients with hormone-sensitive MBC. The overall response rate was higher in the exemestane treatment arm than the tamoxifen arm, whereas OS was similar between the two treatment arms. OS was not significantly different from

that for tamoxifen in the different individual trials of the three third-generation AIs, but a meta-analysis indicated an OS benefit of AIs compared to tamoxifen as a first-line therapy for HR+ breast cancer [119]. Thus, AIs can be considered more efficacious than tamoxifen as first-line therapy, which is very significant for quality of life in palliative settings. AIs are also superior to megestrol acetate. Megestrol acetate was previously administered as a standard second-line hormonal therapy in patients resistant to tamoxifen, but these findings indicate that the overall ORRs were higher for exemestane than for megestrol acetate as second-line treatment following tamoxifen failure [118, 120].

Comparing Steroidal AIs with Nonsteroidal AIs

An indirect comparison revealed that exemestane administered at 25 mg daily appeared to inhibit aromatization as efficiently as anastrozole administered at 1 mg daily [121]. Furthermore, 2.5 mg of letrozole daily appeared to be a more potent AI than either exemestane or anastrozole [122]. These results should be interpreted carefully in light of plasma estrogen level measurements. Because the methods to evaluate such low plasma estrogen levels in patients require high sensitivity, obtaining measurements in vivo is very difficult. Assays with a sensitivity limit of 5–7 pM for estrone and 1–2 pM for E2 are required to detect more than 90% inhibition in vivo. Pauwels et al. developed a sensitive liquid chromatography-tandem mass spectrometry method for measuring low estrogen levels [123]. The limit of quantification was 1.2 and 1.3 ng/l for estrone and E2, respectively. Exemestane, however, is metabolized into several steroidal compounds. These steroidal molecules may interact nonspecifically during the measurement of estrogen levels and consequently cause cross-contamination [115]. As a result, chromatographic sample purification is required.

There are a limited number of randomized clinical studies comparing two different classes of AIs as first-line or sequential endocrine therapy for patients with hormone-dependent MBC. In one trial, 130 postmenopausal women were randomized to receive anastrozole or exemestane for at least 8 weeks. Another trial randomized 103 postmenopausal women with advanced breast cancer to anastrozole or exemestane until disease progression. Both studies demonstrated no difference in clinical efficacy between exemestane and anastrozole [124, 125].

A systematic review performed by Riemsma et al. indirectly compared different first-line AIs, including anastrozole, letrozole, and exemestane, in postmenopausal women with HR+ (±ErbB2 positivity) advanced breast cancer [126]. Four of 25 randomized controlled trials met the inclusion criteria. A narrative synthesis analysis was used when a meta-analysis using direct or indirect comparisons was not suitable for some or all of the data. These three AIs were compared to tamoxifen based on available data and to each other using a network meta-analysis. Based on direct evidence, the time to progression was significantly better in the letrozole arm than the tamoxifen arm (hazard ratio, 0.70 with 95% CI, 0.60–0.82). Furthermore, a better overall response rate (RR, 0.65 with 95% CI, 0.52–0.82), and quality-adjusted time without symptoms or toxicity (Q-Twist difference = 1.5; $p < 0.001$) were obtained. Exemestane was significantly superior to tamoxifen in terms of the objective response rate (RR, 0.68; 95% CI, 0.53–0.89). Anastrozole was significantly superior to tamoxifen in terms of the time to tumor progression in one trial (hazard ratio, 1.42; 95% CI, 1.15-NR) but not the other (hazard ratio, 1.01; 95% CI, 0.87-NR). There were no significant differences in adverse events between letrozole and tamoxifen. However, tamoxifen caused more serious adverse events than exemestane (OR, 0.61; 95% CI, 0.38–0.97), whereas exemestane was associated with more arthralgia than tamoxifen (OR = 2.33). Anastrozole resulted in a higher incidence of total adverse events (OR = 1.04) and hot flashes (OR = 1.39) compared to tamoxifen in one trial [126]. The indirect comparison of AIs with one another in postmenopausal women with HR+ advanced breast cancer demonstrated that letrozole and exemestane were superior to anastrozole in terms of the objective response rate, whereas OS and PFS, the more clinically relevant outcomes, did not differ significantly among AIs. A class effect of all AIs may explain the similar survival rates.

Although these are the best available data, these findings should be interpreted with appropriate caution because the basic assumptions of homogeneity, similarity, and consistency were not fulfilled for this network analysis and the findings are based on indirect comparisons. Head-to-head comparisons of these three AIs in patients with MBC in first-line settings are warranted.

Taken together, these data indicate that exemestane as a first-line treatment is effective, is well tolerated, and can be considered, similarly to NSAIs, as a valid first-line option for the treatment of HR+ cancers in postmenopausal women. As far as hormonal suppression is concerned, exemestane appears slightly less efficacious compared to the other AIs, whereas the clinical antitumoral efficacy of NSAIs and SAIs appears to be similar. In second-line treatment, the sequence of AIs appears to be irrelevant due to the total lack of cross-resistance.

Switching Between Third-Generation AIs

As emphasized previously, steroidal AIs bind irreversibly to the active site of aromatase; thus, new enzyme production is required for estrogen synthesis. However, nonsteroidal AIs reversibly bind to the active site of aromatase. Although the clinical relevance of these differences is unclear, a lack of cross-resistance between steroidal and nonsteroidal AIs was suggested. Thus, upon the progression of metastatic disease following treatment with NSAIs, exemestane may be

effective as sequential hormone therapy or vice versa [127–130]. The subsequent findings of several trials demonstrated that breast cancer patients who have become resistant to NSAIs may experience benefit from SAIs [131–135]. The clinical benefit of exemestane after progression on a nonsteroidal AI is supported by the findings of a systemic review published in 2011 [136]. On average, 25–30% of patients in the crossover studies experienced an objective response or stable disease for 6 months or more. In addition, the administration of NSAIs after failing SAIs appears to be effective. Several potential mechanisms have been suggested to underlie this nontotal cross-resistance, and studies to confirm these mechanisms are eagerly awaited [127–136].

Fulvestrant

Tamoxifen and its derivatives have partial agonist activity on ERs located in certain tissues in addition to having antagonistic activity on ERs. The well-defined agonistic effects that limit their clinical efficacy are endometrial stimulation and the induction of tumor growth after previous response to tamoxifen [47]. Fulvestrant (ICI 182,780 Faslodex produced by AstraZeneca Cheshire, United Kingdom) is a novel, steroidal estrogen antagonist and is devoid of the estrogen agonist effect to block uterotrophic activities characteristic of ER agonists and of partial agonists such as tamoxifen and raloxifene. Fulvestrant has been investigated in several in vitro and in vivo preclinical studies. In animals, fulvestrant has 100 times greater affinity for the ER than tamoxifen, and it significantly reduces the ability of the ER to stimulate or inhibit gene transcription possibly by impairing dimerization, increasing ER turnover, and disrupting nuclear localization. In addition, fulvestrant cannot cross the blood-brain barrier in animal models and is neutral with respect to lipids and bone.

Fulvestrant was also assessed clinically in patients with breast carcinoma preoperatively or after the failure of tamoxifen or a nonsteroidal AI and in patients who underwent hysterectomy for benign conditions [47, 137]. The findings of preclinical and clinical studies demonstrated that fulvestrant functionally blocks and decreases cellular ER levels; thus, ERs become unavailable or unresponsive to estrogen or estrogen agonists in breast cancer. Therefore, fulvestrant is now known as a selective ER downregulator. In addition, fulvestrant is not cross-resistant with tamoxifen or the ER-agonist activity associated with tamoxifen.

Although fulvestrant has been studied in postmenopausal patients with HR+ inoperable locally advanced or advanced breast cancer in several phase II and III trials, the dosage, line of therapy, and comparison groups were not uniform. Initially, a dose-response effect of fulvestrant in the dose range of 50–250 mg for intramuscular use was demonstrated, but later trials evaluating the clinical activity of 125 mg of fulvestrant did not show any objective tumor response after 3 months of treatment [138]. Therefore, the subsequent clinical development of fulvestrant in advanced breast cancer was performed with monthly dosages of 250 mg, although 500 mg was later tested and compared to 250 mg [139].

Fulvestrant Versus Tamoxifen

Howell et al. conducted a multicenter, double-blind, randomized trial to compare the efficacy and tolerability of fulvestrant with tamoxifen as a first-line endocrine therapy in postmenopausal women with advanced breast cancer [140]. The tumors of the patients were required to be ER+ and/or PR+ or of unknown receptor status. Patients were randomized to 250 mg of fulvestrant (once-monthly intramuscular injection; $n = 313$) or 20 mg of tamoxifen (once-daily oral tablets; $n = 274$). In 2004, with a median follow-up of 14.5 months, the median time to progression was similar between fulvestrant and tamoxifen (6.8 months and 8.3 months, respectively; HR, 1.18; 95% CI, 0.98–1.44; $p = 0.088$). A prospectively planned subgroup analysis of patients with known HR+ tumors (78%) revealed that the median time to progression was also similar between the two treatment arms (8.2 months for fulvestrant and 8.3 months for tamoxifen; HR, 1.10; 95% CI, 0.89–1.36; $p = 0.39$). For the overall population, the objective response rate was 31.6% with fulvestrant and 33.9% with tamoxifen, and in the known HR+ subgroup, the objective response rate was similar between the two treatment arms (33.2% and 31.1%, respectively, OR, 1.10; 95% CI, 0.74–1.63; $p = 0.64$). In addition, the clinical benefit rate was similar among the treatment arms (57% for fulvestrant, 62.7% for tamoxifen; OR, 0.79; 95% CI, −15.01–3.19; $p = 0.22$). Both tamoxifen and fulvestrant were well tolerated. The median time to treatment failure was longer in patients who were treated with tamoxifen than in fulvestrant-treated patients (7.8 months vs. 5.9 months; HR, 1.24; 95% CI, 1.03–1.50; $p = 0.026$). Among patients with HR+ breast cancer, the median time to treatment failure was similar between the treatment arms (7.5 months for fulvestrant and 8 months for tamoxifen: HR, 1.15; 95% CI, 0.93–1.42; $p = 0.19$) [140]. The median survival was longer in the tamoxifen arm than in the fulvestrant arm (38.7 months vs. 36.9 months, respectively; HR, 1.29; 95% CI, 1.01–1.64; $p = 0.04$) according to the planned analysis with adjustments for baseline covariates. However, when the analysis was unadjusted for baseline covariates, survival did not differ between the two groups (HR, 1.21; 95% CI, 0.95–1.54; $p = 0.12$). Among the patients with HR+ tumors, the median survival was 39.3 months in the fulvestrant group and 40.7 months in the tamoxifen group (HR, 1.16; 95% CI, 0.88–1.54; $p = 0.30$). The upper limit of the 95% CI was 1.54, which did not satisfy the predefined criterion ($\leq$1.25) to conclude noninferiority of fulvestrant compared to tamoxifen. In total, 12% of the fulvestrant-treated patients and 11% of the tamoxifen-

treated patients died without "breast cancer," and these deaths represented approximately a quarter of all deaths in both treatment arms [140].

The results from this trial indicate that differences in efficacy favored tamoxifen, and in the first-line setting, the noninferiority of fulvestrant could not be demonstrated. Nevertheless, in patients with potentially hormone-sensitive breast cancer (HR+ tumors), the efficacy of fulvestrant was at least similar efficacy to that of tamoxifen, without significant differences between end points and a favorable overall tolerability profile. The survival analysis revealed similar results for time to progression, that is, patients with both ER+ and PR+ breast cancer appeared to gain the most benefit from fulvestrant.

Fulvestrant Versus Anastrozole

A phase III clinical trial (trial 0020) was performed to compare the efficacy and tolerability of fulvestrant at a dose of 250 mg in a once-monthly intramuscular injection with anastrozole at a dose of 1 mg once daily in tablets in postmenopausal women with advanced breast cancer whose disease had progressed after prior endocrine therapy [141]. Trial 0020 was an open-label, nonblinded, randomized, multicenter, parallel-group study conducted in South Africa, Europe, and Australia. The time to progression was the primary end point, and overall response rates, duration of response, and tolerability were determined as secondary end points. The median time to disease progression was similar between the fulvestrant and anastrozole arms (5.5 months and 5.1 months, respectively; HR, 0.98; 95% CI, 0.80–1.21; $p = 0.84$) with a median follow-up of 14.4 months. Although the overall response rates indicated a numerical benefit of fulvestrant (20.7%) over anastrozole (15.7%), this difference did not reach statistical significance (OR, 1.38; 95% CI, 0.84–2.29; $p = 0.20$). The clinical benefit rates were 44.6% in the fulvestrant arm and 45.0% in the anastrozole arm. The median duration of response was also similar in the two groups (14.3 months for fulvestrant and 14 months for anastrozole). Both fulvestrant and tamoxifen were well tolerated; treatment was terminated because of an adverse event in 3.2% of fulvestrant-treated patients and 1.3% of anastrozole-treated patients [141].

Another phase III, randomized, double-blind trial entitled "trial 0021" was conducted in North America concurrently with trial 0020 [142]. The main aim of the trial was to compare two doses of monthly fulvestrant (125 mg and 250 mg) as an intramuscular injection with anastrozole (1 mg/d oral dose) in the treatment of patients with advanced breast cancer whose disease had progressed during prior endocrine therapy. The end points of this study were the same as those of trial 0020. To determine the clinical activity of 125 mg of fulvestrant, a planned preliminary data summary and an interim analysis were conducted. After the first 30 patients in the fulvestrant 125 mg group (combined from both trials) were enrolled into the studies and followed up for 3 months, both trials conducted a preliminary data summary. This interim assessment demonstrated insufficient evidence for 125 mg of fulvestrant in terms of clinical activity without any objective tumor response at 3 months. Thus, the independent data monitoring committee offered to stop recruitment to the fulvestrant 125 mg treatment arm. The patients who were already randomized into the 125 mg arm in trial 0021 were permitted to continue the 125 mg of fulvestrant or to withdraw from the trial and receive the other treatments at the discretion of the clinician. These patients were not monitored further for efficacy. As a consequence, the protocol for the study was amended to compare 250 mg of fulvestrant with 1 mg of anastrozole [142].

With a median follow-up of 16.8 months, fulvestrant was shown to be as effective as anastrozole with respect to time to progression (5.4 months with fulvestrant vs. 3.4 months with anastrozole: HR, 0.92; 95.14% CI, 0.74–1.14; $p = 0.43$). Both treatments resulted in 17.5% overall response rates and statistically similar clinical benefit rates (42.2% for fulvestrant and 36.1% for anastrozole; 95% CI, −4.00–16.41%; $p = 0.26$). In all patients, fulvestrant caused a longer duration of response compared to anastrozole (ratio of average response durations: 1.35; 95% CI, 1.10–1.67; $p < 0.01$). In responding patients, the median duration of response was 19 months for fulvestrant and 10.8 months for anastrozole. Both treatments were shown to be well tolerated [142].

In 2003, the authors performed the prospectively planned combined analysis of data from these two phase III trials comparing 250 mg of fulvestrant monthly ($n = 428$) and 1 mg of anastrozole daily ($n = 423$) in postmenopausal women with advanced breast carcinoma whose disease had previously progressed after receiving endocrine therapy [143]. The main aim of both trials was to demonstrate the superiority of fulvestrant over anastrozole. At a median follow-up of 15 months, disease progression occurred in approximately 83% of patients in each arm. The median time to progression (5.5 months in the fulvestrant arm and 4.1 months in the anastrozole arm; HR, 0.95; 95.14% CI, 0.82–1.10; $p = 0.48$) and overall response rates (19.2% for fulvestrant and 16.5% for anastrozole; 95.14% CI, 2.27–9.05%; $p = 0.31$) were similar between the two treatment arms. In responding patients, to obtain more complete information on the duration of response, further follow-up (median of 22.1 months) was performed; the median duration of response was determined (from randomization to disease progression). A statistical analysis of all randomized patients revealed a significantly longer duration of response in fulvestrant-treated patients compared to anastrozole-treated patients. Both drugs were well tolerated with few withdrawals due to drug-related adverse events (0.9% in the fulvestrant group and 1.2% in the anastrozole group). However, there

was a lower incidence of joint disorders in the fulvestrant arm (p = 0.0036). These data further supported the use of fulvestrant as an additional, effective, and well-tolerated treatment option in postmenopausal women whose disease progressed during prior endocrine therapy, with efficacy end points slightly favoring fulvestrant [143].

Fulvestrant Plus Anastrozole Versus Anastrozole

Some patients eventually become resistant to single-agent endocrine therapy and experience disease progression, as observed for many other cancer therapies. It was hypothesized that fulvestrant combined with an AI might lead to better outcomes compared to anastrozole alone in patients with HR+ MBC. Subsequent, preclinical work precluded the potential synergy of fulvestrant with AI therapy to delay the development of endocrine resistance.

Bergh et al. performed an open-label randomized phase III clinical trial entitled "FACT" to compare the efficacy of anastrozole with that of combined fulvestrant and anastrozole therapy in women who had experienced a first relapse of breast cancer after the primary treatment of early disease [144]. Postmenopausal women or premenopausal women receiving an LHRH agonist were included. A total of 514 patients were randomized to receive fulvestrant (initiated with a loading dose followed by monthly injections) plus anastrozole (1 mg daily and n = 258) or to anastrozole (1 mg daily, n = 256) alone. Although two-thirds of the patients had been treated with adjuvant antiestrogens, only eight women had received an AI. The median time to progression, which was the primary end point of the study, was similar in the experimental and standard arms (10.8 vs. 10.2 months, respectively; hazard ratio, 0.99; 95% CI, 0.81–1.20; p = 0.91). The median OS was also similar among the two treatment groups (37.8 and 38.2 months, respectively; hazard ratio, 1.0; 95% CI, 0.76–1.32; p = 1.00). The incidences of prespecified adverse events were also similar. Hot flashes were more common in the experimental arm than in the standard arm (24.6 vs. 13.8%, p = 0.0023). Death due to adverse events occurred in 4.3% of the patients treated with the experimental regimen and 2% of the patients in the standard arm [144].

The Southwest Oncology Group (SWOG) performed a similarly designed randomized phase III trial [145]. Treatment-naive postmenopausal women with MBC were randomized to receive either anastrozole (group 1) (1 mg orally every day with permission to cross over to fulvestrant alone as disease progressed) or anastrozole in combination with fulvestrant (group 2). The stratification was performed based on the absence or presence of prior adjuvant tamoxifen therapy. Fulvestrant was administered at a dose of 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter as an intramuscular injection. The clinical benefit rate was 73% for the combination therapy and 70% for single-agent anastrozole (p = 0.39). Stable disease was the most frequent response type. In patients who had measurable disease, the overall response rate was similar in the two arms (27% for combination therapy vs. 22% for anastrozole alone; p = 0.26). Three deaths in group 2 were potentially attributable to the treatment. The median PFS was 13.5 months in the anastrozole-alone arm and 15 months in the combination arm (hazard ratio for progression or death with combination therapy: 0.80; 95% CI, 0.68–0.94; p = 0.007). The combination therapy provided a longer median overall survival (41.3 months vs. 47.7 months for anastrozole vs. the combination; hazard ratio, 0.81; 95% CI, 0.65–1.00; p = 0.05); however, after progression, 41% of the patients in the anastrozole group crossed over to fulvestrant. In general, combination therapy was more effective than single-agent anastrozole in all subgroups, without significant interactions. There was a similar rate of serious side effects between the two groups [145]. These findings indicated that combined use of anastrozole and fulvestrant was superior to anastrozole alone or the sequential administration of anastrozole with fulvestrant for the treatment of HR+ MBC, although the dose of fulvestrant in this trial was below the current standard.

In subgroup analyses that were not prespecified, among 414 women (59.7%) who were not treated with prior tamoxifen, the median PFS was longer with combination therapy (12.6 months vs. 17 months in groups 1 and 2, respectively; hazard ratio for progression or death with combination arm: 0.74; 95% CI, 0.59–0.92; P = 0.006) [145]. Among women with a prior tamoxifen history, the estimated median PFS was similar (14.1 months vs. 13.5 months, respectively; hazard ratio, 0.89; 95% CI, 0.69–1.15; P = 0.37). There was no significant interaction between therapy and a history of prior adjuvant tamoxifen. Among women without prior tamoxifen, the OS was significantly different between the groups with a hazard ratio for death with the combination therapy of 0.74 (95% CI, 0.56–0.98; p = 0.04); however, OS was similar among women with prior tamoxifen history (hazard ratio, 0.91; 95% CI, 0.65–1.28; p = 0.59), and the combination therapy resulted in a benefit for both groups [145].

A possible explanation for the conflicting results in terms of efficacy between the FACT and SWOG S0226 studies is that the primary end point of FACT was time to disease progression, whereas the primary end point of SWOG S0226 was PFS. Although these end points appear similar, death without progression would only be captured in the SWOG S0226 study, thereby potentially increasing the progression numbers. Furthermore, the percentage of patients without a history of endocrine therapy was higher in the SWOG S0226 study than in the FACT study (59.7% vs. 32.2%, respectively) [144, 145].

Tan et al. performed a meta-analysis of these prospective randomized clinical trials and compared the effectiveness of fulvestrant + anastrozole with anastrozole alone as first-line treatment in postmenopausal women with HR+, HER2-negative MBC [146]. The pooled hazard ratio for PFS was 0.88 (95% CI,

0.72–1.09; 95% PI, 0.65–1.21), the pooled OS was 0.88 (95% CI, 0.72–1.08; 95% PI, 0.68–1.14) and the pooled odds ratio for the response rate was 1.13 (95% CI, 0.79–1.63; 95% PI, 0.78–1.65). A nonsignificant trend of marginal superiority was observed for anastrozole + fulvestrant compared to anastrozole alone for the end points of PFS, OS, and response rates.

Based on these data, the evidence for combining monthly fulvestrant at a dose of 250 mg with anastrozole is insufficient to recommend this combination as a first-line therapy for all women with postmenopausal HR+ breast cancer. However, recently the final survival outcomes of SWOG study was reported. In the final analysis, the addition of fulvestrant to anastrozole was associated with increased long-term survival as compared with anastrozole alone, despite substantial crossover to fulvestrant after progression during therapy with anastrozole alone. The results suggest that the benefit was particularly notable in patients without previous exposure to adjuvant endocrine therapy [147].

In 2013, Al-Mubarak et al. [138] performed a systematic review of eight randomized trials comparing fulvestrant vs. other endocrine therapies. The hazard ratios for time to progression and the odds ratios for serious adverse events, drug discontinuation because of toxicity, and commonly observed toxicities were pooled in this meta-analysis. The meta-regression analysis was conducted to explore the heterogeneity of the study populations and fulvestrant dosing. No significant differences were observed in the time to progression between fulvestrant and the other treatment groups (HR, 0.94; $p = 0.18$). The meta-regression analysis demonstrated that fulvestrant, when used as a first-line treatment, reduced the hazard ratios for time to progression compared to AIs in studies in which fewer patients were administered adjuvant endocrine therapy and at higher doses. The rates of serious adverse events and treatment discontinuation were similar between the fulvestrant and other groups, but fulvestrant monotherapy was associated with less frequent arthralgia (OR, 0.73; $p = 0.02$). Combining fulvestrant with AI did not improve the time to progression, but it did increase toxicity. Fulvestrant monotherapy was associated with similar efficacy but reduced arthralgia compared to other endocrine therapy options in unselected patient populations. High-dose fulvestrant monotherapy, when used as a first-line treatment or in patients with limited prior exposure to adjuvant endocrine therapy, may delay progression compared to AIs [138].

Another mode of action of fulvestrant that differs from that of other currently used antiestrogens is that fulvestrant consistently reduces PR levels in the tumor in a dose-dependent manner.

Similar to many other antiestrogens, resistance to fulvestrant occurs in the majority of patients with advanced breast cancer after prolonged therapy, although the underlying mechanisms are poorly understood and may include overexpression of the microRNA miR-221/222.

Combined Use of Endocrine Agents with Other Targeted Agents in the First-Line Setting

Cyclin-Dependent Kinases 4 and 6 Inhibitors

Analysis of the Cancer Genome Atlas revealed the associations of deregulated cyclin D, CDK4/6 and retinoblastoma (Rb) interactions with luminal B cancer [148]. Cyclin D activates CDK4/6 and induces Rb phosphorylation and progression of the cell cycle into the S phase, eventually resulting in endocrine resistance [149]. PD 0332991, called palbociclib, is a highly selective, orally administered inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). Preclinical studies demonstrated that palbociclib inhibits the proliferation of ER+ breast cancer cell lines, and early clinical trials suggested that it improves PFS when combined with an endocrine agent [150]. Ribociclib and abemaciclib are other oral small-molecule inhibitors of CDK4/6 with preclinical and clinical evidence of growth-inhibitory activity in HR+ breast cancer cells and synergy with anti-estrogens.

Palbociclib in combination with letrozole received US Food and Drug Administration (FDA) accelerated approval as a first-line treatment option for HR+ advanced breast cancer in February 2015 [48]. The approval was based on a randomized, multicenter, open-label phase I/II trial (PALOMA-1) in which 165 patients were randomized to receive palbociclib (125 mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5 mg orally daily) or letrozole alone [151]. A significant improvement in PFS was observed in patients receiving palbociclib plus letrozole (median 20 months) compared with patients receiving letrozole alone (median 10 months) (HR, 0.49; 95% confidence interval, 0.32–0.75). An improvement in OS was observed in the combination arm vs. the letrozole-alone arm (median 37.5 vs. 33 months, respectively, $p = 0.819$), although this improvement did not reach statistical significance. The most common adverse reaction in patients receiving palbociclib plus letrozole was neutropenia (grade ¾ toxicity 54% in the combination arm vs. 15% in the letrozole-alone arm) [152].

The results from the phase III trial PALOMA-2, which compared letrozole with letrozole plus palbociclib in the first-line setting for HR+ HER2- metastatic breast cancer, supported the findings of previous trials [153, 154]. At a median follow-up of 23 months, the median PFS of the combination arm was longer than that of the letrozole-alone arm (HR: 0.58, 24.8 months vs. 14.5 months, respectively). A consistent benefit of palbociclib–letrozole was demonstrated across all subgroups. The subgroups were visceral disease (HR, 0.63; 95% CI, 0.47–0.85), nonvisceral disease (HR, 0.50; 95% CI, 0.36–0.70), presence of previous hormonal therapy (HR, 0.53; 95% CI, 0.40–0.70), no history of prior hormonal therapy (HR, 0.63; 95% CI, 0.44–0.90), a disease-free interval of 12 months or less (HR, 0.50; 95% CI, 0.33–

0.76), a disease-free interval of more than 12 months (HR, 0.52; 95% CI, 0.36–0.73), and newly metastatic disease (HR, 0.67; 95% CI, 0.46–0.99). The rate of clinical benefit response was 84.9% in the palbociclib–letrozole group and 70.3% in the placebo–letrozole group [154]. However, overall survival data are immature.

Ribociclib (LEE011) has been evaluated in a phase III clinical trial (MONALEESA-2) in association with letrozole as a first-line treatment in postmenopausal women with HR+ advanced breast cancer [155]. Patients were randomized to ribociclib (600 mg/day; 3 weeks-on/1 week-off) plus letrozole (2.5 mg/day; continuous) or placebo plus letrozole until disease progression, unacceptable toxicity, death, or treatment discontinuation. The median PFS was 25.3 months [95% confidence interval (CI) 23.0–30.3] for ribociclib plus letrozole and 16.0 months (95% CI 13.4–18.2) for placebo plus letrozole (hazard ratio 0.568; 95% CI 0.457–0.704; log-rank $P = 9.63 \times 10^{-8}$). The ribociclib treatment benefit was maintained irrespective of PIK3CA or TP53 mutation status, total Rb, Ki67, or p16 protein expression, and CDKN2A, CCND1, or ESR1 mRNA levels. The ribociclib benefit was more pronounced in patients with wild-type vs. altered receptor tyrosine kinase genes. OS data remain immature. The ORR was 54.5% vs. 38.8%, respectively, for patients with measurable disease. In conclusion, in MONALEESA-2, ribociclib plus letrozole showed improved progression-free survival compared with letrozole alone as a first-line treatment for postmenopausal patients with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer. The improved efficacy outcomes and manageable tolerability observed with first-line ribociclib plus letrozole were maintained with a longer follow-up relative to that of letrozole monotherapy [155].

MONALEESA-7 aimed to assess the efficacy and safety of ribociclib plus endocrine therapy in premenopausal women with advanced, HR-positive breast cancer. This phase 3, randomized, double-blind, placebo-controlled trial was performed at 188 centers in 30 countries. Eligible patients were premenopausal women aged 18–59 years who had histologically or cytologically confirmed HR-positive, HER2-negative, advanced breast cancer and who had not received previous treatment with cyclin-dependent kinases 4 and 6 inhibitors. Patients were randomly assigned (1:1) to receive oral ribociclib (600 mg/day on a 3-weeks-on, 1-week-off schedule) or matching placebo with either oral tamoxifen (20 mg daily) or a nonsteroidal aromatase inhibitor (letrozole 2·5 mg or anastrozole 1 mg, both oral, daily), all with goserelin (3·6 mg administered subcutaneously on day 1 of every 28-day cycle). A total of 672 patients were randomly assigned. The median PFS was 23.8 months (95% CI 19.2-not reached) in the ribociclib group and was 13.0 months (11.0–16.4) in the placebo group (hazard ratio 0.55, $p < 0{\cdot}0001$). Grade 3 or 4 adverse events reported in more than 10% of patients in either group were neutropenia (61% in the ribociclib group and 4% in the placebo group) and leucopenia (14% and 1%). Serious adverse events occurred in 18% of patients in the ribociclib group and 12% in the placebo group. No treatment-related deaths occurred. In conclusion, ribociclib plus endocrine therapy improved progression-free survival compared with that of placebo plus endocrine therapy and had a manageable safety profile in patients with premenopausal, HR-positive, HER2-negative, advanced breast cancer [156].

Abemaciclib: Abemaciclib (Verzenio™) is an orally administered inhibitor of cyclin-dependent kinases 4 and 6 that is being developed by Eli Lilly and Company. In the MONARCH-3 trial, abemaciclib in combination with an aromatase inhibitor (letrozole or anastrozole) was compared with aromatase inhibitor monotherapy in endocrine treatment naïve first-line HR+ advanced breast cancer patients [157]. The median PFS was found to be significantly prolonged in the abemaciclib arm (HR, 0.54; $p = 0.000021$; median: not reached in the abemaciclib arm, 14.7 months in the placebo arm). In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm ($p = 0.004$). Comparing abemaciclib and placebo, the most frequent grade 3 or 4 adverse events were neutropenia (21.1% vs. 1.2%), diarrhea (9.5% vs. 1.2%), and leukopenia (7.6% vs. 0.6%).

Although increased expression of cyclin D1 and pRb and decreased expression of p16 (a natural CDK4/6 inhibitor) were found to be associated with response in in vitro preclinical studies, patient selection on the basis of cyclin D1 amplification or p16 loss was not associated with an improved outcome from palbociclib treatment in the PALOMA-1/TRIO-18 trial [150, 151].

Except for ER positivity, there is no biomarker that predicts the response to CDK4/6 inhibitors. Based on mechanistic insights evaluated in many preclinical and clinical trials, CDK4/6 inhibitors are currently being explored in combination with other agents, including targeted therapies, immunotherapy, and chemotherapy.

Anti-VEGF monoclonal antibody, bevacizumab: preclinical findings have indicated that estradiol regulates angiogenesis under both physiological and pathological conditions. High VEGF levels in breast tumors have been shown to be related to a decreased response to endocrine agents [158]. Bevacizumab has been extensively evaluated in the treatment of HR+ and negative breast cancer in several trials. In 2014, Kümler et al. performed a meta-analysis of 14 phase III trials in which bevacizumab was investigated [159]. More than 4400 patients with advanced breast cancer had benefits in the relapse rate and PFS; however, no trial demonstrated an OS advantage. Recently, the results of 2 phase III trials have been published [160, 161]. In the LEA trial, the addition of bevacizumab to letrozole or fulvestrant in the first-line

setting was studied for postmenopausal women with HR+ HER2-negative advanced breast cancer [160]. The time to treatment failure and OS were comparable in the treatment arms, although ORR was improved with the bevacizumab combination. In the CALGB 40503 trial, bevacizumab plus letrozole was compared with letrozole monotherapy. PFS was improved with the combination (20 months vs. 16 months, HR: 0.74; $p = 0.016$) [161]. Unfortunately, OS was similar between the 2 treatment arms at the cost of a higher frequency of grade 3 or 4 toxicities with bevacizumab-based treatment regimens. Thus, bevacizumab is not currently recommended in combination with ET in HR+ advanced breast cancer patients.

CDK4/6 Inhibitors in Second or Further Lines of Treatment

There is no evidence to recommend a CDK4/6 inhibitor as monotherapy or in combination with other drugs in patients who received another CDK4/6 inhibitor in previous lines. However, CDK4/6 inhibitors are among the most effective treatment options in patients who are CDK4/6 inhibitor naïve and have progressive disease under prior antiestrogen treatment.

CDK4/6 Inhibitors in Combination with Fulvestrant

The PALOMA-3 trial was a phase III randomized trial that included patients with HR+ and HER2− advanced breast cancer to compare palbociclib plus fulvestrant with placebo plus fulvestrant [162]. Premenopausal women who were treated with goserelin were also included in the study. Patients were required to have progressive disease during, be within 12 months after completion of adjuvant ET or on prior ET in the metastatic setting (with progression from prior AI required for postmenopausal women). The study was stopped early due to significant efficacy results reported at interim analysis favoring fulvestrant plus palbociclib (median PFS: 9.2 vs. 3.8 months; HR: 0.42, 95% CI 0.32–0.56; $p < 0.001$). Although higher rates of neutropenia and fatigue were reported in the combination arm, the rates of discontinuation and febrile neutropenia were similar between the two arms. Although a longer follow-up is required to determine the impact of combination therapy on OS, the available PFS data support the use of palbociclib in combination with fulvestrant.

Abemaciclib with fulvestrant: Abemaciclib at 150 mg twice daily plus fulvestrant has been approved in the United States for the treatment of HR+, HER2− advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy as well as a monotherapy in adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting based on the findings obtained in the phase 3 MONARCH 2 trial [163]. PFS was significantly longer with abemaciclib plus fulvestrant than with fulvestrant alone (median, 16.4 vs. 9.3 months; HR, 0.553; $p < 0.001$). In patients with measurable disease, abemaciclib plus fulvestrant achieved an ORR of 48.1% (95% CI, 42.6–53.6%) compared with the ORR of 21.3% (95% CI, 15.1–27.6%) in the control arm. The most common adverse events were diarrhea (86.4% vs. 24.7%), neutropenia (46.0% vs. 4.0%), nausea (45.1% vs. 22.9%), and fatigue (39.9% vs. 26.9%) in the abemaciclib vs. placebo arms.

In the MONARCH 1 trial, a phase II single-arm open-label study, patients with HR+/HER2− MBC who had progressed on or after prior endocrine therapy and had one or two chemotherapy regimens in the metastatic setting were treated with abemaciclib 200 mg two times daily on a continuous schedule until disease progression or unacceptable toxicity [164]. Patients had a median of three (range, 1–8) lines of prior systemic therapy in the metastatic setting, 90.2% had visceral disease, and 50.8% had ≥3 metastatic sites. At the 12-month final analysis, the objective response rate was 19.7%, clinical benefit rate (CR + PR + SD ≥6 months) was 42.4%, median PFS was 6.0 months, and median OS was 17.7 months. Diarrhea, fatigue, and nausea were the most frequent side effects, but discontinuations due to AEs were infrequent (7.6%). In this poor-prognosis, heavily pretreated population with refractory HR+/HER2− metastatic breast cancer, continuous dosing of single-agent abemaciclib was well tolerated and approved by the FDA.

Other Targeted Agents for Endocrine-Resistant Hormone Receptor-Positive Breast Cancer

Preclinical studies have suggested that acquired AI resistance may be a result of the upregulation of several growth factor receptors, such as HER2 and IGFR1. The increased expression of these receptors may promote the activation of downstream protein kinases, such as mitogen-activated protein kinase and Akt, which in turn, could result in increased ER phosphorylation and activation and sensitization of tumor cells to estrogen. The combination of endocrine agents with a molecular-targeted agent continues to be explored in several currently active or recently finalized clinical trials with the aim of overcoming endocrine resistance.

PI3K-Akt-mTOR Signaling Pathway

Accumulating evidence suggests that both the levels and activity of ER and PR are dramatically influenced by growth-factor receptor (GFR) signaling pathways and that this cross-talk is a major determinant of both breast cancer progression and response to therapy [165–168]. The activation of the PI3K-Akt-mTOR signaling pathway, which includes PI3K, a

key mediator of GFR signaling, is one of the most altered pathways in breast cancer [148, 150]. For example, breast tumors may have mutation or loss of PTEN or both, amplification and activating mutations in PIK3CA, amplification of Akt2 and p70S6kinase, and overexpression of Akt3 [169]. Consistent with the mutational spectrum of PI3K signaling intermediates in breast cancer, direct analysis of PI3K activation has shown an association with poor outcomes [170]. Similarly, loss of PTEN is associated with low ER and PR and poor outcomes [171]. Recently, Generali et al. demonstrated the significance of downregulation of key molecules in the PI3K pathway in response to letrozole, further emphasizing the predictive and therapeutic role of this pathway in ET [172].

The inhibition of proliferation could be synergistically enhanced by the addition of an mTOR inhibitor to endocrine treatment [173]. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study investigated the safety and efficacy of the mTOR inhibitor everolimus in combination with exemestane in breast cancer patients who had been previously treated with NSAIs [174]. Patients were randomly assigned to receive 25 mg of exemestane daily or exemestane plus 10 mg of everolimus daily. The study demonstrated that concomitant use prolonged PFS (median of 7 vs. 3 months; hazard ratio for mortality: 0.43, 95% CI, 0.35–0.54) and provided a higher overall response rate (9.5 vs. 0.4%). Nonetheless, combination therapy was associated with a higher incidence of serious adverse events, including stomatitis (8%), dyspnea (4%), noninfectious pneumonitis (3%), and elevated liver enzymes (3%), compared to that of exemestane monotherapy. However, combination therapy led to a higher percentage of treatment discontinuation. There was no statistically significant improvement in OS [175]. Given the remarkable PFS benefit, everolimus was approved by the FDA for the treatment of HR+ advanced breast cancer in combination with exemestane after failure with NSAIs. Currently, activity of the mammalian target of rapamycin inhibitor everolimus in combination with letrozole and goserelin is under assessment in premenopausal patients after progression on tamoxifen (MIRACLE trial) [176].

A phase III trial (HORIZON) was conducted in the first-line setting with temsirolimus, another mTOR inhibitor. Unfortunately, adding temsirolimus to letrozole did not improve PFS (median, 9 months; HR, 0.90; 95% CI, 0.76–1.07; $P = 0.25$) as first-line therapy in patients with AI-naïve advanced breast cancer nor in the 40% patient subset with prior adjuvant endocrine therapy [177].

In a randomized phase II study of neoadjuvant everolimus and letrozole vs. placebo and letrozole, the addition of everolimus marginally improved the sonographic response rate (68% vs. 59%, respectively; $P = 0.062$), but markedly enhanced the antiproliferative response (defined as the natural logarithm of percentage positive for Ki67 < 1 on day 15 vs. baseline; 57% vs. 30%, respectively; $P < 0.01$) [178]. In TAMRAD, which was conducted by Groupe d'Investigateurs Nationaux pour I'Etude des Cancers Ovariens et du sein (GINECO) as a randomized phase II trial of everolimus and tamoxifen vs. tamoxifen alone in postmenopausal patients with advanced disease pre-exposed to AIs, the addition of everolimus was associated with a four-month improvement in time to progression (median 9 vs. 5 months, HR = 0.54, 95% CI 0.36–0.81) and reduced risk of death (HR 0.45, 95% CI 0.24–0.81) [178]. However, the ORRs of the two arms were similar (14 vs. 13%). Furthermore, grade 3–4 stomatitis (11 vs. 0%), anorexia (7 vs. 4%), and the incidence of pneumonitis were higher with combination therapy.

Drugs targeting other components of these pathways, including Akt inhibitors, PIK3CA inhibitors (e.g., pictilisib) and dual kinase inhibitors targeting both mTOR and PI3KCA, are currently in development.

Next-generation sequencing of BOLERO-2 did not show any relationship between somatic mutation patterns, particularly in the catalytic subunit of PI3K3CA, and clinical outcomes [179]. The PFS benefit of everolimus was maintained regardless of the alteration status of PIK3CA, FGFR1, and CCND1 or the pathways of which they are components. However, quantitative differences in everolimus benefit were observed between patient subgroups defined by exon-specific mutations in PIK3CA (exon 20 vs. 9) or by different degrees of chromosomal instability in the tumor tissues [179]. The data from this exploratory analysis suggest that the efficacy of everolimus is largely independent of the most commonly altered genes or pathways in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer. The potential impact of chromosomal instabilities and low-frequency genetic alterations on everolimus efficacy warrants further investigation. Thus, the identification of predictive markers for PIK3CA/mTOR inhibition still needs to be addressed prospectively. Furthermore, PIK3CA mutational status has been shown to be discordant between the primary tumor and metastases [150]. In fact, mutational status is mainly analyzed in primary tumor samples. Thus, alterations in molecular pathways should be re-analyzed in the metastatic setting.

The combination of everolimus with tamoxifen was studied by the Groupe d'Investigateurs Nationaux pour I'Etude des Cancers Ovariens et du sein (GINECO) [180]. Postmenopausal women ($n = 111$) who progressed on an AI were randomly assigned to receive tamoxifen with or without everolimus. The combination therapy resulted in an improved time to progression (median of 9 vs. 5 months; hazard ratio, 0.54; 95% CI, 0.36–0.81) and risk of death (hazard ratio, 0.45; 95% CI, 0.24–0.81). However, the overall response rates of the two arms were similar (14 vs. 13%). Furthermore, grade 3–4 stomatitis (11 vs. 0%), anorexia (7 vs. 4%), and the incidence of pneumonitis were higher in the combination therapy arm.

Insulin-Like Growth Factors (IGF-1 and IGF-2)

The binding of insulin-like growth factors (IGF-1 and IGF-2) to the IGF-1 receptor (IGF-1R) enhances cell proliferation and prolongs cell survival. Ganitumab is a monoclonal immunoglobulin G1 (IgG1) antibody that blocks IGF-1R. In a phase II double-blind randomized controlled trial, the efficacy and safety of ganitumab in combination with endocrine therapy was investigated in postmenopausal patients with HR+ locally advanced or MBC previously treated with endocrine agents [181]. The median PFS was similar between the ganitumab and placebo arms (3.9 months vs. 5.7 months; $p = 0.44$). However, OS was shorter in the ganitumab arm than in the placebo arm (HR, 1.78; 80% CI, 1.27–2.50; $p = 0.025$). With the exception of hyperglycemia (11 vs. 0%), adverse events were generally similar between the groups. Because the addition of ganitumab to endocrine treatment in women with previously treated HR+ locally advanced or MBC did not improve outcomes, further studies of ganitumab in this patient subgroup have not been designed.

Class I Histone Deacetylase Inhibitors

Entinostat is a small-molecule inhibitor of class I histone deacetylase that plays a key function in the control of gene expression. It exerts antiproliferative effects and promotes apoptosis in breast cancer cell lines and has been evaluated as a second or later line of therapy in women with ER+ breast cancer. In the ENtinostat Combinations Overcoming REsistance (ENCORE 301) randomized phase II trial, 130 women who had previously progressed on AI therapy were randomly assigned to receive 25 mg of exemestane daily with 5 mg of entinostat daily or with placebo [182]. The patients included in the trial had undergone multiple prior lines of therapy including chemotherapy and endocrine agents. The preliminary findings demonstrated that exemestane + entinostat therapy improved PFS (median of 4 vs. 2 months) at the expense of more fatigue (46 vs. 26%) and uncomplicated neutropenia (25 vs. 0%).

HER2-Positive Hormone Receptor-Positive Metastatic Breast Cancer

Premenopausal and Postmenopausal

Several are the mutual effects of ER and HER2. In experimental models, despite initially lacking EGFR or HER2, hormone-sensitive ER+ breast cancer cells usually develop endocrine resistance over time via the enhanced expression of receptors involved in cross-talk with ER [183]. Therefore, the overexpression of HER2 results in resistance to established endocrine therapies [184]. Combined therapeutic strategies might enhance endocrine effectiveness in patients with HR+, HER2+ breast cancer, and delay disease progression for those with HR+ and HER2-negative tumors at risk of early relapse. This treatment strategy has been evaluated in many clinical studies.

Endocrine Treatment with or Without Trastuzumab

Mackey and colleagues compared the AI anastrozole with combination anastrozole + trastuzumab in an open-label, multicenter, two-arm phase III trial [185]. A total of 208 HER2+, ER+ patients were randomized to receive either anastrozole alone (1 mg daily) or anastrozole (1 mg daily) + trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly) until disease progression. Patients who had not received prior chemotherapy in the metastatic setting were also included. Patients who received tamoxifen either in the adjuvant or first-line metastatic setting were included. PFS was the primary end point. The median PFS was two-fold longer in the anastrozole + trastuzumab arm: 4.8 months vs. 2.4 months with anastrozole alone ($p = 0.0016$). More than 15% of the patients in the anastrozole+trastuzumab arm had PFS exceeding 2 years. The overall response rate was significantly better in the anastrozole + trastuzumab arm (58%) than the anastrozole-alone arm (45%), although the individual rates were similar [185]. In the anastrozole-alone arm, 70% of the patients were allowed to proceed to trastuzumab later in the course of disease. OS, although not statistically significant, was numerically superior in the combination arm (28.5 vs. 23.9 months, $p = 0.325$). Treatment with anastrozole + trastuzumab was associated with manageable toxicity with no unexpected adverse events, although the frequency of common adverse events was increased [185].

Kaufman et al. investigated endocrine therapy in combination with anti-HER2 therapy in a randomized trial entitled "The Trastuzumab and Anastrozole Directed Against ER+ HER2+ Mammary Carcinoma (TAnDEM)" [186]. Postmenopausal women with HR+ and HER2+ MBC were randomized to receive anastrozole alone ($n = 104$) or combination therapy with anastrozole and trastuzumab ($n = 103$), and patients treated with anastrozole alone were allowed to cross over to the combination therapy after disease progression in the anastrozole arm. Approximately two-thirds of the patients on anastrozole alone received the combination treatment at progression. At the central laboratory, receptor analyses were repeated, and HR positivity was confirmed in 150 patients (77 in the trastuzumab + anastrozole arm; 73 in the anastrozole-alone arm). However, 44 patients (21 in the trastuzumab + anastrozole arm; 23 in the anastrozole-alone arm) were identified as ER/PR negative by the central laboratory [186]. Treatment with trastuzumab + anastrozole resulted in significantly longer PFS compared to treatment with anastrozole alone (4.8 vs. 2.4 months, respectively; hazard ratio 0.63; 95% CI, 0.47–

0.8; log-rank p = 0.0016). Among patients with centrally confirmed HR positivity, the median PFS was 5.6 months in the combination arm and 3.8 months in the anastrozole-alone arm (log-rank p = 0.006) [186]. However, the median OS was statistically similar between the two treatment groups in either the overall or centrally confirmed HR+ subgroups, which may be attributable in part to the high crossover rate [186].

The addition of an AI to HER2-targeted therapy may delay the use of chemotherapy in some patients and provides an important advantage. Based on these positive results, trastuzumab used concurrently with an AI has been approved for the treatment of postmenopausal patients with HR+ and HER2+ MBC who have not received prior trastuzumab. Based on the results of clinical trials, nonsteroidal AIs have become one of the standard treatment options in this patient population; however, there is no reason to believe a different result would be obtained with a steroidal AI.

Endocrine Treatment with or Without Lapatinib

In the first-line setting, the combination of lapatinib with letrozole was compared to letrozole + placebo in 1286 patients with HR+ MBC. In HER2+ patients, lapatinib + letrozole led to a longer median PFS than letrozole + placebo (8.2 vs. 3 months; HR, 0.71; 95% CI, 0.53–0.96; p = 0.019) [153]. In patients with centrally confirmed HR+, HER2-negative disease (n = 952), lapatinib + letrozole did not improve PFS [187].

In 2012, a systematic review analyzed outcomes including OS, PFS, time to progression, and ORR of first-line hormone therapy in combination with an anti-HER2 agent in HR+, HER2+ MBC patients [188]. Relevant interventions were combination regimens with endocrine agents including AIs (letrozole, anastrozole, and exemestane), tamoxifen, and an anti-HER2 agent (lapatinib or trastuzumab). They searched randomized controlled clinical trials reported in six databases until January 2009 to assess the safety and efficacy of first-line treatments for postmenopausal women with HR+ and HER2+ MBC without prior therapy for advanced or metastatic disease. Eighteen studies (62 papers) were included in the systematic analysis. Lapatinib + letrozole was significantly superior to letrozole alone based on a direct head-to-head study in terms of PFS/time to progression and overall response rate. In terms of PFS/time to progression and ORR, tamoxifen (hazard ratio, 0.45 [95% CI, 0.32–0.65]) and anastrozole (hazard ratio, 0.53 [95% CI, 0.36–0.80]) were significantly worse (tamoxifen, OR, 0.25 [95% CI, 0.12–0.53]; anastrozole, OR, 0.27 [95% CI, 0.12, 0.58]) compared to lapatinib + letrozole. The combination also appeared significantly superior to exemestane in terms of PFS/time to progression (hazard ratio, 0.52 [95% CI, 0.34, 0.79]). Lapatinib + letrozole was also superior, although not significantly, in terms of OS to tamoxifen, hazard ratio, 0.74 (0.49, 1.12); anastrozole, hazard ratio, 0.71 (0.45, 1.14); and exemestane, hazard ratio, 0.65 (0.39, 1.11). Although the p value was statistically nonsignificant, when compared to trastuzumab + anastrozole, lapatinib + letrozole was superior in terms of OS (hazard ratio, 0.85 [0.47, 1.54]), PFS/time to progression (hazard ratio, 0.89 [0.54, 1.47]), and ORR (OR, 0.92 [0.24, 3.48]). Based on a direct head-to-head study, lapatinib+letrozole was significantly superior to letrozole in terms of PFS/time to progression and ORR. Consequently, indirect comparisons appeared to favor lapatinib + letrozole vs. other first-line treatments in this patient population in terms of three main outcomes: OS, PFS/time to progression, and ORR.

The FDA approved lapatinib + letrozole for the treatment of postmenopausal women with HR+ MBC overexpressing the HER2 receptor for whom hormonal therapy is indicated. However, it is important to note that lapatinib in combination with an AI has not yet been compared to a trastuzumab-containing chemotherapy regimen for the treatment of MBC.

The results of the CALGB 40302 trial were recently published. The authors investigated whether lapatinib improved PFS among women with HR+ MBC treated with fulvestrant [189]. Eligible women had ER+ and/or PR+ tumors, regardless of HER2 positivity and prior AI treatment. Five hundred milligrams of fulvestrant was administered to patients intramuscularly on day 1, followed by 250 mg on days 15 and 28 and every 4 weeks thereafter with either 1500 mg of lapatinib or placebo daily. The study planned to accrue 324 patients and was powered for a 50% improvement in PFS with lapatinib from 5 to 7.5 months. At the third planned interim analysis, the futility boundary was crossed, and the data and safety monitoring board recommended study closure, having accrued 295 patients. No difference was detected in PFS (hazard ratio of placebo to lapatinib: 1.04; 95% CI, 0.82–1.33; p = 0.37); the median PFS was 4.7 months for fulvestrant + lapatinib vs. 3.8 months for fulvestrant + placebo at the final analysis. There was no difference in OS (hazard ratio, 0.91; 95% CI, 0.68–1.21; p = 0.25). The median PFS was similar among the treatment arms (4.1 vs. 3.8 months for HER2-normal tumors) in HER2+ MBC patients, and lapatinib was associated with longer median PFS (5.9 vs. 3.3 months), but the differential treatment effect by HER2 status was not significant (p = 0.53). Diarrhea, fatigue, and rash were the most frequently experienced toxicities associated with lapatinib. Adding lapatinib to fulvestrant did not improve PFS or OS in ER+ advanced breast cancer and increased toxicity [189].

Table 30.2 Endocrine therapy in hormone receptor-positive, HER2-negative advanced breast cancer

Ovarian suppression (GnRH agonist) or ablation in all premenopausal patients			
Endocrine Treatment Naive		Previous Endocrine Treatment	
No contraindication to CDK inhibitors	Contraindication to CDK inhibitors	Under endocrine treatment or within 12 months after the end of adjuvant endocrine treatment	Disease recurrence at least 1 year after the end of adjuvant endocrine treatment
CDK inhibitors[a] and aromatase inhibitor	Fulvestrant	CDK inhibitors and aromatase inhibitor	Treat as patients who are endocrine treatment naive
CDK inhibitors and fulvestrant	Aromatase inhibitors	CDK inhibitors and fulvestrant	
Fulvestrant	Tamoxifen	Abemaciclib and tamoxifen	
		Fulvestrant	
		Everolimus and exemestane	
		If an aromatase inhibitor used previously, switch to other (steroidal to nonsteroidal or vice versa)	
		Tamoxifen	
		Progestins	
		Estrogens or androgens	

[a]Paalociclib, ribociclib, abemaciclib

In premenopausal women with HR+ HER2+ breast cancer, data are insufficient to conclude the overall benefit of tamoxifen therapy in combination with an anti HER2 agent. However, based on the data obtained in postmenopausal women, tamoxifen + trastuzumab is widely used in premenopausal breast cancer patients. In conclusion, the combination of an anti-HER2 agent with endocrine therapy is an active and safe method with favorable response rates and survival advantages in patients with HR+ and HER2+ advanced breast cancer.

Conclusion

Endocrine therapy should be considered for patients with hormone-sensitive advanced breast cancer without life-threatening visceral involvement. Premenopausal women with HR+ advanced breast cancer should receive ovarian ablation or functional suppression therapy in combination with other endocrine agents recommended to postmenopausal women. Nonsteroidal AIs comprising anastrozole and letrozole; steroidal AIs (exemestane), fulvestrant, tamoxifen, or toremifene; progestins such as megestrol acetate and fluoxymesterone; and estrogens such as ethinyl estradiol can be used sequentially. Exemestane in combination with everolimus may be offered to patients whose disease progressed under nonsteroidal AIs. Trastuzumab or lapatinib can be combined with other endocrine agents, particularly AIs or tamoxifen, in patients with both HER2− and HR-positive breast cancer. Several targeted agents are currently being studied in patients with HR+ and endocrine-resistant disease, and in the near future, there may be many other treatment options for HR+ endocrine therapy-resistant advanced breast cancer. A summary of treatment recommendations is presented in Table 30.2.

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Treatment of HER2-Negative Metastatic Breast Cancer: Chemotherapy

31

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Introduction

Breast cancer is the most common cancer in women, with more than 200,000 new cases in 2014, and it is the second leading cause of cancer death in women [1]. Although often curable when localized to the breast and local lymph nodes, if the disease becomes metastatic, it is usually not curable. Breast cancer is a heterogeneous disease comprising several molecular subtypes, which are commonly extrapolated into clinical subtypes based on receptor status [2]. The specific receptors that are assessed in standard clinical practice are the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2-neu (HER2) receptor. These receptors are both prognostic but also predictive of the response to targeted therapy; thus, when metastasis is suspected, it is crucial to perform a biopsy not only to confirm recurrent disease but also to confirm receptor status [3]. In addition, tissue availability may increase clinical trial access because many studies now assess targetable molecular aberrancies.

Systemic Chemotherapy of HER2-Negative Metastatic Breast Cancer

Considerable advances have been made in the treatment of certain subtypes of breast cancer, such as HER2-positive disease. In this subtype, targeted therapies against HER2 have changed the clinical outcome for patients with metastatic disease by providing them with several effective therapies that can extend survival by many years [4]. The ER- and PR-positive subtypes also have several targeted therapies available that use endocrine therapies; however, when the disease becomes metastatic, all patients eventually develop endocrine resistance and eventually require cytotoxic chemotherapy [5]. Patients with ER-, PR-, and HER2-negative tumors, so-called triple-negative breast cancers (TNBCs), biologically tend to display an aggressive phenotype, currently do not have targeted therapy options as a standard of care, and have only a limited number of cytotoxic agents available to treat their disease [6]. This chapter narrates and expands on some of the recent efforts in drug development for HER2-negative metastatic breast cancer (MBC), and the current standard of care of these different subtypes of breast cancer is summarized.

Treatment of ER/PR-Positive HER2-Negative Metastatic Breast Cancer

Two-thirds of all women diagnosed with breast cancer have a disease that is ER/PR+. These tumors are highly responsive to antiestrogen therapeutic strategies. However, despite the widespread use of hormonal adjuvant therapy, a quarter of women with ER+ disease will relapse. In this situation, a determination regarding further hormonal therapy versus chemotherapy as the next step must be made. Patients whose disease is viscerally relatively "low"-volume, bone/soft tissue-predominant, and asymptomatic are reasonable candidates for upfront endocrine therapy. The current standard practice for these patients has been discussed in Chap. 30.

Treatment of ER/PR-Positive HER2-Negative Endocrine-Refractory Metastatic Breast Cancer

Mechanisms of Endocrine Therapy Resistance in ER-Positive Breast Cancer

Acquired resistance (defined as recurrence at least 6–12 months after completion of adjuvant therapy or disease progression of more than 6 months after endocrine therapy initiated in the metastatic setting) and occasionally primary

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Sidebar 31.1. Mechanisms of Resistance to Endocrine Agents

Primary Resistance

- Receptor tyrosine kinase/growth factor signaling pathway
- *FGFR* amplification
- *EGFR*/*ERBB2* mutations
- Cell-cycle control signaling pathway
- Cyclin D1 amplification or expression
- *MYC* amplification and overexpression
- Hormone-signaling pathway
- Loss of ERα
- Posttranslational modification of ERα
- Expression of ER coactivation/corepression factors

Acquired Resistance

- PI3K/AKT1/MTOR signaling pathway
- PI3K/AKT/mTOR pathway activation
- Mitogen-activated protein (MAP) kinase pathway
- MAPK/ERK pathway activation
- Hormone signaling pathway
- *ESR1* mutations
- Changes in the tumor microenvironment

resistance (recurrence either during adjuvant therapy or within 6–12 months of completion of adjuvant therapy or disease progression of less than 6 months after treatment in the metastatic setting) to antiestrogen therapy is inevitable in patients with ER+ metastatic breast cancer (MBC).

A variety of mechanisms have been implicated in primary and acquired resistance to endocrine agents (Sidebar 31.1). In the following text, we review some strategies for overcoming endocrine therapy resistance. The current standard practice for these patients has been discussed in Chap. 30.

mTOR Inhibitors

The PI3K–Akt–mTOR signaling pathway is a major intracellular signaling pathway that plays a significant role in cell growth and proliferation and has been implicated in resistance to endocrine therapy [7]. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study [8] demonstrated that inhibiting mTOR with everolimus in combination with exemestane improved progression-free survival (PFS) compared with exemestane alone in patients with ER-positive MBC previously treated with a nonsteroidal anti-inflammatory (NSAI). However, the phase III HORIZON trial [9] found no survival benefit of combining temsirolimus with letrozole in the first-line setting, suggesting that mTOR signaling may have a specific role in acquired resistance to endocrine therapy. Although the BOLERO-2 study combination has become a standard of care in patients whose disease has progressed after treatment with an NSAI, it is unknown if everolimus has meaningful single-agent activity that could explain the results [10, 11]. Several ongoing trials will better define the role of everolimus in advanced disease: BOLERO-6 (NCT01783444), a phase II trial comparing exemestane/everolimus to capecitabine in ER+/HER2-negative disease refractory to AI, and BOLERO-4 (NCT01698918), a phase II single-arm study evaluating the role of everolimus as a first-line treatment. Everolimus is also being evaluated in the adjuvant setting in two studies using two different approaches: (1) SWOG1207 (NCT01674140), which will randomly assign high-risk premenopausal and postmenopausal patients to add everolimus or placebo to their standard adjuvant endocrine therapy; and (2) NCT01805271, which will evaluate the addition of everolimus to adjuvant endocrine therapy in high-risk ER+/HER2-negative patients with breast cancer who remain disease free after at least 1 year of treatment.

PI3K Inhibitors

PI3K inhibitors consist of pan-PI3K targeting all class I isoforms, isoform-specific PI3K inhibitors, and dual PI3K/mTOR inhibitors. Compounds may also display differential activity for wild-type and mutant PI3K proteins. The response rates for single-agent PI3K inhibitors are far below than those for other kinase inhibitors in other cancer types (such as EGFR, ALK, or BRAF inhibitors).

Buparlisib (BKM120) is a pan-PI3K inhibitor with potent activity against mutant PI3Kα [12]. Early-phase trials of buparlisib plus endocrine therapy reported activity and a manageable safety profile characterized by transaminitis, hyperglycemia, diarrhea, and mood disorders (anxiety, depression, irritability) [13]. The randomized phase III BELLE-2 trial studied fulvestrant 500 mg plus buparlisib 100 mg daily or placebo in postmenopausal MBC progressing on AIs [14]. Buparlisib increased the median PFS by 1.9 months (6.9 months vs. 5.0 months, $P < 0.001$). For patients with PI3K/AKT pathway activation (defined as PIK3CA mutation or PTEN loss, assayed in the archival primary tumor for the majority of patients), there was no difference in the benefit of buparlisib. However, in the subset of patients in whom PIK3CA mutation was assessed by circulating tumor DNA at trial entry, buparlisib plus fulvestrant increased PFS in PIK3CA-mutant cases compared with fulvestrant alone (7 months vs. 3.2 months; HR, 0.56; $P < 0.001$).

Using the same treatment arms as BELLE-2, the phase III BELLE-3 trial enrolled AI-experienced patients with disease progression in the past 30 days on an mTOR inhibitor plus endocrine therapy [15]. The median PFS for patients in the buparlisib arm was 3.9 months versus 1.8 months for fulvestrant/placebo, and the 6-month PFS rates were 30.6% and 20.1%, respectively. Of the 349 patients for whom PIK3CA mutation status from circulating tumor DNA was available, 147 had mutations in the gene. Among those with PIK3CA

mutations, PFS was 4.7 months in the buparlisib arm versus 1.6 months in the placebo arm. A similar result was obtained for PIK3CA status in tumor tissue.

In a phase III clinical trial, taselisib, a pan-PI3K inhibitor, combined with fulvestrant (FULV) halted the growth of advanced breast cancer for 2 months longer than hormone therapy alone and decreased the chance of cancer worsening by 30%. The SANDPIPER trial was the first and largest phase III clinical trial of taselisib and enrolled 516 postmenopausal women with locally advanced or metastatic ER-positive, HER2-negative MBC progressing on AIs. The women were randomly assigned to receive fulvestrant and placebo (176 women) or fulvestrant and taselisib (340 women). Taselisib + FULV significantly improved PFS (hazard ratio [HR] 0.70) as mPFS was 5.4 months with placebo versus 7.4 months with taselisib. The ORR more than doubled when taselisib was added (28% vs. 11.9%). Overall survival (OS) was still immature. The most common grade ≥3 adverse events in the taselisib + FULV arm in safety-evaluable patients who received ≥1 dose of treatment were diarrhea (12%), hyperglycemia (10%), colitis (3%), and stomatitis (2%). Adverse events led to more taselisib discontinuations (17% v 2%) and dose reductions (37% v 2%) versus placebo [16].

Fulvestrant

Another strategy used to overcome resistance to single-agent endocrine therapy is to target the ER. Fulvestrant binds to the ER, causing its downregulation; thus, estradiol may compete for receptor site occupancy. Preclinical studies [17] have suggested that the antitumor effects of fulvestrant can be increased in a low-estrogen environment, and studies in breast cancer xenografts have found the combination of an AI with fulvestrant to have synergistic antitumor effects. Combination endocrine therapy using AIs and fulvestrant in the metastatic setting has been studied in large randomized clinical trials with discordant results [18, 19]. The Southwest Oncology Group (SWOG) 0226 study demonstrated a median PFS of 13.5 months (95% CI, 12.1–15.1 months) for the anastrozole arm compared with 15 months (95% CI, 13.2–18.4 months) for the combination arm (HR, 0.8; $P = 0.007$), with overall survival (OS) favoring the combination arm as well (HR, 0.81; $P = 0.049$). However, subgroup analysis demonstrated that the benefit was restricted to patients who had not received prior tamoxifen (HR, 0.74; $P = 0.006$), rather than those previously treated with tamoxifen (HR, 0.89; $P = 0.39$) [19]. The fulvestrant and anastrozole combination therapy (FACT) study [18] and the study of faslodex with or without concomitant arimidex versus exemestane following progression on NSAIs (SoFEA) [17], on the other hand, showed no difference in median PFS. These results therefore have had limited applicability in clinical practice. However, neither the SWOG 0226 study nor the FACT study investigated fulvestrant alone as a control arm, although data from SoFEA suggest that fulvestrant and exemestane are equivalent in patients whose disease progressed during treatment with an NSAI (HR, 0.95; $P = 0.56$). Notably, these studies used the 250-mg dose of fulvestrant, which was subsequently shown to be inferior to the 500-mg dose in the comparison of faslodex in recurrent or metastatic breast cancer (CONFIRM) study. The 500 mg dose is now the standard of care dose. In addition, in the front-line setting, the fulvestrant first-line study comparing endocrine treatments (FIRST) suggested that 500 mg of fulvestrant compared with anastrozole may improve median time to progression (TTP) (HR, 0.63; $P = 0.049$), and a recent update at the 2014 SABCS suggested a similar benefit in median OS (HR, 0.7; $P = 0.04$). The results from a confirmatory phase III study are anticipated because these findings may ultimately affect clinical practice (NCT01602380).

Cyclin-Dependent Kinases 4 and 6 Inhibitors

A new strategy in treating patients with ER-positive breast cancer is to target cyclin-dependent kinases 4 and 6 (CDK4/6), a key pathway involved in regulating the G1/S transition of the cell cycle. Preclinical studies combining tamoxifen with the CDK4/6 inhibitor palbociclib demonstrated synergistic antitumor effects, which led to a phase II study randomizing 165 women with ER-positive MBC to front-line letrozole alone or in combination with palbociclib. This study showed a significant difference in PFS between the letrozole arm (10.2 months; 95% CI, 5.7–12.6 months) and the combination arm (20.2 months; 95% CI, 13.8–27.5 months) (HR, 0.488; 95% CI, 0.139–0.748; $P < 0.001$) [20]. The confirmatory phase III PALOMA-2 study randomized a total of 666 postmenopausal patients with ER-positive MBC and no prior systemic therapy to receive letrozole with palbociclib or letrozole with placebo. Median PFS (the primary endpoint) was 24.8 months versus 14.5 months in favor of the palbociclib arm (hazard ratio [HR], 0.58; 95% CI, 0.46–0.72; $P < 0.000001$) [21]. The response rate was also improved in the palbociclib arm (42.1% vs. 34.7%, $P = 0.031$), and the clinical benefit rate was 84.9% versus 70.3% ($P < 0.0001$). Similar evidence of efficacy was observed in the phase III PALOMA-3 trial for the combination of fulvestrant plus palbociclib, in which PFS was 9.2 months versus 3.8 months with fulvestrant plus placebo (HR, 0.42; $P < 0.000001$) in patients with disease progression after at least one line of hormonal therapy and at most one line of chemotherapy but naive to CDK4/6 inhibitors [22, 23]. In both phase III trials, the most common grade 3 or 4 adverse event in the palbociclib arms was neutropenia (incidence 62–65%), but treatment was otherwise well tolerated. Both palbociclib with letrozole for first-line treatment and palbociclib with fulvestrant for second-line treatment of patients with ER+/HER2-negative MBC are approved by the U.S. Food and Drug Administration (FDA).

Treatment of Endocrine-Refractory or Triple-Negative Metastatic Breast Cancer that Presents with Visceral Threat

Admittedly, using receptor status and sensitivity to guide management of therapy in MBC oversimplifies the discrete molecular subtypes identified through advances in genomic analysis. For example, the biological behavior and drivers of an ER+ luminal breast cancer that becomes hormone insensitive are presumably distinct from those of triple-negative basal-like subtypes, as evidenced by different patterns of relapse and response to treatment [24].

A guiding principle of treatment of metastatic disease is to respect the palliative goal of this therapy given the absence of data demonstrating superior survival benefit with combination cytotoxics rather than sequential strategies. Sequential administration of single agents has been considered a viable and acceptable standard of care, and this is due, in part, to Intergroup trial E1193, in which, despite increased response rate (RR) and time to treatment failure with combination paclitaxel and doxorubicin in metastatic disease, sequential doxorubicin followed by paclitaxel and vice versa showed similar efficacy and no difference in survival benefit [25]. Many patients will require multiple lines of therapy for advanced disease, and consequently, use of combination chemotherapy regimens rather than sequential use of single-agent cytotoxics should be limited to specific circumstances in which performance status permits it and rapid response is critical, as with impending organ failure. Cytotoxics that have FDA-approved indications in MBC and activity as single agents include anthracyclines, taxanes, nontaxane microtubule inhibitors, and antimetabolites (Table 31.1).

Anthracycline Single-Agent Cytotoxic Therapy: Doxorubicin, Epirubicin, and Pegylated Liposomal Doxorubicin

Many patients will have been exposed to anthracyclines in the adjuvant setting; however, with the advent of docetaxel/cyclophosphamide as a standard adjuvant doublet, more patients may present with recurrent disease without having been exposed to these agents. Women with metastatic disease (receptor status not reported) exposed to alkylators in the adjuvant setting or to, at most, one line of therapy in the advanced setting or to both were randomly assigned to doxorubicin 75 mg/m^2 versus docetaxel 100 mg/m^2 every 3 weeks. Although docetaxel resulted in a higher objective RR in this pretreated population with visceral disease, there was no statistically significant difference in median TTP or OS. Neutropenic fever, infection, cardiac toxicity, nausea, and vomiting were more likely with anthracycline therapy, whereas the primary toxicities caused by docetaxel consisted of diarrhea, neuropathy, fluid retention, and skin and nail changes [27]. In a trial designed to establish the optimal dose of first-line epirubicin in MBC, women who had mostly

Table 31.1 Selected phase III clinical trials of single-agent and synergistic combination therapies in ER-positive, endocrine-refractory, or triple-negative MBC

Drug/Regimen	Line of therapy	Number of patients included	Findings
Doxorubicin 60 mg/m^2 every 3 weeks vs. liposomal doxorubicin 50 mg/m^2 every 3 weeks [26]	+/− adjuvant anthracycline or endocrine	509	PFS: 7.8 vs. 6.9 mo OS: 22 vs. 21 mo
Doxorubicin 75 mg/m^2 every 3 weeks vs. docetaxel 100 mg/m^2 every 3 weeks [27]	Prior alkylator	326	RR: 33% vs 48%[a] TTP: 21 vs. 26 weeks OS: 14 vs 15 mo
Docetaxel 100 mg/m^2 every 3 weeks vs. paclitaxel 175 mg/m^2 every 3 weeks [28]	First- and second-line	449	TTP: 5.7 vs. 3.6 mo[a] OS: 15.4 vs.12.7 mo[a]
Nab-paclitaxel 260 mg/m^2 every 3 weeks vs. paclitaxel 175 mg/m^2 every 3 weeks [29]	Unlimited, no prior taxane in metastatic setting	225	RR: 33% vs. 19%[a] TTP: 23 vs. 16.9 weeks[a] OS: 60.5 vs. 55.7 weeks
Docetaxel 100 mg/m^2 every 3 weeks vs. capecitabine 1250 mg/m^2 twice a day × 14 days every 3 weeks + docetaxel 75 mg/m^2 every 3 weeks [30]	First- or second-line	511	RR: 30% vs. 42%[a] TTP: 6.1 vs. 4.2 mo[a] OS: 14.5 vs. 11.5 mo[a]
Paclitaxel 175 mg/m^2 every 3 weeks vs. paclitaxel 175 mg/m^2 every 3 weeks + gemcitabine 1250 mg/m^2 D1 and D8 every 3 weeks [31]	First-line	529	RR: 41% vs. 26%[a] TTP: 6.14 vs. 3.98 mo[a] OS: 18.6 vs. 15.8 mo[a]
Eribulin 1.4 mg/m^2 every week × 2 weeks every 3 weeks vs. physicians' choice [32]	Median 4 prior	762	PFS: 3.7 vs. 2.2 mo OS: 13.1 vs. 10.6 mo[a]
Capecitabine 1250 mg/m^2 twice a day × 14 days every 3 weeks vs. ixabepilone 40 mg/m^2 every 3 weeks + capecitabine 1000 mg/m^2 twice a day × 14 days every 3 weeks [33]	Third-line	1221	RR: 29% vs. 43%a PFS: 4.2 vs. 6.2 mo[a] OS: 15.6 vs. 16.4 mo

Mo months, *OS* overall survival, *PFS* progression-free survival, *RR* response rate, *TTP* time to progression
[a]Statistically significant

positive/unknown hormone receptor status and whose adjuvant regimens were nonanthracycline based were randomly assigned to four dose levels of epirubicin, including 90 mg/m^2, which is hematologically equivalent to the maximum tolerated dose of 75 mg/m^2 of doxorubicin. This dose was found to afford the greatest TTP with the least toxicity and is further evidence of the efficacy of single-agent anthracyclines [34]. Pegylated liposomal doxorubicin (PLD) has also been examined in the hope that preferential accumulation in tumor tissue would limit cardiotoxicity. In a noninferiority trial designed to assess efficacy and cardiac safety, women who could have received prior adjuvant anthracycline were randomly assigned to either PLD or doxorubicin. Noninferiority was achieved; however, not surprisingly, significantly more doxorubicin-treated patients met the protocol-defined criteria for cardiotoxicity [26].

Taxane Single-Agent Cytotoxic Therapy: Paclitaxel, Docetaxel, and Tesetaxel

Single-agent taxanes are an effective option in metastatic patients, particularly in those who were treated with only anthracycline-based adjuvant therapy. Taxanes induce mitotic arrest by inhibiting depolymerization of the microtubules. Although the mechanisms of binding to tubulin and cell-cycle arrest through stabilization of microtubules of paclitaxel and docetaxel are similar, preclinical studies have shown that docetaxel has greater affinity, longer retention time, and higher intracellular concentration in target cells [28]. The side-effect profiles are also different because fluid retention and fatigue are more characteristic of docetaxel toxicity, whereas hypersensitivity and neurotoxicity are more common with paclitaxel. This difference is thought to be related to the solvents required for the stabilization of these hydrophobic compounds. Several studies have examined the optimal dosing regimens of taxanes. Weekly paclitaxel appears to be as effective as or more effective than every-21-day dosing [35, 36]. Docetaxel administered every 3 weeks has better efficacy compared with either weekly or every-3-week paclitaxel but at the expense of greater toxicity [28]. Docetaxel on a weekly schedule still results in some fatigue, fluid retention, and excess lacrimation but less myelosuppression and neuropathy [37]. Nab-paclitaxel appears to be more effective and convenient than paclitaxel and docetaxel and affords the benefit of taxane therapy without steroid premedication [29].

Tesetaxel is a novel, oral taxane that has potential advantages over currently available taxanes, including oral administration and once every 3 weeks dosing, no history of hypersensitivity reactions, and improved activity against chemotherapy-resistant tumors [38]. A total of 555 patients have been treated with tesetaxel in clinical studies (492 monotherapy; 63 in combination with capecitabine). In MBC, tesetaxel had robust single-agent activity in two multicenter, phase II studies. In the TOB203 clinical trial, 38 patients with HER2-, HR+ MBC received single-agent tesetaxel; the confirmed ORR in all 38 patients was 45% (95% CI: 29–62%), and the median PFS was 5.7 months (95% CI: 4.1–9.8 months). In a phase I study, the combination of tesetaxel plus a reduced dose of capecitabine was associated with a tolerable adverse effect profile with minimal overlapping toxicity. Combining the approved dose of capecitabine with currently available taxanes resulted in robust efficacy but significant toxicity, and preclinical and clinical studies suggest that reducing the dose of capecitabine in combination with a taxane may result in reduced toxicity without a reduction of efficacy. Therefore, the CONTESSA clinical trial is investigating tesetaxel plus a reduced dose of capecitabine as an all-oral regimen in HER2-, HR+ MBC patients. CONTESSA is a multinational, multicenter, randomized phase III registration study comparing tesetaxel (27 mg/m^2 on day 1 of a 21-day cycle) plus a reduced dose of capecitabine (1650 mg/m^2/day on days 1–14 of a 21-day cycle) to the approved dose of capecitabine alone (2500 mg/m^2/day on days 1–14 of a 21-day cycle) in patients with HER2-, HR+ MBC previously treated with a taxane in the (neo)adjuvant setting. Where indicated, patients must have received endocrine therapy with or without a CDK 4/6 inhibitor. The primary endpoint is PFS as assessed by an Independent Radiologic Review Committee (IRC). Secondary endpoints are OS and ORR as assessed by the IRC. Enrollment was initiated in Dec 2017 (Clinical trial NCT03326674).

Nontaxane Microtubule Inhibitor Single-Agent Cytotoxic Therapy: Vinorelbine, Ixabepilone, and Eribulin

Other microtubule inhibitors efficacious in the treatment of metastatic disease in those exposed/resistant to anthracyclines and taxanes include vinorelbine, ixabepilone, and eribulin. Nearly a quarter of patients who progressed through anthracyclines and taxanes treated with weekly vinorelbine (dose modified to 25 mg/m^2 because of hematological toxicity and neurotoxicity) had an objective response [39]. Vinorelbine binds to tubulin, inhibiting tubulin polymerization, and this may explain why sensitivity to vinorelbine is retained among patients pretreated with taxanes because excess depolymerized tubulin has been noted in vitro.

Ixabepilone is an epothilone B analog that increases polymerization but, unlike taxanes, has the capacity to bind to multiple isomers of tubulin. Ixabepilone has been evaluated in the setting of patients pretreated with anthracyclines, taxanes, and capecitabine as well as in the first-line metastatic treatment of patients treated with adjuvant anthracyclines. In the first-line setting, women with MBC achieved an overall RR of 41.5% and a median survival of 22 months [40, 41]. Modifications in the administration

schedule of ixabepilone in a group of women who had not had prior taxane exposure did reduce neurotoxicity while maintaining RRs comparable to those of historical controls of docetaxel or paclitaxel in the first- or second-line metastatic setting [42]. Women with taxane-resistant MBC or those pretreated with taxanes and capecitabine had RRs ranging from 11% to 12% and a durable response of nearly 6 months [43, 44]. In this heavily pretreated population with prior exposure to taxane therapy, half experienced reversible sensory neuropathy.

Eribulin is the latest nontaxane microtubule inhibitor with a mechanism distinct from that of taxanes, epothilones, and vinca alkaloids in that it affects centromere dynamics and sequesters tubulin into nonfunctional aggregates. Like vinorelbine, eribulin decreases polymerization of microtubules [45]. Phase II studies have shown efficacy in populations pretreated with anthracyclines and taxane as well as capecitabine. Despite a median of four prior regimens, women still achieved RRs ranging from 9% to 14% and a PFS of approximately 2.6 months [46]. A phase III trial randomly assigning heavily pretreated patients to eribulin showed an improvement in OS of 13.1 months compared with 10.6 months in women treated according to the physician's choice. Neutropenia (52%), fatigue (54%), and neuropathy (35%) were common toxicities [32].

Antimetabolite Single-Agent Cytotoxic Therapy: Capecitabine and Gemcitabine

Antimetabolite therapy should be considered in women with prior exposure to anthracycline and taxane therapy. Capecitabine is an orally administered precursor of 5-deoxy-5-fluorouridine monotherapy that is preferentially converted to 5-fluorouracil in tumor tissue by exploiting the high intratumoral concentrations of thymidine phosphorylase. A group of women who had received over three prior cytotoxic regimens, including prior anthracycline and taxane therapy, achieved an objective RR of 26% and a median survival of 12.2 months with capecitabine monotherapy, even though nearly half required dose reduction. Retrospective analysis suggested that dose reduction for palmar-plantar erythrodysesthesia, diarrhea, and nausea did not affect efficacy [47]. Capecitabine monotherapy was also tested in the first-line setting against cyclophosphamide/methotrexate/fluorouracil with comparable RRs, although palmar-plantar erythrodysesthesia induced by capecitabine required treatment interruptions and dose reductions in one-third of the patients [47]. Capecitabine at a lower dose of 1000 mg/m^2 daily for 14 days of a 21-day cycle was compared with previously tested regimens of 1250 mg/m^2 to assess safety in women at least 65 years of age, half of whom had received prior systemic treatments. The lower dose afforded similar rates of tumor response with better tolerability in the lower-dose group [48].

Gemcitabine has also been evaluated as a single-agent therapy in multiple trials in both the first-line and refractory/resistant settings at doses ranging from 800 to 1200 mg/m^2 weekly for 3 weeks on a 28-day cycle. RRs varied from 14.5% to 37% with an OS of 21 months in the first-line setting to RRs of 20% to 37.1% with an OS of 11 months in a pretreated setting [49, 50].

Platinum Agents

The efficacy of platinum agents in TNBC documented in the neoadjuvant setting has made them attractive agents for consideration in the metastatic setting [51]. A retrospective study [52] has shown that in patients with metastatic TNBC, platinum-based chemotherapy is associated with improved survival. The triple-negative breast cancer trial (TNT), recently presented at the 2014 SABCS, randomized 376 unselected patients with metastatic TNBC to carboplatin versus docetaxel. In the overall analysis, median PFS was not statistically significant ($P = 0.29$; 3.1 vs. 4.5 months for the carboplatin and docetaxel arms, respectively). However, for patients with breast cancer susceptibility gene (BRCA) germline mutations, the ORR for the carboplatin arm was more than double that of the docetaxel arm (ORR, 68.0% vs. 33.3%; $P = 0.03$); homologous recombination deficiency (HRD) scores did not predict a benefit [53]. Moving forward, it will also be important to delineate which patients are most likely to derive benefit from platinum-based therapy and whether BRCA germline mutations or HRD biomarkers can predict who is most likely to benefit.

New Approaches for Triple-Negative Breast Cancer (TNBC): PARP Inhibitors and Beyond

Subtypes of TNBC have been described on the basis of histopathological features and gene expression profiling, highlighting the heterogeneity, and complexity of these tumors [54]. Four distinct breast cancer subtypes (luminal A, luminal B, HER2 enriched, and basal-like) of prognostic and predictive significance were first described by Perou et al. [2] in 2000 using microarray analysis. Of the four subtypes, basal-like tumors are typically of the triple-negative phenotype, and the vast majority (approximately 80%) of TNBCs are of the basal-like subtype [55]. In analyzing gene expression profiles of TNBC, Lehmann et al. [56] identified six distinct molecular subtypes (basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor). These molecular subtypes were refined into four tumor-specific subtypes (basal-like 1, basal-like 2, mesenchymal, and luminal androgen receptor) following histopathology and laser capture microdissection, which identified infiltrating lymphocytes and tumor-associated stromal cells contributing to the immunomodulatory and mesenchymal stem-like subtypes, respectively [55]. In addition to microarray-based studies, the genomic landscape of

this disease has been extensively interrogated, resulting in the identification of alterations that add to our burgeoning knowledge of TNBC [57]. The features and alterations unique to these various subtypes have been incorporated into many ongoing, rationally designed trials to refine treatment strategies. In this section, we discuss notable novel approaches in the treatment of TNBC.

PARP Inhibitors

The effectiveness of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors has been of great interest in TNBC, especially in women with BRCA germline mutations. Iniparib, initially thought to be a PARP inhibitor, was studied in a phase II study in an unselected population of patients with metastatic TNBC and showed improved PFS (3.6–5.9 months) and OS (7.7–12.3 months), prompting a larger phase III study that did not show improved PFS or OS [58, 59]. Subsequent definitive preclinical studies, however, demonstrated that in fact iniparib has weak, if any, PARP inhibitory effects [60]. Although these studies nearly put an end to the development of PARP inhibitors in breast cancer, several agents, including olaparib and veliparib among many others, are now being actively developed [61]. An ongoing phase III trial evaluating PARP inhibition in BRCA-mutant MBCs including olaparib, OlympiAD (NCT02000622), has reached its primary endpoint. In this trial, 302 patients with inherited BRCA mutations who had MBC that was either ER-positive or triple-negative were randomly assigned to receive olaparib tablets or standard chemotherapy (capecitabine, vinorelbine, or eribulin) until the cancer worsened or the patient developed severe side effects [62]. Tumors shrank in approximately 60% of the patients who received olaparib, compared with 29% of those who received chemotherapy. At a median follow-up of approximately 14 months, patients who received olaparib had a 42% lower chance of cancer progression than those who received chemotherapy. The median time to progression was 7 months with olaparib and 4.2 months with chemotherapy. For women who have a BRCA germline mutation with metastatic ovarian cancer, the first PARP inhibitor, olaparib, has already been approved based on a phase II study and compelling ORR [63].

Ongoing efforts are focused on molecular diagnostics beyond BRCA testing to predict benefit from PARP inhibition, as well as the application of PARP inhibitors in a broader population. Recently, the efficacy of olaparib monotherapy in patients with HER2-negative metastatic breast cancer with germline BRCA mutation (gBRCAm) or lesional BRCA mutation (lBRCAm) was reported [64]. Retrospective review charts for patients with MBC who had received ≥2 chemotherapy lines for MBC were compared with genomic studies. lBRCAm was detected in 12 of 19 patients (8 Foundation One, 3 Foundation Act, and 1 Guardant 360), although somatic versus germline nature was not determined, and gBRCAm was detected in 7 of 19 patients. In this retrospective analysis conducted from March 2014 to August 2017, 319 patients with MBC were treated with targeted therapy based on molecular abnormality. Overall, 19 of 319 (6%) patients who received olaparib for MBC had gBRCAm or lBRCAm. The median age was 45.1 years (range, 31–67), and the median number of previous lines of treatment for MBC was 4 (range, 2–8). Olaparib was dosed at 300 mg orally twice daily until disease progression. For 12 of 19 patients (63%), the PFS ratio was ≥1.3 (95% CI: 0.7–3). For 9 of 12 patients (75%) with lBRCAm, the PFS ratio increased. Six-month PFS was 69.4% [95% CI: (40%, 86.4%)], and 6-month OS was 88.8% [95% CI: (62.1%, 97.1%)]. There was no grade 3–4 toxicity. Olaparib monotherapy provided a statistically significant increment of PFS in nearly two-third (63%) of heavily pretreated MBC patients harboring gBRCAm and lBRCAm. Interestingly, 75% of the patients with lBRCAm experienced an improvement in PFS with minimal toxicity. Further research is necessary to extend olaparib approval for lBRCAm in MBC patients.

A recent meta-analysis was conducted to better evaluate the activity, efficacy, and safety of single-agent PARPi in patients with BRCA-mutated HER2-negative MBC [65]. A systematic search of MEDLINE, Embase, and conference proceedings up to January 31, 2018 was conducted to identify randomized controlled trials investigating single-agent PARPi versus chemotherapy in BRCA-mutated HER2-MBC. Two randomized controlled trials with 733 patients were included: OlympiAD (olaparib) and EMBRACA (talazoparib). In both trials, physician's choice monochemotherapy (i.e., capecitabine, eribulin, gemcitabine, or vinorelbine) was the comparator. Compared with monochemotherapy, PARPi significantly improved PFS (HR 0.56, 95% CI 0.45–0.70) and ORR (OR 4.15, 95% CI 2.82–6.10); however, there was no difference in OS (HR 0.82, 95% CI 0.64–1.05). Adverse events of any grade (OR 1.37, 95% CI 0.49–3.85) and of grade 3–4 (OR 0.76, 95% CI 0.43–1.33) were not significantly different between the arms. Use of PARPi was associated with a significantly increased risk of anemia (any grade: OR 3.07, 95% CI 1.16–8.10; grade 3–4: OR 7.69, 95% CI 2.55–23.19) and any grade of headache (OR 1.57, 95% CI 1.06–2.33), but was associated with a reduced risk of neutropenia (any grade: OR 0.53, 95% CI 0.29–0.96; grade 3–4: OR 0.40, 95% CI 0.23–0.67) and any grade of palmar-plantar erythrodysesthesia syndrome (OR 0.04, 95% CI 0.02–0.10). No significant differences in other types of adverse events were observed between PARPi and monochemotherapy. Patients treated with PARPi experienced a significantly delayed time to clinically meaningful quality of life deterioration (HR 0.40, 95% CI 0.29–0.54). Although the optimal sequence is still to be determined, PARPi will likely be considered a standard of care in this patient population in the upfront setting.

Androgen Receptor Blockers

The androgen receptor (AR) has been identified as a possible predictive biomarker for antiandrogen therapy in breast cancer. The Translational Breast Cancer Research Consortium (TBCRC) 011 study [66], a phase II study investigating bicalutamide in AR-positive, ER-negative breast cancer, found a clinical benefit rate (defined as complete or partial response or stable disease for >6 months) of 19% (95% CI 7–39%), suggesting an antitumor effect even though only 12% of the 424 patients tested had AR positivity. Similarly, in a phase II trial of enzalutamide, a potent AR inhibitor, the 24-week clinical benefit rate was 29% (95% CI 20–41%), and a median PFS of 14 weeks (95% CI 8–19 weeks) was observed in the 57 evaluable patients [67]. In this study, an androgen-driven diagnostic gene signature was associated with greater clinical benefit, and the phase III ENDEAR trial of paclitaxel plus enzalutamide/placebo and enzalutamide monotherapy has been initiated in diagnostic signature-positive TNBC (NCT02929576) [68].

Antibody–Drug Conjugates

Antibody–drug conjugates (ADCs) are a novel class of cancer therapeutics that combine the selectivity of a targeted treatment with the cytotoxicity of chemotherapy, resulting in an improved therapeutic index. Sacituzumab govitecan (IMMU-132) is an anti-Trop-2 ADC consisting of humanized IgG antibody against Trop-2 linked to SN-38, an active metabolite of irinotecan. The Trop-2 protein is an epithelial cancer antigen that is highly expressed in a majority of TNBC compared with normal tissues and is associated with a poor prognosis and aggressive disease [69]. In the first in-human phase I trial, sacituzumab govitecan had an acceptable safety profile and evidence of efficacy, including one confirmed response and two minor responses in three of four patients with TNBC [70].

In the ongoing multicenter phase II trial, promising PFS of 5.6 months (95% CI 3.6–7.1 months), OS of 14.3 months (95% CI 10.5–18.8 months), and a response rate of 29% were observed in a heavily pretreated (median of five prior therapies) population of TNBC [71]. Sacituzumab govitecan has been given breakthrough therapy and fast-track designation from the FDA, and a phase III international multicenter randomized trial versus treatment of physician's choice in refractory mTNBC is planned for initiation in 2017 (NCT02574455).

A phase I/II basket trial (NCT01631552) investigated the activity of sacituzumab govitecan in patients with HR+/HER2-negative MBC who had ≥1 prior hormonal therapy. Patients received sacituzumab govitecan at a dose of 10 mg/kg on days 1 and 8 of a 21-day cycle until progression or unacceptable toxicity. Fifty-four patients with HR+/HER2-MBC were accrued between February 2015 and June 2017. For metastatic disease, all patients received at least two prior treatments, with a median of three prior hormonal agents and two prior chemotherapy regimens. Prior treatments in any setting included taxane (93%), anthracycline (69%), and CDK 4/6 inhibitors (69%). Sixteen patients died, 27 are in long-term follow-up, and 11 are still on treatment. The median number of doses was 11 (range 1–74). Treatment was generally well tolerated, with no treatment-related deaths. Based on the currently available adverse event data, grade ≥3 toxicity (≥10%) included neutropenia and leukopenia; there was 1 case each of grade ≥3 diarrhea and febrile neutropenia. As of data cutoff on 31 December 2017, ORR was 31% (17 PRs/54) by local assessment, and the clinical benefit rate (CBR: PR + SD > 6 months) was 48%. For patients who received CDK inhibitors, ORR was 24% (9 PRs/37). In conclusion, sacituzumab govitecan as a single agent induced objective responses in heavily pretreated HR+/HER2neg MBC and was well tolerated with a safety profile consistent with previous reports [72].

Glembatumumab vedotin (CDX-011) is a fully human IgG2 monoclonal antibody with a high affinity for the extracellular domain of glycoprotein nonmetastatic B linked to the microtubule inhibitor monomethyl auristatin E (MMAE). Glycoprotein nonmetastatic B is highly expressed in TNBC compared with normal tissue, predicts breast cancer recurrence, and is associated with reduced overall survival [73]. Early activity was observed in mTNBC and high-gpNMB-expressing tumors in the phase II EMERGE study [58]. The METRIC trial, a randomized phase III study evaluating glembatumumab vedotin versus capecitabine, is ongoing in gpNMB overexpressing TNBC (NCT01997333).

Combination Cytotoxic Therapy

Combination therapies generally increase RR and TTP but with a concomitant increase in toxicity. Moreover, a critical shortcoming of studies in this area is the use of study designs in which the combination is compared with one or the other of the agents alone. The lack of comparison between sequential use of both agents and the combination biases these studies in favor of the combination. Many cytotoxic combinations have been assessed in the metastatic setting; however, only a few have shown synergy in phase III studies to prolong OS over single-agent cytotoxics with manageable toxicities, and these regimens will be reviewed here.

The low myelotoxicity of capecitabine makes it an attractive agent for combination with other cytotoxics, and preclinical work showing tumor overexpression of thymidine phosphorylase by taxanes suggested that this was an opportunity for synergy. Patients pretreated with anthracycline (prior paclitaxel was permitted) were randomly assigned to capecitabine/docetaxel or docetaxel monotherapy, and the combination resulted in an increased RR, TTP, and OS. However, the improvement in efficacy was at the cost of more grade 3 adverse events (71% vs. 49%) in the

combination arm. The 1250 mg/m^2 twice-daily dose of capecitabine may have been too high to use in combination with docetaxel given evidence that 1000 mg/m^2 twice daily of capecitabine monotherapy is equivalent to higher doses in women at least 65 years old. Treatment interruption was required in 34% of capecitabine cycles and 27% of docetaxel cycles compared with 20% in the single-agent arm [30]. This trial did not answer the question of whether sequential administration would have had equivalent benefit with less toxicity.

Another study compared the combination of gemcitabine plus paclitaxel to gemcitabine alone in the first-line treatment of metastatic disease. Median survival was 18.6 versus 15.8 months (P = 0.0489) with a longer TTP (6.14 vs. 3.98 months; P = 0.0002) and a higher RR (41.4% vs. 26.2%; P = 0.0002). However, the 22% improvement in OS and 43% improvement in TTP were at the expense of more neutropenia, fatigue, and neuropathy. Again, the trial did not answer the question of whether sequential single-agent therapy would have yielded equivalent results [31]. The study design also precluded comparison with a weekly paclitaxel schedule, which appears preferential to a three-weekly schedule in the advanced setting [31, 74].

Given the proposed deficiency of DNA-repair mechanisms in triple-negative and basal-like tumors, platinum-based chemotherapy combinations have been presented as a strategy to treat these subtypes of MBC. Although phase II studies of carboplatin- or cisplatin-based combination regimens have demonstrated overall RRs ranging from 29% to 41% in triple-negative MBC, these responses are often at the expense of significant hematological and nonhematological side effects, including peripheral neuropathy, nephrotoxicity, and nausea [75, 76]. In light of the high rates of grade 3/4 toxicities for a palliative regimen and absence of prospective phase III data showing improvement in PFS and OS, the use of combination platinum-based therapy in triple-negative MBC warrants further study [77].

In summary, women whose MBC requires cytotoxic therapy have multiple alternatives. Monotherapy is preferable to minimize side effects given the paucity of data comparing combination regimens to sequential use of single agents. Presuming adequate performance status, women with prior exposure to anthracyclines should only receive paclitaxel, albumin-bound paclitaxel, or docetaxel as the first-line treatment for their triple-negative or endocrine-refractory metastatic disease. Women who have progressed through taxane therapy can be treated with alternative microtubule inhibitors such as vinorelbine or eribulin if they do not have prohibitive residual neuropathy. A reasonable alternative is to treat these women with either capecitabine or gemcitabine. Combination cytotoxic regimens should be reserved for women who have good performance status and whose organ function is threatened by rapidly progressive disease.

New Directions in Targeting Angiogenesis

Although numerous studies investigating [78] anti-vascular endothelial growth factor (VEGF) therapy in the neoadjuvant setting have suggested improved pathologic complete response rates, especially in TNBC, studies to date have not demonstrated a survival benefit in the adjuvant setting or metastatic setting. Multiple studies have now been conducted in unselected patients with MBC. The Eastern Cooperative Oncology Group (ECOG) 2100 study [79] found that adding bevacizumab to paclitaxel in unselected patients with MBC improved PFS (11.8 vs. 5.9 months; HR, 0.60; $P < 0.001$) but not OS (26.7 vs. 25.2 months; HR, 0.88; P = 0.16). The regimens in bevacizumab for breast oncology-1 (RIBBON-1) trial [80, 81] showed that adding bevacizumab to chemotherapy in HER2-negative MBC also improved PFS but not OS in the first-line setting; the RIBBON-2 study had similar results in the second-line setting. Subgroup analysis, however, suggested that in patients with TNBC, there may be a trend toward OS benefit (HR, 0.624; P = 0.05) [82].

The phase III IMELDA study randomized patients with HER2-negative MBC to bevacizumab with or without capecitabine after induction with docetaxel and bevacizumab and found that the addition of capecitabine improved PFS (11.9 vs. 4.3 months; $P < 0.001$) and OS (39.0 vs. 23.7 months; P = 0.003) despite premature termination of the study [83]. A recent update [84] at the 2014 SABCS meeting revealed no differences among different subgroups in terms of OS and no significant changes in quality-of-life measures. These results are difficult to apply in clinical practice because there was no control arm investigating capecitabine without bevacizumab. The TANIA phase III study, an investigation of bevacizumab continuation through second-line therapy in patients with HER2-negative MBC, reported that PFS was improved in those continuing bevacizumab (6.3 vs. 4.2 months; P = 0.007); however, OS has not been reported to date [85]. A recent subgroup analysis of the TANIA study presented at the 2014 SABCS meeting suggested a slight benefit in the TNBC populations (median PFS, 4.9 vs. 2.1 months) and that plasma-based VEGF biomarkers did not predict efficacy [86, 87]. The fact there are no data suggesting an improvement in OS in patients receiving bevacizumab compared with those who do not and the failure to identify patients who are more likely to benefit from anti-VEGF therapy have hindered the development of these drugs for MBC.

A key growth factor in angiogenesis is the fibroblast growth factor receptor (FGFR) gene, and this may be an important mechanism of resistance to anti-VEGF therapy. Many genetic aberrations in FGFR have been identified in breast cancer. Approximately 10% of breast cancers will have FGFR aberrations, which are associated with inferior prognosis, especially in luminal-type breast cancers [88]. Several targeted drugs are currently under development to target tumors that have FGFR amplification [89].

Promises of Immune Therapies

The immune system can identify tumor antigens through immune surveillance, a process in which antigen-presenting cells present non–self-antigens to T cells, allowing them to recognize and destroy cells expressing such antigens. A hallmark of oncogenesis is that tumor cells can develop mechanisms to evade such immune recognition [90]. The success of immune checkpoint blockade in certain cancers has served as a proof of concept that immune therapy is a viable therapeutic strategy. Cytotoxic T-lymphocyte antigen (CTLA) inhibitors have shown significant and sustained antitumor activity in melanoma [91]. Blockade of programmed cell death 1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) has also been found to have antitumor activity in certain cancers, with 6–17% overall response rates [92]. The effects of single-agent checkpoint blockade are modest, with only a small fraction of patients having clinically significant responses; however, combination checkpoint blockade with CTLA and PD-1 inhibitors has recently demonstrated synergistic activity, with an ORR of 40% and 31% of patients achieving greater than 80% reduction in their tumors by 12 weeks [93]. These results suggest that combination immune therapy may improve antitumor responses.

Approximately 20% of TNBCs express PD-L1, and the expression of PD-L1 is associated with poor prognosis in patients with breast cancer, particularly those with luminal B and basal-like subtypes, thus making the aggressive phenotype ER-positive and TNBC attractive subtypes in which to investigate PD-L1 blockade [94]. A recent early-phase study [95] presented at the 2014 SABCS meeting demonstrated clinical activity of the anti-PD-L1 monoclonal antibody pembrolizumab in patients with heavily treated TNBC. In this phase IB study of monotherapy with pembrolizumab, the ORR was 18.5% in evaluable patients with TNBC displaying PD-L1 expression (positive staining in stroma or on at least 1% of tumor cells by immunohistochemistry). The median duration of response was not reached, and three responders remained on the study for at least 1 year. These promising results led to the initiation of KEYNOTE-086 (NCT02447003), a larger single-arm phase II study to evaluate the role of pembrolizumab in advanced TNBC and identify the biomarkers of efficacy. The preliminary results of this study were reported at the 2017 ASCO annual meeting. Of the 170 patients enrolled, 44% had ≥3 prior lines of therapy, 74% had visceral metastases, and 62% had PD-L1+ tumors. ORR was 5% regardless of PD-L1 expression: 0.6% CR, 4% PR, 21% SD. The disease control rate was 8% (95% CI: 4–13). Median PFS and OS were 2.0 months (95% CI: 1.9–2.0) and 8.9 months (95% CI: 7.2–11.2), with 6-month rates of 12% and 69%, respectively. ORR was numerically lower in patients with poor prognostic factors (e.g., high LDH and liver/visceral metastases) [96]. In addition, KEYNOTE-119 (NCT02555657), a randomized phase III study of pembrolizumab versus physician's choice single-agent chemotherapy in pretreated advanced TNBC, is estimated to complete recruitment in late 2017. Finally, atezolizumab has also shown efficacy as a single agent in PD-L1-positive tumors in a phase IA trial, in which a cohort of 12 patients with mTNBC were treated, with an ORR of 33% [97].

Abemaciclib, a selective inhibitor of CDK4/6, is approved to treat HR+, HER2- metastatic breast cancer patients as monotherapy and in combination with fulvestrant. In preclinical models, abemaciclib administered with PD-L1 antibody therapy synergistically induced an antitumor response and immunological memory. A phase I study (NCT02079636) of abemaciclib plus pembrolizumab, a programmed death receptor 1 (PD-1) antibody, demonstrated stable disease in 65% of patients with stage IV MBC along with a generally manageable safety profile. The results were updated at the ASCO 2018 annual meeting [98]. Patients received the maximum tolerated dose of abemaciclib 150 mg twice daily orally plus pembrolizumab 200 mg on day 1 of each 21-day cycle. Twenty-eight patients with HR+, HER2- MBC with 1–2 prior chemotherapy regimens, measurable disease, adequate organ function, ECOG PS ≤1, and no prior treatment with CDK4/6 or PD-1/PD-L1 inhibitors were enrolled in the MBC cohort. Abemaciclib plus pembrolizumab demonstrated a generally manageable safety profile in patients with HR+, HER2- MBC. The single-agent toxicity profiles reported previously were not exacerbated, and no new safety signals were detected. Initial ORR was 14.3%. Assessment of the effectiveness of this novel combination with reference to PD-L1 status for the treatment of patients with HR+, HER2- MBC is ongoing (Clinical trial NCT02779751).

At the 2018 ESMO annual meeting, Schmid et al. presented the results of the phase III trial in triple-negative metastatic breast cancer [99]. In this phase III trial, patients with untreated metastatic, triple-negative breast cancer were randomized to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Atezolizumab plus nab-paclitaxel prolonged progression-free survival in both the intention-to-treat population and the PD-L1-positive subgroup. In the intention-to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; $P = 0.002$); among patients with PD-L1-positive tumors, the median progression-free survival was 7.5 months and 5.0 months, respectively (hazard ratio 0.62; $P < 0.001$). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69–1.02; $P = 0.08$); among patients with PD-L1-positive tumors, the median overall sur-

vival was 25.0 months and 15.5 months, respectively (hazard ratio 0.62; 95% CI, 0.45–0.86).

The combination of paclitaxel and a LAG-3 fusion protein (eftilagimod alpha) as a first-line chemoimmunotherapy in patients with MBC was recently reported at the 2018 ASCO annual meeting [100]. Eftilagimod alpha (Efti, previously IMP321) is a recombinant LAG-3Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. The activation of the dendritic cell network with Efti the day after chemotherapy may lead to stronger antitumor CD8 T-cell responses. The authors have reported the final results of the safety run-in of a phase IIb trial in patients with hormone receptor-positive MBC receiving weekly paclitaxel as first-line chemotherapy. In the safety run-in phase, 15 patients with MBC received paclitaxel (80 mg/m^2; D1, D8, D15; IV) in a 4-week cycle in conjunction with either 6 mg (n = 6; cohort 1) or 30 mg (n = 9; cohort 2) of Efti injections (D2 and D16; SC) for 6 cycles. Patients without progressive disease could continue for a maximum of 12 additional Efti injections every 4 weeks. Blood samples for pharmacokinetics and immunomonitoring were taken at cycles 1, 4, and 6. The primary endpoint was the determination of the recommended phase II dose of this combination. Between January and October 2016, 15 patients were enrolled. A majority (67%) of the patients were pretreated with hormonal therapy. Nine (67%) patients had a serious adverse event, of which 1 was related to paclitaxel (dizziness grade 3) and 1 to Efti (cytokine release syndrome grade 1). No grade 4 adverse events were observed, and four grade 3 adverse events in 4 patients were related to Efti. Grade 1 and 2 injection site reactions were the most common Efti-related adverse events and occurred in 14 patients (93%). Increased numbers of circulating monocytes, dendritic cells, and CD8 T-cells as well as increased cellular activation were observed. This sustained (≥6 months) activation of the cellular response was associated with increased Th1 marker levels (IFN-g, CXCL10) in the plasma. Seven patients (47%) had a partial response (mean duration of 9 months). The disease control rate was 87%. Overall, 30 mg of Efti SC is the recommended phase II dose and is currently being investigated in the ongoing phase II of the study.

Conclusion

An understanding of the biology of breast cancer has led to important advances in the development of targeted therapies; however, MBC remains an incurable disease for most patients. As we learn to use genomic medicine and harness the immune system to guide drug development, it is important to start combining drugs using biologically informed translational science to optimize patient outcomes.

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Treatment of HER2-Overexpressing Metastatic Breast Cancer

32

Adnan Aydiner

Introduction

Human epidermal growth factor receptor-2 (HER2) is amplified or overexpressed in 15–25% of breast cancers. Historically, the overexpression of HER2 has been associated with an increased risk of disease recurrence and worse overall prognosis. Therapies that target HER2 have become important in the treatment of metastatic breast cancer (MBC) and have altered the natural course of HER2-positive breast cancer. HER2 protein overexpression and/or gene amplification remain the most important predictors of response to HER2-targeted therapies. Quality HER2 testing is required for the appropriate identification and management of HER2-positive patients. The initial success of trastuzumab in improving survival rates led to the clinical development of lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) [1–3]. HER2- and estrogen-targeted treatment combinations improve progression-free survival (PFS) but not overall survival (OS) [4, 5]. Chemotherapy (CT) regimens combined with HER2-targeted therapy can induce high overall response rates (ORR), extend the time to progression (TTP)/PFS, and prolong OS. When the best treatment response has been obtained (usually after 6–12 months of combined therapy), cytotoxic chemotherapy is stopped, and anti-HER2 therapy is continued, although the optimal duration of treatment is unknown. Following discontinuation of chemotherapy, endocrine therapy must be added to an HER2-directed therapy of patients whose tumors are also hormone receptor-positive. Further treatments for patients with MBC who progress on an HER2-directed therapy must be based on individual considerations [1–3].

A key first step in appropriately deciding on the use of HER2-targeted therapy is the accurate determination of HER2 overexpression by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). The current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, updated in 2018, define HER2 positivity as 3+ on IHC (defined as uniform intense membrane staining of >10% of invasive tumor cells) or amplified on FISH (an HER2: chromosome enumeration probe [CEP] 17 ratio of ≥2.0, or <2.0 plus average HER2 copy number ≥6 signals/cell) [6].

First-Line Treatment

The trial by Slamon et al. and other randomized controlled trials of trastuzumab observed a benefit for HER2-targeted therapy combinations [7]. Other agents that improve survival include lapatinib and the combination of trastuzumab plus pertuzumab.

There are a number of effective options: single-agent chemotherapy and anti-HER2 agent(s). Taxanes [7], vinorelbine [8], and capecitabine [9, 10] are generally preferred regimens with anti-HER2 partners. Double-agent chemotherapy with HER2-targeted agents is generally avoided because PFS is improved at the cost of significantly increased toxicity [11].

Many clinically important randomized trials of first-line treatments for HER2 MBC, including trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine (T-DM1), and mammalian target of rapamycin (mTOR) inhibitor (everolimus), have affected medical practice (Table 32.1).

Trastuzumab

The HER2 proto-oncogene encodes a 185-kDa transmembrane receptor protein that is structurally related to the epidermal growth factor receptor (EGFR). HER2 in cancer cells can be activated by either heterodimerization with other ligand-bound HER family members (including HER1, HER3, and HER4) or, when overexpressed, by homodimerization. Upon binding, ligand-induced receptor homo- or heterodimerization activates a phosphorylation-signaling

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Table 32.1 First-line randomized phase III studies in HER2-positive metastatic breast cancer patients

Trial	Study arms	ORR		PFS		OS	
		%	*P*	Months		Months	
Slamon [7]	Trastuzumab + chemotherapy	50	$P < 0.001$	7.4	RR = 0.51 $P < 0.001$	25.1	RR = 0.80 $P = 0.046$
	Chemotherapy	32		4.6		20.3	
HERNATA [8]	Trastuzumab + docetaxel	59.3	NS	15.3	HR = 0.94 $P = 0.67$	35.7	HR 1.01 $P = 0.98$
	Trastuzumab + vinorelbine	59.3		12.4		38.8	
NCIC CTG MA-31 [22]	Lapatinib + taxane	54	NS	9.0	HR 1.37 $P = 0.001$	NR	HR 1.28 $P = 0.11$
	Trastuzumab + taxane	55		11.3		NR	
CLEOPATRA [27]	Pertuzumab + trastuzumab + docetaxel	80.2	$P = 0.0001$	18.7	HR 0.69 $P < 0.0001$	56.5	HR 0.66 $P = 0.0001$
	Placebo + trastuzumab + docetaxel	69.3		12.4		40.8	
MARIANNE [33]	Trastuzumab + taxane	67.9	NR	13.7	HR 0.91 $P = 0.31$	NR	HR 0.86 *P*=NR
	T-DM1 + placebo	59.7		14.1	HR 0.87 $P = 0.14$	NR	HR:0.82 *P*=NR
	T-DM1 + pertuzumab	64.2		15.2		NR	
BOLERO-1 [37]	Everolimus + trastuzumab + paclitaxel	NR	NS	15 ER(−) 20.3	HR 0.89 $P = 0.11$ ER(−) HR: 0.66 $P = 0.049$	NR	NR
	Placebo + trastuzumab + paclitaxel	NR		14.5 ER (−) 13.1		NR	

ORR objective response rate, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *RR* relative risk, *ER* estrogen receptor, *NR* not reported, *NS* nonsignificant, *T-DM1* trastuzumab emtansine

cascade, leading to enhanced responsiveness to stromal growth factors and oncogenic transformation. Downstream signaling regulates the transcription of genes responsible for cell proliferation, survival, angiogenesis, invasion, and metastasis [12]. Trastuzumab inhibits the proliferation of human tumor cells that overexpress HER2 in vitro and in animals. Trastuzumab binds to subdomain IV of HER2 to disrupt ligand-independent signaling and mediate antibody-dependent cellular cytotoxicity [12]. The EGFR family is composed of four homologous receptors: ERBB1 (EGFR/HER1), ERBB2 (HER2/*neu*), ERBB3 (HER3), and ERBB4 (HER4). Three receptors have been implicated in the development of cancer; the role of ERBB4 is less clear. Six different ligands, known as EGF-like ligands, bind to EGFR. After ligand binding, the ERBB receptor is activated by dimerization between two identical receptors (i.e., homodimerization) or between different receptors of the same family (i.e., heterodimerization). Dimerization leads to the phosphorylation of several intracellular catalytic substrates, including members of the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt/PTEN family, and other important signaling pathways that regulate apoptosis, protein synthesis, and cellular proliferation. The morphologies of the extracellular domains of the four EGFRs are nearly identical, but the EGFRs vary considerably in functional activity. For instance, ERBB3 lacks inherent kinase function but can heterodimerize with other ERBB receptors. The ERBB2-ERBB3 dimer, which is considered the most active ERBB signaling dimer, is fundamental for ERBB2-mediated signaling in tumors with ERBB2 amplification [12].

Single-agent trastuzumab treatment may be reasonable when avoiding the cytotoxic side effects of chemotherapy is desirable but may result in poorer outcomes compared with trastuzumab administered in combination with chemotherapy. In the HERTAX trial, patients who were randomly assigned treatment with trastuzumab followed by docetaxel had lower median OS (20 vs. 31 months) and significantly lower ORR (53% vs. 79%) than those receiving docetaxel plus trastuzumab [13]. However, sequential treatment was associated with lower toxicity. This trial did not address the efficacy of transitioning from single-agent trastuzumab to trastuzumab plus single-agent chemotherapy at the time of disease progression.

The JO17360 trial evaluated the efficacy and safety of sequential therapy versus combination therapy as first-line therapy. Trastuzumab was continued along with docetaxel in the sequential arm. The Independent Data Monitoring Committee recommended stopping enrollment because PFS and OS were greater in the combination arm than in the sequential arm [14].

In another phase III randomized trial (SAKK 22/99) 175 patients with measurable/evaluable HER2-positive advanced disease without the previous HER2-directed therapy were randomized to trastuzumab alone followed, at disease progression, by the combination with chemotherapy or upfront trastuzumab plus chemotherapy. The outcomes of patients receiving sequential trastuzumab-chemotherapy or upfront combination were similar, and they failed to demonstrate superiority of the sequential approach. Nevertheless, these results suggest that chemotherapy and its toxicity can be deferred [15].

These clinical data suggest that a monoclonal antibody-chemotherapy combination is preferable to initiating treatment with single-agent trastuzumab. If a patient progresses on single-agent trastuzumab therapy, adding single-agent chemotherapy to trastuzumab is an option. The main characteristics and efficacy findings from these trials are summarized in Tables 32.1 and 32.2.

Trastuzumab Plus Chemotherapy

Trastuzumab is more active when used in combination with many chemotherapeutic agents, resulting in significantly improved ORR and OS. In the only first-line phase III trial to compare an HER2-targeted therapy plus chemotherapy with chemotherapy alone, Slamon et al. observed improved survival, TTP, and ORR in the trastuzumab arm (Fig. 32.1) [7]. Patients were randomly assigned to receive standard chemotherapy alone or standard chemotherapy plus trastuzumab. Those who had not previously received adjuvant therapy with an anthracycline were treated with an anthracycline and cyclophosphamide with or without trastuzumab. Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone or paclitaxel with trastuzumab. The addition of trastuzumab to chemotherapy was associated with a longer PFS (7.4 months vs. 4.6 months; $P < 0.001$), a higher ORR (50% vs. 32%, $P < 0.001$), a longer duration of response (9.1 months vs. 6.1 months; $P < 0.001$), a lower rate of death at 1 year (22% vs. 33%, $P = 0.008$), longer survival (25.1 months vs. 20.3 months; $P = 0.046$), and a 20% reduction in the risk of death. The most important adverse event was cardiac dysfunction. The addition of trastuzumab was not associated with increases in other chemotherapy-associated toxicities. The cardiac dysfunction was New York Heart Association class III or IV and occurred in 27% of the group administered anthracycline, cyclophosphamide, and trastuzumab; 8% of the group administered anthracycline and cyclophosphamide alone; 13% of the group administered paclitaxel and trastuzumab; and 1% of the group administered paclitaxel alone. This trial demonstrated that trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic HER2-overexpressing breast cancer. The combination of an anthracycline and trastuzumab is not recommended because of the risk of significant cardiotoxicity [7].

The HERNATA study compared taxane- and non-taxane-based chemotherapy backbones in association with trastuzumab [8]. A total of 284 patients were randomized to trastuzumab plus either docetaxel or vinorelbine. OS was similar in both arms, but vinorelbine was much better tolerated; significantly, more patients in the docetaxel arm experienced grade 3–4 toxicities and discontinued therapy.

Table 32.2 Chemotherapy (CT) plus trastuzumab (Tras) versus Tras followed by CT in HER2-positive metastatic breast cancer

TRIAL Author	J017360 Inoue [14]	HERTAX Hamberg [13]	SAKK 22/99 Pagani [15]
Number of patients	112	101	175
Treatment	Tras + Doc vs Tras → Tras + Doc	Tras + Doc vs Tras → Doc	Tras + CT vs Tras → Tras + CT
Line of treatment	1st line	1st line	1st, 2nd, or 3rd line
Response rate	67.9% (comb) vs. 47.2% (seq)	58% (comb) vs 38% (seq)	Not reported
Median PFS or TTP following both Tras and CT	PFS 14.6 mo (comb) vs PFS 12.4 mo (seq) HR 4.24; $P < 0.01$	PFS 9.4 mo (comb) vs. PFS 9.9 mo (seq)	TTP 10.3 mo (comb) vs TTP 12.2 mo (seq)
Median overall survival	Not reached. HR 2.72; ($P = 0.04$) in favor of comb	30.5 mo (comb) vs 19.7 mo (seq)	36.3 mo (comb) vs 35.6 mo (seq)

Doc Docetaxel, *PFS* progression-free survival, *TTP* time to progression, *mo* month, *comb* combination, *seq* sequential, *HR* hazard ratio

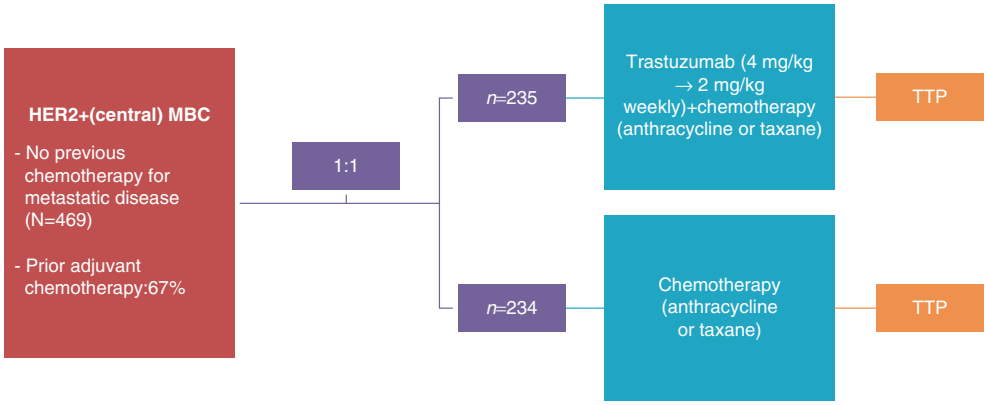

Fig. 32.1 "Trastuzumab plus chemotherapy (anthracycline or taxane)" versus "chemotherapy (anthracycline or taxane)" (SLAMON) [6]. *HER2* human epidermal growth factor receptor-2, *MBC* metastatic breast cancer, *TTP* time to disease progression

Efficacy was similar. In a smaller study that compared trastuzumab with either vinorelbine or a weekly taxane (paclitaxel or docetaxel), vinorelbine was associated with greater hematological toxicity [16]. Weekly paclitaxel has less toxicity and is better tolerated than three-weekly docetaxel. Data for patients who cannot use a taxane are limited, and the selection of an appropriate chemotherapy agent should be guided by patient and provider preferences.

Trastuzumab is generally not given in combination with multi-agent chemotherapy because of the excess risk of toxicity [17, 18]. No trials have demonstrated that this approach improves OS. Two phase III trials explored the value of combination chemotherapy plus trastuzumab. The Breast Cancer International Research Group 007 study investigated the addition of carboplatin to docetaxel and trastuzumab [17]. The response rates were identical in both arms, with no significant differences in OS.

Robert et al. randomized 196 patients to trastuzumab and paclitaxel with or without carboplatin [18]. The response rate was higher in the triple-therapy arm; no significant difference in OS was observed. The increased toxicity of doublet chemotherapy limits the clinical role of this treatment strategy.

The single most important contraindication to HER2-targeted therapy is decreased left ventricular ejection fraction (LVEF) and/or clinical evidence of congestive heart failure arising from low LVEF [19]. The University of Texas M.D. Anderson Cancer Center evaluated the cardiac safety of a long-term trastuzumab therapy in patients with HER2-overexpressing MBC. The median cumulative time of trastuzumab administration was 21.3 months. The median follow-up was 32.6 months (range, 11.8–79.0 months). Among the patients, 28% experienced a cardiac event (CE): 15.6% with grade 2 cardiac toxicity and 19 patients (10.9%) with grade 3 cardiac toxicity. With trastuzumab discontinuation and appropriate therapy, all but three patients had improved LVEF or diminished symptoms of congestive heart failure. Baseline LVEF was significantly associated with CEs (hazard ratio, 0.94; $P = 0.001$). The risk of CE among patients receiving concomitant taxanes was higher early in the follow-up period and subsequently declined. This toxicity was reversible in the majority of patients. Additional treatment with trastuzumab can be considered after the recovery of cardiac function among patients who experience CE (Tables 32.3 and 32.4).

In conclusion, HER2-targeted therapy in combination with chemotherapy in the first-line setting is associated with improvements in the response rate, PFS, TTP, and OS when compared with chemotherapy alone. These data support the use of HER2-targeted therapy in combination with chemotherapy for the first-line treatment of MBC.

Table 32.3 Dosage dose modification of trastuzumab based on asymptomatic left ventricular ejection fraction decrease from baseline

Relationship of left ventricular ejection fraction (LVEF) to the lower limit of normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	≤10 percentage points	10–15 percentage points	≥15 percentage points
Within a facility's normal limits	Continue	Continue	Hold and repeat MUGA/ECHO after 4 weeks[c]
<6% below LLN	Continue[a]	Hold and repeat MUGA/ECHO after 4 weeks[a, b]	Hold and repeat MUGA/ECHO after 4 weeks[c]
≥6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks[c]	Hold and repeat MUGA/ECHO after 4 weeks[b, c]	Hold and repeat MUGA/ECHO after 4 weeks[b, c]

[a]Consider cardiac assessment. Cardiotoxicity associated with trastuzumab typically responds to appropriate medical therapy but may be severe and lead to cardiac failure
[b]After two holds, consider permanent trastuzumab discontinuation
[c]Refer to cardiologist

Table 32.4 Dosage dose modification of trastuzumab and pertuzumab combination based on asymptomatic left ventricular ejection fraction decrease from baseline

	Trastuzumab and pertuzumab		
Left ventricular ejection fraction	Action	LVEF at reassessment	Dose
<40% and asymptomatic	Pause and repeat MUGA in 3 weeks[b]	>45% or 40–45% and <10% ↓ from baseline	Restart[b]
40–50%[a] and ≥10% points below baseline and asymptomatic		<40% or 40–50%[a] and ≥10% points below baseline or symptomatic	Discontinue[b] Consider for restart.
Symptomatic	Consider discontinuing[b]	Not applicable	Not applicable

[a]In the CLEOPATRA trial, trastuzumab and pertuzumab treatments were paused if LVEF was 40–45% and ≥10% below baseline and asymptomatic. At LVEF reassessment, pertuzumab and trastuzumab may be restarted if LVEF "≥46%" or "40–45% and <10% ↓ from baseline"; otherwise, discontinue
[b]Refer to cardiologist

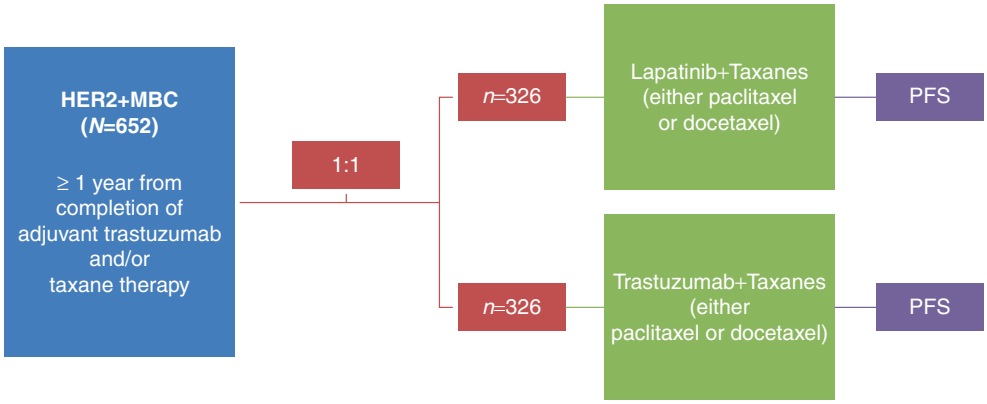

Fig. 32.2 "Taxane plus trastuzumab" versus "taxane plus lapatinib" (NCIC CTG MA-31) [22]. *HER2* human epidermal growth factor receptor 2, *MBC* metastatic breast cancer, *PFS* progression-free survival

Lapatinib

Lapatinib is a small-molecule tyrosine kinase inhibitor that dually targets human epidermal growth factor receptors 1 (EGFR) and HER2. In contrast to trastuzumab, lapatinib enters the cell and binds to the intracellular domain of the tyrosine kinase receptor, completely blocking the autophosphorylation site and halting the downstream cascade. After oral administration, lapatinib reaches peak plasma levels within approximately 4 h and steady-state levels within 6–7 days and has a half-life of 24 h [20].

Single-agent lapatinib is not approved. As a second-line combination therapy, lapatinib and capecitabine improve TTP compared with capecitabine monotherapy for the treatment of HER2-positive MBC refractory to anthracycline-, taxane-, and trastuzumab-containing regimens [20]. Lapatinib plus chemotherapy is also active as a first-line treatment compared with chemotherapy alone but may be inferior to trastuzumab-based therapy [21, 22]. Two phase III trials have explored the use of lapatinib in the first-line setting, one of which compared lapatinib against placebo.

Guan et al. randomized patients who had not been treated with chemotherapy for metastatic disease to weekly paclitaxel (80 mg/m^2 weekly for 3 weeks every 4 weeks) plus either lapatinib (1500 mg daily) or placebo [21]. The addition of lapatinib to paclitaxel significantly improved OS versus paclitaxel plus placebo (treatment hazard ratio, 0.74; P = 0.0124); median OS times were 27.8 months versus 20.5 months, respectively. Median PFS was prolonged by 3.2 months, from 6.5 months with placebo plus paclitaxel to 9.7 months with lapatinib plus paclitaxel (hazard ratio, 0.52; stratified log-rank $P < 0.001$). ORR was significantly higher with lapatinib plus paclitaxel compared with placebo plus paclitaxel (69% vs. 50%, respectively; $P < 0.001$). The incidence rates of grade 3 and 4 diarrhea and neutropenia were higher in the lapatinib plus paclitaxel arm. Only 4% of patients in this group reported febrile neutropenia. Cardiac events were low grade, asymptomatic, and mostly reversible. The incidence rates of hepatic events were similar in both arms. There were no fatal adverse events in the lapatinib plus paclitaxel arm.

The MA.31 trial compared a combination of first-line anti-HER2 therapy (lapatinib or trastuzumab) and taxane therapy (paclitaxel 80 mg/m^2 weekly or docetaxel 75 mg/m^2 3 weekly) for 24 weeks, followed by the same anti-HER2 monotherapy until progression (Fig. 32.2) [22]. A total of 652 patients were accrued, including 537 patients with centrally confirmed HER2-positive tumors. Median follow-up was 21.5 months. Median intention-to-treat (ITT) PFS times were 9.0 months with lapatinib and 11.3 months with trastuzumab. ITT analysis indicated that PFS for lapatinib was inferior to trastuzumab, with a stratified hazard ratio of 1.37 (P = 0.001). In patients with centrally confirmed HER2-positive tumors, median PFS times were 9.1 months with lapatinib and 13.6 months with trastuzumab (hazard ratio, 1.48; $P < 0.001$). More grade 3 or 4 diarrhea and rash were observed with lapatinib ($P < 0.001$). The PFS results were supported by the secondary end point of overall survival, with an ITT hazard ratio of 1.28 (P = 0.11); in patients with centrally confirmed HER2-positive tumors, the hazard ratio was 1.47 (P = 0.03).

In conclusion, as a first-line therapy for HER2-positive MBC, lapatinib combined with taxane was associated with a shorter PFS and more toxicity compared with trastuzumab combined with taxane. Taken together, the evidence suggests that trastuzumab-based regimens should still be considered the standard of care in this setting.

Neratinib

Some reports describe the mechanism of action of neratinib in breast cancer. A pioneering work from Rabindran et al. showed that neratinib inhibited proliferation and EGFR, HER2, HER4, AKT, and MEK phosphorylation in HER2-overexpressing breast cancer cell lines. Upon administration, neratinib targets and covalently binds to the cysteine residues in the ATP-binding pockets of both HER2 and EGFR, which inhibits their activity and results in the inhibition of down-

stream signal transduction events, induces cell cycle arrest and apoptosis, and decreases cellular proliferation in HER2- and EGFR-expressing tumor cells [23].

Neratinib is an oral, irreversible TKI, known as a pan-inhibitor because it interacts with the catalytic domains of several EGFR family members. In the NEfERT-T trial, 479 women with previously untreated recurrent and/or metastatic HER2-positive breast cancer were randomized to neratinib-paclitaxel or trastuzumab-paclitaxel [24]. Women received neratinib (240 mg/d orally) or trastuzumab (4 mg/kg then 2 mg/kg weekly), each combined with paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days). Median progression-free survival was similar in both arms (12.9 months; hazard ratio, 1.02; $P = 0.89$). With neratinib-paclitaxel, the incidence of central nervous system (CNS) recurrences was lower (relative risk, 0.48; $P = 0.002$), and the time to central nervous system metastases was delayed (hazard ratio, 0.45; $P = 0.004$). Common grade 3 to 4 adverse events were diarrhea (30.4% with neratinib-paclitaxel and 3.8% with trastuzumab-paclitaxel), neutropenia (12.9% vs. 14.5%), and leukopenia (7.9% vs. 10.7%). In conclusion, in first-line HER2-positive metastatic breast cancer, neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of PFS. In spite of similar overall efficacy, neratinib-paclitaxel may delay the onset and reduce the frequency of central nervous system progression, a finding that requires confirmation [24].

Pertuzumab

The pairing of HER receptors on the cell surface is referred to as dimerization. HER2 dimerizes with the other members of the HER family, including HER1, HER3, and HER4. HER2–HER3 dimerization is believed to produce the strongest mitogenic signal, resulting in the activation of two key pathways that regulate cell survival and growth: mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) [12]. The humanized monoclonal antibody pertuzumab prevents the dimerization of HER2 with other HER receptors, particularly the pairing of the most potent signaling heterodimer HER2/HER3, thus providing a potent strategy for dual HER2 inhibition. Pertuzumab binds to the extracellular domain of HER2 at a different epitope than trastuzumab [25]. Preclinical data indicated that the combination of pertuzumab and trastuzumab was more active than either antibody alone because the antibodies bind different HER2 epitopes, resulting in a more comprehensive signaling blockade [25]. Phase II studies demonstrated that pertuzumab was generally well tolerated as a single agent or in combination with trastuzumab and/or cytotoxic agents and implied that the combination of pertuzumab and trastuzumab has improved clinical efficacy for early and advanced HER2-positive breast cancer [26].

In the CLEOPATRA trial, the survival of patients with HER2-positive MBC was significantly improved after the first-line therapy with pertuzumab, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel (Fig. 32.3) [27]. In this trial, patients with MBC who had not received previous chemotherapy or anti-HER2 therapy for their metastatic disease were randomly assigned to receive the pertuzumab or placebo combination. The median OS was 56.5 months in the group receiving the pertuzumab combination, compared with 40.8 months (95% CI, 35.8–48.3) in those receiving the placebo combination (hazard ratio favoring the pertuzumab group, 0.68; $P < 0.001$). Median PFS, as assessed by the investigators, improved by 6.3 months in the pertuzumab group (hazard ratio, 0.68; 95% CI, 0.58–0.80). Pertuzumab extended the median duration of response by 7.7 months, as independently assessed. Dual HER2 blockade did not increase the risk of cardiac toxicity. Febrile neutropenia was more common with pertuzumab (13.8% vs. 7.6%), driven mostly by a high incidence in Asian patients (26% vs. 10%), for reasons not currently clearly understood. The rate of grade 3 and 4

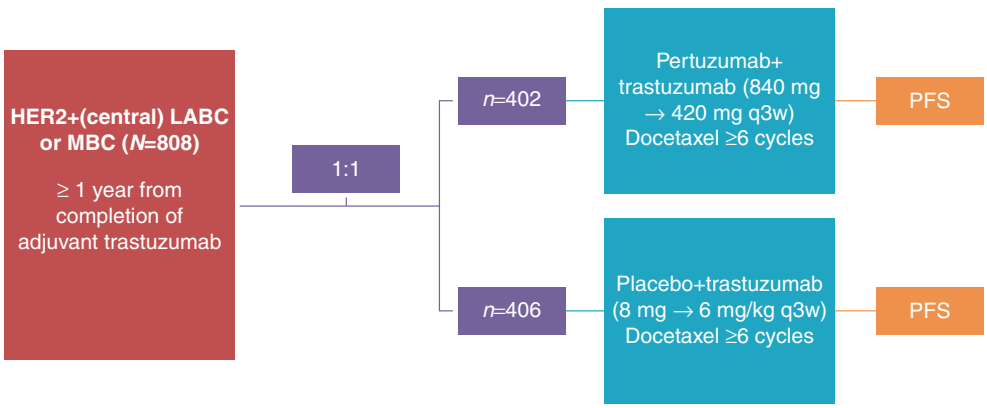

Fig. 32.3 Docetaxel plus trastuzumab versus docetaxel plus trastuzumab plus pertuzumab (CLEOPATRA) [28]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *q3w* every 3 weeks, *PFS* progression-free survival

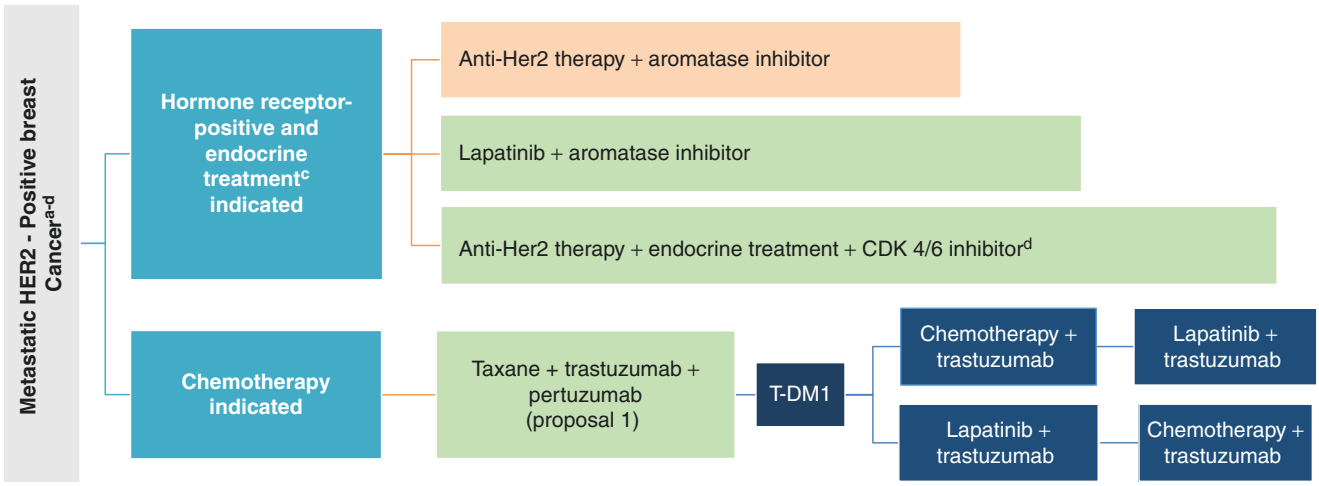

Fig. 32.4 Systemic treatment of recurrent or metastatic HER2-overexpressing breast cancer*

* In HER2-positive metastatic breast cancer (MBC), decision pathways provide recommendations based on the best evidence available at the time of this book edition. Because new data from randomized clinical trials are published continuously, decision pathways must be subject to change. ASCO, ESMO, CCO, and NCCN guidelines are continuously updated and revised to reflect new data and clinical information that may add to or alter current clinical practice standards

[a] Administration of ado-trastuzumab emtansine and pertuzumab was not superior to treatment with chemotherapy + trastuzumab or ado-trastuzumab alone as the first choice treatment in HER2-positive disease. According to the PERTAIN trial, addition of pertuzumab to trastuzumab and endocrine treatment in the first choice prolonged progression-free survival. The addition of pertuzumab in the second choice in patients who did not receive pertuzumab in the first choice provided a minor clinical benefit

[b] T-DM1 may be used as the front-line therapy if the patient develops metastasis within 6 months of finishing adjuvant therapy with anti-HER2 treatment

[c] In premenopausal patients, medical or surgical oophorectomy must be performed

[d] Clinical trials are ongoing for anti-HER2 therapy + endocrine treatment + CDK 4/6 inhibitor, or anti-HER2 therapy + immunotherapy

diarrhea (7.9% vs. 5.0%) was increased in the pertuzumab arm. In conclusion, compared with the addition of placebo, the addition of pertuzumab to trastuzumab and docetaxel significantly improved median OS of patients with HER2-positive MBC (Figs. 32.3 and 32.4).

In the CLEOPATRA study, pertuzumab consistently showed a PFS benefit, independent of biomarker subgroups (hazard ratio < 1.0), including the estrogen receptor-negative and estrogen receptor-positive subgroups [28]. The prognosis was significantly better for patients with high HER2 protein, high HER2 and HER3 mRNA levels, wild-type phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and low sHER2 ($P < 0.05$). PIK3CA was the strongest prognostic indicator, with longer median PFS for patients whose tumors expressed wild-type versus mutated PIK3CA in both the control (13.8 months versus 8.6 months) and pertuzumab groups (21.8 months vs. 12.5 months). The biomarker data demonstrate that HER2 is the only marker suited for patient selection for the trastuzumab plus pertuzumab-based regimen in HER2-positive MBC. HER2, HER3, and PIK3CA were relevant prognostic factors. Interestingly, mutated PIK3CA was associated with worse prognosis when patients were treated with lapatinib plus capecitabine but not with T-DM1, suggesting that T-DM1 might overcome the negative implications of PIK3CA mutations. Novel biomarkers could help refine and optimize therapy for specific subsets of patients in the future.

Antibody-Drug Conjugate (ADC): T-DM1

Most ADC targets are cell surface proteins that are much more abundant on tumor cells than normal cells or tissues. ADCs selectively deliver targeted chemotherapy and could be important components of combination treatment regimens. The three components of ADCs, antibody, linker, and drug must be stable in the circulation for days or weeks. Antibody conjugates are a diverse class of therapeutics comprising a cytotoxic agent linked covalently to an antibody or antibody fragment directed toward a specific cell surface target expressed by tumor cells. Patients whose tumors express high levels of the target antigen are most likely to benefit from treatment. An appropriate antibody for ADC therapeutics allows the antibody-target complex to be internalized by the target cells, followed by drug release [29]. After T-DM1 binds HER2, the HER2/T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin, preventing microtubule polymerization and

suppressing microtubule dynamic instability. T-DM1 retains the mechanisms of action of trastuzumab, including disruption of the HER3/PI3K/AKT signaling pathway and Fcγ receptor–mediated engagement of immune effector cells, which leads to antibody-dependent cellular cytotoxicity [30].

Drugs targeting tubulin or DNA are most often employed to form ADCs. ADCs are an effective method to increase the therapeutic index of these highly potent cytotoxic agents. The drugs used in ADCs must conjugate with a linker that can influence their circulating half-life and safety by minimizing the release of the drug molecule in the circulation. The goal is to optimize the delivery of the conjugate to the target tissue. An under-conjugated antibody decreases ADC potency, whereas a highly conjugated antibody markedly decreases circulating half-life and impairs binding to the target protein, thus decreasing ADC potency and efficacy [31].

T-DM1 is the first ADC to gain regulatory approval for HER2-positive MBC. T-DM1 binds HER2: the complex is internalized and degraded in lysosomes. The mechanisms of ADC action for T-DM1 include all of the effects of trastuzumab plus the effects of the conjugated maytansine derivative.

Evidence supporting a potential role for T-DM1 comes from a phase II trial involving 137 women with HER2-positive MBC who were randomly assigned to trastuzumab plus docetaxel (HT) or T-DM1 [32]. Median PFS times were 9.2 months with HT and 14.2 months with T-DM1 (hazard ratio, 0.59; 95% CI, 0.36–0.97); median follow-up was approximately 14 months in both arms. ORR rates were 58.0% (95% CI, 45.5–69.2) with HT and 64.2% (95% CI, 51.8–74.8) with T-DM1. T-DM1 had a favorable safety profile versus HT, with fewer grade ≥3 adverse events (adverse events; 46.4% vs. 90.9%), adverse events leading to treatment discontinuations (7.2% vs. 34.8%), and serious adverse events (20.3% vs. 25.8%). Grade 3–4 adverse events included neutropenia (6% vs. 62%), febrile neutropenia (0% vs. 24%), and epistaxis (1% vs. 5%) and were less common with T-DM1. T-DM1 was associated with a higher incidence of serious pneumonias (6% vs. 0%) and increased liver transaminases (aspartate aminotransferase, 9% vs. 0%; alanine aminotransferase, 10% vs. 0%). In conclusion, in this randomized phase II study, first-line treatment with T-DM1 for patients with HER2-positive MBC provided a significant improvement in PFS versus HT with a favorable safety profile.

After obtaining regulatory approval for T-DM1 when progression develops after trastuzumab treatment, the logical next step was to evaluate the efficacy of this novel ADC as a first-line treatment in a phase III randomized study. The MARIANNE (NCT01120184) trial recruited more than 1000 patients with HER2-positive MBC who had not received any chemotherapy in the metastatic setting (Fig. 32.5) [33]. In this phase III study, patients with centrally assessed HER2-positive (IHC3+ or ISH+) progressive/recurrent locally advanced BC or previously untreated MBC with a ≥6-month interval since treatment in the (neo) adjuvant setting with taxanes or vinca alkaloids were randomized 1:1:1 to HT (docetaxel or paclitaxel plus trastuzumab), T-DM1 (T-DM1 plus placebo, hereafter T-DM1), or T-DM1 plus pertuzumab at standard doses. The primary end point was PFS assessed by independent review. Comparisons between HT and T-DM1 or T-DM1 plus pertuzumab were considered separately. In each arm, approximately 31% of patients had prior (neo)adjuvant treatment with an HER2-directed therapy, and approximately 37% overall had de novo disease. The response rates were 67.9% in patients who were treated with trastuzumab plus taxane, 59.7% with T-DM1, and 64.2% with T-DM1 plus pertuzumab; median response durations were 12.5, 20.7, and 21.2 months, respectively. PFS and OS were similar across treatment arms. T-DM1 and T-DM1 plus pertuzumab demonstrated noninferior PFS compared with HT but were not superior to HT. The addition of pertuzumab to T-DM1 did

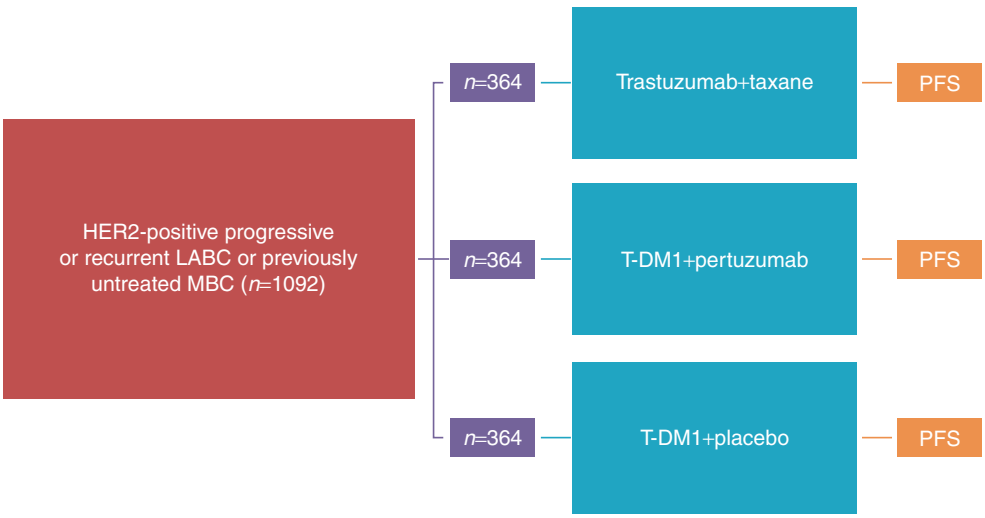

Fig. 32.5 Docetaxel/paclitaxel plus trastuzumab versus T-DM1 versus T-DM1 plus pertuzumab (MARIANNE) [33]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *T-DM1* trastuzumab emtansine, *PFS* progression-free survival

not improve PFS. T-DM1-containing regimens were associated with different toxicity profiles than the control regimen. T-DM1 was better tolerated than HT, with fewer grade 3–4 adverse events and fewer adverse event-related treatment discontinuations. The incidence of grade ≥3 adverse events was numerically higher in the control arm (54.1%) versus the T-DM1 arm (45.4%) and the T-DM1 plus pertuzumab arm (46.2%). No febrile neutropenia and less neuropathy, diarrhea, and alopecia were observed with T-DM1, though these subjects had greater transaminase elevation and thrombocytopenia. Health-related quality of life was maintained for longer with T-DM1. These results suggest that T-DM1 may be an alternative to HT in previously untreated HER2-positive MBC. However, this trial did not include a comparator arm with taxane, trastuzumab, and pertuzumab, which is the standard first-line therapy for HER2-positive MBC.

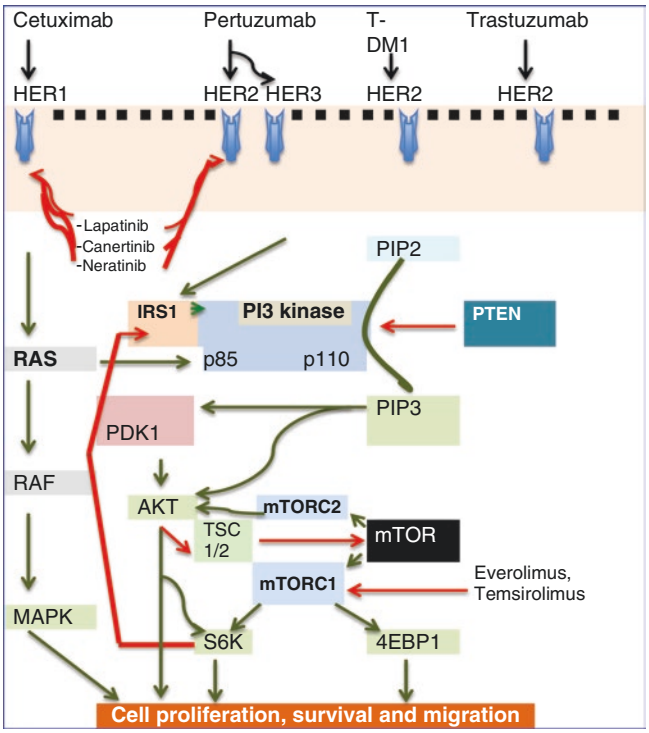

Fig. 32.6 PI3K and mTOR pathways

mTOR Inhibitor: Everolimus

The PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway is an established driver of oncogenic activity in human malignancies and regulates cell growth and proliferation (Fig. 32.6) [34]. In breast cancer, the PI3K/Akt/mTOR pathway has been associated with resistance to endocrine therapy, HER2-directed therapy, and cytotoxic therapy. Therapeutic targeting of this pathway holds significant promise as a treatment strategy. In the BOLERO-2 trial, the mTOR inhibitor everolimus was the first of this class of agents approved for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer [35]. In early studies, everolimus showed antitumor activity in breast cancer and synergy with both trastuzumab and paclitaxel [36].

S6K, ribosomal protein S6 kinase; TSC, tuberous sclerosis protein; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; p85, phosphoinositide-3-kinase regulatory subunit; PDK, phosphoinositide-dependent kinase 1; mTOR, mammalian target of rapamycin; mTORC1/2, mTORC complex 1/2; PI3 kinase, phosphoinositide-3-kinase; AKT, akt murine thymoma viral oncogene; RAS, rat sarcoma; and RAF, rapidly accelerated fibrosarcoma. Epidermal growth factor receptor (EGFR) family is composed of four homologous receptors: *ERBB1* (EGFR/HER1), *ERBB2* (HER2/*neu*), *ERBB3* (HER3), and *ERBB4* (HER4). Three receptors have been implicated in the development of cancer; the role of ERBB4 is less clear. After ligand binding, the ERBB receptor is activated by dimerization between two identical receptors (i.e., homodimerization) or between different receptors of the same family (i.e., heterodimerization).

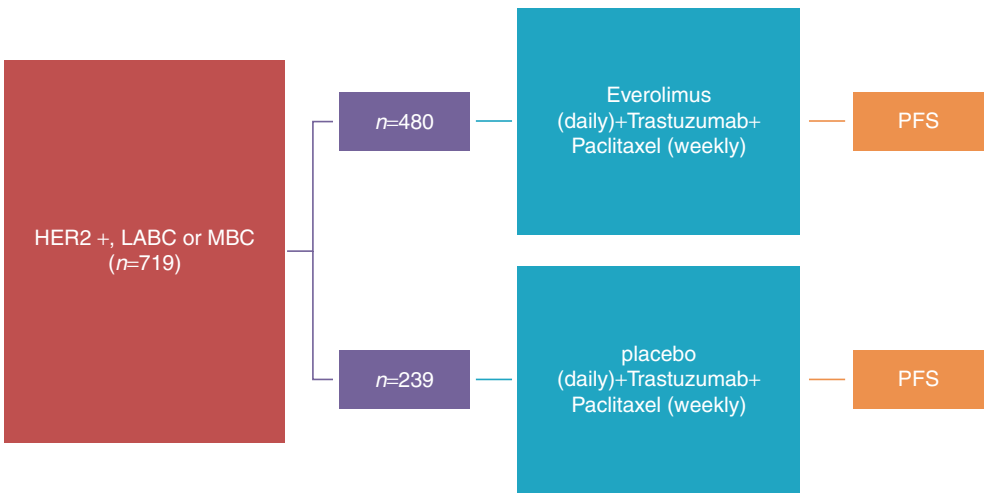

Fig. 32.7 Paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab plus everolimus (BOLERO-1) [32]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *PFS* progression-free survival

Dimerization leads to the phosphorylation of several intracellular catalytic substrates, like Ras/Raf/mitogen-activated 3-kinase (PI3K)/Akt/PTEN family, and other important signaling pathways. PI3K signaling through AKT in breast cancer, including multiple clinically relevant feedback loops. Common drugs that inhibit specific members of the signaling pathway are shown in the figure. Red lines represent inhibition. The morphologies of the extracellular domains of the four EGFRs are nearly identical. The ERBB2-ERBB3 dimer, which is considered the most active ERBB signaling dimer, is fundamental for ERBB2-mediated signaling in tumors with ERBB2 amplification. The mammalian target of rapamycin (mTOR) signaling network regulates cell proliferation and metabolism in response to environmental factors. The growth factor receptor is linked to mTOR signaling via the phosphatidylinositol-3-kinase (PI3K)/Akt family. *PTEN* plays an important role in this pathway; loss of *PTEN* function through mutation, deletion, or epigenetic silencing results in increased activation of AKT and mTOR. The mTOR proteins regulate the activities of the translational regulators 4EBP1 and S6K.

The BOLERO-1 trial evaluated the combination of everolimus with trastuzumab plus paclitaxel as a first-line treatment for women with HER2-positive, locally advanced, or MBC (Fig. 32.7) [37]. In this phase III randomized trial, women with HER2-positive advanced breast cancer, without prior trastuzumab or chemotherapy for advanced disease, were randomized 2:1 to receive either everolimus (10 mg/day) or placebo and weekly paclitaxel plus trastuzumab. The two primary objectives were to compare the investigator-assessed PFS between everolimus plus trastuzumab plus paclitaxel and placebo plus trastuzumab plus paclitaxel in the full population and the hormone receptor-negative subpopulation. A total of 719 patients were randomized to receive everolimus or placebo. Baseline characteristics/prior therapies were balanced between the two treatment arms. The median age was 53 years; 70.5% had visceral metastases, and 43.3% were hormone receptor-negative. Prior therapy included trastuzumab (10.8%) and taxane (24.9%). The baseline characteristics for the hormone receptor-negative subpopulation were generally balanced between the two treatment arms and similar to the overall population. Median study follow-up at the time of analysis was 41.3 months. The study did not meet its primary objective in the full population: median PFS was 15 months (95%: 14.6–17.9) in the everolimus arm versus 14.5 months (95% CI: 12.3–17.1) in the placebo arm (hazard ratio, 0.89; $P = 0.1166$). The hormone receptor–negative subpopulation ($n = 311$) achieved a clinically relevant 7.2 months of benefit in median PFS in the everolimus arm (20.3 months) versus the placebo arm (13.1 months); (hazard ratio, 0.66; $P = 0.0049$), just short of the protocol pre-specified level of statistical significance ($P = 0.0044$). An additional sensitivity analysis of PFS without censoring patients at the start of new antineoplastic therapy yielded a hazard ratio consistent with the primary analysis ($P = 0.0043$). PFS based on a central assessment corroborated the investigator-assessed PFS in both the full population and the hormone receptor-negative subpopulation. OS data were not complete at the time of this publication. The most common adverse events in the everolimus versus placebo arms were stomatitis (66.5% vs. 32.4%), diarrhea (56.6% vs. 46.6%), and alopecia (46.8% vs. 52.5%). Suspected drug-related serious adverse events were reported for 21.8% versus 7.6%, and on-treatment adverse event-related deaths were reported for 3.6% versus 0% of patients, respectively. In conclusion, first-line therapy with everolimus plus trastuzumab plus paclitaxel did not show a PFS benefit in patients with HER2-positive advanced breast cancer; the hormone receptor-negative subpopulation derived a clinically robust benefit to median PFS of 7.2 months, suggesting that everolimus may have a role in this patient subpopulation.

To identify biomarkers to predict the clinical efficacy of everolimus treatment, BOLERO-1 and BOLERO-3 data were retrospectively analyzed. In both studies, differential PFS benefits of everolimus were consistently observed in patient subgroups defined by their PI3K pathway status. When analyzing combined data sets of both studies, everolimus was associated with a decreased hazard of progression in patients with PIK3CA mutations (hazard ratio, 0.67), PTEN loss (hazard ratio, 0.54), or hyperactive PI3K pathway (hazard ratio, 0.67). This analysis, although exploratory, suggests that patients with human epidermal growth factor receptor 2-positive advanced breast cancer having tumors with PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway could derive a PFS benefit from everolimus [38].

Hormone Receptor–Positive Tumors

Anti-HER2 Treatment Plus Endocrine Treatment

HER2- and hormone receptor-positive breast cancer is a distinct subtype associated with a good prognosis but a lower response to standard chemotherapy plus anti-HER2 agents. Concurrent blockade of the HER2 and estrogen receptor pathways has been a successful strategy to increase ORR and PFS in patients with advanced disease [4, 5].

For select patients with HER2-positive and hormone receptor-positive (ER positive/PgR positive or negative) breast cancer, endocrine treatment with either trastuzumab/pertuzumab or lapatinib/trastuzumab may be an acceptable first-line treatment [4, 5]. We do not typically recommend endocrine therapy alone for hormone receptor-positive, HER2-positive disease. Management could conceivably

include combinations of available endocrine therapies such as aromatase inhibitors (AIs), selective estrogen receptor down-regulators, or tamoxifen, with one or more of the currently approved HER2-targeted agents, including trastuzumab, pertuzumab, or lapatinib.

Several trials have examined the addition of HER2-targeted agents to aromatase inhibitors in postmenopausal women [5, 39, 40]. TAnDEM is the first randomized phase III study to combine a hormonal agent and trastuzumab without chemotherapy as treatment for HER2/hormone receptor–positive MBC [5]. Postmenopausal women with HER2/hormone receptor–positive MBC were randomly assigned to anastrozole with or without trastuzumab until progression. Patients in the trastuzumab plus anastrozole arm experienced significant improvements in PFS compared with those receiving anastrozole alone. In patients with centrally confirmed hormone receptor positivity, median PFS times were 5.6 and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively (log-rank $P = 0.006$). OS did not differ significantly between treatments. The most common toxicities in the combination arm were fatigue (21%), vomiting (21%), and diarrhea (20%). The incidence rates of grade 3 and 4 adverse events were 23% and 5%, respectively, in the trastuzumab plus anastrozole arm, and 15% and 1%, respectively, in the anastrozole-only arm.

The eLEcTRA trial compared the efficacy and safety of letrozole combined with trastuzumab to letrozole alone in patients with HER2-positive and hormone receptor-positive MBC [39]. Patients were randomized to either letrozole alone (arm A, $n = 31$) or letrozole plus trastuzumab (arm B, $n = 26$) as first-line treatments. An additional 35 patients with HER2-negative and hormone receptor–positive tumors received letrozole alone (arm C). Median time to progression in arm A was 3.3 months compared to 14.1 months in arm B (hazard ratio, 0.67; $P = 0.23$) and 15.2 months in arm C (hazard ratio, 0.71; $P = 0.03$). The clinical benefit rate was 39% for arm A compared to 65% in arm B (odds ratio 2.99, 95% CI 1.01–8.84) and 77% in arm C (odds ratio 5.34, 95% CI 1.83–15.58). The eLEcTRA trial demonstrated that the combination of letrozole and trastuzumab is a safe and effective treatment option for patients with HER2-positive and hormone receptor-positive MBC.

Both of these trials observed PFS and TTP benefits but no OS benefit in the combination arm. In another more recent trial [41], postmenopausal women with hormone receptor-positive MBC were randomized to daily oral treatment with letrozole plus lapatinib versus letrozole plus placebo. Of the 1286 patients enrolled in the phase III study, 219 had HER2-positive tumors. In the hormone receptor-positive HER2-positive population, adding lapatinib to letrozole significantly lowered the risk for disease progression compared to letrozole alone (hazard ratio, 0.71; 95% CI, 0.53–0.96). PFS was 8.2 months versus 3.0 months. ORR (28% vs. 15%), and the clinical benefit rate (48% vs. 29%) was also significantly greater in lapatinib-treated women. The most common adverse events in the lapatinib group were diarrhea (68%) and rash (46%), primarily grade 1 and 2. In conclusion, the risk for disease progression among women with hormone receptor-positive HER2-positive MBC was a statistically significant 29% lower risk for treatment with letrozole plus lapatinib compared with letrozole alone. The combination therapy was well tolerated, with primarily grade 1 and 2 toxicities. This trial further confirms that sustained HER2 inhibition benefits patients with HER2-positive MBC. Moreover, the addition of oral lapatinib provides a convenient option for women who receive oral endocrine therapy for an extended time.

Although adding HER2-targeted therapy to endocrine therapy does not seem to benefit OS, the reported studies did show a PFS benefit for the combination therapy groups [5, 39, 40]. Patients with ER-positive breast cancer have been included in first-line chemotherapy trials, such as CLEOPATRA, which showed an OS benefit from the chemotherapy and HER2-targeted therapy combinations [27]. No studies have directly compared endocrine plus HER2-targeted therapies with chemotherapy plus HER2-targeted therapy.

These results suggest that anti-HER2 treatment is less effective in HER2- and hormone receptor-positive breast cancer. There is no clear evidence that only the ER/PgR status of patients with HER2-positive advanced breast cancer affects their response to HER2-targeted therapy. Loibl et al. combined individual patient data from five clinical trials evaluating PIK3CA mutations. Patients received either trastuzumab (T), lapatinib (L) or the combination T/L in addition to a taxane-based chemotherapy. Within the hormone receptor-positive (HR+) subgroup, the PIK3CA mutant group had a lower pCR rate. HR+/PIK3CA mutant patients seemed to have significantly worse DFS (hazard ratio 1.56; $P = 0.05$) [42].

A dual HER2-targeted approach plus an aromatase inhibitor was evaluated in two randomized trials. In the Phase III ALTERNATIVE trial, 355 women with metastatic HER2-positive hormone receptor-positive disease, most of whom had been treated with adjuvant trastuzumab, were randomized to receive lapatinib/trastuzumab plus an aromatase inhibitor, trastuzumab plus an aromatase inhibitor, or lapatinib plus an aromatase inhibitor. Median PFS without chemotherapy was "quite respectable" at approximately 11 months with the triplet therapy, versus <6 months with the single agents. OS was numerically but not significantly improved (46 vs. 40 months) [43].

The benefit to adding pertuzumab to trastuzumab and an aromatase inhibitor was evaluated in a phase II PERTAIN study. The preliminary results of this study, in which 258 postmenopausal women were assigned to first-line pertu-

zumab plus trastuzumab and an AI (anastrozole or letrozole) or trastuzumab plus an AI, suggest improved PFS with the three-drug combination (hazard ratio, 0.65; 95% CI 0.48-0.89) [44]. The study demonstrated a 3-month PFS improvement with the triplet (18.9 months). Grade 3 or higher adverse events were observed in 50% of patients receiving trastuzumab and pertuzumab versus 39% of those receiving trastuzumab alone. Although these results are arguably strong for a regimen excluding chemotherapy, it must be noted that half of the women received induction therapy with a taxane for 18–24 weeks prior to the initiation of endocrine therapy.

Both of these two trials suggest that a dual HER2-targeted approach plus an aromatase inhibitor will improve PFS, which is now above and beyond 11–12 months and certainly above the 5–6 months we were seeing before, with the addition of trastuzumab alone to endocrine treatment. Patients who could be considered for this nonchemotherapy approach are those with minimal disease, elderly patients, and patients with severe comorbidities. We do not typically recommend endocrine therapy alone for hormone receptor-positive, HER2-positive disease [40]. These patients can receive an AI in combination with lapatinib/trastuzumab or trastuzumab/pertuzumab.

Although the clinician may discuss using endocrine therapy with HER2-targeted therapy, most patients will receive chemotherapy plus HER2-targeted therapy. When chemotherapy is discontinued, clinicians may recommend that patients start endocrine therapy, which is typically administered in conjunction with HER2-targeted therapy.

In conclusion, initial therapy with endocrine agents with HER2-targeted therapy is a reasonable option for patients who are not good candidates for chemotherapy or for those who wish to avoid the toxicity of chemotherapy, especially in elderly patients and patients with severe comorbidities, low-volume disease, a long disease-free interval, or indolent disease.

Second-Line Therapy

Multiple phase III clinical trials have demonstrated that continuation of anti-HER2 therapy in the second-line setting improves the clinical outcome of patients whose disease has recurred or progressed on first-line trastuzumab-based therapy (Tables 32.4 and 32.5). All studies have demonstrated a benefit of continuing some form of HER2-targeted therapy

Table 32.5 Second-line randomized phase III studies in HER2-positive metastatic breast cancer patients

Trial	Study arms	ORR (CR/PR)		PFS		OS	
		%	*P*	Months	Hazard ratio (95% CI), *P*	Months	Hazard ratio (95% CI), *P*
GBG26/BIG03-05 [10] (von Minckwitz 2009).	Capecitabine + trastuzumab	48.1	OR = 2.5 *P* = 0.0115	8.2	HR = 0.69 *P* = 0.0338	25.5	HR = 0.76 *P* = 0.257
	Capecitabine	27		5.6		20.4	
EGF100151 [49] (Cameron, 2010)[a]	Lapatinib + capecitabine	NR	NR	31.3 (weeks)	HR 0.5 *P* < 0.001	71.4 (weeks)	HR = 0.79 *P* = 0.077
	Capecitabine	NR		18.6 (weeks)		56.6 (weeks)	
EMILIA [51] (Dieras, 2017)	T-DM1	43.6	*P* < 0.001	9.6	HR 0.65 *P* < 0.001	29.9	HR 0.75 *P* < 0.001
	Lapatinib + capecitabine	30.8		6.4		25.9	
BOLERO-3 [48] (Andre, 2014)	Everolimus + trastuzumab + vinorelbine	41	*P* = 0.210	7	HR 0.78 (0.65–0.95) *P* < 0.001	NR	
	Trastuzumab + vinorelbine	37		5.8		NR	
TH3RESA [63] (Krop, 2017)	T-DM1	31	*P* = 0.0001	6.2	HR 0.53 *P* < 0.0001	22·7	HR = 0·68; *P* = 0·0007
	Physicians' choice[b]	9		3.3		15·8	
EGF104900 [41] (Blackwell, 2012)	Lapatinib + trastuzumab	NR		11.1	HR 0.74 (0.58–0.94)	14	HR 0.74 (0.57–0.97)
	Lapatinib[c]	NR		8.1		9.5	
LUX Breast I [58] (Harbeck, 2016)	Afatinib + vinorelbine	46.1	*P* = 0.851	5.5	*P* = 0.43	20.5	*P* = 0.0048
	Trastuzumab + vinorelbine	47		5.6		28.6	

MBC metastatic breast cancer, *ORR* objective response rare, *CR* complete response, *PR* partial response, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *T-DM1* T-DM1, *NE* not evaluable, *NS* nonsignificant

[a]The lapatinib plus trastuzumab study did include a heavily pretreated population. The results of patients receiving only one prior trastuzumab-based regimen is written in the table

[b]Physician's choice could have been single-agent chemotherapy, hormonal therapy, or an HER2-directed therapy or a combination of an HER2-directed therapy with chemotherapy, hormonal therapy, or other HER2-directed therapy: 68.1% chemotherapy + trastuzumab, 10.3% trastuzumab + lapatinib, 2.7% chemotherapy + lapatinib

[c]Lapatinib is not approved as a single agent

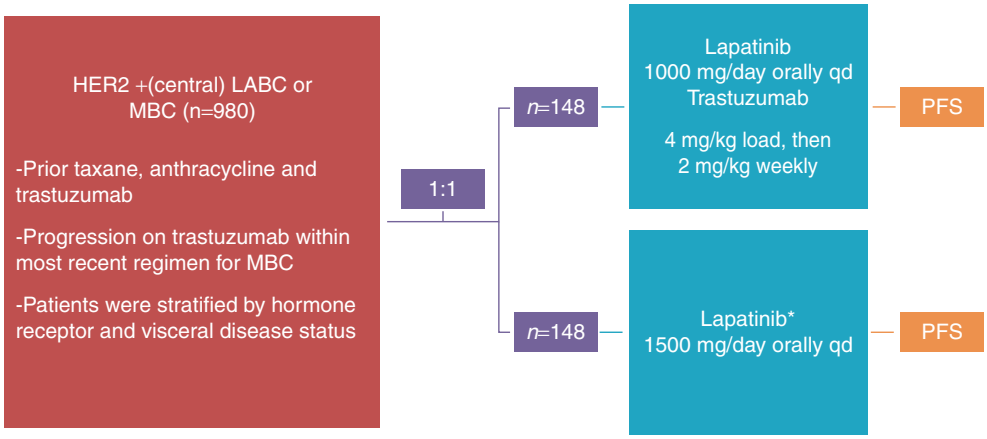

Fig. 32.8 Lapatinib plus trastuzumab versus. lapatinib alone (EGF 104900) [41]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *qd* once daily, *PFS* progression-free survival; *Lapatinib is not approved for use as a single agent

in the second-line setting as either a combination of HER2-targeted therapy and chemotherapy, a combination of two HER2-targeted therapies, or T-DM1. These therapies were associated with improved outcomes.

The evaluated therapeutic options included continuing trastuzumab with a different chemotherapy partner, switching to T-DM1, adding the mTOR pathway inhibitor everolimus, or switching to a regimen of capecitabine plus lapatinib.

Hormone Receptor-Positive Disease in Second or Later Lines

Management of hormone receptor-positive and HER2-positive metastatic disease without chemotherapy could conceivably include combinations of available endocrine therapies with anti-HER2 drugs.

Dual HER2 blockade enhances clinical benefit versus single HER2 blockade. The ALTERNATIVE study evaluated the efficacy and safety of dual HER2 blockade plus AI in postmenopausal women with HER2-positive/HR-positive MBC who received prior endocrine therapy and prior trastuzumab plus chemotherapy [43]. Patients were randomly assigned to receive lapatinib + trastuzumab + AI, trastuzumab + AI, or lapatinib + AI. All patients had received prior trastuzumab and prior endocrine therapy, either in the adjuvant or metastatic disease setting. PFS was significantly increased with the AI in combination with lapatinib plus trastuzumab as compared with trastuzumab without lapatinib (hazard ratio, 0.62; 95% CI 0.45-0.88). The ORR was also increased with the combination (31.7% vs. 13.7%). Diarrhea was the most common adverse event with lapatinib. Serious adverse events were reported similarly across the three groups. This combination offered an effective and safe chemotherapy-sparing alternative treatment regimen for this patient population. It is uncertain whether the best strategy is to use the three-drug regimen of an AI plus lapatinib plus trastuzumab first, or whether it would be equally acceptable to first use an AI plus trastuzumab with or without pertuzumab and add lapatinib at the time of disease progression.

Assuming patients may have received trastuzumab, pertuzumab, and an AI in the first line, based on the ALTERNATIVE trial, it would be reasonable in patients whose disease is not rapidly progressive or symptomatic, or is not characterized by significant visceral involvement to consider discontinuing pertuzumab and adding lapatinib and/or an alternative endocrine therapy at the time of disease progression to further postpone the use of chemotherapy [43].

Continuing Trastuzumab

The strategy of continuing trastuzumab while switching its chemotherapy partner was evaluated in two phase III trials. Continuation of trastuzumab in conjunction with lapatinib without cytotoxic chemotherapy was investigated in the EGF104900 study (Fig. 32.8) [41]. Heavily pretreated patients were randomized to lapatinib plus trastuzumab or to lapatinib alone. The improvement in response rate was not significant. In the updated final analysis of all patients randomly assigned with strata (n = 291), lapatinib plus trastuzumab continued to be superior to lapatinib monotherapy in PFS (hazard ratio, 0.74; P = 0.011) and offered a significant OS benefit (hazard ratio, 0.74; P = 0.026). The improvements in absolute OS rates were 10% at 6 months and 15% at 12 months in the combination arm compared with the monotherapy arm. Multiple baseline factors, including an Eastern Cooperative Oncology Group (ECOG) performance status of 0, nonvisceral disease, <3 metastatic sites, and shorter time from initial diagnosis to random assignment, were associated with improved OS. The incidence of adverse events was consistent with previously reported rates. These data demonstrated a significant 4.5-month median OS advantage of the lapatinib and trastuzumab combination and support dual HER2 blockade in patients with heavily pretreated HER2-positive MBC.

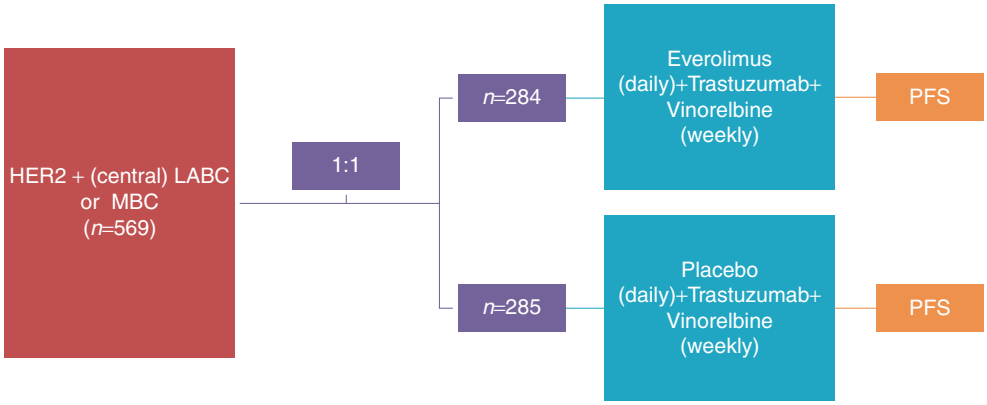

Fig. 32.9 Everolimus in combination with vinorelbine and trastuzumab (BOLERA-3) [48]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *PFS* progression-free survival

In a German Breast Group/Breast International Group study, 156 patients with HER2-positive breast cancer that progressed during treatment with trastuzumab were randomly assigned to receive capecitabine (2500 mg/m^2 body-surface area on days 1 through 14 [1250 mg/m^2 semi-daily]) alone or with continuation of trastuzumab (6 mg/kg body weight) in 3-week cycles [10]. Median times to progression were 5.6 months in the capecitabine group and 8.2 months in the capecitabine-plus-trastuzumab group, with an unadjusted hazard ratio of 0.69 (two-sided log-rank P = 0.0338). OS times were 20.4 months (95% CI: 17.8–24.7) in the capecitabine group and 25.5 months (95% CI: 19.0–30.7) in the capecitabine-plus-trastuzumab group (P = 0.257). ORR rates were 27.0% with capecitabine and 48.1% with capecitabine plus trastuzumab (odds ratio, 2.50; P = 0.0115). The continuation of trastuzumab beyond progression was not associated with increased toxicity, and the continuation of trastuzumab plus capecitabine resulted in a significant improvement in ORR and TTP compared with capecitabine alone.

Trastuzumab and Pertuzumab Combination

A study of the combination of trastuzumab and capecitabine with or without pertuzumab in patients with HER2-positive MBC (PHEREXA) was reported [45]. This randomized, two-arm study evaluated the efficacy and safety of a combination of trastuzumab and capecitabine with or without pertuzumab in patients with HER2-positive MBC. The study population consisted of female patients whose disease progressed during or following previous trastuzumab therapy for metastatic disease. All patients in Arms A and B received trastuzumab plus capecitabine oral twice daily for 14 days every 3 weeks (1250 mg/m^2 twice daily in Arm A and 1000 mg/m^2 twice daily in Arm B). In addition, patients in Arm B received pertuzumab every 3 weeks. The study treatment continued until disease progression or unacceptable toxicity. Median PFS was 9.0 months in Arm A versus 11.1 months in Arm B (hazard ratio, 0.82; P = 0.0735). Interim OS was 28.1 months in Arm A versus 36.1 months in Arm B (hazard ratio, 0.68; 95% CI: 0.51–0.90). Adverse events were reported in 98.2% in Arm A versus 97.4% in Arm B; grade ≥3 adverse events were 59.6% versus 51.8%; and treatment discontinuations due to adverse events were 19.3% versus 21.1%. In conclusion PHEREXA did not meet its primary endpoint of PFS. An 8-month improvement in median OS with pertuzumab to 36.1 months was observed. Statistical significance for OS cannot be claimed due to the hierarchical testing; however, the magnitude of benefit is in keeping with prior experience of pertuzumab in MBC.

mTOR Inhibitors to Target Resistance

Although HER2-targeted therapy in the clinic has significantly improved patient outcomes, treatment resistance remains a problem. The causes of resistance include pathway redundancy, reactivation, or the utilization of escape pathways [46, 47]. Understanding the mechanisms of resistance can lead to better therapeutic strategies to overcome resistance and optimize outcomes.

In breast cancer, the PI3K/Akt/mTOR pathway has been associated with resistance to endocrine therapy, HER2-directed therapy, and cytotoxic therapy [34, 46]. Disease progression in patients with HER2-positive breast cancer receiving trastuzumab might be associated with activation of the PI3K/Akt/mTOR intracellular signaling pathway. Adding the mTOR inhibitor everolimus to trastuzumab might restore sensitivity to trastuzumab (Figs. 32.6 and 32.7) [46, 47].

In the BOLERO-3 trial, women with HER2-positive, trastuzumab-resistant, advanced breast cancer who had previously received taxane therapy were randomized to daily everolimus (5 mg/day) (n = 284) plus weekly trastuzumab (2 mg/kg) and vinorelbine (25 mg/m^2) or to placebo (n = 285) plus trastuzumab plus vinorelbine in 3-week cycles, stratified by previous lapatinib use (Fig. 32.9) [48]. Median fol-

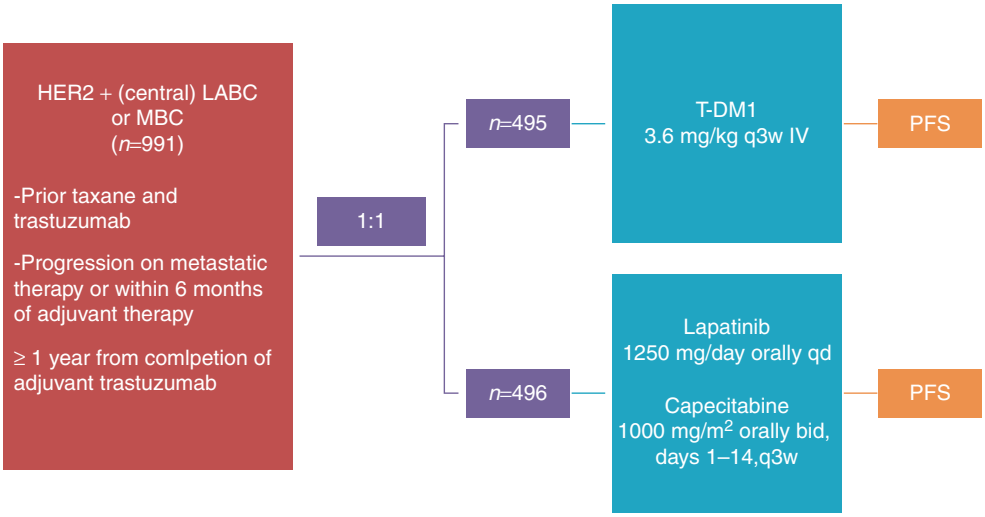

Fig. 32.10 T-DM1 versus "capecitabine plus lapatinib" (EMILIA) [50]. *HER2* human epidermal growth factor receptor 2, *LABC* locally advanced breast cancer, *MBC* metastatic breast cancer, *T-DM1* trastuzumab emtansine, *q3w* every 3 weeks, *IV* intravenous, *PD* progressive disease, *qd* once daily, *bid* twice daily

low-up at the time of analysis was 20.2 months. Median PFS times were 7.0 months with everolimus and 5.8 months with placebo (hazard ratio, 0.78; $P = 0.0067$). The greatest benefit was to patients with hormone receptor-negative tumors. The most common grade 3–4 adverse events were neutropenia (73% in the everolimus group vs. 62% in the placebo group), leukopenia (38% vs. 29%), anemia (19% vs. 6%), febrile neutropenia (16% vs. 4%), stomatitis (13% vs. 1%), and fatigue (12% vs. 4%). Serious adverse events were reported in 42% of patients in the everolimus group and 20% in the placebo group.

Capecitabine Plus Lapatinib

Geyer et al. conducted a phase III study comparing capecitabine plus lapatinib with capecitabine alone in patients who had progressed on prior trastuzumab-based therapy [9, 49]. Patients were randomized to lapatinib (1250 mg/day) plus capecitabine (2000 mg/m^2) or capecitabine monotherapy (2500 mg/m^2) on days 1–14 of a 21-day cycle. In total, 207 and 201 patients were enrolled to combination therapy and monotherapy, respectively. The median OS times were 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (hazard ratio, 0.87; $P = 0.210$). This study showed significant clinical benefits, including a trend toward OS in favor of the combination versus monotherapy in patients with trastuzumab-pretreated HER2-positive MBC. These results led to the premature termination of accrual to the study, and 36 patients receiving monotherapy were permitted to crossover to combination therapy. A Cox regression analysis considering crossover as a time-dependent covariate suggested that there may have been a 20% lower risk for death in the combination therapy arm (hazard ratio, 0.80; $P = 0.043$). Although premature termination and crossover resulted in insufficient power to detect an OS benefit, these updated analyses confirm a trend toward an OS advantage in the combination arm. The incidence rates of diarrhea (60% vs. 39%) and rash (27% vs. 15%) were higher in the combination arm, but the incidence rates of severe toxicities were comparable between the two arms. Lapatinib was approved by the FDA for the treatment of HER2-positive breast cancer in combination with capecitabine for patients who progressed after anthracycline, taxane, and trastuzumab.

T-DM1

T-DM1 is an antibody-drug conjugate incorporating the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (Fig. 32.5) [50]. The superiority of T-DM1 to capecitabine plus lapatinib in the second-line setting was established in the EMILIA trial (Fig. 32.10) [50]. Patients with HER2-positive advanced breast cancer who had previously been treated with trastuzumab and a taxane were randomly assigned to T-DM1 or lapatinib plus capecitabine. Among 991 patients, median PFS as assessed by independent review was 9.6 months for T-DM1 versus 6.4 months for lapatinib plus capecitabine (hazard ratio for progression or death from any cause, 0.65; $P < 0.001$), and median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months; hazard ratio for death from any cause, 0.68; $P < 0.001$). ORR was higher with T-DM1 (43.6%, vs. 30.8%; $P < 0.001$). Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%). The incidence rates of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1, whereas the incidence rates of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus

capecitabine. The incidence rates of grade 3 or worse thrombocytopenia were 12.9% in the T-DM1–treated group and 0.2% in the lapatinib/capecitabine group. Patients treated with T-DM1 in the EMILIA trial experienced an overall higher rate of bleeding compared with those treated with capecitabine plus lapatinib (30% vs. 16%, respectively), although the rate of serious bleeding events was low in both arms (1.4% vs. 0.8%). However, the etiology of bleeding was not entirely explained by other risk factors (e.g., the use of anticoagulants or concomitant thrombocytopenia). Platelets do not overexpress HER2, and the thrombocytopenia may be mediated in part by DM1-induced impairment of megakaryocytic differentiation. For most patients receiving T-DM1, thrombocytopenia can be monitored without any changes in treatment. T-DM1 can cause liver failure and death. If serum transaminases or total bilirubin are increased, the dose of T-DM1 should be reduced or discontinued. All patients should undergo evaluation of LVEF before and during treatment with T-DM1. If a patient develops a clinically meaningful decrease in left ventricular function, the treatment should be discontinued. Additional treatment with T-DM1 can be considered after recovery of cardiac function among patients who experience cardiac events (Tables 32.5 and 32.6).

In the final descriptive analysis, median OS was longer with T-DM1 than with the control (29.9 months versus 25.9 months; hazard ratio, 0.75). This descriptive analysis of final OS in the EMILIA trial shows that T-DM1 improved OS in patients with previously treated HER2-positive metastatic breast cancer, even in the presence of crossover treatment. The safety profile was similar to that reported in previous analyses, reaffirming T-DM1 as an efficacious and tolerable treatment in this patient population [51].

Table 32.6 Dosage dose modification of T-DM1 based on asymptomatic left ventricular ejection fraction decrease from baseline

Criteria	Left ventricular ejection fraction (LVEF)	Action	Action at LVEF reassessment
1	>45%	Continue and follow routine monitoring guidelines	Follow actions based on criteria
2	40–45% AND <10% below baseline and asymptomatic	Continue and repeat LVEF in 3 weeks	Discontinue permanently if no recovery. If improved to criteria # 1 (for # 2, 3, or 4) or # 2 (for # 3 or 4), it may be restarted; monitor closely
3	40–45% AND ≥10% below baseline, and asymptomatic	Pause and repeat LVEF in 3 weeks	
4	<40% and asymptomatic		
5	Symptomatic or confirmed CHF	Discontinue	Not applicable

Patient-reported outcomes from EMILIA have also been published [52]. A secondary endpoint of the EMILIA study was time to symptom worsening, which was delayed in the T-DM1 arm versus the capecitabine-plus-lapatinib arm (7.1 months vs. 4.6 months, respectively; hazard ratio, 0.796; $P = 0.012$). In the T-DM1 arm, 55.3% of patients developed clinically significant improvement in symptoms from baseline versus 49.4% in the capecitabine-plus-lapatinib arm ($P = 0.084$). Although similar at baseline, the number of patients reporting diarrhea increased 1.5- to 2-fold during treatment with capecitabine and lapatinib but remained near baseline levels in the T-DM1 arm. Together with the EMILIA primary data, these results support the view that T-DM1 has greater efficacy and tolerability than capecitabine plus lapatinib, which may translate into improvements in health-related quality of life. Based on the available data, the ASCO guideline recommends the use of anti-HER2 therapy including T-DM1 in the second-line setting [53].

The capacity of ADCs to deliver chemotherapy selectively to the tumor not only offers the potential for greater efficacy and reduced toxicity as monotherapy but also expands the potential for combination regimens. Virtually any agent that one would consider adding to a trastuzumab/chemotherapy backbone could be considered for addition to T-DM1. The order of treatment may be important; in preclinical models, pretreatment with pertuzumab appeared to blunt the efficacy of T-DM1 [54]. T-DM1 is an ideal candidate for combination with agents that, because of overlapping toxicities, have been difficult to combine with chemotherapy. Ongoing trials are combining T-DM1 with a variety of downstream inhibitors of signaling or other molecular pathways, including inhibitors of heat shock proteins, cyclin-dependent kinases, PI3K/AKT, and mTOR. Ongoing trials are exploring the potential of combining T-DM1 with a variety of chemotherapy agents, including paclitaxel, docetaxel, and capecitabine, among others.

MM-302

MM-302 (HER2-Targeted Antibody-Liposomal Doxorubicin Conjugate) is a novel, HER2-targeted antibody-liposomal doxorubicin conjugate that specifically targets HER2-overexpressing cells. HERMIONE is an open-label, multicenter, randomized phase II trial of MM-302 plus trastuzumab versus chemotherapy of physician's choice (gemcitabine, capecitabine, or vinorelbine) plus trastuzumab that plans to enroll 250 anthracycline-naïve patients with locally advanced/metastatic HER2-positive breast cancer. The HERMIONE study will evaluate the efficacy and safety of MM-302 plus trastuzumab in patients with refractory HER2-positive advanced/metastatic breast cancer for whom there are no standard of care therapies with a proven survival advantage [55].

MM-111

MM-11 is a bi-specific monoclonal antibody that reversibly targets the HER2 and HER3 heterodimer. A phase I-II study is currently evaluating its efficacy as a single agent in HER2-positive advanced breast cancer patients who have received prior trastuzumab or lapatinib therapy (clinical trials.gov, NCT00911898). Another phase I trial is studying MM-111 plus trastuzumab in HER2-positive, heregulin-positive, advanced, and refractory breast cancer (clinical trials.gov, NCT01097460).

Tyrosine Kinase Inhibitors

Afatinib is an oral ErbB family blocker that covalently binds and irreversibly blocks all kinase-competent ErbB family members. A phase II, open-label, single-arm study explored afatinib activity in HER2-positive breast cancer patients progressing after trastuzumab treatment [56]. Patients had stage IIIB/IV HER2-positive MBC with progression following trastuzumab or trastuzumab intolerance and an ECOG performance status of 0–2. Patients received 50 mg of afatinib once daily until disease progression. The primary endpoint was ORR using RECIST 1–0 (Response Evaluation Criteria in Solid Tumors 1.0) criteria [57]. Forty-one patients who had received a median of three prior chemotherapies (range, 0–15), including 68.3% who had received trastuzumab for >1 year, were treated. Four patients (10% of 41 treated; 11% of evaluable patients) had a partial response. Fifteen patients (37% of 41) had stable disease as the best response, and 19 (46% of 41) achieved clinical benefit. Median PFS was 15.1 weeks (95% CI: 8.1–16.7), and median OS was 61.0 weeks (95% CI: 56.7–not evaluable). The most frequent grade 3 treatment-related adverse events were diarrhea (24.4%) and rash (9.8%).

In the LUX-Breast 1 phase III trial, patients with HER2-positive MBC and failure of one trastuzumab-based regimen (adjuvant/first-line) were randomized 2:1 to afatinib plus vinorelbine (AV) or trastuzumab plus vinorelbine (TV). Treatment continued until disease progression or unacceptable adverse events [58]. A total of 508 patients were randomized (AV:339, TV:169). A pre-planned risk/benefit assessment was found unfavorable. Recruitment was stopped after a benefit-risk assessment by the independent data monitoring committee was found unfavorable for the afatinib group. Patients on afatinib plus vinorelbine had to switch to trastuzumab plus vinorelbine. In this trial, AV and TV demonstrated similar PFS and ORR. Median OS times were 19.6 months with AV and 28.6 months with TV (hazard ratio, 1.76; $P = 0.0036$). The most common drug-related adverse events were diarrhea (80.1%), neutropenia (75.1%), and rash with AV and neutropenia (78.7%) and anemia with TV. In conclusion, the OS diverged and was shorter for AV compared with TV, and AV tolerability compared unfavorably with that of TV. The LUX-Breast 1 trial was a negative trial for afatinib.

Neratinib is an oral, irreversible inhibitor of HER1, HER2, and HER4. A phase II trial evaluated neratinib in 136 HER2-positive patients [59]. The median PFS times were 22.3 and 39.6 weeks, and the ORRs were 24% and 56% in the pretreated and trastuzumab-naïve patients, respectively. Diarrhea was the most common grade 3/4 adverse effect. A phase I-II trial evaluated neratinib plus vinorelbine in trastuzumab or lapatinib pretreated patients ($n = 77$). ORRs were 41% (no prior lapatinib) and 8% (prior lapatinib) [60].

A multinational, open-label, phase I/II trial was conducted to determine the maximum-tolerated dose (MTD) of neratinib plus capecitabine in patients with solid tumors (part one) and to evaluate the safety and efficacy of neratinib plus capecitabine in patients with HER2-positive MBC (part two) [61]. Part one was a 3+3 dose-escalation study in which patients with advanced solid tumors received oral neratinib once per day continuously plus capecitabine twice per day on days 1–14 of a 21-day cycle at predefined dose levels. In part two, patients with trastuzumab-pretreated HER2-positive MBC received neratinib plus capecitabine at the MTD. In part one ($n = 33$), the combination of neratinib 240 mg per day plus capecitabine 1500 mg/m^2 per day was defined as the MTD, which was further evaluated in part 2 ($n = 72$). The most common drug-related adverse events were diarrhea (88%) and palmar-plantar erythrodysesthesia (48%). In part two, the ORRs were 64% ($n = 39$ of 61) in patients with no prior lapatinib exposure and 57% ($n = 4$ of 7) in patients previously treated with lapatinib. Median PFS times were 40.3 and 35.9 weeks, respectively. Neratinib in combination with capecitabine had a manageable toxicity profile and showed promising antitumor activity in patients with HER2-positive MBC pretreated with trastuzumab and lapatinib.

Third-Line Therapy and Beyond

The lapatinib plus trastuzumab study did include a heavily pretreated population and showed a benefit for continuing trastuzumab in combination with lapatinib after progression during previous trastuzumab-containing regimens. These data support the continuation of HER2-targeted therapy in the third-line setting and beyond.

Patients with progressive disease after two or more HER2-directed regimens for recurrent or MBC have few effective therapeutic options. Th3Resa is a phase III trial to specifically address the efficacy of anti-HER2 therapy in this third-line setting (Fig. 32.11) [62]. Patients with progressive HER2-positive advanced breast cancer who had

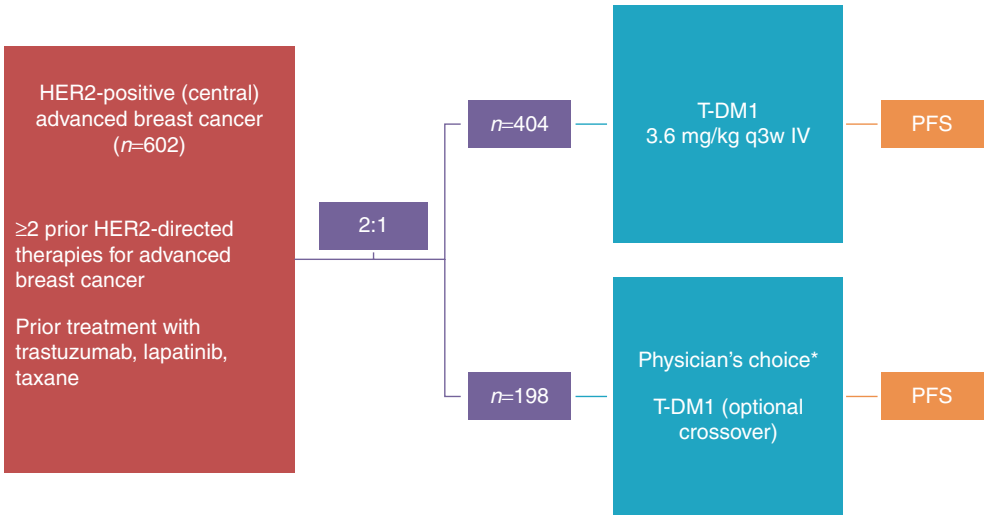

Fig. 32.11 T-DM1 versus physician treatment of choice (TH3RESA) [63]. *Physician's choice could be single-agent chemotherapy, hormonal therapy, or HER2-directed therapy or a combination of an HER2-directed therapy with chemotherapy, hormonal therapy, or other HER2-directed therapies: 68.1% chemotherapy + trastuzumab, 10.3% trastuzumab + lapatinib, and 2.7% chemotherapy + lapatinib. *HER2* human epidermal growth factor receptor 2, *T-DM1* trastuzumab emtansine, *IV* intravenous, *q3w* every 3 weeks, *PFS* progression-free survival

received two or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting were randomly assigned (in a 2:1 ratio) to T-DM1 (3.6 mg/kg intravenously every 21 days) or the physician's choice. A total of 602 patients were randomly assigned (404 to T-DM1 and 198 to physician's choice). At data cutoff, 44 patients assigned to physician's choice had crossed over to T-DM1. After median follow-up times of 7.2 months in the T-DM1 group and 6.5 months in the physician's choice group, PFS was significantly improved with T-DM1 compared with physician's choice (median 6.2 months vs. 3.3 months) (stratified hazard ratio, 0.53; $P < 0.0001$). Interim overall survival analysis showed a trend favoring T-DM1 (stratified hazard ratio, 0.55; $P = 0.0034$). Results from the final overall survival analysis of the TH3RESA trial are reported [63]. Overall survival was significantly longer with trastuzumab emtansine versus treatment with physician's choice (median 22·7 months vs. 15·8 months; hazard ratio, 0·68; $P = 0·0007$). A lower incidence of grade 3 or worse adverse events was reported with T-DM1 than with physician's choice (32% vs. 43%). Grade 3 or worse adverse events, including neutropenia, diarrhea, and febrile neutropenia, were more common in the physician's choice group than in the T-DM1 group. Thrombocytopenia (5% vs. 2%) was the principal grade 3 or worse adverse event in the T-DM1 group. Serious adverse events were reported by 18% of patients in the T-DM1 group and 21% in the physician's choice group. T-DM1 should be considered as a new standard for patients with HER2-positive advanced breast cancer, who have previously received trastuzumab and lapatinib.

Trastuzumab deruxtecan (ds-8201a), a HER2-targeting antibody-drug conjugate, demonstrated significant clinical activity in heavily pretreated patients with HER2-expressing MBCs who previously received T-DM1. Whereas T-DM1 is a tubulin-targeting chemotherapy, trastuzumab deruxtecan is a topoisomerase 1 inhibitor. It is highly potent, with a drug-to-antibody ratio (DAR) of 7.8, compared with 3.5 for T-DM1.

In a 2-part phase I study, the ORR to trastuzumab deruxtecan in 57 evaluable patients with HER2-positive tumors was 61.4%. In the HER2-positive cohort, the ORRs were 56.4% among those with ER-positive disease and 75.0% in those with ER-negative disease. Notably, the ORR was 62.5% among the 50 patients in this cohort with prior pertuzumab treatment. The disease control rate (DCR) was 94.7% overall in the HER2-positive subset: 92.3% in the ER-positive group, 100.0% in the ER-negative group, and 94.0% among those who had received prior pertuzumab. Median PFS was not yet reached in the ER-positive group and was 10.3 months in the ER-negative group. Median PFS was 10.3 months in the HER2-positive cohort who had received prior pertuzumab. The main toxicity was grade 1/2 gastrointestinal toxicity. Grade 1/2 nausea was reported by 67.9%. Grade 3 and 4 events were hematologic in nature. The rates of grade 3/4 anemia were 8.7% in the HER2-positive group. The rates of grade 3 decreases in neutrophil count and white blood cell count were each 10.4%. Across the study, 5 patients (4.3%) had a grade 4 decrease in neutrophil count [64].

In August 2017, trastuzumab deruxtecan received an FDA breakthrough therapy designation for the treatment of patients with HER2-positive, locally advanced, or MBC who have been treated with trastuzumab and pertuzumab and

have disease progression after T-DM1. An ongoing pivotal phase II trial called DESTINY-Breast01 is examining the efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive unresectable and/or MBC who are resistant or refractory to T-DM1.

The ASCO guidelines for HER2-positive advanced breast cancer recommended anti-HER2 therapy, including T-DM1, pertuzumab, and capecitabine plus lapatinib in the third-line setting, with hormonal therapy in patients with ER-positive and/or PgR-positive disease [53]. Additionally, if a patient's HER2-positive advanced breast cancer has progressed during or after the second-line or greater HER2-targeted therapy, clinicians should offer T-DMI if she has not received T-DM1, pertuzumab if she has not received pertuzumab, or the third-line or greater HER2-targeted therapy-based treatment if she has received both T-DM1 and pertuzumab. Options include lapatinib plus capecitabine and other combinations of chemotherapy with trastuzumab, lapatinib, and trastuzumab or hormonal therapy (in patients with ER- and/or PgR-positive disease). There is insufficient evidence to recommend one regimen over another (Fig. 32.4) [53].

Treatment Influence of Previous HER2 Therapy

First-Line Treatment

For patients who received adjuvant trastuzumab and develop MBC, decisions are based on the time that elapsed from the end of adjuvant treatment to the diagnosis of MBC. We do not have a predictive biomarker to tell us which patients are more likely to benefit from ado-trastuzumab emtansine or pertuzumab. There are a few prognostic biomarkers, but no predictive ones, to guide the treatment selection of metastatic HER2 therapy. For patients with a treatment-free interval of 6 months or longer, pertuzumab, trastuzumab, and a taxane can be preferred. For patients with a treatment-free interval of less than 6 months, T-DM1 can be preferred. This recommendation is based on the phase III EMILIA trial, which demonstrated that T-DM1 improves clinical outcomes and is better tolerated than lapatinib plus capecitabine [50]. An alternative trastuzumab-containing regimen or a lapatinib-based combination can be used if T-DM1 is not available (Tables 32.6, 32.7, 32.8 and 32.9). Initial therapy with endocrine agents with HER2-targeted therapy is a reasonable option for patients who are not good candidates for chemotherapy or for those who wish to avoid the toxicity of chemotherapy, especially in elderly patients and patients with low-volume disease, a long disease-free interval, or indolent disease. Endocrine therapy alone for hormone receptor-positive, HER2-positive disease is not recommended. Typically, we administer endocrine therapy following induction chemotherapy plus HER2-directed therapy, although in some cases, cytotoxic chemotherapy may be deferred to a later time. For premenopausal women in whom an HER2-directed therapy, such as lapatinib/trastuzumab or trastuzumab/pertuzumab and endocrine therapy, is appropriate, the typical approach is to offer ovarian suppression or ablation in combination with endocrine therapy (AI) and an HER2-directed therapy. For postmenopausal women in whom an HER2-directed therapy and endocrine therapy are appropriate, administration of an HER2-directed therapy plus an AI is an effective treatment strategy.

1. *For patients with recurrence ≤12 months after adjuvant treatment*:

   If a patient finished trastuzumab-based adjuvant treatment ≤12 months before recurrence, clinicians should follow the second-line HER2-targeted therapy-based treatment recommendations. For patients who progress 6 months or longer after the completion of adjuvant trastuzumab (without pertuzumab), trastuzumab plus pertuzumab in combination with a taxane can also be suggested [53].
2. *For patients with recurrence >12 months after adjuvant treatment*:

   If a patient finished trastuzumab-based adjuvant treatment >12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations [53].

Table 32.7 Combined usage of cytotoxic drugs with dual anti-HER2 inhibition for HER2-positive advanced breast cancer

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
Trastuzumab plus Pertuzumab with docetaxel	Trastuzumab	8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
	Pertuzumab	840 mg IV day 1 followed by 420 mg	Intravenous	Cycled every 21 days
	Docetaxel	75–100 mg/m^2	Intravenous	Cycled every 21 days
Trastuzumab plus Pertuzumab with paclitaxel	Trastuzumab	8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days OR
		4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
	Pertuzumab	840 mg IV day 1 followed by 420 mg	Intravenous	Cycled every 21 days
	Paclitaxel	175 mg/m^2	Intravenous	Cycled every 21 days OR
	Paclitaxel	80–90 mg/m^2	Intravenous	Cycled every 7 days

Table 32.8 Combined usage of cytotoxic drugs with trastuzumab for HER2-positive advanced breast cancer

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
Trastuzumab plus the following cytotoxic(s)	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
Paclitaxel/carboplatin	Carboplatin	AUC 6	Intravenous	Day 1 Cycled every 21 days
	Paclitaxel	175 mg/m^2	Intravenous	Day 1 Cycled every 21 days
Weekly paclitaxel/ carboplatin	Carboplatin	AUC 2	Intravenous	Days 1, 8, and 15 Cycled every 28 days
	Paclitaxel	80 mg/m^2	Intravenous	Days 1, 8, and 15 Cycled every 28 days
Paclitaxel	Paclitaxel	175 mg/m^2	Intravenous	Day 1 Cycled every 21 days
	Paclitaxel	80–90 mg/m^2	Intravenous	Day 1 Cycled every 7 days
Docetaxel	Docetaxel	80–100 mg/m^2	Intravenous	Day 1 Cycled every 21 days
	Docetaxel	35 mg/m^2	Intravenous	Day 1 Cycled every week
Vinorelbine	Vinorelbine	25 mg/m^2	Intravenous	Day 1 weekly Cycled every 21 days
	Vinorelbine	30–35 mg/m^2	Intravenous	Days 1 and 8 Cycled every 21 days
Capecitabine	Capecitabine	1000–1250 mg/m^2	Peroral	Twice daily days 1–14 Cycled every 21 days

Table 32.9 Systemic therapy for previously trastuzumab-treated HER2-positive advanced breast cancer patients

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
T-DM1	Ado-trastuzumab emtansine	3.6 mg/kg	Intravenous	Day 1
				Cycled every 21 days
Lapatinib + capecitabine	Lapatinib PO daily	1250 mg	Peroral	Days 1–21
				Cycled every 21 days
	Capecitabine	1000 mg/m^2	Peroral	Twice daily days 1–14
				Cycled every 21 days
Trastuzumab + capecitabine	Capecitabine	1000–1250 mg/m^2	Peroral	Twice daily days 1–14
				Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
Trastuzumab + lapatinib (without cytotoxic therapy)	Lapatinib	1000 mg	Peroral	Days 1–21 Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days

Patients Who Require Second- or Later-Line Treatment

In general, trastuzumab can be continued across treatment regimens for women who experience disease progression on an HER2-directed agent, regardless of the line of treatment. There are no high-quality data available to support the continued use of pertuzumab through multiple lines of therapy.

For patients with HER2-positive MBC who experience disease progression on a regimen that includes an HER2-directed agent, available options include the following (Fig. 32.4) (Tables 32.8 and 32.9):

1. Trastuzumab plus an alternative cytotoxic agent
2. T-DM1, if not previously administered
3. Lapatinib plus capecitabine or trastuzumab, if not previously administered

When lapatinib is administered, it must be combined with another agent (e.g., capecitabine or trastuzumab) because combination therapies have better clinical outcomes than monotherapy. Lapatinib plus capecitabine is an option for patients who experience disease progression on trastuzumab, particularly if they prefer oral medications [53]. The combination of lapatinib and trastuzumab is a chemotherapy-free option for patients with HER2-positive MBC whose disease has progressed on trastuzumab [53].

For patients who progress after initial trastuzumab and a taxane in the metastatic setting or after both trastuzumab- and lapatinib-containing regimens, T-DM1 is an active agent, provided they have not received it previously. This recommendation is based on both the EMILIA trial and the second-phase III Th3Resa trial.

The optimal selection of anti-HER2 therapy and personalization of treatment remain active areas of research. Trials to examine the utility of newer agents in various settings are under way and may change our future clinical practice.

Duration of Chemotherapy or HER2-Targeted Therapy

If a patient is receiving a HER2-targeted therapy and chemotherapy combination, the chemotherapy should continue for approximately 6 months (or longer) and/or to the time of maximal response, depending on toxicities and the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy: no further change in the regimen is needed until the time of progression or unacceptable toxicities. There are insufficient data to make a single statement on when to stop administering HER2-targeted therapy [53].

In most trials, an HER2-targeted therapy was administered until disease progression or until toxic adverse events caused the clinician and patient to decide to discontinue this therapy. For patients who have an optimal treatment response and for whom cytotoxic chemotherapy has been discontinued, the decision to discontinue an HER2-directed therapy should be individualized because there are no prospective data to provide guidance. Anti-HER2-directed therapy can be continued for many years in such patients without disease progression. However, the same can be said for patients who discontinue treatment. While continuation of an HER2-directed treatment can increase the risk of cumulative toxicity (particularly cardiotoxicity) and healthcare costs and may be inconvenient, these considerations must be balanced by the potential benefit of treatment in delaying (or preventing) disease progression [53]. After stopping chemotherapies, especially in patients with complete response, we do not know how long we should add pertuzumab to trastuzumab. It is possible that after a period of time, treatment can be continued with trastuzumab alone with or without endocrine treatment according to the receptor status.

Monitoring Therapy

The receptor status of metastasis or a recurrent tumor can change. Curigliano et al. evaluated the discordance rates of ER, PgR, and HER2 status between the primary tumor and liver metastases, which would potentially impact treatment choices [65]. They identified 255 consecutive patients with matched primary and liver tissue samples and observed changes in ER status in 14.5% and in PgR status in 48.6% of cases. Changes in HER2 status were observed in 24 of 172 assessable patients (13.9%). HER2 status changed from positive to negative in 17 of 54 patients (32%) and from negative to positive in 7 of 118 patients (6%). The study also revealed that a change in HER2 status from negative to positive was associated with a certain decrease in ER and PgR expression between the primary tumor and liver biopsy. A discordance in receptor status (ER, PgR, and HER2) between the primary tumor and liver metastases led to a change in therapy in 31 of 255 patients (12.1%). Biopsy of metastases for reassessment of biological features should be considered in all patients when safe and easy to perform because it is likely to impact treatment choice.

The continuous evaluation of patients during therapy should be individualized according to patient and provider preferences. A careful assessment for response to treatment requires serial clinical examinations, repeat laboratory evaluation (including tumor markers when initially elevated), and radiographic imaging. Although there is no standard schedule for evaluation during treatment, a reasonable approach would be as follows: history and physical exam prior to the start of each treatment cycle, serial assay for serum tumor markers (e.g., cancer antigen [CA] 15-3 or carcinoembryonic antigen [CEA] if they were elevated at baseline), and repeat imaging studies (using the same imaging modality throughout) every two to three cycles of therapy.

Patients on an HER2-directed therapy require regular monitoring of cardiac function with echocardiogram (ECHO) or multigated acquisition (MUGA) scan. We typically follow the recommendations for cardiac monitoring presented in the drug label (every 3 months) for the first year of therapy, and if there has been no evidence of cardiac toxicity after a year of treatment, we decrease the frequency of monitoring to every 6 months for patients remaining on treatment (Look Tables 32.3, 32.4, and 32.6).

Definition of Treatment Failure

Briefly, we monitor for treatment failure by considering serial changes in tumor markers, evidence of disease progression (new or growing metastases) based on serial imaging, and evidence for clinical deterioration in the patient (e.g., increasing disease-related symptoms, intolerable treatment toxicity, or declining performance status). We generally use "Response Evaluation Criteria in Solid Tumors"

Table 32.10 RECIST 1.1 criteria

Minimum target lesion size	≥10 mm (CT + MRI)
	≥15 mm lymph nodes
	≥20 mm chest X-ray
Measurement	Unidimensional
	Lymph nodes = short axis
Progressive disease	20% increase in sum of diameter (SOD)
	+ minimum 5-mm increase from nadir
Nonmeasurable assessment	Substantial worsening
	Tumor burden has increased sufficiently
Lymph node measurements	Specific instructions
	≥15 mm, 10–14 mm, <10 mm
PET	May be considered to support CT
	For progressive disease and confirmation of CR

(RECIST) criteria for the definition of progression (Table 32.10). However, RECIST applies to imaging of metastatic disease and does not include clinical deterioration as a measure of progression. RECIST 1.1 exists to standardize the reporting of results on clinical trials. According to RECIST 1.1, disease progression on imaging is simply defined as any of the following: the appearance of any new lesions, a 20% or greater increase in the sum of measurable target lesions compared with the sum previously recorded, or a worsening of existing nontarget lesions such as bone metastases [57] (Table 32.10).

Overview of RECIST Criteria

RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), remain the same ("stabilize"), or worsen ("progress") during treatment. Important points of RECIST are summarized as follows:

(a) Measure in the plane of the longest diameter.
(b) Do not measure lesions across normal, nontumor tissue.
(c) Do not necessarily select the largest lesions as targets. Select those that are best defined and reproducibly measurable.
(d) Use consistent imaging quality.
(e) Precise and consistent visualization of lesions is essential. Scanning without intravenous contrast usually is useless in a clinical study and typically makes the patient nonevaluable.
(f) Typically, the same anatomy must be imaged for all time points. Keep it consistent and always scan all anatomy with disease so that the reviewer can make consistent comparisons.
(g) Measure where the target lesion is the largest.
(h) A slight increase in existing nontarget lesions alone does not justify progressive disease. The progression shall be clear and obvious to determine a substantial worsening.
(i) If a target lesion separates, measure the longest diameter of each lesion separately. The individual longest diameters of all the resulting lesions shall contribute to the sum of diameters (SOD).
(j) If target lesions become confluent, calculate the longest diameter of the resulting lesion.
(k) Include the hypervascular "enhancing rim," if present, in the longest diameter measurement. Measure the longest diameter irrespective of a central necrosis.
(l) Continue measuring target lesions in their longest diameter, even when they develop central cavities or necrosis. If the sum of diameters does not accurately reflect the patient's response assessment, a different assessment may be needed.

Lymph nodes Identify the longest diameter of a lymph node or nodal mass (e.g., 18 mm), and then measure the longest perpendicular diameter to that as the short axis (e.g., 12 mm). A short axis of 12 mm defines this lymph node as being pathological but not measurable (to be measurable, it must be ≥15 mm). As such, it shall be recorded as a nontarget lesion.

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or magnetic resonance imaging (MRI), can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability. Blastic bone lesions are nonmeasurable.

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI that greatly impact image quality, lesion conspicuity, and measurement. Chest MRI is not recommended. Measurements are possible on isotropic reconstructions and nonaxial MRI planes: sagittal, coronal, or oblique. Always measure in the same plane.

Evaluating a PET-CT for progression It is sometimes reasonable to incorporate FDG-PET to complement CT scanning in assessment of progression.

Negative PET at baseline with a positive PET at follow-up is progressive disease based on a new lesion.

No PET at baseline and a positive PET at follow-up:

- If the positive PET at follow-up corresponds to a new site of disease on CT, this is progressive disease.
- If the positive PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site.
- If the positive PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease (See Box 32.1).

Box 32.1 Summary of the Optimal HER2-Targeted Therapy for Advanced Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

- Clinicians should recommend HER2-targeted therapy-based combinations for the first-line treatment. If HER2-positive advanced breast cancer progresses during or after the first-line HER2-targeted therapy, clinicians should recommend the second-line HER2-targeted therapy-based treatment.
- If HER2-positive advanced breast cancer progresses during or after the second-line or greater HER2-targeted treatment, clinicians should recommend the third-line or greater HER2-targeted therapy-based treatment.
- If available, clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for the first-line and trastuzumab emtansine (T-DM1) as the second-line treatment. If HER2-positive advanced breast cancer progresses during or after the second-line or greater HER2-targeted treatment but the patient has not received pertuzumab, clinicians may offer pertuzumab.
- If the patient has already received trastuzumab, pertuzumab, and T-DM1, clinicians should recommend the third-line or greater HER2-targeted therapy-based treatment (lapatinib plus chemotherapy, trastuzumab plus lapatinib, trastuzumab plus chemotherapy, trastuzumab or lapatinib plus hormonal therapy in patients with hormone receptor-positive disease).
- If a patient is receiving HER2-targeted therapy and chemotherapy combinations, chemotherapy should continue to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy ends, clinicians should continue the HER2-targeted therapy, and no further change in the regimen is needed until the time of progression or unacceptable toxicities.
- If a patient finished trastuzumab-based adjuvant treatment >12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations.
- If a patient's cancer is hormone receptor-positive and HER2-positive, clinicians may recommend either HER2-targeted therapy plus chemotherapy or in select cases endocrine therapy plus trastuzumab/pertuzumab or lapatinib/trastuzumab. Clinicians may add endocrine therapy to the HER2-targeted therapy when chemotherapy ends and/or when the cancer progresses.
- Management of hormone receptor-positive and HER2-positive metastatic disease without chemotherapy could conceivably include combinations of available endocrine therapies, with one or more of the currently approved HER2-targeted agents, including trastuzumab, pertuzumab, or lapatinib.

Targeting HER2 in Breast Cancer Brain Metastases

Brain metastases occur in one-third of the patients with HER2-positive MBC and are responsible for death in half of these patients. Patients with brain metastases should receive appropriate local and systemic therapies. Local therapies include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS). Treatments depend on factors such as patient prognosis, presence of symptoms, resectability, number and size of metastases, prior therapy, and whether metastases are diffuse [66]. Other options include systemic therapy, best supportive care, enrollment onto a clinical trial, and/or palliative care. Recommendations in the National Comprehensive Cancer Network (NCCN) guidelines for patients with one to three brain metastases are surgery or SRS, and consider WBRT in advanced systemic disease [1] and, for >3 brain metastases, WBRT, or consider SRS in select cases.

In a retrospective study, 176 breast cancer patients underwent SRS for brain metastases, and median survival times were 16 months for 95 newly diagnosed patients and 11.7 months for 81 patients with recurrent brain metastasis. There was no association between the number of treated brain metastases and survival. Longer survival was associated with age <50 years, Karnofsky performance status >70, primary tumor control, ER positivity, and HER2 overexpression [67].

There are currently no systemic therapies approved to treat patients with breast cancer and brain metastases. Data primarily stem from single-arm prospective trials and from case series and/or retrospective studies. Large monoclonal antibody agents such as trastuzumab, T-DM1, and pertuzumab may not penetrate the blood-brain barrier (BBB) because of their molecular size. A few hours after trastuzumab infusion, the serum levels achieved were, as expected, in the range of 10,000–100,000 ng/mL, whereas cerebrospinal fluid levels were 300-fold lower [68]. However, when metastatic tumors grow and after radiation therapy (RT), the BBB loses those structural features that are critical for its function. The serum- and cerebrospinal fluid-level ratio of trastuzumab is altered in patients with HER2-positive breast

cancer and impairment of the BBB. In a study by Stemmler et al., the ratios of median trastuzumab levels in the serum and cerebrospinal fluid were 420:1 before and 76:1 after the completion of cranial radiotherapy [69]. With concomitant meningeal carcinomatosis, the trastuzumab serum to cerebrospinal fluid ratio was 49:1 after radiotherapy.

In another small trial, the authors performed a feasibility study to determine the optimal dosage and time of administration of the zirconium-89 ((89)Zr)-trastuzumab monoclonal antibody to enable PET imaging of HER2-positive lesions. The patients underwent at least two PET scans between days 2 and 5 [70]. The results of the study demonstrated that the best time to assess (89)Zr-trastuzumab uptake by tumors was 4–5 days after the injection. PET scanning after the administration of (89)Zr-trastuzumab at appropriate doses allows visualization and the quantification of uptake by HER2-positive lesions in patients with MBC, suggesting that trastuzumab can cross a disrupted BBB and that continuation of trastuzumab after the development of brain metastases may benefit these patients.

registHER is a prospective, observational study of 1012 patients with confirmed HER2-positive tumors, including 377 (37.3%) patients with central nervous system (CNS) metastases [71]. Compared with patients with no CNS metastases, those with CNS metastases were younger and more likely to have hormone receptor-negative disease and a higher disease burden. Median time to CNS progression among patients without CNS disease at initial MBC diagnosis was 13.3 months. Treatment with trastuzumab, chemotherapy, or surgery after CNS diagnosis was associated with a statistically significant improvement in median OS following the diagnosis of CNS disease (trastuzumab vs. no trastuzumab, 17.5 vs. 3.8 months; chemotherapy vs. no chemotherapy, 16.4 vs. 3.7 months; and surgery vs. no surgery, 20.3 vs. 11.3 months). The results of multivariable proportional hazards analyses confirmed the independent significant effects of trastuzumab and chemotherapy (hazard ratio, 0.33; $P < 0.001$; hazard ratio, 0.64; $P = 0.002$, respectively). The effects of surgery and radiotherapy did not reach statistical significance ($P = 0.062$ and $P = 0.898$, respectively). In conclusion, patients with HER2-positive MBC evaluated in registHER survived longer after CNS metastases if treated with trastuzumab, chemotherapy, and surgery.

Lapatinib is the first HER2-directed drug to be validated in preclinical mouse models for activity against brain metastases of breast cancer. Lapatinib belongs to the family of small-molecule tyrosine kinase inhibitors of HER1 and HER2 and can cross the BBB. In a phase II study [72] of 242 patients, eligible patients had HER2-positive breast cancer, progressive brain metastases, prior trastuzumab, and cranial radiotherapy. Objective CNS responses to lapatinib were observed in 6% of patients. In an exploratory analysis, 21% of patients experienced a $\geq$ 20% volumetric reduction in their CNS lesions. An association was observed between volumetric reduction and improvements in PFS and neurological signs and symptoms. During disease progression in the same study, 10 of 50 patients (20%) who received a combination of lapatinib and capecitabine exhibited an objective response in the brain.

In the LANDSCAPE study, a combination of lapatinib plus capecitabine was administered to previously untreated patients with HER2-positive breast cancer and brain metastasis [73]. Twenty-nine patients had objective CNS responses (65.9%, 95% CI: 50.1–79.5), all of which were partial responses. Twenty-two (49%) patients had grade 3 or 4 treatment-related adverse events, including diarrhea in nine patients (20%) and hand-foot syndrome in nine patients (20%). The median time to RT was 8.3 months. Thirty-six (82%) patients had received RT to the brain at the time of analysis. Median time to progression was 5.5 months (95% CI: 4.3–6.0). The 6-month survival rate was 90.9% (95% CI: 77.4–956.5), and the median OS was 17 months (95% CI: 13.7–24.9). At least one severe adverse event was reported by 31% of patients; treatment was discontinued because of the toxicity in four patients. In conclusion, lapatinib plus capecitabine is highly active for untreated brain metastasis, and treatment on this protocol delayed the start of RT.

In the CEREBEL trial, patients without baseline CNS metastases were randomly assigned to receive lapatinib-capecitabine or trastuzumab-capecitabine [74]. The primary endpoint was incidence of CNS metastases as the first site of relapse. The relapse rates were 3% (8 of 251 patients) for lapatinib-capecitabine and 5% for trastuzumab-capecitabine ($P = 0.360$). PFS and OS were longer with trastuzumab-capecitabine versus lapatinib-capecitabine (hazard ratio for PFS, 1.30; 95% CI: 1.04–1.64; hazard ratio for OS, 1.34; 95% CI: 0.95–1.64). CEREBEL is inconclusive for the primary endpoint, and no difference was detected between lapatinib-capecitabine and trastuzumab-capecitabine for the incidence of CNS metastases. A better outcome was observed with trastuzumab-capecitabine in the overall population.

Results from the phase III CLEOPATRA trial in HER2-positive first-line MBC demonstrated significant improvements in PFS and OS with pertuzumab, trastuzumab, and docetaxel versus placebo, trastuzumab, and docetaxel [27]. The incidence rates of CNS metastases as the first site of disease progression were similar (placebo, 12.6%, pertuzumab, 13.7%) between the two arms. The median times to development of CNS metastases as the first site of disease progression were 11.9 months in the placebo arm and 15.0 months in the pertuzumab arm (hazard ratio, 0.58; $P = 0.0049$). OS in patients who developed CNS metastases as the first site of disease progression showed a trend in favor of pertuzumab, trastuzumab, and docetaxel (hazard ratio, 0.66; 95% CI 0.39–1.11). Median OS was 26.3 versus 34.4 months in the placebo and pertuzumab arms, respec-

tively. The differences in the survival curves were not statistically significant in the log-rank test ($P = 0.11$) but were significant in the Wilcoxon test ($P = 0.04$). While the incidence of CNS metastases was similar between arms, the results suggest that pertuzumab, trastuzumab, and docetaxel delay the onset of CNS disease compared with placebo, trastuzumab, and docetaxel.

In the EMILIA trial [75], patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane were randomized to T-DM1 or capecitabine-lapatinib until disease progression. Among 991 randomized patients, 95 (T-DM1 = 45; capecitabine-lapatinib = 50) had CNS metastases at the baseline. Among patients with CNS metastases at baseline, a significant improvement in OS was observed in the T-DM1 arm compared with the capecitabine-lapatinib arm (hazard ratio, 0.38; $P = 0.008$; 26.8 vs. 12.9 months).

These data strongly support the hypothesis that the best overall treatment also improves survival in cases of brain metastases. Other conventional cytotoxic agents that can cross the BBB may act with anti-HER2 therapy on CNS metastases, and further research is needed.

In a phase I trial combining temozolomide plus lapatinib for the treatment of brain metastases in patients with HER2-positive MBC (LAPTEM trial), 18 patients were enrolled (16 patients with recurrent or progressive brain metastases) [76]. Temozolomide orally once daily at three dose levels, 100, 150, and 200 mg/m^2/day, was given on days 1–5 of a 28-day cycle. Lapatinib was given orally once daily at three dose levels: 1000, 1250, and 1500 mg/day. Both agents were administered until disease progression or intolerable toxicity, with a maximum of six cycles. The most common adverse effects were fatigue, diarrhea, and constipation. Disease stabilization was achieved in 10 of 15 assessable patients. The estimated median survival time for the 16 patients with brain metastases was 10.9 months, and the median PFS was 2.6 months.

Neratinib, is an irreversible pan-ERBB tyrosine kinase inhibitor. Forty patients were enrolled in a phase II trial of neratinib for patients with HER2-positive breast cancer and brain metastases [77]. Neratinib 240 mg orally was given once daily. Follow-up was every 4 weeks, and brain MRI and body CT restaging were performed at week 8. Therapy was continued in CR, PR, and SD. Continued therapy with the addition of trastuzumab is allowed for progressive disease not affecting the CNS. Of the patients, 78% had prior WBRT. The median number of cycles was 2 (range 1–7), and the median PFS was 1.9 months. The most common grade 3 event was diarrhea (23%), which decreased after loperamide prophylaxis was implemented. There was no complete response, but three patients (8%) had a partial response. Progressive disease in only the CNS was observed in ten (25%) patients. To enhance CNS activity, the authors evaluated the combination of neratinib + capecitabine in a subsequent cohort. During 21-day cycles, patients received capecitabine 750 mg/m^2 twice daily × 14 days followed by 7 days off + neratinib 240 mg orally once daily. Thirty-nine patients were enrolled, the median prior metastatic line was 2, and 65% had prior whole brain radiotherapy. Overall 12-month survival was 63% (95% CI 43%-77). No patients had grade 4 toxicity; 18 (49%) had grade 3 toxicity, with diarrhea being most common (32%).

In a randomized trial, in first-line ERBB2-positive metastatic breast cancer, neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of PFS. With neratinib-paclitaxel, the incidence of central nervous system recurrences was lower (relative risk, 0.48; $P = 0.002$), and the time to CNS metastases was delayed (hazard ratio, 0.45; $P = 0.004$). In spite of a similar overall efficacy, neratinib-paclitaxel may delay the onset and reduce the frequency of CNS progression, a finding that requires a larger study to confirm [24].

Tucatinib (ONT-380) is a potent selective small-molecule inhibitor of HER2 with minimal EGFR-like side effects. Nine patients with CNS metastases (four with asymptomatic metastases and five with progressive disease) were treated with ONT-380 in combination with other systemic therapies [78]. ONT-380 was given as 300 mg twice daily with approved doses of T-DM1, trastuzumab, or trastuzumab plus capecitabine. There were three partial remissions (two patients with T-DM1, one with trastuzumab plus capecitabine). Four patients had stable disease (two patients with T-DM1, two patients with trastuzumab).

Ongoing studies of patients with HER2-positive breast cancer with brain metastasis include a randomized, phase II study of WBRT with or without lapatinib. This study (NCT01622868) is evaluating lapatinib as a radiosensitizer in combination with WBRT. ARRY-380, a HER2-selective inhibitor with some capacity to cross the BBB and activity in intracranial tumor models, is undergoing evaluation in combination with trastuzumab [https://clinicaltrials.gov/ct2/]. Several trials are also in progress combining different drugs such as ONT-380 and abemaciclib.

In conclusion, treatment options that have demonstrated some brain-specific benefit in clinical trials include capecitabine/lapatinib, the continued use of trastuzumab, ado-trastuzumab emtansine, neratinib, and the experimental agent tucatinib. Capecitabine/lapatinib would generally be considered for CNS disease only in those patients who we are not able to control with local measures. Generally, the preferred option among them is ado-trastuzumab emtansine, based on a subset of the large EMILIA trial that achieved a doubling in OS. An exploratory analysis of the single-arm KAMILLA study also found a median time to disease progression in the brain of 11.3 months with ado-trastuzumab emtansine [79] (See Box 32.2).

Box 32.2 Summary of Recommendations on Disease Management for Patients with Advanced HER2-Positive Breast Cancer and Brain Metastases

- For patients with a favorable prognosis for survival and limited (one to four) metastases, treatment options include ± surgery and radiation therapy (RT) (whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) or both.
- For other patients with diffuse disease/extensive metastases, options include WBRT and, in select cases, only the best supportive care and/or palliative care.
- For patients with leptomeningeal metastases options include involved field RT to bulky disease or symptomatic sites and intrathechal treatment for select cases with normal cerebrospinal fluid flow (consider placing ventricular catheter and subcutaneous reservoir).
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, the same systemic therapy should be continued, and for patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should use the algorithms for the treatment of HER2-positive metastatic breast cancer.
- If a patient does not have a known history or the symptoms of brain metastases, routine surveillance with brain magnetic resonance imaging (MRI) should not be performed. Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurological symptoms suggestive of brain involvement.

Intrathecal (IT) Anti-HER2 Treatment

Breast cancer is one of the most common tumors to involve the leptomeninges. Leptomeningeal carcinomatosis (LCM) of HER2-overexpressing breast carcinoma remains potentially sensitive to HER2-type receptor inhibition if the meningeal blood-brain barrier is bypassed. Importantly, the receptor status of a metastasis can change [65]. Several studies and case reports of intrathecal (IT) trastuzumab to treat LCM have been published. Extremely low levels of the antibody are detected in the CSF after intravenous trastuzumab; much higher levels can reached after intraventricular or IT administration, which might reach therapeutic concentrations.

Seventeen patients were evaluable for the efficacy and safety of IT trastuzumab for the treatment of metastatic cancer in HER2-positive breast cancer patients. The mean age at IT trastuzumab administration was 48 years, and the mean total dose was 400 mg. IT trastuzumab alone or as part of combination therapies seemed to be safe; no serious adverse events were reported in 88% of cases. In 69% of cases, there was a significant clinical improvement, whereas 31% exhibited stabilization or progression of the disease. A CSF response was observed in 67% of cases. The median OS was 13.5 months, whereas the median CNS-PFS was 7.5 months. In 24% of cases, IT trastuzumab was administered after CNS progression, with a response observed in 75% of cases and a CNS-PFS of 9.4 months. The cumulative dose of IT trastuzumab given was 1040 mg (median 1215; range 55–1675). Clinical improvement (hazard ratio, 0.14; 95% CI 0.02–0.91) and CSF response (hazard ratio, 0.09; 95% CI 0.01–0.89) were associated with longer CNS-PFS [80].

Thus, IT trastuzumab might be a promising treatment for leptomeningeal involvement in HER2-positive breast cancer patients, and further studies are warranted to optimize the dose, interval, duration, and combination of drugs for treatment. A role for IT trastuzumab for leptomeningeal metastases in HER2-positive breast cancer was evaluated in a phase I trial [81]. The protocol planned IT administration of trastuzumab (30-, 60-, 100-, or 150-mg dose levels) once a week, over the course of at least 4 weeks. The authors did not observe dose-limiting toxicity of IT trastuzumab. Eleven patients (11/16) had no toxicity attributed to IT trastuzumab. For 60 mg or higher dose levels, minor toxicities attributed to IT trastuzumab. Two patients experienced immediate toxicity, including headache or vomiting. The mean residual intracerebrospinal fluid concentration of trastuzumab was 27.9 mg/L for the 150-mg dose level. Three patients achieved a clinical response, seven patients had stable disease, and four patients had progressive disease. The MTD and recommended phase II weekly dose of IT trastuzumab in patients with HER2-positive metastatic breast cancer was 150 mg. A phase II trial using this dose regimen is ongoing.

Immunotherapy

Several immunotherapies are under development and show promise in the treatment of aggressive breast cancer [82]. Breast cancer vaccines, such as peptide vaccines, DNA vaccines, and cell-based vaccines (including dendritic cells), are the most prevalent immunotherapy strategies. HER2 antigen is one of the most common targets of these therapies. However, a strong efficacy signal has been lacking, and the benefit of vaccination against HER2 may be low in HER2-amplified tumors. There have been mixed results in the trials of peptide-based breast cancer vaccines, which have targeted HER2 [83].

The E75 HER2-derived peptide together with GM-CSF as an adjuvant was tested in a phase I/II trial with early-stage breast cancer with a range of HER2-positive expression. With the E75 vaccine, the benefit of vaccination seems the highest in tumors that are HER2 1+ or 2+ [84].

A similar result was seen with the AE37 vaccine [85]. Despite eliciting a measurable immune response, combination therapies and alternative methods of antigen delivery have been developed [86]. Robust immune responses were noted with the combination of an anti-HER2 vaccine and trastuzumab [87].

Clinical trials of DNA vaccines against HER2 [88] have shown promise in stimulating immune responses against these tumor antigens. Development of immune tolerance, or the failure to mount an immune response to the vaccine antigen due to immunoregulation, is the main problem. Peptides that have higher T cell-binding efficiency and checkpoint blockade are in progress [89]. HER2 has also been one of the most studied antigens targeted by dendritic cell vaccines [90, 91].

Strategies that target regulatory T cells, immunosuppressive macrophages, or myeloid cells are some new promising immunotherapy approaches for the breast cancer treatment [92, 93]. Targeting regulatory T cells focuses on the suppressive lymphocyte subset due to the accumulation of these cells in the solid tumor mass, which have been shown to correlate with a poor clinical outcome for patients with breast cancer. Targeting myeloid cells has primarily been aimed at inhibiting localization of immunosuppressive myeloid cells at tumor sites.

Immune checkpoint blockade is another strategy. However, trials have demonstrated modest responses in breast cancer patients to PD-1 and PD-L1 blockade as monotherapy or in combination with conventional chemotherapy [82, 94]. The expression of PD-1/PD-L1 is more prevalent in TNBC, and this strategy may be more important in this subtype. On March 2019, FDA granted accelerated approval to atezolizumab (PD-L1 inhibitor) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PDL-1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test (IMpassion130 study). Tumor-targeting therapy by the anti-HER2 monoclonal antibody is mediated by CD8(+) T-cell responses. Analysis of the tumor microenvironment has demonstrated that tumor tissues are heavily infiltrated by immunosuppressive macrophages and that most tumor-infiltrating T cells, particularly CD8(+) T cells, express high levels of the inhibitory co-signaling receptor programmed cell death-1 (PD-1). The term "immune evasion" refers to the capacity of a tumor to suppress and change the host's antitumor immune responses. The PD-1 pathway may be engaged by tumor cells to overcome active T-cell immune surveillance. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors. High expression of these ligands (particularly PD-L1) on tumor cells correlates with poor prognosis and survival. Avoidance of destruction by the host's immune system must contribute importantly to tumor growth and progression. These data suggest that the tumor microenvironment is dominated by immunosuppressive responses that prevent antitumor immunity. Removing inhibitory signals from the tumor microenvironment in combination with other therapies should be a successful tumor therapy [95, 96]. Investigating the therapeutic potential of agents that inhibit the suppression of T-cell targeting and combining them with anti-HER2 agents is a promising treatment approach. This approach was confirmed in mouse models of HER2-positive mammary tumors, in which a combination of trastuzumab with anti-PD-1 and anti-PD-L1 antibodies achieved the greatest tumor regression [95, 96]. These observations suggest that the PD-1/PD-L1 pathway plays a critical role in immune evasion by tumors and could be considered an attractive target for therapeutic intervention in several solid organ types.

In an ongoing phase I/II study of HER2-positive disease (PANACEA), the investigators propose to determine whether adding an immunotherapy can reverse trastuzumab resistance and improve clinical outcomes. This trial is evaluating the combination of the anti-PD-1 antibody pembrolizumab with trastuzumab in patients with metastatic HER2-positive breast cancer that has progressed after at least one line of therapy (NCT02129556). The randomized phase II KATE2 study is comparing T-DM1 plus the anti-PD-L1 antibody atezolizumab to T-DM1 plus placebo in patients with prior trastuzumab and taxane treatment (NCT02924883).The combination of T-cell checkpoint inhibitors and vaccines may also be a viable strategy. HER2 has also been explored as an antigen for vaccine development in HER2-positive breast cancer in many other trials: the results could change our future clinical practice.

Adoptive chimeric antigen receptor T cell (CAR T) therapy is a promising approach in immunotherapy. HER2 overexpression represents an accessible target for CAR T cells. This therapy could be an option in advanced refractory HER2-positive breast cancers. The identification of potential antigen targets will be important in the application of CAR T cell therapy to breast cancer. However, the tumor microenvironment of solid tumors is immunosuppressive, which may limit the potency of CAR T cells [97].

Other than trastuzumab and pertuzumab, several antibodies are currently being studied for the treatment of breast cancer. Patritumab is a fully human anti-HER3 monoclonal antibody. In a phase IB study of patritumab, trastuzumab, and paclitaxel in patients with metastatic HER2-positive breast cancer previously treated with trastuzumab, the objective response rate was 38.9%, with a median PFS of 274 days [98]. Margetuximab, another anti-HER2 antibody, has been engineered with an Fc domain that promotes more potent ADCC activity [99]. The currently recruiting phase III SOPHIA trial is comparing margetuximab plus physician's choice chemotherapy to trastuzumab plus chemotherapy after previous treatment with pertuzumab, trastuzumab, and

T-DM1 (NCT02492711). The XMT-1522 ADC targets an HER2 epitope and is conjugated with the cytotoxic agent auristatin and showed synergistic activity when combined with trastuzumab and pertuzumab. A phase IB study is being conducted in both HER2 1–3+ and HER2-amplified advanced breast cancers and other HER2-expressing tumor types (NCT02952729).

Future Directions

Successful targeting of HER2 has improved outcomes in HER2-positive breast cancer, but treatment resistance remains a problem. Many patients have tumors that exhibit de novo or acquired resistance, and most progress within a year. Treatment resistance can be caused by pathway redundancy or reactivation or by escape pathways. The use of combination anti-HER2 treatments for potent inhibition of HER family signaling is biologically sound and offers great clinical promise. ER is a potential resistance pathway for anti-HER2 treatments. Concomitant inhibition of ER with potent HER2 inhibition is being investigated in clinical trials. PI3K pathway activation is also a potential mechanism for resistance and is an attractive therapeutic target to overcome or prevent resistance to anti-HER2 treatment. Other proposed markers of trastuzumab resistance include a truncated form of HER2 (p95), HER2/IGF-IR dimerization, and Src activation [47].

Preclinical data in mouse models of HER2-positive breast cancer have shown that CDK4/6 inhibitors can restore sensitivity to anti-HER2 therapy in resistant tumors [100]. Although still in early phases of development, Rb disruption strategies and the use of CDK-4/6 inhibitors may be clinically useful. In a phase IB trial of palbociclib and T-DM1 (NCT01976169), the TDM-1 and palbociclib combination was well tolerated, with reversible hematologic toxicity and evidence of clinical efficacy. The recommended dose for further study is TDM-1 (3.6 mg/kg) day 1, with 150 mg of palbociclib on days 5–18 of a 21-day cycle [101]. The phase II PATRICIA trial is delivering palbociclib and trastuzumab with or without letrozole in postmenopausal patients with advanced HER2-positive breast cancer (NCT02448420). The PATINA trial will explore the effect of adding palbociclib to standard treatments for patients with HR/HER2-positive metastatic breast cancer (PATINA: NCT02947685). This trial is a randomized phase III study of maintenance palbociclib with endocrine therapy, pertuzumab, and trastuzumab after chemotherapy in advanced ER/HER2-positive disease. The randomized phase II monarcHER trial compares abemaciclib plus trastuzumab plus fulvestrant versus abemaciclib plus trastuzumab versus physician's choice, in ER/HER2-positive MBC with at least two prior anti-HER2 therapies (NCT02675231). A phase I/II trial of ribociclib and trastuzumab or T-DM1 (NCT02657343) is ongoing.

PI3K/AKT pathway aberrations are common in breast cancer. The PI3K/AKT pathway is a powerful downstream signaling pathway activated by HER2 signaling. The resulting downregulation of the PI3K/AKT pathway signaling leads to apoptosis in human tumors. Hyperactivation of the PI3K pathway by activating mutations or loss of PTEN expression has been associated with resistance to trastuzumab-based chemotherapy [95, 102, 103]. Metastatic tumors arising in patients who had previously been treated with trastuzumab expressed lower levels of PTEN compared with the primary tumor [102]. Inhibiting the PI3K/AKT pathway (as with anti-HER2 drugs) leads, by feedback mechanisms, to a rebound in HER3 activity, which is one of the main pathways to resistance. Combining targeted therapies (dual HER2 inhibition) with HER3-targeting drugs might inhibit this feedback response. Even with dual HER2 inhibition, a proportion of patients do not respond to therapy, as observed in the CLEOPATRA study [27, 28]. The BOLERO1 and BOLERO2, 3 trials investigated the addition of the mTOR inhibitor everolimus to trastuzumab and paclitaxel in the first-line therapy and trastuzumab and vinorelbine following trastuzumab resistance, respectively. A combined analysis of these studies found that tumors lacking PIK3CA mutations, PTEN loss, and PI3K pathway activation did not benefit from everolimus [38].

Several PI3K inhibitors are in phase I/II stage development. A phase I/II study of pilaralisib (SAR245408) in combination with trastuzumab or paclitaxel and trastuzumab in patients with HER2-positive MBC who progressed on a previous trastuzumab-based regimen has been completed. Other PI3K inhibitors are also under investigation. Other ongoing studies are evaluating novel therapeutic approaches to overcome primary and secondary drug resistance in tumors, including inhibition of PI3K/TOR, heat shock protein 90 (HSP90), IGF-IR, and angiogenesis. Several early phase trials are also in progress combining alpelisib (NCT02038010), taselisib (NCT02390427), or pictilisib (NCT00960960) with various combinations of trastuzumab, pertuzumab, and T-DM1.

ADCs represent an exciting frontier in cancer medicine [104, 105]. ADCs currently on the market or in clinical trials are predominantly based on two drug classes: auristatins and maytansinoids. Both are tubulin binders and block cell progression through mitosis. A newly developed class of linker-drugs is based on duocarmycins, which are potent DNA-alkylating agents with DNA-alkylating and DNA-binding moieties that bind the minor groove of DNA. SYD985 displayed high antitumor activity in two patient-derived xenograft models of HER2-positive MBCs. These data indicate that this new HER2-targeting ADC has a favorable safety profile and great potential for patients with HER2-positive cancers.

Studies comparing ADCs with different average drug-to-antibody ratios (DARs) have demonstrated that a higher average DAR leads to increased efficacy but also somewhat less

favorable physicochemical and toxicological properties. SYD985 combines several favorable properties of unfractionated ADCs with improved homogeneity. SYD985 was selected for further development and recently entered clinical phase I evaluation [106]. Preliminary evidence suggests that SYD985 could have an efficacy superior to that of T-DM1, particularly for tumors that are HER2-negative by fluorescence in situ hybridization and 1+ to 2+ for HER2 by immunohistochemistry [104]. If confirmed in the clinic, this could extend the target population of patients with breast and gastric cancers who may respond to this treatment modality to include those with fluorescence in situ-negative or immunohistochemistry-negative HER2 2+ and HER2 1+ disease.

Finally, there is a broad array of ongoing breast cancer immunotherapy clinical trials. A deeper understanding of normal and aberrant interactions between malignant and immune cells has allowed researchers to harness the immune system with novel immunotherapy strategies, many of which have shown promise in breast cancer. Both basic science and clinical trial data are rapidly developing in the use of immunotherapy for breast cancer. A search for trials of immunotherapies yielded more than 90 clinical trials that are currently enrolling breast cancer patients. The application of immunotherapeutic strategies to the treatment of breast cancer holds promise.

Conclusion

Therapies that target HER2 have altered the natural course of HER2-positive MBC. The initial success of trastuzumab in improving survival rates led to the clinical development of lapatinib, pertuzumab, and T-DM1. HER2 protein overexpression and/or gene amplification remains the most important predictive factor of response to HER2-targeted therapies. Although successful targeting of HER2 has improved outcomes in HER2-positive breast cancer, treatment resistance and brain metastases remain problematic. As in the first-line setting, multiple choices exist for second- and third-line therapies. The choice is often based on patient preferences, prior toxicities, and drug availability. Ongoing studies are evaluating novel therapeutic approaches to overcome primary and secondary drug resistance in tumors.

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End-of-Life Considerations in Patients with Breast Cancer

33

Nazim Serdar Turhal and Faysal Dane

Introduction

Most patients in the terminal status of a serious and/or life-threatening illness such as cancer develop remarkable physical and psychosocial symptoms in the last weeks to months before death. Effective treatment may successfully alleviate the majority of symptoms that may arise in terminally ill cancer patients. Here, we will discuss common issues confronted in daily practice during the end of life of advanced cancer patients.

Discussing Prognosis

Prognosis may be defined as the estimation of the likelihood that a particular health event will occur. The prognosis discussion ideally should occur when the patient is not acutely ill and therefore can process the information free of acute distress. Unfortunately, on many occasions, this discussion occurs near the final stages of illness. There is a tendency toward unrealistic aggressive intervention demands that are unlikely to benefit the patient when these discussions are conducted at the final stage [1, 2].

A proper private setting for this conversation is also of utmost importance. Particular attention should be paid to interference, such as cell phones. A typical strategy is to first determine what the other party understands about the situation and begins the conversation at that level, providing small amounts of information and frequently stopping to ensure that the other side grasps the facts [3, 4].

In cancer patients, discussing prognosis may often refer to estimating the expected life span, but this is not the only outcome that the physician is expected to know. The patient or the family may also ask the doctor to estimate the time span for other events such as losing the ability to care for himself/herself. Obviously, the doctor cannot know the course of an illness precisely for a particular patient, but the patient or relatives expect that the doctor has likely faced similar occurrences many times in the past and is thus familiar with the average course and can provide a reasonable estimate. A reasonable estimate allows the patient and family to prepare for the unwanted circumstance in a timely manner. It is important for the physician to reiterate the fact that "every patient is different" and that the exact timing and sequence of events are unknowable. This perspective may also help the patient and the loved ones maintain hope. Several studies have demonstrated that physicians are poor at guessing the life spans of terminally ill patients and even poorer at communicating such estimates frankly to the patient and family [5, 6].

Even though discussions of prognosis are an essential part of a physician's daily tasks, particularly when caring for cancer patients, they represent a miniscule portion of medical education and are not discussed extensively in standard textbooks. This lack of training may also explain why physicians frequently avoid this conversation unless forced by the counterpart or under a sense of obligation as part of good clinical practice [6–8].

Growing interest in palliative care is increasing the importance of grasping the significance of this subject matter by practicing physicians, particularly in the oncology community [6–8].

Every intervention, including laboratory tests for screening and medications, should be guided by the expected prognosis of the patient. The clinical decision-making process may be much easier for the clinician if the patient is also aware of the prognosis. There are no established and commonly agreed upon guidelines for best practices for specific stages of life expectancy [6–8].

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Discussing End of Life

When patients approach the end of life and the expected time of death is near, many practical issues regarding patient care surface, particularly if the patient is not fully capable of making decisions on his/her own. There may be some conflict between healthcare providers and family members on subsequent steps. Ideally, the patient's preferences will be discussed in advance to facilitate decision-making by the doctor and family. However, such discussions frequently do not occur, and conflicts may arise, particularly if the different parties involved in the patient's care have different expectations. A surrogate is essential under these circumstances to make decisions on the patient's behalf. Detailed advance care planning should be determined long before the crisis arises in the final days or weeks. This approach can prevent arguments both between family members and between loved ones and healthcare providers. The doctor should remember that both the family and the legal surrogate have the right to refuse any further medical interventions, and the doctor must respect that decision [5–8].

Hope

Hope is an important emotion that is highly valued by patients and relatives. Patients or their loved ones frequently reiterate that they did not lose hope or seek traces of hope because of the physician's verbal and nonverbal communication, partly because there is a common belief that success in treatment is not possible if there is no hope on behalf of the patient. Although the correlation between treatment success and hope can work both ways, the physician is frequently expected to speak in a manner that keeps hope "alive" in the patient. We, as physicians, must be honest with our patients about the facts of the disease without doubt. However, emphasizing the positive aspects of the clinical disease course, pathology or laboratory reports in no way harms the patient and, on the contrary, may increase the patient's cooperation with treatment. An essential distinction is to avoid outright lies to give hope to other parties. The patient or the family's frequent discussion of the hope "issue" may be a strong indicator that this is an issue that must be addressed; thus, the physician should appropriately bring it up during the visit [3–7].

Healing Versus Curing

It is important for the physician to inform the patient about the expected outcome of the intended therapy. The patient may not want to know the full details, and the physician must respect this while demonstrating a readiness to provide answers to the patient's questions anytime they are required. Again, providing information in small chunks and waiting for the information to "sink in" are essential. If the patient does not want to talk about this despite invitation, the physician must respect this decision as well. It is important to know that there is a significant discrepancy between a physician's intentions regarding a particular therapy and how the patient and the family perceive it. Thus, every effort should be made to bring these views closer together. In a developing world healthcare setting, the physician caring for the cancer patient must pitch in to fulfill the role of social worker, psychologist, psychiatrist, and occasionally even chaplain [9, 10].

How to Tell the Children

Every time there is a need to share bad news, there is a dilemma on how to communicate that properly with the patient and/or family, including children. Although there is no one-size-fits-all approach, there are some general rules a practitioner must follow. The explanation must begin at a level the other side currently knows or accepts. In particular, if small children are involved, we must learn about them and their level of understanding, which is of utmost importance. We as doctors must respect whether the patient does not want to know or is ready to hear what we are about to share. Sharing the information in an appropriate setting is also a prerequisite. Giving the facts in honest but small chunks and waiting for the recipients to "come to grips" with what has been said are also important. It may be necessary to stop frequently to answer questions. In addition, the explanation may also take more than one session. Children, particularly at younger ages, may feel guilty about what has happened to their parents or believe that their behavior caused the condition; therefore, this area may require detailed attention to clarify. Concluding the session with a wrap-up of what has been said and the proper communication for the next step for the other party are also important. Perceptions and reactions to bad news can vary widely based on personality and cultural factors, and the above techniques should be adjusted accordingly. However, in general, frankly answering all questions at a level that the other party is ready to understand is essential [11, 12].

Cultural and Religious Considerations

The cultural and religious backgrounds of both the physician and the patient are important aspects of disease perception as well as end-of-life care. The physician must be aware and take proper steps to avoid unnecessary confrontation if

background is going to be an important issue at that stage of the patient's care. The physician may not know in full detail how different cultures and/or religions can affect the way that an individual perceives disease and death, but careful observation of the person throughout the duration of care is certainly important and enables an appropriately individualized approach. A proper interpreter if the clinician is not fluent in the patient's language is also an important consideration [12–14].

Care Without Chemotherapy

There are times when the clinical condition requires the patient to be observed and managed for symptoms rather than administering chemotherapy or direct cancer-related treatment. This may cause patient anxiety, although this scenario is not necessarily an issue toward the terminal part of the disease course. Proper communication is also essential when this occurs. The message should not be conveyed, as "I have nothing else to offer you." Instead, the physician should state, "I am concentrating on offering you an approach that would put your quality of life above everything else" [13–16].

Hospice Programs

When a patient is admitted to the hospital, the care is based on intervening in most if not all laboratory anomalies. The house staff is trained at detecting these anomalies and correcting them appropriately and immediately. Toward the end of life, this approach may not be in the patient's best interest, and other institutions that concentrate on comforting the patient with dignity rather than correcting chart abnormalities have consequently been established. Although in some developed countries, including the USA, such palliative care teams are available both in the hospital and in hospices, in the developing world, these specialized services do not exist. As major care providers to cancer patients, medical oncologists and staff nurses usually assume this task. Palliative care providers are also an essential part of terminal care, and their presence certainly improves patient satisfaction [17, 18].

Hospices provide terminal care to patients with a life expectancy of less than 6 months. They provide services such as family education, practical support, and counseling. These services are frequently not a top priority in hospitals, which are also not equipped to provide these services. Hospice is also quite costly, and societies with limited resources are inclined to let families handle this difficult task and provide various levels of outside support to ease the work associated with it [17, 19, 20].

Relief of Suffering

Fatigue

Fatigue is the most common and one of the most disregarded and undertreated symptoms in terminally ill cancer patients. The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to activity and that interferes with usual functioning" [21]. Cancer-related fatigue differs from normal fatigue, which is usually short term and improved by rest. There are many contributing factors that influence fatigue. These factors and the fatigue itself should be assessed and managed appropriately because they significantly affect the quality of life of the patients who are receiving palliative care. Up to 75% of patients with cancer present with fatigue [21]. At the end of life, its prevalence increases to 85% in patients with life-threatening illnesses [22].

Some studies have demonstrated an association between fatigue and pain, dyspnea, anorexia, psychological symptoms, and gastrointestinal symptoms such as abdominal discomfort, bloating, abdominal distension, and constipation [23, 24]. The essential factors contributing to cancer-related fatigue are cancer therapy; metabolic/nutritional/hormonal issues such as anemia, poor nutrition, hypothyroidism, menopause, and dehydration; or other comorbidities such as heart problems or pulmonary diseases. Pain and its treatment, emotional distress, and sleep disturbances may also contribute to cancer-related fatigue. Although as a general rule anemia is considered the most important contributor to fatigue in patients experiencing cancer treatment, its importance is diminished toward the end of life for cancer patients. During that stage, other factors, including psychological symptoms such as anxiety and depression, pain, cachexia, adverse effects of medications, physical inactivity, and infection, may play a greater role.

A comprehensive history and physical examination are indicated to identify potentially reversible etiologies. A review of all medications, including alternative therapies, is important to identify side effects and potential drug interactions that may contribute to fatigue. In these cases, altering the dose interval may significantly improve fatigue.

The optimal management of fatigue involves aggressive treatment for potentially treatable etiologies. If a specific reversible etiology cannot be identified, symptomatic treatment is appropriate. There are limited data to support the hypothesis that one pharmacological approach is superior to another for fatigue [25]. Patients who have a high cancer burden with fatigue may be given a 2-week trial of corticosteroids (20–40 mg of prednisone) or megestrol acetate (480–800 mg/day). In cancer patients with severe fatigue

who do not respond to steroids or have fatigue that is considered to be related to opioids, methylphenidate or modafinil may be recommended [25]. Moderate exercise, cognitive behavioral therapy, and yoga may be helpful. In most cases of advanced cancer, because of the multidimensional nature of fatigue, a combination of both pharmacological and non-pharmacological interventions may be beneficial.

The increasing cancer burden and declining functional reserve result in fatigue and a decrease in routine daily activities at the end of life. Patients may not be able to even move in their home to access a bedroom or toilet. In such cases, creating space for care on an accessible level or providing a portable toilet may improve patient comfort.

Loss of the ability to move or transfer independently is one of the most significant aspects of functional inadequacy. The period between independent mobility and bed confinement entails a high risk of falls. During this period, assistive equipment may be required. In hospitalized patients, family members should be allowed to stay with the patient for comfort and to promote safety. Bed alarms may help hospital staff to respond to patients' needs promptly to avoid injuries.

A prolonged period of lying on a flat bed on the same part of the body may result in skin ulcers. To decrease these ulcers, turning and repositioning may be beneficial. If these maneuvers are not comfortable for the patient, adequate cushioning may improve comfort.

In Turkey, home healthcare is not widely available. Thus, family members should be educated in transfers, turning, changing, feeding, and other personal care issues to ensure safety.

Insomnia

Insomnia is observed in the majority of terminally ill cancer patients. Insomnia in dying patients may commonly result from undertreated pain, depression, anxiety, delirium, dyspnea, nocturnal hypoxia, nausea and vomiting, or pruritus. Drugs such as steroids and antiemetics may cause insomnia. Apart from adversely affecting the quality of life, insomnia can heighten the intensity and awareness of other symptoms such as pain, anxiety, or fatigue. One study indicated that the most common causes of insomnia in patients receiving palliative care are uncontrolled pain, urinary symptoms, and dyspnea [26]. In this study, 62% of patients who were prescribed hypnotic drugs reported improvement in sleep disturbance. Another study reported that many terminally ill advanced cancer patients are chronically prescribed hypnotic drugs for unclear indications [27]. In the majority of these patients, discontinuation of the hypnotic drugs may significantly improve cognition without adversely affecting insomnia.

Meta-analyses of randomized, placebo-controlled trials indicate that benzodiazepines are effective in improving sleep duration and sleep quality [28]. A newer class of sleep-promoting medications called nonbenzodiazepines such as zaleplon or zolpidem has also been shown to be effective in patients with insomnia [29].

Anecdotal evidence suggests that taking a warm bath or drinking a glass of warm milk prior to bedtime and avoiding caffeinated beverages following dinner may improve the quality of sleep.

Gastrointestinal Symptoms

Nausea and Vomiting

Nausea in palliative care patients with advanced cancer may have many causes. Although there have been many randomized clinical studies in the field of chemotherapy- or radiation treatment-induced nausea and vomiting, evidence is lacking for terminally ill advanced cancer patients who have nontreatment-related nausea [30]. Great effort should be made to identify and manage the treatable etiologies. The correction of metabolic abnormalities, overviewing medications, opioid rotation, rational bowel care, and, in the case of brain involvement, treating the metastasis may provide relief.

If a potentially treatable etiology cannot be identified and if the bowel obstruction is not the cause, symptomatic treatment may be started with a prokinetic agent. In these cases, because of its central antiemetic and peripheral gastric-emptying effects, metoclopramide would be an ideal option for symptomatic treatment [31]. Dexamethasone and other steroids may augment the effects of metoclopramide. In cases in which steroids and metoclopramide are contraindicated, other centrally acting antiemetic agents can be administered. Serotonin antagonists are very useful for chemotherapy-, radiation treatment-, or operation-induced nausea and vomiting. For patients with contraindications for oral administration, metoclopramide, dexamethasone, or haloperidol may be given intravenously. In patients with bowel obstruction, prokinetic agents are contraindicated. In these circumstances, dexamethasone and haloperidol are good options. In addition, because of its reduced effects on gastrointestinal secretions and motility, subcutaneous octreotide may be beneficial in patients with bowel obstruction.

Dry Mouth

More than two-thirds of patients with advanced cancer complain of thirst or dry mouth. Dry mouth in this population is usually a result of opioids and is not because of dehydration and serum sodium; in contrast to healthy individuals, it is unrelieved by fluid therapy [32]. Most palliative care clinicians promote the use of good mouth care and sips of water when desired rather than parenteral hydration in this setting [33].

Decreased Oral Intake

The great majority of patients with advanced stage cancer have reduced oral intake before death. The inability to swallow is a common symptom in these cases. It might occur as a part of weakness or generalized fatigue or as a result of sedation related to medications or metabolic disturbances. The inability to consume sufficient food or fluids generally causes emotional stress for family members and other caregivers. In the final days or weeks of advanced terminal cancer, high caloric intake has not been shown to improve functional status or prolong survival. Thus, parenteral nutrition or tube feeding is not recommended for the nutritional supply of cancer patients in the dying days or hours. Case-based reports and retrospective series support the idea that adequate hydration in terminally ill patients is related to the amelioration of symptoms and a comfortable death. To improve mouth irritation and symptoms of thirst, good mouth care should be performed. In a randomized study, 129 cancer patients were enrolled to receive either 1 l of normal saline over 4 h or a placebo (100 ml per day) to determine whether parenteral hydration was superior in improving symptoms of dehydration and delaying the onset or severity of delirium and whether it had any effects on quality of life [34]. The study demonstrated that there was no difference between the treatment and placebo groups in dehydration symptoms, quality of life, or survival.

Loss of Bowel Control

The loss of bowel control in the last days of life may cause incontinence of the urine and/or stool. The incontinence of stool or urine is commonly distressing for the patient and family members. In the case of urinary incontinence, a urinary catheter may minimize the need for frequent cleaning and changing. However, the use of catheters should be considered carefully and may not be used if urine flow is minimal and can be managed with absorbent pads.

Respiratory Symptoms

Upper Airway Secretion

For most patients, problematic airway secretions occur late in the dying process. The loss of the ability to swallow upper airway secretions may result from weakness and decreased neurological function. The gag reflex and clearing of the oropharynx decline, and secretions from the tracheobronchial tree accumulate. Increased airway secretions may interfere with a patient's ability to sleep, worsen dyspnea, precipitate uncomfortable coughing spells, and predispose the patient to infections.

In addition to a professional explaining and reassuring the patient's family, proper positioning and encouraging the family to cleanse the mouth with sponge sticks might be beneficial. Some patients may benefit from suctioning to clear excessive secretions if they have many secretions. However, deep suctioning should be avoided.

A recent review failed to demonstrate that any intervention was superior to placebo in patients with death rattle [35]. Although pharmacological agents have not been demonstrated to be beneficial in these patients, to relieve suffering, clinical judgment must be used to determine whether a pharmacological agent should be used to facilitate drying of secretions. Therefore, for patients managed at home, a scopolamine patch or glycopyrrolate may be recommended. For hospitalized patients, glycopyrrolate may be preferred due to its rapid onset of action and low central nervous system side effects.

Dyspnea in the End of Life

Dyspnea is defined as an uncomfortable awareness of breathing and is observed in approximately 70% of dying patients [36]. Dyspnea encompasses multiple somatic perceptions that are described as air hunger, increased effort for breathing, chest tightness, rapid breathing, incomplete exhalation, or a feeling of suffocation. Dyspnea is a multidimensional symptom consisting of affective and physical aspects. Dyspnea is a major detriment to quality of life [37]. Dyspnea has prognostic impact for survival, mainly in terminally ill cancer patients [38]. One study found that the presence of dyspnea was associated with a median survival of less than 30 days [39]. The goal in treating dyspnea is to reduce the distress. Among patients receiving palliative care for advanced cancer, the causes of dyspnea are often irreversible. However, if a treatable cause of dyspnea, such as pulmonary emboli, airway obstruction, or pleural effusion, is identified, the specific treatment of the underlying cause may be appropriate depending on the invasiveness of the therapy. Studies of supplemental oxygen for the relief of dyspnea have shown controversial results in hypoxemic patients with cancer. The benefit of oxygen has not been demonstrated in nonhypoxemic patients [40]. A systematic review of controlled trials that included both hypoxemic and nonhypoxemic patients concluded that there was no consistent benefit of oxygen over air inhalation for dyspnea in patients with end-stage cancer [41]. Supplemental oxygen is a standard therapy for the symptomatic management of patients who are hypoxemic on room air. In patients who are not hypoxemic, supplemental oxygen appears no more likely than room air to provide relief of dyspnea. A randomized trial of 239 patients found no difference between oxygen and room air for the treatment of refractory dyspnea in nonhypoxemic adult outpatients [42].

The use of noninvasive positive pressure ventilation (NPPV) at the end of life is a variable practice. In a randomized study, NPPV was shown to improve dyspnea much faster than passive oxygen therapy in 200 hospitalized

patients with end-stage cancer and severe respiratory failure [43]. In addition, the dose of morphine required to control dyspnea was significantly less in the NPPV group. Nevertheless, NPPV can be uncomfortable for patients with dyspnea. In addition, decreased mental status is thought to be a contraindication to NPPV because of the risk of aspiration.

Opioid agonists are the best-established pharmacological treatment for the management of dyspnea in patients with advanced disease. Randomized trials and systematic reviews have demonstrated the benefits of opioids in treating dyspnea [44, 45]. In a phase II study, the beneficial dose of sustained-release morphine was 10 mg daily for 70% of patients, and the benefit at any dose was sustained for 3 months in 53% of patients [46].

Systematic reviews of a small number of trials have concluded that benzodiazepines do not have a major role in the management of dyspnea in the absence of anxiety [47]. However, benzodiazepines are important drugs when anxiety is significant. Bronchodilators, glucocorticoids, and diuretics may provide relief of dyspnea in some clinical situations.

Psychiatric Disorders in Cancer Patients

Depression and Suicidal Ideation

The prevalence of major depression in cancer patients is as high as 40% [48]. In cancer patients, depression is the most common mental health problem. Certain cancer drugs, such as steroids and vinca alkaloids, may cause depressive symptoms. Factors that are associated with an increased risk of depression are prior history of depression, young age, and uncontrolled cancer symptoms. If the diagnosis of depression is missed, then the quality of life of dying patients is impaired, and the burden of suffering increases. Individuals who have depression are also at increased risk for suicide. Although depressed mood and sadness are normal responses in patients facing death, feelings of hopelessness, helplessness, loss of interest, excess guilt, and suicidal ideation are among the indicators of depression in advanced cancer patients.

A careful diagnostic interview is the gold standard method for assessing whether patients are clinically depressed. Major depression is a treatable condition, even in terminally ill patients. The first step in treating depression is to relieve uncontrolled symptoms. For patients with major depression, supportive psychotherapy should be initiated and is sometimes sufficient to treat the condition. However, most experts recommend an approach that combines supportive psychotherapy with patient and family education and the use of antidepressant medication. In terminal care, the psychostimulants methylphenidate, dextroamphetamine, and modafinil have a rapid onset of antidepressant action and are preferred to other agents, such as selective serotonin reuptake inhibitors, which may require weeks to achieve full effectiveness [49].

Delirium

Delirium is one of the most frequent neuropsychiatric disorders observed in patients with advanced cancer [50]. The incidence ranges from 15% to 75% depending on the clinical condition. In a study conducted in terminally ill patients, delirium was reported in more than 75% of patients [51]. Delirium is multifactorial in origin. It might be a result of either the cancer itself or a result of treatments, electrolyte imbalances, or infection, etc. The identification of the reversible causes of delirium is essential because cognitive improvement may occur rapidly with treatment. Symptomatic and supportive therapies such as fluid and electrolyte balance, nutrition, and vitamins are also important. Haloperidol is the drug of choice for delirium in terminally ill patients [52]. Lorazepam plus haloperidol may be more effective than haloperidol alone in sedating the delirious patient.

Stopping Nutrition and Hydration in End-of-Life Care

As mentioned above, the great majority of terminally ill cancer patients have reduced oral intake before death. The reasons for insufficient oral intake include loss of appetite, nausea, vomiting, dysphagia, generalized fatigue, gastrointestinal obstruction, or impaired cognitive function. Family members usually become distressed when the cancer patient is unable to consume sufficient food and fluids, and they fear that the condition will result in more suffering and death [53].

In general, there are no clear indications for artificial nutrition or hydration when supporting palliative care at the end of life. Artificial hydration is the provision of water and electrolytes by any route other than the mouth. Artificial nutrition involves nonoral, enteral, or parenteral delivery of nutrients. Studies suggest that artificial nutrition has no effect on prolonging life or improving functional status in many advanced diseases [54]. Retrospective and case series studies conducted in advanced cancer patients have demonstrated that decreased protein synthesis and increased protein degradation are associated with the release of cytokines [55].

Therefore, providing nutritional supplements by either the enteral or parenteral route does not improve functional status, improve symptoms, or prolong survival in advanced cancer populations. Indeed, there are no randomized trials comparing nutritional support to no nutritional support in patients receiving palliative care for a terminal illness. However, the consistent lack of benefit from retrospective trials argues against the routine use of enteral or parenteral nutrition in patients receiving palliative care.

The practice of administering hydration near the end of life differs widely. Although the majority of cancer patients who die in acute care hospitals receive hydration until death, most patients who die at home receive no fluids. There are conflicting data on the association between symptoms and fluid deficits in terminally ill patients. Decisions regarding the use of hydration should be individualized. Some symptoms, such as delirium, sedation, or myoclonus, are thought to be aggravated by dehydration. In these cases, there may be a role for a trial of a small amount of parenteral fluids. Otherwise, it is inappropriate to routinely use hydration in terminally ill patients.

Palliative Sedation

Palliative sedation aims to relieve severe and refractory symptoms at the end of life. The aim of palliative sedation is to reduce the severity of intolerable suffering for terminally ill patients. It is usually used for the treatment of pain, dyspnea, agitated delirium, and convulsions. In a systematic review of observational studies including more than 1000 patients, there was no statistically significant difference in survival between patients who underwent sedation and those who did not [56]. The sedative medications used for palliative sedation include midazolam, levomepromazine, chlorpromazine, phenobarbital, and propofol. Once adequate relief has been achieved, dose titration of the sedative drugs may be determined by the clinical situation.

The Final Days

The final days are usually defined as the last few days to weeks of a patient's life. The patient may have many severe symptoms ranging from dyspnea to incontinence, and observing their loved ones suffering from these symptoms may place an unbearable burden on the families.

If the patient is in the hospital, every effort should be made to comfort the patient, and family concerns and demands should be properly addressed. Particular attention should be paid to ensure that the family does not feel "abandoned." This period may be the appropriate time to make arrangements for final visits and for cultural and religious requirements following death [13, 14, 16, 19].

After the Death

The family should be able to spend as much time as needed after the death. Small acts of respect to the family after death, such as offering condolences, may facilitate the acceptance and closure of the process in their own mind [57–59].

Grief and Bereavement

The level of grief may depend on many issues; some are generalizable, such as culture and religion, but some are not, such as personal guilt and coping difficulties. Grief usually begins even before the patient dies; thus, supporting measures should start with the anticipated loss. Suffering should begin to ease by approximately 6 months after the death, but reminders such as anniversaries may remind families of the loss for years after. As resources allow, support for families should continue for at least 1 year after the loss and be available thereafter in case of need. If not supported adequately, grieving individuals are expected to have higher rates of psychiatric illnesses, substance abuse, etc. [57–59].

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Part VI

New Breast Cancer Therapeutic Approaches

Angiogenesis Inhibition in Breast Cancer

34

Kerem Okutur and Gokhan Demir

Introduction

Breast cancer is the most frequently occurring malignant tumor among women. Although there have been many impressive advances in systemic therapies that have translated to significant improvements in survival, postoperative recurrence and distant metastasis remain unsolved problems. Although adjuvant therapies maintain significant decreases in local recurrence and distant metastasis in early-stage breast cancer, nearly one-third of these patients eventually develop metastatic disease. In advanced breast cancer, however, the aim of treatment is palliation, and the mean survival ranges from 24 to 48 months [1].

Angiogenesis is a process with important roles in all stages of cancer, including growth, invasion, progression, and metastasis. Tumors require new blood vessel formation to supply oxygen and nutrients. However, tumor-associated angiogenesis shows structural and functional differences from physiological angiogenesis. In tumor-associated new vessel formation, structural anomalies and vascular anarchy are distinctive, and these differences allow increased oxygen and nutrient diffusion and resistance to chemotherapeutic agents and radiation treatment compared with normal tissues [2].

With the shift in cancer treatment from chemotherapeutic agents to targeted treatments in the late 1990s, antiangiogenic strategies were discovered. Since then, preclinical and clinical studies using monoclonal antibodies and small-molecule agents with a role in the angiogenic process have accelerated.

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Breast Cancer and Angiogenesis

Tumor angiogenesis is a complex process that involves the interaction of stimulatory and inhibitory factors in multiple steps. The appearance of new vessels during the period of tumor growth (angiogenic switch) occurs when the level of stimulatory factors surpasses the level of inhibitory factors [3]. The vascular endothelial growth factor (VEGF) pathway is the most important pathway; VEGF, as the main element of this pathway, is the most important stimulatory factor in the proliferation of the vascular endothelial cells [4].

There are six molecules in the VEGF family: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor (PGF)-1, and PGF-2 [5]. VEGF receptors (VEGFR) comprise three cell-membrane receptors (VEGFR-1/Flt-1, VEGFR-2/Flt-1 (KDR), and VEGFR-3/Flt-4) and a soluble form of VEGFR-1 (sVEGFR-1). These receptors are mainly expressed by endothelial cells and are activated by VEGF [6]. The VEGF gene is situated on the short arm of the sixth chromosome (6p21.3). There are many factors that stimulate VEGF gene expression, including hypoxia; certain growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF); tumor necrosis factor (TNF); transforming growth factor β (TGF-β); interleukin 1 (IL-1); nitric oxide; tumor suppressor genes, such as p53; oncogenes, such as K-ras, H-Ras, and v-scr; HER2; and HER1/EGFR [7]. Among these, the most effective stimulant for angiogenesis is hypoxia.

VEGF receptors contain seven immunoglobulin (Ig)-like domains in the extracellular region, a transmembrane region, and a tyrosine kinase domain. While VEGFR-1 is mainly activated by VEGF-A, VEGF-B, and PIGF, the main stimulant of VEGFR-2 is VEGF-A. The binding of VEGF-C and VEGF-D to VEGFR-3 stimulates lymphangiogenesis [5]. The binding of VEGF to the extracellular domain of the receptor leads to conformational changes in the structure of the receptor and to dimerization. Dimerization of the receptor initiates cytoplasmic catalytic activation, resulting in autophosphorylation of the tyrosine

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kinase. This autophosphorylation activates the phosphatidylinositol 3-kinase (PI3-K)-Akt pathway and the Ras-Raf-MEK-mitogen-activated protein kinase (MAPK)-dependent pathway [8]. The activation of these pathways triggers many processes that lead to new vessel formation, such as endothelial cell survival, mitogenesis, migration, differentiation, vascular permeability, and endothelial progenitor cell mobilization from the bone marrow into the peripheral circulation.

The first systematic study to draw attention to the importance of angiogenesis in breast cancer came from Folkman and colleagues. From the results of this study, it was determined that angiogenesis is one of the basic requirements for tumor progression (angiogenic switch) [9]. The transfection of breast cancer cells with angiogenic stimulatory peptides increases tumor growth, invasiveness, and metastasis [10]. Furthermore, it has been shown that the inhibition of VEGF in breast cancer cell lines reduces the microvessel density and decreases the infiltration of tumor-related macrophages but, conversely, increases the infiltration of tumor-related neutrophils [11].

Clinical studies show that angiogenesis begins to develop in the early stages of breast cancer and is particularly responsible for progression into an invasive form. In the studies conducted on patients with preinvasive breast lesions (ductal or lobular hyperplasia and carcinoma in situ), angiogenesis and VEGF levels are significantly increased compared with those of normal breast tissue in the preinvasive stage [12]. Similarly, in patients with invasive tumors, angiogenesis and VEGF expression are significantly increased compared with patients with preinvasive lesions [13]. Furthermore, some VEGF polymorphisms significantly increase the risk of developing breast cancer [14]. Increased microvascular density and aggressive biological behavior are linked with breast cancer progression in patients with benign and premalignant lesions [15, 16]; additionally, in cases with higher microvascular density, the risks of distant metastasis and recurrence are higher [17].

A better understanding of the relationship between angiogenesis and tumor development and progression has accelerated the development of treatment strategies targeting these processes. In 1993, VEGF inhibition was shown for the first time to cause an in vivo antitumor effect; this was the start of the studies focused on angiogenesis inhibitors [18]. The angiogenic treatments developed since 1993 can be divided into two groups. The first group comprises antibody treatments targeting VEGF or VEGFR. This group includes the monoclonal anti-VEGF antibody bevacizumab, the VEGF-trap agent aflibercept, and the anti-VEGF agent ramucirumab. The other group features small-molecule tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib, and others) that exert their effects by binding the tyrosine kinase domain of VEGFR and targeting the intracellular signal transduction system.

Bevacizumab

Bevacizumab is a humanized recombinant IgG1 monoclonal antibody that selectively binds to all isoforms of VEGF. Upon binding, it prevents the VEGF-VEGFR interaction, thereby neutralizing VEGF activity. As a result, the endothelial cells are driven toward apoptosis, and a significant regression in tumor-related abnormal vascularization occurs [19]. The inhibition of VEGF leads not only to a regression of the vascular structure of the tumor but also to a normalization of vasculogenesis by removing the structural and functional anomalies in existing vessels [20]. The normalization of angiogenesis, the removal of tumor-linked vascularization, and the amelioration of bloodstream anomalies all lead to better penetration by chemotherapeutic agents into the tumor tissue, which increases the response rates to and the antitumor efficiency of chemotherapy [21]. Furthermore, the proliferation of endothelial cells and the decrease in migration inhibit new vessel formation by the tumor. VEGFR-1 and VEGFR-2 are expressed on the surface of not only endothelial cells but also tumor cells; therefore, the direct antitumor effect of bevacizumab can be discussed. In the last few years, evidence of the effect of bevacizumab on the immune system has also been found. Bevacizumab increases the activity of B and T lymphocytes and the number of natural killer cells; in particular, as a result of T lymphocyte activation, the antigen presentation capacities of dendritic cells improve, and these changes contribute to the antitumor effects of the drug [22].

The pharmacokinetics of bevacizumab have been evaluated in different studies with doses of 1–20 kg (weekly, once in 2 weeks or 3 weeks). With a dose of 1–10 kg, the pharmacokinetic effects of bevacizumab appear to be linear. The half-life of the drug is approximately 20 days. The time to reach a stable plasma concentration is approximately 100 days [23]. The most frequent side effects of bevacizumab are hypertension, proteinuria, and hematuria, and the less frequent but potentially lethal side effects are arterial thrombosis and gastrointestinal perforation [24].

The first FDA approval for bevacizumab was obtained in February 2004 after a study showed that its addition to a first-line treatment regimen in metastatic colorectal cancer including 5-fluorouracil significantly improved overall survival (OS), progression-free survival (PFS), and response rate (RR) [25]. Later, its efficacy as a second-line therapy was also shown [26]. As a result of subsequent studies, it was also approved for the treatment of non-small cell lung cancer with non-squamous cell histology, renal cell carcinoma, ovarian cancer, high-grade glial tumors, and cervical cancer [27–31].

In phase I studies, no serious toxicity of bevacizumab was observed when used as monotherapy or in combination with other chemotherapeutic agents at a dose ranging from 1 to 10 mg/kg for several tumor types [32–34]. In a phase I–II

study that included 75 patients with metastatic breast cancer who received anthracycline and taxane treatment before using bevacizumab at doses of 3 mg/kg, 10 mg/kg, or 20 mg/kg, the overall response rate was 9.3%, and the median response time was 5.5 months [35]. Four patients left the study because they experienced side effects; hypertension (22%) was the most frequently observed adverse effect. For subsequent studies, the ideal dosage for bevacizumab was reported to be 10 mg/kg.

Studies in HER2-Negative Advanced Breast Cancer

The results of the XCALIBr study, which was the first multicenter phase II nonrandomized study of the efficacy and safety of bevacizumab in metastatic breast cancer, were presented at the 2007 ASCO annual meeting [36]. In this study, 103 patients with HER2-negative metastatic breast cancer were treated with capecitabine at 100 mg/m^2 twice daily on days 1–14 every 21 days and bevacizumab 15 mg/kg on day 1 every 21 days. The endpoint of the study was set as PFS, and patients who progressed under the study regimen continued their treatment with second-line paclitaxel or vinorelbine combined with bevacizumab. The overall response rate was 38.5% (stable disease (SD) rate 42.99%), PFS was 5.7 months, and OS was 10 months. The median time to progression (TTP) was longer in patients with estrogen receptor-positive than estrogen receptor-negative tumors (8.9 months vs. 4 months, $p < 0.0001$). The treatment was generally well tolerated; the most frequently observed grade III adverse effects that were reported are hand-foot syndrome (13%) and pain (10%). Grade IV pulmonary embolism stood out as the most serious side effect in 2% of the patients. In a phase II study of 56 metastatic breast cancer patients published by Burstein et al., weekly treatment with vinorelbine and bevacizumab (10 mg/kg every 14 days) was done; the general response rate was 34%, and the median TTP was 5.5 months [37]. The median TTP was significantly longer in patients with low base-line VEGF levels; therefore, it was reported that the plasma VEGF level could be used as a prognostic parameter for patients receiving anti-VEGF treatment. In another phase II study, 45 metastatic breast cancer patients (NCCTG N0432) were treated with a combination of docetaxel (75 mg/m^2 on day 1 every 21 days), capecitabine (825 mg/m^2 twice daily on days 1–14 every 21 days), and bevacizumab (15 mg/kg on day 1 every 21 days) [38]. The general response rate was 49%, the median response time was 11.8 months, and the median PFS and OS were 11.1 months and 28.4 months, respectively. Grade II/IV side effects were frequently related to chemotherapy; bevacizumab-related side effects included grade III gastrointestinal bleeding in one patient (2%), grade III hypertension in two patients (4%), and grade IV thrombosis in one patient (2%).

The ATHENA trial, a phase II trial that includes 2251 patients and involves a median 12.7-month follow-up, is researching the efficacy of bevacizumab addition to the first-line treatment of recurrent or metastatic HER2-negative breast cancer with taxane-based regimens or other non-anthracycline chemotherapeutic agents (capecitabine and vinorelbine) [39]. The median age of the patients in this study is 53, 95% of the patients who are involved have an ECOG 0–1 performance status, and 65% of the patients are estrogen receptor positive. Regarding the treatment regimens, 35% of the patients received paclitaxel, 33% received docetaxel, and 10% were given a combination regimen including taxane. The median TTP was 9.5 months, and the ORR was 52%. TTP in combination with bevacizumab and taxane regimens appeared to be longer (10.9–6.8 months) compared to bevacizumab in regimens lacking taxane. In the triple-negative group, the median TTP was 7.2 months, leading us to believe that the effect of bevacizumab in HER2-related disease is independent of the hormone receptor status. The toxicity observed in the study was consistent with the data from the phase III studies of bevacizumab combined with taxane-based chemotherapy in terms of the side-effect profile. The median OS of the study population after a median of 20 months of follow-up was 25.2 months. The median OS was 18.3 months in the triple-negative group and 20.5 months in the group over 70 years of age. The survival results of triple-negative patients were similar to those of other phase III studies, demonstrating the efficacy of bevacizumab in this subgroup. In the subgroup analysis, the TTP and OS of the patients who continued to use bevacizumab after regression were significantly longer than those of the patients who stopped using bevacizumab before or when chemotherapy was halted (for TTP, median 11.6 months vs. 6.7 months; for OS, median 30 months vs. 18.4 months) [40]. In addition to the longer TTP and OS, prolonged treatment with bevacizumab was also associated with no increase in toxicity. These results raise the question whether bevacizumab can improve the results of metastatic breast cancer in a similar manner as in advanced ovarian cancer. In a few studies that aimed to answer this question, maintenance bevacizumab treatment was tolerated and was linked to a longer period of stabilized disease [41–43]. In the randomized phase III IMELDA trial, 185 patients without disease progression after three to six cycles of first-line docetaxel (75 mg/m^2 every 3 weeks) plus bevacizumab (15 mg/kg) were randomized to receive either capecitabine (1000 mg/m^2, twice per day on days 1–14 every 21 days) plus bevacizumab (15 mg/kg) or bevacizumab alone [44]. In the maintenance arm, the median PFS and OS were significantly longer in the capecitabine + bevacizumab group (11.9 months vs. 4.3 months, $p < 0.0001$; and 39 months vs. 23.7 months,

$p = 0.0003$, respectively). The IMELDA trial confirmed the efficacy of the capecitabine-bevacizumab combination as a maintenance therapy in HER2-negative advanced breast cancer as in metastatic colorectal cancer.

In the first randomized phase III study of breast cancer that included bevacizumab, 462 metastatic breast cancer patients who had been previously treated with anthracycline and taxane were treated with capecitabine alone (2500 mg/m^2 on days 1–14 every 21 days) or with a combination of capecitabine + bevacizumab (15 mg/kg on day 1 every 21 days) (AVF2119 trial) [45]. HER2-positive patients comprised 20–25% of the study group, and approximately 75–80% of the patients have visceral metastases. According to the results of the study, although adding bevacizumab to capecitabine resulted in a twofold increase in the response rate (19.8% vs. 9.1%, $p = 0.001$), no change occurred in PFS and OS. Because the increasing response rate did not reflect the primary endpoint of the study, the short response times of the cases that were responsive to bevacizumab and the effect of bevacizumab being masked by previous treatments were emphasized. The authors also suggested that angiogenic pathways become more complex during disease progression; therefore, using antiangiogenic treatments at the earlier stages of metastatic disease (in other words, as the first-line treatment) is likely the best approach.

Directed by this new information, a new phase III study has begun (E200 trial) [46]. In this study, using weekly paclitaxel monotherapy as the first-line treatment of metastatic breast cancer was compared with the same regimen including bevacizumab. HER2-negative cases comprised 90% of the patients. The primary endpoint of the study was PFS, which was significantly longer in the bevacizumab arm (median 11.8 months vs. 5.8 months, $p < 0.001$). Additionally, the objective response rate was higher in the bevacizumab arm (36.9% vs. 21.2%, $p < 0.001$). Conversely, no OS difference was found between the two groups. OS is generally accepted as a reliable cancer endpoint; however, PFS is not accepted by many researchers as an important endpoint in metastatic disease. Nevertheless, the relative benefits of both OS and PFS as primary endpoints are being discussed, especially in cancers, such as breast cancer, that have long post-progression survival times. However, the FDA passed an accelerated approval for bevacizumab in 2008 for the first-line treatment of metastatic HER2-negative breast cancer based on the significant benefit on PFS shown in this study and noting that analyzing the improvement of OS requires a longer period of time for follow-up and larger studies including many more patients.

In the double-blinded, placebo-controlled phase III AVADO (Avastin and docetaxel) study, 736 patients with recurrent, metastatic HER-negative breast cancer who did not receive any treatment were randomized into three groups [47]. The first group received docetaxel and placebo, the second group received docetaxel and bevacizumab (7.5 mg/kg), and the third group received docetaxel and bevacizumab (15 mg/kg). All patients whose disease progressed continued to the second-line treatment, which included bevacizumab. The ORR was 46% in the placebo group, 55% in the low-dose bevacizumab (7.5 mg/kg) group, and 64% in the high-dose bevacizumab (15 mg/kg) group. A significant improvement was observed in PFS in the groups receiving 7.5 mg/kg and 15 mg/kg doses compared with the placebo group (9 months, 10 months, and 8.1 months, respectively). However, this improvement does not reflect the OS because no OS differences were found between treatment groups. The researchers tried to explain this lack of effect on OS as being due to insufficient power of the study for a survival analysis and to one-third of the patients in the placebo group being crossed over to the second-line treatment that included bevacizumab. However, the FDA has withdrawn the previous accelerated approval that it had granted because of the much lower PFS benefit compared with the E2100 study and because no improvement in OS was achieved. In a meta-analysis, the biggest improvement in PFS with bevacizumab was observed in patients who received weekly chemotherapeutic regimens [48]; this may explain why the improvement in PFS observed in the E2100 study is bigger than that in the AVADO trial and in the other trial discussed below, RIBBON-1. According to the biomarker results of the AVADO study, plasma VEGF-A and VEGFR-2 are potential markers for the efficacy of bevacizumab [49]. In the prospective MERiDiaN study, plasma VEGF-A was evaluated as a predictive biomarker for bevacizumab in HER2-negative breast cancer [50]. The results indicated that the PFS improvement with bevacizumab was similar to that for other first-line studies, but plasma VEGF-A did not correlate with the PFS benefit and did not identify patients who benefitted the most from bevacizumab.

The RIBBON-1 trial is a randomized, double-blind, placebo-controlled phase III trial researching the efficacy and safety of bevacizumab in combination with other chemotherapy regimens for the first-line treatment of metastatic breast cancer [51]. A total of 1237 patients with HER2-negative recurrent or metastatic disease were randomized into two groups. The first group comprised patients who received placebo or bevacizumab added to capecitabine monotherapy, and the other group consisted of patients who received placebo or bevacizumab added to taxane (paclitaxel or docetaxel)-based or anthracycline-based chemotherapy. The dose of bevacizumab was 15 mg/kg, and the endpoint of the study was PFS. A total of 75% of the patients were hormone receptor positive. In the case of disease progression, patients were provided second-line treatment that included bevacizumab. Similarly to the AVADO study, a sig-

nificant improvement in PFS was observed in both groups; however, no change in OS was found. Additionally, in this study, nearly half of the patients crossed over to second-line treatment with bevacizumab in the placebo group, which makes OS analysis more difficult.

RIBBON-2 is another randomized, double-blind phase III study that was designed to compare single-agent chemotherapy (taxane, gemcitabine, capecitabine, or vinorelbine) with either bevacizumab (15 mg/kg for 3 weeks, 10 mg/kg for 2 weeks) or placebo added to the chemotherapeutic regimen [52]. In this study including 684 patients, the ratio of hormone receptor-positive patients was 72%, the ratio of HER2-negative patients was 85%, and the ratio of triple-negative patients was approximately 23%. The addition of bevacizumab to the treatment regimen increased PFS from 5.1 to 7.2 months (p = 0.0072). The improvement in PFS was most significant in the hormone receptor-negative and triple-negative groups. When investigated with regard to the chemotherapeutic agents, PFS was increased by the addition of bevacizumab in the patients receiving taxane, gemcitabine, and capecitabine, but no improvement was observed in the vinorelbine group. ORR and OS were improved in the bevacizumab arm compared with the placebo arm, but this improvement was not statistically significant. Researchers suggested that in the AVF2119 study, there was no PFS benefit from the addition of bevacizumab to capecitabine because the patient population comprised a majority of heavily pretreated patients with poor prognostic factors. In the open-label phase III TANIA trial, 494 patients with HER2-negative advanced breast cancer who had progressed during/after ≥12 weeks of first-line bevacizumab-containing chemotherapy were randomized to receive second-line single-agent chemotherapy with or without bevacizumab [53]. The primary endpoint of the trial was PFS, and no crossover was allowed. PFS was significantly longer in the bevacizumab arm (6.3 months vs. 4.2 months, p = 0.0068). In the final analysis of the trial, there was no PFS improvement with continuing bevacizumab in the third line [54]. The results supported that the PFS benefit of bevacizumab use beyond progression seems to be limited to the second-line setting and that bevacizumab has no long-term efficacy.

The TURANDOT (capeciTabine and bevacizUmab Randomized Against avastiN anD taxOl Trial) study is designed to compare the combination regimens of capecitabine + bevacizumab and paclitaxel + bevacizumab as the first-line treatment for metastatic breast cancer in terms of efficacy and safety [55]. A total of 564 patients were randomized into two groups receiving paclitaxel (90 mg/m^2 on days 1, 8, and 15 every 4 weeks) plus bevacizumab (10 mg/m^2 on days 1 and 15 every 28 days) or capecitabine 1000 mg/m^2 twice daily on days 1–14 every 21 days plus bevacizumab 15 mg/m^2 on day 1 every 28 days. At the first interim analysis, the HR for OS was 1.04 (p = 0.059), and the noninferiority criteria were not achieved. The objective RR was higher with the paclitaxel-bevacizumab combination than with the capecitabine-bevacizumab combination (44% vs. 27%, $p < 0.0001$). Similarly, PFS was longer in the paclitaxel group than in the capecitabine group (median 11 months vs. 8.1 months, $p > 0.0052$). The final analysis of the study showed noninferiority of the paclitaxel-bevacizumab combination (median OS 30·2 months for the paclitaxel group versus 26·1 months for the capecitabine group; HR 1.02, p = 0.0070) [56].The proportion of the patients whose treatment was stopped due to side effects was twofold higher in the paclitaxel group than in the capecitabine group, showing that capecitabine is more tolerable and safer. In the subgroup analysis of the TURANDOT study, the 1-year OS in the triple-negative patient group was 78% (with paclitaxel + bevacizumab), which is a very high ratio for triple-negative patients [57]. The high frequency of side effects with paclitaxel + bevacizumab has resulted in the proposal of strategies to reduce toxicity. The first of two studies designed for this purpose and for which results were announced at ASCO 2014 was the phase III SAKK 24/09 study, which was designed in the framework of the following question: "could sufficient antitumor efficacy be ensured with low toxicity by adding metronomic chemotherapy to bevacizumab?" [58]. In this study, a regimen of first-line paclitaxel (90 mg/m^2 on days 1, 8, and 15 every 4 weeks) added to first-line bevacizumab (10 mg/kg, every 2 weeks) (Arm A) was compared with metronomic oral chemotherapy (capecitabine 1500 mg/day + cyclophosphamide 50 mg/day, continuous) (Arm B) in 147 patients with metastatic HER2-negative breast cancer. No difference was detected between the two arms in terms of ORR and PFS. Additionally, no difference was detected between the two groups in the frequency of grade 3–5 side effects (febrile neutropenia, infection, neuropathy, mucositis, and hand-foot syndrome), which was the primary endpoint of the study. In another phase III study (the AROBASE study), maintenance with exemestane + bevacizumab or treatment and maintenance with paclitaxel + bevacizumab were compared in 113 patients with ER-positive, HER2-negative, locally advanced/metastatic breast cancer previously controlled by first-line paclitaxel + bevacizumab combination therapy [59]. Although the rate of side effects was low with the hormonal therapy + bevacizumab combination, patient recruitment for the study was discontinued due to the failure to achieve a PFS advantage, which was the primary endpoint. At the final analysis of the study, maintenance with exemestane + bevacizumab did not achieve longer PFS compared with continuation with paclitaxel + bevacizumab [60].

Studies in HER2-Positive Advanced Breast Cancer

In most of the studies that evaluate the efficacy of bevacizumab in metastatic breast cancer, HER2-positive patients are not included; therefore, information on the role of bevacizumab in HER2-positive disease is limited. However, in preclinical studies, an active interaction between angiogenesis and the HER2 signal has been shown [61–63]. In experimental models, HER2 overexpression increases hypoxia-inducible factor (HIF)-α and VEGF mRNA expression [63]. Heregulin and neuregulin, which are HER ligands, increase the synthesis of VEGF in breast cancer cells and thereby increase the migratory and invasive potential [64, 65]. In a cohort study that included 611 breast cancer patients, a significant correlation was established between HER2 and VEGF expression [66]. HER2, by inducing the release of VEGF, upregulates the COX-2 gene, which plays an important role in angiogenesis [67]. Furthermore, in xenograft models of breast cancer, the antitumor effect is significantly increased by the combined blockage of VEGF and HER2 [68].

In a phase II study including 50 patients with HER2-positive metastatic breast cancer that was conducted in light of these preclinical data, trastuzumab and bevacizumab combination therapy was used, and a high OR of 48% was obtained [69]. Additionally, both agents had safe side-effect profiles. In another phase II study that included 88 patients, bevacizumab 15 mg/kg was added to the combination of capecitabine plus trastuzumab [70]. The response rate in the study was 73% (77% complete response (CR) and 66% partial response (PR)) with a median TTP of 14.4 months and median PFS of 14.4 months. Upon assessing the toxicity profile, ≥grade 3 side effects were observed in 44% of the patients, and most of these were related to capecitabine. Treatment was stopped in 13 patients because of side effects, but these patients went on to receive trastuzumab and bevacizumab treatments. In two patients, heart failure was observed. In other phase I–II studies, the concomitant use of bevacizumab with docetaxel + trastuzumab, lapatinib, and lapatinib + trastuzumab was reported to be safe and effective [71–74].

The AVEREL [Avastin (bevacizumab) in combination with hERceptin (trastuzumab)/docetaxEL in patients with HER2-positive metastatic breast cancer] study is the first randomized, open-label phase III study of the efficacy of anti-HER2 + anti-VEGF combination chemotherapy in HER2-positive breast cancer as a first-line treatment [75]. A total of 424 patients were included in the study and were randomized into two arms—the BTH arm (bevacizumab 15 mg/kg, docetaxel 100 mg/m^2, and trastuzumab 8 mg/kg loading dose followed by 6 mg/kg thereafter) and the TH arm (docetaxel 100 mg/m^2, trastuzumab 8 mg/kg loading dose followed by 6 mg/kg thereafter). After 26 months of follow-up, the primary endpoint of the study, PFS improvement, was not met (HR 0.82; p = 0.0775; median PFS 13.7 months for TH vs. 16.5 months for BTH). The HR for the independent review committee-assessed PFS was 0.72 (p = 0.0162), with a similar 3-month increase in the median PFS. The ORR was 74% in the BTH arm and 70% in the TH arm. No significant difference for the median OS was found between the two groups. The frequencies of grade ≥3 neutropenia and hypertension were higher in the BTH group. According to the biomarker analysis of the study, similarly to the AVADO study, the improvement in PFS was higher in patients with higher plasma VEGF levels.

The ECOG 1105 study is a randomized phase III study designed to test the efficacy of adding bevacizumab (10 mg/kg every 2 weeks) to weekly paclitaxel-trastuzumab combination therapy (days 1, 8, and 15 (±carboplatin) [76]. Patients responding after treatment with six cycles in the bevacizumab arm continued with bevacizumab plus trastuzumab until disease progression or unacceptable toxicity occurred. Unfortunately, the study ended early because of poor patient accrual. When the 88 patients in the study were analyzed, no differences between the two groups for ORR, PFS, or OS were found. Bevacizumab added to paclitaxel-trastuzumab combination therapy did not increase the toxicity, and the treatment was generally well tolerated.

Taking the results of the AVAREL and ECOG 1105 studies into account, it seems inappropriate at present to use bevacizumab in place of the standard treatment protocols for HER2-positive metastatic disease. Biomarker studies appear to be necessary to define the subgroups that will benefit from bevacizumab in this patient group.

Data regarding the phase III studies of bevacizumab in HER2-negative and HER2-positive advanced breast cancer are summarized in Table 34.1.

Studies in Early-Stage Breast Cancer

After it was shown that angiogenesis develops in the early stages of breast cancer and that within the cases of early-stage breast cancer, the ones with highly angiogenic features have a higher ratio of local recurrence and metastasis, the idea of antiangiogenic agents being effective as adjuvant therapy was promoted, and studies were designed to assess this idea [12, 17]. The ECOG 2014 study was one of the first of these studies and included 226 patients with node-positive, early-stage, HER2-negative breast cancer who had undergone surgery [77]. Patients were randomized into two groups. Group A (n = 104) received four cycles of dose-dense AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, every 2 weeks) with bevacizumab 10 mg/kg (every 2 weeks) followed by 4 cycles of paclitaxel (175 mg/m^2 every 2 weeks)

Table 34.1 Efficacy outcomes from randomized phase III trials of bevacizumab in advanced breast cancer

Trial	Design	Patient population	Patients enrolled	HER2 positive (%)	Chemotherapy regimen	B dose (kg)	Primary endpoint	ORR (%)	Median PFS (months)	Median OS (months)
Miller [45] AVF2119g	Randomized, phase III	Metastatic breast cancer, tax/anthr pretreated	462	26.3	Cape q3w + B vs. Cape alone	15	PFS	19.8 vs. 9.1, $p = 0.001$	4.86 vs. 4.17 ($p = 0.98$)	15.1 vs. 14.5
Miller [46] E2100	Open-label, randomized, phase III	Metastatic breast cancer, first-line	722	44.7	Pac weekly+B vs. Pac weekly alone	10	PFS	36.9 vs. 21.2, $p < 0.001$	11.8 vs. 5.9, $p < 0.001$	26.7 vs. 25.2, $p = 0.16$
Miles [47] AVADO	Randomized, double-blind, placebo-controlled phase III	Metastatic or locally recurrent breast cancer, first-line	736	0	Docet q3w+B vs. Docet q3w+P	7.5 or 15	PFS	55 vs. 46, $p = 0.07$ 64 vs. 46, $p < 0.001$	9.0 vs. 8.2, $p = 0.12$ 10.1 vs. 8.2, $p = 0.006$	30.8 vs. 31.9, $p = 0.72$ 30.2 vs. 31.9, $p = 0.85$
Robert [51] RIBBON-1	Randomized, double-blind, placebo-controlled phase III	Metastatic or locally recurrent breast cancer, first-line	1237	Cape arm: 4.2 Tax/anthr arm: 1.0	Cape q3w+B/ tax q3w or anthr q3w-based regimen+B vs. same regimens+P	15	PFS	Cape+B arm: 35.4 vs. 23.6, $p = 0.0097$ Tax/anthr+ B arm: 51.3 vs. 37.9, $p = 0.0054$	Cape arm: 8.6 vs. 5.7, $p < 0.001$ Tax/anthr arm: 9.2 vs. 8.0, $p < 0.001$	Cape arm: 29.0 vs. 21.2 Tax/anthr arm: 25.2 vs. 23.8
Brufsky [52] RIBBON-2	Randomized, double-blind, placebo-controlled phase III	Metastatic or locally recurrent breast cancer, second-line	684	0	Chemo [Cape q3w or tax (docet q3w or pac weekly) or gem weekly or vin q3w-based regimen]+B vs. Same regimens+P	10 or 15	PFS	Chemo+B arm: 39.5 vs. 29.6, $p = 0.0193$	Chemo+B arm: 7.2 vs. 5.1, $p = 0.0072$	Chemo+B arm: 18 vs. 16.4, $p = 0.0072$
Lang[a] [55], Zielinski [56] TURANDOT	Open-label, randomized, phase III, noninferiority	Metastatic or locally recurrent breast cancer, first-line	564	0	Cape q3w+B vs. Pac weekly+B	Cape arm: 15 Pac arm: 10	OS	Cape +B arm: 27 vs. Pac+B arm: 44, $p < 0.0001$	Cape +B arm: 8.1 vs. Pac+B arm: 11, $p = 0.0052$	Cape +B arm: 26.1 vs. Pac+B arm: 30.2, $p = 0.0070$
Arteaga[b] [76] E1105	Randomized, double-blind, placebo-controlled phase III	Metastatic HER2(+) breast cancer, first-line	96	100	Pac weekly+T+B vs. Pac+T+P	10	PFS	52 vs. 52, $p > 0.05$	12.2 vs. 11.1, $p = 0.10$	NR
Gianni [75] AVAREL	Open-label, randomized, controlled phase III	Metastatic or locally recurrent HER2(+) breast cancer, first-line	424	100	Docet+T+B q3w vs. docet+T	15	PFS	74 vs. 70, $p = 0.3492$	16.5 vs. 13.7, $p = 0.0775$	NR
Gligorov [44] IMELDA	Open-label, randomized, phase III, maintenance	Metastatic breast cancer, progression-free after 3–6 cycles of docetaxel+bevacizumab, second-line	185	0	Cape q3w+B vs. B alone	15	PFS	86 vs. 77	11.9 vs. 4.3, $p < 0.0001$	39.0 vs. 23.7, $p = 0.0003$
von Minckwitz [53], Vrdoljak [54] TANIA	Open-label, randomized, phase III, beyond-progression	Metastatic or locally recurrent breast cancer, progression during/after ≥12 weeks of bevacizumab+chemotherapy, second-line	494	0	Single-agent chemo+B vs. Single-agent chemo alone	10 or 15	PFS	20.9 vs. 16.8, $p = 0 \cdot 3457$	6.3 vs. 4.2, $p = 0 \cdot 0068$	19.7 vs. 18.7, $p = 0 \cdot 7253$

B bevacizumab, *ORR* objective response rate, *PFS* progression-free survival, *OS* overall survival, *tax* taxane, *anthr* anthracycline, *cape* capecitabine, *pac* paclitaxel, *docet* docetaxel, *gem* gemcitabine, *vin* vinorelbine, *T* trastuzumab, *P* placebo, *NR* not reported

[a]Interim analysis

[b]The study was terminated early due to poor patient accrual

with bevacizumab (10 mg/kg every 2 weeks) and then 18 cycles of bevacizumab1 0 mg/kg alone (every 2 weeks). Group B ($n = 122$) received 4 cycles of dose-dense AC without bevacizumab followed by 4 cycles of paclitaxel (175 mg/m^2 every 2 weeks) with bevacizumab (at the same dosage as group A) and then 22 cycles of bevacizumab alone (10 mg/kg every 2 weeks). The primary endpoint of the study was clinically apparent cardiac dysfunction (CHF). When results were evaluated in both groups, three patients had developed CHF. No significant difference between the decrease in left ventricular ejection fraction was found between the two groups. However, in 30% of the patients, treatment had to be paused due to side effects; these side effects mainly occurred during bevacizumab maintenance. However, grade ≥3 side effects related to bevacizumab were rarely observed. Following this phase II pilot ECOG study, a randomized, double-blind, phase III study was initiated. In the ECOG 5103 study, 4950 node-positive or high-risk, node-negative, operated, early-stage, HER2-negative patients were randomized into three groups [78]. The first group (group A) received four cycles of AC (in every 2–3 weeks) with placebo followed by weekly paclitaxel (days 1, 7, and 15, every 21 days for four cycles) with placebo. Four cycles of AC combined with bevacizumab followed by weekly paclitaxel combined with bevacizumab were applied to the second group (group B). To the third group (group C), the treatment plan for the second group was given followed by bevacizumab maintenance (every 3 weeks for ten cycles). The primary endpoint of the study is disease-free survival (DFS). Chemotherapy-associated side effects and their frequencies were similar in all three groups. Of the grade 3–5 adverse effects associated with bevacizumab, the frequencies of hypertension, thrombosis, proteinuria, and hemorrhage were 8%, 3%, <1%, and <1%, respectively. However, a significant portion of patients in the study groups prematurely discontinued bevacizumab (24% of patients in group B and 55% of patients in group C); therefore, the period of bevacizumab use in most of the patients was shorter than expected. The cumulative frequencies of clinical cardiac failure detected in month 15 in the study groups were 1%, 1.9%, and 3%, respectively. No differences were detected among the three groups for DFS or OS. The 5-year DFS rates were similar among the groups (77%, 76%, and 80%, respectively).

Another phase III study studying the role of adjuvant bevacizumab in triple-negative breast cancer is BEATRICE [79]. A total of 2991 patients were randomized to receive ≥4 cycles of anthracycline- or taxane-based adjuvant chemotherapy with or without adding a year-long treatment regimen of bevacizumab (5 mg/kg/week). At the end of a median 32 months of follow-up, no DFS improvement, which was the primary endpoint of the study, was obtained (HR 0.87, $p = 0.181$). No difference in fatal adverse effects was found between the bevacizumab and chemotherapy groups; however, the addition of bevacizumab to the adjuvant chemotherapy was correlated with an increased frequency of grade ≥3 hypertension (12% in the bevacizumab arm, 1% in the chemotherapy arm) and severe cardiac events (1% in the bevacizumab arm, <0.5% in the chemotherapy arm). No difference was detected between the two groups for OS (HR 0.86, $p = 0.23$); however, patients with high plasma VEGFR-2 levels may benefit from the addition of bevacizumab to their treatment. An updated analysis of the study showed no difference between the two groups regarding DFS and OS [80].

Adequate data regarding the status of bevacizumab for adjuvant therapy in HER2-positive early-stage breast cancer has not been reported. The BETH study was a phase III study in which bevacizumab was added to systemic chemotherapy + trastuzumab combination therapy, which is the standard therapy in this patient group [81]. A total of 3509 patients were included in the study and were assigned to two treatment groups: six cycles of docetaxel/carboplatin plus trastuzumab (TCH) with or without trastuzumab or three cycles of docetaxel plus trastuzumab with or without bevacizumab followed by three cycles of FEC. In both regimens, patients used trastuzumab (with or without bevacizumab) for a total of 1 year. When all patients were considered or when the TCH and chemotherapy with anthracycline groups were individually analyzed, it was observed that the addition of bevacizumab to the treatment did not cause a significant change in DFS. However, it was also observed that the rates of grade 3–4 adverse effects were higher in the patient group receiving bevacizumab (hypertension 19% vs. 4%, $p < 0.001$; congestive heart failure 2.1% vs. 1%, $p = 0.0621$; hemorrhage 2% vs. <1%, $p < 0.0001$; proteinuria 1% vs. <1%, $p < 0.0001$; and gastrointestinal perforation 11 cases vs. 1 case, $p = 0.0031$).

Neoadjuvant Studies

Many studies have researched the efficacy of adding bevacizumab to systemic chemotherapy in HER2-negative locally advanced breast cancer. In these studies, pathological complete response (pCR) rates range from 9% to 42% [82–85]. The results of two large randomized trials based on the data of phase II studies are contradictory. In the large, randomized NSABP B40 study, patients were randomized into three groups: docetaxel alone, docetaxel plus capecitabine, and docetaxel plus gemcitabine [86]. After four cycles of chemotherapy, four cycles of AC were applied to all patients. Additionally, the patients in the study were divided into two groups: those who received bevacizumab in their first six cycles of chemotherapy followed by ten cycles of bevacizumab 15 mg/kg postoperatively and those who did not. When the results were evaluated, it was observed that add-

ing bevacizumab to chemotherapy significantly increases the pCR in the breast (28.4% vs. 34.5%, $p = 0.02$). When both the breast and axillary nodes were examined in the bevacizumab-treated group, the pCR was higher but did not reach statistical significance (23% vs. 27.6% $p = 0.08$). When the effect of bevacizumab added to chemotherapy was analyzed according to the hormone receptor status, the pCR rates of the breast and breast + axillary lymph nodes were significantly higher in the hormone receptor-positive group compared with the hormone receptor-negative group. The addition of bevacizumab to chemotherapy increased the frequency of hypertension, left ventricular dysfunction, hand-foot syndrome, and mucositis. Moreover, an apparent increase was also observed in the frequency of postoperative complications (especially in patients with reconstruction administration) [87, 88]. In the survival analysis of the study, OS was significantly improved in the bevacizumab group, but DFS was not [89]. Patients with hormone-receptor positive tumors seemed to derive a greater benefit from bevacizumab.

Another phase III study related to neoadjuvant bevacizumab is the GeparQuinto study designed by von Mincwits et al. [90]. Patients were randomized into two groups, one in which bevacizumab 15 mg/kg was added to four cycles of epirubicin plus cyclophosphamide followed by four cycles of docetaxel and one in which bevacizumab was not added. In the bevacizumab arm, the pCR rate was significantly higher (14.9% vs. 18.4%, $p = 0.04$). In contrast to the NSABP B40 study, the effect of bevacizumab on pCR was most significant in the triple-negative group (27.9% vs. 39.3%, $p = 0.003$), whereas bevacizumab was not effective in the hormone receptor-negative group (7.8% vs. 7.7%, $p > 0.05$). This variation could be the result of differences between the designs, treatment regimens, and patient populations of the NSABP B40 and GeparQuinto studies. Although the frequency of hypertension, mucositis, and febrile neutropenia was higher in the bevacizumab group, no difference in terms of heart failure was found between the two groups. In the survival analysis of the study, in contrast to the results for pCR, there was no OS or DFS benefit in the bevacizumab group [91]. Moreover, no subgroup showed a significant benefit from bevacizumab (triple negative; HR+/HER2-; locally advanced or not; pCR or not). When the effects of BRCA 1/2 mutation status were examined, the pCR rate among patients treated with bevacizumab was 61.5% for *BRCA1/2* mutation carriers and 35.6% for those without mutations (odds ratio 2.90, $p = 0.004$) [92]. pCR was a strong predictor of DFS for patients without *BRCA1/2* mutations (HR 0.18, $p < 0.001$) but not for patients with *BRCA1/2* mutations (HR 0.74, $p = 0.129$). The addition of bevacizumab did not significantly improve DFS in either BRCA1/2 mutation-positive patients or BRCA1/2 mutation-negative patients.

In the CALGB 40603 study, which recruited stage II and stage III triple-negative patients, the effect of carboplatin and/or bevacizumab was examined when added to weekly neoadjuvant paclitaxel and subsequent dose-dense AC [93]. When the results were examined, the addition of carboplatin to neoadjuvant therapy elevated the pCR rate in the breast from 44% to 60% ($p = 0.0018$), and the addition of bevacizumab increased the rate from 48% to 59% ($p = 0.0089$). At 3 years, overall event-free survival (EFS) was 74.1%, and OS was 83.2% [94]. Patients who achieved pCR had a 3-year EFS of 84.8% versus 61.8% for those who did not (HR 0.33, $p < 0.001$). Patients assigned to bevacizumab versus not had 3-year EFS of 75.5% versus 72.9% (HR 0.80; $p = 0.25$) and OS of 85.5% versus 80.9% (HR 0.76; $p = 0.23$). The results of a meta-analysis are consistent with the findings that the addition of carboplatin and bevacizumab to neoadjuvant therapy significantly increased the pCR rates in patients with triple-negative breast tumors [95]. However, it remains unknown whether this approach improves survival results.

The ARTemis study is a phase III study in which bevacizumab was added to neoadjuvant chemotherapy with docetaxel and anthracycline in HER2-negative patients [96]. In total, 800 patients were randomized in the study, and the pCR rate was higher in the arm treated with bevacizumab (22% vs. 17%, $p = 0.03$). When subgroups were analyzed, the groups that benefited most from neoadjuvant therapy with bevacizumab were ER-negative or minimally ER-positive patients. The pCR results were consistent with the results of the GeparQuinto and CALGB 40603 studies. At a median follow-up of 3.5 years, DFS and OS were higher in *patients who reached pCR* versus those without pCR (HR for DFS 0.38, $p < 0.001$; HR for OS 0.43, $p = 0.003$) [97]. However, similar to the results of the survival analyses in GeparQuinto and CALGB 40603, OS and DFS were not different between groups receiving or not receiving bevacizumab.

Because VEGFR expression was shown to be related to adjuvant antihormonal treatment failure, we thought that using antiangiogenic therapy together with hormonal therapy might be effective [98, 99]. In a pilot study of 25 patients, the objective clinic response rate of neoadjuvant letrozole and bevacizumab combination therapy was 68%, and the pCR rate was 16% [100]. Neoadjuvant studies including hormone therapy and anti-VEGF treatment combinations in hormone receptor-positive patients are currently being conducted.

Our knowledge regarding neoadjuvant bevacizumab in HER2-positive disease is limited. In a phase II study including 26 patients who received weekly bevacizumab (5 mg/kg) added to weekly neoadjuvant paclitaxel + carboplatin + trastuzumab and who underwent surgery, 14 of the 26 patients had pCR (54%), but bevacizumab-related complications (most frequently, wound-healing delay and infections)

were observed during neoadjuvant therapy and postoperatively in a significant number of patients [101]; this is most likely linked to the prolonged usage of bevacizumab/trastuzumab. The BEVERLY-2 study is another phase II study that included 52 patients with HER2-positive nonmetastatic inflammatory breast cancer [102]. Patients received FEC + bevacizumab (one to four cycles) and docetaxel + bevacizumab + trastuzumab (five to eight cycles) before surgery and adjuvant radiotherapy trastuzumab and bevacizumab after surgery. The pCR rate with neoadjuvant therapy was 63.5%; a grade 3 bevacizumab-related side effect (hypertension) was observed in only one patient. In the survival and biomarker analysis of the study, 3-year DFS and OS rates were 68% and 90%, respectively, and pCR, circulating tumor cell presence and matrix metalloproteinases (MMP) 2 and 9 were predictive of survival [103, 104]. In the AVANTHER study, bevacizumab (15 mg/kg given four times every 3 weeks) was added to weekly neoadjuvant paclitaxel and trastuzumab (12 cycles) [105]. In 18 out of 42 patients, pCR was obtained (42.9%), and grade 3 side effects (hypertension and mucositis) were observed in only two patients. The AVATAXHER study was designed to evaluate the ability of positron emission tomography (PET) to predict the effect of an early response of the addition of bevacizumab to the treatment regimen in patients who failed to respond to neoadjuvant therapy [106]. Patients were initially administered two cycles of neoadjuvant docetaxel + trastuzumab, and their metabolic responses were assessed by PET immediately before cycles 1 and 2. Patients were assigned to two groups, responders and nonresponders, according to their PET response. In the nonresponder group, bevacizumab was added to the current treatment, and responders continued to receive standard treatment. The pCR response rate was higher in the PET responders group of patients receiving bevacizumab compared with patients not receiving bevacizumab (43.8% vs. 24%).

Aflibercept

Aflibercept (VEGF-Trap) is a recombinant protein composed of the VEGFR-1 extracellular domain fused with the VEGFR-3 extracellular domain in combination with the Fc(a) domain of human IgG1. It binds to VEGF-A, VEGF-B, PGF-1, and PGF-2 in circulation [107]. Its fusion protein structure provides many advantages, including binding to VEGF with higher affinity than other anti-VEGF agents (800 times higher than bevacizumab), long plasma half-life (18 days), and the ability to bind to PGF-1 and PGF-2 [108, 109]. In preclinical studies, aflibercept regresses tumor vascularization and simultaneously stimulates the normalization of the existing vascular structure [110, 111]. In phase I studies that include different tumor groups, aflibercept appears to possess clinical antitumor efficiency and to be well tolerated [112–114]. Aflibercept received approval for second-line treatment of metastatic colorectal cancer after its ability to prolong survival was shown [115]. In the only phase II study for aflibercept, metastatic breast cancer patients who received less than two chemotherapy regimens received aflibercept at a dose of 4 mg/kg every 21 days; however, after the partial response rate was found to be 4.8% and the median PFS was found to be 2.4 months, the trial was closed [116].

Ramucirumab

Ramucirumab (IMC-1121B) is a humanized monoclonal antibody that specifically binds to the extracellular VEGF-binding domain of VEGFR-2 with high affinity. As a result of that binding, it blocks all VEGFs that bind to VEGFR-2, unlike bevacizumab, which only binds to VEGF-A [117, 118]. Its objective antitumoral and antiangiogenic effects were observed in a phase I trial [119]. Ramucirumab has currently approved FDA indications for lung cancer, colorectal cancer and gastric or gastroesophageal junction adenocarcinoma. In a phase III study (TRIO-012) comparing ramucirumab + docetaxel combination therapy with docetaxel alone as a first-line treatment for advanced HER2-negative breast cancer, no significant improvement was detected in either PFS or OS upon the addition of docetaxel to ramucirumab [120].

Antiangiogenic Tyrosine Kinase Inhibitors

Small-molecule tyrosine kinase inhibitors have been developed to inhibit the intracellular catalytic function of the VEGF family. Sunitinib, sorafenib, pazopanib, motesanib, vandetanib, vatalanib, and axitinib are among the tyrosine kinase inhibitors for which the efficacy in treating breast cancer is being investigated (Table 34.2).

Sunitinib

Sunitinib is an oral tyrosine inhibitor that blocks not only VEGFR-1, 2, and 3 but also PDGFR-α, PDGFR-β, c-kit, FMS-like tyrosine kinase-3, RET, and colony-stimulating factor-1 receptors [121, 122]. It has received FDA approval for the treatment of advanced renal cell cancer, neuroendocrine cancer, and gastrointestinal stromal tumors. In experimental studies, it has been shown to have significant antitumor activity in breast cancer and bone metastases of breast cancer when given alone; it also enhances the antitumor effects of other chemotherapeutic agents, including taxanes and fluoropyrimidines [123, 124]. In phase I studies in

Table 34.2 Phase II and III trials of antiangiogenic TKIs in advanced breast cancer

Trial	Design	Patient population	Patient enrolled	HER2 positive (%)	Chemotherapy regimen	TKI dose (day)	Primary endpoint	ORR (%)	Median PFS (months)	Median OS (months)
Burstein [128]	Phase II	Metastatic breast cancer, tax/anthr pretreated	46	19	S (monotherapy)	50	ORR	11	2.3	8.9
Robert [130]	Open-label, randomized, phase III	Metastatic or locally recurrent breast cancer, first-line	485[a, b]	0	Pac weekly+S vs. Pac weekly+B	25–37.5	PFS	32.2 vs. 32.1, $p = 0.525$	7.4 vs. 9.2, $p = 0.999$	17.6 vs. NR
Mayer [131] SABRE-B	Open-label, randomized, phase II	Metastatic breast cancer, first-line	46	0	Pac weekly+B+S vs. Pac weekly+B	25	PFS	71 vs. 61	NR[c]	NR[c]
Bergh [132]	Open-label, randomized, phase III	Metastatic or locally recurrent breast cancer, first-line	296	0	Docet q3w +S vs. Docet q3w alone	37.5	PFS	55 vs. 42, $p = 0.001$	8.6 vs. 8.3, $p = 0.265$	24.8 vs. 25.5, $p = 0.904$
Barrios [134]	Open-label, randomized, phase III	Metastatic or locally recurrent breast cancer, tax/anthr pretreated	482[a, b]	0	S (monotherapy) vs. Cape q3w	37.5	PFS	11 vs. 16, $p = 0.109$	2.8 vs. 4.2, $p = 0.002$	15.3 vs. 24.6, $p = 0.350$
Crown [135]	Open-label, randomized, phase III	Metastatic or locally recurrent breast cancer, tax/anthr pretreated	442	13	Cape q3w+S vs. Cape q3w alone	37.5	PFS	19 vs. 18, $p = 0.490$	5.5 vs. 5.9, $p = 0.941$	16.4 vs. 16.5, $p = 0.494$
Moreno-Aspitia [147] N0336	Phase II	Metastatic breast cancer, tax/anthr pretreated	23	13	Sor (monotherapy)	2 × 400	RR	0	2.0	NR
Bianchi [148]	Phase II	Metastatic breast cancer, heavily pretreated	56	20	Sor (monotherapy)	2 × 400	RR	2	1.5	8.6
Baselga [149]	Open-label, randomized, placebo-controlled phase IIB	Metastatic or locally advanced breast cancer, first- and second-line	229	0	Cape q3w+Sor vs. Cape q3w+P	2 × 400	PFS	38 vs. 31, $p = 0.25$	6.4 vs. 4.1, $p = 0.001$	22.2 vs. 20.9, $p = 0.42$
SOLTI-0701 Baselga [150] RESILIENCE	Randomized, double-blind, placebo-controlled phase III	Metastatic or locally advanced breast cancer, tax/anthr pretreated	537	0	Cape q3w+Sor vs. Cape q3w+P	3 × 200	PFS	13.5 vs. 15.5, $p = 0.51$	5.5 vs. 5.4, $p = 0.811$	18.9 vs. 20.3, $p = 0.14$
Gradishar [151]	Randomized, double-blind, placebo-controlled phase IIB	Metastatic or locally recurrent breast cancer, first-line	237	0	Pac weekly+Sor vs. Pac weekly+P	2 × 400	PFS	67 vs. 54, $p = 0.0468$	6.9 vs. 5.6, $p = 0.0857$	16.8 vs. 17.4, $p = 0.904$
Jonhston [164]	Open-label, randomized, phase II	Metastatic/advanced breast cancer, first-line	190	100	Lap+Paz vs. Lap alone	400	PDR	36.2 vs. 22.2	36.2% vs. 38.9%, $p = 0.37$ (PDR at week-12)	NR

(continued)

Table 34.2 (continued)

Trial	Design	Patient population	Patient enrolled	HER2 positive (%)	Chemotherapy regimen	TKI dose (day)	Primary endpoint	ORR (%)	Median PFS (months)	Median OS (months)
Martin [169]	Randomized, double-blind, placebo-controlled phase II	Metastatic or locally recurrent breast cancer, first-line		0	Pac weekly+M vs. Pac weekly+B vs. Pac weekly+P	125	RR	49 vs. 41 (placebo arm), $p = 0.31$	9.5 vs. 9.0 (placebo arm), $p = 0.31$	NR
								49 vs. 52 (B-arm), $p = 0.75$	9.5 vs. 11.5 (B-arm), $p = 0.15$	
Rugo [173]	Randomized, double-blind, placebo-controlled phase II	Metastatic or locally recurrent breast cancer, first-line	168	0	Docet q3w+Ax vs. Docet q3w+P	2 × 5	TTP	41.1 vs. 23.6, $p = 0.011$	8.1 vs. 7.1, $p = 0.0091$ (TTP)	NR
Boér [179]	Randomized, double-blind, placebo-controlled phase II	Advanced breast cancer, second-line	64	Van-arm: 11 Placebo-arm: 17	Docet q3w+Van vs. Docet q3w+P	100	NPE	40 vs. 17	8.2 vs. 5.6, $p = 0.25$	NR

TKI tyrosine kinase inhibitor, *ORR* objective response rate, *PFS* progression-free survival, *OS* overall survival, *tax* taxane, *anthr* anthracycline, *S* sunitinib, *Sor* Sorafenib, *Paz* pazopanib, *M* motesanib, *Ax* axitinib, *Van* vandetanib, *cape* capecitabine, *B* bevacizumab, *Lap* lapatinib, *pac* paclitaxel, *docet* docetaxel, *P* placebo, *PDR* progressive disease rate, *NPE* number of progression events (by the data cutoff), *NR* not reported

[a]Interim analysis

[b]This trial was terminated early because of the futility of reaching the primary endpoint, as determined by the independent data monitoring committee during an interim futility analysis

[c]Due to serious toxicity, the study was terminated early. Therefore, follow-up was short, and the median PFS and OS were not reached

different tumor types, it has been shown that using sunitinib at a dose of 37.5–50 mg/day has a safe toxicity profile [125–127]. The most frequent adverse effects are fatigue, hypertension, and skin changes. In a phase II study that included 64 heavily treated breast cancer patients who had previously received taxane and anthracycline, PR was achieved in 7 patients (11%), and SD longer than 6 months was obtained in 3 patients (5%) [128]. The patients who were responsive were either triple-negative or HER2-positive patients who had previously received trastuzumab. A group study for sunitinib in combination with chemotherapy was then initiated. In a pilot study with 22 advanced breast cancer patients receiving first-line treatment with a paclitaxel-sunitinib combination, an objective response was found in seven patients (two CR and five PR, 38.7%) [129]. In a phase II study that followed this study, paclitaxel-sunitinib and paclitaxel-bevacizumab combinations were compared [130]. In the interim analysis of this study, which included 485 patients, the study was terminated because of the inferior results of the paclitaxel-sunitinib arm compared with the paclitaxel-bevacizumab arm (median PFS 7.4 months vs. 9.2 months). In both arms, the objective response rate was calculated as 32%, but the response time was shorter in the sunitinib arm (6.3 months vs. 14.8 months). The SABRE-B study is a phase II dose-escalation study in which sunitinib was added to the paclitaxel-bevacizumab combination therapy [131]. The sunitinib dose began at 25 mg/day and was intended to be increased if the toxicity was tolerable. However, the randomization of the 46 patients included in the study was ended early due to the frequency of serious grade ≥3 side effects in the triple combination therapy arm compared with the paclitaxel-bevacizumab arm (83% vs. 57%), and the treatment time required to calculate PFS and OS was not reached because of the side effects. In a phase III study with 296 HER2-negative patients for whom docetaxel-sunitinib combination therapy was compared with docetaxel alone as a first-line treatment, the ORR was found to be higher in the sunitinib arm (55% vs. 42%, $p = 0.001$), but no difference was found between the two arms in terms of PFS or OS [132]. In an exploratory study that included 26 HER2-positive patients, the objective RR was 76% with docetaxel-trastuzumab-sunitinib (37.5 mg) combination treatment, which was well tolerated [133]. In another phase III study, HER2-negative advanced breast cancer patients who previously received taxane and anthracycline were randomized to a capecitabine or sunitinib arm for monotherapy, but this study was also closed due to sunitinib having a high side-effect frequency compared with capecitabine and because in terms of PFS, the primary endpoint could not be reached at the first interim analysis [134]. In a phase III study, capecitabine-sunitinib combination therapy and capecitabine monotherapy were compared in breast cancer patients who had received taxane and anthracycline and at least one treatment in a metastatic setting [135]. According to the results, the addition of sunitinib to capecitabine did not result in an advantage in terms of PFS, ORR, or OS, and all side effects except hand-foot syndrome were more frequent in the sunitinib arm. It appears that adding sunitinib to chemotherapy for breast cancer does not elicit a positive effect. The possible explanations for this situation include the heterogeneity of the patient groups; the changes in the signaling mechanisms of pretreated patients; the fact that antiangiogenic agents sometimes cause hypoxia by inhibiting vascularization more than is necessary, thereby resulting in the formation of more aggressive and invasive cell types; and the uncertainty of both the optimal biological dose of sunitinib and the sequence of drug application. Because side effects occurred in many studies, the optimal dose was never reached, and endpoints were thus affected. The efficacy of sunitinib monotherapy has been evaluated in HER2-negative patients for whom an objective response was achieved with chemotherapy; however, in this study, PFS improvement was not obtained, and toxicity developed in many patients [136]. Sunitinib also led to serious hematological toxicity in a phase II study in which it was used as a neoadjuvant concomitantly with weekly paclitaxel-carboplatin therapy [137]. Additionally, two studies, one in a metastatic setting and the other in a neoadjuvant setting, investigated the combination of sunitinib with exemestane in hormone receptor-positive breast cancer and found that the current regimen was safe [138, 139].

Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits the Ras/Raf/mitogen-activated protein kinase (MAPK) signaling pathway by blocking VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, RET, Flt3, and c-kit [140]. In preclinical studies, its wide-spectrum antitumor activity has been observed [141–143]. Based on phase II and III studies, it is currently approved for hepatocellular carcinoma and renal cell carcinoma [144–146]. When no response was observed in a phase II study with 23 metastatic breast cancer patients who received anthracycline or taxane before, the study was terminated prematurely [147]. In another phase II trial with 56 patients who received at least one treatment in a metastatic setting, sorafenib monotherapy in one patient (2%) achieved a partial response, and stable disease was achieved in 20 patients (37%) [148]. In both studies, 800 mg/day was well tolerated; fatigue, rash, hand-foot syndrome, and diarrhea were the most common side effects. Because its efficacy is low as monotherapy, combination with chemotherapy has been attempted. In the trial of Baselga et al. (SOLTI-0701 trial), 229 HER2-negative patients were randomized into capecitabine-sorafenib and capecitabine-placebo groups in

first- or second-line treatment [149]. Adding sorafenib to capecitabine significantly improved PFS (median 6.4 months vs. 4.1 months, $p = 0.001$). However, no difference was shown in terms of ORR (38% vs. 31%, $p = 0.25$) or OS (median 22.2 vs. 20.9 months, $p = 0.42$) between the two groups. In the sorafenib arm, the frequency of side effects such as hand-foot syndrome, rash, mucosal inflammation, neutropenia, and hypertension was significantly higher compared with the placebo arm. Based on these results, a new phase II study (RESILIENCE trial) has been initiated in which the dose of sorafenib added to capecitabine was reduced to 600 mg/day and a more aggressive treatment for hand-foot syndrome was planned [150]. Unfortunately, the capecitabine plus reduced-dose sorafenib regimen was not found to be superior to capecitabine plus placebo regarding PFS (5.5 versus. 5.4 months; HR 0.973, $p = 0.81$), OS (18.9 vs. 20.3 months; HR 0.195, $p = 0.14$) or ORR (13.5% vs. 15.5%, $p = 0.515$). As the first international multicenter phase II study in which paclitaxel-sorafenib and paclitaxel-placebo treatments were compared, the median TTP and ORR were superior in the sorafenib arm (median 8.1 months vs. 5.6 months, $p = 0.0343$, and 67% vs. 54%, $p = 0468$, respectively). However, no difference in PFS or OS was observed between the two groups [151]. Similarly, the second study was terminated early because the interim analysis revealed shorter PFS in the paclitaxel-sorafenib group [152]. In a multi-institutional phase I/II study that included patients showing progression under aromatase inhibitors, PR was achieved by the addition of 800 mg sorafenib to anastrozole treatment in one patient, and SD was achieved in seven patients [153]. However, 77% of the patients required dose reduction, and 31% had to stop taking sorafenib because of its unacceptable toxicity. A phase II study researching the efficacy of sorafenib-bevacizumab treatment ended early due to serious toxicity [154]. The results of two meta-analyses individually examining the randomized and retrospective studies of sorafenib have shown that sorafenib in combination with chemotherapy improved PFS and TTP compared with chemotherapy alone and had no effect on ORR or OS [155, 156]. Other studies combining sorafenib with vinorelbine or ixabepilone have failed [157, 158].

Pazopanib

Pazopanib is a small-molecule oral tyrosine kinase inhibitor that exerts its effects by blocking VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, c-kit, and mast-stem cell growth factor receptor [159]. In its phase I study that included many tumor types, it had both antitumor and anticytostatic effects [160]. The antitumor effect appeared at a dose of 800 mg/day, and no increase in the plasma concentration was observed at higher doses; therefore, the suggested dose is 800 mg/day. The side effects are generally grade 1 or 2, and the most frequently observed side effects are hypertension, diarrhea, skin hypopigmentation, and nausea. In a phase II study, pazopanib, which has been approved for use in renal cell carcinoma and leiomyosarcoma, was evaluated in 20 recurrent or metastatic breast cancer patients who received two or more treatments (including adjuvant or neoadjuvant); PR was achieved in 1 patient (5%), and SD was achieved in 11 patients (55%) (in 4 of the 11 SD patients, the time of response was longer than 6 months) [161]. The median PFS was 5.3 months. In half of the patients, shrinking of the target lesion was observed, and treatment was generally well tolerated. In the neoadjuvant treatment of HER2-negative locally advanced breast cancer, the pCR rate was 17% with pazopanib added to four cycles of AC and subsequent weekly paclitaxel (9% in ER-positive patients and 38% in triple-negative patients) [162].

In a phase I study conducted based on information regarding the additive antitumor effect of anti-HER2 treatment with antiangiogenic treatment, the combination of lapatinib (1000–1500 mg) and pazopanib (400–800 mg) had a notable antitumor effect and a safe toxicity profile [163]. However, in subsequent studies of the combination of lapatinib 1500 mg + pazopanib, serious toxicity and predominant diarrhea were reported [164]. In a phase II study comparing lapatinib 1000 mg + pazopanib 400 mg in combination with lapatinib 1500 mg monotherapy, the combination therapy increased the ORR (58% vs. 47%) but had no effect on PFS [165]. Furthermore, with the combination therapy, grade ≥3 side effects were observed at a high frequency (50% vs. 17%).

Motesanib

Motesanib is a small-molecule tyrosine kinase inhibitor that very selectively blocks VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, and c-kit [166]. In preclinical and clinical studies, it has been shown that it has a broad antitumoral effect [166, 167]. In tumor xenograft models of breast cancer, motesanib decreases tumor growth and, when used with tamoxifen or docetaxel, significantly increases the antitumor efficacy [167]. In a phase I study based on these data that included 45 patients, motesanib was added to weekly paclitaxel or docetaxel every 3 weeks [168]. The maximum tolerated dose of motesanib was 125 mg/day. When toxicity was considered, the treatment was generally well tolerated; in seven patients (16%), motesanib-related grade 3 adverse effects were found (cholecystitis in two patients and hypertension in two patients). The ORR was 56% with motesanib added to taxane-based chemotherapy. In a phase II study, combinations of paclitaxel-motesanib, paclitaxel-placebo, and paclitaxel-bevacizumab were compared [169]. No difference

in terms of ORR was found between the motesanib and placebo groups (49% vs. 41%, $p = 0.31$). In the bevacizumab arm, ORR was 51%, which was similar to the motesanib arm. The serious adverse event ratio in patients taking motesanib was higher than that in the other two groups; the most common adverse events were diarrhea, hypertension, fatigue, and peripheral neuropathy.

Axitinib

Axitinib (AG013736) is an oral tyrosine kinase inhibitor that inhibits VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, c-kit, and colony-stimulating factor-1 [170]. Axitinib regresses tumor vasculature in human breast cancer xenograft models and, in parallel, inhibits tumor growth [171]. In a phase I study, axitinib was shown to have a clinical antitumor effect in solid tumors [172]. The suggested dose is 5 mg twice daily. In a phase II study including 168 patients with metastatic breast cancer, axitinib and placebo added to docetaxel were compared [173]. TTP was found to be longer in the axitinib arm compared with the placebo arm (8.1 months vs. 7.1 months), but the difference was not statistically significant. The ORR was significantly higher in the combination arm (41.4% vs. 23.6%, $p = 0.011$). Adverse effects, including neutropenia, stomatitis, diarrhea, mucositis, and hypertension, were more frequent in the axitinib arm. In the subgroup analysis of the study, TTP in the axitinib arm was significantly better in patients who previously received adjuvant treatment (9.2 months vs. 7.0 months, $p = 0.043$).

Vandetanib

Vandetanib (ZD6474) is an oral receptor tyrosine kinase inhibitor that competitively binds to and blocks the ATP-binding site of VEGFR-2 (flk-1/KDR). In contrast to the other antiangiogenic tyrosine kinase inhibitors, vandetanib shows an anti-EGFR effect at sub-micromolar concentrations by simultaneously blocking HER1 [174]. Vandetanib not only inhibits endothelial cell proliferation and angiogenesis but also regresses cancer cell growth by affecting the autocrine EGFR signal [175, 176]. In its phase I study, it was well tolerated at a dose of 300 mg/day, and the most frequent side effects were diarrhea, rash, and hypertension [177]. In a phase II study that included 46 patients with metastatic breast cancer who received anthracycline and taxane, no objective response was observed [178]. The authors proposed that this could be due to changes in the tumor biology that could have made the patients unresponsive to anti-VEGF treatment or to the fact that the adequate plasma concentration for the antitumor effect of vandetanib was not reached. In a small phase II study comparing vandetanib or placebo added to docetaxel, no difference in the risk of disease progression was found between placebo and vandetanib [179]. One of the two studies combining vandetanib and fulvestrant in patients with hormone receptor-positive metastatic breast cancer was discontinued due to low patient participation. In the other study, no significant change was detected in PFS or OS with vandetanib added to fulvestrant compared with placebo in patients with bone-only or bone-predominant metastatic disease [180, 181].

Vatalanib

Vatalanib (PTK787/ZK-222584) is a new class of oral small-molecule tyrosine kinase inhibitor. It blocks all VEGFRs (VEGFR-1 (flt-1), VEGFR-2 (flk-1/KDR), and VEGFR-3 (flt-4)), PDGRF, c-kit, protein tyrosine kinase, and c-fms, but its affinity is highest for VEGFR-1 and VEGFR-2 [182]. According to preclinical studies, in addition to its antiangiogenic activity, vatalanib also has an aromatase inhibitory effect [183, 184]. In a phase I study, the maximum tolerated dose was 750 mg given twice daily; conversely, the biologically active dose was 1000 mg twice daily [185]. Phase I/II studies of vatalanib combined with trastuzumab and letrozole were closed prematurely due to low patient enrollment and toxicity [186].

Conclusion

Although targeting tumor angiogenesis represents an active treatment modality for many solid tumors, several studies have indicated that this approach is not an accepted standard treatment for early-stage or advanced breast cancer. There are numerous ongoing trials examining the effectiveness of various new agents, especially TKIs, including nintedanib, lenvatinib, apatinib, cabozantinib, and cediranib. To integrate antiangiogenic therapy into the standard treatment options for breast cancer, biomarker studies should be performed to determine which patients most benefit from this strategy. In the coming years, the identification of effective combinations and predictive markers according to molecular subgroups will permit the use of antiangiogenic therapy as an effective treatment option for breast cancer patients.

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Tyrosine Kinase Inhibitors

35

Burcu Cakar and Erdem Göker

Introduction

Tyrosine kinase is an enzyme that phosphorylates tyrosine residues in proteins to regulate signals within a cell. Under normal conditions, tyrosine kinase activity is regulated by strict mechanisms. However, this tight control is lost in cancer cells due to uncontrolled cell proliferation, differentiation, apoptosis, and invasion [1]. As tyrosine kinase is the driving step in cell signaling, tyrosine kinase inhibitors (TKIs) can serve as a therapeutic option for breast cancer patients. In this chapter, we will review monoclonal antibodies targeting tyrosine kinase receptors and small-molecule TKIs that serve as anticancer agents and discuss newer therapeutic options for overcoming drug resistance in breast cancer.

Receptor tyrosine kinases have three different major domains: extracellular domains (domains I–IV), transmembrane domains, and juxtamembrane domains. Upon ligand binding, two receptor tyrosine kinases homo- or heterodimerize, and tyrosine residues are phosphorylated to activate the downstream signaling cascade. Nearly 90 tyrosine kinases have been identified in humans, including receptor tyrosine kinases and cellular tyrosine kinases [2].

Among these, the epidermal growth factor receptor family (EGFR, ErbB) and VEGF are the primary targets investigated for breast cancer. Four members of the ErbB receptor family have been identified: (1) HER1 (EGFR), (2) HER2 (ErbB2), (3) HER3 (ErbB3), and (4) HER4 (ErbB4).

In the ErbB family, HER2 is the preferred dimerization partner as its kinase catalytic activity is the most potent and also does not require a ligand for dimerization. HER2 overexpression is observed in 15–30% of breast cancers and is associated with a poorer prognosis. Trastuzumab, a humanized monoclonal anti-HER2 monoclonal antibody, binds to the extracellular domain of HER2 (subdomain IV) and induces a conformational change. Previous studies have confirmed that trastuzumab exhibits antitumor activity via different mechanisms: antibody-dependent cell-mediated cytotoxicity, inhibition of downstream pathways, and prevention of dimerization. Although this agent shows efficacy via a variety of effects, the majority of HER2-positive patients develop resistance to treatment. Increased expression of MUC-4, alternative downstream PI3K-AKT pathway activation, PTEN loss, expression of truncated p95, and downregulation of p27 are possible causes of trastuzumab resistance.

The majority of targeted therapy studies have attempted to overcome these resistance mechanisms by targeting various steps of the tyrosine kinase activation cascade or combining new anti-HER2 therapies targeting the HER2 signaling network at multiple points.

Anti-HER2 Therapies

Lapatinib

Lapatinib is orally active dual inhibitor of EGFR and HER2 (Fig. 35.1). Preclinical studies have demonstrated that lapatinib inhibits trastuzumab-resistant HER2(+) breast cancer by binding truncated p95 [3, 4]. In the metastatic first-line setting, lapatinib/chemotherapy combinations are approved following disease progression in patients previously treated with trastuzumab. In this setting, the paclitaxel-lapatinib combination significantly improved event-free survival (EFS), time to progression (TTP), and the clinic benefit rate (CBR) without an OS advantage compared with those of paclitaxel-placebo in a phase III study [5]. In subsequent settings, lapatinib/capecitabine and lapatinib/trastuzumab are possible therapeutic options [6, 7]. Lapatinib and trastuzumab, which block HER2 via different mechanisms, appear to be a good combination choice. However, it is not clear whether sequential or combined use of these agents

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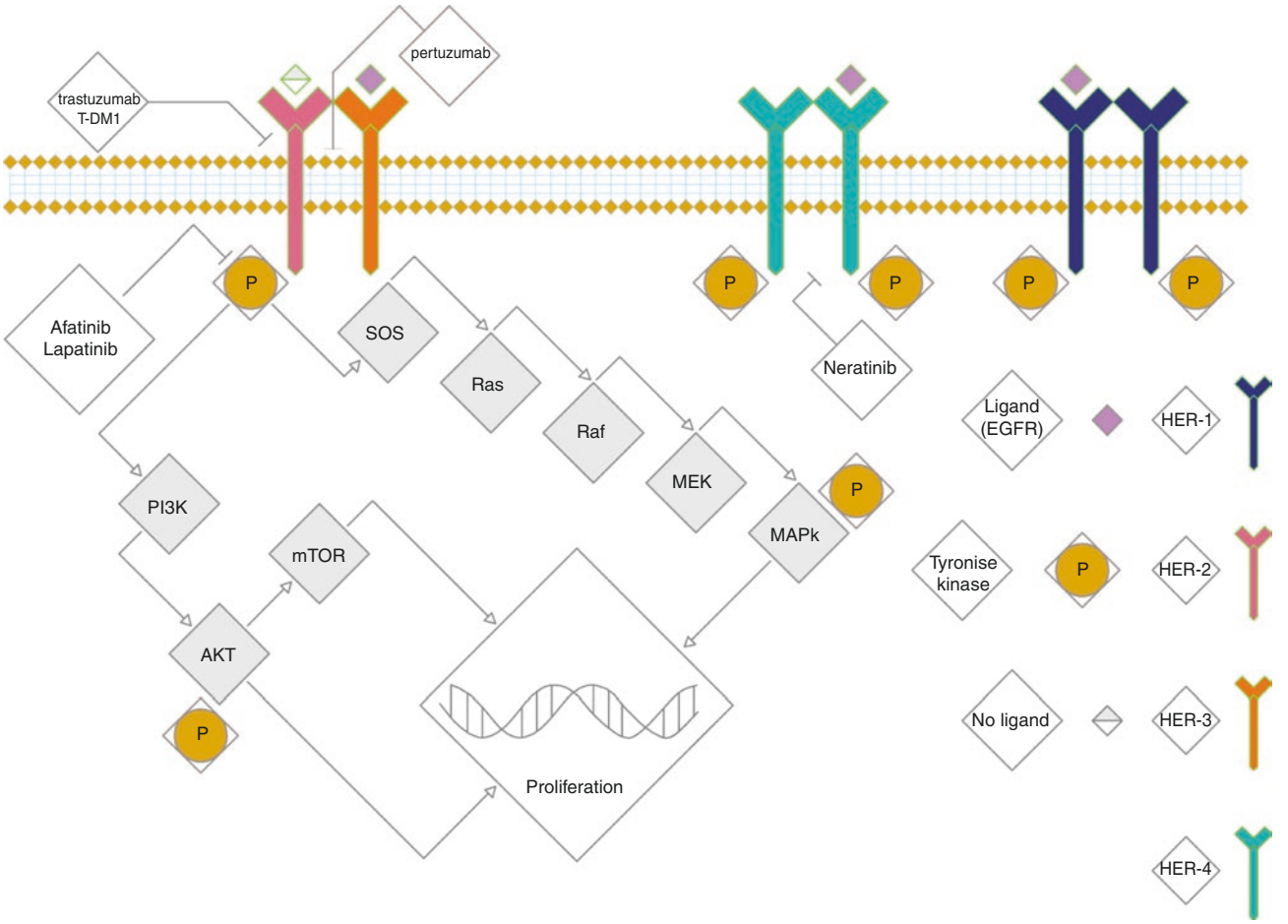

Fig. 35.1 Therapies targeting HER signaling

will produce better results. An ongoing phase III study, NCT00968968, is evaluating the efficacy of lapatinib plus trastuzumab versus trastuzumab as continued HER2 suppression after the first- or second-line trastuzumab-based chemotherapy combination and will clarify whether dual blockage in maintenance achieves better results in the metastatic setting. As a first-line therapy, lapatinib combined with taxane was associated with shorter PFS and greater toxicity compared with those of the trastuzumab and taxane combinations [8].

In the neoadjuvant setting, although the lapatinib/trastuzumab combination improved pCR significantly compared with that of trastuzumab alone (51.3% vs. 29.5%) in the NEO-ALTTO study [9], a head-to-head comparison of trastuzumab and lapatinib with chemotherapy combination in the GeparQuinto study showed that trastuzumab achieved better pCR compared with that of lapatinib (31.75 vs. 21.7%, respectively) [10]. In a randomized phase II CHERLOB trial, preoperative taxane and anthracycline chemotherapy in combination with trastuzumab, lapatinib, or the combination were evaluated in stage II–IIIA breast cancer patients. The pCR rates were 28%, 32%, and 48% in the trastuzumab, lapatinib, and combination arms, respectively [11]. The present data confirm that the combination of these agents results in better pCR, whereas single-agent trastuzumab appears to be superior to single-agent lapatinib.

In HER2 hormone receptor (HR) copositive tumors, inhibiting both the HER2 and ER pathways might be a more reasonable option. There is cross talk between these pathways. In lapatinib-exposed cells, continuous inhibition of the PI3K/Akt pathway can lead to upregulation of the transcription factor FOX03A, which can increase ER signaling [12]. Two large randomized trials have evaluated AIs and anti-HER2 therapy combinations. In postmenopausal hormone receptor-positive and HER2-positive breast cancer patients, lapatinib in combination with letrozole achieved a significantly better median PFS (8.2 months vs. 3 months), ORR (28% vs. 15%), and CBR (48% vs. 29%) compared to those of letrozole alone [13]. In the TAnDEM study, the trastuzumab and anastrozole combination versus anastrozole alone showed a significantly superior median PFS (4.8 months vs. 2.4 months) and ORR (20.3% vs. 6.8%) in the metastatic breast cancer setting [14]. An ongoing study, NCT01160211, is recruiting participants to compare AIs in combination with

lapatinib, trastuzumab, or both for the treatment of hormone receptor-positive, HER2-positive metastatic breast cancer as first- or second-line therapy in postmenopausal subjects.

Pertuzumab

Pertuzumab is a recombinant humanized monoclonal antibody that binds to the extracellular subdomain II of HER2 and prevents HER2 dimerization. In contrast to trastuzumab, which is effective on HER2 homodimers, pertuzumab can affect HER2/EGFR and HER2/HER3 interactions (Fig. 35.1). After preclinical studies as a single agent and in combination with trastuzumab confirmed activity [15], a phase II study evaluated the role of the pertuzumab with trastuzumab combination in HER2-positive metastatic breast cancer patients who progressed on prior trastuzumab therapy. The objective response rate (ORR) and CBR were 24% and 50%, respectively. The median progression-free survival was 5.5 months [16]. A subsequent phase III CLEOPATRA study evaluated the role of the docetaxel, trastuzumab, and pertuzumab combination compared with docetaxel, trastuzumab, and placebo in a HER2-positive metastatic breast cancer patient group. The majority of the group (90%) did not receive an anti-HER2 agent previously, and the triple combination showed a significant median PFS, OS, and ORR advantage (19 months vs. 12 months, HR 0.68; 95% CI 0.58–0.80; 56.5 months vs. 40.8 months, HR 0.68; 95% CI 0.56–0.84; 80% vs. 69%, respectively) [17]. Based on this study, pertuzumab received approval from the FDA as a combination therapy for HER2-positive metastatic breast cancer in the first-line setting in June 2012.

For HR-positive and HER2-positive metastatic breast cancer, the phase II PERTAIN study evaluated the pertuzumab, trastuzumab, and aromatase inhibitor triple combination against trastuzumab plus aromatase inhibitor in the first-line setting. However, half of these patients received induction therapy with taxane prior to the initiation of endocrine therapy. The three-drug combination improved PFS (18.9 vs. 15.8 months; HR 0.65, 95% CI 0.48–0.89) with higher grade ≥3 AEs (50% vs. 39%) [18]. The role of pertuzumab in the second-line setting is not clear.

Among neoadjuvant studies, the NEOSPHERE trial randomized operable, locally advanced or inflammatory HER2-positive breast cancers to four different treatment groups: (a) docetaxel plus trastuzumab, (b) docetaxel plus trastuzumab plus pertuzumab, (c) pertuzumab plus trastuzumab, and (d) docetaxel plus pertuzumab [19]. pCR in these four groups was 29%, 45.8%, 16.8%, and 24%, respectively. In this study, the triple combination showed superior pCR, but a subgroup of arm C also seemed to benefit from dual blockade without chemotherapy. The randomized phase II TRYPHAENA trial compared pertuzumab and trastuzumab (HP) with or without an anthracycline-based chemotherapy regimen. Patients with operable, locally advanced, or inflammatory breast cancer were randomized 1:1:1 to receive six neoadjuvant cycles q3w (Arm A: 5-fluorouracil, epirubicin, cyclophosphamide [FEC] + H + P × 3 → docetaxel [T] + H + P × 3; Arm B: FEC × 3 → T + H + P × 3; Arm C: T + carboplatin + H [TCH] + P × 6). pCR was assessed at surgery, and adjuvant therapy was given to complete 1 year of H. FEC-HP followed by D(docetaxel)-HP, FEC followed by D-HP, and DC(docetaxel-carboplatin) followed by HP were the three treatment arms. The pCR rates were 62%, 57%, and 66%, respectively, with no significant difference [20].

T-DM1

T-DM1 is an antibody drug conjugate composed of trastuzumab and an antimitotic agent derivative, maytansine, that targets HER2-expressing cells directly [21] (Fig. 35.1). The FDA approved the drug in February 2013 based on the Emilia Study. This phase III study enrolled 991 HER2-positive MBC patients with prior trastuzumab and taxane therapy and compared T-DM1, 3.6 mg/kg IV, D1 in combination with capecitabine (1000 mg/m2 orally twice daily, days 1 to 14) and lapatinib (1250 mg orally daily) every three weeks. Significant improvements in the median PFS (10 months vs. 6 months, respectively; HR 0.65; 95% CI 0.55–0.77), OS (31 months vs. 25 months, respectively; HR 0.68; 95% CI 0.55–0.85) and ORR were achieved (44% vs. 31%, respectively) [22, 23].

A recently published phase II study of HER2-positive MBC/locally advanced patients showed that in the first-line setting, T-DM1 showed a superior median PFS (14.2 months vs. 9.2 months, respectively; HR 0.59; 95% CI 0.36–0.97) and ORR (64.2% vs. 58%, respectively) compared with that of the docetaxel and trastuzumab combination [24]. The phase III MARIANNE study randomized previously untreated locally advanced/metastatic breast cancer patients to trastuzumab plus taxane, T-DM1 plus placebo, or T-DM1 plus pertuzumab. The median PFS for arms 1, 2, and 3 was 13.7, 14.1, and 15.2 months, respectively. Neither experimental arm showed PFS superiority to trastuzumab plus taxane. The response rates were similar, and grade ≥3 adverse events were numerically higher in the control arm (54.1%) than in the T-DM1 (45.4%) and T-DM1 plus pertuzumab arms (46.2%) [25].

In the first-line setting, a phase II trial comparing taxane plus trastuzumab or T-DM1 also demonstrated that T-DM1 provided a significant improvement in PFS, with a better safety profile than taxane plus trastuzumab [26].

The activity of T-DM1 was also demonstrated after multiple HER2-directed therapies. In the TH3RESA trial,

patients who had progressed on at least two lines of HER2-directed regimens were randomized to T-DM1 and the clinician's choice of therapy. Patients treated with T-DM1 had improved PFS (median 6.2 vs. 3.3 months; HR 0.53, 95% CI 0.42–0.66) and OS (median, 22.7 versus 15.8 months; HR 0.68, 95% CI 0.54–0.85) [27, 28].

The agents mentioned above target the dimerization and activation of HER1, HER2, and HER3; however, there are various cascades downstream of the ErbB family before the proliferation signal reaches the nucleus.

Neratinib

Neratinib is an oral covalent drug that irreversibly inhibits the active ATP site of the ErbB family (Fig. 35.1) [29]. In a phase II study, advanced HER2-positive breast cancer patients received oral neratinib 240 mg once daily. The median PFS was 39.6 and 22.3 weeks for patients with prior trastuzumab or without trastuzumab, respectively. The objective response rates were 24% among patients with prior trastuzumab treatment and 56% in the trastuzumab-naïve cohort [30]. Another study comparing neratinib monotherapy versus lapatinib plus capecitabine demonstrated a median PFS of 4.5 versus 6.8 months in the neratinib (240 mg/day) and combination arms, respectively. ORR was 29% and 41%. The non-inferiority of neratinib could not be demonstrated in this study [31]. Another study evaluated the neratinib (240 mg/day) and capecitabine combination (1500 mg/m^2/day) in HER2-positive breast cancer. The ORR for patients who received prior treatment with lapatinib and lapatinib-naïve patients was 57% and 64%, respectively. The median PFS was superior in the lapatinib-naïve group (40.3 weeks vs. 35.9 weeks) [32]. The NEfERT-T trial compared neratinib plus paclitaxel versus trastuzumab plus paclitaxel in treatment-naïve metastatic HER2-positive breast cancer patients. Overall efficacy was similar and CNS recurrence was slightly lower in the neratinib arm. However, neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of progression-free survival [33].

In the neoadjuvant setting, contradictory results have been reported. The I-SPY2 trial evaluated neratinib in combination with weekly paclitaxel with or without trastuzumab followed by doxorubicin and cyclophosphamide (AC) for women with HER2-positive locally advanced breast cancer. Neratinib achieved a pCR rate of 56% vs. 33% in the trastuzumab arm [34]. However, in the NSABP FB-17 neoadjuvant trial comparing paclitaxel-trastuzumab and paclitaxel-neratinib in HER2-positive breast cancer, the trastuzumab-based arm was associated with a higher pCR rate (38% vs. 33%) [35].

In the adjuvant setting, the FDA approved neratinib in July 2017 for the extended adjuvant treatment of early-stage HER2-positive breast cancer. Approval was based on the ExteNET trial, a multicenter, placebo-controlled trial of 1 year of neratinib after trastuzumab-based treatment. Neratinib improved 5-year invasive disease-free survival (iDFS) after trastuzumab-based adjuvant treatment in women with HER2 breast cancer. The 5-year iDFS was 90.2% (95% CI 88.3–91.8) in the neratinib group and 87.7% (85.7–89.4) in the placebo group. The benefit was significant only in HR-positive patients, and the most prominent adverse event in the neratinib arm was diarrhea [36].

Afatinib

Afatinib is an oral small-molecule inhibitor of the ErbB receptor family that covalently binds and irreversibly blocks ErbB family members (Fig. 35.1). For advanced HER2-positive breast cancer patients after trastuzumab failure, afatinib 50 mg was administered once daily until progression. In 37% of patients, SD was the best response, and 46% achieved clinical benefit. The median PFS and OS were 15.1 and 61 weeks, respectively [37]. In HER2-negative patients, the activity seems to be limited according to a previous study [38].

Dual blockade and pan-HER blockade of tyrosine kinases and drug conjugate anti-HER2 agents are being studied in early-phase clinical studies that will explain the exact roles of these agents in the near future.

EGFR Inhibitors

EGFR (HER1) is member of the ErbB family that enhances tumorigenicity in breast cancer and is also associated with poorer survival and resistance to hormonotherapy [39, 40]. EGFR is not only related to ER(+) tumors but was also found to be overexpressed in basal-like breast cancers [41]. The small-molecule tyrosine kinase inhibitor gefitinib is being investigated in combination with endocrine therapy in hormone receptor-positive tumors, whereas cetuximab was evaluated in triple-negative patients.

Gefitinib

Gefitinib is a small-molecule tyrosine kinase inhibitor that inhibits the phosphorylation of downstream signaling pathways. The efficacy of the drug could not be demonstrated as monotherapy in taxane- and anthracycline-pretreated metastatic breast cancer patients [42], but gefitinib was shown to be a reasonable option in the neoadjuvant setting in combination with anastrozole in ER(+) and EGFR(+) tumors [43]. A phase II study in the advanced breast cancer setting demonstrated that paclitaxel and carboplatin combined with

gefitinib (250 mg/day orally) achieved CR (10.3%), PR (44.1%), and SD (30.9%) in advanced breast cancer patients [44]. In another study, first-line therapy in MBC with gefitinib and docetaxel achieved an ORR of 54%, with better partial and complete responses in the ER(+) versus ER(−) group (70% vs. 21%) [45]. Although the combination of gefitinib with various chemotherapies had an acceptable toxicity profile, adding gefitinib to chemotherapy or to trastuzumab did not significant improve response rates or survival [46–48]. These results support the combination of the drug with hormonotherapy options.

Based on current data, adding gefitinib to anastrozole has no additional clinical effect in the neoadjuvant setting [49]; however, the same combination is associated with improved PFS (17.4 vs. 8.4 months) and CBR (49% vs. 34%) compared with that of anastrozole alone in the metastatic setting [50]. A recent study comparing anastrozole plus gefitinib versus fulvestrant plus gefitinib in postmenopausal HR-positive MBC showed that both combinations had similar clinical benefit rates (44.1% vs. 41%), median PFS (5.3 vs. 5.2 months), and OS (30.3 vs. 23.9 months) [51]. However, the benefit rates of both combinations are not clearly superior to those of gefitinib or endocrine therapy alone.

As EGFR expression is related to endocrine resistance, it is rational to suggest that gefitinib with endocrine therapy might overcome hormonotherapy resistance. A phase II study examined two patient groups with initial hormonotherapy who received gefitinib. Stratum 1 included women with newly diagnosed metastases or who had recurred 1 year after stopping adjuvant therapy with tamoxifen. Stratum 2 involved patients with recurrent disease during or after AI adjuvant therapy or who progressed after first-line hormonotherapy with AI in the metastatic setting. Patients were randomized to tamoxifen plus gefitinib (250 mg/day orally) versus tamoxifen plus placebo. The median PFS (10.9 vs. 8.8 months) was better in the combination arm in Stratum 1. No objective responses were detected in Stratum 2 with the combination [52]. In a recent phase II study, HR-positive pretreated advanced breast cancer patients were randomized to anastrozole plus gefitinib or placebo. The study closed prematurely due to slow recruitment, and no PFS advantage could be confirmed by adding gefitinib to anastrozole. Moreover, in the gefitinib arm, one-third of the patients interrupted therapy due to gastrointestinal and skin adverse events [53].

These conflicting results indicate that the present data are insufficient for identifying the exact setting of this agent.

Cetuximab

Cetuximab is a epidermal growth factor (EGF) antagonist that binds specifically to EGFR on both normal and tumor cells. Binding of cetuximab to EGFR blocks the phosphorylation and activation of receptor-associated kinases. Signal transduction through EGFR activates the k-Ras protein; however, mutant k-Ras protein is continuously active and does not depend on EGFR regulation. The majority of cetuximab studies have included triple-negative breast cancers (TNBCs) because they have high EGFR expression. A phase II study evaluating weekly irinotecan/carboplatin with or without cetuximab in patients with metastatic breast cancer showed antitumor activity but with significant associated toxicity [54]. The TBCRC001 study evaluated the cetuximab and carboplatin combination in metastatic TNBCs; the clinical benefit ratio of the combination was higher (27% vs. 10%), although due to rapid disease progression, the median PFS was only 2 months in all study groups. BALI-1, the largest EGFR trial in metastatic TNBC, compared cetuximab with cetuximab and cisplatin combinations. For the combination, the progression risk reduction was 32.5%, and PFS was longer in the cetuximab arm (3.7 months vs. 1.5 months, HR 0.67, $p = 0.03$) without any significant improvement in OS [55].

In the first-line metastatic setting, adding cetuximab to ixabepilone did not improve PFS in TNBC patients [56]. The N0436 (Alliance) study aimed to evaluate the irinotecan and cetuximab combination in MBC patients who previously received anthracycline and/or taxane but closed early due to low overall activity [57].

In addition to these two agents, erlotinib was shown to have minimal activity in unselected previously treated women [58], limited activity in combination with bevacizumab in MBC after first- or second-line chemotherapy [59], and preliminary evidence of anticancer activity in combination with trastuzumab [60]. Among EGFR inhibitors, cetuximab and gefitinib have been well studied but have not shown encouraging activity in these patients.

Targeting the PI3K Pathway in Breast Cancer to Overcome TKI Resistance

The phosphoinositide-3-kinases (PI3Ks) are a family of lipid kinases that function as dimeric enzymes and consist of catalytic (p 110 α, β, ɣ, and δ) and regulatory subunits (p85). Following binding of a growth factor or a ligand to a tyrosine kinase receptor, the inhibitory effect of p85 on p110 is removed, and PI3K is activated (Fig. 35.1). The activated kinase phosphorylates phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3) to recruit proteins such as Akt and PDK1 to cellular membranes [61]. Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) acts as a catalytic antagonist of PI3K by hydrolysis of PIP3 to PIP2. Class 1 PI3Ks are the major subgroup involved in cancer. Mutational activation or overexpression of PI3K or PTEN inactivation by genetic

or epigenetic alterations result in enhanced PI3K signaling. The majority of mutations are in PIK3CA, which encodes the p110 alpha catalytic subunit, in three hot spots and are gain-of-function mutations. Two of these mutations are on the helical domain and one is on the kinase domain of p110α.

A paper published in *Nature* highlighted the genomic and proteomic features of breast cancer subtypes and showed that the PIK3CA mutation was more common in luminal tumors, whereas PTEN mutation/loss was most common in basal-like breast cancers [62]. PIK3CA mutation was observed in 49%, 32%, 7%, and 42% of luminal A, luminal B, basal-like, and HER2-positive patients, respectively, whereas PTEN mutation/loss was found in 13%, 24%, 35%, and 19%, respectively.

These previous studies confirmed that PI3KCA mutations might confer favorable clinical outcomes. Luminal A–B tumors have more frequent mutations and slower disease progression, especially luminal A tumors; it is possible that these mutations are related to less aggressive disease. However, these mutations are also related to trastuzumab and lapatinib resistance in HER2-positive breast cancer and hormonotherapy resistance in HR-positive tumors by directly inducing ER transcription [63, 64]. Retrospective analyses of HER2-positive MBC have shown that tumors with PIK3CA mutations or PTEN loss are associated with low efficacy of trastuzumab and lapatinib and have also suggested that anti-HER2 drug-resistant tumors might still benefit from PI3K inhibitors [65, 66]. By contrast, PTEN-deficient HER2-positive cells still have upstream input from HER2, and therefore dual blockade might be effective in this patient group [67].

PI3K pathway inhibitors can be divided into subgroups according to their targets: (1) pan-PI3K inhibitors, (2) mTOR inhibitors, (3) Akt inhibitors, and (4) PI3K/ mTOR dual inhibitors.

PI3K Inhibitors

Clinical trials with PI3K inhibitors are ongoing and still in early phases. The efficacy of buparlisib, an oral panPI3K inhibitor, was evaluated in two phase III trials.

The BELLE-2 trial randomized postmenopausal women with HR-positive/HER2-negative locally advanced/metastatic patients with progression on/after AI therapy to buparlisib 100 mg/day plus fulvestrant or placebo plus fulvestrant. The median PFS was 6.9 months (95% CI 6.8–7.8) in the buparlisib group versus 5.0 months (4.0–5.2) in the placebo group (HR 0.78 [95% CI 0.67–0.89], one-sided $p = 0.00021$). In the PI3K-activated group, the median PFS was 6.8 (95% CI 4.9–7.1) and 4 (95% CI 3.1–5.2) months in the buparlisib and placebo arms, respectively (HR 0.76, $p = 0.014$). The main problem of the drug is tolerability. Hepatotoxicity, hyperglycemia, and depression were the most common AEs in the buparlisib arm. Dose reduction or discontinuation occurred in 70% of patients in the buparlisib arm versus 10% in the placebo arm due to AEs [68].

The BELLE-3 trial, which had a similar design, included HR-positive/HER2-negative locally advanced/metastatic patients who had relapsed on/after endocrine therapy and mTOR inhibitors. The median PFS was significantly longer in the buparlisib arm versus the placebo arm (3.9 months vs. 1.8 months, HR 0.67, 95% CI 0.53–0.84, $p = 0.0003$) with similar toxicity issues. The poor safety profile will probably not support its further evaluation in breast cancer patients [69].

The activity of taselisib, an alpha-specific PI3K-selective inhibitor, was first shown in a neoadjuvant trial. The LORELEI study included 334 postmenopausal patients with ER-positive/HER2-negative, stage I–III, operable early breast cancer who were randomized to letrozole plus either taselisib or placebo. ORR was better in patients who received taselisib compared to that in those who received placebo (50% vs. 39.3%, odds ratio [OR] 1.55, 95% CI 1.00–2.38, $p = 0.049$), but there was no significant difference in pCR between the groups [70].

The phase III Sandpiper study randomized patients with HR-positive/HER2-negative locally advanced/MBC who progressed on aromatase inhibitors to taselisib plus fulvestrant versus placebo plus fulvestrant. The primary objective was PFS, and the results will be presented at ASCO 2018.

mTOR Inhibitors

mTOR is one of the major mediators of cell growth, mainly via two downstream messengers: P70-S6 kinase 1 and 4E-BP1, which show activity at the translational level (Fig. 35.1). As previous studies have shown that PI3K/Akt/mTOR pathway activation contributes to trastuzumab and hormonotherapy resistance, the addition of mTOR inhibitors to chemotherapy and hormonotherapy options were investigated for delaying resistance in this patient group [71, 72].

The first studies initiated with temsirolimus. A phase II study exploring the combination of letrozole and temsirolimus compared to letrozole alone showed a longer median PFS in the combination group; however, a subsequent phase III study was stopped early due to toxicity issues [73, 74].

Everolimus, which has a better toxicity profile, became the major agent evaluated in this setting. Everolimus as a monotherapy did not achieve a good objective ORR [75]. However, in HER2-positive MBC patients, trastuzumab in combination with paclitaxel or vinorelbine demonstrated efficacy in trastuzumab-pretreated patients [76, 77]. In a phase I/II study, HER2-positive MBC patients who progressed on trastuzumab-based therapy received everolimus in combination with trastuzumab. Among 47 patients, the

combination of everolimus and trastuzumab provided PR in seven patients (15%) and persistent SD (lasting 6 months or longer) in nine patients (19%), resulting in a clinical benefit rate of 34%. The median PFS was 4.1 months. This study suggests that everolimus may have promising activity in trastuzumab-pretreated patients without cytotoxic chemotherapy [78].

In HR-positive tumors, because endocrine therapy resistance is associated with PI3K/Akt/mTOR pathway activation, the combination of everolimus and hormonotherapy is a rational option to overcome or delay endocrine resistance. The benefit of everolimus plus exemestane was shown in the BOLERO-2 trial of 724 patients who progressed on anastrozole. Patients were randomly assigned to exemestane plus everolimus versus exemestane plus placebo. The combination improved the median PFS (7.8 vs. 3.2 months, HR 0.45, 95% CI 0.38–0.54) and ORR (9.5% vs. 0.4%) without any OS benefit (31 vs. 26.6 months, 95% CI 22.6–33.1 months) [79, 80]. In the phase II GINECO study, 111 HR-positive/HER2-negative MBC patients previously treated with aromatase inhibitors were randomly selected to receive tamoxifen alone or tamoxifen in combination with everolimus 10 mg/day. The CBR (61.1% vs. 42.1%) and TTP (8.6 months vs. 4.5 months) were significantly better in the combination, and the risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 to 0.81) [81]. When patients were stratified according to primary or secondary hormone resistance, the TTP improvement was better in the secondary hormone-resistant patients who received the combination therapy compared to that in those who received tamoxifen alone (17.5 months vs. 5 months, respectively), whereas TTP was slightly improved by combination therapy in primary hormone-resistant patients (5.4 months vs. 3.9 months, respectively).

In a phase II study, ER(+) MBC patients who failed AI therapy within 6 months were randomized to everolimus 10 mg/day in combination with intramuscular fulvestrant 500 mg D1, 250 mg D14, 250 mg D28 and 250 mg once a month. The median PFS was 10.4 months in the everolimus arm versus 5.1 months in the placebo arm (HR 0.61, 95% CI 0.40–0.92; stratified log-rank $p = 0.02$). Grade 3/4 AEs were more common in the everolimus arm (53%/3% vs. 23%/3%), including hyperglycemia (16%/0% vs. 0%), stomatitis (11%/0% vs. 0%), hypertriglyceridemia (9%/2% vs. 0%), lymphopenia (9%/0% vs. 0%), and pneumonitis (6%/2% vs. 0%) [82].

The present data show that everolimus might be an ideal therapeutic option in secondary hormone-resistant patients with hormonotherapy combinations.

In the first-line setting, the BOLERO-1 trial evaluated the combination of everolimus with trastuzumab and paclitaxel in HER2-positive advanced breast cancer patients. PFS was not significantly different between groups; however, in the HR-negative subgroup, everolimus prolonged PFS (20.2 months vs. 13.0 months) [83].

The BOLERO-3 trial recruited women with HER2-positive, trastuzumab-resistant, advanced breast carcinoma who had received taxane previously to everolimus (5 mg/day) plus weekly trastuzumab and vinorelbine or placebo plus trastuzumab and vinorelbine. The median PFS was 7.00 months (95% CI 6.74–8.18) with everolimus and 5.78 months (5.49–6.90) with placebo (hazard ratio 0.78, 95% CI 0.65–0.95, $p = 0.0067$). However, serious AEs were reported in 42% of patients in the everolimus arm and 20% of patients in the placebo arm [84].

Everolimus has also been evaluated in the neoadjuvant setting in combination with letrozole. Newly diagnosed ER(+) localized breast cancer patients were randomized to letrozole 2.5 mg/day plus placebo or letrozole plus everolimus 10 mg/day before surgery. ORR was 59% and 68% in the letrozole and combination arms, respectively [85].

Upon blocking mTOR with everolimus, compensatory Akt activation occurs. Baselga et al. explained in a review that this situation was due to reduced S6 following mTOR inhibition and claimed that reduced S6 could not suppress signaling of IGF-1R via suppression of IRS-1 anymore. Activated IGF-1R increase PI3K signaling [61].

AKT Inhibitors

AKT inhibitors are being investigated in breast cancer. The LOTUS trial investigated the activity of the oral AKT inhibitor ipatasertib in combination with paclitaxel for first-line therapy of triple-negative breast cancers. In this study, patients with locally advanced or metastatic triple-negative breast cancer previously untreated with systemic therapy were randomly assigned to receive intravenous paclitaxel 80 mg/m2 (days 1, 8, 15) with either ipatasertib 400 mg or placebo once per day (days 1–21) every 28 days until disease progression or unacceptable toxicity [86]. The combination improved mPFS vs. placebo + paclitaxel in TNBC. The greatest PFS benefit was observed in patients with PIK3CA/AKT/PTEN alterations (mPFS:9 vs. 4.9 months; HR 0.44 (90% CI 0.22–0.87). The most common AE was diarrhea in the ipatasertib arm, which was generally manageable. This drug combination is being evaluated for MBC in phase III trials and as a neoadjuvant treatment for TNBC in the randomized phase II FAIRLANE trial.

Concluding Remarks

Targeted therapies in breast cancer have had a remarkable effect on patient survival since the introduction of the first representative, trastuzumab, in HER2-positive breast cancer.

However, patients develop resistance to these drugs during the treatment period. This resistance is mainly due to the use of alternative pathways by cancer cells to continue proliferation signaling. To delay resistance to these therapies, combined modalities targeting the different steps of signaling cascades have been investigated. The main restriction in this approach is tumor heterogeneity; we cannot predict the driving pathway to be blocked in a tumor by simple standard analysis techniques. In recent decades, genomic analyses have revealed that by analyzing tumor characteristics, individualized therapies can be designed for each patient. The use of individual therapies is also evident in the study protocols of ongoing trials that mainly include patients with mutations demonstrated to be targeted by a specific drug. Future studies should not only confirm the efficacy of targeted combinations but should also stratify the selected patient groups for each developed drug.

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Immunotherapy in Breast Cancer

36

Soley Bayraktar

Introduction

Evading immune destruction is an emerging hallmark of cancer. The immune system plays a dual role in cancer: it not only suppresses tumor growth by destroying cancer cells or inhibiting their outgrowth but also promotes tumor progression either by selecting for tumor cells that are more fit to survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth. The conceptual framework called "cancer immunoediting" integrates the immune system's dual host-protective and tumor-promoting roles. Nonetheless, numerous studies have shown that tumors can be recognized and contained for extended periods of time by the immune response through the concerted action of the innate (via chronic inflammation orchestrated by the innate immune system) and adaptive immune responses [1]. Despite these efforts, cancer still develops, at increased frequency with age, as a consequence of selecting less immunogenic tumor cells (immunoediting) or the increased effectiveness of tumor-mediated immunosuppression (immune subversion) or both [2, 3].

Our understanding of the complex interplay between cancer and the immune system has improved substantially by moving from the concept of "immune surveillance" [4] to that of "immunoediting" [3], a term that appropriately describes the dual host-protecting and tumor-sculpting actions of the immune system. Immunoediting has three phases: elimination, equilibrium, and escape. The elimination phase in the immunoediting hypothesis corresponds to the immune surveillance function. In the equilibrium phase, although the immune system has failed to eliminate all clinically detected tumors, it can be actively and effectively engaged to keep the tumor under control, for instance, reducing the risk of metastatic spread [5]. During the equilibrium phase, the immune system can select cancer cells with a particular genotype and phenotype through evolutionary pressure to favor the development of immunological anergy, tolerance, or indifference (escape phase) [2]. An example of tumor immunoediting in triple-negative breast cancer (TNBC) is provided by the presence of CASP8 mutations [6], which can abrogate the death induced by cytolytic CD8+ T cells and has been described as a common mechanism of immune escape in many solid tumors [7]. Figure 36.1 presents the major functions and components of the immune system relevant for potential breast cancer (BC) therapy.

Immune Checkpoints

T cells are activated by foreign antigens presented on the major histocompatibility complex and coexpression of the T-cell receptor (TCR) or by concurrent coactivation of costimulatory and/or coinhibitory signals (Fig. 36.2). The latter include members of the CD28/B7 family, which are known as "immune checkpoints" [8, 9].

Immune checkpoints are involved in T-cell tolerance as well as activation and play a crucial role in maintaining self-tolerance and immune homeostasis under physiological conditions, thereby protecting tissues from unnecessary damage when the immune system has efficiently cleared the pathogen [10]. Even maternal immune tolerance towards the fetus is in part regulated by checkpoint inhibitors [11].

Tumors may express immune inhibitory signals, resulting in an attenuated immune reaction against the pathologic antigens [12]. Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), the axis of programmed cell death-1 and its ligands (PD-1/PD-L1/2), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin mucin-3 (TIM-3) are negative signals inhibiting the T-cell immune response. In the context of tumor immunology, CTLA-4 signaling is more involved in limiting the initiation of a T-cell response in the lymph nodes, whereas PD-1 features more prominently later on in the process and

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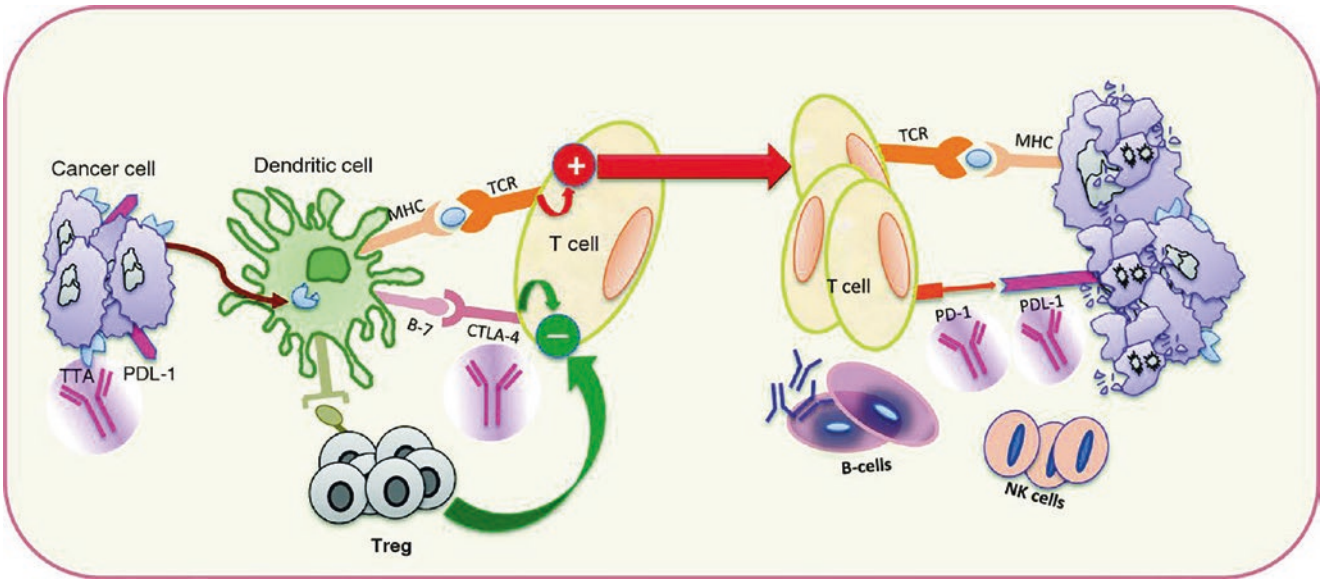

Fig. 36.1 Immune system functions and components relevant to breast cancer therapy. CTLA-4 cytotoxic T lymphocyte-associated antigen 4, MHC major histocompatibility complex, NK natural killer, PD-1 programmed death-1, PDL-1 PD-1 ligand 1, TAA tumor-associated antigen, TCR T-cell receptor, Treg regulatory T. (Reproduced with permission from Criscitiello et al. Breast Cancer Research 2014, 16:204)

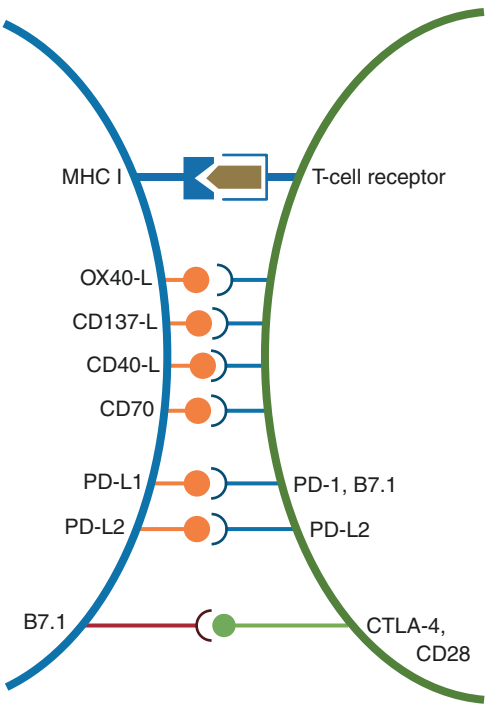

Fig. 36.2 Costimulatory and coinhibitory receptors expressed by T cells (green) and target cells (rose). (Reproduced with permission from Schutz F. et al. PD-1/PD-L1 Pathway in Breast Cancer, Oncol Res Treat 2017)

serves to limit T-cell activity in the tumor microenvironment [13]. After TCR engagement, CTLA-4 is upregulated to attenuate T-cell responses and prevent expansion of autoreactive T cells, primarily during the priming phase within the lymph nodes. Anti-CTLA antibodies, such as ipilimumab and tremelimumab, were tested in solid tumors, including breast cancer, with limited efficacy [14, 15].

PD-1/PD-L1 Pathway

PD-1 is an inhibitory immune checkpoint inhibitor that is expressed on the surface of T cells, B cells, natural killer T cells, T-cell lysis, and induction of tolerance to antigens [16–18]. In vitro blockade of PD-1 with monoclonal antibodies led to a 2-fold increase in cytokine production [19]. However, the in vivo activity also depends on T-cell motility as well as the duration of the interaction with antigen-presenting cells and target cells [20]. When T cells have been activated by their TCR, PD-1 is expressed simultaneously to offer the attacked cell a way of escaping the immune reaction. PD-1 decreases once the immune response has eliminated the pathologic antigen [21].

In solid tumors, the PD-1/PD-L1 inhibitory pathway can be (mis-)used to silence the immune system by increasing the expression of PD-L1 on the tumor cell surface [22]. PD-L1 expression has been associated with large tumor size, high-grade, high-proliferation, estrogen receptor-negative status, and HER2-positive status [23], and it is inversely correlated with survival in ovarian [24] and breast cancer [25]. PD-L1 is expressed in 20% of triple-negative breast cancers (TNBCs) [26]. This pattern indicates that although antitumor immunity is elicited against many solid tumors, it is counterbalanced by immunosuppressive factors. In vivo,

PD-L1 increases tumorigenesis and invasiveness and makes tumor cells less susceptible to specific CD8+ T cells [27]. Melanoma tumor growth is widely suppressed in PD-1 knockout mice. Furthermore, blockade of the PD-1/PD-L1 pathway in vivo using specific antibodies leads to stronger tumor regression in cellular immunotherapies [28]. The goal of immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1/anti-PD-L1, is to "release the brakes" and enhance T-cell activation by blocking negative pathways.

Prognostic Value of Immune-Related Gene Signatures

In recent years, gene expression profiling has been used in an effort to more precisely define BC taxonomy and identify prognostic and predictive signatures [29]. The common denominator in the majority of the "first-generation" signatures is their overall capacity to detect subtle differences in the cell cycle and proliferation. For this reason, they have not been found to be prognostic in the TN or HER2+ subtypes since these tumors are, by nature, highly proliferative. Several investigators have attempted to overcome the limitations of these first-generation signatures by focusing on the BC microenvironment or immune response (or both) to define promising "second-generation" prognostic signatures [30]. Unsupervised gene expression profiling of cancer-associated stroma revealed a signature enriched for CD8+ T-cell responses that was predictive of good prognosis [31]. An immune response module, the STAT1 module, has been shown to be associated with survival in patients with TNBC and HER2+ breast cancer [32, 33], and in the same BC subtypes, the overexpression of immune-related genes was able to identify subgroups of patients with a better prognosis [34, 35]. Similarly, in other studies, the high expression of B-cell and immunoglobulin-based metagenes has been associated with a low risk of developing distant metastases in patients with untreated ER-negative breast tumors [33, 36], whereas in patients with untreated breast cancer, elevated expression of the STAT1-related and T-cell-related metagenes is associated with a low risk of distant metastasis [37]. These studies suggest that effective engagement of the immune system, although insufficient to eliminate the tumor, can help to reduce the risk of tumor spread or maintain tumor dormancy [5].

The Role of Lymphocytic Infiltrate in Breast Cancer

The presence of tumor-infiltrating lymphocytes (TILs) is observed in some breast tumors and has been reported to be a good prognostic feature for certain types of breast cancer [34, 38], particularly estrogen receptor (ER)-negative tumors and HER2-positive subtypes [39]. Additionally, TILs have been negatively correlated with the patient's age at diagnosis [40]. More recently, the nature of TILs has been better characterized. Ruffell and colleagues [41] reported that TILs were mainly composed of CD3+/CD56− T cells, but a minority consisted of natural killer (NK) cells or CD20+ cells. The majority of CD3+ cells were either CD4+ or CD8+ T cells. Interestingly, CD8+ cells did not express Granzyme B at baseline, indicating that they did present inactivation status, but did express Granzyme B after neoadjuvant chemotherapy in one-third of the patients. Finally, a minority of TILs presented T and NK cell features [41]. The genomic characteristics of TIL+ tumors are important for understanding which molecular mechanisms lead to lymphocyte infiltration. Genomic instability may promote an anti-tumor immune response through tumor-associated antigens. Some mechanisms of chemokine release by the tumor have been described and correlated with lymphocyte attraction. TILs have been associated with CXCL9 and CXCL13 expression by the tumor [39]. TIL+ tumors present a specific methylation pattern on immune-related genes, including CCL5 [42]. A cluster of chemokines is lost in a subset of BC [43].

In TNBC and HER2-positive breast cancer, the association between the presence of TILs or the expression of immune markers and the likelihood of achieving a pCR after neoadjuvant chemotherapy is consistent and strong. A high level of expression of immune markers is associated with different immune cell types and functions and has been associated with benefit from chemotherapy in TNBC [23, 37, 44]. This association has also been confirmed by evaluation of the TIL density [39, 45]. Overall, these data suggest that the immune system collaborates with the action of chemotherapy in TNBCs, as suggested by data from preclinical studies [46, 47]. However, whether drug-specific immunomodulation properties [47], such as inducing immunogenic tumor cell death (postulated for anthracyclines) or engaging different immune effector mechanisms, are associated with different clinical outcomes is unknown and is currently an active area of investigation. Interestingly, assessments of the immune milieu modulation after neoadjuvant chemotherapy in patients with TNBC with residual disease have shown that the immune microenvironment can be turned from "cold" (containing few TILs) to "hot" (higher TIL presence) in some patients [48]. Tumors that remain or become "cold" after chemotherapy have a higher risk of relapse compared with that of tumors that remain or become "hot" [48]. These data also support the concept of chemotherapeutic agents having immunomodulatory activity and thus acting as an immunological adjuvant in the tumor microenvironment to stimulate vaccination-induced antitumor immunity [48]. Whether the immune system has different prognostic and predictive roles in different molecular subtypes of TNBCs has not been defined yet.

Overall, considering that, in TNBCs, a "hot" immune microenvironment is associated with a better prognosis and a higher likelihood of benefit from chemotherapy, it should not be surprising that many investigators have identified a strong association between high levels of immune markers or TILs and a low risk of relapse and/or death in patients with early-stage TNBC treated with systemic chemotherapy [49]. These results suggest that, in TNBC, the risk of recurrence in the early disease setting can be effectively defined by adopting appropriate immune markers for risk stratification. These results also distinguish a subgroup of patients with TNBC characterized by a "cold" immune microenvironment that has a high risk of relapse, despite treatment, and a low likelihood of benefit from cytotoxic chemotherapy [37]. Evidence for the clinical utility of TIL evaluation, however, remains scarce, in part because the TIL assessment lacks sufficient standardization; however, efforts to improve consistency and reproducibility are under way [50].

Immunogenicity of Breast Cancer

Breast cancer has not traditionally been considered immunogenic, as opposed to melanoma and renal cell carcinoma, which have traditionally been considered more responsive to immunotherapies. However, it appears that, despite a weak influence on primary tumor growth, the immune system is effective in preventing BC metastasis [51, 52]. Moreover, the tumor microenvironment releases immune-suppressive factors that make antigen presentation difficult and that have a negative impact on the immune response [53]. Furthermore, by blocking endogenous immune checkpoints that normally terminate immune responses after antigen activation, it is possible to evade immune destruction.

Nonetheless, it seems that any tumor could be immunogenic with appropriate immune activation. In a neoadjuvant clinical trial (Trial of Principle [TOP] study) in which patients with ER-negative BCs were treated with anthracycline monotherapy, high immune module scores were associated with sensitivity to anthracyclines [44]. The immune system also appears to be pivotal in determining the response to monoclonal antibodies (mAbs) and tyrosine kinase inhibitors, and some evidence indicates a possible role in the response to endocrine treatment. Antibody-dependent cellular cytotoxicity (ADCC) has long been implicated as one of the mechanisms of action of trastuzumab [54, 55]. Therefore, a complete tumor response after molecular targeted therapies requires a functioning immune system, pointing the way toward radically new combination therapies with a targeted and immune approach [56]. mAbs against an antigen tumor target or immune-regulatory molecules; cell-based therapies, including adoptive transfer of ex vivo-activated T cells and NK cells; or blockade of Treg cells could be useful for amplifying the antitumor response.

Tumor Mutational Burden (TMB) and Mutational Signatures in Breast Cancer

The use of immunotherapy is exponentially increasing in the treatment of patients with advanced solid tumors. However, the response rates vary significantly between different tumor types and even within the same tumor type (e.g., in lung cancer, approximately 1 in 4 patients respond to immunotherapy). To better identify patients who will respond to immunotherapy, several markers have been proposed. TMB has emerged more recently as a quantitative marker that can help predict responses to immunotherapies across different cancers, including melanoma, lung cancer, bladder cancer, and breast cancer [57]. TMB is a measure of the overall number of somatic protein-coding mutations occurring in the tumor specimen. Bonta et al. [58] analyzed 54 patients with solid tumors treated with immunotherapy for which genomic sequencing was available (FoundationOne). There were 39 lung cases and 15 non-lung (GI, GU, sarcoma, breast). Among patients with known TMB, 60% (18/30) had a favorable response (stable disease or response to therapy). Higher TMB values were correlated with increased probability of a favorable response. In their study, a TMB cutoff value of 8 mutations (mut)/megabase (MB) yielded a sensitivity of 95% and a specificity of 58% for predicting a favorable response. At the 2018 ASCO annual meeting, Barroso-Sousa et al. [59] presented an evaluation of the mutational load across breast cancers. Samples were classified as having high TMB if they had >10 mut/MB. The analysis included 3689 samples. The median TMB was 1.55 mut/MB. TMB varied significantly according to histology (ductal > lobular, $p = 4.6 \times 10^{-13}$), tumor subtype (HR−/ HER2+ > TNBC > HR+/HER2+ > HR+/HER2–, $p < 0.05$), staging (metastatic > primary, $p = 2.2 \times 10^{-16}$) and site of metastasis (higher in soft tissue and lowest in lung, $p < 0.05$). They identified a total of 70 (~2%) hypermutated tumors (62.8% metastatic vs. 37.2% primary samples). Mutational signature analysis of the hypermutated samples showed the presence of dominant APOBEC (77.1%), homologous recombination (HR; 2.9%), defective DNA mismatch repair (MMR; 18.6%), and POLE hypermutation (1.4%) signatures. The median TMB was higher for samples with the POLE and HR signatures, followed by those with MMR and APOBEC (93.1, 38.7, 14.6, and 12.4 mut/MB, respectively). Among hypermutated tumors, eight samples had somatic mutations in the POLE gene, but only the case with a high POLE signature had a characterized POLE driver mutation. In addition, 80% of the hypermutated tumors with an APOBEC signature had

PIK3CA mutations, in contrast to 31% of hypermutated tumors with other signatures ($p = 0.0005$). In another study, Xu et al. [60] aimed to predict the level of TMB in patients with breast cancer based on the expression of ER, PR, HER2, and Ki-67, thereby anticipating the prognosis of patients and the possible response to immunotherapy. HER2 expression positivity was significantly associated with TMB (HER2 positive vs. HER2 negative, odds ratio [OR] =34.81, 95% confidence interval [CI]: 3.711-821.689, $p = 0.0065$). In addition, TMB was higher in patients who were Ki-67 expression positive (>14%) than in those who were Ki-67 expression negative (≤14%) (OR = 0.217, 95% CI: 0.054-0.806, $p = 0.0242$). However, no significant differences in TMB were observed between the ER-positive group and ER-negative group (OR = 3.133, 95% CI: 0.124-127.687, $p = 0.4954$) and between the PR-positive group and PR-negative group (OR = 1.702, 95% CI: 0.162-20.335, $p = 0.6492$). In a multivariate analysis, high TMB (>5.56) was an independent predictive factor for decreased DFS (adjusted hazard ratio [HR], 5.594; 95% CI: 1.694-18.473; $p = 0.005$). These results suggest that the level of TMB value can be predicted based on the expression levels of ER, PR, HER2, and Ki-67, which may indicate the prognostic and predictive value of immunotherapy in patients with breast cancer.

Therapies Affecting the Immune System

Immunotherapy with checkpoint inhibitors has made a significant impact in the treatment of melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC) in recent years [61–64]. New agents such as nivolumab and pembrolizumab [a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody] selectively block the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation [65]. There is preliminary evidence of a positive correlation between high mutational burden of tumors and clinical benefit from immunotherapy strategies (i.e., the checkpoint inhibitors anti-CTLA-4 and anti-PD-1 antibodies), with remarkable effects observed in tumors displaying the highest rates of mutations, such as melanoma [66, 67]. These effects are also illustrated by the antitumoral immunologic response to anti-PD-1 antibody in patients with colorectal cancer and an increased mutational burden secondary to mismatch repair deficiency [68]. In recent years, the improved knowledge of BC biology has provided an opportunity to develop immunotherapies for overcoming the relatively nonimmunogenic properties of BC and improve the immune response.

TNBCs have a higher number of tumor-infiltrating lymphocytes (TILs) [69] and higher programmed cell death 1 ligand 1 (PD-L1), protein [70, 71], or mRNA [26, 49] expression compared with those of other breast cancer subtypes. PD-L1 expression is significantly associated with the presence of TILs [71], which suggests that the most common mechanism of regulation of PD-L1 expression in TNBC is regulatory feedback (acquired resistance) to immune engagement. An extremely heterogeneous pattern of immune infiltration, however, has been described among TNBC subtypes [72]. A significant association has also been observed between PD-L1 mRNA expression and the presence of PD-L1 copy-number alterations, with basal-like breast cancer having the highest frequency of PD-L1 gains/amplifications (17%) [23]. In addition, the loss of PTEN expression in TNBCs is associated with PD-L1 overexpression [26], confirming an association between increased PI3K signaling and the presence of PD-L1.

The finding that a population of TNBC is immunogenic and actively engaged by the immune system provides a strong rationale for testing immunotherapies in this type of breast cancer. The potential importance of immune checkpoint-guided therapy in TNBC is underscored by recent reports. Two phase I trials with immune-checkpoint inhibitors in patients with advanced-stage TNBC have been reported [73]. In one, 188 patients with advanced-stage TNBC positive for PD-L1 expression were treated with the anti-PD-1 monoclonal antibody pembrolizumab with a response rate of 18.5% (5 of 27 patients). Seven additional patients had stable disease. Of the screened patients, ≥1% PD-L1 expression was detected using IHC labeling of stromal or tumor cells in archival specimens from 58% of patients with the 22C3 antibody. Avelumab, an anti-PD-L1 IgG1 antibody, showed modest anti-tumor activity among 57 patients with TNBC, with only five partial responses (8.8%; 95% CI: 2.9, 19.3) [74]. In patients with TNBC who had PDL1+ immune cells within the tumor, 44.4% (4 of 9) had partial responses, compared with 2.6% (1 of 39) in those with PD-L1-negative immune cells. Different trials are ongoing to establish the roles of immune-checkpoint inhibitors alone or in combination and of other immunotherapies in TNBC (Table 36.1).

At the 2018 ESMO annual meeting, Schmid P. et al. presented the results of the phase 3 trial in triple-negative metastatic breast cancer [101]. In this phase 3 trial, patients with untreated metastatic triple-negative breast cancer were randomized to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Atezolizumab plus nab-paclitaxel prolonged progression-free survival in both the intention-to-treat population and the PD-L1-positive subgroup. In the intention-to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; $p = 0.002$); among patients with PD-L1-positive

Table 36.1 Clinical trials testing immunotherapies in patients with breast cancer

Disease setting	Phase	Clinical trial reference number	Breast cancer	Immunotherapies (alone or in combination)	Control arm treatment
Trials including only patients with TNBC					
Metastatic	I/II	NCT02513472	TNBC	Pembrolizumab[a]/eribulin mesylate	NA
	II	NCT02499367	TNBC	Nivolumab[a]/doxorubicin (low dose) or cyclophosphamide metronomic or radiation therapy or cisplatin	NA
		NCT02447003	TNBC	Pembrolizumab	NA
	III	NCT02555657	TNBC	Pembrolizumab	Single-agent CT (capecitabine, eribulin, gemcitabine, or vinorelbine)
		NCT02425891	TNBC	Atezolizumab[b]/nab-paclitaxel	Nab-paclitaxel
Adjuvant	II	NCT02539017	TNBC	Vaccine (DC-CIK)/EC followed by docetaxel	EC followed by docetaxel
Neoadjuvant	I/II	NCT02489448	TNBC	Durvalumab[b]/nab-paclitaxel followed by ddAC	NA
	II	NCT02530489	TNBC	Atezolizumab/nab-paclitaxel	NA
	III	NCT02620280	TNBC (LABC only)	Atezolizumab/nab-paclitaxel/carboplatin	Nab-paclitaxel/carboplatin
Trials including patients with breast cancer					
Metastatic	I	NCT02303366	All	Pembrolizumab/stereotactic ablative body radiosurgery	NA
	I/II	NCT00003432	All (CEA-positive only)	Vaccine (CEA RNA-pulsed DC)	NA
		NCT01421017	All with skin metastasis	Imiquimod (TLR7 agonist)/radiotherapy or cyclophosphamide	NA
	II	NCT02536794	HER2-negative	Durvalumab/tremelimumab[c]	NA
		NCT02411656	HER2-negative	Pembrolizumab	NA
		NCT02563925	All with brain metastasis	Tremelimumab/brain radiotherapy or stereotactic	NA
		NCT00083278	All	Ipilimumab[c]	NA
		NCT01792050	HER2-negative	Indoximod (IDO inhibitor)/paclitaxel or docetaxel	Paclitaxel or docetaxel
		NCT02491697	All	Vaccine (DC-CIK)/capecitabine	Capecitabine

BC breast cancer, *CEA* carcinoembryonic antigen, *CT* chemotherapy, *DC* dendritic cells, *DC-CIK* dendritic cells cocultured with cytokine-induced killer cells, *ddAC* dose-dense doxorubicin and cyclophosphamide, *EC* epirubicin and cyclophosphamide, *LABC* locally advanced breast cancer. *TLR7* Toll-like receptor 7, *NA* not applicable, *TNBC* triple-negative breast cancer

[a]Antiprogrammed cell death protein 1 (PD-1) monoclonal antibodies (mAbs): nivolumab and pembrolizumab (anti-PD1)

[b]Antiprogrammed cell death 1 ligand 1 (PD L1) mAbs: atezolizumab and durvalumab

[c]Anti cytotoxic T lymphocyte protein 4 (CTLA 4) mAbs: ipilimumab and tremelimumab

tumors, the median progression-free survival was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; $p < 0.001$). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI 0.69 to 1.02; $p = 0.08$); among patients with PD-L1-positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI 0.45 to 0.86).

In light of the promising preliminary results obtained with immune-checkpoint inhibitors, their expected curative potential [75] and their beneficial safety profile, these agents are already being assessed for the treatment of patients with early-stage TNBC. Three trials in patients with stage I–III TNBC are currently ongoing to evaluate the potential activity of immune-checkpoint inhibitors in combination with chemotherapy in the neoadjuvant setting. In the phase III trial NeoTRIPaPDL1 (NCT02620280), patients with locally advanced TNBC will be randomly assigned to receive nab-paclitaxel and carboplatin with or without a PD-L1-inhibitor (atezolizumab). Notably, the primary end point will be event-free survival. A phase II trial will evaluate atezolizumab in combination with nab-paclitaxel (NCT02530489). Finally, a phase I/II trial will test the safety and efficacy of durvalumab, another anti-PD-L1 antibody, in combi-

Table 36.2 Results of clinical trials using immune checkpoint inhibitors in TNBC

Drug	Phase	Population	Number	Results in TNBC
Pembrolizumab [73]	Ib	Solid tumors, including heavily pretreated metastatic TNBC, PDL1 positive	27 patients with TNBC evaluable for efficacy	ORR 18.5% (1 CR, 4 PR), median duration of response not reached (longest 47 weeks and ongoing)
Atezolizumab [92]	Ia	Solid tumors, including heavily pretreated metastatic TNBC	27 patients with TNBC evaluable for efficacy	ORR 19% (2 CR, 2 PR), median duration of response not reached (longest 84 weeks and ongoing)
Avelumab [74]	I	Locally advanced or metastatic breast cancer	58 patients with TNBC	ORR for all patients 4.8% (5 of 8 responses were in TNBC)
Atezolizumab plus nab-paclitaxel [93]	I	Metastatic TNBC	32 patients evaluable for efficacy	ORR 46% in 1st line, 22% in 2nd line, 40% in the 3rd line setting (0 CR, 4 PR)

CR complete response, *ORR* overall response rate, *PR* partial response, *TNBC* triple-negative breast cancer, *PDL1* programmed death cell ligand

nation with weekly nab-paclitaxel followed by dose-dense chemotherapy containing cyclophosphamide and doxorubicin (NCT02489448). The results of clinical trials using immune checkpoint inhibitors in TNBC are shown in Table 36.2.

Another interesting immune molecule is CTLA-4 (CD152), which is similar to PD-1 but has different immune inhibitory signals. CTLA-4 knockout mice display early lethality, in contrast to PD-1 knockouts, which exhibit late-onset and organ-specific autoimmunity. Anti-CTLA4 mAb treatment has shown robust tumor responses in phase III trials, albeit with considerable adverse events [76]. Still, combining anti-CTLA-4 mAb with trastuzumab has shown synergy in preclinical mouse models [77].

Hence, immunotherapeutics that augment CD8 T-cell anti-tumor activity—such as anti-PD1 and anti-CTLA4 mAbs—given in combination with trastuzumab in patients with HER2+ BC may improve outcomes by invoking and enhancing critical host immunity [56, 78, 79]. Given this evidence, the evaluation of the baseline immune response and the identification of easy-to-define surrogate markers of immune system activation could be helpful in the management of BC to identify patients who may benefit from these combination therapies, even eliminating the need for combination cytotoxic chemotherapy.

Forkhead box P3 (FOXP3)+ Treg cells are crucial for the induction and maintenance of peripheral tolerance to self-antigens. While exerting their function, Treg cells can also suppress immune responses to tumor antigens, alloantigens, and allergens [80]. FOXP3 expression in BC was associated with worse distant metastasis-free survival but not local recurrence risk, and the risk increased with increasing FOXP3 immunostaining intensity [81]. According to these data, Treg cells may play an important role in BC immunopathology because of their potent suppression of both T-cell activation and effector functions. The blockade of Treg cells could be useful for enhancing the immune response and improving patients' clinical outcomes.

Importantly, a subset of patients treated with immune checkpoint inhibitors experience an accelerated tumor growth rate (TGR) compared with that of the pretreatment kinetics, known as hyper-progression. Kanjanapan et al. [82] explored the relationship among hyperprogressive disease (HPD), treatment-related toxicity and clinical factors. They observed a 7% rate of HPD within a range of solid tumors treated with immune checkpoint inhibitors, comparable to that in other reports. There were no associations between HPD and clinically significant adverse events, age, tumor type, and type of therapy. Further studies are needed to identify predictors of HPD.

Immunotherapy for ER-Positive Breast Cancer

Immunotherapy has thus far shown more limited responses in ER-positive breast cancer compared to those in TNBC, which tends to overexpress PDL1 as outlined above. ER+ breast cancers may be less immunogenic, with inadequate activation of immune effector cells and/or other adaptations in the tumor microenvironments that suppress antigenicity and/or suppress activation of the adaptive or innate immune effector systems. Studies to determine how to reestablish immune-based host elimination of tumors offer potential, particularly for the eradication of the many small foci of growth-arrested but surviving cells that remain during treatment with endocrine therapies and are the source of distant recurrences in ER+ cancers. The results of clinical trials using immune checkpoint inhibitors in non-TNBC are shown in Table 36.3.

Table 36.3 Results of clinical trials using immune checkpoint inhibitors in non-TNBC

Phase	Population	Enrolled	Evaluable	Regimen	Clinical outcomes
I/II [94]	First-line MBC, Her2(-)	33	30	IMP321+paclitaxel	ORR: 50%, 15 PR
I [14]	Metastatic ER+/PR+	26	26	Tremelimumab (Anti-CTLA-4)+exemestane	SD ≥12 weeks: 42%
Ib [95]	Metastatic ER+/PR+	261 screened	25	Pembrolizumab	ORR: 12%, 3 PRs, SD: 16%
Ib [74]	Metastatic BC	168	168	Avelumab	Overall population: ORR: 4.8%, 1 CR and 7 PRs, SD: 23% By subtype: TNBC ORR: 8.6%, Her2+ ORR: 3.8%, ER+ Her2(-) ORR: 2.8%

BC breast cancer, *CR* complete response, *ORR* overall response rate, *PR* partial response, *Her2* human epidermal growth factor receptor type 2, *TNBC* triple-negative breast cancer, *SD* stable disease, *CTLA-4* cytotoxic T-lymphocyte antigen-4

Immunotherapy for Inflammatory Breast Cancer (IBC)

The role of immune infiltrate and immune checkpoints was also investigated in relation to genomic abnormalities in IBC samples [83]. The pathological examination of 20 IBC tissue samples identified a subset of IBC tumors associated with infiltration of immune cells. IHC staining identified the majority of infiltrating cell populations as CD8+ cytotoxic T cells, and high levels of CD8+ infiltration were observed in 5/12 tumors. To explore the possible role of PD-L1 in IBC, the investigators performed IHC staining of IBC tissues. Evaluation of PD-L1 staining revealed low-intensity tumor cell staining in 3/12 tumors studied and high-intensity tumor cell staining in 1/12 tumors. PD-L1 mRNA expression has been reported to be as high as 38% among patients with IBC, higher than the rate in non-IBC (28%), and correlates positively with pCR [84]. Notably, somatic mutation rates were significantly higher in high-infiltration versus low-infiltration tumors ($p < 0.05$) [83]. The authors speculated that this correlation between the somatic mutation rate and immune cell infiltration might be related to the exposure of tumor neoantigens to the immune system. A phase 2 clinical trial for patients with metastatic IBC assessing the efficacy of an anti-PD-1 inhibitor monoclonal antibody (pembrolizumab) is under development (NCT02411656).

Maintenance Immunotherapy in Patients with Metastatic Breast Cancer (MBC) Who Have a Clinical Benefit with Chemotherapy

Recchia et al. [85] investigated the effect of maintenance immunotherapy with the aim of prolonging PFS and OS through immune-mediated mechanisms in patients with hormone-resistant MBC who had not progressed with chemotherapy. From 1996 to 2009, 74 patients with MBC were entered in the study and received the following maintenance immunotherapy regimen: IL-2 (1.8 M UI) and oral retinoic acid (0.5 mg/kg), 5 days/week, 3 weeks/month for 1 year. Therapy was continued with an intermittent schedule until progression. The median age was 55 years (range 31–75); 30% of patients were premenopausal; 60% were ER+ and had progressed after two or more lines of hormonal therapy. The 74 patients had received 368 courses of chemotherapy regimens (median of 6 courses each patient). Thirty-six patients had also received high-dose chemotherapy with peripheral blood progenitor cell transplantation. After a median follow-up of 100 months (range 96–200), each patient had received a median of 8 courses of immunotherapy (total of 924 courses delivered). No WHO grade 3 or 4 toxicity was observed; grade 2 cutaneous toxicity and autoimmune reactions occurred in 19% and 16% of patients, respectively. Statistically significant improvements were observed in the number of lymphocytes ($p < 0.001$), natural-killer cell count ($p < 0.001$), and the CD4+/CD8+ ratio ($p < 0.01$). Ten-year PFS and OS were 25% and 31%, respectively. Although these data need to be matured in the breast cancer field, this approach has already been proven significant in improving PFS and OS in stage 3 non-small cell lung cancer patients. In February 2018, the FDA approved durvalumab as a maintenance therapy for patients with unresectable stage III non-small cell lung cancer whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy [86].

Vaccine-Based Therapies for Breast Cancer

Vaccines constitute an active and specific immunotherapy designed to stimulate the intrinsic antitumor immune response by presenting tumor-associated antigens (TAAs) that are expressed on normal tissues but overexpressed on tumor cells. Malignant cells can express both normal self-antigens and specific TAAs that arise from genetic mutations or epigenetic changes or both, which are recognized by the

Table 36.4 Reported clinical trials of therapeutic breast cancer vaccines

Vaccine	Population	Sample size	Biomarkers	Clinical activity	References
STn-KLH+CY vs KLH+CY	Stage 4 BC	1028	New vaccine-specific ab	No difference	Miles et al. [98]
hTERT peptide+montanide and GM-CSF adjuvant	Stage 4 BC	19	New TILs post vaccine, hTERT CD8+T cells	Improved OS with hTERT immunity	Emens [96]
GLOBO-H-KLH+QS21 adjuvant	Stage 4 BC	27	IgM, CDC, ADCC	2-year DFS in 56%	Emens [96]
CEA-MUC1-TRICOM poxvirus	Stage 4 BC	26	Inconsistent	Possible CB in pts with MRD	Emens [96]
Survivin peptide+IFA	Advanced/ recurrent BC	14	Survivin-specific T cells	SD in 14%	Emens [96]
Mammaglobin cDNA	Stage 4 BC	14	Mammaglobin-specific T cells	Possible benefit	Triveedhi et al. [97]
Her2-DC(lapuleucel-T)	Stage 4 BC	18	Her2-specific T-cell population	SD in 17%	Park et al. [79]
P53-DC	Stage 4 BC	26	P53-specific T cells and Ab in 38% and 42%	SD in 42%	Svane et al. [99]
Allogeneic GM-CSF-secreting breast tumor cells+low-dose CY and DOX	Stage 4 Her2+ BC	20	Her2-specific DTH and polyfunctional CD8+ T cells	6-month clinical benefit 55%; PFS:7 months; OS:42 months	Chen et al. [100]
DC-autologous tumor fusion	Stage 4 BC	23	Increased CD4+ and CD8+T cells	SD or PR in 43%	Emens [96]

BC breast cancer, *CEA* carcinoembryonic antigen, *DC* dendritic cell, *DTH* delayed-type hypersensitivity, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *Her2* human epidermal growth factor receptor type 2, *hTERT* human telomerase reverse transcriptase, *ICD* intracellular domain, *IFA* incomplete Freund's adjuvant, *KLH* keyhole limpet hemocyanin, *MUC-1* mucin 1, *MRD* minimal residual disease, *TILs* tumor-infiltrating lymphocytes, *TRICOM* triad of costimulatory molecules, *STn* sialyl-Tn

immune response through either their loss or de novo aberrant expression. Many TAAs (including MUC1, HER2, CEA, hTER, and WT1) have been identified and shown to be specifically recognized by T cells [87]. Induction of strong immunity by cancer vaccines is expected to lead to the establishment of immunological memory, thereby preventing tumor recurrence.

Cancer vaccines are more effective when given in combination with standard cancer treatments, which appear to increase their effectiveness [88, 89]. The elimination of Treg cells potentially provides a basis for a synergistic effect between cancer vaccines and chemotherapy [89]. To improve immunotherapy trials, investigators have to take into account the ability to initiate tumor-specific immunity by providing tumor-associated antigens; the capacity to recruit effector immune cells within the tumor site; and the ability to preserve immune cell functionality within the tumor microenvironment through the subversion of immune-escape mechanisms. Table 36.4 summarizes the clinical trials of breast cancer vaccines.

Conclusion

Immunomodulation appears to be a promising strategy for solid tumors. High immunogenicity has been described in breast cancer subtypes with a high proliferation index (TNBC, HER2). Immune checkpoints are one of the major mechanisms of immune escape. Expression of PD-L1 on tumor cells leads to lower activity of CD8+ T cells. Antibodies against PD-1 or PD-L1 are being investigated in clinical trials. The first results are promising, but only a subset of patients (20%) respond to immune checkpoint inhibitory treatment. Predictive markers are urgently needed to select patients who have the best chance for receiving an effective treatment [90]. One possible avenue is immuno-molecular therapy, which integrates immune and molecular features to devise novel combinatorial approaches based on targeting intracellular molecular alterations and modulating the immune response [91].

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Part VII

Site-Specific Therapy of Metastatic Breast Cancer

Neurological Metastases

37

Sule Karaman and Seden Kucucuk

Parenchymal Brain Metastases of Breast Cancer

Metastases are the most common malignancy (50%) of the brain parenchyma. They are ten times more common than primary brain tumors [1, 2]. Metastases to the brain develop in approximately 20–40% of all cancers [3, 4], including lung cancer, breast cancer, melanoma, colon cancer, and renal cell tumors [4–8]. In breast cancer patients, the clinical incidence of brain metastasis (BM) is 10–15%, whereas in autopsy series, the rate has been reported as 18–30% [9]. In patients with breast cancer, BMs are diagnosed with localized disease at the time of diagnosis in 2.5% of patients, in systemic disease in 5–10% of patients, as a solitary disease in 5–10% of patients, and metachronous with known systemic disease in ≥80% of patients. Potential risk factors of metastasis in general have been investigated in many studies, including BM patients. Young age, short disease-free survival, presence of visceral metastases, hormone negative and high grade disease are potantial risk factors of parankimal BM which have been investigated in many studies [10]. In the RTOG "Recursive Partitioning Analysis" (RPA) model, which included 1200 patients, three prognostic categories for BM were identified (Table 37.1). According to this model, the patients with the best prognosis were under 65 years of age, had a Karnofsky performance score (KPS) higher than 70, and had no extracranial disease, and the primary tumor was under control.

There were no differences between solitary and multiple BM models; however, being solitary or multiple BM has extra prognostic value for RPA 1 and RPA 2 [11]. Sperduto et al. updated RTOG's RPA data and proposed a new prognostic scoring system called the "graded prognostic assessment" (GPA) [12]. The GPA scoring system consists of four categories ranging between 2.6 and 11 months (Table 37.2). The GPA system has shown that patients with one to three metastases have a more favorable outcome than patients with >4 metastatic lesions.

Table 37.1 Median survival in patients treated with WBRT according to the RPA

RPA	Clinical features	Median survival for all primary tumors (months)	Median survival for brain metastatic breast cancer (months)
1	KPS ≥70	7.1 (13.5 with a single BM)	15
	Age <65		
	Primary cancer controlled		
	No extracranial disease		
2	KPS ≥70	4.2 (6 with a single BM)	11
	Age ≥65		
	Primary cancer not controlled or extracranial disease exists		
3	KPS <70	2.3	3

RPA recursive partitioning analysis score, *KPS* Karnofsky performance status, *BM* brain metastasis

If the BM can be controlled or the disease can be eradicated, the GPA scoring system results suggest that patients with a better prognosis can be treated more aggressively. In high-performance patients with a solitary BM, stereotactic radiation therapy (SRT) + whole-brain radiotherapy (WBRT) is recommended instead of WBRT (evidence level I).

The CNS metastasis risk is two to four times higher in patients with epidermal growth factor 2-positive (HER-2 (+)) breast cancers than those with HER-2 (−) breast cancers. This increase may be due to the aggressive nature of HER-2 (+) breast cancers, but it may also be related to the use of trastuzumab in these patients, which prolongs survival enough for BMs to develop [13] Another hypothesis is that HER-2 positivity activates the VEGF pathway and causes a biological predisposition for CNS metastases [14]. Recently, triple-negative breast cancers and HER-2 (+) breast cancers have been shown to have a similar risk of CNS metastases. Lin et al. have reported that 46% of metastatic triple-negative

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Table 37.2 GPA score

Score				
(A)				
	0	0.5	1	
Age	>60	50–59	<50	
KPS	<70	70–80	90–100	
Number of CNS metastases	>3	2–3	1	
Extracranial disease	Present	–	None	
(B)				
GPA	0–1	1.5–2	2.5–3	3.5–4
General survival for all primary cancers (months)	3.1	5.4	9.61	6.7
General survival for breast cancer (months)	3.4	7.7	15.1	25.3

KPS Karnofsky performance status, *CNS* central nervous system, *GPA* graded prognostic assessment

patients will be diagnosed with a CNS metastasis [15]. In a 2012 study by Sperduto et al. which only included breast cancer patients, tumor subgroup (luminal, A, B, HER-2), KPS (under or over 70), and age (under or over 60) were significant prognostic factors for BM [16, 17].

The diagnosis of BMs begins with a clinical suspicion. The most common symptom is headache (24–48%) [18]. Mental and cognitive changes, motor deficits, seizures, nausea, and vomiting are some of the other possible symptoms. Contrasted computed tomography (CT) and contrasted brain magnetic resonance imaging (MRI) are used for radiological diagnosis. The most specific diagnostic method for BMs is MRI [19]. In Fig. 37.1a–c, MRI of multiple BMs is shown in three planes. Approximately 20% of patients with solitary metastases on CT scans have multiple metastases as determined by MRI. Primary brain tumors (benign/malign) should be differentiated from infections, cerebral infarcts, arteriovenous malformations, hemorrhages, demyelinating diseases, and radiation necrosis. To assess the disease status, full systemic scans (such as PET-CT and CT) should be performed simultaneously with BM imaging. There is no survival advantage of early diagnosis when still asymptomatic; however, early diagnosis significantly decreases post-WBRT cerebral deaths.

The aim of breast cancer BM treatment is controlling symptoms, decreasing morbidity caused by potential neurological damage, and increasing local control (LC) and survival without disrupting the quality of life as much as possible.

Treatment methods are symptomatic treatment and treatment of life-threatening problems, such as obstruction or hydrocephalus, with surgery, RT, chemoradiotherapy (CRT), chemotherapy (CT), hormonal treatment (HT), and targeted treatments.

After a diagnosis of BM, the first step is planning symptomatic medical treatment. The aim of symptomatic treatment is to relieve and prevent neurological symptoms caused by edema and to control seizures. Symptomatic patients should immediately be administered steroid treatment (dexamethasone or methylprednisolone). Generally, dexamethasone is chosen because its mineralocorticoid effects are low, it has mild effects on cognitive functions, and it readily penetrates the cerebrospinal fluid (CSF). The only randomized trial to address steroid dosage is Vecht et al.'s trial, which included 96 patients [20]. In this study, the first arm was randomized to 8 mg/day or 16 mg/day doses, which gradually decreased over 4 weeks. The second arm was randomized to 4 mg or 16 mg for 4 weeks, after which the dose was gradually decreased. To prevent gastritis, an H2 receptor agonist was administered simultaneously with dexamethasone. In both arms, there were similar improvements of the KPS on days 7 and 28. The dosing recommendation from this study resulted in a set 4 mg/day dosage with dose tapering over 4 weeks. Starting with a high 16 mg dexamethasone dose and tapering over 4 weeks caused a better improvement in KPS. This effect can be explained by the maximal anti-inflammatory effect of initiating treatment with high doses and the minimization of delayed steroid-related toxicities with dose tapering. In symptomatic patients, treatment can be initiated with an intravenous bolus of 10 mg followed by 4–6 mg of dexamethasone every 6–8 h. In asymptomatic patients with minimal peritumoral edema or mass effect, the steroid dose can be kept at a lower level until neurological symptoms appear. In BM patients, the doses should be arranged individually based on the patient, the clinical features, edema, and mass effect caused by the tumor. Patients presenting with seizures should be given anticonvulsants. Phenytoin, carbamazepine, and sodium valproate are commonly used anticonvulsants. For metastases that are located on the motor cortex and metastases that are concomitant with leptomeningeal metastases, prophylactic anticonvulsant therapy may decrease the risk and frequency of seizures [21]. Valproic acid is the primary anticonvulsant used in chemotherapy patients.

In patients with BMs, the median survival with supportive treatment only is 1–3 months. The clinical response rate of WBRT is 50%, and survival increases twofold (3–6 months). Patients who receive systemic hormonal treatment or chemotherapy after local treatment of the BM have a longer survival than patients who do not receive systemic treatment (7–8 months vs 3–6 months, respectively) [22]. In oligometastatic disease, the combination of WBRT and local treatments, such as surgery or SRT, results in a higher overall survival rate than WBRT alone.

In our approach to BM treatment, the number and size of the brain lesions, the performance of the patient, and the control of the systemic disease are important factors. If solitary lesions are larger than 1 cm and there are no signs of extracranial metastatic disease, they are called "solitary metastases"; additionally, if the presence of extracranial metastases is unknown, they are called "single metastases."

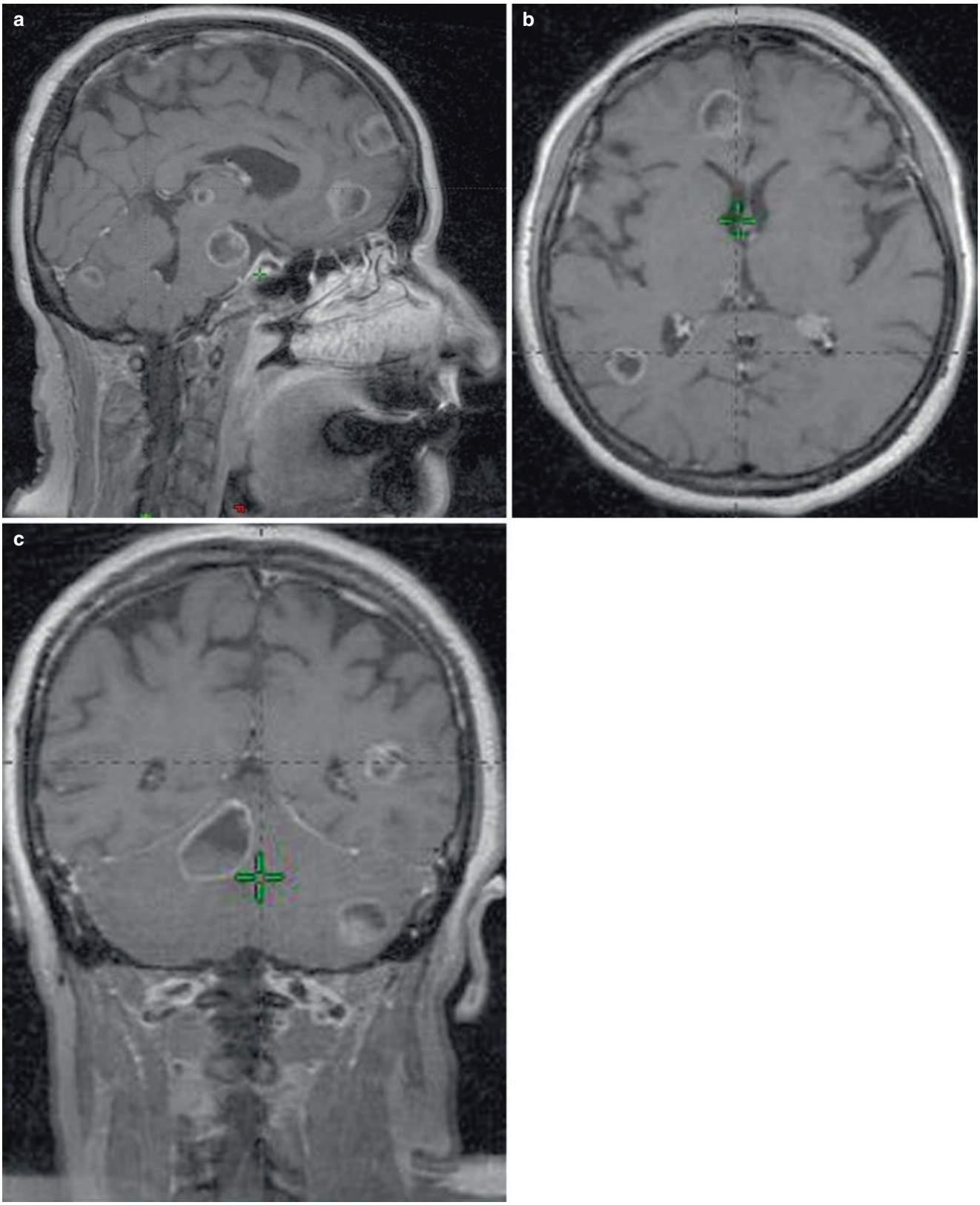

Fig. 37.1 (**a**–**c**) MRI of multiple BMs in three planes

Table 37.3 Primary treatment algorithm of metastatic brain lesions

Number of lesions	Size of lesions	Treatment	
1	<1 cm lesion (asymptomatic, unidentified diagnosis)	Observation or surgery	
		Surgery + WBRT or SRT + WBRT if it grows	
	<1 cm lesion (pathologically verified lesion)	Treated similarly to >1 cm lesions	
	>1 cm lesion	Single	KPS ≥70; if primary is under control
			Surgery ± WBRT or SRT ± WBRT
			KPS <70; if primary is not under control
			WBRT
		Solitary	KPS <70; if primary is not under control
			WBRT
2–3	Any	KPS ≥70; if primary is under control	
		S ± WBRT or SRT ± WBRT	
		KPS <70; if primary is not under control	
		WBRT	
>3	Any	WBRT	

KPS Karnofsky performance score, *RT* radiotherapy, *SRT* stereotactic radiotherapy, *cm* centimeter, *S* surgery, *WBRT* whole-brain RT

A single metastasis is found in 20–30% of BM patients, two to three oligometastatic metastases are found in 20–30%, and two third of the patients are polymetastatic and have three or more metastases.

If a solitary metastasis is present, a biopsy should be performed if possible. The diagnosis changes after the biopsy in 11% of the solitary metastasis. It may be difficult to differentiate these lesions from abscesses, gliomas, and meningiomas, and the incidence of meningiomas is higher in breast cancer patients than in the normal population [23]. CT scans may not be able to detect occult metastases, and incorrect surgical decisions may be made. To avoid this potential problem, preoperative MRI is necessary. The standard treatment for single BMs is surgery. Single small brain lesions suspected to be metastases are treated surgically or are monitored with MRI and treated surgically if growth is detected. The algorithm for the primary treatment of BM is shown in Table 37.3.

Whole-Brain Radiotherapy

Although systemic treatment has advantages for the treatment of metastatic breast cancer (MBC), local treatments continue to be more effective in newly diagnosed patients presenting with BMs. Breast cancer metastases to the brain are hematogenous, so there can be micrometastases anywhere in the brain. Therefore, WBRT is the mainstay of the standard treatment of MBC with BM. This treatment has the advantages of preventing or delaying neurological deficits, regaining lost functions, and decreasing steroid dependency, and it is the best supportive treatment method for BM. Reciprocal and multiple field three-dimensional conformal planning samples are shown in Figs. 37.2 and 37.3.

Randomized trials investigating BM treatments include BM patients in whom BM is caused by various primary cancers. The primary cancer of BM patients in these trials is lung cancer in 50–77% of patients and breast cancer in 8–19% of patients. In other words, the international guidelines for breast cancer patients are based on only approximately 10% of the patients in these randomized trials [18]. In addition, low-performance patients (KPS <70) have been excluded from these studies. Because no randomized trials have included only breast cancer BM patients, we must evaluate the characteristics of BMs of lung and breast cancers individually before using the information provided by these randomized trials for the treatment of breast cancer BM [24]. When the epidemiologic data are reviewed, the prognosis of low-performance breast cancer BM (KPS <70) is two times worse than the prognosis of small-cell lung cancers.

The benefit of WBRT for breast cancer BM has been evaluated for survival and the level of care (hospital or home) following radiation. Between 1999 and 2012, 241 patients were mostly treated with 5 × 4 Gy. Median survival was 2.9 months, and 24% of patients were never discharged from the hospital. The decision-making criteria for WBRT are the WHO score, level of care before WBRT, and patient's choice of level of end-of-life care [25].

In addition, the probability of the metastasis developing in the brain alone is 20–25% in breast cancers and 60–75% in NSCLC [26]. Thus, SRT alone is not always a good option for the treatment of breast cancer BM, and WBRT still plays a very important role.

The studies on breast cancer BM patients who were treated only with WBRT are summarized in Table 37.4 [26–29].

An updated Cochrane meta-analysis in 2018 that included 11,898 patients from 54 published phase III randomized controlled trials (RCTs) compared WBRT versus other treatments for newly diagnosed multiple BM. Altered higher biological WBRT dose-fractionation schemes did not show any benefit for OS, neurological function improvement (NFI), or symptom control compared with those for standard care. However, OS and NFI were worse for lower biological WBRT schemes than standard schemes. The addition of WBRT to radiosurgery improved local and distant brain control in selected people with brain metastases, but the data showed worse neurocognitive outcomes and no differences in OS. Selected patients with multiple brain metastases from non-small-cell lung cancer may show no difference in OS when OSC is given and WBRT is omitted. The use of radiosensitizers, chemotherapy, or molecular-targeted agents in

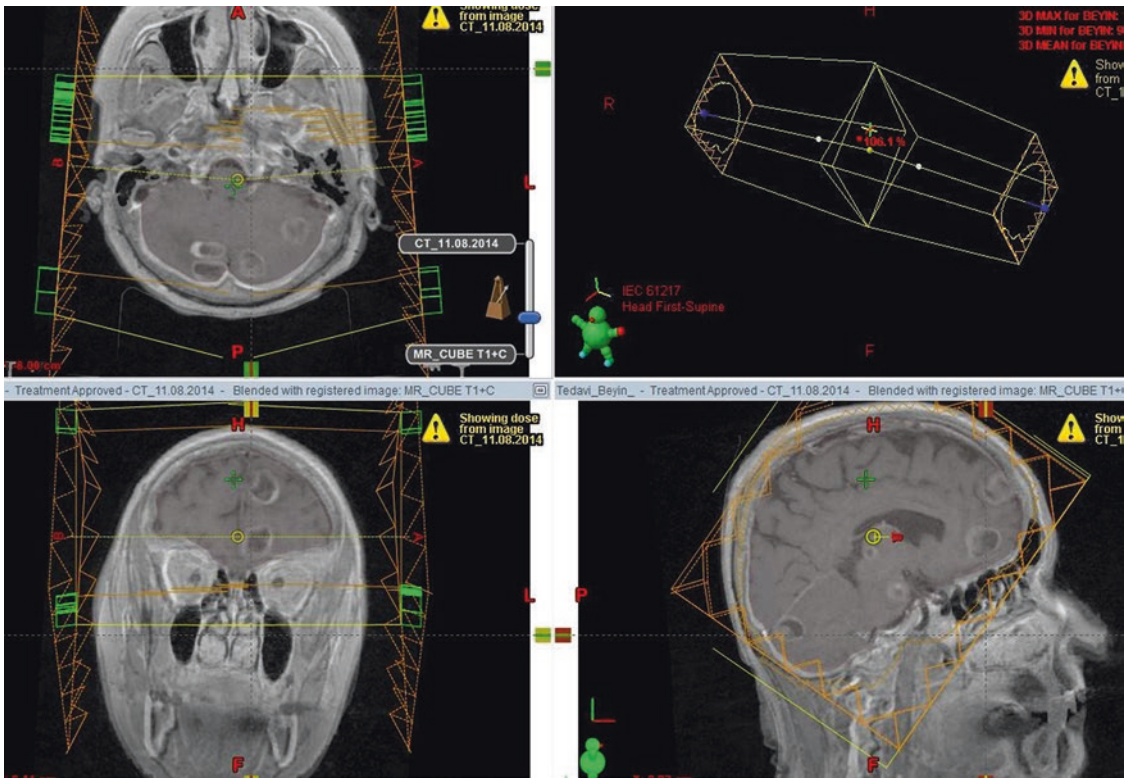

Fig. 37.2 Treatment plan for WBRT with reciprocal fields

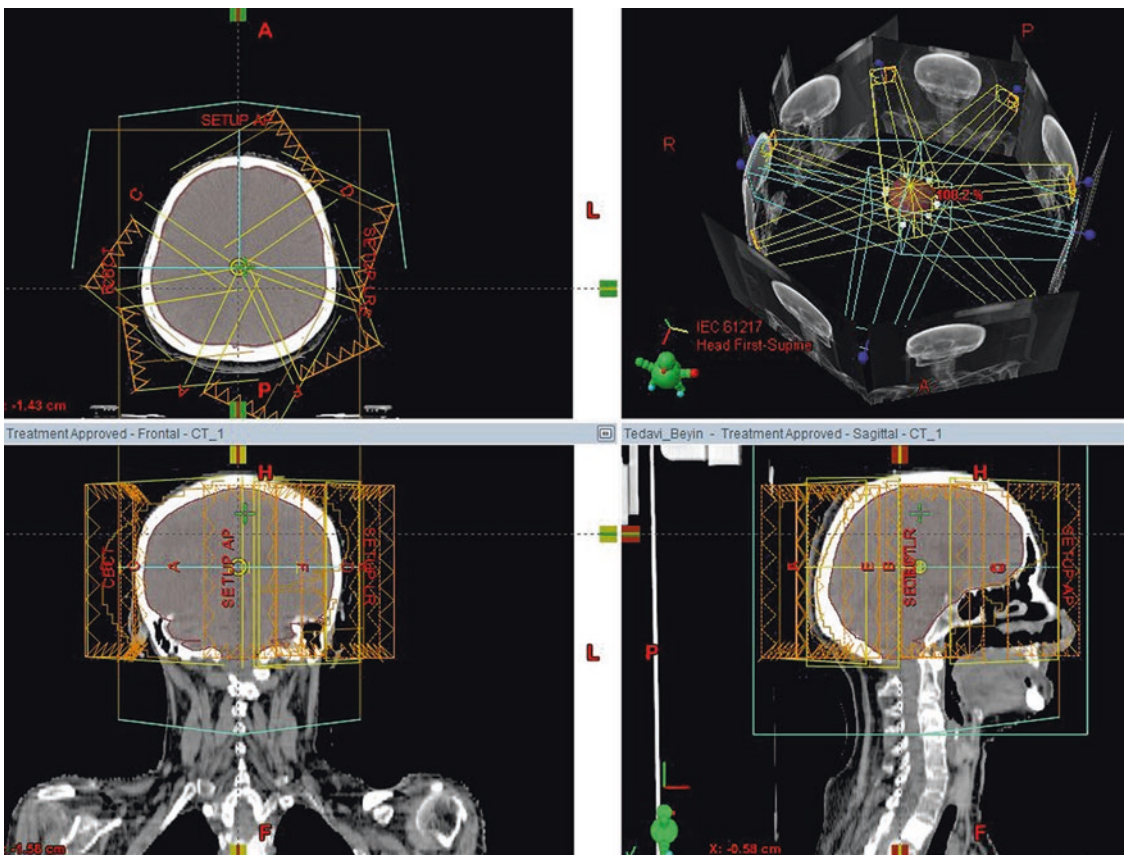

Fig. 37.3 Whole-brain radiotherapy planning in multiple fields

Table 37.4 Breast cancer BM studies in which patients were treated with WBRT alone

Study	*N*	RT plan (Gy/fr)	Response rate (%)	Recurrence rate (%)
Nieder et al. [26]	46	30/10	65	0
Ogura et al. [27]	36	30/10	82	32
		50/25		
		10 pts boost RT		
Mahmoud-Ahmed et al. [28]	116	30/10	NR	50
Le Scodan et al. [29]	117	30/10	NR	42.5

RT radiotherapy, *Gy* gray, *fr* fraction, *NR* not relevant

Table 37.5 Some randomized trials on various BM radiotherapy plans

Study	*N*	RT plan (Gy/fr)	Median survival (w)	P
RTOG 6901	910	30/10	21	NS
Borgelt et al. [31]		30/15	18	
		40/15	18	
		40/20	16	
Haide-Meder et al. [32]	226	25/10	16.8	NS
		36/6	21.2	
Royal College of Radiology [33]	533	30/10	12	NS
		12/2	11	
RTOG 91–04 [34]	429	30/10	18	NS
		54.4/34	18	
Graham et al. [35]	113	40/20	24.4	NS
		20/4	26.4	

RT radiotherapy, *Gy* gray, *fr* fraction, *N* patient number, *w* weeks, *NR* not relevant

conjunction with WBRT remains experimental. Further trials are needed to evaluate the use of neurocognitive protective agents and hippocampal sparing with WBRT in homogeneous patient groups with brain metastases [30].

To determine the optimal WBRT dose for BMs, various RT plans, which aimed to increase LC and survival while decreasing delayed side effects, have been compared (Table 37.5) [31–35]. No difference in general survival and acute toxicity was shown in these studies. Disease-free survival, tumor response rate, and quality of life results were not analyzed. These trials failed to provide a consensus on a single fractionation and dosage. However, fundamental radiation oncology knowledge suggests that plans with lower doses per fraction will result in less delayed neurocognitive side effects. Currently, a commonly used RT plan is 30 Gy, delivered via ten fractions of daily 300 cGy doses. If fractionation is determined according to the patient's prognosis, the long-term side effects of WBRT can be minimized in patients with longer survival expectancy. In RPA III patients who are resistant to chemotherapy, short plans (e.g., 20 Gy/5 fr) may be preferred.

Table 37.6 Trials comparing WBRT alone and WBRT + CT in the treatment of breast cancer BMs

Study	*N*	Primary distribution (%)	Randomization (Gy/fr)	Median survival (m)	Response rate %
Antonadou et al. (2002) [40]	23	Lung: 83	40/20	7	67
		Breast: 11			
	25	Ovaries: 6	40/20 + TMZ	8.6	96
				NS	(*p*: 0.017)
Verger et al. (2005) [41]	41	Lung: 51	30/10	3.1	
		Breast: 16			54
	41	Ovaries: 33	30/10 + TMZ	4.5	72
				NS	(*p*: 0.03)

RT radiotherapy, *Gy* gray, *fr* fraction, *TMZ* temozolomide, *NS* nonspecific

Although chemotherapeutic agents traditionally have a limited role in BM due to their low potential to pass the blood-brain barrier, they have been used in combination with WBRT in some studies. Many randomized trials have investigated the use of WBRT in combination with radiation sensitizers, such as misonidazole, motexafin gadolinium (MGd), efaproxiral, thalidomide, and temozolomide (TMZ), for treating the BMs of various primary cancers, most of which were lung cancers [36–39]. However, in most of these studies, the frequency of toxicities had increased, and no difference was found in LC and median survival. In some studies, an increased response rate was observed with radiation sensitizers (especially TMZ) and WBRT [40, 41].

In a phase II randomized study of WBRT with or without concurrent TMZ for BM from breast cancer, 100 patients were randomized to WBRT (3 Gy × 10–30 Gy) with or without concomitant 75 mg/m(2)/day TMZ during the radiation course. WBRT combined with TMZ did not significantly improve LC and OS in patients with BMs from breast cancer compared to those of WBRT alone (median PFS, 7.4 vs 11.1 months; median OS, 7.4 months vs 9.4 months) [42].

Two randomized trials that compared WBRT alone and with concomitant TMZ use in BMs are summarized in Table 37.6. These trials have shown that TMZ improves LC and delays cerebral progression. However, toxicity was increased, and no change in general survival was reported. The results of these two small trials must be reviewed in larger series. In patients with bulky BMs who are not suitable candidates for SRT, with registration limited to prospective studies, WBRT and concomitant TMZ use may be considered.

In breast cancer patients with BM, treatments targeting the HER-2 receptor are currently being used in combination

with WBRT, and research is ongoing. A retrospective trial including 31 patients showed that trastuzumab and WBRT combinations are tolerated well, and the responses have been encouraging [43]. Lapatinib combined with WBRT has been tested in HER-2 (+) brain cancer patients in a phase I trial. However, the study did not meet the predefined criteria for feasibility [44]. As a dual inhibitor of EGFR/HER2 tyrosine kinases, lapatinib has demonstrated effectiveness in HER2-overexpressing breast cancer brain metastases. Lapatinib also appears to sensitize EGFR-expressing cell lines to radiation. In the phase II HeCOG trial, 81 patients were treated with lapatinib 1250 mg once daily and WBRT (30 Gy/10 fr), followed by 6 weeks of lapatinib. For 25.9% of the patients, the primary site of cancer was the breast. The response was stable disease for 15 patients (34.9%) and disease progression for only one patient (2.3%). Response was not related to EGFR protein expression. Four of eight deaths were considered related to the study drugs. Nine patients had serious infections. The potential for a survival benefit from the HER2- and hormone-positive phenotypes is important. Therefore, we should pay attention to potential delayed toxicity in deciding treatment. Future trials should include participants with homogeneous prognostic features and specific molecular markers with BM with a focus on determining the use of chemotherapy and targeted treatments in combination with WBRT [45].

In oligometastatic disease, surgery or SRT followed by WBRT has shown no improvement in neurological symptoms and overall survival. This outcome has raised doubts concerning the ability to decrease potential long-term side effects by withholding WBRT and the benefit of initiating treatment of BMs with systemic therapies. Currently, initiating treatment with systemic treatment instead of WBRT is an approach that has been considered in HER-2 (+) breast cancer BM patients because lapatinib has significant efficacy in treating CNS metastases. If life expectancy is longer than 2 years, the long-term side effects of WBRT must be considered. The results of the LANDSCAPE trial suggest that WBRT can be withheld and that systemic treatment can be initiated in patients with multiple BMs. However, specific patient groups, such as asymptomatic patients at baseline, were also included in the trial. Another randomized trial is warranted to demonstrate the possibility of withholding WBRT in HER-2 (+) BM patients. Advancements that reveal the pathobiological processes in BM formation may aid the identification of prophylactic strategies to prevent BM formation in high-risk HER-2 (+) or triple-negative breast cancer patients. We previously mentioned that overexpression of the HER-2 protein is associated with a high brain relapse rate in HER-2 (+) locally advanced breast cancer. Duchnowska et al. reported that 13 gene signatures can be predictive in HER-2 (+) patients and that this feature can be used in further predictive research [46]. A retrospective single-center experience with 547 breast cancer BM patients treated with radiation-targeted therapies showed that the molecular subtypes appeared to be prognostic for survival and predictive of the response to radiotherapy. TKIs were found to improve OS and LC. For BM in HER2-amplified breast cancer patients, to preserve neurocognition, we can consider upfront radiosurgery and HER2-directed therapy and reserve WBRT for salvage [47]. Tumor cells cause brain involvement by integrin-mediated growth along the basal vascular membrane or by inducing neoangiogenesis and nodular growth. An appropriate approach to prevent BM development is the suppression of these growth factors with specific drugs (e.g., integrin inhibitors or antiangiogenic drugs). In preclinical animal trials, intracardiac administration of these drugs prevents the development of BM. The Angle-Celtic VII and Tsarine 0602 trial is an ongoing trial investigating the role of prophylactic brain irradiation in Her-2 (+) breast cancer patients with no BM. However, these trials were not well received by clinicians and patients because of the long-term neurotoxicity caused by RT and have been halted due to low patient participation. A more accepted alternative for WBRT planning is hippocampus-sparing PCI. In this approach, better memory preservation is possible. Future trials will be designed to report the results of this technique. An example of hippocampus-sparing conformal WBRT planning is shown in Fig. 37.4.

Surgery

The surgical treatment of BMs provides fast relief of symptoms, LC, and histopathological confirmation of the diagnosis. Developments in cortical mapping and stereotactic techniques and the use of ultrasonography (USG) have made metastatic lesions easily accessible. Surgery is not an appropriate approach in patients with multiple metastases, uncontrolled primary disease, comorbidities, or inaccessible lesions. Three randomized trials have questioned whether WBRT should be used alone or if it should be combined with surgery. One of these randomized trials was from Patchell et al. and included 48 patients, only 10% of whom were breast cancer patients. Patients were randomized to WBRT alone and surgery with WBRT arms. Functional improvement (38 weeks versus 8 weeks, respectively) and the survival advantages (40 weeks versus 15 weeks, respectively, $p < 0.005$) were significantly better, and recurrence significantly decreased in the combined treatment (surgery + WBRT) arm (20% versus 52%, respectively, $p < 0.02$) [48].

The second randomized trial was from Vecht et al. and included 64 BM patients (with primary breast cancer in 19%) [49]. Similar results with combined treatment were reported in this trial. This study has shown that clinically stable patients without extracranial disease benefit from combined

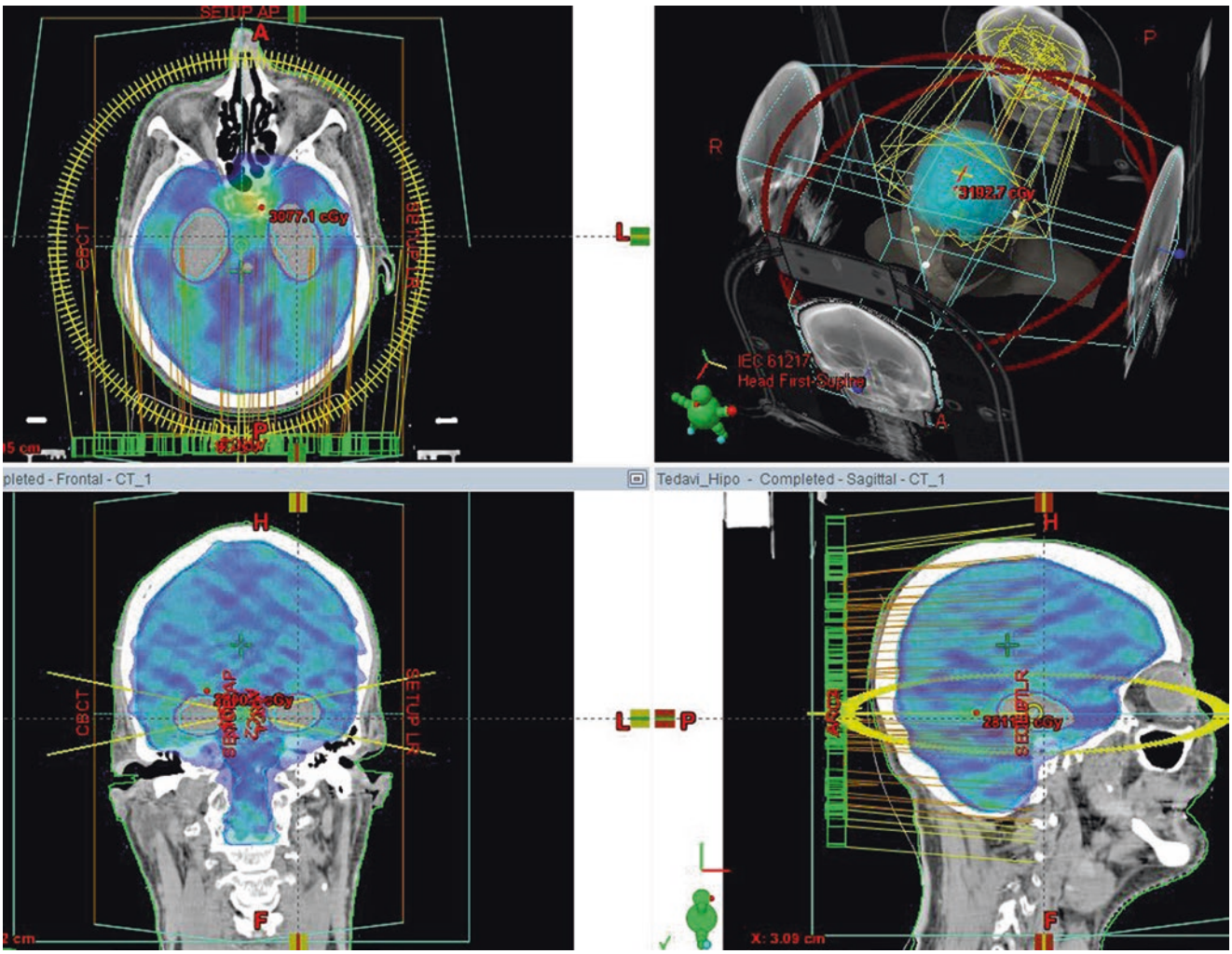

Fig. 37.4 Hippocampus-sparing WBRT planning

treatment. The median survival was only 5 months in patients with progressive extracranial disease. In a randomized trial by Mintz et al. studying similar arms in 84 patients, no difference in survival was reported [50]. However, 73% of the patients had extracranial disease and were low performance, and the definition of single metastases was inadequate due to the absence of cranial MRI.

The specifics of the three randomized trials are summarized in Table 37.7. These randomized trials showed that longer survival rates were achieved in patients treated with surgery and WBRT when compared with WBRT alone [48–50]. However, these results were explained by high-performance patients being treated with surgery. All three of these trials suggested that surgical treatment should be limited to high-performance status patients with BMs that can potentially cause life-threatening complications.

In the Cochrane Review of these randomized trials, including 195 patients, an increase in functionally independent survival and a significant decrease in neurological deaths were observed in patients treated with surgery plus WBRT when compared with patients treated with WBRT alone. However, there was no significant difference in overall survival [51].

A postoperative hippocampus-sparing three-dimensional conformal WBRT planning example is shown in Fig. 37.5.

In many retrospective studies, surgery alone has been reported to have more favorable results than WBRT alone [52]. However, surgery patients have high-performance statuses, single metastases, and minimal extracranial diseases. These features are indicative of good prognoses in many multivariate analyses. Surgery alone and WBRT alone have been compared in two randomized trials. In only 10% of these patients, the primary cancer was breast cancer.

In a study by Patchell et al., the recurrence rates for surgery patients were calculated as 46% at the initial BM location and 70% in the whole brain. A total of 44% of the patients treated with surgery alone died due to neurological symptoms caused by BM recurrence. The similarity of sur-

Table 37.7 Randomized trials comparing WBRT and Surgery + WBRT

Study	*N* #	Randomized arms	RT plan (Gy/fr)	Median survival (m)	FIS
Patel et al. [48]	48	WBRT S + WBRT	36/12	3.4 9.2 $p < 0.01$	–
Vecht et al. [49]	64	WBRT S + WBRT	40/20	6 10 *p*: 0.04	3.5 7.5 *p*: 0.06
Mintz et al. [50]	84	WBRT S + WBRT	30/10	6.3 5.6 *p*: 0.24 (NS)	32% 32% (NS)

RT radiotherapy, *Gy* gray, *fr* fraction, *S* surgery, *WBRT* whole-brain radiotherapy, *NS* nonspecific, *FIS* functionally independent survival

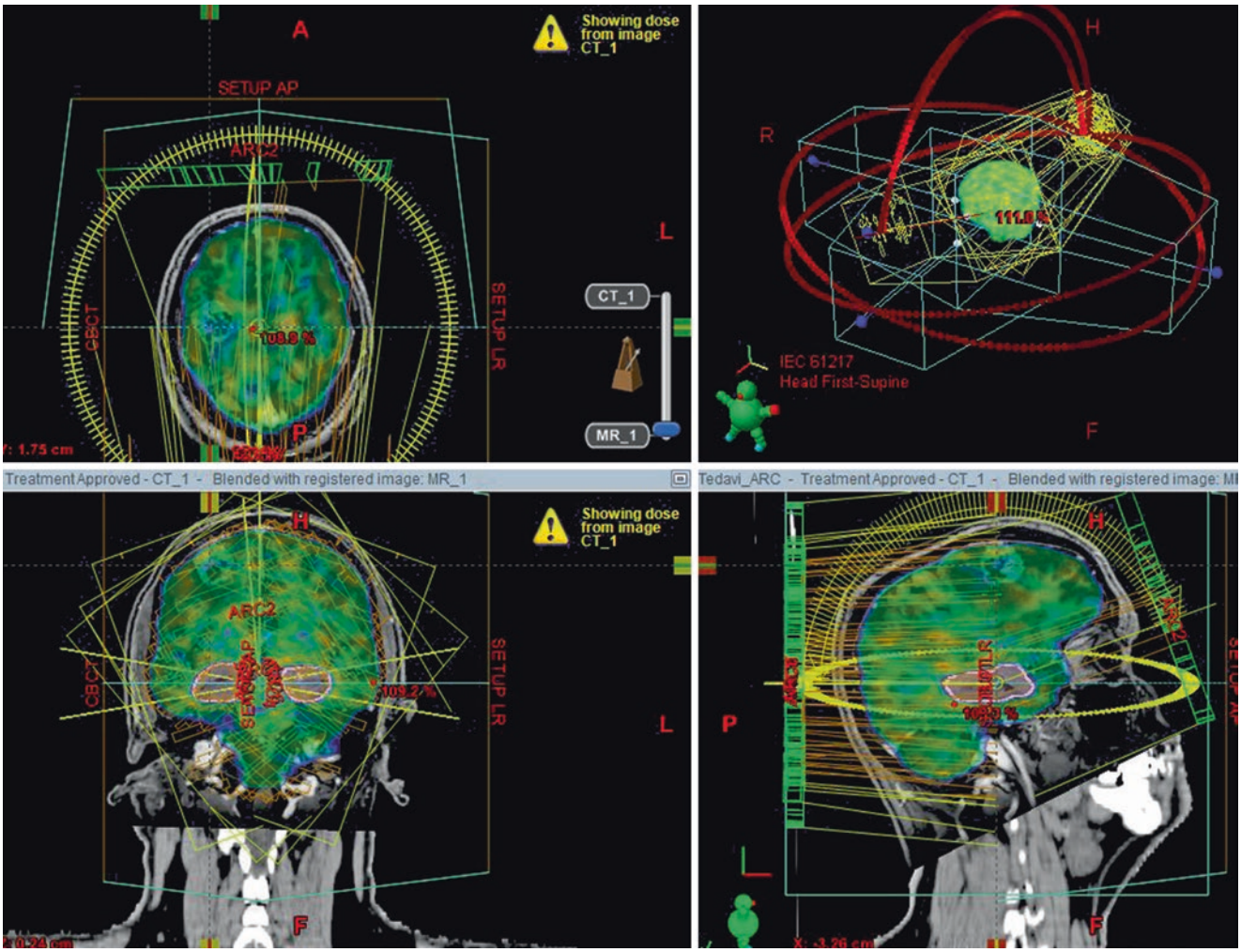

Fig. 37.5 Postoperative hippocampus-sparing WBRT (the surgical cavity is shown with an *arrow*)

vival rates has led to some studies concluding that surgery alone may be sufficient. However, the primary end point of this trial was recurrence rates, not survival. A statistical analysis of survival results would require 2000 patients, whereas this trial only included 94 patients. This sample size is not enough for survival analyses [53].

The phase III EORTC 22952–26,001 trial published in 2001 by Kocher et al. included 359 patients with one to three BMs who were treated with surgery or SRS (20 Gy/1 fr) and were randomized to observation or WBRT (30 Gy/10 fr) arms. LC was 41% in the surgery group and 73% in the S and WBRT group. The addition of WBRT decreased intracranial recurrences and neurological deaths but did not increase functionally independent survival or overall survival. Based on the results of this trial, WBRT may be withheld in high-performance patients with stable disease and a limited number

of BMs, and these patients may be monitored with frequent imaging studies [54].

In these two trials, no difference in survival was shown in WBRT patients, but brain recurrence rates and neurological deaths decreased. In both trials, less than 50% of patients had controlled extracranial disease, and subgroups were not analyzed. We can expect a survival advantage in patients with controlled extracranial disease. In addition, the rate of neurological death was significantly higher when RT was delayed. Delayed RT (salvage therapy) seems to be less effective than upfront WBRT.

The surgical approach to single BMs in breast cancer is a treatment option to be considered in patients with a single metastasis, no extracranial disease, and controlled disease. However, this approach is still unclear because the literature about BMs in breast cancer is limited.

With multiple BMs, the role of surgery remains controversial. There are single-center results in the literature [52]. In the retrospective data provided by Bindal et al., the postoperative median survival in patients with multiple metastases is 14 months. However, the survival reported by Hazuka et al. in the same patient group was only 5 months. The difference between the data may be due to differences in the distribution of the primary cancers. The surgical approach to multiple BMs of breast cancer is limited due to the morbidity of multiple craniotomies. The use of surgery must be limited to large and symptomatic lesions.

WBRT is one of the treatment options for patients with one to three BMs. WBRT increases LC and intracerebral control but may decrease the quality of life and impair neurocognitive function. Additionally, combined treatment offers no survival benefit. This inadequacy has focused attention on postoperative SRT. With SRT being used in BM, postoperative SRT has been questioned in many retrospective trials. Surgical resection followed by SRT was analyzed by Kelly PJ et al. in 2012 using retrospective data from seven centers. However, there were no BM patients with primary breast cancer among the patients who were evaluated. The median dose was 18 Gy [15–19], and LC was 74–100%. The median survival was 15 months, and WBRT use could be decreased by 70%. SRT was administered 4–6 weeks later, with the goal of delivering RT to a smaller cavity after surgery; however, tumor progression may occur during this period. In these series, SRT to the resection cavity was generally offered as an alternative RT option in patients with RPA <3, KPS >70%, and ≤3 metastases [55].

In the study published in 2012 by Choi et al., SRT was delivered to 120 cavities in 112 patients with a median dose of 20 Gy (12–30 Gy). In 16% of these patients, the primary cancer of the BM was breast cancer. Univariate analysis showed that LC was better in patients with margins for the target volume. LC is an independent factor for distant metastasis (DM) in breast cancer. SRT is suggested as an alternative to WBRT in patients who can be monitored closely [56]. NCCTG N107C/CEC·3 is a study that randomized 194 patients with a resection cavity of less than 5·0 cm 1:1 to the postoperative SRS (12–20 Gy /1 fr) or WBRT (30 Gy/10fr or 37·5 Gy/ 15 fr) arms. The median cognitive-deterioration-free survival was longer, and cognitive deterioration at 6 months was less frequent in the SRS arm than that in the WBRT arm (3.7 vs 3 months; $p < 0.0001$; 52% vs 85%; $p < 0.00031$), and there was no difference in overall survival (12.2 vs 11.6 months; $p = 0.70$). After resection of a brain metastasis, SRS can be considered to be a less toxic alternative to WBRT for some patients [57].

Stereotactic Radiotherapy

WBRT is the mainstay of treatment for BM. However, serious neurocognitive impairments caused by WBRT have been reported in the last decade [4]. In two randomized trials, the survival and local control rates of surgery combined with WBRT were better than those for WBRT alone. This improvement has raised hopes that similar results can be achieved when WBRT and SRT are used in combination to treat BM [58]. Examples of photon-based SRT techniques include gamma knife (GK), linear accelerators (LINACs), and CyberKnife. Lars Leksell developed the idea of sending radiation beams to a specific target in the cranium and implemented it using a stereotactic frame. Leksell initially used orthovoltage X-rays, and in 1967, he started using the gamma rays produced by 201 cobalt-60 with Larsson. He named the method “radiosurgery” because it combines surgery and RT and allows the total X-ray dose of classical RT to be delivered to a specific target in one session. The beam he used inspired him to name the system he uses the GammaKnife.

Generally, the tumor diameter must be smaller than 3.5 cm to use the GammaKnife. With increased clinical use of the GammaKnife, LINACs have been modified to the stereotactic RT system to treat tumors of various sizes and locations with stereotactic radiosurgery. In LINAC-based systems, LINAC devices and micro-multileaf collimators or circular collimators are used to shape the beam according to the target volume. The CyberKnife radiosurgery system mainly consists of a linear accelerator generating 6 MV X-rays that is placed on an industrial robot with six joints and a robotic patient bed that can move in six directions. In SRT, the dose that reaches the surrounding brain tissue is clinically insignificant, and a higher dose is delivered to the target volume. SRT has many advantages: the hemorrhaging and infection risks are low, the seeding potential of the tumor is low, and the duration of the hospital stay is shorter, thus reducing hospital costs. Proton modality is not a common way to treat BM with SRT because it is not available in every facility and increases treatment costs. This modality is the

first reported series of proton SRS for the management of brain metastases. Their retrospective experience was that proton SRS treatment is well-tolerated and that LC outcomes were comparable with conventional photon SRS treatment. Although proton SRS remains resource-intensive, future strategies evaluating its benefit due to integral dose reduction should be investigated [59]. JLGK0901 was a prospective observational study of Gamma Knife SRS with 1–10 newly diagnosed BMs in 2009–2012. A total of 1194 patients were categorized as 1 tumor ($n = 455$); 2–4 tumors ($n = 531$); and 5–10 tumors ($n = 208$). However, in JLGK0901, the primary tumor was the breast in only 10% of all patients; results for patients with five to ten brain metastases were similar to those for patients with two to four BMs when treated with SRT without WBRT. Considering the minimal invasiveness of SRT and its lower toxicity compared with those of WBRT, SRT might be a suitable alternative for patients with up to ten brain metastases [60].

Surgery and SRT have not been compared in any randomized trials. Retrospective studies report controversial results due to patient selection. In a nonrandomized trial by Bindal et al., 31 patients were treated with SRT, and 62 patients were treated with surgery; 16% of all these patients had primary breast cancer. In the surgery arm, overall survival increased, and neurological deaths decreased [61]. In contrast, no survival advantage was shown in similar groups in a study conducted by the Mayo Clinic [62]. Auchter et al. reported a 1-year local control of 85% and a median survival of 56 weeks in 122 single BM patients treated with SRT (11% primary breast cancer) [63]. The results for surgery were similar.

In both studies, the authors concluded that the results for SRT and surgery were equivalent. Due to the lack of randomized data, the decision to treat with SRT or surgery should be made according to the lesion size, current symptoms, and functional status. The neurotoxicity and local failure rates are assumed to increase as the lesion size increases so the use of SRT is suggested for lesions smaller than 3 cm. Surgery should be performed for large and symptomatic lesions that require emergency decompression. For small and asymptomatic lesions, both treatment methods can be used. A planning sample for a patient with a single metastasis is shown in Fig. 37.6.

Three randomized studies and one review have compared WBRT alone and WBRT combined with an SRT boost.

In a randomized study by Kondziolka et al., 27 patients with two to four BMs that were 2.5 cm or smaller were evaluated. WBRT alone and WBRT + SRT were compared. In the WBRT and SRT combined treatment arm, LC and whole-brain control results were more favorable, but no difference in survival was reported [64].

In the RTOG 9508 study conducted by Andrews et al., which included 333 patients with one to three BMs, WBRT alone and WBRT + SRT were compared. The WBRT dose was 37.5 Gy/15 fr, and the SRT dose was 15–24 Gy/1 fr. Although 3–4 cm tumors were included in this study, a survival advantage was reported for single metastasis and RPA 1 cases in the WBRT + SRT arm when compared with the WBRT-alone arm (6.5 and 4.9 months; $p = 0.04$; 9.6 and 11.6 months, respectively). This advantage was not demonstrated for multiple metastases. Performance status improved at 6 months (43% and 27%, respectively; $p = 0.03$), and LC increased (82% and 71%, respectively; $p = 0.01$) in the WBRT + SRT arm when compared with the WBRT-alone arm [3].

The results of a randomized trial with three arms by Chagule et al. from Brown University have only been published in summary [65]. Although the survival rates were similar in all three arms, and better LC rates and less brain recurrence were reported, the statistical results were not published. In addition, symptomatic lesions were surgically resected from 51 patients before randomization, and the effect of these patients on the results was not specified as a subgroup in any of the analyses. The patient number was also insufficient for statistically significant results. The SRT doses used were not changed in accordance with the tumor size. The summary of this three-armed trial is shown in Table 37.8 [3, 64–66]. It is the only study that has included two arms comparing WBRT and SRT.

The Cochrane review included three randomized trials that compared WBRT with WBRT + SRT in 385 patients with BM. No difference in overall survival was shown between the two arms. In single BM patients treated with WBRT + SRT, survival significantly increased in comparison with WBRT alone (6.5 months and 4.9 months, respectively; $p = 0.04$). When compared with the WBRT arm, local failure rates were lower (HR 0.27; 95% CI 0.14–0.52), the improvement of performance status was significantly higher (43% versus 27%, $p = 0.05$), and steroid dependency decreased (RR 0.64; 95% CI 0.42–0.97; $p = 0.03$) in the WBRT + SRT arm [66]. In light of these studies, the SRT boost is indicated in single metastases, but it is hard to recommend routine use in patients with multiple metastases.

The results of the three randomized studies and the review on WBRT and WBRT + SRT are shown in Table 37.8.

Three randomized studies have investigated the combination of SRT with WBRT and SRT alone [54, 67, 68]. In the EORTC 22952–26,001 study, 359 patients treated with surgery or SRT (20 Gy/1 fr) were randomized to observation or WBRT (30 Gy/10 fr) arms. Patients with stable systemic disease, controlled primary tumors, and high KPS were included in the trial. Compared with observation, the results of adding WBRT showed a decrease in intracranial relapse (surgery 59% vs 27% and SRT 31% vs 19%, respectively) and death rates due to neurological symptoms. However, no differences were reported in overall survival or functionally inde-

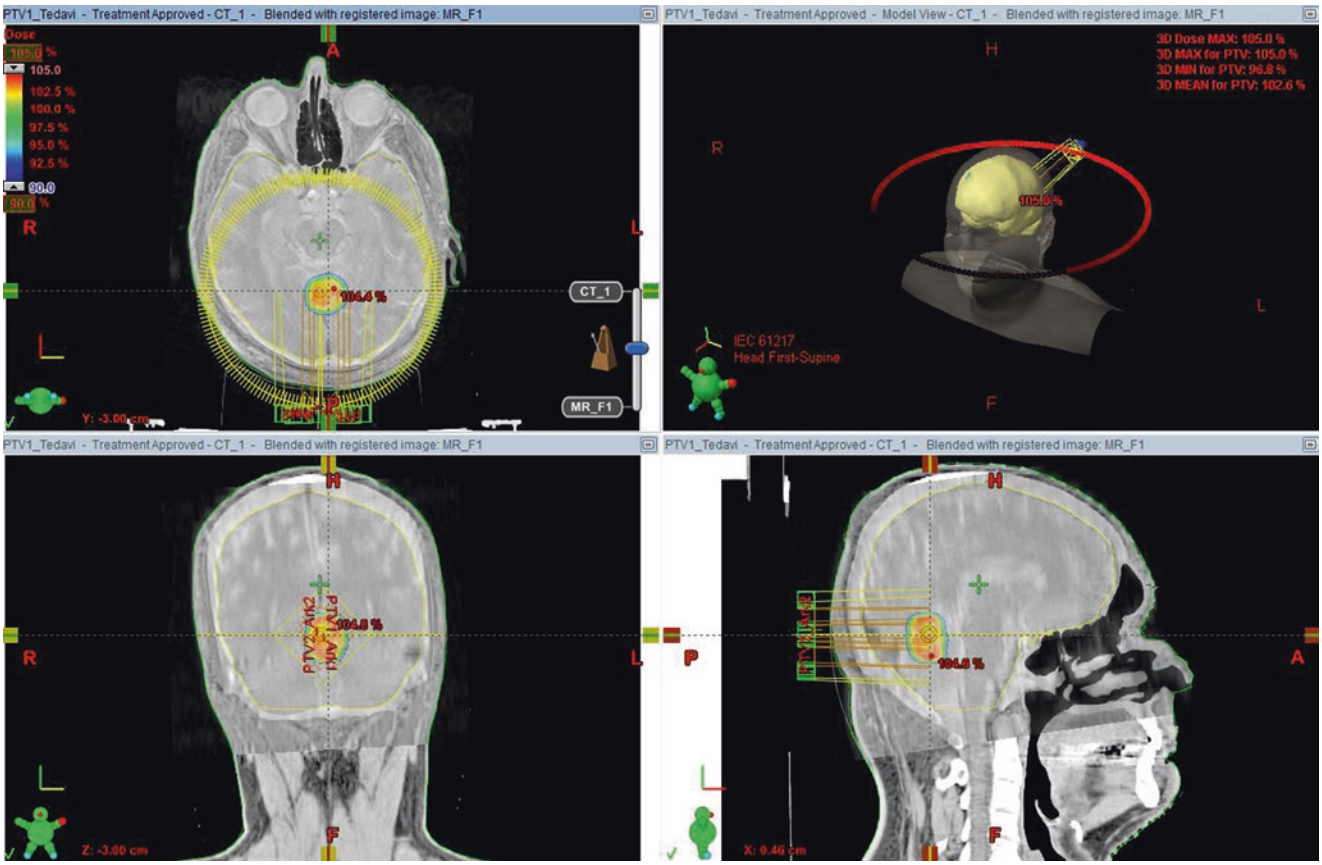

Fig. 37.6 Planning of SRT with MR fusion in a patient with a single metastasis

Table 37.8 A summary of the randomized trials and the review that compare WBRT only and WBRT + SRT boost

Study	*N* #	Randomization	LC (%)	Overall survival (m)	Time to failure (m)	Time to any brain failure (m)	New brain lesion (%)	Performance improvement at 6 months (%)
Kondziolka et al. [64]	27	WBRT + SRT WBRT	96 0 *p*: = 0.016	11 7.5 NS	36 6 *p* = 0.005	34 5 *p* = 0.02	–	
Chagule et al. [65]	109	WBRT + SRT WBRT SRT	91 62 87 NS	5 9 7 NS	–		19 23 43 NS	
RTOG 9508 [3]	333	WBRT + SRT WBRT	82 71 *p* = 0.01					43 23 *p* = 0.03
Cochrane [66]	385	WBRT + SRTWBRT	–	Single BM 6.5 4.9 *p* = 0.04	–	–	–	34 27 *p* = 0.05

LC local control, *WBRT* whole-brain radiotherapy, *SRT* stereotactic radiotherapy, *BMs* brain metastases, *NS* not specified

pendent survival. Just as with surgery, the contribution to disease control in other areas of the brain and overall survival is minimal. In conclusion, in locally treated (SRT) BM patients with one to three metastases, the addition of adjuvant WBRT decreases intracranial relapses and death due to neurological symptoms but makes no difference in functionally independent survival (FIS) and overall survival [49]. In a study by Chang et al., 58 patients with one to three metastases were randomized to SRT followed by WBRT or observation arms [67].

In the JROSG 99–1 study conducted by Aoyama et al., which included the participation of 11 centers in Japan, 132 patients with one to four metastases were randomized to SRT followed by observation or WBRT arms. The 1-year survival

rate was significantly higher in the SRT arm compared with the SRT + WBRT arm (76% and 46.8%, respectively; $p < 0.001$). In the SRT-alone arm, the brain salvaging treatment requirement was significantly higher in comparison with that in the SRT + WBRT arm (29 patients and 10 patients, respectively; $p < 0.001$). No differences were observed between the two arms in terms of survival (7.5 and 8 months) and neurological deaths [68].

Tsao et al. updated the Cochrane review. This update included three randomized trials that compared SRT and SRT + WBRT. Combined therapy increased LC in the whole brain when compared with patients treated with SRT alone but had no effect on overall survival [69].

Randomized participants (SRS alone, $n = 111$; SRS plus WBRT, $n = 102$) were studied to evaluate cognitive deterioration. SRS is suggested for <3 cm brain lesions for resection cavity and nonresected metastases because of in less cognitive deterioration at 12 months. WBRT is good when there is a risk of meningeal disease, ventricle violation, and poor PS, not good candidate for SRT for technical issues [70].

Until further research is performed, the use of combined SRT and WBRT should be limited to patients with good performance statuses, long life expectancy, and controlled extracranial disease. A sample hippocampus-sparing WBRT and SRT plan for metastases is shown in Fig. 37.7.

The benefit of the addition of SRT to WBRT in multiple BMs is being investigated in four ongoing prospective studies.

No prospective randomized studies have compared surgery + WBRT and SRT + WBRT. In retrospective data, no overall survival difference was noted, apart from one study with patient selection bias.

Adjuvant WBRT After Surgery or SRT

Adjuvant WBRT after surgery or SRT is generally recommended to prevent local recurrence and to target micrometastases that cannot be detected with imaging methods. The basis of this recommendation is the 1998 trial by Patell et al., which demonstrated a larger decrease in local recurrences in patients who received WBRT after surgery than in patients treated only with surgery [53]. The role of surgery followed by WBRT in breast cancer BM has been investigated in many retrospective trials, but no trial has reported a survival benefit. These studies contained heterogeneous groups of BM patients with various primary cancers. In the prospective study by Patell et al., only nine patients had a single BM due to primary breast cancer. In this trial, 95 patients with a single BM were allocated to surgery fol-

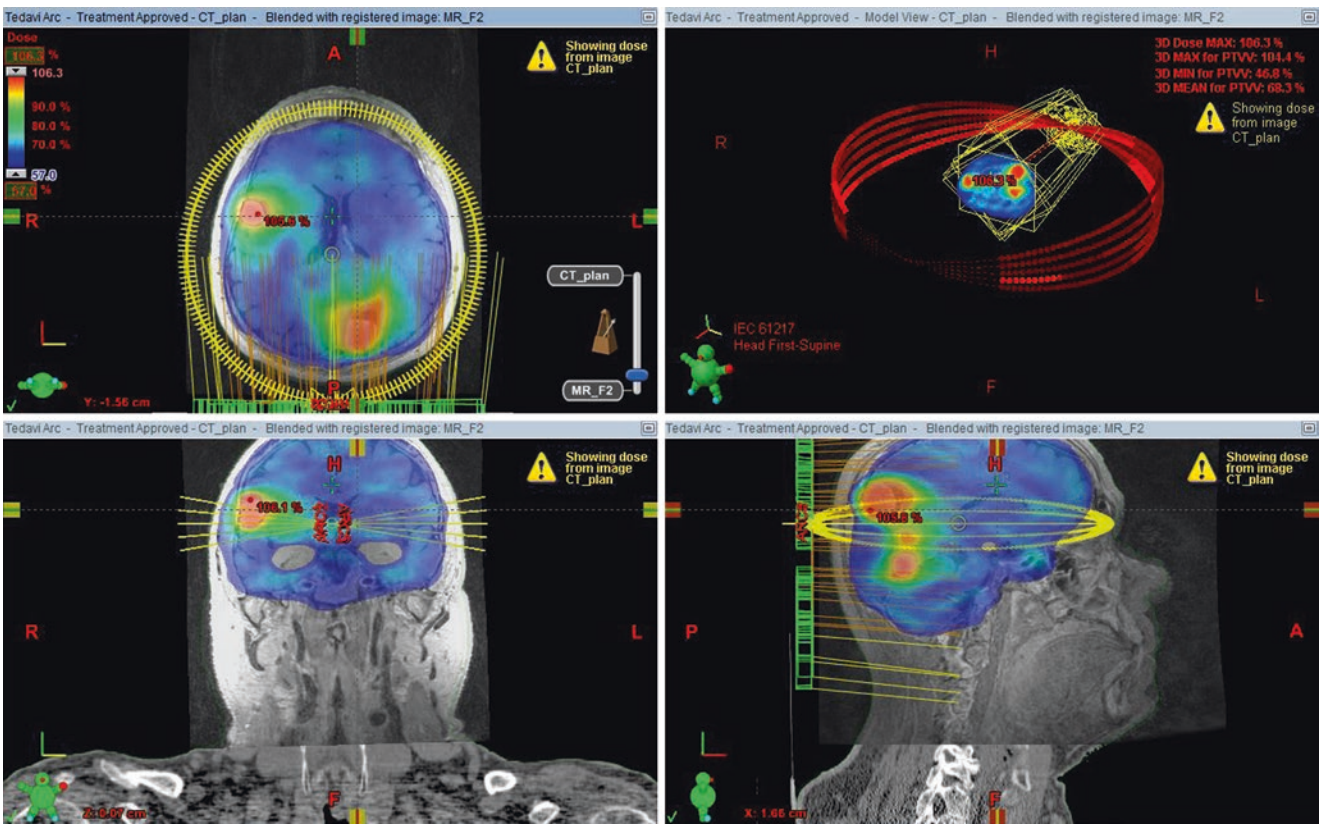

Fig. 37.7 Hippocampus-sparing WBRT and SRT planning for BMs

lowed with observation and postoperative WBRT (50.4 Gy/5.5 weeks) arms. In the postoperative WBRT arm, there was a significant decrease in the recurrence (18% and 70%, $p < 0.001$) and neurological death rates compared with the surgery followed by observation group (14% and 44%, $p = 0.003$, respectively). However, the normal WBRT dose was not used in this study. WBRT has a survival advantage but also increases cognitive side effects. Recent studies have questioned its routine use after SRT and surgery [67, 68, 71, 72].

A Cochrane meta-analysis evaluated 663 patients from five randomized trials comparing SRT with WBRT, surgery, and SRT alone in the treatment of BM. In this meta-analysis, the 1-year intracranial progression risk decreased by 53% in patients treated with adjuvant WBRT in comparison with patients who were not treated with WBRT ($p < 0.0001$). No differences were shown in overall survival or disease-free survival ($p = 0.08$ and $p = 0.28$, respectively) [51]. The effect of WBRT on neurocognitive functions, the quality of life, and neurological events is unclear due to study bias. In light of the five randomized trials on adjuvant RT, following local treatments (SRT, surgery) with adjuvant WBRT should be a standard.

Intracavitary and Interstitial Brain Irradiation

Brachytherapy with the GliaSite Radiation Therapy System has only been approved for the intracavitary treatment of primary brain tumors. One multi-institutional phase II study has defined its use in resectable single BMs. In this study, 62 patients who were at risk for recurrence were treated with a single-use applicator system at doses of 60 Gy RT to a depth of 10 mm. There is a dual silicone balloon at the edge of the applicator. The internal balloon serves as a lotrex (125 I) reservoir, and the external balloon is a backup reservoir. No patients received WBRT, and 43% of the patients had extracranial disease. In the results of the trial, LR was 82–87% in MRI follow-ups, and the median survival was 10 months. Thus, the GliaSite results were similar to WBRT for LC, overall survival, and functional independence [73].

Cosgrove et al. treated 14 brain cancer patients with lesions smaller than 3.5 cm with doses of 15 Gy. At the 12-month follow-up, LC was successful in 10 of 13 patients. However, interstitial procedures are not very popular for BM [74].

Second Course Brain Irradiation in Recurrent BMs (Re-irradiation)

If too many recurrent lesions are present for treatment with SRT, the WBRT decision must be made very carefully. As a general principle, SRT must be prioritized and used whenever possible because it preserves normal brain tissue. An SRT planning sample for a patient with a new BM who was previously treated with WBRT 1 year prior is shown in Fig. 37.8.

Wong et al. reported the largest series, which included 86 patients treated with a second course of WBRT. During the first course of WBRT, 30 Gy doses were delivered, and during the second course, an average dose of 20 Gy was delivered. The median survival was 4 months after the second course of irradiation. Among the patients, 27% experienced full relief of symptoms, 43% experienced partial relief, and 29% experienced worsening symptoms. Multivariate analyses of patients with no extracranial disease showed better survival [75]. In a similar study, 17 patients who were initially treated with 35 Gy were treated with 21 Gy WBRT for brain recurrence. In 80% of the patients, symptomatic improvements were observed. The median survival was 5.2 months. In patients with stable extracranial disease, the median survival was 19.8 months, and in those with progressive extracranial disease, it was 2.5 months.

For patients who will be irradiated for a second course, SRT or WBRT is chosen according to the systemic disease status, recurrent metastatic brain lesion size, the prior treatment method, and patient performance. The treatment algorithm for recurrent BM patients is shown in Table 37.9.

The RTOG 90–05 trial by Pirzkall et al. is a dose escalation study that included 156 patients with recurrent primary brain tumors or recurrent BMs. This study recommended 24 Gy for ≤2 cm, 18 Gy for 2–3 cm, and 15 Gy for 3–4 cm tumors. Grade 3–5 neurotoxicity was related to tumor size, dose, and KPS [76]. Second WBRT courses should be delivered with a minimum daily dose of 1.8–2 Gy, with a total dose of 20 Gy.

Systemic Treatment

The role of chemotherapy has not been precisely defined in BM. Chemotherapy is rarely part of the BM treatment plan due to the blood-brain barrier (BBB). The agents that penetrate the BBB are temozolomide, topotecan, capecitabine, nitrous urea, thioTEPA, trastuzumab, tamoxifen, liposomal doxorubicin, methotrexate, and gefitinib [77]. Although breast cancer is sensitive to chemotherapy, the contribution of chemotherapy in BM is controversial. Chemotherapy can be used in cases of multiple BMs, extracranial disease, and inadequate local control. Rosner et al. reported 100 breast cancer patients with BM who were treated with cyclophosphamide, fluorouracil, prednisolone, methotrexate, and vincristine. This was the largest series reported [78]. In 50% of the patients, an objective response was achieved (10% complete, 40% partial). The median remission duration was 7 months in partially responsive patients and 10 months in fully responsive patients. The intracranial and extracranial

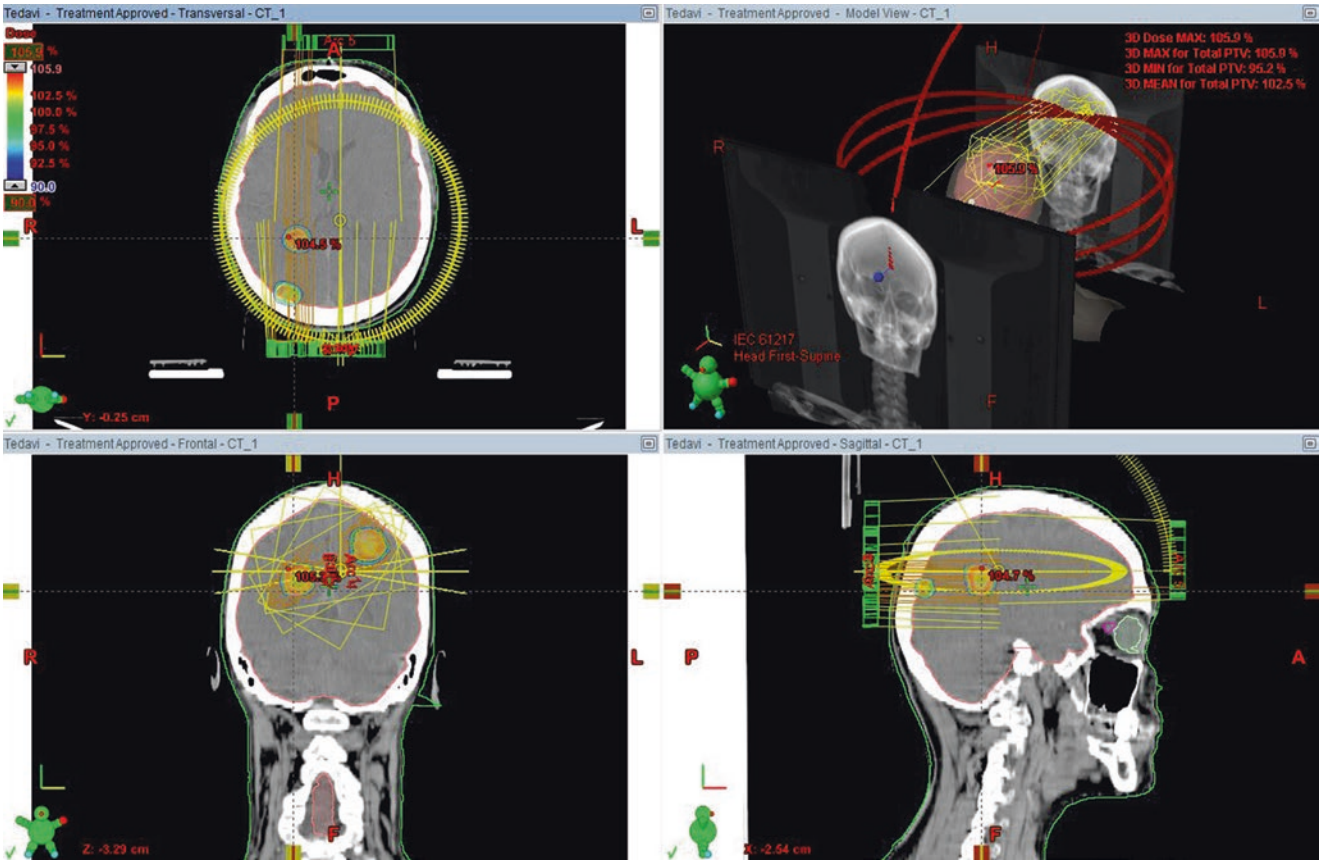

Fig. 37.8 An SRT planning sample for a patient with a new BM, treated with WBRT 1 year prior

Table 37.9 Salvage treatment during BM treatment

Systemic disease status	Recurrent metastatic brain lesion number	Treatment
None or stable	1–3	SRT if lesions are suitable
		Surgery for mass effect
		WBRT if not performed previously
None or stable	>3	If not delivered before WBRT
		If previously responsive to WBRT, if longer than 4 months has passed since the second WBRT
		Limited field RT
		CT
Progressing	Any	If WBRT was not performed previously, WBRT with accelerated plans (4 Gy × 5 or 3 Gy × 10)
		Supportive treatment
		CT

WBRT whole-brain radiotherapy, *SRT* stereotactic radiotherapy, *RT* radiotherapy, *CT* chemotherapy

Table 37.10 Systemic chemotherapy protocols shown to be active in breast cancer CNS metastases

Study	Protocol	*N*	Median survival (m)
Rosner et al. [78]	Cyclophosphamide, fluorouracil, prednisone, methotrexate, and vincristine	100	10
Lange et al. [79]	RT + Ifo/BCNU	61	8
Boogerd [80]	Cyclophosphamide, doxorubicin, and fluorouracil	20	6.3
Rivera et al. [81]	Temozolomide + capecitabine	24	3
Kouvaris et al. [82]	Temozolomide + WBRT	33	12
Kurt et al. [83]	Capecitabine	20	7.3
Cocconi et al. [84]	Cisplatin and etoposide	22	14.5

response rates were equivalent. The studies that used systemic chemotherapy protocols that have been proven to be effective in treating CNS metastases of breast cancer are listed in Table 37.10 [78–84]. The most commonly used protocol is CFP (cyclophosphamide, 5-FU, and prednisolone). No protocol was superior to the others.

The hormonal therapy agents that can penetrate the BBB in BM are tamoxifen and megestrol acetate. The BBB is dis-

rupted in contrast-enhancing metastases. Targeted treatments with trastuzumab and lapatinib can penetrate the BBB. Lapatinib is a small molecule that can pass the BBB. In a lapatinib study by Lin et al. that included 241 patients, a partial response was reported in seven patients, and a 20–50% reduction in tumor volume was achieved in 19 patients [85].

Leptomeningeal Metastases

Leptomeningeal metastases (LMs) are common complications of BM, and their occurrence rate is gradually increasing. The clinical LM occurrence rate in breast cancer patients is 2–5%; in autopsy data, this rate is 3–6%. The approach to LM differs from the approach to parenchymal BMs. In clinical and autopsy series, lobular carcinomas are more likely to spread to the leptomeninges for unknown reasons. In cancers other than breast cancer, LMs generally occur in widespread metastatic stages, whereas in breast cancer, LMs can occur even when the disease is under control and without any systemic metastases. LMs may develop within weeks or up to 15 years after the diagnosis of breast cancer [86].

The most common presentation of LM is spinal symptoms, weakness in the legs, and paresthesia. Sudden multifocal abnormalities in multiple levels of the neuroaxis (cerebellum, cranial nerves, and spine) suggest an LM diagnosis. Neck stiffness is present in 2–13% of cases. Obstruction of the CSF may cause headaches, mental status changes (such as lethargy, confusion, and memory loss), nausea, vomiting, and/or ataxia. Seizures are rare. Mental status changes indicate cerebral dysfunction, and hearing loss is a sign of cranial nerve involvement. To diagnose LM, malignant cells must be found in the CSF. Increased protein levels and mononuclear pleocytosis are often observed in the CSF. Sometimes, the glucose level in the CSF may be <70% of the normal serum glucose level. Carcinoembryonic antigen (CEA) may be increased in CSF; in this case, the serum CEA levels must also be checked because CEA can penetrate the BBB. Increased CEA in the CSF may be due to increased serum CEA. The extent of the disease must be established with MRI of the whole spinal cord, including the cauda equina and the brain (Fig. 37.9a–e). In these patients, cranial MRI must also be performed to scan for BMs.

Whole craniospinal irradiation is not recommended because it can cause myelosuppression. RT is delivered to the area where the bulky or symptomatic lesion is located in the craniospinal axis. After RT, intrathecal (IT) chemotherapy is administered in three phases, induction, consolidation, and protection, by lumbar punctures or an Ommaya reservoir. Administration via an Ommaya reservoir has a lower infection risk. If the CSF flow is blocked, RT may be delivered first and followed with intrathecal chemotherapy. The agents that are frequently used for intrathecal chemotherapy are methotrexate, thioTEPA, and liposomal cytarabine. In a series of 48 breast cancer patients with LM metastases, intrathecal methotrexate was delivered twice a week until CSF was clean and was continued as a protection plan once every 2–4 weeks. In this study, the response rate was 61%, and the median survival was 7.2 months [87]. Although standard cytarabine has a limited effect on breast cancer metastases, the response rate of liposomal cytarabine is 28%. In a phase II randomized trial comparing methotrexate and liposomal cytarabine, 21 of 61 patients were primary breast cancer patients. There was no difference in the response rates between the two arms (liposomal cytarabine 26%, methotrexate 20%). Although statistically insignificant, there was a tendency toward increased survival [88]. Liposomal cytarabine was used every 2 weeks for induction and once every 4 weeks for consolidation. Many agents, such as mafosfamide, topotecan, interferon, and interleukin-2, have been used to treat LM in experimental study protocols. The results of the combined use of chemotherapy agents were similar to singular use, and combined use is not recommended. The most common long-term neurotoxicity caused by LM treatment after brain irradiation is leukoencephalopathy. It appears on MRI as a hyperintensity in periventricular white matter in T2 slices and as brain atrophy and ventricular dilatation in FLAIR imaging (fluid attenuation inversion recovery). The clinical signs are cognitive deterioration, behavioral changes, gait abnormalities, and seizures. The use of RT and methotrexate together increases the occurrence of leukoencephalopathy, but in LM patients, it may not be clinically apparent due to poor prognosis. The relationship between the order of RT and chemotherapy administration and the frequency of leukoencephalopathy is not entirely understood. Some studies state that the risk increases when RT is prioritized. Intrathecal chemotherapy may cause aseptic meningitis in 20% of patients; it presents 12–72 h later with headaches, nausea, vomiting, lethargy, and fever. Other serious complications are neutropenia, sepsis, mental impairment, and increasing myelopathy. The death rate due to treatment is 5%.

Epidural Metastases

Epidural metastases (EMs) are mostly caused by the tumor entering the epidural space from the vertebral column (85% of cases) and less frequently caused by entry from the paravertebral space. The frequency of epidural spinal compression fractures in breast cancer patients is reported to be 4%. The vertebral column is the most frequent site of bone metastases. The frequency is 60% in brain cancer patients, and approximately 84% of these patients are advanced-stage

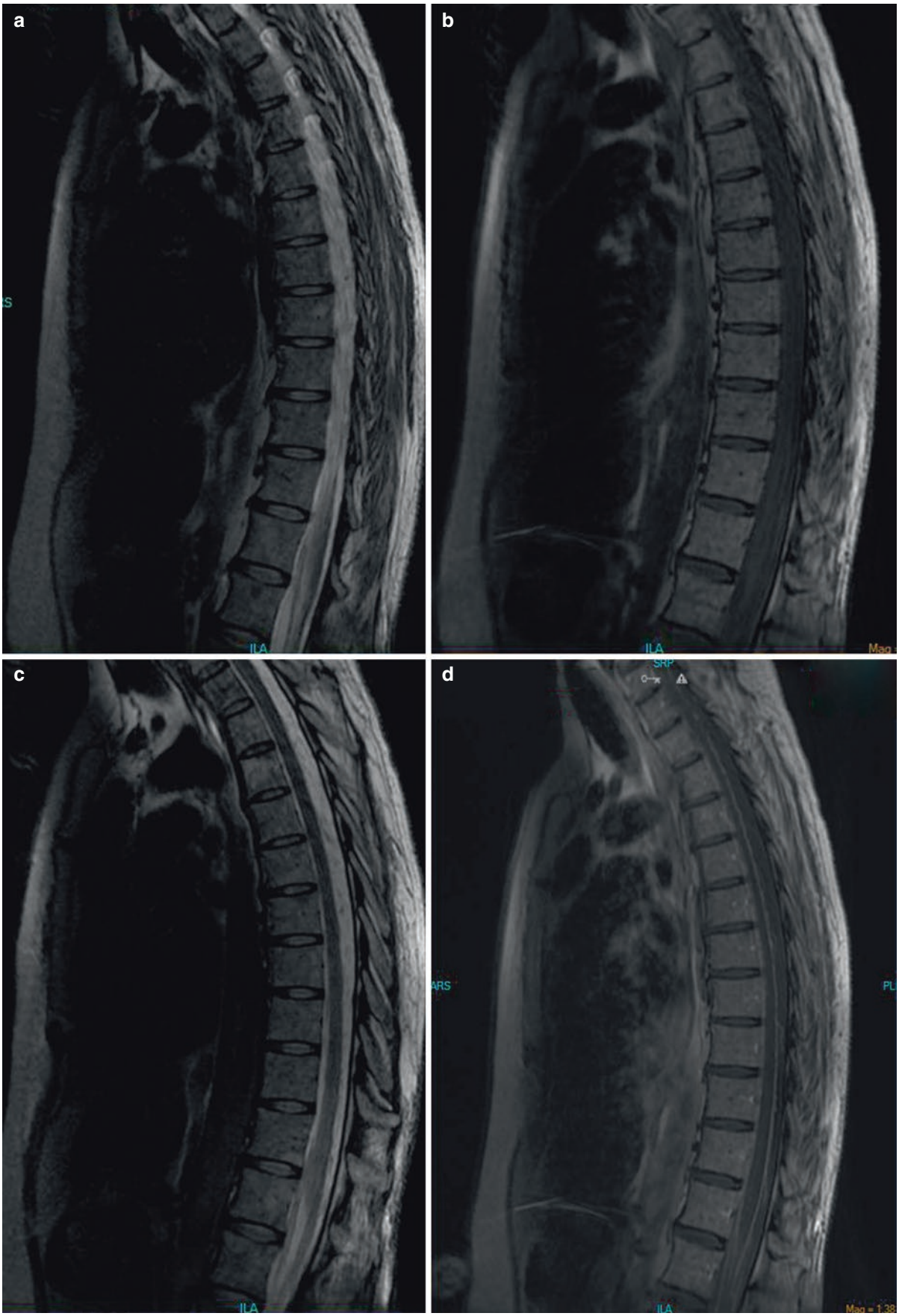

Fig. 37.9 (**a**–**e**) LM metastases at t1 and t2; precontrast and postcontrast sagittal MR images

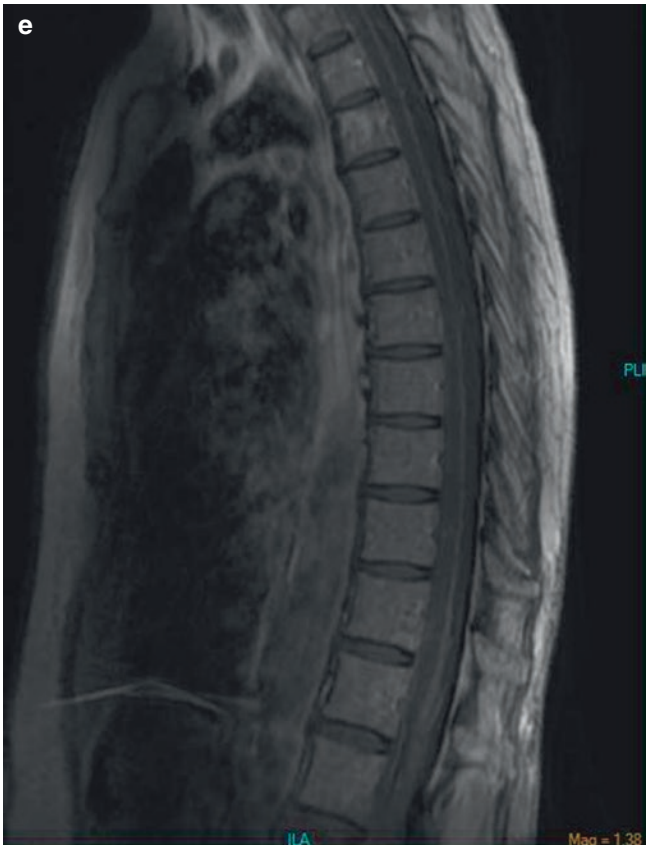

Fig. 37.9 (continued)

breast cancer patients [89]. The epidural spinal cord compression frequency in breast cancer patients is 4%. Spinal cord damage caused by direct spinal cord compression is more common than damage caused by radicular artery compression. The time between breast cancer diagnosis and EM is 43 months. The median survival is 4–13 months. The most important prognostic factor is discharging the patient in an ambulatory status. Whole spinal canal MRI must be performed (Fig. 37.10). If EMs are left untreated, they may cause paraplegia or quadriplegia, depending on the level of the lesion. If the suspicion of an EM arises, an emergency evaluation is necessary. After diagnosis, steroids and RT must be initiated immediately. In EM patients with no cord compression, patients are given low steroid doses (10 mg dexamethasone); in patients with cord pressure, steroid therapy should be initiated with a bolus dose (100 mg dexamethasone). The continuation steroid dose is 4 mg of dexamethasone every 6 h. It is tapered when radiotherapy is completed or symptoms are stabilized. In progressive or recurrent spinal cord compressions due to the risk of myelopathy caused by a second irradiation course, surgery is recommended. The recommended surgical treatment is "vertebral resection and stabilization with methyl methacrylate cement" [90]. EMs are generally located anterolaterally, and a posterior approach (laminectomy) is not very efficient and may lead to even more weakness. The results of IGRT and SRT trials in EM are expected to be similar to the results of SRT in intracranial lesions [91].

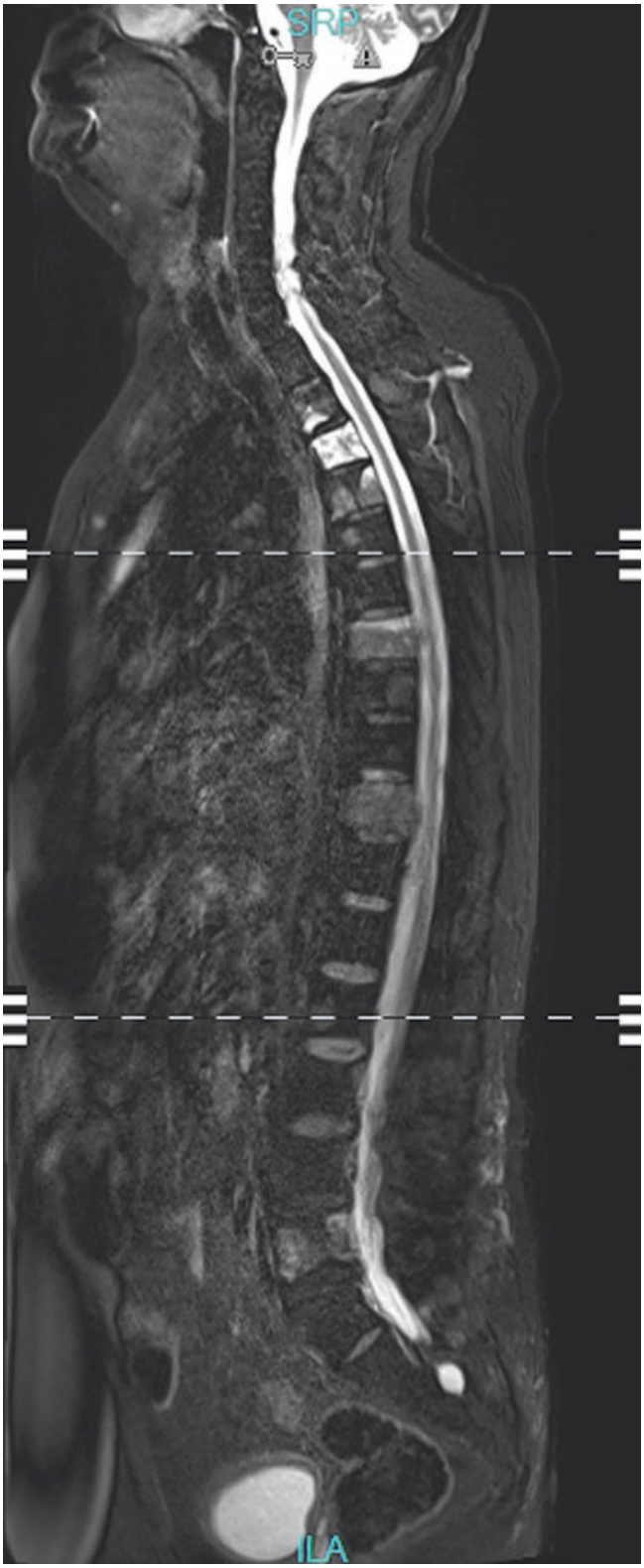

Fig. 37.10 Sagittal MRI of epidural metastases

Brachial Plexopathy

The neoplastic invasion of the brachial plexus is quite rare, but it is still a common cause of plexopathies. MBCs and lung cancers are the second most common causes of non-traumatic brachial plexopathies. Brachial plexus lesions are caused by the direct extension of the tumor to the plexus (Pancoast tumor) or are secondary to a neoplasia that metastasizes from the axillary lymph nodes to the plexus. The axilla apex is one of the lymphatic drainage locations of the breast; thus, brachial plexus involvement is not rare in MBCs. It may develop as a result of neoplastic invasion, but it may also develop as a long-term side effect of breast cancer RT if the treatment falls in the supraclavicular or axillary treatment zones. RT causes the fibrosis of tissues surrounding the brachial plexus, which may result in the compression of nerve fibers and a loss of function (Fig. 37.11a–c). When RT is being planned, the brachial plexus must be defined, and the doses it receives must be evaluated and recorded carefully, as for every organ that is at risk of RT damage [92].

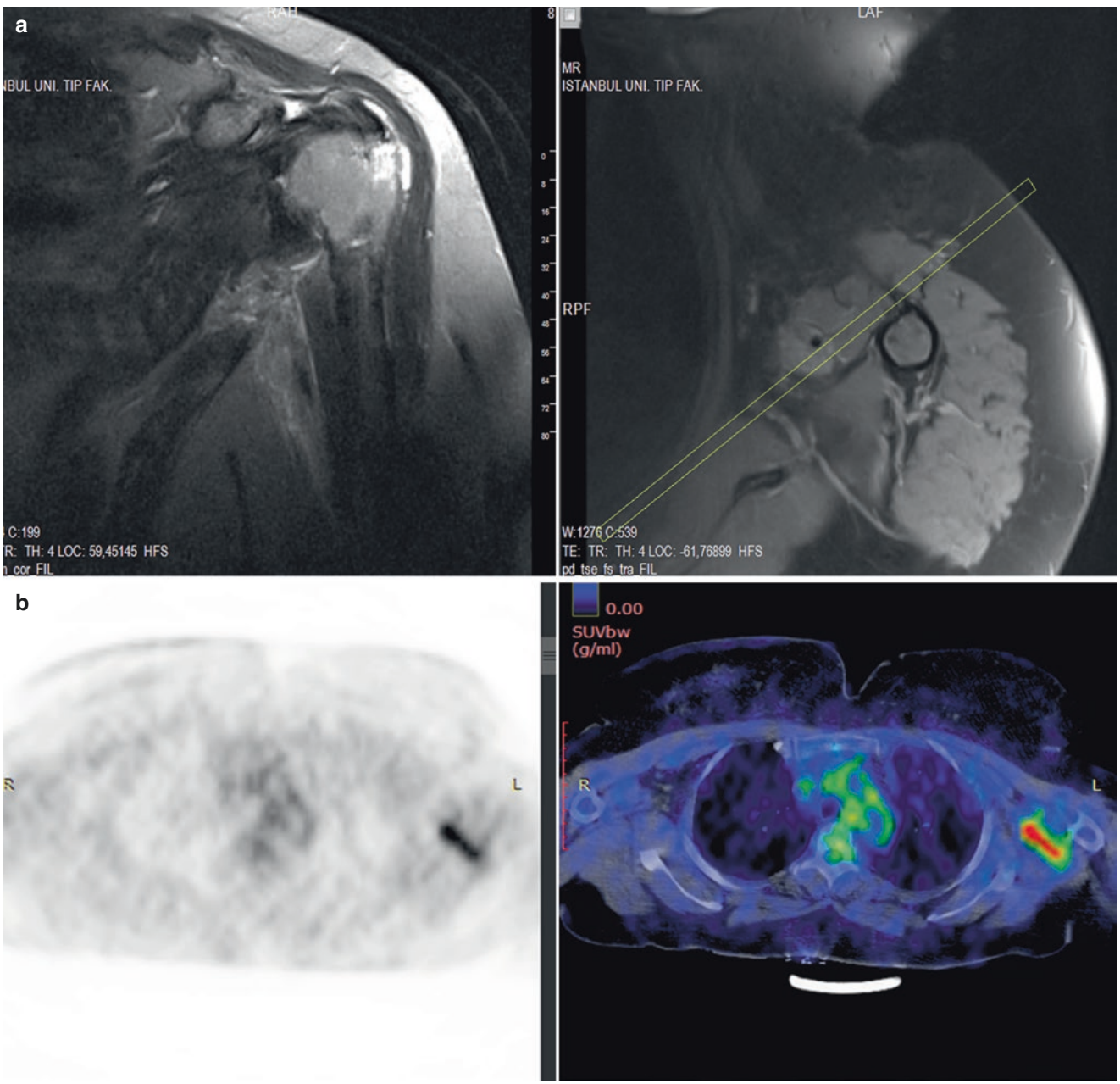

Fig. 37.11 (**a**) Coronary and axial view of brachial plexopathy in MRI. (**b**) Axial view of brachial plexopathy in PETCT. (**c**) Coronary view of brachial plexopathy in PET-CT

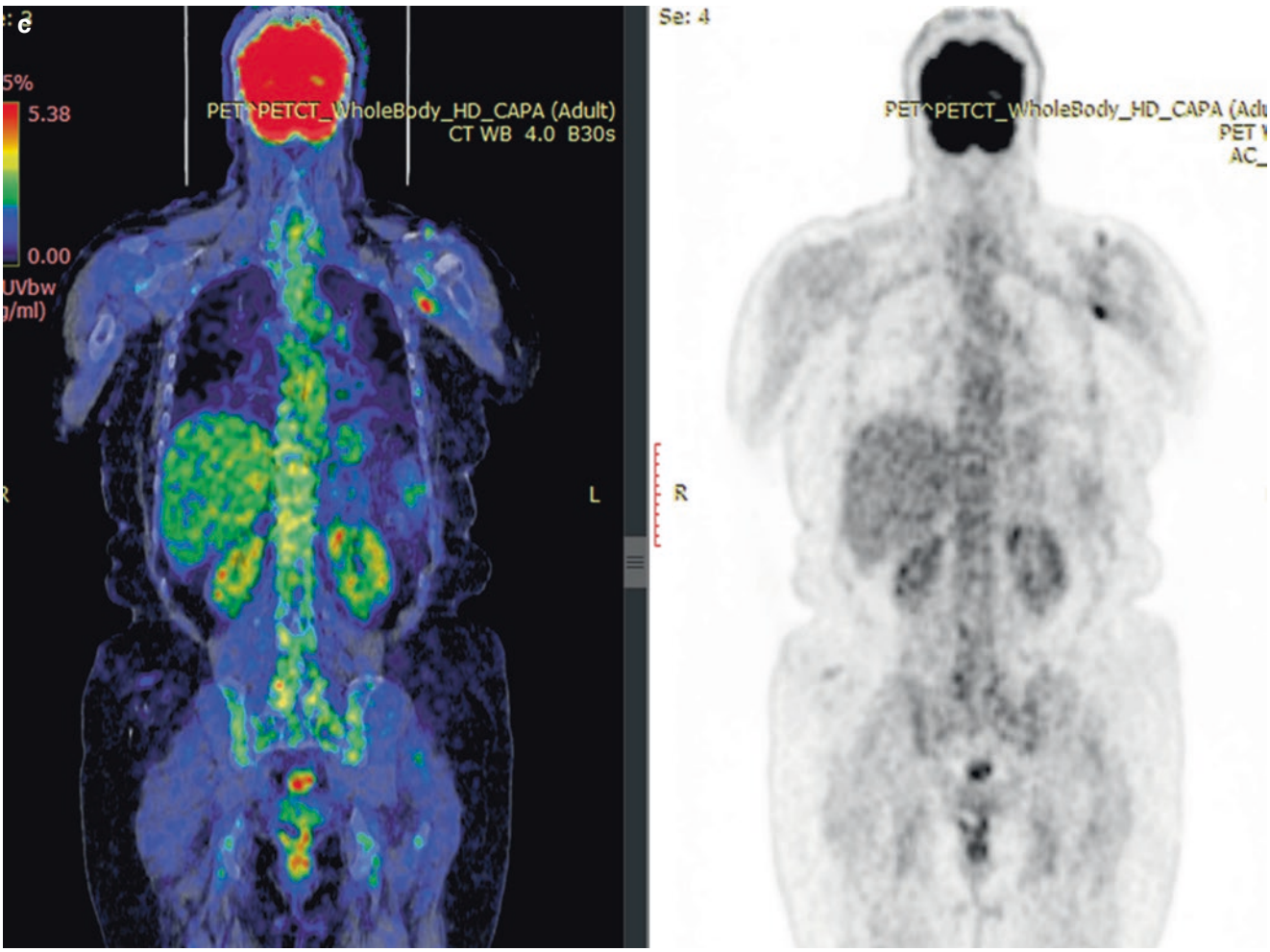

Fig. 37.11 (continued)

In retrospective reviews, the RT dose, treatment technique, and chemotherapy administration affect the development of brachial plexopathy. In a study by Pierce et al., the risk of brachial plexopathy was 3% when the axillary dose was <50 Gy and 8% when the dose was >50 Gy. Approximately 20% of the brachial plexopathy cases were permanent [93].

Brachial plexopathy is a progressive and potentially permanent clinical picture that disrupts the quality of life, consisting of severe shoulder pain and pain radiating to the medial areas of the hand and forearm. Symptoms may be diffuse, but they frequently include symptoms of the C8–T1 dermatome and myotomes and imitate ulnar neuropathy and C8–T1 radiculopathy. The incidence is less than 0.5% [94].

Nerve damage in the plexus is determined in a neurological examination and EMG, and the plexopathy is graded. Imaging methods such as CT, MRI, and PETCT can be used in the diagnosis and differential diagnosis (Fig. 37.10). Visually guided fine-needle aspiration biopsy may be performed. Steroids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and physical therapy can be used in the treatment.

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Ocular Metastases

38

Nergiz Dagoglu and Anand Mahadevan

Introduction

Metastatic carcinoma of the eye is the most common malignant ocular neoplasm [1]. Among all cases, breast cancer is responsible for most of these metastases, making it a significant sequel [2]. Breast cancer as a cause is followed by lung carcinoma and carcinoma of an unknown primary. Gastrointestinal, genitourinary, and other carcinomas are infrequently responsible for ocular metastasis (Table 38.1) [3, 4]. Metastatic disease to the eye from the breast was first described by Johann Friedrich Horner in 1864 [5]. Since then, reports of ocular involvement have steadily increased in living patients as well as in histopathological studies on postmortem subjects. However, the true incidence of ocular metastases is underestimated because subclinical disease is frequently overlooked, especially in patients with metastatic disease in other life-threatening organs that affect the patient's performance status [1].

Because of differences in the diagnostic rate, the prevalence of ocular metastases in patients with breast carcinoma shows a large range between 10% and 38% [6, 7]. In a study of 250 patients with breast carcinoma, 38% of 152 patients with ocular symptoms and 9% of 98 asymptomatic patients had ocular metastases [7]. All asymptomatic patients had stage IV disease. Bilateral involvement is common and ranges between 20% and 40% [8]. Multifocal involvement of a single eye is also common, occurring in 20–28% of affected eyes [9, 10].

The globe itself is the anatomic structure that is the most frequently diagnosed site for ocular metastasis. In the globe, the uveal tract of the eye, which is composed of the iris, the ciliary body, and the choroidal layer with its rich vascular network, is involved in the large majority of ocular metastatic disease (Fig. 38.1) [3, 4].

Table 38.1 Primary sites for patients with ocular metastases [4]

Breast	47%
Lung	21%
Gastrointestinal	4%
Kidney	2%
Skin	2%
Prostate	2%
Unknown	17%
Other	5%

The reasons for the propensity of breast carcinoma to cause ocular metastases rather than other tumors are unclear. Possible hypotheses include the ability of such cells to survive in relatively inhospitable microenvironments, the tendency to cause metastases many years after the diagnosis of the primary tumor, and the prolonged survival of many patients with metastatic disease [7, 10, 11].

Ocular metastasis from breast cancer usually occurs or is diagnosed after metastasis to other organs, primarily the lungs. At the time of ocular metastasis diagnosis, 85% of patients also have pulmonary involvement. The reported interval from breast cancer diagnosis to ocular metastasis is 2–5 years [10, 12], and the interval from the detection of non-ocular metastases to the detection of ocular metastasis is 10 months in most cases. In rare cases, ocular metastasis can be perceived as the first sign of metastatic spread in breast cancer [13] or may even be the initial symptom of breast carcinoma [14].

The expected median survival time of patients with ocular metastases is short and ranges between 4 and 12 months [15, 16]. As expected, breast cancer patients with ocular metastases survive significantly longer than patients with other primary tumors. This survival correlates with the results of modern multimodal therapy strategies for breast cancer [16, 17].

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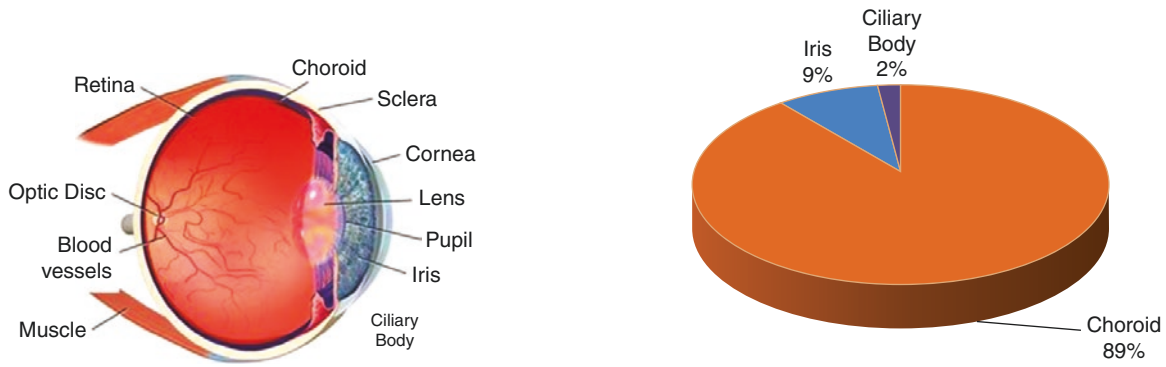

Fig. 38.1 Anatomic structures of the eye and anatomic locations of ocular metastases [4]

Given the increasing survival rates of cancer patients, the incidence of ocular metastasis is expected to increase. This point brings up the need for more focused attention on the importance of the patient quality of life.

Symptoms and Signs

The most common presenting symptom recorded in patients with ocular metastasis is blurred vision [18]. In contrast, either proptosis or visual loss frequently is the first complaint for most other ocular neoplasms [19]. However, this difference rarely assists the differential diagnosis.

More specific symptoms and signs may be present depending on the affected area. For example, choroidal involvement may induce blurry vision or vision field loss because these tumors cause retinal detachment, which leads to lens and iris displacement and secondary angle-closure glaucoma [20]. Optic disc metastases often produce rapid, profound visual loss. Iris metastases frequently cause secondary open-angle glaucoma when the trabecular meshwork becomes clogged with tumor cells [21]. Although some authors have stressed pain as a typical symptom for metastatic lesions, any primary malignancy that has perineural invasion and some benign processes will present with pain [22, 23].

The differential diagnosis with ocular melanoma or other ocular lesions can be made by clinical evaluation, including a previous cancer history. The standard workup includes direct ophthalmoscopy, Goldmann perimetry, and ultrasonography (USG) [3, 24]. Computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) imaging are also utilized [25–27].

USG is useful for determining the extent of retinal detachment and outlining any underlying choroidal masses. MRI has several advantages. Most importantly, it may provide some indication regarding tissue specificity and, therefore, be helpful in distinguishing between benign and malignant lesions. MRI also provides additional information for small metastases or choroidal masses that are often missed by other modalities. Nevertheless, incorporating MRI or a CT scan of the brain as part of the initial evaluation is also essential because the risk of synchronous brain metastases for these patients is 25–30% [25, 26].

SPECT imaging with technetium-99 m-MIBI is another method that can be used if more conventional techniques fail to distinguish the nature of the lesions. It is a highly sensitive technique (92%) for detecting malignant ocular tumors [27].

The majority of intraocular tumors can be diagnosed based on clinical examination and radiographic features, which lessens the need for diagnostic ophthalmic fine-needle aspiration biopsy (FNAB). In general, the diagnostic precision of ophthalmic FNAB is high but still limited because cellularity can confound the results. Furthermore, surgical biopsy may cause a significant risk of visual loss or other ocular morbidity and presents a significant risk of seeding along the biopsy track [28].

Treatment

If ocular metastasis is detected early enough, it can be treated effectively to prevent vision loss and therefore to maintain quality of life [3]. The short-term prognosis for vision is usually good, but the systemic prognosis is poor. Treatment requires an individualized approach in which both the tumor and patient characteristics are considered. Tumor characteristics include the size, extent, and location of the tumor; the number of tumors; the laterality of involvement; and the effects on normal intraocular tissues. Patient characteristics involve the visual status of the affected eye or eyes, the visual status of the contralateral eye in unilateral cases, the extent of primary disease, and the age and general health of the patient [29].

Treatment requires a multidisciplinary approach with close communication between the patient's ophthalmologist, medical oncologist, radiation oncologist, and neuroradiolo-

gist. Indications for treatment of uveal metastases include visual symptoms attributable to the lesion (e.g., blurred vision, scotoma, flashes, floaters, and dysmorphopsia), lesions close to the optic nerve or macula with signs of active disease, enlargement despite systemic chemotherapy, and painful lesions [30].

Since its first application in 1979, radiotherapy (RT) has become a well-established and widely available treatment for uveal metastases [31]. RT can be applied as a conventional external beam RT (EBRT), plaque brachytherapy, stereotactic body RT (SBRT), or proton beam. Other local therapies include intravitreal injection, laser therapy, and cryotherapy.

Though timely treatment with RT typically anticipates a higher probability for better vision and organ preservation, some patients with hormone-sensitive lesions may benefit from chemotherapy (CT) or hormone therapy (HT) [32]. Manquez et al. [33] found choroidal metastasis regression with aromatase inhibitor treatment in 10 of 17 patients with hormone receptor-positive breast cancer over a mean follow-up of 20 months.

In patients who are already on CT or HT when the metastatic carcinoma of the eye is detected, a regimen change may be recommended. An appropriate drug regimen often produces satisfactory regression of all tumors and preservation or recovery of useful vision in the affected eye or eyes [34].

Because the choroid is the most common site of ocular metastasis and has a vascular structure, anti-vascular endothelial growth factor (anti-VEGF) has been tested as part of the treatment in several case reports. Preliminary results support the use of anti-VEGF [35, 36], emphasizing the ease of administration and the minimal time commitment required. However, there are still many uncertainties, such as the optimal dose, the interval and number of injections, the indications for use, and maintenance therapy.

Surgical resection can be reserved for a minority of carefully chosen patients [34]. Resection may be indicated particularly when the metastases cause pain or proptosis and if RT, CT, or management approaches fail to relieve symptoms [37].

The optimal therapy for asymptomatic ocular metastases is controversial. Data in the literature regarding the treatment of asymptomatic metastasis are rare, and the best time for treatment initiation is arguable. A careful "watchful waiting" strategy and systemic CT in patients with breast cancer seem reasonable [22, 23, 38].

Radiotherapy Doses

RT is effective in relieving symptoms and controlling tumor growth. Though the reported series address the application of different techniques and doses, more current protocols suggest a total dose of 30–40 Gy, delivered in fractionated doses of 2–5 Gy [23, 39].

Doses of less than 30 Gy are less effective. Maor et al. reported that none of the nine patients in their study who received 30 Gy in ten fractions had tumor regrowth after therapy, but two of ten patients treated with 25 Gy in ten fractions had tumor regrowth [40]. In another series reported by Reddy et al. [41], 30% of tumors did not respond to treatment with doses of 21–30 Gy. Importantly, for most patients, the benefit in vision produced by RT lasted for the remainder of their lives.

Rudoler et al. [8] reported the results of the largest series of 188 patients with 233 ocular metastases over a 23-year time period. A wide range of doses, from 4 to 63 Gy, were used, but most (72%) patients were treated with 30–40 Gy total doses in 2–3 Gy fraction sizes. Their results showed an improvement or stabilization of visual acuity in 57% of all patients.

One of the most recent reports evaluating a more uniform treatment was presented by Wiegel et al. [22, 23]. They evaluated 65 eyes that were treated with a total dose of 40 Gy in 20 fractions that was applied with asymmetric fields, resulting in increased visual acuity for 36% of the patients. This was thought to correspond with the finding that doses higher than 30 Gy were strongly correlated with better or more stable visual acuity because almost 90% of the patients showed an increase or stabilization during their lifetime.

However, doses higher than 40 Gy are not used because of the possible increase in side effects.

A total of 15–20% of patients with unilateral metastasis develop symptomatic contralateral metastasis later. Additionally [22, 23, 42, 43], a unilateral field for unilateral choroidal metastasis without sparing the contralateral choroid is an effective technique in destroying possible contralateral micrometastasis and may lower the risk of late side effects compared with bilateral fields.

Radiotherapy Techniques

Most metastatic carcinomas are responsive to RT delivered by the external beam (EB) or plaque methods. These tumors generally show rapid regression after RT, and vision in the eye is frequently stabilized, if not improved [32].

EBRT is particularly applicable to patients with large tumors that involve the optic nerve or macula and either cause substantial visual disturbance or affect multiple areas in both eyes. Unilateral RT with a lateral electron portal of sufficient energy is adequate to treat most ocular metastases. The anterior border should be placed just behind the anterior chamber of the eye, and a posterior tilt should be utilized to avoid the lens. For bilateral metastases, posteriorly tilted opposing photon fields may be an option [44, 45].

Furthermore, single small-to-medium-sized tumors can occasionally be treated effectively by radioactive plaque therapy. This treatment consists of suturing a radioactive device (plaque) to the sclera directly overlying the intraocular tumor. The plaque is left in place for several days, generally until a radiation dose of 40–50 Gy has been delivered to the apex of the tumor, and then, the plaque is removed [46, 47].

Considering the risk of ocular toxicity, other techniques, such as stereotactic body radiotherapy (SBRT) [48] or proton beam therapy (PBT) [49], that promise less toxicity or shorter treatment times are applied to choroidal metastases.

Although SBRT has not been used to a great extent to treat choroidal metastases, evidence supporting its use is mounting. SBRT can deliver precisely targeted radiation in fewer high-dose treatments than conventional therapeutic techniques, thus preserving healthy tissue [48]. Reports have shown reduction of recurrence and high local control rates.

PBT, because of its physical characteristics, allows for more focused irradiation, with less scatter to nearby tissues (49) Tsina et al. showed regression of choroidal metastases in 84% and stability of the lesion in 14% of eyes treated with PBT over a mean follow-up period of 5 months. The average dosage administered was 28 Gy delivered over two treatments.

Side Effects

The rate of severe late side effects after EBRT is low. Approximately 30–50% of the patients died after 5–7 months; therefore, late side effects did not appear [50]. Referring to data from Wills Eye Hospital [32], patients who live significantly longer seem to have more late side effects, as expected. The small number of side effects, however, did not allow multivariate analysis of possible risk factors.

Radiation-induced ocular side effects have been well described. Thus far, cataracts, keratopathy, retinopathy, neovascularization of the iris, and optic neuropathy have been described [51]. Mild skin erythema and conjunctivitis occur frequently. Cataracts are particularly common in patients with irradiation of anterior segment metastases.

The retinal vasculature may also be damaged by RT [52]. Clinical manifestations are typically delayed in onset for a median of approximately 8 months after treatment and are progressive. The incidence of radiation-induced retinopathy and papillopathy is 8%. The severity of retinopathy does not correlate with the RT dose and may occur with doses as low as 50 cGy.

In particular, a significant influence of additional chemotherapy on retinopathy could not be demonstrated.

Course and Outcome

If untreated, most ocular metastases are progressive [22, 23]. They tend to grow faster when compared with primary malignant intraocular neoplasms. If the patient survives long enough, many of the untreated metastatic carcinomas ultimately yield to blindness and pain. Factors used to predict the potential for the preservation or recovery of vision in the affected eye or eyes include the number and size of tumors, their locations relative to the optic disc and fovea, the severity of their effects on the retina and other ocular tissues, and their response to treatment. Moreover, the treatment response is also dependent on the site of the primary tumor and its pathological features.

Ocular metastases do not affect overall survival because the eye is not a vital structure. The prognosis for a patient's survival is dependent on the presence and extent of metastatic tumors in vital organs.

Conclusion

As the survival time of breast cancer patients increases, the incidence of ocular metastasis is expected to rise. With the new therapeutic regimes used in the modern treatment of breast cancer, the range of ocular and visual problems that may be observed will undoubtedly increase. Both ophthalmologists and oncologists should be aware of the range of disorders that may be directly or indirectly caused by breast cancer, not only for the palliation of symptoms but also because the first signs of breast cancer may present as eye symptoms in some cases. Early diagnosis may positively affect the long-term prognosis for patients.

Physicians who treat patients with breast cancer should maintain a high degree of suspicion of ocular metastases. Because patients with breast cancer often have prolonged survival after the diagnosis of ocular metastases, early diagnosis and treatment of this lesion is a primary concern to maximize their quality of life [10].

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Management of Malignant Pleural Effusions in Breast Cancer

39

Jelena Grusina Uyumaz, Tugba Cosgun, and Alper Toker

Introduction

Carcinomatous pleurisy often manifests in malignant disease as an indicator of the terminal stage of disease. However, the optimal strategy for palliation of malignant pleural effusions (MPE) is not well understood and partially depends on the nature of the cancer and the performance status of the patients. Some recent studies have investigated the ability of possible markers to predict the fate of pleurodesis and survival in patients with malignant pleural effusion. For example, survivin is a member of the inhibitor of apoptosis family that is related to increased tumor aggressiveness both in tissue and in pleural fluid [1].

Breast carcinoma is one of the most common neoplasms and causes approximately one third of all MPEs [2]. The majority of patients with recurrent MPE die within 6 months [3, 4], whereas patients with pleural effusion due to breast carcinoma have a longer median survival time ranging from 6 to 36 months [5, 6]. A clinical cohort study that included 145 breast carcinoma patients with MPE also showed that the mean survival after the diagnosis of MPE was 6 months; survival was especially shortened in patients with triple-negative breast carcinoma and in those who tested positive for malignant cells in the pleural fluid [7].

Although there are exceptions, such as the studies mentioned above, the long life expectancy has generally led to the development of surgical strategies and palliative strategies for controlling dyspnea during the first intervention in MPE associated with breast cancer [8, 9]. Pleural progression-free survival in breast carcinoma patients is improved if patients receive systemic therapy following initial pleurodesis rather than systemic therapy alone [10].

The ideal treatment is to remove the fluid and prevent re-accumulation. No methods has been shown to be most effective. Various methods, such as thoracentesis, chest tube drainage, permanent catheter placement, talc or other molecule use, and video-assisted thoracoscopic surgery (VATS), have been used to create pleural symphysis. Whole-chest radiotherapy, decortication, and pleurectomy have also been considered in previous years [11].

The outcome of pleurodesis might depend on the tumor type: Bielsa and colleagues [12] demonstrated that pleurodesis outcomes are better for breast carcinoma patients than for lung cancer or mesothelioma patients.

Symptoms

Dyspnea is one of the most widespread symptoms and decreases the quality of life. Medical treatment does not have any effect on dyspnea linked to pleural effusion. Less than 30% of patients with metastatic pleural effusion from breast carcinoma will benefit from hormonal or chemotherapeutic treatment. The remaining patients with long-lasting pleural effusion or who experience incomplete re-expansion due to insufficient thoracentesis may develop a peel and a trapped lung. These patients are often the most difficult to treat.

Treatment with Thoracentesis

Previous studies have shown that the immunophenotype of breast cancer metastases and/or pleural and peritoneal effusions may be different from that of the primary tumor ("receptor conversion"), and thus, there may be a need to

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investigate and biopsy the new metastatic locations, such as pleural effusions [2].

Determination of receptor status in malignant effusion specimens may help optimize patient-tailored hormonal treatment. AR-targeted therapies represent the advent of a new era for solving the problem of malignant pleural effusions in metastatic breast cancer [2].

Patients treated with nonsurgical methods, especially repeated thoracentesis, may live for a considerable length of time, but their quality of life is suboptimal due to recurring effusions. Furthermore, this modality leads to a low percentage of success, with possible complications that may worsen the symptomatology. Repeated thoracentesis controls less than 15% of effusions. In addition to the risk of empyema, loss of function of the lung due to incomplete expansion and the persistence of symptoms may occur.

Treatment with Thin Pleural Catheters

Because the long-term benefit of thoracentesis is low, chronic TIPC use has gained popularity in the past two decades. Van Meter and colleagues [13] analyzed 19 studies with a total of 1370 patients and concluded that TIPC may improve the symptoms of patients with MPE and does not appear to be related to major complications. This method does not require hospitalization and also avoids the pain and complications associated with chemical agents [14]. Spontaneous pleurodesis can occur in up to 50% of patients [15, 16] and is more likely in patients with primary breast or gynecologic tumors [17]. However, in the absence of sufficient data, the longer time for pleurodesis, risk of infection, and potential for nutritional loss that can occur with ongoing drainage reduce the evidence supporting TIPC use. Furthermore, some patients may develop unpleasant feelings due to a distorted body image and the extra responsibility faced by them or their family members. In 2003, Ohm and colleagues [18] performed a study of MPE patients. They divided their patients into two groups and performed VATS and talc pleurodesis on patients with an expanded lung and used TIPC for those with a trapped lung. The TIPC patients experienced a shorter hospital stay. The authors concluded that TIPC is safe and effective and has a role in the treatment of patients with a trapped lung [18].

TIPC patients also had better survival with effusion control at 30 days compared with those who underwent bedside talc pleurodesis (82% vs. 52%, respectively; $p = 0.024$) [19]. Sioris and colleagues [20] recommended the use of an indwelling pleural catheter as a safe alternative for patients with MPE who are unsuitable for talc pleurodesis.

Thomas and colleagues did not observe a difference between indwelling pleural catheter patients and talc pleurodesis patients in terms of improvements in breathlessness and quality of life [21].

The most popular TIPC drainage systems are the PleurX and Jackson Pratt systems. The PleurX (CareFusion Corporation, San Diego, CA, USA) tunneled pleural catheter system was developed to control symptomatic, recurrent MPE, and trapped lung syndrome. The PleurX comprises a fenestrated silicone catheter (15.5 Fr diameter) with a valve mechanism and a polyester cuff. The PleurX shows good results for spontaneous pleurodesis and relieves patients of dyspnea [17]. Another type of TIPC is the Jackson Pratt 10 Fr drain, which is easily and effectively used in breast cancer MPE and shows good results in patients with a trapped lung [22].

Chemical Pleurodesis

The most popular chemical agents for pleurodesis are asbestos-free talc, tetracycline, doxycycline, silver nitrate, iodopovidone, and bleomycin.

Chemical pleurodesis by the instillation of asbestos-free talc is an effective and safe procedure for the palliation of symptoms related to metastatic pleural effusions [23, 24] and is strongly recommended in patients with an expected median survival greater than 6 months [25, 26]. Studies comparing chemicals for use in pleurodesis have been performed for more than two decades. Talc is the most effective and widely used sclerosing agent. However, talc has side effects, including severe and fatal complications. Recent chemotherapy, oxygen supplementation, and peripheral edema are independent prognostic factors for the development of complications [27]. Such patients are recommended to be reserved for TIPC. One of the most interesting studies compared doxycycline pleurodesis versus TIPC; in this study, the initial success rate was 68% with doxycycline but 97% with TIPC [14]. Recurrence rates of 21% and 13% have been reported in doxycycline and TIPC patients, respectively.

Talc poudrage and pleurodesis via chest tube drainage have lower success rates, with risks associated with infection of the pleural cavity. Thus, they should only be used in cases with poor prognosis and for a short period of time.

Large-particle talc, which is available from Bryan Corporation, is reported to cause less deposition in the lung and liver than normal or mixed particle talc [28].

Other sclerosing agents—tetracycline and bleomycin—are available, with different success rates and side effects, such as fever and pleuritic chest pain [29]. Sedrakyan and colleagues [30] analyzed 46 randomized clinical trials and concluded that talc tended to be associated with fewer recurrences compared to those for bleomycin and, with less certainty, for tetracycline. Tetracycline (or doxycycline) was not superior to bleomycin.

Furthermore, Balassoulis and colleagues [31] recommended intrapleural erythromycin as an effective and safe

sclerosing agent for pleurodesis. They observed a complete response rate (no re-accumulation of pleural fluid after 90 days) for erythromycin pleurodesis of 79.4%, but all patients suffered chest pain.

According to Light, the two most promising agents are silver nitrate and iodopovidone.

In a study of outpatient malignant pleural effusion patients, pleural catheter insertion followed by 0.5% silver nitrate pleurodesis showed good results, with a recurrence rate of only 4% after 30 days [32, 33]. Fifty to one hundred milliliters of 2% iodopovidone through a chest tube is recommended, and low re-accumulation rate has been observed [34, 35].

Surgical Methods

Surgical options include medical thoracoscopy, video-assisted thoracoscopic (VATS) pleurodesis, partial and/or total pleurectomy by VATS, additional decortication, extended pleurectomy/decortication, and extrapleural pneumonectomy (EPP). However, no operation has been shown to be beneficial in a prospective randomized controlled clinical trial [36].

In our practice, we often use VATS for the management of MPE, and we have developed an optimal surgical technique to obtain successful results.

The aim of the VATS technique is to differentiate ideal candidates for complete lung expansion and to employ talc pleurodesis. Those patients whose lungs do not have the ability to completely expand can either undergo VATS decortication, if possible, or receive a TIPC.

We perform VATS procedures under general anesthesia by single lumen tube intubation or under sedation. Patients are placed in the lateral decubitus position. Two thoracoscopic ports are opened: one port for the camera and one port for biopsies and instrumentation. We use a 30-degree optical camera to assess the pleura and the lung surface by asking the anesthesiologist to maintain the patient in an apneic state. Before the apneic state is achieved, it is expected that the anesthesiologist will ventilate the patient with 100% FiO_2 for a period of time to permit apnea if the patient is intubated. At least four different biopsy specimens are obtained, including 2 × 2-cm specimens from abnormal areas, and a frozen section examination is performed by collecting the remainder of the specimens for further pathological evaluation. If intraoperative complete lung re-expansion is achieved with contact between the parietal and visceral pleura, talc poudrage is accomplished under direct vision by nebulization into the pleural cavity of 4–6 g of asbestos-free sterilized talc when the lung is deflated. At the end of the procedure, one chest tube is kept in site through the thoracoscopic access ports to drain both the apex and the base of the pleural cavity. If lung re-expansion is not completely achieved or if a partial expansion is achieved in the apex but not in the basal part of the hemithoracic cavity, we consider the following two options: first, performing a VATS decortication, and second, leaving a TIPC. After observing lung re-expansion in a postoperative chest X-ray, we can remove the silicon catheter. We do not recommend prescribing anti-inflammatory medication, which could possibly prevent adhesions.

Another primary advantage of the surgical approach is the possibility of obtaining significant surgical specimens, thereby enabling complete tumor characterization at the final pathologic evaluation with reassessment of estrogen, progesterone, and *c-ErbB2* status [37]. Pleural biopsy performed under optic vision has 100% diagnostic accuracy.

Pleurodesis with VATS has very high efficacy in terms of effusion control if preoperative indications (complete pulmonary expansion) are respected. The advantage of pleurodesis in VATS is the possibility of conducting the procedure in direct view, which permits the distribution of the talc in a uniform manner, even in the most inaccessible areas. Additionally, talc pleurodesis has a high success rate when thoracoscopy is unavailable [30].

This VATS approach has a success rate of approximately 90% with the first attempt. Evacuative thoracentesis or drainage of the pleural cavity and subsequent assessment of pulmonary re-expansion are predictive factors for the success of the procedure [36]. The re-expansion capacity may be observed during surgery by inflating the lung with 30 cm of H_2O. Recurrent pleural effusion with bulky mediastinal lymph node involvement and lymphangitic pulmonary carcinomatosis demonstrated by computerized tomography may indicate unsuccessful surgical performance. The cytologic analysis of pleural effusion almost always depends on the quantity/quality ratio of the material; generally, the obtained effusion is not sufficient to perform immunohistochemical analysis [26].

Moreover, the biological patterns of the tumor in breast carcinoma may be useful for obtaining new, updated information to predict the response to specific drugs. High hormone receptor expression levels (negative in primary breast carcinoma) represent a determining factor in prescribing endocrine agents [37], and the presence of *c-ErbB2* overexpression is a determining factor in prescribing monoclonal antibodies, such as trastuzumab [38]. Completely new information might also be obtained when the diagnosis is performed in a rural area where efficient diagnostic modalities are absent (histological exam lost or not available).

In some series with VATS and chemical pleurodesis, an overall median survival time of 17 months was obtained [39]. These data are more sensitive than the median survival times reported by Fentiman et al. [6] (105 patients) and Raju and Kardinal [5] (122 patients) of 13 and 6 months, respectively. Chi-square test analysis of tumor characteristics did

not show any significant prognostic effect of pleural effusion recurrence. In addition, the survival time was negatively affected by the number of metastatic sites. In patients with a single metastatic site (pleura) at the time of recurrent pleural effusion, the median survival was 20 months, compared with a median survival of 12 months in those with multiple sites of metastatic disease ($p = 0.0003$).

A study that compared tunneled pleural catheters and talc pleurodesis via VATS showed that placement of tunneled pleural catheters was associated with a significantly reduced postprocedure length of hospital stay [40].

However, indwelling pleural catheters placed for drainage offered on an ambulatory basis are an alternative treatment option for these patients. Administration of talc through an indwelling pleural catheter for the treatment of malignant pleural effusion resulted in a significantly higher rate of pleurodesis than an indwelling catheter alone with no adverse effects [41].

Conclusions

The appropriate management plan should be based on patient characteristics, such as the rate of re-accumulation, disease prognosis, and severity of symptoms [36]. Pleurodesis via VATS is a safe and effective procedure for treating pleural effusion that is associated with a low recurrence rate, and this method should be considered the standard treatment for achieving complete lung re-expansion. Pleural biopsy is a determining factor for assessing high hormone receptor expression levels together with the presence of *c-ErbB2* overexpression. In breast carcinoma patients, this information may be useful in predicting the response to specific drugs, such as endocrine agents and trastuzumab. The management of MPE is palliative for patients with terminal-stage disease, and our goal is to choose the most effective and adequate way to help these patients.

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Management of Discrete Pulmonary Nodules

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Introduction

Pulmonary metastases following surgery for breast cancer usually present as multiple lesions and/or pleural effusion or lymphatic carcinomatosis. When chemotherapy fails to show adequate efficacy in a patient with multiple pulmonary lesions that were thought to be metastases, the possibility of changes in the molecular biological properties of the metastatic tumor and the possibility of a (second) primary lung cancer should be considered. The immunohistochemical profiles of cytokeratin such as CK7 and CK20 along with TTF-1 and the breast cancer marker GCDFP-15 are useful in determining the origin of cancer. Solitary pulmonary lesions in breast cancer patients are candidates for transthoracic fine needle aspiration or wedge resection for accurate tissue diagnosis, and treatment should be planned after a final diagnosis is made. Nevertheless, we suggest that patients with primary breast cancer and indeterminate pulmonary nodules or questionable metastases be offered treatment with curative intent.

There is a broad spectrum of thoracic manifestations in patients with breast cancer [1]. The thorax is a common site for metastasis, which can include local or regional recurrence, bone metastases, spinal cord compression, solitary or multiple pulmonary nodules with or without cavitation, an airspace pattern (lepidic), endobronchial metastasis, lymph node metastasis, and pleural or pericardial involvement complicated by their effusions. Treatment-related complications are numerous, and modalities such as chemo- and radiotherapy may adversely affect the cardiopulmonary system, presenting as pneumonitis, cardiotoxicity, and pericardial effusion. Taken together, physicians dealing with this disease should be familiar with pulmonary/thoracic radiology. In contrast to this issue, the American Society of Clinical Oncology (ASCO) does not recommend chest radiographs or CT scans for routine follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination [2].

The topic of this chapter is the isolation of pulmonary nodules from all other thoracic manifestations.

Diagnosis

Breast cancer progresses from local tumor invasion to axillary lymph nodes and then to organs such as the brain, bone, liver, and lungs. Once a breast cancer case presents with a pulmonary mass, it must be evaluated for metastatic disease [3]. We must not forget that most lung metastases are asymptomatic and are found incidentally. Symptoms occur in 15–20% of patients and usually reflect proximity to the central airways; these symptoms include cough, hemoptysis, or dyspnea [4]. A chest CT is the recommended diagnostic tool to evaluate a pulmonary nodule and is best performed within 4 weeks of resection. However, positron emission tomography is helpful to determine if there is evidence of other metastatic disease not detected on physical examination or other imaging [5, 6].

Histological diagnosis is important in disease management because of the possibility of primary lung cancer or a benign, inflammatory, or infectious pulmonary process. Although results vary between series of breast cancer patients with pulmonary nodules, most nodules are metastatic lesions (34.2–75%), 11.5–48% are primary lung cancer, and 13.5–17.7% are benign lesions [7, 8]. There are also many case reports that present examples of the possible combination of two distinct diseases in the same organ, especially in patients in whom the pulmonary nodule increases in size during anticancer therapies [9, 10]. The probable reactivation of tuberculosis should be kept in mind even in people without tuberculosis symptoms and not only from endemic regions

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[11]. Although lymphangitic metastasis was the most frequently observed pulmonary manifestation in a series of patients who died of disseminated breast cancer [12, 13], it is not easy to distinguish a median value of the incidence of pulmonary nodules found in breast cancer patients. This is in contrast to the increasing number of patients with other cancers who undergo routine staging using CT or PET-CT; only a subset of (802/1578) patients were assessed with CT scans in a large series of breast cancer patients [14]. Evangelista showed that the inclusion of PET-CT in the diagnostic algorithm of evaluated patients helped to avoid unnecessary overtreatment in 12 of 29 patients [15].

Hong et al. conducted a meta-analysis to assess the performance of PET/CT for diagnosis of metastases in breast cancer. In this analysis, across 8 studies including 748 patients, the sensitivity and specificity of PET/CT were 0.96 and 0.95, respectively. As a conclusion, across six comparative studies, they emphasized that FDG PET-CT has higher sensitivity for diagnosis of distant metastases in breast cancer patients, comparing to conventional imaging studies [16].

Additional valuable data are sometimes provided during radiotherapy. Simulation CT scans for three-dimensional radiotherapy planning offer clinical information, including the postoperative status of the breast, lungs, and liver [17]. Because simulation CT scans is of poorer image quality than diagnostic scans due to lower resolution, no enhancement, and thicker image slices, and because they are not routinely interpreted by diagnostic radiologists, the incidence of incidental findings in that study is reportedly low; however, they recommend that the suspicious findings be further evaluated [17].

Among breast cancer patients with pulmonary nodules, biopsy was performed in 30 of 54 patients; breast cancer was presumed in 21, but biopsy showed primary lung cancer in 12 [18]. These two groups did not differ in age, stage, breast tumor size, nodal involvement, or estrogen receptor positivity. In conclusion, it was valuable to evaluate patients with one or more pulmonary lesions without evidence of other metastatic diseases. Aggressive workup can allow for the treatment of lung cancer and can impact survival.

In a retrospective study, Matsuura and colleagues evaluated 53 patients who developed pulmonary nodules in the follow-up period after breast cancer surgery and underwent lung surgery or needle biopsy procedure. The diagnoses were breast cancer metastases in 25 (47%) patients, primary lung malignancy in 21 (40%), and benign disease in 7 (13%). They also observed phenotype discordance in six patients (24%) and estrogen or progesterone receptor upregulation in three patients among the pathologically proven metastatic patients. Eventually they emphasized on the value of diagnostic effort in patients who developed lung nodules after breast cancer surgery, in order to define or modify the treatment [19].

Transthoracic fine needle aspiration biopsy is the most frequently used method for histological diagnosis when multiple nodules are present that are not eligible for resection. The metastatic nodules occur via hematogenous tumor spreading and are generally spherical or ovoid, vary in size, are sharply marginated, and are mostly peripherally located [20]. Among CT findings, presence of a solid opacity, well-defined tumor, and absence of an air bronchogram were significantly associated with metastatic breast tumor [21].

Okasaka reported the evaluation of pulmonary nodules that appeared in 48 patients after mastectomy [22]. Differential diagnosis was obtained by morphopathological methods alone in 32 patients and by immunohistochemical and molecular marker examination in the remaining 16. The molecular marker mammaglobin 1 was used for differential diagnosis. The final diagnosis was metastatic breast cancer in 40 patients (83.3%) and primary lung cancer in 8 patients (16.7%).

A total of 1703 patients with primary breast cancer were reviewed to investigate the clinical value of preoperative chest CT in detecting lung and liver metastases [23]. Abnormal CT findings, including suspected metastases and indeterminate nodules in the lung or liver, were found in 266 patients (15.6%). True metastases were found in 26 patients (1.5% of all patients and 9.8% of patients with abnormal CT findings), including 17 in the lungs, 3 in the liver, and 6 in both. The largest group having true metastases comprised 24 patients with stage III disease. The sensitivity, specificity, and positive predictive value of chest CT were 100%, 89.1%, and 11.3%, respectively, for lung metastasis and 100%, 97.6%, and 18.4%, respectively, for liver metastasis. All true metastatic lung lesions were small nodules, ranging from 0.2 to 1.5 cm, that could not be detected on chest X-rays. It was not possible to demonstrate the usefulness of routine preoperative chest CT in detecting asymptomatic liver and lung metastasis in patients with early breast cancer. However, chest CT upstaged 6.0% of stage III patients to stage IV.

Immunohistochemistry staining is performed in nearly all cases to distinguish between primary and metastatic lesions and to compare the hormonal receptor status with the tumor resected from the breast. Thyroid transcription factor-1 (TTF-1) is a sensitive marker for thyroid and pulmonary adenocarcinomas as well as a highly specific method in the differential diagnosis of primary and metastatic lung adenocarcinomas [24].

There are many studies in the literature in which the authors simply resect the pulmonary nodule without conducting a biopsy. Kitada reported 1226 patients who had breast cancer surgery [25]. A total of 49 patients had pulmonary nodules before or after surgery, and 14 of them had video-assisted thoracoscopic surgery to remove this solitary pulmonary nodule for diagnosis. Evaluation of the immunohistochemical cytokeratin profile and the TTF-1 and

GCDFP-15 levels of the lesion were useful when distinguishing between pulmonary cancer and a metastatic pulmonary tumor.

Treatment

In the case of pulmonary metastases in breast cancer patients, resection is advocated if there are no other distant metastases, if the primary tumor is under control, if complete resection can be performed, and if the disease-free interval is longer than 36 months [26]. Estrogen, progesterone, and Her-2 receptor positivity are also good prognostic and predictive factors that enable the continuation of endocrine therapy and/or anti-Her2 therapy after metastasectomy.

Table 40.1 shows the different series of breast cancer patients, indicating the series that are retrospective and those in which complete resection was mostly associated with long-term survival. Staren evaluated 5143 patients with breast cancer [27] and found that 284 patients had metastases, including lung metastasis; 63 (1.2%) had only lung metastasis. Furthermore, 33 patients had resection of the metastatic pulmonary nodule, and 23 patients were given adjuvant chemotherapy. The 5-year survival of the metastasectomy group was 36%, whereas that of the non-resection group was 11%. The Mayo Clinic reported their experience in 13,502 breast cancer patients, of whom 60 (0.4%) were metastatic only to the lungs [28]. Patients with complete resection achieved 42% 5-year survival in contrast to those with incomplete resection, who achieved 36%. The study, however, did not mention the other potential prognostic factors related to prolonged survival. A large series reporting lung metastasectomy in breast cancer patients included 467 patients; complete resection was performed in 84%, and the median survival was 37 months compared with 25 months in incompletely resected patients [29]. Complete resection and a disease-free interval of more than 36 months were the two most significant factors associated with prolonged survival.

Table 40.1 Pulmonary metastasectomy in breast cancer patients

Author	Number of patients	Median survival (months)	5-year overall survival (%)
Mountain, 1978	21	27	14
Mc Cormick, 1978	28	20	15
Lanza, 1992	37	47	49.5
Staren, 1992	33	58 (single lesion)	36
McDonald, 1994	60	42	37.8
Girard, 1994	32	–	–
Friedel, 1994	91	–	27
Livartowski, 1998	40	70	54
Murabito, 2000	62 (28 CR)	79 CR,15.5 IR	80 CR
Friedel, 2002	467	35	35
Ludwig, 2003	21	96.9	53
Planchard, 2004	125	50	45
Tanaka, 2005	39	32	30.8
Rena, 2007	27	–	38
Welter, 2008	47	32	36

CR complete resection, *IR* incomplete resection

A more recent meta-analysis of the prognostic factors for resection of isolated pulmonary metastases in breast cancer patients was conducted in 2015. A total of 1937 patients across 16 studies were evaluated in this analysis. The poor prognostic factors were disease-free interval (≤3 years), incomplete resection of metastases, hormone receptor status (negative), and number of lung metastases (>1). In this study, the five-year overall survival rate was 46% after pulmonary metastasectomy, in light of which surgery of pulmonary metastases was mentioned as a promising treatment for breast cancer patients [30].

In another study that was published in 2017, Song et al. stated that breast cancer patients with solitary lung metastases who underwent lung metastasectomy had a longer progression-free interval THAN patients who did not received metastasectomy. In terms of overall survival, there was no significant difference between these groups of patients. In conclusion, they highlighted surgery for metastasectomy as an independent factor for improved progression-free survival in patients with isolated lung metastases of breast cancer [31].

After complete resection of all visible metastases is achieved (NED: no evidence of disease), there are no prospective data regarding the addition of chemotherapy to improve survival. The goal of systemic therapy should be to fight against micrometastasis. Studies from the MD Anderson Cancer Center that summarize and update the data from the last 30 years note that the addition of newer chemotherapy agents may improve long-term survival after recurrence. Hanrahan showed that patients who receive anthracycline-based chemotherapy at primary diagnosis could benefit from the local treatment of isolated recurrences followed by docetaxel-based chemotherapy [32]. The median follow-up for this docetaxel-based trial ($n = 26$ patients) was 45 months. The early outcomes of this study are promising. The median disease-free survival (DFS) was 44 months, and the 3-year DFS and overall survival (OS) rates were 58% and 87%, respectively.

The major goal of pulmonary resection (metastasectomy) is to differentiate the primary tumor from metastatic disease and to reevaluate the hormonal status and biological changes of breast cancer. Although there are no prospective data, radical resection may lead to long-term survival for selected patients with good prognostic factors.

Algorithm from the Perspective of a Thoracic Surgeon

Approach to a discrete pulmonary nodule in a breast cancer patient.

Breast cancer patient with pulmonary nodule in chest X-ray (CT or PET-CT?)

Extrapulmonary metastatic site?

If yes, go on with medical oncology and follow the nodule after chemotherapeutic response.

If no, define the lesion.

1. One nodule with FDG(+), SUVmax >5 without mediastinal FDG uptake: perform sublobar resection (lobectomy, if primary).
2. One nodule with low FDG (SUVmax <5) without mediastinal FDG uptake: consider Noguchi classification [32]; follow or perform resection.
3. At least two nodules: diagnose with bronchoscopy/transthoracic biopsy/wedge resection.
4. Single nodule with mediastinal enlarged lymph nodes (FDG+): perform endobronchial ultrasonography (EBUS) or mediastinoscopy.
5. Cavitary nodule in a smoker: perform sublobar resection (lobectomy, if primary).
6. Calcified, popcorn-shaped single lesion: radiologic follow-up.
7. Nodule increasing in size during chemotherapy: perform sublobar resection (lobectomy, if primary).
8. Nodule with pleural effusion: perform VATS-wedge resection/biopsy with/without talc pleurodesis.

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Management of Isolated Liver Metastasis

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Abdullah Igci and Enver Özkurt

Management of Isolated Liver Metastases

A solitary first metastasis of the liver in breast cancer is an uncommon presentation. Nearly half of all patients with metastatic breast cancer develop liver metastases [1–3], but a minority of patients present with metastatic breast cancer limited to the liver (5–12%) [3–6]. Among patients who have died of breast cancer, hepatic metastases are found in 55–75% of autopsies [7]. Overall, the 5-year survival of patients with stage IV breast cancer is currently 23% [8] and drops to 8.5% for those patients with liver metastases [4].

Hepatic metastases generally occur at later stages of disseminated disease and carry a very poor prognosis, with a median survival of 6 months [9]. However, the median survival of patients with isolated liver metastases is approximately 1 year, if untreated [10]. Even with systemic chemotherapy, the median survival time is approximately 19 months for patients with metastatic breast cancer to the liver only or with limited disease elsewhere [11].

Published studies have evaluated the safety and benefit of hepatic resection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or intra-arterial chemotherapy, stereotactic body radiation therapy (SBRT), and interstitial laser therapy (ILT) to treat liver metastases from breast cancer. Because no randomized controlled trials have been performed, the comparative efficacies of these approaches remain controversial. Moreover, identifying appropriate patients for treatment remains a challenge [3, 12, 13], and the carefully selected patients in published series may represent good prognosis subgroups independent of the therapeutic approach.

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Patient Selection Criteria

Palliative liver-directed therapy may be beneficial if the hepatic disease adversely affects the patient's quality of life. Most oncologists consider this a palliative situation in which surgical treatment is reserved for symptomatic cases only. The risks and benefits of liver-directed therapies should be compared with systemic treatment options [5]. However, various retrospective studies have noted a survival benefit for aggressive local treatment of the primary tumor in select patients even in the presence of distant metastases [14–16].

In particular, candidates should have limited metastatic disease in the liver, controlled primary disease, younger age, longer disease-free intervals, and higher performance status [3, 5, 17–20]. The presence of extrahepatic metastatic or residual primary breast cancer is commonly [21, 22], but not always [23, 24], considered a contraindication to liver-directed therapy.

To aid in risk assessment and decision-making, the pre-procedure work-up should define the extent of disease and its responsiveness to systemic therapy. For this critical decision-making, a pathologic examination and some imaging modalities should be performed. A computed tomography (CT) scan of the abdomen and pelvis should be used to evaluate the number and location of liver metastases to facilitate procedure planning and to rule out other intra-abdominal diseases. Further, CT imaging of the chest should be performed to rule out pulmonary and mediastinal disease. Additionally, a bone scan should be undertaken to rule out bone metastases, and a positron emission tomography (PET) scan may be useful to identify extrahepatic disease.

Surgical Treatment Options

Liver resection for metastases that derive from non-portal vein-associated organs is still controversial even though it is widely accepted in colorectal cancer and neuroendocrine tumors. In those cases, liver metastases may be regarded as a

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sign of systemic tumor spread that is only amenable to systemic chemotherapy [25]. Increasing evidence suggests that patients with breast cancer liver metastases (BCLMs) may receive survival benefits from liver metastasectomy associated with systemic treatment [26]. Moreover, the 5-year survival rate is comparable to that after colorectal cancer liver metastasis resection [27].

Most published studies are designed as retrospective single-arm and single-center analyses. The limited number of eligible cases in these centers leads to an average caseload of two to three patients per year [8]. Independent prognostic factors that are predictive of survival are still not clearly defined. Because only patients with a limited number of liver lesions seem to benefit from surgical therapy, liver resection is rarely performed [8]. If the patients' physical performance is good enough for surgery, perioperative morbidity and mortality rates are low [21, 28–30].

Candidates for Surgical Treatment

Patient selection and operative criteria for hepatic resection remain controversial. The important criteria seem to be that patients have fewer than four hepatic metastases, no extrahepatic disease, and demonstrated disease regression or stability with systemic therapy before resection [31]. At a minimum, a patient should have a normal performance status and normal hepatic function tests [32]. Pocard and Selzner indicated that the size and number of hepatic metastases were an important factor [17]. Patients in whom hepatic metastases were found more than 1 year after resection of the primary cancer had significantly better outcomes than those with early (<1 year after resection) metastatic disease. Younger patients with a limited number of tumor locations seem to be good candidates for this option, and hepatic metastasectomy may lead to prolonged survival [33].

Increasing evidence in the literature also suggests that patients with oligometastases (metastases limited to one organ with a small number of lesions) may be good candidates for surgical therapy. Furthermore, the pattern of oligometastases may result from a distinct biological behavior with a specific gene expression and tumor metabolism [34].

Chua et al. indicated that the response to chemotherapy might predict a better outcome for patients who undergo liver resection for hepatic metastases [8]. To select patients who will benefit from surgical treatment, a better understanding of the individual biological behavior of BCLM is warranted. This study should include molecular markers, metabolic activity, and the response to chemotherapy [35, 36].

Presurgical Evaluation

Before hepatic resection, patients should be examined to rule out extrahepatic, intra-abdominal disease. Metachronous metastases must be regarded as tumor recurrence. There is a broad variety of secondary tumor growth in distant organ systems, most frequently in the bone, liver, lungs, and brain. Among these different metastatic locations, the liver is the second most frequent site of metachronous metastases (40–50%) [33]. Intraoperative ultrasound (US) may be beneficial for identifying additional liver lesions and determining the exact location of the lesions concurrently with their proximity to venous structures.

Hepatic resection candidates must have enough liver remnant after resection of the lesion(s). Because the function and architecture of the liver are integrated, adequate liver function can be maintained if there is a critical volume of intact liver and a contiguous bile duct system (20% of a normal liver, 40% of the liver if steatosis is present). If a small liver remnant is anticipated, the patient may benefit from preoperative portal vein embolization of the lobe to be resected. This embolization causes hypertrophy of the opposite lobe that will be the remnant, thereby decreasing the risk of postoperative hepatic insufficiency [37].

In the absence of prospective data, the role and effectiveness of hepatic metastasectomy in BCLM have not been defined. In terms of safety, mortality was 0% in the large majority of studies [18, 21, 26, 29–31, 38–42], and morbidity ranged between 0% [43] and 35.9% [44]. Regarding survival, the median survival after hepatectomy ranged between 27 and 63 months (Table 41.1) [43]. Other authors have also noted that repeat hepatectomy for BCLM is associated with improved survival [31]. Large disease-free intervals between primary breast cancer surgery and liver metastases diagnosis [18, 20], positive hormone receptor status [38], response to chemotherapy, and R0 resection [29] are all favorable prognostic factors in patients with BCLM [49, 50]. The variables associated with poor outcomes after liver resection for BCLM include the presence of the extrahepatic disease at the

Table 41.1 The 5-year survival rates after curative liver resection

Reference	Number of patients	5-year survival rate (%)	Median survival (months)
Raab et al. [43]	34	18	27
Carlini et al. [45]	17	46	53
Arena and Ferrero [46]	17	41	–
Vlastos et al. [21]	31	61	63
Sakamoto et al. [28]	34	21	36
Yedibela et al. [47]	17	50	62
Adam et al. [31]	85	43	43
Elias and Di Pietroantonio [48]	54	34	34
Thelen et al. [29]	39	61	73
Hoffmann et al. [49]	41	48	58
Dittmar et al. [41]	21	38	52

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time of resection [28], multiple liver metastases, and estrogen receptor (ER)-negative status [30, 51].

Vlastos et al. studied the long-term survival of 31 patients with breast cancer with metastases limited to the liver who underwent hepatic resection at the MD Anderson Cancer Center [21]. The hepatic metastases had developed after a median of 22 months from the initial diagnosis. Solitary hepatic metastases were found in 20 patients, and multiple hepatic metastases were found in 11 patients. Major hepatic resections (3 or more segments resected) were performed in 14 patients, and minor resections (fewer than 3 segments resected) with or without radiofrequency ablation were performed in 17 patients. The median size of the largest hepatic metastasis was 2.9 cm. A total of 87% of the patients received either pre- or postoperative systemic therapy, with a median survival of 63 months. The overall 2- and 5-year survival rates were 86% and 61%, respectively, while the 2- and 5-year disease-free survival rates were 39% and 31%, respectively. Vlastos et al. were unable to identify any treatment- or patient-specific variables associated with the survival rates. They concluded that in select patients with hepatic metastases from breast cancer, an aggressive surgical approach was associated with favorable long-term survival and that hepatic resection should be considered as a component of the multimodality treatment of breast cancer in these patients.

In a prospective study of 50 patients with hepatic metastases of breast cancer, 34 patients underwent laparotomy with the intention of undergoing a curative liver resection [41]. Liver resection was performed in 34 patients. Resection margins were clear in 21 cases (R0). Nine patients with clear resection margins lived for more than 60 months after liver resection. The observed 5-year survival rate was 21% for all 50 patients, 28% for resected patients, and 38% after R0 resection. On univariate analysis of their results, the survival rates of the resected patients were significantly influenced by R classification, age, extrahepatic tumor at the time of liver resection, size of metastases, and HER2 expression of liver metastases. Multivariate analysis revealed an absence of HER2 expression, the presence of extrahepatic tumor, and a patient's age ≥50 years as independent factors of poor prognosis. They concluded that breast cancer patients who were younger than 50 years with technically resectable hepatic metastases, minimal extrahepatic tumor, and positive HER2 expression appear to be suitable candidates for liver resection with curative intent, and an aggressive multidisciplinary management of those patients, including surgical treatment, may improve long-term survival.

In another single-center study from Bucharest, Romania [52], 52 female patients underwent surgery for BCLM between 2002 and 2013. Only patients with liver resections ($n = 43$) were included in their analysis. The median survival of the 43 patients with liver resection was 32.2 months. The factors that were significantly associated with overall post-hepatectomy survival were estrogen/progesterone receptor (ER/PR) status ($p = 0.002$), node involvement of the primary tumor ($p = 0.049$), and the size ($p = 0.005$) and number ($p = 0.006$) of the metastatic lesions. The 1-, 3-, and 5-year survival rates after curative liver resection were 93.02%, 74.42%, and 58.14%, respectively. They emphasized that BCLM resection is a safe procedure and offers a survival benefit, especially in patients with reduced liver metastatic burden (solitary metastases, diameter of the metastases <5 cm) and positive ER/PR status.

Polistina et al. retrospectively reviewed 26 women with isolated BCLM and without any sign of disease progression after a cycle of chemotherapy [53]. Women were treated with hepatic resection for unilobar disease or surgical "open" RFA for bilobar disease. The overall survival from the breast cancer diagnosis was 47.69 ± 22.25 months (range 33–84, median 45.5 months); these rates were 52.25 ± 14.57 months (range 33–84, median 48.5 months) for the hepatic resection patients and 43.79 ± 27.14 months (range 9–101, median 39 months) for the RFA patients. Overall survival from the BCLM treatment was 21.12 ± 12.78 months (range 9–64, median 15.5 months); specifically, it was 29.42 ± 14.53 months (range 12–64, median 29.5 months) for the resected patients and 14 ± 4.45 months (range 9–24, median 13.5 months) for patients treated with RFA, with a strongly significant survival difference for surgically treated patients ($p = 0.001$). The overall disease-free survival from BCLM was 15.96 ± 13.16 months (range 3–64, median 12 months), disease-free survival for resected patients was 23.22 ± 16.2 months (range 8–64, median 18.5 months), and for patients treated by RFA was 9.64 ± 4.22 months (range 3–18, median 9 months). The overall 1-, 2-, and 5-year (actuarial) survival rates were, respectively, 80.7, 57, and 31%. When calculated for the two groups, these rates were, respectively, 100, 66.6, and 34% (actuarial) for the resected group patients and 64.2, 21.4, and 11.5% (actuarial) for the RFA patients. These data indicate that aggressive treatment of isolated BCLMs may improve survival for these patients.

Finally, in a systemic review about hepatic resection for metastatic breast cancer, Terence et al. searched the MEDLINE and PubMed databases (January 2000–January 2011) to identify studies that reported the outcomes of hepatectomy for BCLM [8]. Nineteen studies were examined, comprising 553 patients. Hepatectomy for BCLM was performed at a rate of 1.8 (range, 0.7–7.7) cases per year in the reported series. The median time to liver metastases occurred at a median of 40 (range, 23–77) months. The median mortality and complication rates were 0% (range, 0–6%) and 21% (range, 0–44%), respectively. The median overall survival was 40 (range, 15–74) months, and the median 5-year survival rate was 40% (range, 21–80%). Potential prognostic factors associated with a poorer overall survival include a positive liver surgical margin and hormone refractory dis-

ease. Consequently, the authors indicated that, for selected patients with isolated liver metastases and in those with well-controlled minimal extrahepatic disease, hepatectomy has a superior 5-year survival. Thus, to evaluate its efficacy and control for selection bias, a randomized trial of standard chemotherapy with or without hepatectomy for BCLM is warranted.

When we reviewed all of the studies of the surgical treatment of isolated BCLM, we confirmed that hepatic resection has not been compared in a randomized trial with systemic chemotherapy or with nonsurgical, liver-directed options (Table 41.1) [21, 28, 29, 31, 41, 43, 45–49]. This lack of comparison could be due to a low number of cases per year. Nevertheless, multicenter prospective randomized studies are needed to specify the exact efficacy of surgery among this specific group of patients.

Nonsurgical Treatment Options

BCLM usually indicates the presence of hematogenous disseminated cancer with a very poor prognosis [54]. Apart from hepatic resections, minimally invasive therapy methods, such as RFA, TACE, SBRT, and ILT, have been used for effective and relatively simple treatment of BCLM for patients who are not good candidates for resection or do not desire surgical procedures [55–60].

Radiofrequency Ablation Therapy

Radiofrequency ablation uses a high-frequency electrical current (375–480 kHz) that is applied through one or more needle electrodes that are electrically insulated along all but the distal 1–3 cm of the shaft. The radiofrequency current produces ionic agitation that leads to heat production. Heating results in cellular destruction and protein denaturation at temperatures above 50 °C when applied for 4–6 min and within a few seconds at temperatures above 75 °C [61]. Temperatures higher than 100 °C may result in tissue water boiling and gas formation within the target. Although these bubbles allow visualization using B-mode diagnostic US imaging, it may retard the transmission of the radiofrequency current. Most work has been performed using simple monopolar radiofrequency probes that consist of an electric generator, a needle electrode(s), and a grounding pad attached to the skin of the patient.

Surgical resection with or without chemotherapy is considered the best treatment option in selected cases with solitary BCLM and has a low surgical risk. Solitary liver metastases in breast cancer patients are rare, occurring in only approximately 5% of all cases. Most patients are unsuitable for surgery because of their poor general condition or the stage of disease. RFA is an alternative to resection and the preferred adjunctive treatment (instead of surgery) to systemic chemotherapy for hepatic metastases and in patients with hepatic disease after chemotherapy [62]. Many patients are not eligible for surgery, and a review of the major surgical studies shows that RFA of hepatic metastases has a lower mortality and periprocedural complication rate compared with surgery. Additionally, RFA offers clear advantages with regard to the length of hospital stay and costs compared with surgery. However, due to the poor local effectiveness of RFA in treating metastases larger than 3 cm in diameter, surgery remains better for larger lesions [63].

RFA is a relatively simple technique that constitutes an effective local treatment for hepatic metastases, with minimal invasiveness and few adverse events [62]. Hepatic RFA has been primarily used to treat hepatocellular carcinoma and metastases from colorectal cancer, but a small number of reports also concern metastases from the breast, stomach, kidney, and lung carcinoma and from cholangiocarcinoma and melanoma [64].

Veltri et al. analyzed 45 patients (mean age 55 years) with 87 metastases (mean size 23 mm), examining adverse events, complete ablation at the initial follow-up assessment and during the subsequent follow-up (mean 30 months), time to progression, and survival [63]. They investigated the correlation between local effectiveness and metastasis size. They also analyzed possible predictors of 3-year survival, including the local effectiveness of RFA (complete ablation maintained at 1 year versus treatment failure). Nine adverse events occurred in their series (two major complications, 2.3%). Complete ablation at initial follow-up was obtained in 90% of patients; in 19.7%, the complete ablation relapsed, with a time to progression of 8 months. The difference between the mean diameter of maintained complete ablation (22 mm) and that of the treatment failures (30 mm) was highly significant ($p = 0.0005$), as was the 30 mm threshold ($p = 0.0062$). The overall survival rates at years 1, 2, and 3 were 90, 58, and 44%. In the univariate analysis, the local effectiveness of RFA did not reach significance, so the authors concluded that RFA of hepatic metastases from breast cancer has high local effectiveness in tumors up to 30 mm but that it is not relevant in determining survival.

In another study from Italy [65] that aimed to evaluate the effectiveness of RFA of liver metastases from breast cancer and its impact on survival, 13 female patients (age range 36–82 years; median 54.5 years) underwent RFA for the treatment of 21 liver metastases from breast cancer. The procedures were performed under ultrasound guidance using an RF 2000 or RF 3000 generator system and Le Veen monopolar needle electrodes. Follow-up was performed by CT after 1, 3, 6, and 12 months. The technical success was 100%. No major or minor complications occurred at the end of the procedure. In their series, 7/21 lesions in 7/13 patients increased

in size at 7, 18, 19, and 38 months. This increase resulted in a mean disease-free interval of 16.6 months. The mean overall survival after RFA was 10.9 months. The authors noted that RFA appears to be a useful adjunct to systemic chemotherapy and/or hormone therapy in the locoregional treatment of hepatic metastases from breast cancer. RFA may also be a less invasive alternative to surgery in the locoregional treatment of liver metastases from breast cancer.

After a median follow-up of 16 months, 64% of patients were alive in a group of 14 patients with 16 tumors who were treated with RFA [66]. In a larger case series of 24 breast cancer patients with 64 liver metastases treated with RFA and followed for a median of 19 months, 58% developed new metastases, the majority of which occurred in the liver (71%) [56]. However, most patients with disease limited to the liver were disease-free at the last follow-up.

Sites that are treated with RFA frequently cavitate after the procedure, forming a distinctive scar band. The risk of complications increases with proximity to the porta hepatis. Hepatitis, infection, and injury to larger bile ducts and nearby bowels rarely occur. Patients with preexisting liver damage, such as cirrhosis, and those with larger tumors are more likely to experience complications [67]. Although it is uncommon, needle track seeding has been reported [68]. Aside from the risks mentioned above, RFA can be performed as an outpatient procedure.

In most reported cases for metastatic breast cancer, RFA was used in combination with systemic chemotherapy, and very few side effects (mild right upper quadrant discomfort and asymptomatic pleural effusion) were noted; however, none required specific treatment [24, 66]. RFA has also been combined with surgical resection [21].

Even in light of the lack of correlation between local effectiveness and survival, hepatic RFA should not be used as the only treatment for metastatic breast cancer. To produce a positive effect on medium-term survival, a systemic therapeutic approach is required. Nonetheless, RFA may be proposed as an alternative to surgery in the context of a multimodal strategy because it is safe and effective in achieving local control of limited disease, especially when the burden of systemic therapy needs to be decreased, in part to improve the quality of life of the patient. Based on these data and the experience with other malignancies, RFA for metastatic breast cancer limited to the liver may be beneficial for select patients.

Transarterial Chemoembolization and Intra-arterial Chemotherapy

TACE is a local, catheter-based, minimally invasive therapeutic option for unresectable liver tumors and is defined as the selective administration of chemotherapy, usually in combination with embolization of the vascular supply of the tumor [69]. In contrast with the normal liver parenchyma, which is primarily fed by the portal vein, tumors in the liver are supplied by the hepatic artery. TACE takes advantage of this blood supply pattern by instilling cytotoxic agents mixed with iodized oil into the hepatic artery feeding the tumor and then embolizing this vessel (often with gelatin sponge particles) to cut off the tumor blood supply [70].

The technical success of TACE is demonstrated by the presence of hyper-attenuating iodized oil within the tumor on unenhanced CT [71]. Because of the size of the liver, the tumor may not change after liver-directed therapy [72]; thus, the European Association for the Study of the Liver (EASL) has been proposed as an alternative to the Response Evaluation Criteria in Solid Tumors (RECIST). A surrogate end point for response is the apparent diffusion coefficient (ADC), which measures the mobility of water in tissues: viable tumor cells restrict the mobility of water, while necrotic tumor cells allow increased diffusion [71]. In one study of TACE for patients with metastatic breast cancer (n = 14, prospective chart review), no tumors met the RECIST criteria for complete response, but the ADC increased by a mean of 27% after treatment [71].

Indications for TACE

Indications for the TACE treatment of liver metastases in patients with breast cancer were primarily palliative or symptomatic. During the course of treatment in some patients, the indication changed to neoadjuvant. Palliative chemoembolization was defined as therapy for asymptomatic patients intended mainly to prolong survival and to preserve and improve the quality of life without curing the disease. Symptomatic treatment was defined as a therapy intended to alleviate or decrease tumor-related symptoms (e.g., pain or bulk-related symptoms). Neoadjuvant TACE was defined as a clinical scenario in which TACE resulted in a relevant downsizing of the size and number of metastases, resulting in a situation where the criteria for local thermal ablation via laser-induced thermotherapy (LITT) were met. These criteria were defined as ≤5 metastases and ≤5 cm in diameter. Patients who met such inclusion criteria for LITT treatment before chemoembolization also received chemoembolization before LITT to decrease the tumor activity and to decrease tumor vascularity (based on findings of contrast-enhanced magnetic resonance imaging [MRI] performed at first presentation) to maximize the ablative effect of the LITT on the tumor [73].

Contraindications for TACE

Contraindications for treatment with TACE were poor performance status (Karnofsky status, ≤70%), nutritional impairment, the presence of marked ascites, high serum total bilirubin level [>3 mg/dL (51.3 μmol/L)], poor hepatic

synthesis [serum albumin level < 2.0 mg/dL (20 g/L)], and renal failure [serum creatinine level > 2 mg/dL (176.8 μmol/L)]. Partial or complete thrombosis of the main portal vein was a further exclusion criterion for the procedure, as were cardiovascular or respiratory failures. The tumor load of the liver was restricted to not more than 70% of the total liver volume [73].

A chart review of eight patients treated with TACE demonstrated a median overall survival of 6 months, with no patient surviving longer than 14 months [72]. A study of 14 patients with 27 lesions using MRI showed a median survival of 25 months and a 35% overall survival at 3 years [71].

Li et al. [74] compared the results of TACE (n = 28) and systemic chemotherapy (n = 20) and concluded that there was a significant difference between the two groups in terms of response rates and survival rates. The 1-, 2-, and 3-year survival rates for the TACE group were 63.04, 30.35, and 13.01%, whereas those for the systemic chemotherapy group were 33.88, 11.29, and 0%.

In another study, 208 patients (mean age 56.4 years, range 29–81) with unresectable hepatic metastases from breast cancer were repeatedly treated with TACE at 4-week intervals [73]. In total, 1068 chemoembolizations were performed with lipiodol and starch microspheres. Tumor response was evaluated by MRI according to the RECIST criteria. For all protocols, local tumor control was defined as a partial response in 13% (27/208), stable disease in 50.5% (105/208), and progressive disease 3 in 6.5% (76/208) of patients. The 1-, 2-, and 3-year survival rates after TACE were 69%, 40%, and 33%, respectively. The median and mean survival times from the start of TACE were 18.5 and 30.7 months, respectively. Treatment with mitomycin-C only showed median and mean survival times of 13.3 and 24 months, respectively; with gemcitabine only, they were 11 and 22.3 months, and with a combination of mitomycin-C and gemcitabine, they increased to 24.8 and 35.5 months, respectively. These authors emphasized that TACE is an optional therapy for the treatment of liver metastases in breast cancer patients with better results from the combined chemotherapy protocol.

An open-label, prospective nonrandomized single-center phase II study evaluated the efficacy and tolerability of transarterial chemoembolization with gemcitabine in patients with inoperable BCLM [75]. Forty-three patients were enrolled. Tumor response was evaluated by MRI and CT imaging. All patients tolerated the treatment well, with no dose-limiting toxicities. Imaging follow-up according to the RECIST criteria revealed a partial response in 3 patients, stable disease in 16 patients, and progression in 22 patients. The progression-free survival was 3.3 months. A significant correlation existed only with vascularization: strongly vascularized tumors show a significantly worse response. Patients with complete or partial response and the main fraction of the stable disease group showed only moderate vascularization in the MRI and angiography. The resulting estimate of the total survival rate amounts to a median of 10.2 months. The authors concluded that transarterial chemoembolization with gemcitabine is well tolerated and provides an alternative treatment method for patients with liver metastases of breast cancer.

Overall treatment efficacy may be improved by combining TACE with other localized treatments, such as RFA [76] and SBRT. Once again, it is difficult to establish a survival benefit for TACE in the absence of randomized, controlled trials.

Stereotactic Body Radiation Therapy

SBRT is similar to central nervous system stereotactic radiosurgery, except that it addresses tumors outside of the central nervous system. A stereotactic radiation treatment for the body means that a specially designed coordinate system is used for the exact localization of the tumors in the body to treat it with limited but highly precise treatment fields. SBRT involves the delivery of a single high-dose radiation treatment or a few fractionated radiation treatments (usually up to five treatments). A highly potent biological dose of radiation is delivered to the tumor, improving the cure rates for the tumor, in a manner that was not previously achievable by standard conventional radiation therapy.

SBRT for liver lesions must be performed cautiously, given the challenges of the low toxicity tolerance of the neighboring liver tissue and organ motion. Because SBRT relies on imaging to precisely define the target lesion or lesions to accommodate physiologic motion, candidates for this approach should have tumors with well-delineated borders and must also be willing and able to have fiducials placed. The primary size limitation for SBRT is the size of the remaining liver after treatment. This critical liver volume is approximately one-third of the liver (approximately 500–700 cm^3) [77, 78], and damaging more than this amount may cause liver failure [79]. Early CT follow-up to assess the response after SBRT can be hindered by a zone of hypodensity corresponding to the normal tissue volume that received approximately 30 Gy [77, 80].

Data for the SBRT of breast cancer metastatic to the liver are limited. However, several prospective trials of SBRT have included a mix of primary tumor types, including metastatic breast cancer. After retrospective results showed promise for SBRT [79, 81], 37 patients with 60 lesions (4 primary liver tumors and 56 metastatic tumors, 14 of which were from breast cancer) were prospectively treated with a single fraction of SBRT (dose escalated from 14 to 25 Gy) [82]. No major complications were reported, and the actuarial freedom from local failure rate at 18 months was 67%, with failures mainly occurring in patients who were treated with

lower doses. However, an updated report with long-term follow-up showed high rates of recurrence [83].

A higher dose (approximately 30 Gy in 3 fractions) was used in a series of 23 patients who received SBRT for liver metastases, 6 (26%) of which were metastatic breast cancer, and this dose achieved actuarial local control rates at 1 and 2 years of 76% and 61%, respectively [84]. Although there was one case of self-limited grade 2 hepatitis at 6 weeks, no patient experienced a grade 3 or higher toxicity.

A prospective SBRT study of 69 patients (16 [23%] with metastatic breast cancer) with a total of 174 metastases in the liver achieved a local control rate of 57% at 20 months and a median survival of 14.5 months [85]. Subsequent subset analysis suggested that breast cancer lesions had better survival and control compared with metastases from other primary sites: 2- and 4-year survival rates were 72% and 64%, respectively, in patients with breast cancer compared with 38% and 18%, respectively, for other primary sites [85]. With the high radiation doses, SBRT may offer a benefit to selected patients.

Early results from a phase II trial for SBRT of one to three metastases in the liver have been reported by Scorsetti et al. [86]. A total of 61 patients (76 lesions) were treated in 3 fractions of up to 75 Gy using volumetric modulated arc therapy by RapidArc (Varian, Palo Alto, CA). After a median of 12 months, the in-field local control rate was 94%, the median overall survival was 19 months, and the actuarial survival at 12 months was 83.5%. No acute toxicity higher than G3 (one patient) and no radiation-induced liver disease were observed. The authors noted that SBRT for unresectable liver metastases can be considered an effective, safe, and noninvasive therapeutic option, with excellent rates of local control and low treatment-related toxicity.

A randomized study comparing the major nonsurgical ablative techniques, namely, SBRT and RFA, is still lacking. However, outcomes in terms of local tumor recurrence rates from recent published trials compare very favorably with RFA [87]. A prospective comparison of RFA versus SBRT is being addressed by a currently ongoing trial (Radiofrequency Ablation Versus Stereotactic Radiotherapy Trial) [88].

Interstitial Laser Therapy

Localized tumor destruction can also be achieved through hyperthermic coagulative necrosis caused by laser light delivered through quartz-diffusing laser fibers that are placed directly in the tumor [57]. ILT has been used to treat tumors up to 5 cm and can be performed through a variety of modalities: percutaneously with local anesthesia in the outpatient setting, laparoscopically, or intraoperatively [57]. Accurate positioning of the laser can be ensured using real-time imaging; MRI is preferred over CT and ultrasonography due to the heat sensitivity of the MRI sequence and its ability to demonstrate the degree of necrosis by rapidly depicting temperature changes. Monitoring with MRI also minimizes radiation exposure, thereby increasing safety [57].

Previous studies have already focused on ablative methods such as ILT and their survival data, particularly for hepatic metastases from colorectal cancer [89, 90]. However, no studies have addressed patients with other non-colorectal primary tumors; only a few briefly focused on breast cancer [57, 91].

The largest published study with ILT for metastatic breast cancer was published by Mack et al. and included 232 patients with 578 liver metastases from breast cancer. The mean survival rate for all treated patients, with calculation started on the date of diagnosis of the metastases that would be treated with ILT, was 4.9 years (95% confidence interval, 4.3, 5.4). The median survival was 4.3 years, with 1-, 2-, 3-, and 5-year survivals of 96%, 80%, 63%, and 41%, respectively. The mean survival after the first ILT treatment was 4.2 years (95% confidence interval, 3.6, 4.8) [57]. Although ILT may be promising, data are limited for BCLM.

Vogl et al. designed a study that evaluated prognostic factors for long-term survival and progression-free survival after the treatment of non-colorectal cancer liver metastases through MR-guided ILT [92]. They included 401 patients (mean age, 57.3 years) with liver metastases from different primary tumors who were treated with ILT. The median survival was 37.6 months starting from the date of ILT. The 1-, 2-, 3-, 4-, and 5-year survival rates were 86.5%, 67.2%, 51.9%, 39.9%, and 33.4%, respectively. The median progression-free survival was 12.2 months. The 1-, 2-, 3-, 4-, and 5-year progression-free survival rates were 50.6%, 33.8%, 26%, 20.4%, and 17%, respectively. The initial number of metastases, the volumes of metastases, and the quotient of the volumes of metastases and necroses influenced the long-term and progression-free survival. The authors stated that ILT shows good results in long-term survival and progression-free survival. The initial number of metastases and their volume are the most important prognostic factors. The status of the lymph nodes, the existence of other extrahepatic metastases, the location of the primary tumor, and different neoadjuvant therapies have no prognostic value.

Minimally invasive ablation treatments such as ILT have limits. For example, numerous hepatic lesions with excessively large dimensions make it impossible to induce sufficient necrotic areas. For these cases, TACE is the most common treatment with good results. In one study, repeated TACE in 161 patients with liver metastases resulted in a reduction of approximately 27% in the tumor size [93]. Based on those insights, neoadjuvant TACE is a budding possibility for effective downsizing and reduction of the number of metastases, thus making the patients eligible for ILT [94].

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Bone-Directed Therapy and Breast Cancer: Bisphosphonates, Monoclonal Antibodies, and Radionuclides

42

Bulent Erdogan and Irfan Cicin

Introduction

The bone is the most common site of breast cancer metastasis, and up to two-thirds of patients who die of breast cancer have bone metastases [1]. Breast cancer patients with only bone metastases have a good prognosis relative to visceral organ metastases [1]. However, bone metastasis seriously impairs the quality of life because patients with bone metastases subsequently develop complications related to the bone metastases and generally need medical and surgical intervention. These skeletal-related complications, also called skeletal-related events (SREs), include pain, pathologic fractures, spinal cord, and other nerve compression syndromes and life-threatening hypercalcemia, and they are sources of devastating morbidity.

All metastases develop in a stepwise fashion. First, the proliferation and invasion of cancer cells occur at the breast. Then, cancer cells migrate and attach to the bone. Following attachment, cancer cells colonize the bone and cause destruction. All of these steps are very complicated and not yet completely understood. However, we know that epithelial cell adhesion molecules, matrix metalloproteinases (MMPs), integrins, chemokines, and several growth factors play crucial roles in this complicated process. More than 100 years ago, Paget [2] proposed that cancer cells metastasize to organs in which the microenvironment is appropriate for their survival. This theory is called the seed-and-soil hypothesis and still remains valid. Bone is a metabolically active tissue. Therefore, it has a huge source of growth factors, cell adhesion molecules, and cytokines that make it fertile soil for the survival of metastasized breast cancer cells.

Normal Bone Physiology

The bones give shape and support to the body and protect vital organs from external damage. Bone is essentially composed of collagen that is mineralized with hydroxyapatite crystals. To protect its strength and renew minor damage that occurs throughout life, bone constantly undergoes remodeling. Under normal conditions, osteoclast-mediated bone resorption and osteoblast-mediated bone formation continue in equilibrium.

The precursors of osteoblasts are multipotent mesenchymal stem cells. Under the influence of growth factors, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and bone morphogenetic proteins (BMPs), mesenchymal stem cells proliferate and differentiate to form osteoblasts. In addition to new bone formation, they also control osteoclast formation by expressing receptor activator for nuclear factor κB ligand (RANKL) and producing osteoprotegerin (OPG). Osteoclastogenesis occurs under the influence of RANKL, which is produced by osteoblasts and stromal cells, and macrophage colony-stimulating factor (M-CSF). These two molecules are necessary for the development and survival of osteoclasts. The binding of RANKL to the RANK receptor, which is found on the surface of mononuclear precursors of the monocyte/macrophage lineage, in the presence of M-CSF promotes the fusion of mononuclear precursors to form osteoclasts [3]. OPG, a decoy receptor for RANKL, inhibits osteoclast differentiation by competitively binding to RANKL [4]. The balance between RANKL and OPG determines osteoclastic activity and the extent of bone resorption. Parathyroid hormone, parathyroid hormone-related peptide (PTHrP), prostaglandin E2 (PGE2) through the receptor EP4, interleukin 6 (IL-6), and IL-11 also stimulate osteoclast

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production [5–7]. Activated osteoclasts adhere to the bone and degrade bone matrix by secreting acid and lysosomal enzymes. The life-span of an osteoclast ends with apoptosis.

Metastasis of Breast Cells to the Bone

Red marrow-containing bones and bones with a rich vascular supply, including the vertebrae, and the metaphysis of long bones and ribs are generally the preferred sites for metastasis. In this metaphyseal bone, the vascular bed is composed of specialized sinusoids that aid the passage of hematopoietic and blood cells in and out of bone marrow. These sinusoids lie in a close proximity with trabecular bone. Endothelial cells lining the sinusoids express cell adhesion molecules, including intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), P-selectin, and E-selectin, without any inflammatory stimulus [8]. This sinusoidal structure and the pooling of blood in the sinusoids provide an advantage to cancer cells for extravasation and homing [9].

Not all breast cancer cells have the ability to metastasize to the bone. Breast cancer cells that express specific adhesion molecules for bone matrix proteins preferentially metastasize to the bone. Integrins are transmembrane glycoproteins that mediate cell-cell and cell-extracellular matrix interactions. Integrin $\alpha\nu\beta3$, which is expressed by breast cancer cells, mediates the attachment to trabecular bone by binding matrix proteins, including vitronectin, osteopontin, and bone sialoprotein [10]. Pecheur et al. [11] suggested that breast cancer cells expressing integrin $\alpha\nu\beta3$ have an increased ability to invade and adhere to mineralized bone; therefore, these cells accelerate bone metastasis. Another transmembrane protein, cadherin-11, is expressed in stromal osteoblastic cells in the bone marrow and mediates homophilic cell-cell adhesion. Breast cancer cells also express cadherin-11. Cadherin-11-expressing breast cancer cells interact with stromal osteoblastic cells, thus enhancing invasion and adhesion. Cadherin-11 expression may be a sign of more aggressive, bone-metastasizing tumors [12].

Under normal physiologic conditions, bone matrix production and degradation are well balanced. When breast cancer cells settle in the bone, this balance is impaired in favor of bone degradation. Tumor-secreted PTHrP is the main regulator of excess bone degradation. It triggers a vicious cycle that causes osteoclastogenesis, osteolysis, and improved malignant cell survival and proliferation [13]. Breast cancer cells indirectly activate stromal cells and osteoblasts to produce RANKL through the stimulation of parathyroid hormone receptor 1 (PTHR1) by tumor-derived PTHrP; concurrently, the OPG level decreases. Together, the RANKL-RANK interaction and decreased OPG levels induce osteoclast production. Then, mature osteoclasts begin to degrade the bone. As bone degradation occurs, bone-stored growth factors, including insulin-like growth factor 1 (IGF1) and TGF-β, are released into the bone microenvironment [14]. IGF-1 plays an important role in stimulating breast cancer cell migration and growth. The TGF-β-TGF-β receptor interaction facilitates PTHrP production by tumor cells [15]. IL-6, IL-11, PGE2, M-CSF, tumor necrosis factor alpha (TNF-α), and PDGF produced by cancer cells or released in the course of osteolysis all contribute to the enhancement and continuation of this vicious cycle (Fig. 42.1). In fact, this process is much more complicated, and several other molecules are involved. All medical treatment modalities are directed to breaking this vicious cycle (Fig. 42.1).

Bone-Directed Therapy

Bisphosphonates

Structure and Mode of Action

As the name implies, bisphosphonates contain two phosphorous atoms that are attached to a central carbon atom (P-C-P) (Fig. 42.2) and thus are analogs of inorganic pyrophosphate, in which the phosphorus atoms attach to a central oxygen atom. Based on this similarity, bisphosphonates can affect various enzymes and metabolic activities in the bone. The P-C-P structure makes up the backbone of a bisphosphonate molecule. This backbone is highly resistant to hydrolysis; therefore, bisphosphonates are resistant to biologic degradation. In addition to the phosphorus molecules, two side chains, the R1 and R2 groups, also bind to the central carbon atom. These side chains distinguish the different bisphosphonates, which have different biochemical properties based on the side chains bound to the central carbon atom [16] (Fig. 42.2).

The main role of bisphosphonates is to inhibit bone degradation. They are also used in several benign diseases, including osteoporosis, Paget's disease of bone, primary hyperparathyroidism, and osteogenesis imperfecta. Based on the nitrogen content of the side chain, bisphosphonates are divided into two classes, including non-nitrogen containing and nitrogen containing (Table 42.1) [17].

When bisphosphonates are administered, they selectively bind to bone mineral. The acidic environment provided by osteoclastic activity causes dissolution of the bisphosphonate molecules. Dissociated bisphosphonate molecules are taken up by osteoclasts via endocytosis [18]. Non-nitrogen-containing bisphosphonates are metabolized to non-hydrolyzable ATP analogs that cause osteoclast dysfunction and apoptosis [19]. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway, which produces important molecules for the posttranslational modification (prenylation) of GTP-binding signaling proteins, including Ras, Rho, Rab, and Rac [20]. The main target of nitrogen-containing bisphosphonates in this

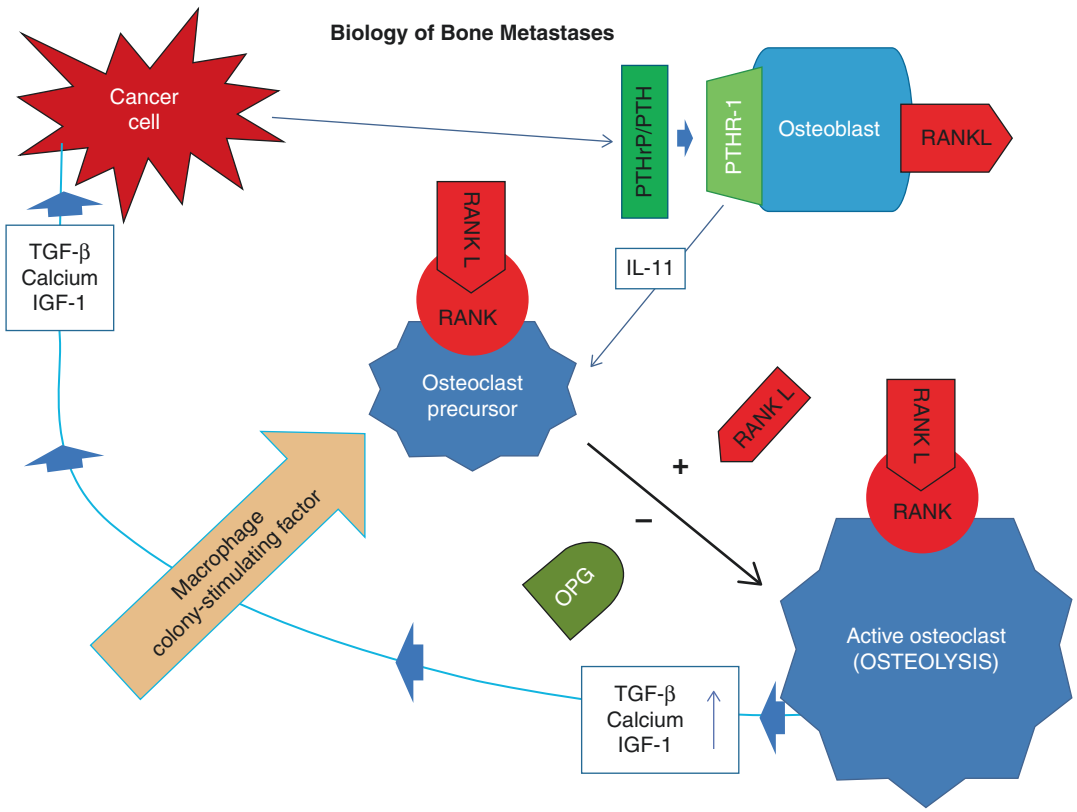

Fig. 42.1 PTHrP produced by cancer cells induces the RANKL-RANK pathway. Specifically, the TGF-β, calcium, and IGF-1 that increased as a result of bone degradation stimulate cancer cells. The vicious cycle is mainly created by PTHrP (*PTH* parathyroid hormone, *PTHrP* parathyroid hormone-related peptide, *TGF-β* transforming growth factor beta, *RANK* receptor activator for nuclear factor κB, *RANKL* receptor activator for nuclear factor κB ligand, *OPG* osteoprotegerin, *IGF1* insulin-like growth factor 1, *IL-11* interleukin 11)

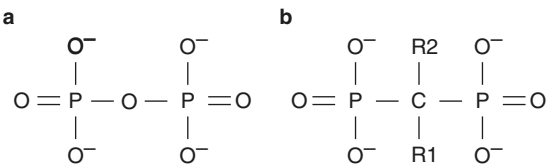

Fig. 42.2 (**a**) Structure of pyrophosphate, (**b**) structure of the bisphosphonate backbone

Table 42.1 Bisphosphonates

Non-nitrogen containing	Nitrogen containing
Etidronate	Pamidronate
Clodronate	Zoledronate
Tiludronate	Ibandronate
	Alendronate
	Risedronate
	Olpadronate

pathway is farnesyl pyrophosphate synthase enzyme. The prenylation of the signaling proteins is essential for osteoclast function and survival. Defective signaling proteins and an excess accumulation of metabolites, which occur due to the blockage of farnesyl pyrophosphate synthase enzyme, lead to osteoclast dysfunction and induce apoptosis [17].

Efficacy of Bisphosphonates in Metastatic Disease

Historically, several studies have suggested that bisphosphonates have beneficial effects in skeletal metastasis of breast cancer [21, 22]. The first placebo-controlled, double-blind randomized study to evaluate the efficacy of oral clodronate in breast cancer patients with bone metastasis was published by Paterson et al. in 1993 [23]. They compared 1600 mg daily oral clodronate (85 patients) with placebo (88 patients) in 173 patients with breast cancer bone metastasis. After a median 14 months of follow-up, there was a significant reduction (27%) in cumulative SREs, including hypercalcemia, radiotherapy needed for bone pain, and vertebral and non-vertebral fractures with the use of clodronate ($P < 0.001$), and there was no survival difference. Two other similar trials have also demonstrated the beneficial effect of clodronate [24, 25]. In these three trials, clodronate therapy significantly delayed the time to the first SRE. Pamidronate is another nitrogen-containing bisphosphonate that is beneficial in breast cancer patients with osteolytic bone metastasis.

In two large multicenter, randomized, placebo-controlled studies, the addition of intravenous pamidronate (90 mg 3–4 weeks intravenous) to patients receiving cytotoxic therapy or patients receiving hormonal therapy reduced skeletal morbidity and delayed the time to the first SRE [26, 27]. A combined follow-up of these two studies at 24 months demonstrated that pamidronate compared to placebo significantly reduced the skeletal morbidity rate (2.4 events vs. 3.7 events, $P < 0.001$) and skeletal complications (51% vs. 64%, $P < 0.001$). The median time to the first SRE was significantly longer (12.7 months vs. 7.0 months, $P < 0.001$), and pain scores were significantly better in the pamidronate arm. The addition of pamidronate to systemic therapy is well tolerated and effective in preventing SRE and symptomatic palliation [28]. Administration of 60 mg pamidronate (four times, given weekly) was also effective in reducing SREs and improving the quality of life of patients with breast cancer bone metastasis [29]. Even lower doses of pamidronate (45 mg every 3 weeks) are beneficial in prolonging the time to progression of bone lesion. In this placebo-controlled trial, marked pain relief has also been achieved [30]. Unfortunately, the researchers did not evaluate its effect on SREs. Although effective at lower doses, the recommended dose is 2-h intravenous infusions of 90 mg pamidronate every 3–4 weeks.

Rosen et al. [31] compared the effects of 4 or 8 mg zoledronic acid with 90 mg pamidronate in patients with breast cancer bone metastasis or multiple myeloma. They analyzed 1130 patients with breast cancer bone metastasis [32]. The 8 mg zoledronic acid dose was reduced to 4 mg, and the infusion time was increased to 15 min because of nephrotoxicity. At the end of 13 months, the proportion of patients with an SRE was similar in both treatment arms. In patients with lytic bone metastasis, 4 mg zoledronic acid achieved a 17% relative reduction in the proportion of patients with an SRE compared with pamidronate; however, this difference was not significant (48% vs. 58%, respectively, $P = 0.058$). Although the primary end point was not reached, 4 mg zoledronic acid delayed the time to first SRE (310 days vs. 174 days, respectively, $P = 0.013$) and yielded a 20% reduction in the risk of SRE (HR, 0.801; $P = 0.037$) compared with pamidronate in this trial. This trial was extended to 24 months, and 412 patients with breast cancer were involved in the extended study [33]. In a subset analysis of patients with breast cancer, the proportion of patients with at least one SRE was still similar in both groups at the end of the extended phase. In multiple event analysis, 4 mg zoledronic acid achieved an additional 20% reduction in the risk of developing SREs compared with pamidronate (RR, 0.799; 95% CI, 0.657–0.972; $P = 0.025$). Zoledronic acid (4 mg, administered via a 15-min intravenous infusion) was as well tolerated as pamidronate (90 mg 2 h intravenous infusion), and the SRE risk was significantly reduced.

Ibandronate is a relatively new bisphosphonate that is effective in the treatment of bone metastasis. It can be given orally or via an intravenous route. The efficacy of intravenous ibandronate was shown in a placebo-controlled phase III trial. Six milligrams of ibandronate every 3–4 weeks for 2 years was superior to placebo in terms of the skeletal morbidity period rate, new SREs, and delaying the time to the first new SRE, and it also reduced pain scores [34]. In another study that used the same dose and schedule of ibandronate, the proportion of patients who developed an SRE was significantly reduced compared with placebo (36% vs. 48%, respectively; $P = 0.027$) [35]. Oral administration is also effective. In a pooled analysis of two randomized, placebo-controlled studies, 50 mg oral ibandronate administered daily reduced the risk of an SRE compared with placebo (HR 0.62; 95% CI, 0.48–0.79; $P = 0.0001$). The need for radiotherapy (0.73 vs. 0.98, respectively, $P < 0.001$) and surgery (0.47 vs. 0.53, respectively, $P = 0.037$) was significantly less in the ibandronate group, and it was well tolerated except for slight adverse upper gastrointestinal effects [36].

In a mixed-treatment analysis of 17 studies, the annual SRE rate was lowest in breast cancer patients treated with zoledronic acid (1.6). The annual SRE rates for oral and intravenous ibandronate were 1.67 and 1.7, respectively. The highest SRE rates were observed with pamidronate (2.07) and clodronate (2.29). According to this analysis, zoledronic acid is the most effective bisphosphonate that reduces the risk of SREs [37].

The results of a Cochrane review showed that bisphosphonates reduce the risk of SRE development by 14% (RR 0.86; 95% CI 0.78–0.95; $P = 0.003$) and delay the median time to an SRE with a median ratio of 1.43 (95% CI 1.29–1.58; $P \leq 0.00001$) compared with those of placebo or no bisphosphonate [38]. All of these large randomized clinical trials and review suggest that the addition of bisphosphonates to systemic therapy, either chemotherapy or hormone therapy, reduces the risk of developing SREs and delays the time to the first SRE in breast cancer patients with bone metastasis. The oral administration of ibandronate can be advantageous for patients who do not want parenteral drugs (Table 42.2).

Despite the proven efficacy of zoledronic acid, the optimal dosing frequency was not established. Zoledronic acid is incorporated into the mineral structure of bone and accumulates in the bone. Consequently, a prolonged dosing interval may be as effective as 3–4 weekly dosing. Three randomized controlled studies investigated the efficacy and safety of reduced-frequency dosing of zoledronic acid. The first published trial was the ZOOM trial [40]. Metastatic breast cancer patients with bone metastasis who were treated with 3–4 weekly zoledronic acid for 12–15 months before enrollment were included in the trial. The patients were randomized 1:1 to receive 4 mg of zoledronic acid every 4 or 12 weeks for 1 year. The primary endpoint was the skeletal morbidity rate.

Table 42.2 Select important clinical trials

Study	Protocol	Important results
Paterson et al. [23]	1600 mg daily oral clodronate vs. placebo	27% reduction in cumulative SRE ($P < 0.001$)
Kristensen et al. [24]	800 mg daily oral clodronate vs. control	Delayed the time to the first SRE ($P = 0.015$)
		Reduced the occurrence of fractures ($P = 0.023$)
Tubina-Hulin et al. [25]	1600 daily oral clodronate vs. placebo	Delayed the time to the first SRE ($P = 0.05$)
		Reduced the pain intensity and analgesic need ($P = 0.01$)
Hortobagyi et al. [26]	90 mg iv. pamidronate every 3–4 weeks vs. placebo	Delayed time to the first SRE ($P < 0.001$)
		Reduced the rate of SREs ($P < 0.001$)
Theriault et al. [27]	90 mg iv. pamidronate every 4 weeks vs. placebo	Delayed time to the first SRE ($P = 0.049$)
		Reduced the skeletal morbidity rate ($P = 0.008$)
Lipton et al. [28] (Pooled analysis of two pamidronate trials at 24 months)	90 mg iv. pamidronate every 3–4 weeks vs. placebo	Delayed time to the first SRE ($P < 0.001$)
		Reduced the skeletal morbidity rate ($P < 0.001$)
Rosen et al. [33]	4–8 mg iv. zoledronic acid vs. 90 mg iv. pamidronate every 3–4 weeks	20% risk reduction for developing SRE compared with pamidronate ($P = 0.025$)
Body et al. [34]	2 mg iv. ibandronate for 3–4 weeks vs. 6 mg iv. ibandronate for 3–4 weeks vs. placebo	6 mg iv. reduced the skeletal morbidity period rate ($P = 0.004$ vs. placebo)
		6 mg iv. delayed time to first the SRE ($P = 0.018$ vs. placebo)
		6 mg iv. 38% reduction in the number of new bone events vs. both 2 mg and placebo
Body et al. [36]	50 mg daily oral ibandronate vs. placebo	Reduced mean skeletal morbidity period rate ($P = 0.004$)
		Reduced risk of SRE ($P = 0.0001$)
Stopeck et al. [39]	4 mg iv. zoledronic acid vs. sc. placebo vs. 120 mg sc. denosumab vs. iv. placebo	Denosumab delayed time to first in-study SRE ($P < 0.001$ for non-inferiority; $P = 0.01$ for superiority)
		Denosumab reduced risk of multiple SREs ($P = 0.001$)
		Denosumab reduced skeletal morbidity rate ($P = 0.004$)

iv Intravenous, *sc* subcutaneous

The skeletal morbidity rate was 0.26 (95% CI 0.15–0.37) and 0.22 (95% CI 0.14–0.29) in the 12-week group and the 4-week group, respectively. Twelve-week dosing was non-inferior to 4-week dosing. On study, SRE was 15% in both arms ($P = 0.89$). In the OPTIMIZE-2 trial, 416 bone metastatic breast cancer patients who were treated with 9 doses or more of intravenous bisphosphonate were randomized 1:1 to receive zoledronic acid at 4-week or 12-week intervals as in the ZOOM trial [41]. The primary endpoint was the SRE rate. One or more SREs were experienced by 22.0% of the patients in the every 4 weeks group and 23.2% of the patients in the every 12 weeks group. The 12-week schedule was non-inferior to the 4-week schedule. The time to first SRE was not different between the schedules (HR, 1.06; 95% CI, 0.70–1.60; $P = 0.79$). In the CALGB 70604 trial, 1822 bisphosphonate-naïve breast, prostate or multiple myeloma patients (855 breast cancer patients) with bone involvement were enrolled. Patients received zoledronic acid for 2 years once every 4 weeks or once every 12 weeks [42]. The primary endpoint was the proportion of patients having at least 1 skeletal-related event within 2 years after randomization. Within 2 years after randomization, 29.5% of patients in the 4-week group and 28.6% of patients in the 12-week group experienced at least one SRE. Administration of zoledronic acid once every 12 weeks was non-inferior to administration every 4 weeks. For patients with breast cancer, the probability of experiencing an SRE within 2 years after randomization was not significantly different between the 4-week group and the 12-week group (between-group difference, −0.02 [99.9%CI, −0.13–0.09]; $P = 0.50$). These three studies demonstrated that zoledronic acid administration once every 12 weeks is non-inferior to standard dosing. Pain scores and analgesic use were also not different in all studies.

Denosumab

Denosumab prevents the RANKL-RANK interaction through binding to RANKL. It is a fully human IgG2 monoclonal antibody that was designed to specifically bind RANKL. The inhibition of the RANKL-RANK interaction prevents osteoclast formation and survival [18]. In a phase II study, five different doses of denosumab were compared with intravenous bisphosphonates in patients with breast cancer bone metastasis. At the end of 13 weeks, denosumab was similar in reducing SREs and suppressing bone turnover when compared with bisphosphonates. The incidence of adverse events was also similar. The most effective course for suppressing bone turnover was four weekly 120 mg administrations of denosumab [43]. The largest clinical trial (2046 patients with breast cancer bone metastasis) that compared denosumab with zoledronic acid was published in 2010 by Stopeck et al.

[39]. Denosumab was superior to zoledronic acid in delaying the time to first in-study SRE (HR, 0.82; 95% CI, 0.71–0.95; $P < 0.001$ for non-inferiority; $P = 0.01$ for superiority) and in reducing the risk of multiple SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; $P = 0.001$). Denosumab also significantly reduced the skeletal morbidity rate ($P = 0.004$). Overall survival was not different (HR, 0.95; 95% CI, 0.81–1.11; $P = 0.49$) between the groups.

Clinical Use of Bone-Modifying Agents

To initiate the administration of a bone-modifying agent, the bone metastasis should be documented with plain radiographs or with other imaging methods (e.g., bone scan, CT scan, or MRI). The American Clinical Society of Oncology (ASCO) considers it reasonable to begin administering bone-modifying agents when bone metastasis is documented with an abnormal bone scan and an abnormal CT or MRI, with a normal plain radiograph. Initiating bone-modifying therapy based only on abnormal findings on bone scan without any evidence of bone metastasis on plain radiograph, CT scan, or MRI outside of a clinical trial is not recommended by ASCO. Even if an extraskeletal metastasis is present, ASCO does not recommend starting a bone-modifying agent in the absence of documented bone metastasis [44]. In patients with advanced breast cancer without bone metastasis, bisphosphonates did not reduce the incidence of bone metastasis (RR 0.96, 95% CI 0.65–1.43; $P = 0.86$) [38]. If bone metastasis is detected with PET/CT, bone scintigraphy may not be needed [45].

The optimal duration and schedule of treatment have not been defined. Generally, clinical trials have evaluated the bone-modifying agents up to 2 years or until there is unacceptable toxicity. In ASCO guideline, every 12 weeks dosing schedule of zoledronic acid is recommended [46]. The ASCO guideline recommends continuing bone-modifying agent until there is an evidence of a substantial decline in the patient's performance status. Bone-modifying agents also reduce the time to the first and subsequent SREs [44]. Therefore, the development of an SRE is not an indication to stop the administration of a bone-modifying agent. Another controversial issue is switching to another bisphosphonate after an SRE develops. In two phase II studies, patients with skeletal progression or the development of an SRE while on clodronate or pamidronate were switched to the more potent bisphosphonate zoledronic acid or ibandronate, which may provide pain palliation and also reduce the expression bone turnover markers [47, 48]. In another phase II study that evaluated switching, switching to denosumab reduced uNTx levels significantly more than continuing zoledronic acid in patients in whom urinary N-telopeptide (uNTx) levels were still elevated despite zoledronic acid treatment, and patients in the switch arm also experienced fewer SREs [49]. These trials do not provide enough evidence to recommend changing bone-modifying agent in cases of treatment failure. However, switching to a more potent agent can be reasonable. Clinicians should decide whether switching to an alternative agent is warranted based on the individual patient. ASCO guideline does not recommend one bone-modifying agent over others. However, in metastatic breast cancer patients, the results of Cochrane review showed that denosumab reduces the risk of SRE development by 22% compared with bisphosphonates (RR 0.78, 0.72–0.85; $P < 0.001$) [38].

Apart from delaying the time to SRE, bone-modifying agents also provide bone pain palliation in patients with breast cancer bone metastasis. All approved bisphosphonates and denosumab can decrease the bone pain caused by breast cancer bone metastasis to some degree. Denosumab and zoledronic acid have similar effects in palliating pain; however, denosumab significantly delays pain worsening in patients who have no or mild pain [50]. Different pain assessment tools and treatment protocols were used in these clinical trials; therefore, it is not possible to determine which one is better [44]. The current standard of care for cancer pain must be applied to all patients with bone pain. Bone-modifying agents are recommended as an adjunctive therapy for bone pain control and not as a first-line treatment by the ASCO guideline [44]. Bisphosphonates and denosumab do not provide any survival advantage in patients with breast cancer bone metastasis [38].

Safety

Osteonecrosis of the Jaw

The incidence of osteonecrosis of the jaw (ONJ) ranges from 0.6 to 6.2% in breast cancer patients who are treated with bisphosphonate. In patients treated with denosumab, the ONJ incidence is similar to that observed with zoledronic acid treatment (2–1.4%, respectively, $P = 0.39$) [39]. A longer duration of therapy, higher cumulative doses, treatment with more potent bisphosphonates (e.g., zoledronic acid and pamidronate), a history of recent alveolar trauma, and inflammatory dental disease are known risk factors for ONJ [51, 52]. Glucocorticoid treatment or antiangiogenic therapy may also contribute to ONJ development [53]. The inhibition of bone remodeling and wound healing through the inhibition of osteoclastic activity are some of the proposed mechanisms of ONJ development. Infection and exposed necrotic bone in the jaw or maxilla are the usual clinical presentations. Pain, suppuration, mucosal swelling, and ulceration may precede clinical presentation. Mild cases are generally controlled with systemic or local antimicrobial therapy and oral rinses. Surgical intervention may be needed for refractory or severe cases [53]. Bisphosphonates accumulate in the bone, and the effect of denosumab on the bone becomes reversible after several months. Therefore, the beneficial effect of stopping a bone-modifying agent is unclear in the case of

ONJ. This decision should be made based on the individual patient after a multidisciplinary assessment of the risk-benefit ratio. ASCO recommends a dental examination and any necessary preventive dentistry before the initiation of bone-directed therapy. If invasive manipulations that affect bone are indicated, the initiation of bone-directed therapy should be delayed for 2–3 weeks. After the initiation of a bone-modifying agent, good oral hygiene should be maintained, and invasive dental procedures should be avoided as much as possible [44].

Nephrotoxicity

Nephrotoxicity is an important adverse event observed with bisphosphonate treatment. Renal toxicity ranges from acute kidney injury with acute renal failure to slowly progressing or non-progressing renal insufficiency [54]. Pamidronate may cause nephrotic syndrome [55, 56]. In a trial that compared 4 and 8 mg zoledronic acid with 90 mg pamidronate, the infusion time for zoledronic acid was extended from 5 to 15 min, and the 8 mg dose was reduced to 4 mg due to the high incidence of nephrotoxicity [31]. Bisphosphonate-related nephrotoxicity depends on the infusion time and dose. Zoledronic acid and pamidronate should not be administered in less than the advised durations of 15 min and 2 h, respectively. Further extension of the infusion time does not provide extra protection [57]. Dose adjustment should be made according to the calculated creatinine clearance (CrCl) in patients with mild to moderate renal failure (CrCl between 30 and 60 ml/min) who will be treated with zoledronic acid. Both zoledronic acid and pamidronate are not recommended for patients with renal failure (CrCl <30 ml/min). Serum creatinine should be monitored prior to every dose of pamidronate or zoledronic acid, and electrolytes, calcium, magnesium, and hemoglobin should also be monitored regularly. If renal function deteriorates during therapy, the drug should be withheld until renal function returns to within 10% of the baseline [44]. In ibandronate studies, including both intravenous and oral administration, the renal adverse effects of treatment were similar with placebo, and no one experienced renal failure [34–36]. Denosumab is a monoclonal antibody; therefore, it is mostly cleared through the reticuloendothelial system and not through the kidney. Although renal-associated adverse effects are nearly equal between zoledronic acid and denosumab, severe renal-associated adverse events (1.5% vs. 0.2%, respectively) and renal failure (1.5% vs. 0.2%, respectively) are more frequent with zoledronic acid [40]. In a meta-analysis, the risk of renal adverse events was significantly higher with zoledronic acid in patients with breast cancer, prostate cancer, and other solid tumors (RR 0.76; 95% CI, 0.59–0.98) [58]. In a small trial involving patients with renal function ranging from normal to dialysis-dependent renal failure, the pharmacokinetics and pharmacodynamics of denosumab (subcutaneous 60 mg single dose) were not affected by renal function. Therefore, dose adjustment is not required. In this trial, the most common adverse event was hypocalcemia. Denosumab may be cautiously given to a patient with renal impairment, and the patient should be closely monitored for hypocalcemia.

Hypocalcemia and Other Adverse Effects

Bone-modifying drugs disrupt bone calcium homeostasis by inhibiting osteoclastic activity. Parathyroid hormone protects the patient from hypocalcemia after the administration of bone-modifying drugs. If any condition that affects parathyroid hormone secretion or calcium metabolism (e.g., surgical hypoparathyroidism, hypomagnesemic hypoparathyroidism, vitamin D deficiency, and renal failure) is present, the patients become prone to hypocalcemia [59, 60]. Hypocalcemia and hypophosphatemia are more common with denosumab [39, 61]. Calcium and vitamin D supplementation were added to treatment protocols in nearly all clinical trials. If no contraindication is present, calcium and vitamin D supplementation is recommended to all patients receiving bone-modifying agents with breast cancer bone metastasis to prevent hypocalcemia.

An acute phase response may occur up to 3 days after the administration of intravenous nitrogen-containing bisphosphonate due to increased cytokine production in 15–30% of patients [62]. Generally, bisphosphonate-naïve patients experience influenza-like symptoms, including fever, chills, myalgia, headache, nausea, and arthralgia, after the first dose. This adverse event is self-limited, resolves after several days, and is not encountered after subsequent doses. Therefore, symptomatic management with anti-inflammatory drugs and acetaminophen is enough [63]. Apart from the acute phase response, severe musculoskeletal pain may occur days or years after initiating bisphosphonate. Discontinuing the causative agent may provide immediate improvement but may not lead to complete improvement [63]. All bisphosphonates, especially pamidronate, may cause ocular inflammation, including conjunctivitis, uveitis, scleritis, episcleritis, and iritis. All patients with ocular inflammation must be evaluated and treated by an ophthalmologist. Conjunctivitis is treated with topical NSAIDs; episcleritis is treated with topical steroid eye drops. The prognosis for both is good, and bisphosphonate treatment can continue. Uveitis, scleritis, and global orbital inflammation are severe conditions and should therefore be treated specifically. Continuing bisphosphonate treatment is not recommended in these cases [64]. Oral bisphosphonates may cause gastric irritation. Anemia was encountered in nearly one-third of patients who were treated with both zoledronic acid and denosumab [61]. Bisphosphonates are associated with an increased risk of cardiac arrhythmias, including atrial fibrillation and supraventricular tachycardia and stroke [65]. Pamidronate rarely may cause skin reaction

and ototoxicity [64]. In osteoporosis trials, the incidence of infectious complications with denosumab was increased [66]. However, in cancer patients treated with denosumab or zoledronic acid, the incidence of infectious complications was similar [61].

Radionuclide Therapy for Breast Cancer Bone Metastasis

Radionuclides are used for the palliation of bone pain secondary to mainly osteoblastic bone metastasis of solid tumors. Radionuclide therapy is indicated in patients with multifocal bone metastasis. If external beam radiation is contraindicated or the patient suffers from severe pain despite adequate analgesia, radionuclide therapy is a reasonable palliative modality. Uncontrolled systemic disease, asymptomatic bone metastasis at fewer than three sites, pure osteolytic metastasis, poor bone marrow reserve, and less than 60 days of life expectancy are relative contraindications for radionuclide therapy. Absolute contraindications are spinal cord compression, a high risk of fracture or pathologic fracture of weight-bearing bones, renal failure, pregnancy, and breast feeding [67]. Strontium-89 hydrochloride (Sr-89), samarium-153 lexidronam (Sm-153), and rhenium-186 hydroxyethylidene diphosphonate (Re-186) are approved radiopharmaceuticals for radionuclide therapy. Phosphorus-32 (P-32) is no longer used because of severe myelosuppression. After administration, radiopharmaceuticals incorporate into newly formed matrix, and the extent of incorporation is determined by osteoblastic activity. Therefore, painful metastatic sites should be visualized on bone scintigraphy before deciding upon radionuclide therapy. Strontium has similar properties to calcium; therefore, it directly incorporates into bone. Other isotopes are chelated to organic phosphates to facilitate incorporation into the bone. These radiopharmaceuticals deliver local radiation by emitting beta particles. Samarium and rhenium also emit gamma radiation, which enables imaging. Another important radiopharmaceutical is alpha-emitter radium 223 (Ra-223). It incorporates into the bone in the same way as strontium. Ra-223 treatment delays the time to first symptomatic SRE, prolongs overall survival, and is also a safe treatment modality in castration-resistant prostate carcinoma patients with only bone metastases [68]. The efficacy of Ra-223 in breast cancer bone metastasis has been shown in vivo and in a mouse model [69].

Most of the studies of radionuclides were performed on patients with prostate cancer [70–72]. Patients with breast cancer were also involved in some of the studies [73, 74]. The previously mentioned radiopharmaceuticals were found to be beneficial in palliating painful breast cancer bone metastasis in randomized clinical trials and in case series. In one study, 92% of breast cancer bone metastasis patients that were refractory to conventional analgesia responded to Sr-89 therapy [73]. Generally, pain relief occurs 1–3 weeks after administration. One or two days after administration, a self-limited pain flare may be experienced. Re-186 provides earlier pain palliation, and the duration of myelosuppression is significantly shorter than with Sr-89 [75]. Repeated administration of these radiopharmaceuticals is also safe and effective in patients who benefited from the previous administration [76–78]. Transient myelosuppression is the most common toxicity. Generally, thrombocytopenia is experienced, and significant neutropenia and anemia develop less frequently than thrombocytopenia [67].

Advances in the Treatment of Bone Metastasis

The current medical treatment of breast cancer bone metastasis is bisphosphonates and denosumab. However, numerous molecules that target this vicious cycle are being investigated. A non-receptor tyrosine kinase, Src, plays an important role in breast cancer bone metastasis and osteoclastogenesis [79]. The Src inhibitor dasatinib, which has been used in chronic myelogenous leukemia, also inhibits osteoclastogenesis in vitro [80]. Another Src inhibitor, saracatinib, decreased bone resorption markers in a phase I study [81]. In two ongoing studies, dasatinib (NCT00566618) and saracatinib (NCT00558272) are still being investigated for the treatment of bone metastasis. In a randomized clinical trial, the cathepsin K inhibitor odanacatib suppressed bone resorption markers, in a manner similar to zoledronic acid, after 4 weeks of treatment and was well tolerated [82]. In the future, antibodies that block PTHrP, TGF-β antagonists, proteasome inhibitors, and many new molecules targeting this vicious cycle are being evaluated for the treatment of bone metastasis.

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The Local Management of Bone Metastases

43

Ahmet Salduz and Levent Eralp

Introduction

Metastatic disease is the most frequently observed malignant lesion of the bone [1]. Breast, kidney, thyroid, and lung cancers have high incidences of bone metastases [1, 2]. Approximately 70% of patients who die of breast cancer have also had bone metastases [3]. Twenty percent of breast cancer bone metastases become symptomatic, and 17% of these symptomatic cases require surgical treatment [4, 5]. Currently, the 5-year survival rate for metastatic breast cancer is 22% [1].

There are two groups of breast cancer bone metastases with regard to the behavioral pattern of the bone cells. Osteolytic lesions, which are the most common form, lead to bone destruction and are a common cause of morbidity and mortality. Osteoblastic lesions lead to new bone formation. Bone metastases can exclusively comprise an osteolytic or osteoblastic phenotype but most likely simultaneously contain osteolytic and osteoblastic activities [2, 4, 6, 7].

Breast cancer bone metastases can lead to bone pain, pathological fractures, hypercalcemia, and spinal cord and other nerve compressions due to pathological fractures (osteolytic activity) or due to direct compression (osteoblastic activity).

Breast cancer patients with bone metastases and extensive bone destruction have significantly increased morbidity and markedly worse prognoses [8, 9].

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Bone Metastasis Pathophysiology

The metastasis of breast cancer involves the progression through complex molecular and cellular stages. An understanding of these stages is very important for modifying therapeutic strategies.

Physiological bone architecture contains a unique microenvironment. The bone extracellular matrix comprises type 1 collagen and hydroxyapatite crystals. The cellular component contains three cell types: osteoblasts, osteocytes, and osteoclasts. These three cell types are controlled by many hormones and growth factors.

Bone is an active tissue that maintains mineral homeostasis through bone resorption via osteoclastic activity and bone formation via osteoblastic activity. Breast cancer cells disrupt this bone turnover.

The metastatic process begins by adhesion to the vessel endothelium and extravasation (via the activities of metalloproteinases and cathepsin K) into the bone tissue. Breast cancer cells produce parathyroid hormone-related peptide (PTH-rP); PTH-rP binds to the parathyroid hormone (PTH) receptor, which results in the expression of receptor activator of nuclear factor κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) by osteoblasts [2, 3]. RANKL binds to the RANK receptor on osteoclast precursors and induces the formation of mature osteoclasts. The excessive activity of osteoclasts due to RANKL and M-CSF results in bone degradation. Bone degradation is conducive to the release of IGF-1 and TGF-β (and possibly PDGF and BMP), which are stored in the bone [2, 3, 8].

IGF-1 stimulates DNA matrix synthesis, thereby stimulating breast cancer cell growth and migration into the bone (Fig. 43.1).

TGF-β potentiates DNA synthesis, inhibits type II collagen synthesis, and, in breast cancer cells, plays a key role in stimulating the secretion of PTH-rP. TGF-β also stimulates COX-2 expression in breast cancer cells, which causes increased PGE2 production [10].

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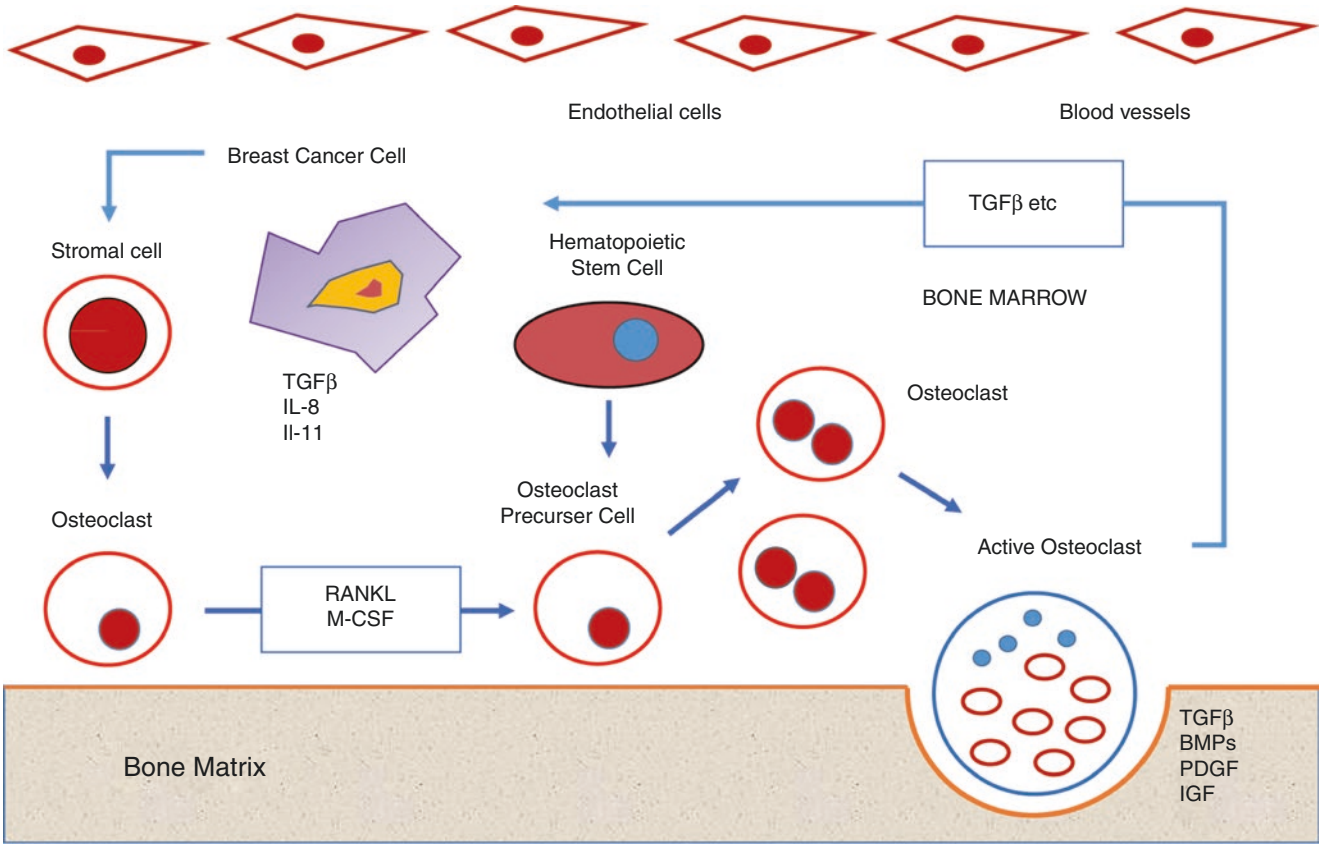


Fig. 43.1 NF-κB ligand (RANKL)/RANK pathway. Breast cancer cells activate osteoblasts with PTH-rP; RANKL is produced by osteoblasts. RANK receptor stimulation results in increasing the maturation of active osteoclasts

Breast cancer cells produce several local factors such as tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-11, M-CSF, and prostaglandin E2. These cytokines activate osteoclastogenesis and suppress osteoblasts.

The hormone estrogen is a mitogenic factor for breast tumor cells; therefore, tumor cells express the estrogen receptor (ER). ER-positive tumors have a higher risk of developing bone metastases. Estrogen has been shown to regulate the level of PTH-rP in some tissues, but whether this regulation occurs in the bone microenvironment remains unclear [2, 11].

Increased blood flow is essential for the survival of metastatic cancer cells; therefore, tumor progression is critically dependent on angiogenesis. When osteoclasts resorb the bone matrix, platelet-derived growth factors (PDGF-1/PDGF-2) and platelet-derived endothelial cell growth factor (PD-ECGF), also known as thymidine phosphorylase (TP), are released. TP is the target of the chemotherapeutic agent 5-fluorouracil [12]. Breast cancer cells also express vascular endothelial growth factor (VEGF); VEGF is angiogenic and, furthermore, promotes osteoclastogenesis [2, 13].

Breast cancer cells induce angiogenesis through the chemotactic and mitogenic effects of PDGF, PD-ECGF, and VEGF on endothelial cells.

Long Bone Metastases

Metastatic bone disease usually causes significant pain and disability. Pain at rest and upon waking indicates a metastatic or primary bone tumor. If a patient with breast cancer has pain at rest in an extremity and a history of disability, a thorough examination, proper imaging, and clinical and pathological diagnoses are crucial.

Clinical Presentation, Evaluation, and Imaging

Patients with symptomatic osseous lesions note localized pain that does not resolve with rest or routine painkillers. The other ominous pain modality is observed only with weight bearing but does not resolve with rest and indicates a probable pathological fracture.

On physical examination, a visual inspection may reveal swelling, ulceration, venous changes, or deformity. Any restriction or pain with joint motion, local tenderness, pathological movement, crepitus, or lymphadenopathy may be established by palpation. Careful neurological and vascular assessments must be performed.

The radiographic evaluation should begin with two-plane X-rays of the affected extremity. When metastatic disease is present, one must determine the localization of the lesion, the relationship with the articular surface, and the distinction between the lesion and normal bone. As much as 50% of the cortical bone must be lost to see plain radiographic evidence of a lytic lesion. The early stages of metastatic disease cannot be observed on plain X-rays. The radiographic appearance of a metastatic lesion may be osteolytic (the most common), osteoblastic, or mixed. The radiographic appearance depends on the balance of osteoclastic (bone destruction) and osteoblastic (bone production) activity levels.

If a patient has a solitary, isolated bone lesion with a history of breast cancer, the most probable diagnosis is metastatic bone disease; however, alternative diagnoses include multiple myeloma, a primary bone tumor, lymphoma, infection, Paget's sarcoma, and hyperparathyroidism. After a careful history has been taken, an examination, proper laboratory tests, and a radiologic evaluation should be performed. The laboratory tests should include the following: a complete blood count, serum protein electrophoresis, the serum calcium level, the prostate-specific antigen level, the C-reactive protein level, and the erythrocyte sedimentation rate (Fig. 43.2). The radiologic evaluation should include the following: two-plane X-rays of the entire long bone; contrast computed tomography (CT) of the chest, abdomen, and pelvis; and a whole body bone scan (although this scan may be negative in myeloma and metastatic renal cancer, a bone scan can detect multiple lesions, which are common in metastatic disease). A bone scan may miss early infiltration into

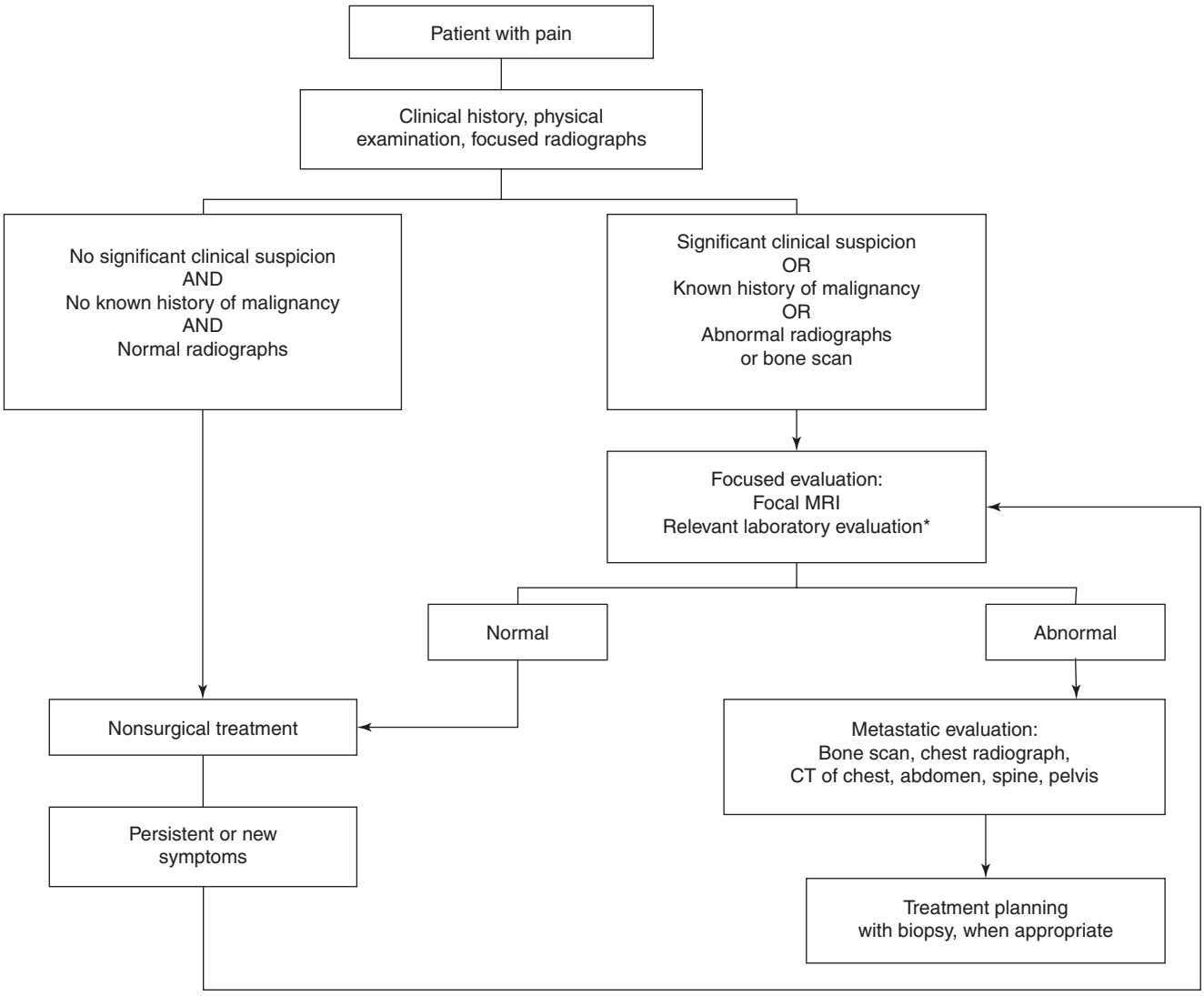


Fig. 43.2 Proposed algorithm for the evaluation of a patient for metastatic disease of the spine. *A relevant laboratory evaluation should include the following: a complete blood count, an erythrocyte sedimentation rate, and the level of C-reactive protein to evaluate reactive processes, as well as a basic metabolic panel with serum calcium level and, where appropriate, markers of specific disease, such as prostate-specific antigen, and serum/urine protein electrophoresis. *CT* computed tomography, *MRI* magnetic resonance imaging

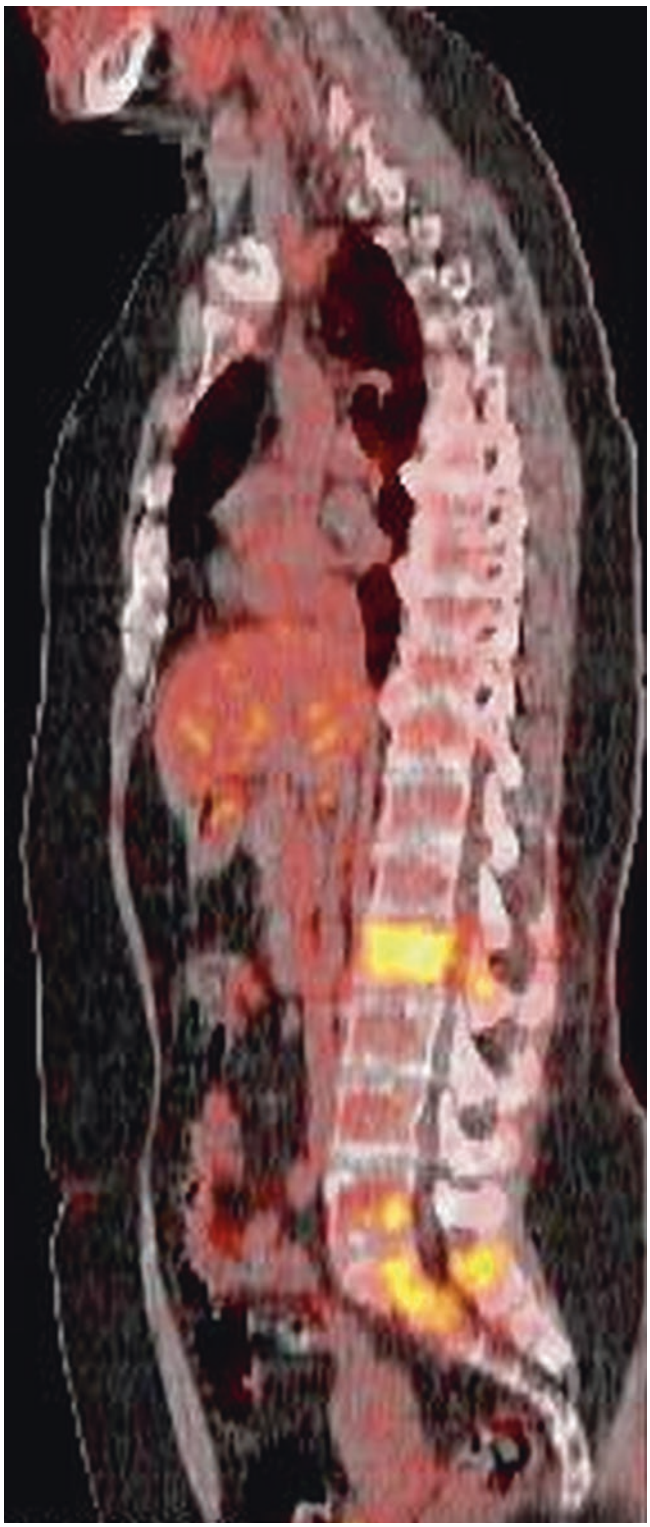


Fig. 43.3 PET-CT scan of a 55-year-old woman revealing a metastatic lesion from breast cancer on the L2 vertebrae and sacrum

the marrow; therefore, despite negative bone scan results in suspect cases, a magnetic resonance imaging (MRI) scan should be performed to detect early-stage bone metastases (Fig. 43.3).

Guidelines

In 1973, Fidler suggested the prophylactic stabilization of long bones. His study indicates that prophylactic stabilization is necessary if long bone metastatic lesions have more than 50% cortical bone destruction [14]. In 1982, Harrington considered three factors in the prophylactic stabilization of the femur: the lesion was ≥2.5 cm, the lesion involved >50% cortical destruction, and the lesion caused persistent pain after a trial of radiotherapy [15].

In 1989, Mirels developed a scoring system according to the anatomic location of the metastatic lesion, the type of bone destruction (osteoblastic, osteolytic, or mixed), the size of the defect, and the degree of pain [16] (Table 43.1). Prophylactic fixation is recommended for a score of ≥9 (33% fracture risk within a year). A Mirels score of 12 indicates a fracture risk of 100% within a year.

Indications

The major indication for prophylactic fixation is improving the quality of life. The purpose of the surgical treatment of a breast cancer patient with long bone metastases and no pathological fracture is to decrease pain, reduce the use of analgesics, restore skeletal stability, regain functional independence, and improve ambulatory and daily routine activity. However, the decision to proceed with surgical intervention is based on several factors and must be individualized. These factors include the following: histology of the primary lesion, the patient's comorbidities and expected life span, the severity of the symptoms, the location of the tumor, the expectations of the patient, and the efficacy of the intervention relative to alternative or adjuvant treatment modalities [17, 18].

The scoring systems are not conclusive and cannot predict all factors. For this reason, the operative decision should be based on both the scoring systems and the individual factors.

In a case where the patient has long bone metastases from breast cancer with a pathological long bone fracture, if the patient's life expectancy is ≥3 months, stabilization of the long bone is necessary for pain relief and for improving movement [18]. In a nonambulatory patient with a pathological long bone fracture, stabilization of the long bone can be performed for painless bed-to-chair transfer.

Asymptomatic lesions require clinical and radiological follow-up. These asymptomatic lesions can be effectively managed with medical treatment (such as bisphosphonate or hormonal therapy) and radiation [12, 18].

Prophylactic fixation results in decreased perioperative morbidity, shorter hospitalization (average of 2 days), fewer hardware complications, and improved survival compared with pathological fracture fixation.

Table 43.1 Mirels scoring system for assessing the risk of pathologic fracture in long bones

Score			
	1	2	3
Anatomic location	Upper limb	Lower limb	Peritrochanteric
Bone destruction type	Blastic	Mixed	Lytic
Size of the defect (as a proportion of shaft diameter)	<1/3	1/3–2/3	>2/3
Pain	Mild	Moderate	Functional

The clear indication for long bone fixation is the presence of a pathological fracture in a weight-bearing long bone.

Medical Treatment

There are five different types of medical treatment: (1) hormone therapy, (2) chemotherapy, (3) bisphosphonates, (4) radiation therapy, and (5) external supports.

For hormone therapy, the response rate is closely related to the activity of the estrogen and progesterone receptors. The most commonly used agent is tamoxifen. Tamoxifen inhibits the effects of estrogen.

Chemotherapy is an effective treatment for bone metastases from breast cancer. For rapidly growing disease, hormonal therapy is ineffective, and chemotherapy use is indicated.

Bisphosphonates inhibit osteoclastic activity (bone resorption).

Upper Extremity Metastases

Twenty percent of breast cancer bone metastases involve the upper extremities, and 50% occur in the humerus [19, 20].

Metastases in the upper extremities can result in the significant impairment of daily functions such as personal hygiene, eating, and the ability to use external aids.

Treatment strategies include both medical treatment (functional bracing, radiation, bisphosphonates, hormone therapy, and chemotherapy) and surgical treatment (resection and reconstruction or stabilization).

Nonsurgical treatment options are usually chosen in cases of limited life expectancy, severe comorbidities, low-demand patients, small lesions, radiosensitive tumors, and asymptomatic lesions.

Lesions of the clavicle and scapula are generally treated nonsurgically with immobilization, radiation, or medical therapy. Nonetheless, destructive lesions of articular parts of the scapula and clavicle may require operative treatment.

A detailed preoperative assessment of the general medical condition is important to minimize complications. Hypercalcemia, sodium-potassium imbalance, anemia, renal and liver dysfunctions, and coagulopathy can be observed in these patients [20].

The cervical spine should be assessed for destructive lesions to avoid any cervical injury during anesthesia and positioning. The cervical spine should be evaluated with cervical X-rays or a bone scan to exclude any cervical metastases.

Surgical Treatment

Surgical treatment strategies include rigid and durable internal fixation for mechanical strength restoration, functional improvement, and pain relief. As a result, the upper extremity can be usable immediately after operation.

A variety of internal fixation or prosthetic devices can be utilized to maintain stable and durable fixation. Healing of the fracture should not be necessary to maintain functional stability.

Surgical treatment of the humerus is reviewed in detail below.

Humerus

Selection of the reconstruction device depends on the anatomic region and the amount of bone destruction. An intramedullary nail (IMN), a plate, hemiarthroplasty, a total shoulder replacement, an intercalary prosthesis, osteoarticular allografts (OAs), and polymethylmethacrylate (PMM) are potential reconstructive devices. PMM supplements poor bone quality when used with reconstruction devices.

Breast cancer metastases in the humerus can be divided into three anatomic regions: the proximal humerus, the humeral diaphysis, and the distal humerus.

Proximal Humerus

Pathological fractures of the proximal humerus usually occur with extensive destruction of the humeral head and metaphysis. A pathological fracture or impending fracture is usually treated with a humeral endoprosthesis. A total shoulder prosthesis is rarely used because intra-articular or glenoid involvement is rare. Resection and proximal humeral replacement achieve excellent pain relief but poor shoulder function [20, 21].

Osteoarticular allografts (OAs) for the reconstruction of the proximal humerus are not a good choice in the long term. The long-term results of OA have been unsatisfactory, and the recovery time is longer than with an endoprosthesis. Benjamin K. does not at all recommend the use of OAs at all due to the unacceptable complication rate [22].

A deltopectoral approach is used to remove the proximal humerus and to curettage all of the tumor tissue. All gross tumor tissue should be removed, but care must be taken not to remove periosteal tissue or the cortical shell. The diaphysis is prepared as the entire canal for the prosthetic stem. The application of the cement is extremely important, and the surgeon should avoid entering soft tissue. Cement extravasation can cause neurovascular injury.

Bos et al. reported the outcomes for 18 patients who underwent proximal humeral reconstruction; 10 underwent subluxation, which indicates a high instability rate [23]. Moeckel et al. reported the outcomes for 22 patients who had good results with proximal humerus reconstruction using a modular hemiarthroplasty; this design allows for an improved soft tissue balance [24].

In this region of the humerus, an intramedullary nail is not stable because of insufficient proximal fixation. Fixation with a plate is also insufficient and associated with extensive bone destruction because there is generally no location for stable screw fixation.

Diaphyseal Region

In the diaphyseal region, the best implant choice is intramedullary nailing (anterograde or retrograde) using a closed technique, and if tumor tissue resection was performed, using a polymethylmethacrylate support to maintain early stable fixation is advised (Fig. 43.4). The humerus has a very small intramedullary canal; thus, applying closed intramedullary nailing can be difficult.

An IMN has some advantages, including that the nail protects the long (almost entire diaphysis) segment of the humerus and that there is a low risk of implant failure and less soft tissue damage.

An anterograde IMN incision may damage the rotator cuff, which would require repair. Many patients complain of rotator cuff tendinitis and weakness. The tip of the nail can cause persistent symptoms.

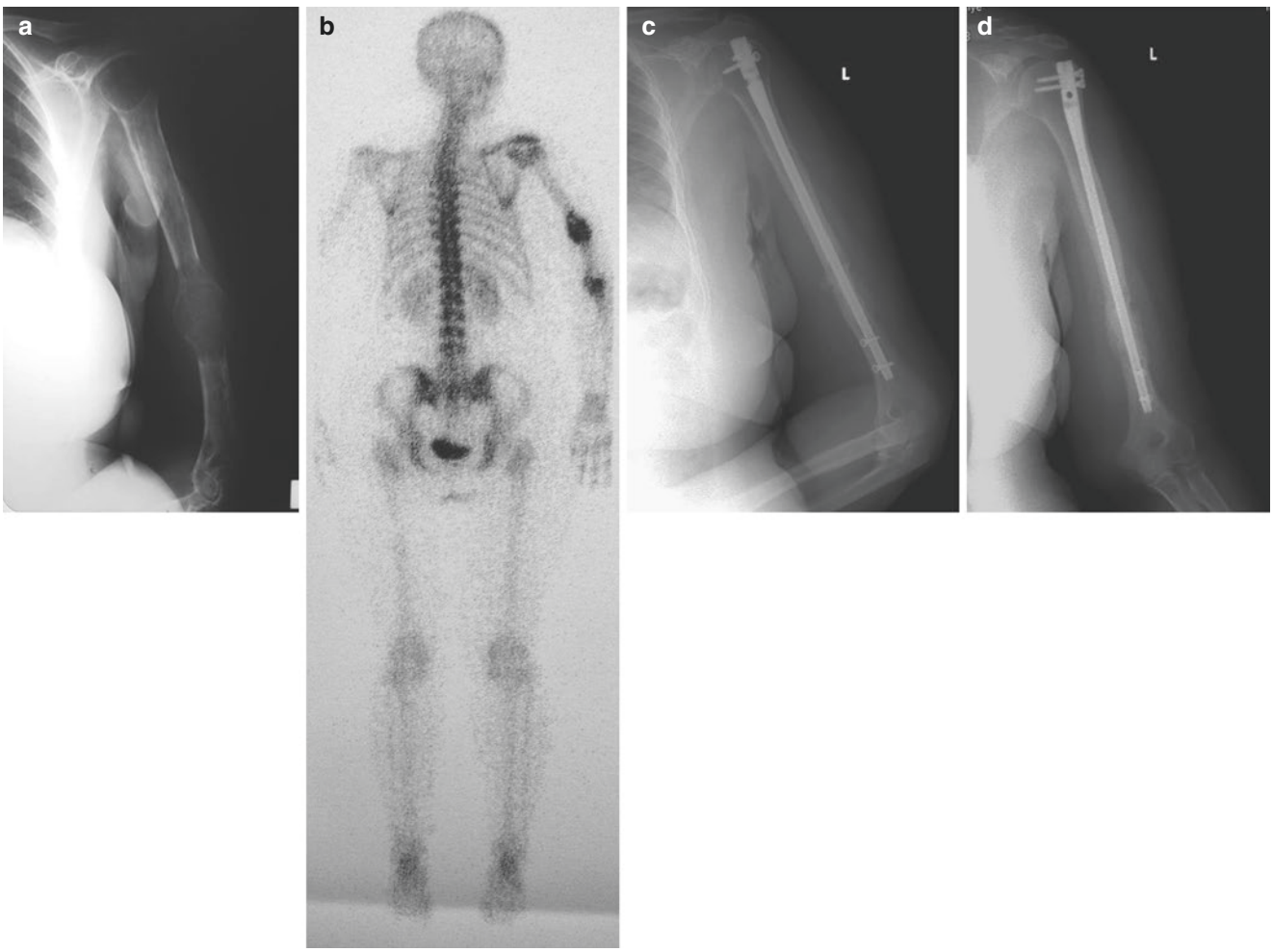


Fig. 43.4 A 59-year-old woman with metastatic breast cancer. (**a**) AP radiograph reveals lytic lesion on the shaft of the left humerus (impending fracture). (**b**) A bone scan with technetium 99 reveals increased uptake in the left humerus diaphysis. (**c**, **d**) Postoperative radiographs after curettage, cementation, and fixation with an intramedullary nail

IMN fixation can be used from between 2 and 3 cm below the greater tuberosity to 5 cm above the olecranon fossa [25]. Outside of these margins, an IMN can be made rigid with interlocking screws or with a polymethylmethacrylate support. To provide rigid fixation, there must be at least 4–5 cm of intramedullary nail on either side of the lesion with intact cortices [20]. However, after nail insertion, at least two locking screws, proximal and distal, are recommended to achieve stable fixation.

Redmond et al. reported 13 patients who underwent intramedullary nailing with the use of a closed technique to treat metastatic disease [25]. As a result, the authors concluded that "interlocking intramedullary nailing of the humerus for pathological fractures provides immediate stability and can be accomplished with a closed technique, brief operative time, and minimum morbidity, with a resultant early return of function to the extremity."

Plate fixation is also a recommended method for impending and complete fractures of the diaphyseal region with some advantages and disadvantages. The major advantage of plate fixation is that the rotator cuff is not as affected as it is with anterograde intramedullary nailing and that fluoroscopy is usually not necessary. The disadvantages of plate usage include the following: extensive soft tissue damage, greater blood loss, possible radial nerve injury, a longer recovery period, and that the long segment is not as well controlled compared with intramedullary nailing. At least three screws should be placed in the normal cortical bone on either side of the fracture. For exposure for plate fixation, an anterolateral or posterior approach is usually used. Care must be taken when resecting the tumor tissue to avoid extensive removal of periosteal tissue or the cortical shell, which would hinder stable fixation in the remaining cortical bone and prolong the healing period.

Intercalary prostheses are suitable for dealing with extensive diaphyseal destruction, segmental defects, or a prior failed device. Intercalary prostheses offer a modular reconstruction option with a transition piece for the resection of large diaphyseal lesions.

Damron et al. reviewed the outcomes of 17 patients who had reconstructions with cemented modular intercalary prostheses; 88% of the patients achieved immediate and stable humeral fixation, pain relief, and an early return of function [26]. Three radial nerve injuries, three implant failures, and two periprosthetic fractures were observed.

Distal Humerus

Metastatic lesions of the distal humerus are rare; breast cancer is one of the most common primary tumors that metastasizes to this location. Distal humeral metastases can be treated with bicondylar plate fixation, flexible intramedullary nails, resection, and prosthetic reconstruction. Additionally, PMM can be added to provide greater and immediate stability to this region. Because of the unique anatomy of this region and the thinning of the bone at the olecranon fossa, supracondylar pathologic fractures are particularly difficult to treat.

In cases of extensive bone destruction and in selected cases after resection of the elbow, arthroplasty provides marked pain relief and functional improvement.

After the prophylactic fixation or surgical treatment of pathological fractures, radiation therapy is recommended. The postoperative use of radiation therapy decreases bone destruction and minimizes the loosening of the fixation material.

Townsend et al. found that the addition of external beam radiation to surgery significantly improved functional outcomes.

Radiation therapy can be started 10 days after surgery. If the patient has previously received radiation, the sutures are left in place for approximately 4 weeks [20].

Lower Extremity Metastases

Metastatic lesions and pathological fractures are more common in the lower extremities than in the upper extremities. The result of a pathologic fracture in the lower extremity is more pronounced than that of a fracture occurring in the upper extremity (Fig. 43.5). Approximately two-thirds of all long bone pathological fractures occur in the femur [27]. The proximal femur (50%) and the intertrochanteric region (20%) are the most commonly involved areas.

Lower extremity metastases can result in significant impairments in daily functions due to the inability to walk. In addition, the inability to walk can cause emboli, lung problems, or infections.

Surgical Treatment

The aims of treatment for the lower extremity long bones are pain relief and ambulatory function restoration. If the life expectancy is longer than 3 months, surgical treatment is a possibility [1, 19, 27].

The surgeon should achieve stable fixation, and local tumor control can be achieved with radiation therapy, chemotherapy, and hormonal therapy. For breast cancer bone metastases, the local control of the tumor is usually provided with the aforementioned methods.

Femoral Head and Neck

For non-pathological fractures in the femoral head and neck region, there are high rates of nonunion and implant failure. For pathological fractures of the femoral neck, there is also a high risk of nonunion; thus, an endoprosthetic replacement is usually the treatment of choice. A long-stem prosthesis is recommended to prevent failure in the case of local tumor progression and to support the femoral shaft (Fig. 43.6). The surgeon should be mindful of the calcar area; when the tumor extends into this region, a special calcar replacement prosthesis

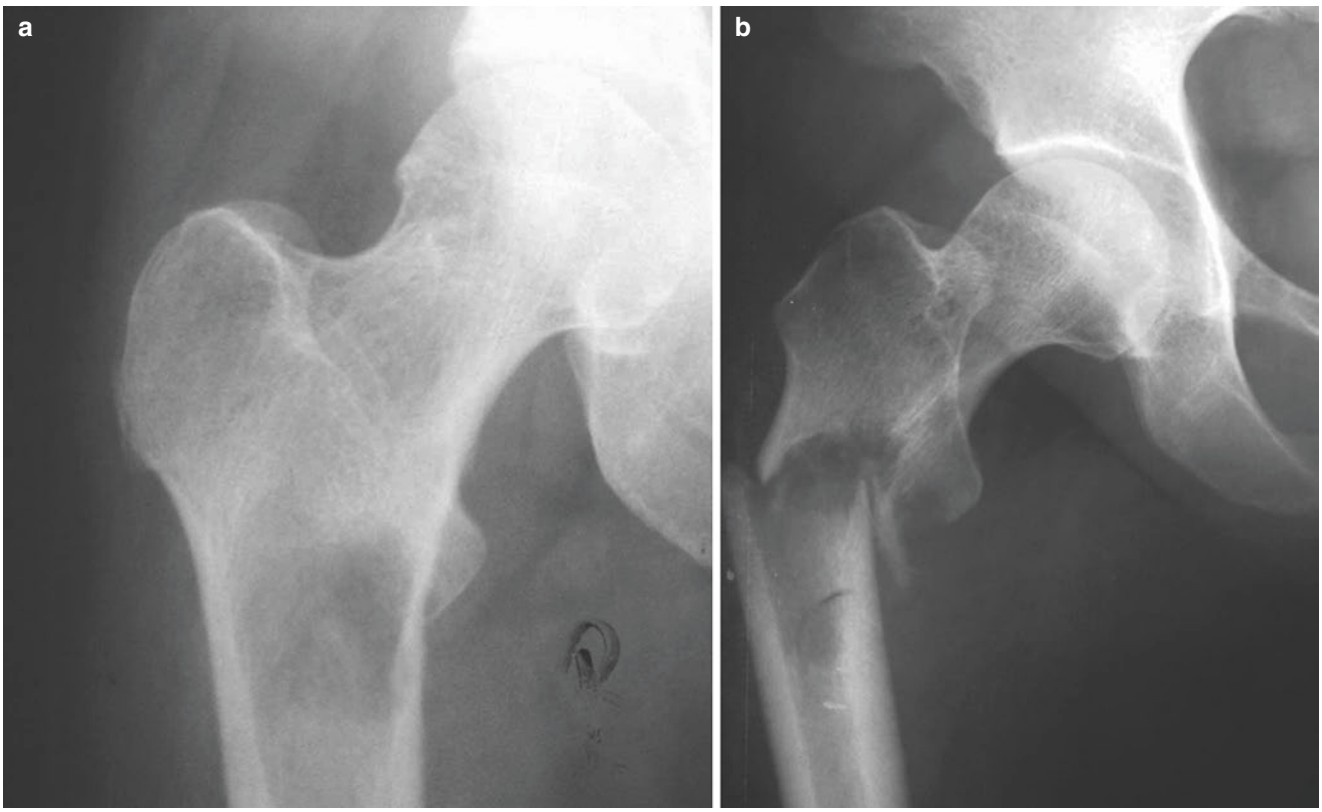


Fig. 43.5 A 41-year-old woman with a metastatic lesion from breast cancer on the subtrochanteric region. (**a**) AP view reveals an osteolytic lesion on the subtrochanteric region; note the lysis on the medial cortex of the femur; patient refused treatment. (**b**) Six months later, the impending fracture evolved to a pathologic fracture

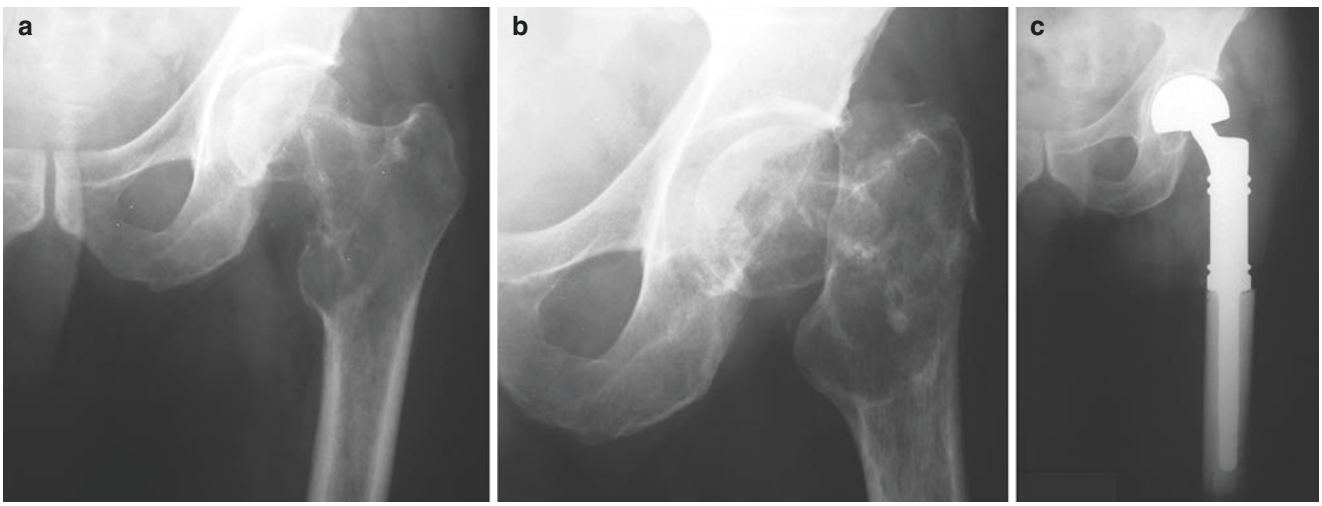


Fig. 43.6 A 61-year-old woman with breast carcinoma metastases to the proximal femur (**a**) AP view demonstrates a lytic lesion on the proximal femur; no pathologic fracture is present. (**b**) Patient received radiation therapy, but tumor progression and a pathologic fracture developed. (**c**) Radiograph of the hip after resection of the proximal femur and reconstruction with a bipolar cemented tumor prosthesis

should be chosen. When the acetabulum is not involved and there is no extensive degenerative joint disease, bipolar cups should be used for increased stability and less morbidity (Fig. 43.7).

Internal fixation with cement has an unacceptably high failure rate [27].

Lane et al. reported the results from 167 patients who were treated with prostheses for impending or complete

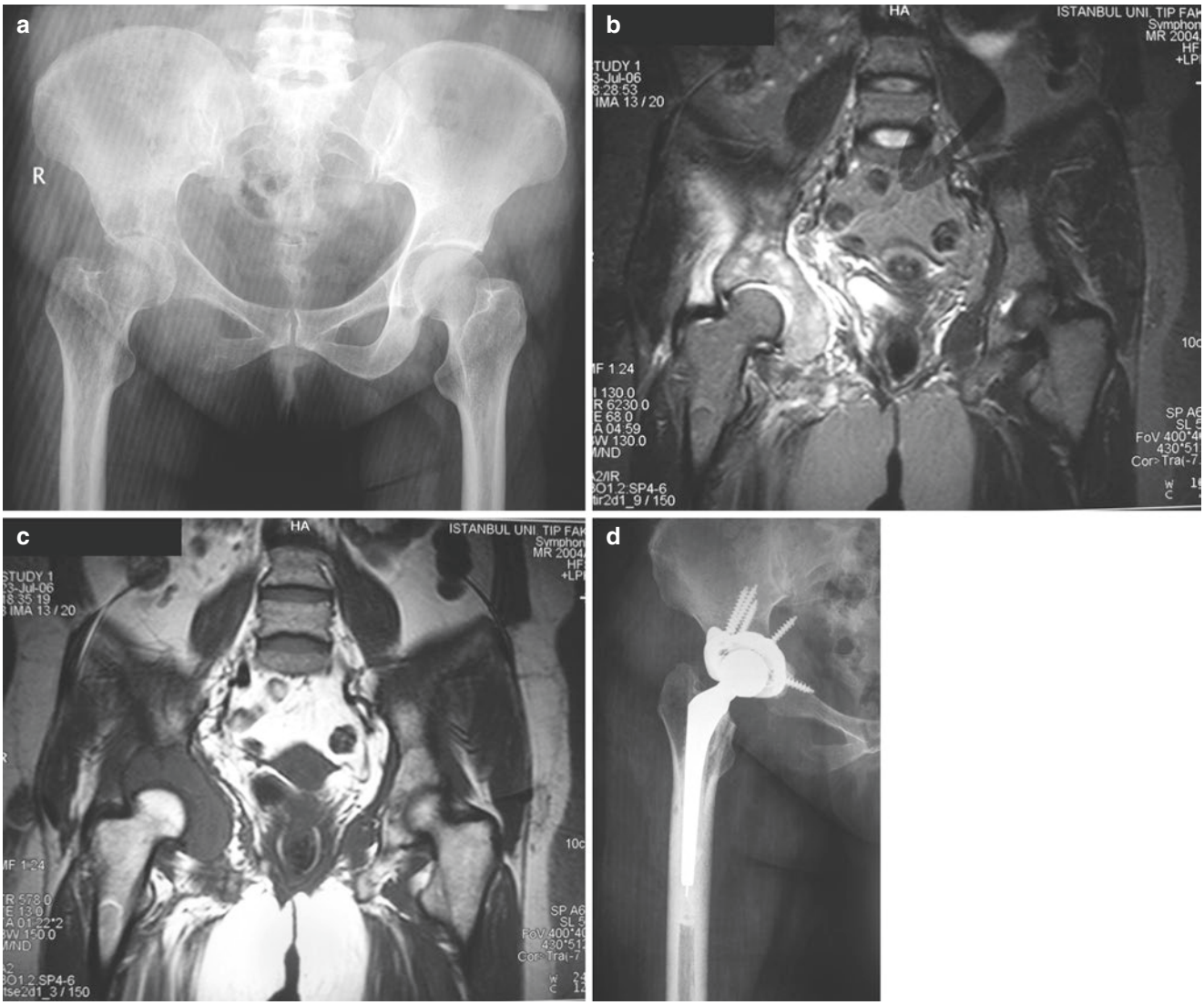


Fig. 43.7 A 41-year-old woman with breast carcinoma metastases to the acetabulum and femoral head. (**a**) AP pelvic radiograph reveals lytic metastatic lesions on the acetabulum, the inferior pubic ramus and the femoral head. (**b**, **c**) T2- and T1-weighted MRI images, respectively, show the metastatic lesion on the acetabulum. (**d**) Radiograph obtained after the resection of the acetabular metastasis and reconstruction with a cemented total hip arthroplasty, acetabulum reconstructed with an antiprotrusio cage

pathological fractures of the hip [28]. All of the patients reported a dramatic relief of pain. The ambulatory status was significantly enhanced in those patients who were able to walk, but the ambulatory status of the gravely ill was not improved.

Intertrochanteric Region

An intramedullary nail (open or closed) should be chosen for most cases. If there is not extensive bone destruction or if there is enough bone stock to fix locking screws, an intramedullary nail is recommended. An intramedullary nail protects the entire femur.

If there is extensive bone destruction, particularly in the medial cortex of the femur, an intramedullary nail and plate-screw fixation cannot provide long-term durability. For better fixation, cement should be added to the osteosynthesis. An implant failure may occur due to high mechanical stress at this level or to femoral head necrosis after irradiation.

If the intertrochanteric region has extensive bone destruction, resection of the proximal femur and reconstruction with a cemented modular megaprosthesis are preferred for better pain relief and immediate ambulatory function. Megaprosthesis for the proximal femur should contain a modular system, be long stemmed and cemented, and have no intramedullary plug.

A calcar replacement prosthesis should be chosen for lesions with extensive bone destruction on the medial side of the proximal femur [27].

The cement acts as an adjuvant chemotherapeutic agent in the medullary canal. Cemented implants are less effective than non-cemented implants along with post- or preoperative irradiation.

Soft tissue coverage is important to avoid prosthetic luxation. A pelvic-hip abduction brace can be used to protect the muscle reattachment sutures during the 6 weeks of soft tissue healing [27].

Subtrochanteric Region

For subtrochanteric impending fractures or pathological fractures, the best treatment choice is an intramedullary nail (nearly the length of the entire femur) fixed with cement (Fig. 43.8). Compared with a plate-nail system (DHS), the nail shares the load and is resistant to bending stresses.

Zickel and Mouradian reported successful results in the treatment of 35 pathological fractures and 11 impending fractures in the subtrochanteric region with a specially designed intramedullary nail [29]. Early mobilization or ambulation was achieved in nearly all of the cases.

The surgeon should avoid creating new fractures during the process of reaming and placing the nail into the canal; for this reason, the nail diameter should be 2 mm smaller than the last reamer used. If there is not enough bone stock, locking screws should be supported with cement.

Proximal femur megaprostheses are potential approaches for lesions that are resistant to medical therapy and have extensive bone destruction of the head, neck, and peritrochanteric region and for which proximal locking screw fixation is not possible.

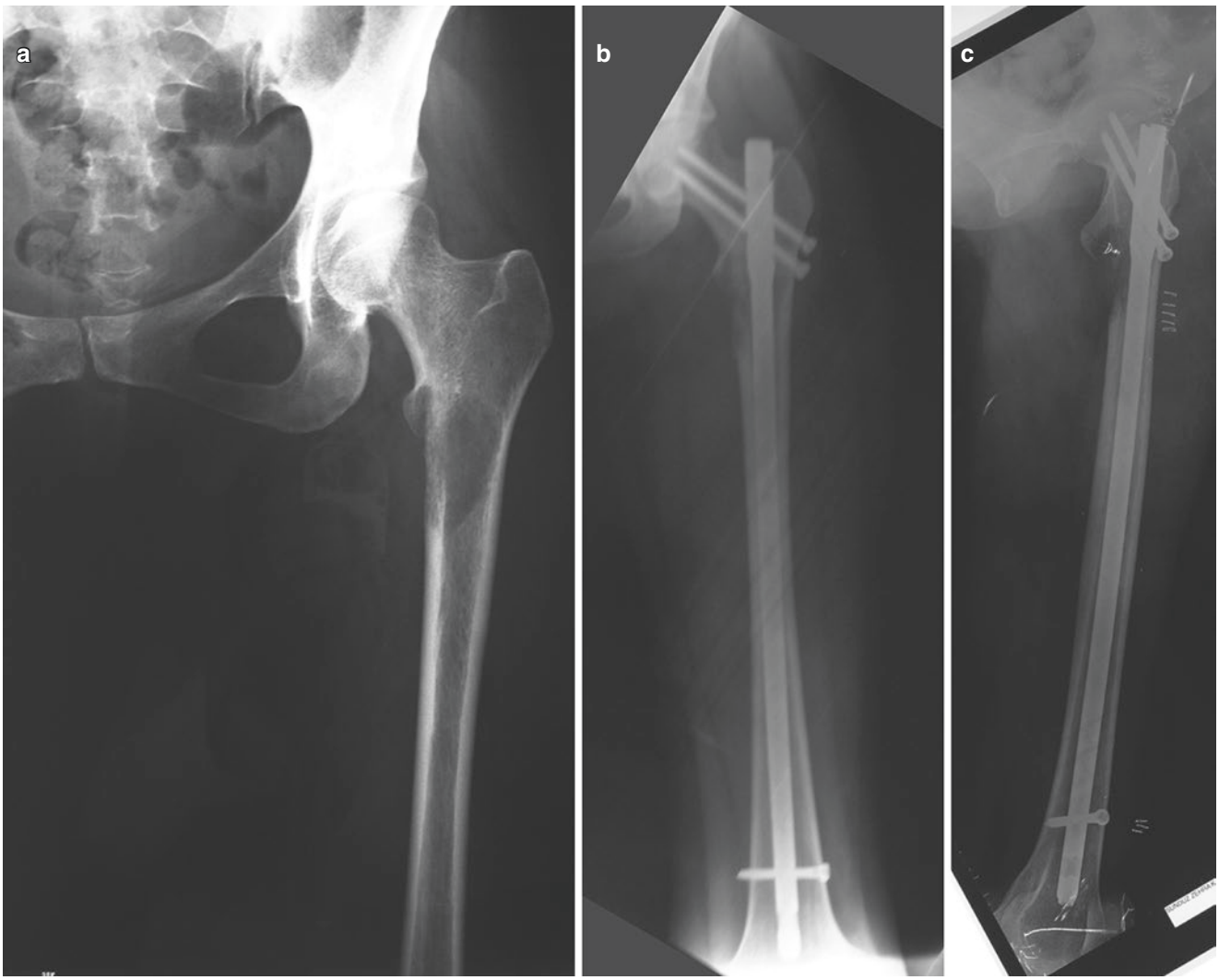


Fig. 43.8 Radiographs of the left femur of a 42-year-old woman with metastatic endometrial carcinoma. (**a**) AP view indicates an osteolytic lesion in the subtrochanteric region. (**b**, **c**) Biplanar radiographs of the entire femur; stabilization was achieved with an intramedullary reconstruction nail

Diaphyseal Region

Pathological fractures or impending fractures of the shaft region should be treated with an intramedullary nail with or without cement. A plate-screw fixation also provides rigid fixation, but a nail fixation system has a greater long-term advantage.

Distal Femoral Region

Metastatic lesions of the distal femoral region are unusual and difficult to treat. The most common treatment option is open reduction, curettage, and plate fixation with cement.

Retrograde intramedullary nailing can be performed if there is no extensive bone destruction. If there is extensive bone destruction, a constrained and cemented total knee prosthesis or modular-type distal femoral knee arthroplasty can achieve immediate stability and full weight bearing.

Tibia

Breast cancer metastases of the tibia are rarely observed and mostly occur in the metaphyseal region. The preferred method of treating metaphyseal region metastases is resection and the use of a cemented tibial prosthesis.

Spinal Metastases

Bone metastases of breast cancer are most commonly observed in the spine. Nearly 16–37% of breast cancer patients develop spinal metastases. Symptomatic vertebral metastatic lesions occur in the thoracic (68–70%), lumbosacral (16–22%), and cervical (8–15%) spine. Vertebrae are common target sites because of the highly vascular vertebral marrow and the extradural Batson's plexus [30, 31]. Some authors believe that the Batson's plexus is the route by which breast cancer cells metastasize to the thoracic spine. Prostate cancer cells similarly use Batson's plexus to metastasize to the lumbar spine.

There is a direct correlation between the vertebral body size and the influence of metastases.

An early diagnosis is essential to improve or preserve neurological function and maximize the quality of life. An early diagnosis is possible with clinical suspicion, and clinical suspicion begins with carefully listening to the patient's history and consequently conducting a detailed clinical examination (Fig. 43.2).

Clinical Presentation, Evaluation, and Imaging

Patients with spinal metastasis primarily complain about axial pain (85–96%) [32]. The pain is characteristically non-mechanical and progressive, includes severe night pain, and does not resolve with routine painkillers. Extension of the tumor or collapse of the involved vertebra can cause neurologic symptoms. The neurological symptoms depend on which area of the medulla spinalis is involved. Nerve root compression leads to radicular pain, whereas spinal cord compression leads to myelopathy. A proper examination, which includes palpation for local tenderness and determining the limitation of motion and signs of nerve root or spinal cord compression and deformity, is critical. Kyphosis is the most common deformity due to vertebral compression fractures.

Plain radiographs must be obtained in two directions. A vertebral collapse and deformities can be easily observed, but at least 50% of the bone must be lost to visualize a lesion in a plain radiograph.

Despite negative plain radiographs for a patient with a suspected or known malignancy, a bone scan is necessary. A bone scan can demonstrate skeletal metastases 3–18 months before their appearance on plain radiographs. A bone scan is a highly sensitive test but is not as specific as an MRI scan. MRI can differentiate between compression fractures resulting from osteoporosis and those caused by metastatic lesions [30, 33].

For evaluating spinal lesions, a CT-guided biopsy is safe and is an intervention with low morbidity. A transpedicular approach under fluoroscopic guidance, similar to that used for kyphoplasty, is also safe and associated with low morbidity. The diagnostic accuracy of CT-guided spinal biopsy ranges from 93% for lytic lesions to 76% for sclerotic lesions [34].

Indications

There are three indications for the surgical treatment of metastatic disease of the spine: a significant or progressive neurological deficit, deformity progression, and intractable pain. The risk factors for a progressive neurological deficit include osteolytic lesions and pedicle and posterior wall involvement. However, the decision to proceed with surgical intervention is not based on these three factors; the surgical decision must be individualized. Indeed, all treatment modalities for spinal metastasis are palliative, not curative; therefore, a general assessment of the patient's overall health, comorbidities, and life expectancy is important for the decision. The main goal is improving the quality of life, as is the case with other metastatic regions.

Most authors agree that a surgical treatment option is appropriate if the estimated life expectancy is longer than 3 months. Tokuhashi et al. published a scoring system for evaluating the prognosis of cancer patients with spinal metastases [35] (Table 43.2). This scoring system is widely acknowledged.

Table 43.2 Tokuhashi scoring system for preoperative evaluation of patients with a metastatic spine tumor [35]

Parameter	Score
General condition	
Poor	0
Moderate	1
Good	2
No. of extraspinal bone metastases	
≥3	0
1 or 2	1
0	2
No. of metastases in the spine	
≥3	0
2	1
1	2
Metastases to major internal organs	
Irremovable	0
Removable	1
No metastases	2
Primary site of cancer	
Lung, stomach	0
Kidney, liver, uterus, other	1
Thyroid, prostate, breast, rectum	2
Myelopathy	
Complete	0
Incomplete	1
None	2

Kostuik et al. developed a system to evaluate the stability of spinal tumors based on the three-column classification of Denis [36]. This model divides each vertebral segment into two (left and right) anterior columns, two middle columns, and two posterior columns. The destruction of fewer than three columns is considered to be stable, whereas the destruction of five to six columns is considered to be markedly unstable.

Nonsurgical Treatment

Known metastatic lesions that are not painful and are not at risk of creating instability may be followed without any treatment.

Site-directed radiation, with or without chemotherapy, is the mainstay for treating painful metastatic lesions that do not compromise neural structures [30]. Breast cancer is moderately sensitive. A radiation oncologist should take care not to compromise potential surgical approaches. Additionally, hormone therapy can be used to support bone structure.

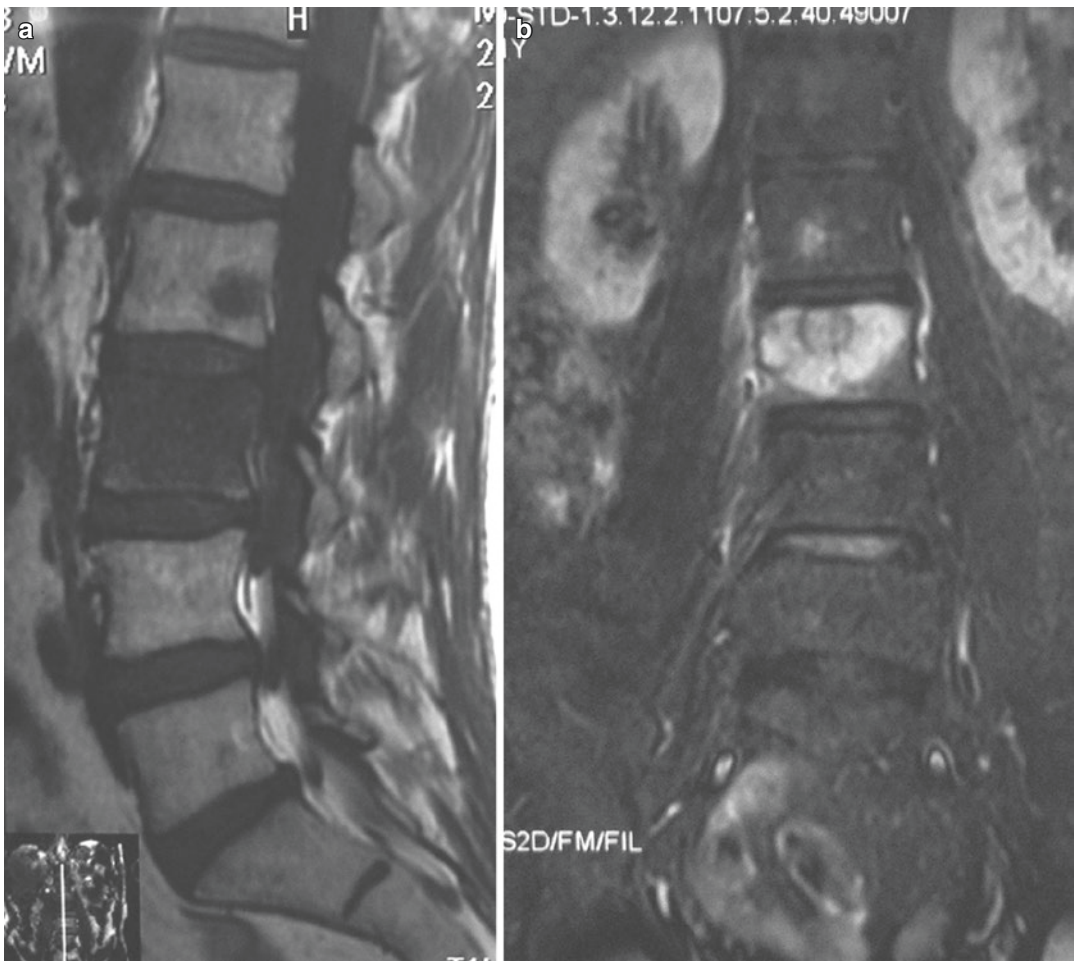
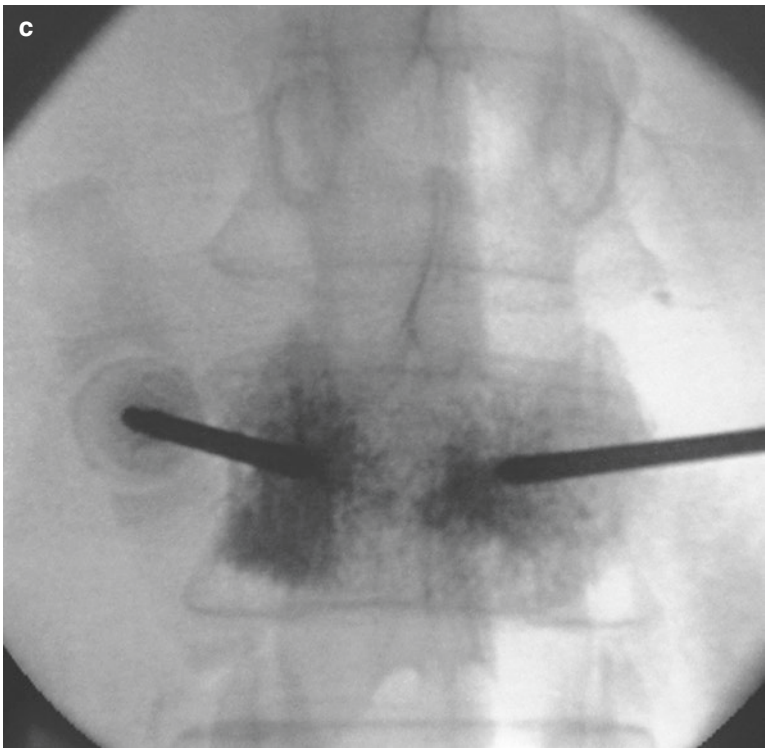


Fig. 43.9 (**a**–**c**) L3 vertebral metastases from breast carcinoma with impending fracture and pain. Percutaneous biopsy, frozen section, and vertebroplasty. Beware of intact posterior wall, no direct neural compression by the tumor

Fig. 43.9 (continued)



Surgical Treatment

The surgical options for treating spinal metastases include the following: an anterior vertebrectomy and stabilization, posterior decompression and stabilization, an anterior/posterior combination approach, vertebroplasty, and kyphoplasty.

Vertebroplasty and kyphoplasty are useful and minimally invasive procedures that can be applied to pathological vertebral compression fractures with minimal deformity, along with the percutaneous injection of bone cement to stabilize the vertebral body. An intact posterior wall and a lack of direct neural compression are important to reduce the risk of complications arising from the extrusion of cement. Furthermore, this procedure is contraindicated in the event that uncorrected coagulopathy is present. A tumor biopsy is often performed with this technique (Fig. 43.9). A study involving 97 cement augmentation procedures performed in 56 patients with various metastatic spinal tumors revealed that an improvement or complete relief of pain was achieved in 84% of the procedures [37].

For an open surgery, the choice of approach depends on the location of the tumor and the goal of the operation; an anterior, posterior, or lateral approach or a combination of these approaches may be used. The majority of tumors invade the vertebral body; therefore, the anterior approach may often represent the most direct route to the lesion [37]. Kostuik et al. reported the return of neurological function in 40% of posterior decompressions and 71% of anterior decompressions [36]. The posterior approach can provide good visualization and allow persistent stabilization, but the anterior approach prevents excessive normal bone loss [21].

Minimally Invasive Treatments

Percutaneous interventions are used for painful bone metastasis with increasing frequency. As mentioned above, these mainly consist of percutaneous cementoplasty for spinal lesions and other long bone lesions. Other image-guided percutaneous interventions can be divided into two main categories; ablation and vascular procedures. Ablation procedures consist of radiofrequency thermal ablation (RFA), microwaves (MW), laser ablation, magnetic resonance-guided focused ultrasound surgery (MRgFUS) and cryoablation (CA).

Vascular procedures can vary according to the field of application. Transarterial embolization, one of the most frequently used vascular procedures, is selective temporary or permanent occlusion of the vessels supplying the tumor to cause ischemia and cell death. Transarterial embolization is mainly employed to reduce operative hemorrhagic risks and is also employed to palliate pain and increase tumor sensitivity to chemo- or radiation therapy.

Although conventional radiotherapy is generally chosen for painful metastatic lesions, ablation procedures can also be chosen instead of conventional radiotherapy. In addition, some patients have experienced recurrent pain at a previously

irradiated site or other side effects of radiotherapy. Ablation techniques have some advantages compared to radiotherapy. The pain decreases immediately after treatment, and lesion size and temperature can be monitored to avoid damage to sensitive structures surrounding the lesion [38]. There are few studies in the literature about ablation techniques for metastasis. Staso et al. showed that radiofrequency ablation and cryoablation with and without radiotherapy are effective in terms of pain relief [39, 40]. Callstrom et al. reported data for 12 patients treated with RFA, and 61.5% experienced pain relief within 4 weeks. In another study of the same group, 61 patients with bone metastasis were treated with CA, and 91% achieved pain relief within 24 weeks [40, 41]. MRgFUS is the most recent technique described in the literature [42, 43]. These studies suggest that this technique can be effectively and safely used not only to control pain related to bone metastases but also for curative treatment of a single or few lesions.

The most appropriate technique for treatment should be chosen according to the characteristics of the lesion. Vascularization is the first condition to be assessed. In the presence of high vascularization, embolization prior to the ablation procedure is indicated. Second, the site of the lesion should be carefully analyzed. MRgFUS can be chosen for a lesion developed on the bone cortex that is well exposed to the penetration of the ultrasound beam. For deep or medullary lesions, RFA can be used for small lesions (up to approximately 4 cm). Larger volumes are treated more successfully with MWs or cryoablation. For the latter, these techniques can be combined with cementoplasty, particularly when consolidation is needed to avoid pathological fracture, particularly weight-bearing bones, such as the vertebral body, acetabulum, and even long bones [38, 44, 45].

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Part VIII

Review of the Breast Cancer Management

A Review of Local and Systemic Therapy in Breast Cancer

44

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Introduction

Breast cancer is the most frequently diagnosed cancer in women. Globally, but particularly in developed countries, breast cancer is a major public health problem, with one million new cases diagnosed annually. Age, family history, and both endogenous and exogenous ovarian hormone exposure have important effects on risk and have been incorporated into models that predict individual risk of breast cancer; diet, alcohol use, and other factors play smaller roles. Inherited mutations play a role in the development of hereditary breast cancer. In this chapter, we have attempted to provide a summary of useful and explicit recommendations for management, but we must stress that these recommendations are subject to change. Some of the recommendations are controversial and the subject of ongoing clinical trials. The gold standard for breast cancer care includes an integrated multidisciplinary team approach comprising pathologists, radiologists, surgical oncologists, medical oncologists, radiation oncologists, oncology nurses, and plastic surgeons.

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Breast Cancer Staging

The tumor-node-metastasis (TNM) staging system for breast cancer described by the American Joint Committee on Cancer (AJCC) applies to invasive and in situ carcinomas with or without microinvasion [1–3]. This classification system was introduced to reflect the risk of recurrence and to be used as a standard prognostic assessment tool for patients with newly diagnosed breast cancer. Improved understanding of prognostic and predictive biological markers, such as estrogen receptor (ER) and HER2 overexpression, has been used to predict the response to systemic therapies (antiestrogen, anti-HER2) [4–6]. Therefore, rapid advances in both clinical and laboratory sciences along with translational research have raised questions about the feasibility of TNM staging as a guide to determine whether to apply systemic therapy based on anatomic prognosis. A validation study has recently been reported emphasizing that the prognostic stage provided more accurate prognostic information than the anatomic stage alone, thereby supporting its use in breast cancer staging [6]. Furthermore, breast cancer therapy has evolved with the increasing application of neoadjuvant therapy, and therefore, additional pretreatment and posttreatment staging was incorporated into this staging system to determine chemotherapy response and treatment efficacy.

In the last update in AJCC Breast Cancer Staging, with advances in personalized medicine, more molecular gene assays and new prognostic and predictive markers were incorporated [2, 7–9]. Lobular carcinoma in situ (LCIS) is removed from TNM staging. The anatomic stage table, clini-

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cal prognostic stage table, and pathological prognostic stage table were added in the eighth edition. The pathological stage table is based on clinical information, biomarker data, and findings from surgery and resected tissue. The largest contiguous tumor or tumor deposit is used for pT and pN; for the primary tumor, for the size of multiple tumors, or for lymph nodes, adjacent satellite tumors are not added. The last edition clarified the postneoadjuvant therapy pathological T category (ypT). It is based on the largest contiguous focus of residual invasive cancer, if present. When multiple foci of residual tumor are present, the (m) modifier is included. Although multigene expression assays may provide additional prognostic and predictive information beyond anatomic TNM staging and ER/PR and HER2 status, there might be difficulties in incorporating these biomarkers into the TNM system. In the AJCC eighth edition, for patients with T1 and T2 hormone receptor-positive, HER-2-negative, and lymph node-negative tumors, a multigene panel is included for pathological prognostic staging. In the low-risk range regardless of T size, these tumors are placed into the same prognostic group category as T1a–T1bN0M0.

Carcinoma In Situ

The most common types of breast carcinoma in situ are LCIS and ductal carcinoma in situ (DCIS). The workup for in situ carcinomas includes patient history, physical examination, bilateral mammography, and careful review of pathology. ER positivity should be assessed in DCIS, whereas it is not recommended in LCIS patients. Breast MRI is not currently a routine workup examination for in situ carcinomas, but it may be useful for select patients.

Lobular Carcinoma In Situ

Because the treatment approach is similar to that for benign disease, LCIS is removed from TNM staging. Disagreement exists about whether a surgical excision should be performed of the area of LCIS diagnosed by core needle biopsy. Most of the studies have shown that around 25% of patients with LCIS diagnosed by core needle biopsy will be upgraded to having invasive cancer or DCIS after excisional biopsy [10]. Determining the subtypes of the LCIS based on core needle biopsy may be helpful to differentiate patients who can be spared a surgical excision. Pleomorphic LCIS and/or multifocal/multicentric LCIS may behave similarly to DCIS; thus, surgical excision with negative margins may be considered [11] (American Pathologists Protocols and Guidelines. Available at http://www.cap.org). More than four foci of LCIS may also strengthen the possibility for upstaging on surgical excision. The usual type of LCIS found on core biopsy (affecting less than four terminal units in a single core), without imaging discordance, may be managed by radiological follow-up. All LCIS patients should be counseled on risk-reduction strategies.

Ductal Carcinoma In Situ

The standard treatment for DCIS is breast-conserving lumpectomy with negative surgical margins (without axillary intervention) and whole-breast radiation (Fig. 44.1). If negative margins cannot be attained by breast-conserving surgery or because of extensive disease (˃4 cm disease or disease in more than one quadrant), mastectomy must be performed [12]. Nonpalpable disease needle localization or other image-guided techniques are utilized to guide surgical resection. Specimen mammography is usually performed for margin assessment. Either aromatase inhibitors (AIs) or tamoxifen can be effective adjuvant treatment options to lower the risk of recurrent DCIS [13, 14].

Patients should be evaluated for hereditary breast cancer risk, and genetic counseling should be provided to DCIS patients with high-risk features. An overall prevalence of 27% was shown for deleterious BRCA1/2 mutations in high-risk women diagnosed with DCIS, supporting the presence of an in situ phase of carcinogenesis in the development of at least some BRCA-associated breast cancers.

Sentinel node biopsy should be routinely performed in patients with high-grade DCIS who will undergo mastectomy or for whom breast-conserving surgery will not allow further sentinel node biopsy in the case of future recurrences [15].

Paget's disease of the breast is characterized by eczema-form changes accompanied by erosion and ulceration of the nipple and areolar epidermis. This condition is primarily correlated with ductal carcinoma in situ (DCIS); additionally, it can be accompanied by invasive ductal carcinoma (IDC). The diagnosis is determined upon microscopic observation of Paget cells in a skin biopsy. The width of the lesion is evaluated via mammography and MRI in patients for whom breast-conserving surgery is planned. Depending on the extent of the lesion, SLNB and axillary curettage for those with axillary metastases are treatment alternatives to breast-preserving surgery or mastectomy (Fig. 44.2).

Surgical Margin

Re-excision is not required for surgical margins of 2–5 mm in DCIS. Multifocality and an increasing number of close or involved margins have been identified as predictive of additional disease on re-excision. These factors may be surrogate markers of an increased extent of disease. If the surgical margin is less than 1 mm at the skin or chest wall, boost radiation at a higher dose to the involved site should be provided instead of re-excision [16]. Recent consensus guidelines

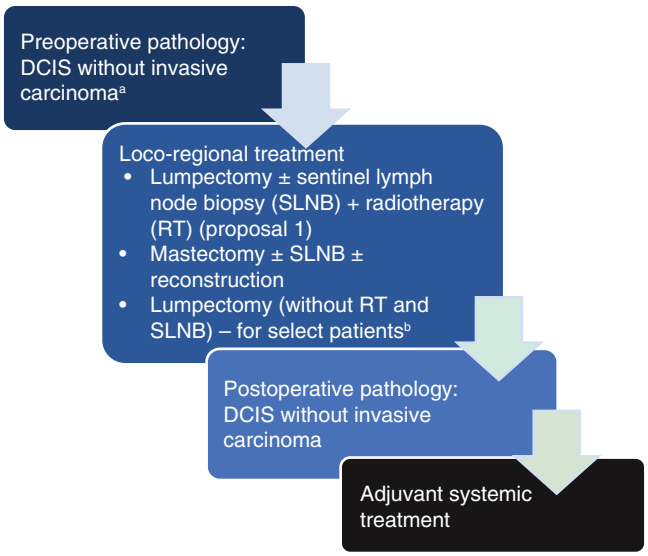

Fig. 44.1 Management of patient with ductal carcinoma in situ (DCIS). [a]Preoperative MR imaging is recommended in DCIS. The specimen should be evaluated with X-ray imaging. Radiation therapy after breast-conserving surgery is the standard treatment in DCIS. The disease-free surgical margin should be adequate. A sufficient surgical margin should be decided together with clinical, radiological, and pathological findings. The decision regarding the "sufficient surgical margin" should be made according to findings such as additional radiological foci (multiple foci, microcalcification), invasive lobular carcinoma, presence of more than one surgical margin, and persistence of surgical marginal proximity in re-excision. [b]ER-positive, postmenopausal case, advanced age, low-grade tumors

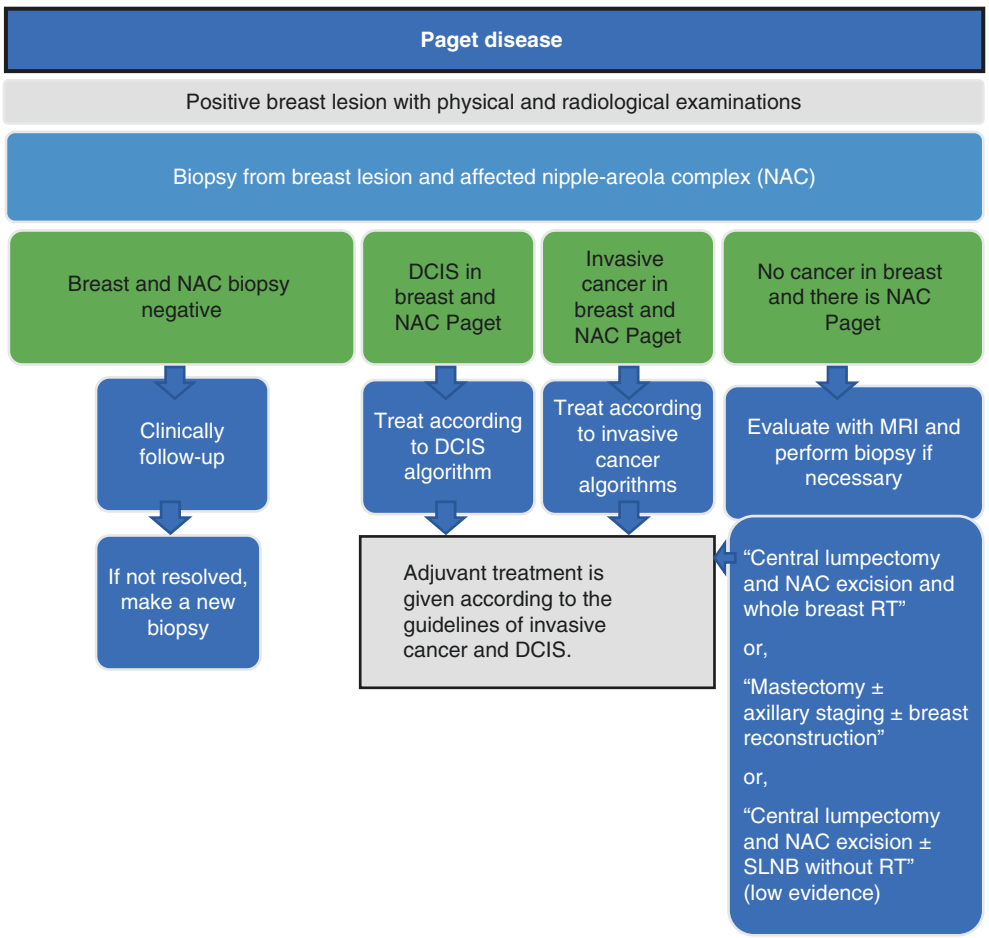

Fig. 44.2 Management of Paget disease

issued jointly by the Society of Surgical Oncology and the American Society for Radiation Oncology, which recommend "no ink on tumor" as the standard for an adequate margin in invasive cancer, caution that these findings cannot be extrapolated to DCIS. The Surgical Society of Oncology (SSO), American Society of Clinical Oncology (ASCO), and American Society for Radiation Oncology (ASTRO) guidelines recommended that a margin of 2 mm is sufficient to avoid re-excision [17]. For pure DCIS, margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths in patients receiving whole-breast radiation treatment. The evidence does not support the routine practice of obtaining negative margin widths wider than 2 mm. DCIS with microinvasion (defined as no invasive focus more than 1 mm in size) should be considered as DCIS when considering the optimal margin width. For patients treated with excision alone (without radiation), regardless of margin width, the risk of IBTR is substantially higher than treatment with excision and whole-breast radiation therapy (even in predefined low-risk patients). The optimal margin width for treatment with excision alone is unknown, but it should be at least 2 mm. Some evidence suggests lower rates of IBTR with margin widths wider than 2 mm.

Radiotherapy

If total mastectomy is performed with negative margins, adjuvant irradiation is not required. If nipple-sparing mastectomy and reconstruction are performed, nipple-areola complex irradiation is not standard. Breast tissue that is inadvertently left under the skin flaps should not be an indication for postoperative radiotherapy.

The recently defined adequate surgical margin for DCIS is 2 mm for patients treated with BCS and whole-breast RT in the consensus guidelines by the SSO, ASCO, and ASTRO [17]. However, close margins at the chest wall or skin do not warrant re-excision for DCIS, but a higher boost dose to the involved lumpectomy site. Moreover, the boost to the tumor bed may be an indication especially for patients ≤50 years of age with negative margins to minimize local recurrence [12, 18].

In cases treated with lumpectomy, adjuvant radiotherapy using partial-breast irradiation (PBI) techniques is under investigation in randomized trials; such an approach should be considered "with caution" according to the American Society for Radiation Oncology and other groups [19–21]. Lumpectomy without radiotherapy has been investigated in prospective and randomized trials in patients considered to be at low risk of local recurrence [17, 22]. In such low-risk DCIS patients, whole-breast radiotherapy should be considered in the decision-making process with the patient, accounting for age, comorbidities, radiation risks, patient preferences, and salvage options [12]. Radiotherapy following breast-conserving surgery is optional in DCIS patients with low-risk features (>60 years of age, ER positive, tumor diameter <1 cm, low grade, negative margins, no palpable mass) [18]. For a patient to be considered a low-risk DCIS case, the following criteria must be present: mammographic detection, no palpable mass, small tumor, ER positive, nuclear grade I or II, and clear surgical margins of at least 2 mm [12]. All other DCIS cases treated with lumpectomy are candidates for whole-breast irradiation [19–25].

The safety and efficacy of hypofractionation (40–42 Gy/15–16 fraction) and boost for DCIS compared with conventional fractionation have been shown in a meta-analysis. The patients with positive margins benefited from a boost to the tumor bed based on this analysis [18]. The results of ongoing randomized trials are pending to clarify the role of hypofractionation (the TROG 07.01 trial) and boost RT [(the TROG 07.01 trial (NCT00470236) and the Bonbis trial (NCT00907868)] in patients with DCIS.

Systemic Treatment

The marked reduction in recurrence rates following tamoxifen for 5 years after diagnosis in women with ER-positive DCIS reported by the NSABP B-17 and B-24 trials resulted in an increased use of tamoxifen as an adjuvant therapy [26]. Despite this reduction ratio, 5-year tamoxifen is not routinely prescribed worldwide. The benefit of tamoxifen in ER-negative DCIS patients to reduce the risk of breast cancer recurrence after breast-conserving surgery and radiotherapy is uncertain, and tamoxifen should not be routinely recommended to ER-negative DCIS patients [26, 27]. Tamoxifen may be given to reduce the contralateral breast cancer risk in both premenopausal and postmenopausal patients with ER-positive DCIS after mastectomy. AI can be a safe and effective alternative endocrine therapy for postmenopausal women (particularly, in patients younger than 60 years of age) with ER-positive or PR-positive DCIS [13, 14].

Conclusion

Classic LCIS does not require surgical treatment. There is evidence to support the existence of histologically aggressive variants of LCIS (e.g., "pleomorphic LCIS"), which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma. Surgeons may consider complete excision with negative margins for pleomorphic LCIS.

Most DCIS patients with limited disease may be treated with wide local excision or with re-excision in which negative margins are achieved. Patients with widespread disease (i.e., disease in two or more quadrants) require total mastectomy with SLN biopsy. Complete ALND is not recommended in the absence of proven axillary metastatic disease in patients with apparent pure DCIS or mammographically detected DCIS with microcalcifications. However, a small proportion of women with pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure

and thus will ultimately require ALN staging. In patients with seemingly pure DCIS to be treated with mastectomy, or with excision in an anatomic location (e.g., tail of the breast), which could compromise the performance of a future SLN biopsy, SLN biopsy may be considered. Endocrine therapy may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast-conserving therapy. The benefit of endocrine therapy for ER-negative DCIS is not established.

Invasive Breast Cancer

Diagnosis

Personal and family histories; physical examination; complete blood count; blood biochemistry, including liver function tests and alkaline phosphatase levels; mammography; and pathology review, including receptor status determination, are the main components of a breast cancer workup.

For clinically early-stage disease (without N2 or T4 and with M0), screening for systemic metastasis in the absence of symptoms or signs of tumor spread should not be routinely performed before surgery in all patients. Only patients with symptomatic stage I–II disease should be screened for systemic metastasis. Before surgery, bone scintigraphy and thoracoabdominal imaging methods such as CT or MRI may be performed in patients with clinically stage IIIA disease (T3N1M0). Positron emission tomography (PET-CT) is not a routine diagnostic or screening test in stage IIIA (T3N1M0) disease unless standard staging tests cannot determine if metastasis is present.

Breast MRI is not a routine diagnostic test for all breast cancer patients, except under special conditions. Breast MRI may be performed to determine the multifocality/multicentricity of the tumor and to screen the contralateral breast for cancer when mammography and breast ultrasonography are inconclusive for malignancy [28]. In patients with occult axillary involvement, breast MRI can be used to detect a primary breast tumor that was not diagnosed with routine diagnostic tests such as mammography and breast ultrasonography [28]. In addition, in patients with Paget's disease who desire breast-conserving surgery, breast MRI may be performed to evaluate the breast for any additional invasive tumor. Patients with dense breast tissue should be routinely examined with breast MRI. Breast MRI must be performed only with breast coil-containing machines and must be evaluated by a radiologist with breast MRI expertise. For suspicious breast lesions, biopsy with wire localization should be performed if possible; otherwise, patients with suspicious lesions must be referred to centers that can provide further investigation.

Pathology

The pathology report must provide uniform information regarding the tumor and should include at least the parameters recommended in the ASCO-CAP guidelines. Ki67 should be included in all breast cancer pathology reports [29].

For surgical margin evaluation, pins, inking, or any other marking should be applied to the surgical specimen for orientation. In addition, the microscopic margin status and tumor type (DCIS or invasive carcinoma) near the surgical margin must be clearly defined [30].

An extensive intraductal component can be defined as breast cancer if the DCIS volume is greater than 25% of the invasive tumor volume and if the DCIS component is spreading to the normal breast parenchyma.

Molecular subtypes of breast cancer can be distinguished with common pathological variables, including ER, progesterone receptor (PR), HER2, and Ki67 index. In HER2-negative breast cancer, the ER and PR statuses are not sufficient to distinguish "luminal A" subtype from "luminal B." However, by including the Ki67 proliferation index status, "luminal A" can be defined as ER+, PR+, HER2−, and low Ki67 proliferation index tumors [31]. "Luminal B" can be defined as ER+, PR− (<20% positive), HER2−, and/or high Ki67 proliferation index tumors [31]. Tumors with Ki67 ≥20–29 should be accepted as having a high proliferation index, and tumors with Ki67 <15 should be accepted as having a low proliferation index, although the standardization of Ki67 tests between laboratories remains problematic. "Basal-like/triple-negative breast cancer" may be CK5/6+ and/or EGFR+.

Chemotherapy should be included in adjuvant regimens according to the intrinsic tumor subtype. The decision regarding cytotoxic treatment (whether to use anthracycline, etc.) as an adjuvant regimen should not be planned based solely on the intrinsic tumor subtype.

Multigene expression array profiling is not required for subtype definition in all cases after clinicopathological assessment. In "luminal B" (HER2-negative) patients and lymph node-negative, ER+, and HER2− patients, multigene signature profiling may be performed, whereas in node-positive, ER+, and HER2− patients, multigene signature profiling is not required. However, the number of involved lymph nodes may change the decision regarding multigene signature [12, 31–34].

The percentage of hormone receptor positivity required for designating a tumor as hormone receptor positive and, consequently, to initiate endocrine therapy should be 1%.

In endocrine-responsive breast cancer patients, multigene expression array profiling should be used to select patients who might benefit from receiving adjuvant chemotherapy [33, 34]. Predicting chemotherapy response differs from predicting prognosis. Thus, the currently used multigene expres-

sion array profiling predicts only the recurrence risk and, thus, should not be directly used to predict the chemotherapy response of a tumor.

In hormone receptor-positive tumors, in the case of inflammatory breast cancer, or the involvement of ≥4 lymph nodes or a low ER% is an indication for adjuvant chemotherapy, and further molecular diagnostic tests can be omitted. Young age, grade III disease, one to three positive nodes, lymphovascular invasion, and large tumor size are not adequate features to omit molecular diagnostics in the decision to apply adjuvant chemotherapy [32] [34]. However, in some patients, combinations of these features may be adequate in the decision to apply chemotherapy.

The data regarding the pathological characteristics of tumor stroma, such as immunocyte infiltration, microvascular density, or stromal p16 staining, are insufficient to influence therapy choice in routine clinical practice.

Determination of the tumor grade should be based on the invasive ductal component of mixed type or metaplastic breast cancer.

Heterogeneous HER2 overexpression, concomitant estrogen receptor expression, and polysomy 17, as well as the degree of tumor proliferation, should not affect the decision to apply anti-HER2 treatment.

Surgical Approach in Invasive Breast Cancer

General Principles

The choice of treatment strategy is based on tumor features (location and size of the tumor, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression) and on the patient's age, general health status, and personal preferences. Patients should be actively involved in all management decisions (Fig. 44.3). The possibility of hereditary cancer should be explored, and, if necessary, prophylactic procedures should be discussed following appropriate genetic counseling and testing of the patient. In younger premenopausal patients, possible fertility issues should be discussed, and guidance regarding fertility preservation techniques should be provided before treatment initiation [35–44].

Breast-conserving therapy, axillary lymph node dissection, and whole-breast irradiation are equivalent to mastectomy with axillary lymph node dissection as the primary treatment for most women with stage I and stage II breast cancers [27, 45–47].

Lumpectomy is contraindicated for patients who are pregnant and would require radiotherapy during pregnancy, who have diffuse disease that cannot be locally removed via a single incision with an acceptable cosmetic result, who have widespread suspicious or malignant-appearing microcalcifications on mammography, or who have positive pathological margins after surgery. Patients with pathologically positive margins generally should undergo re-excision to achieve negative pathological margins. If the margins remain positive after re-excision, mastectomy should be performed to achieve optimal local disease control.

Relative contraindications for lumpectomy include previous radiation therapy to the breast or chest wall, an active connective tissue disease involving the skin such as scleroderma and lupus, tumors larger than 5 cm, and focally positive pathological margins. Those patients with focally positive pathological margins who do not undergo re-excision should be considered for a higher radiation boost dose to the tumor bed. To adequately assess margins following lumpectomy, surgical specimens should be oriented, and the pathologist should provide descriptions of the gross and microscopic margin statuses and the distance, orientation, and type of tumor in relation to the closest margin. A careful histological assessment of resection margins is essential, with the requirement that no tumor be present at the inked margin [48]. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field where appropriate. Acceptably low local recurrence rates remain the major quality assurance target. Current guidelines recommend that local recurrence rates after wide excision and radiotherapy should be <1% per year (with a target of <0.5%) and should not exceed 10% overall.

Contralateral Mastectomy

Only limited data are available on the survival impact of contralateral mastectomy in unilateral breast cancer [49]. Women with breast cancer who are ≤35 years or premenopausal and carriers of a known BRCA1/2 mutation may be recommended additional risk-reduction strategies following appropriate risk assessment and counseling. The lifetime risk of breast cancer in a BRCA1 carrier is 80–85%, with a 10-year actuarial risk of contralateral breast cancer ranging from 25% to 31%. With bilateral mastectomy, the risk of subsequent breast cancer incidence and mortality are both reduced by ~90–95%. A decision should be made by a multidisciplinary team prior to surgery and should include a discussion of the risks associated with the development of contralateral breast cancer compared with the risks associated with recurrent disease from the primary cancer. Except as specifically outlined in some situations, prophylactic mastectomy of the breast contralateral to unilateral breast cancer treated with mastectomy is discouraged. The use of prophylactic mastectomy contralateral to the breast treated with breast-conserving surgery is very strongly discouraged in all patients.

Despite the overall trend toward breast conservation, increasing numbers of breast cancer patients are opting for

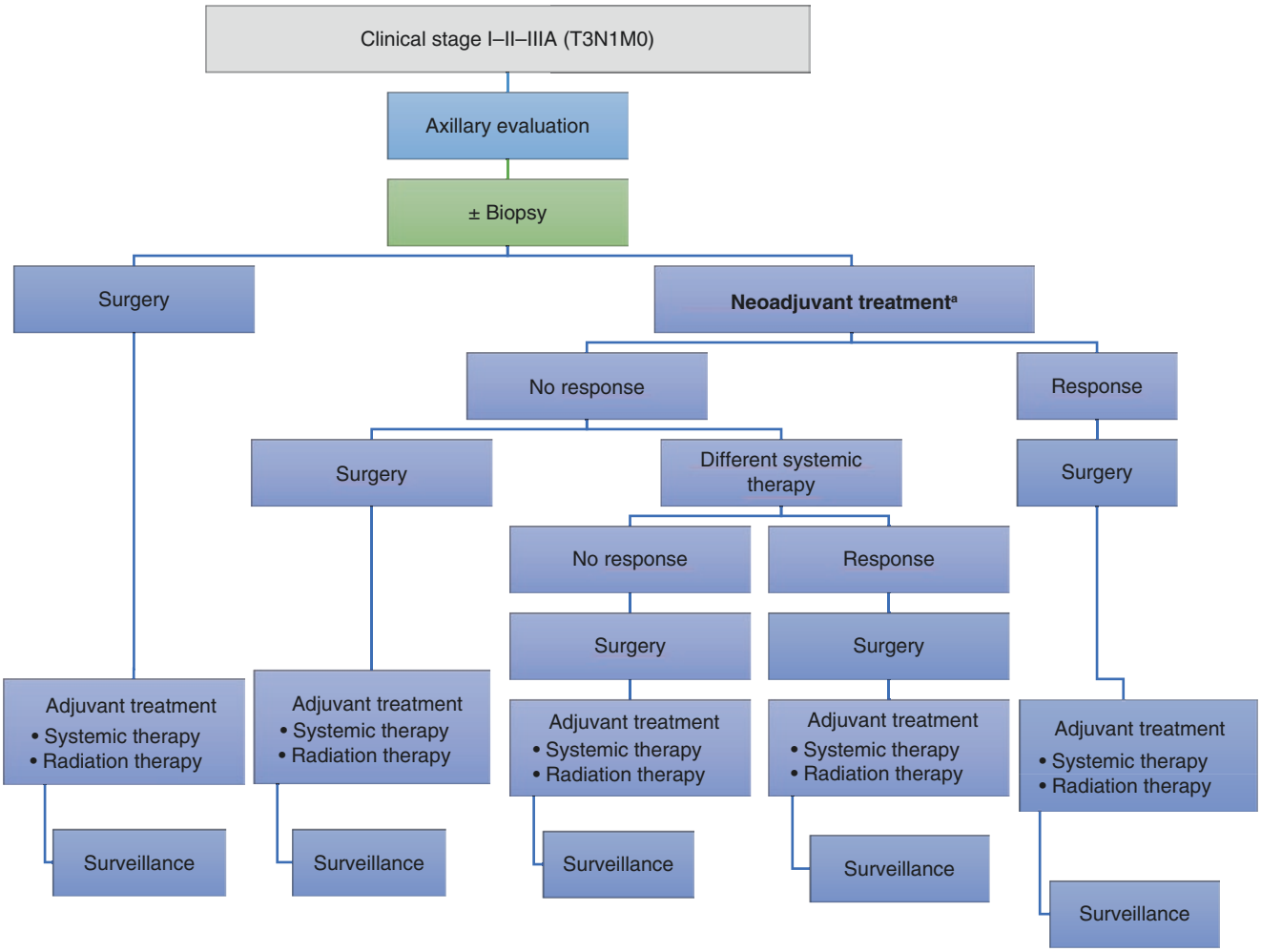

Fig. 44.3 Management of patients for stage I, II, IIIA (T3N1M0) breast cancer. [a]Neoadjuvant chemotherapy should be administered to T2 and T3 tumors (N0–N1) meeting BCS criteria except tumor diameter or to triple-negative and HER-2-positive patients

bilateral mastectomy (incorporating contralateral risk-reducing surgery) over breast conservation and mammographic surveillance of the irradiated breast. These patients should be properly counseled and informed of the finding that patients with early-stage breast cancer may have a superior outcome after breast-conserving therapy compared with mastectomy.

Axillary Staging

Sentinel lymph node (SLN) mapping and surgical excision of clinically lymph node-negative axilla are recommended to evaluate the pathological status of the axillary lymph nodes (ALNs) in patients with stage I or stage II breast cancer [50–56] (Fig. 44.4). This recommendation is supported by the results of randomized clinical trials revealing decreased arm and shoulder morbidity such as pain, lymphedema, and sensory loss in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard ALN dissection [56, 57]. An experienced SLN team is required for SLN mapping and excision [58, 59]. With appropriate training in the dual radiocolloid/blue dye or indocyanine green fluorescence technique, acceptably low false-negative rates and favorable axillary recurrence rates following SLNB are achievable. Women with invasive breast cancer and without access to an experienced SLN team should be referred to an experienced SLN team for definitive surgical breast cancer treatment and ALN staging. Candidates for SLN mapping should have clinically negative ALNs or a negative fine-needle aspiration (FNA) biopsy of any clinically suspicious ALN. There is no consensus for the pathological assessment of SLNB. The significance of occult micrometastases in terms of surgical management and patient outcomes appears to be negligible. Thus, routine IHC or PCR is not recommended for the evaluation of sentinel lymph nodes; treatment decisions should be made based on H&E staining [60].

Multiple attempts have been made to identify cohorts of women with SLN involvement at sufficiently low risk of non-SLN involvement. In these low-risk patients, complete

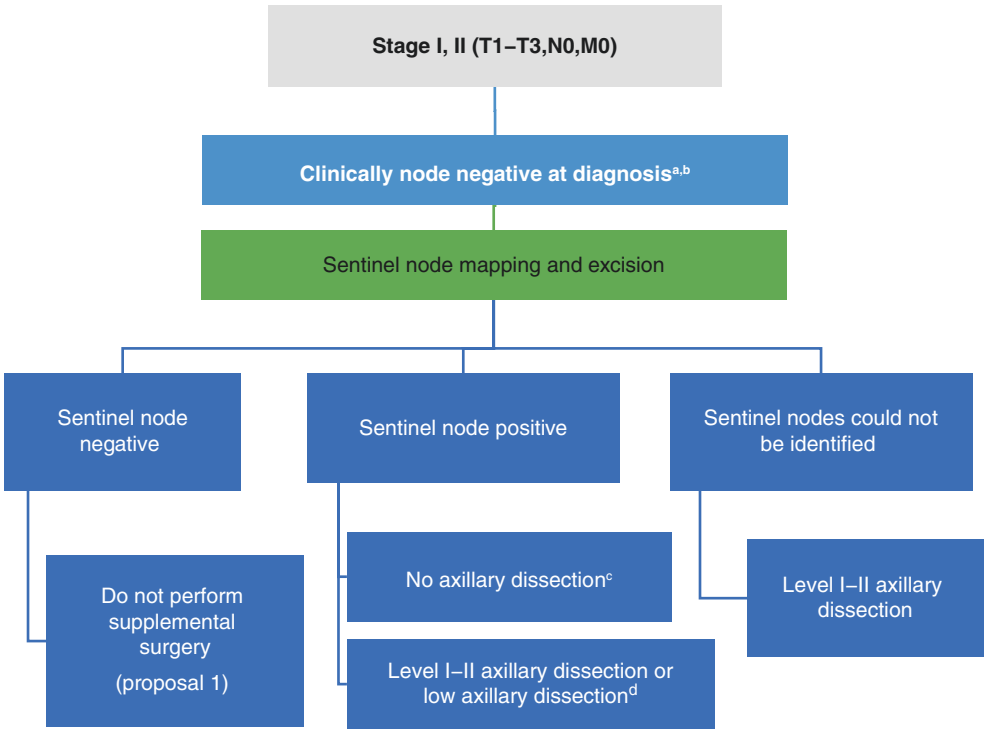

Fig. 44.4 Axillary management of patients with clinical node-negative stages I–II. [a]For breast-conserving surgery (BCS): In patients with macrometastases in 1–2 sentinel lymph nodes (SLNs), complete axillary dissection can be safely omitted when "conservative resection with radiotherapy (RT)" is performed. [b]For mastectomy: In patients with macrometastases in 1–2 SLNs, complete axillary dissection must be performed when "no adjuvant RT is planned"; however, in patients for whom RT is planned, no consensus exists for omitting axillary dissection. [c]In patients with T1 or T2 tumors with BCS and 1–2 positive SLNs, if there is no neoadjuvant chemotherapy and whole-breast irradiation is planned, axillary dissection is not needed. Consider axillary dissection for SLN-positive patients with triple-negative breast cancer. [d]Consider axillary dissection according to preoperative imaging results (mammography, ultrasonography, and PET/CT)

axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low-risk group of patients with positive SLN biopsies but consistently negative nonsentinel nodes [61–66]. Nonetheless, a randomized trial (ACOSOG Z0011) compared SLN resection alone to ALN dissection in women ≥18 years with T1/T2 tumors and fewer than three positive SLNs in women who were undergoing breast-conserving surgery and whole-breast irradiation [67, 68]. In this study, there was no difference in local recurrence, DFS, or OS between the two treatment groups. Only ER-negative status, age <50, and a lack of adjuvant systemic therapy were associated with decreased OS. At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of patients in the ALN dissection group and 2.8% of patients in the SLN dissection group ($p = 0.11$). The median OS was approximately 92% in each group [68]. Long-term follow-up (median 9.25 years) results of this study showed no statistically significant difference in local recurrence-free survival between the groups ($p = 0.13$) [67]. The 10-year cumulative incidence of local-regional recurrence was 6.2% with ALND and 5.3% with SLNB alone ($p = 0.36$). Updated results of the ACOSOG Z0011 trial confirm the previous results that ALND is not needed in women with early-stage breast cancer who will receive whole-breast radiation treatment as part of breast-conserving therapy. In addition to this study, the results of the IBCSG 23-01 trial indicate that further axillary treatment is not required when a sentinel node has micrometastasis (0.2–2 mm) [69].

According to all these results, patients with T1 or T2 tumors and one to two positive SLNs who are undergoing lumpectomy plus breast irradiation may not require any further axillary procedure. However, these results must be confirmed and cannot be extended to patients with characteristics that differ from those of the patient population in the trial [50].

Level I or II axillary dissection should be recommended (1) in patients with clinically positive nodes confirmed by FNA or core biopsy at the time of diagnosis or (2) in patients in whom sentinel nodes are not identified. Traditional level I and level II ALN evaluation requires the removal of at least ten lymph nodes for pathological evaluation to accurately stage the axilla [70, 71]. Level III ALN dissection should be performed only if gross disease is apparent in the level II nodes. Level I–II lymph node dissection should include the tissue that is inferior to the axillary vein from the latissimus dorsi muscle and lateral to the medial border of the pectoralis minor muscle.

Furthermore, without definitive data demonstrating superior survival compared to ALN dissection or SLN resection, these procedures should be considered optional in patients with particularly favorable tumors, in patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, in elderly patients, and in patients with serious comorbidities. Patients with SLN metastasis but no ALN dissection or irradiation are at increased risk of ipsilateral lymph node recurrence [72].

Surgical Approach After Primary Systemic Therapy

Primary systemic chemotherapy (preoperative chemotherapy) is usually utilized in patients with inoperable locally advanced breast cancer. Systemic chemotherapy or hormonal therapy can result in breast tumor size reduction in nearly 80% of patients with locally advanced breast cancer. Systemic therapy can convert inoperable tumors to operable ones and convert the need of a surgical procedure from mastectomy to breast-conserving surgery that will result in favorable cosmesis. Currently, there are clinical trials reporting better aesthetic results in early-stage breast cancer patients. This approach also allows the study of tumor biology before surgery and evaluation of the tumor response to chemotherapy regimens. At the end of systemic therapy, patients may have a complete pathological response both in clinical examination and imaging studies.

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to undergo breast-conserving therapy or for patients with triple-negative and HER2-positive disease (patients with T2–T3 disease or node-positive disease) (Fig. 44.5). In patients anticipated to receive preoperative systemic therapy, core biopsy of the breast tumor and placement of image-detectable marker should be considered to demarcate the tumor bed for any future post-chemotherapy surgical management. Clinically positive ALN should be sampled by FNA or core biopsy, and the positive nodes can be removed following preoperative systemic therapy at the time of definitive operation. Patients with clinically negative ALNs should have axillary ultrasound prior to neoadjuvant treatment. For those with clinically suspicious ALNs, core biopsy or FNA of these nodes is indicated [73].

Sentinel node biopsy or level I/II dissection can be performed as an axillary staging after preoperative systemic therapy. Level I/II dissection should be performed when patients are proven node positive prior to neoadjuvant therapy. However, in T1–T2N1 disease, after neoadjuvant chemotherapy, if three SLNs are negative upon paraffin examination, axillary dissection may not be performed (Figs. 44.6 and 44.7). The false-negative rate of SLNB in either the pre- or post-chemotherapy settings is low [55, 74–77]. The St. Gallen Consensus Panel recommended that patients with a clinically positive axilla or macro-metastases identified in sentinel nodes after neoadjuvant therapy undergo completion axillary dissection [32, 34, 78]. The Panel was split on whether residual micrometastatic lymph node involvement warranted completion dissection after neoadjuvant therapy. Nevertheless, the possibility remains that a pathologic complete response (pCR) following chemotherapy may occur in lymph node metastases previously undetected by clinical exam. An SLN excision can be considered before administering preoperative systemic therapy, because it provides additional information to guide local and systemic treatment decisions. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative systemic therapy is planned.

Because complete or near-complete clinical responses are common, the use of percutaneous-placed clips into the breast under mammographic or ultrasound guidance aids in post-chemotherapeutic resection of the original tumor area and is encouraged. Breast conservation rates are higher following preoperative systemic therapy [79].

Local therapy following a complete or partial response to preoperative systemic therapy is generally lumpectomy, if possible, along with surgical axillary staging. If lumpectomy is not possible or if progressive disease is confirmed, mastectomy is performed along with surgical axillary staging with or without breast reconstruction. Surgical axillary staging may include SLN biopsy or level I/II dissection. If SLN biopsy was performed before administering preoperative systemic therapy and the findings were negative, then further ALN staging is not necessary. If an SLN procedure was performed before administering preoperative systemic therapy and the findings were positive, then a level I/II ALN dissection should be performed.

Patients with stage III disease may be further classified as (1) those for which an initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control and (2) those with disease for which a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those who have clinical T3N1 disease versus those who have clinical T (any), N2, M0 disease based on evaluation by a multidisciplinary team.

In patients with inoperable, locally advanced, noninflammatory disease, anthracycline-based preoperative systemic therapy is the standard therapy. Local therapy following a clinical response to preoperative systemic therapy usually comprises mastectomy or lumpectomy with level I/II ALN dissection [79–81]. Delayed breast reconstruction can be considered in mastectomy patients.

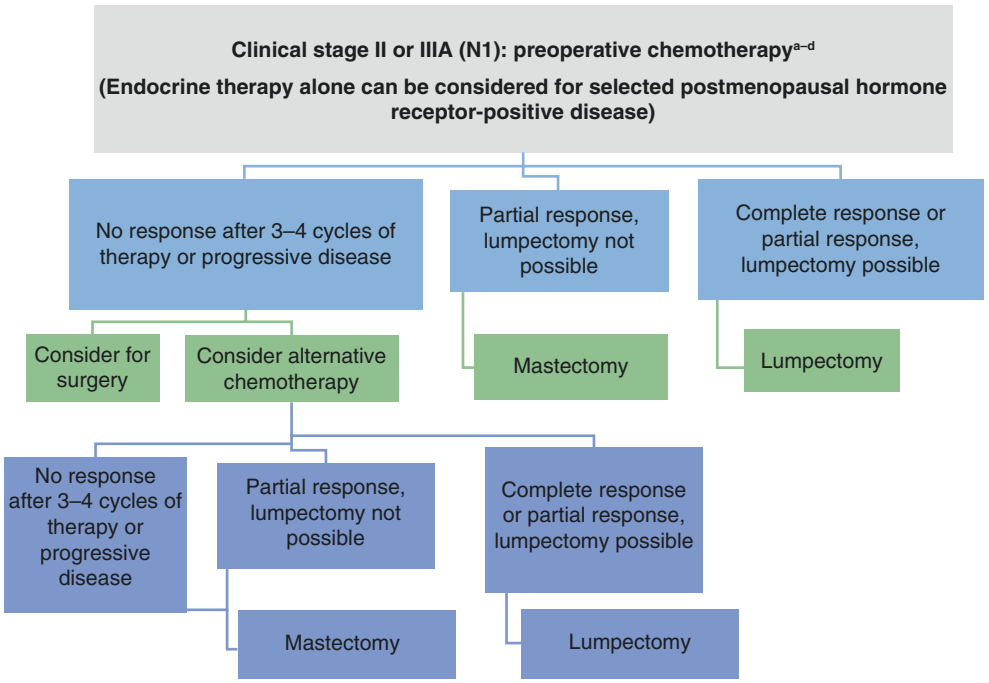

Fig. 44.5 Management of patients receiving neoadjuvant therapy for breast-conserving surgery (stage II or IIIA with N1). [a]HER2-targeted therapy: According to the version 1.0 2019 NCCN Guidelines, patients with HER2-positive disease should receive "pertuzumab + trastuzumab + chemotherapy" in the neoadjuvant setting. [b]Stage II–III triple-negative disease: If provided to patients with triple-negative tumors, the preferred regimen should include an anthracycline and a taxane. Although the available data are insufficient, a platinum-based regimen may be considered in patients with a known BRCA mutation. Anthracyclines followed by taxanes is an acceptable regimen for BRCA-mutant TNBC. Dose-dense chemotherapy requiring growth factor support may also be an option. [c]Neoadjuvant cytotoxic therapy should be discussed as an option and provided frequently to patients with "luminal A-like" tumors, only if conservative surgery would not otherwise be feasible. Neoadjuvant chemotherapy should be administered to T2 and T3 tumors (N0–N1) meeting BCS criteria except tumor diameter or to triple-negative and HER-2-positive patients. [d]Neoadjuvant endocrine therapy without cytotoxics represents a reasonable option for some select postmenopausal patients with endocrine-responsive disease. The duration of treatment must be at least 4–6 months, and treatment can be provided until a maximal response is reached

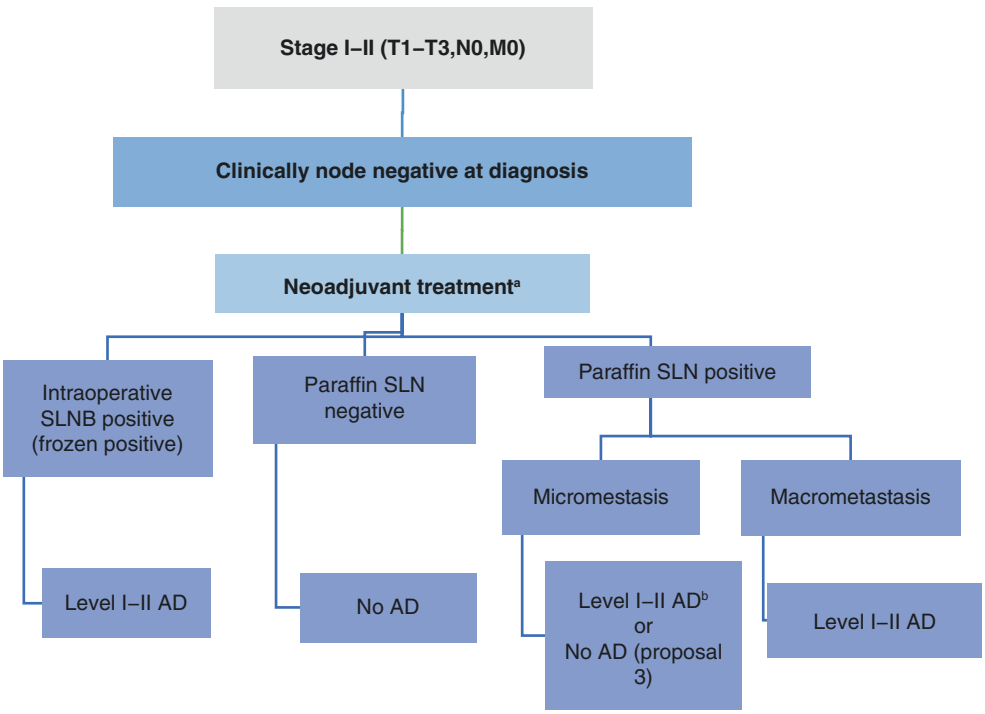

Fig. 44.6 Axillary management of patients with clinical node-negative stages I or II invasive breast cancer. SLNB: sentinel lymph node biopsy. [a]Neoadjuvant chemotherapy (NAC) is recommended for patients with axillary lymph node-negative T2–T3 tumors with triple-negative or HER2-positive tumors. In luminal B tumors, NAC can be considered. [b]Low-volume disease in the SLN after NAC is not an indicator of a low risk of additional positive axillary nodes. These tumor cells are potentially drug resistant and may be an indication of axillary lymph node dissection, even when not detected on intraoperative frozen section

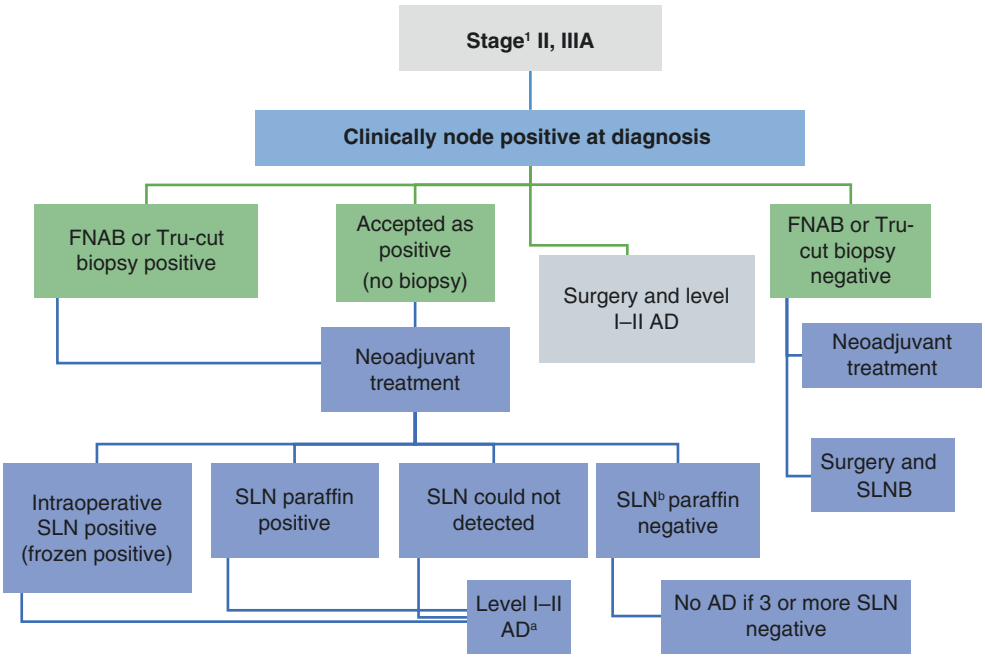

Fig. 44.7 Axillary management of patients with clinical node-positive stage II or IIIA invasive breast cancer. FNAB: fine-needle aspiration biopsy, SLN: sentinel lymph node biopsy; AD: axillary dissection. [1]Clinical stage II (T0, N1, M0; T1, N1, M0; T2, N1, M0); stage IIIA (T3, N1, M0). [a]After neoadjuvant therapy, if the SLN is positive in frozen or paraffin sections, level I–II axillary dissection is recommended. [b]At least three SLNs should be assessed in patients receiving neoadjuvant treatment

Patients with a clinical/pathological diagnosis of inflammatory breast cancer (IBC) should always be treated with preoperative chemotherapy [82, 83]. Primary surgery and SLN dissection are not reliable approaches in patients with IBC [84].

The use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that local recurrence rates may be higher than with mastectomy. Breast-conserving therapy is not recommended for patients with IBC. Mastectomy with level I/II ALN dissection is the recommended surgical procedure for patients with IBC who respond to neoadjuvant chemotherapy. Delayed breast reconstruction is an option for patients with IBC who have undergone a modified radical mastectomy. Early/immediate reconstruction after mastectomy may compromise the postmastectomy radiotherapy outcomes [85].

For patients with IBC who do not respond to preoperative systemic therapy, mastectomy is not generally recommended. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above.

Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options adapted to their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of cancer.

The decision regarding the type of reconstruction includes the patient's preference, body habitus, smoking history, comorbidities, and plans for irradiation, as well as the reconstruction team's expertise and experience. Reconstruction is an optional procedure that does not impact the probability of recurrence or death but is associated with improved quality of life for many patients. It is sometimes necessary to perform surgery on the contralateral breast (e.g., breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

The cosmetic, body image, and psychosocial issues caused by breast loss may be partially overcome by breast reconstruction. Reconstruction can be performed either immediately following mastectomy under the same anesthetic or in a delayed manner following mastectomy. Breast reconstruction usually involves a staged approach requiring more than one procedure.

Many factors must be considered in the decision-making process regarding breast reconstruction following mastectomy. Several different types of breast reconstruction, such as autogenous tissue use, implant use, or both, can be performed following mastectomy [86–88]. Reconstruction with implants can be performed either by immediately placing a permanent subpectoral implant or by initially placing a subpectoral expander and then replacing the expander with a permanent implant. Autogenous tissue reconstruction methods use various combinations of donor sites (e.g., abdomen, buttocks) that may be brought to the chest wall with their original blood supply or as free flaps with microvascular anastomoses to supply blood from the chest wall/thorax. Several procedures using autologous tissue are available, including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap,

and gluteus maximus myocutaneous flap reconstructions. Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast reconstruction, presumably due to underlying microvascular disease.

Skin-Sparing Mastectomy

Possible advantages of skin-sparing mastectomy include improvements in breast cosmesis, body image, and nipple sensation following mastectomy, although the impact of this procedure on these quality-of-life issues has not been well studied [89–91]. Limited data with short follow-up periods are available from surgical series suggesting that the performance of nipple-areolar complex (NAC)-sparing mastectomy in selected patients is associated with low rates of occult NAC involvement in breast cancer and local disease recurrence. NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. The assessment of retroareolar margins is mandatory in patients considering a NAC-sparing procedure [90–93]. Retrospective studies have validated the use of NAC-sparing procedures for breast cancer patients with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable tumors located >2 cm away from the nipple [94, 95]. A meta-analysis of single-center experiences suggests very low risk of local-regional recurrence following nipple-sparing mastectomy [96]. Similarly, the St. Gallen Consensus Panel agreed that nipple-sparing mastectomy was an option for patients following neoadjuvant treatment provided the retroareolar region lacked tumor involvement [32, 97]. Contraindications for nipple preservation include findings of nipple involvement such as Paget's disease or bloody nipple discharge. Prospective trials to assess NAC-sparing mastectomy in the setting of malignancy are ongoing, and participation in these trials is encouraged.

Although no randomized studies have been performed, the results of several retrospective studies have indicated that the risk of local recurrence is not increased in patients receiving skin-sparing mastectomies compared to those undergoing non-skin-sparing procedures. However, strong selection biases almost certainly exist in the identification of patients who are appropriate for skin-sparing procedures [98–102]. NAC reconstruction may also be performed in a delayed fashion if desired by the patient. Reconstructed nipples are devoid of sensation. An experienced breast surgery team working in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedure in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins should perform skin-sparing mastectomy. Postmastectomy radiation should still be applied for patients treated by skin-sparing mastectomy, following the same selection criteria used for standard mastectomy.

Postmastectomy Radiation and Breast Reconstruction

The decision regarding postmastectomy radiation therapy can affect reconstruction strategies because of the increased risk of complications such as capsular contracture following implant irradiation. Postmastectomy radiation therapy may also have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction [103, 104]. Some studies, however, have not achieved a significant compromise in reconstruction cosmesis following irradiation [105]. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, radiation therapy preceding placement of the autologous tissue is generally preferred because of the reported loss in reconstruction cosmesis.

When implant reconstruction is planned in a patient requiring radiation therapy, a two-staged approach with immediate tissue expander placement followed by implant placement is recommended. The exchange of tissue expanders with permanent implants can be performed prior to radiation or after the completion of radiation therapy. The expansion of irradiated skin can result in increased risks of malpositioning, capsular contracture, poor cosmesis, and implant exposure. The use of tissue expanders/implants is relatively contraindicated in patients who have been previously irradiated. Immediate implant placement in patients requiring postoperative radiation has an increased rate of complications such as capsular contracture, malpositioning, poor cosmesis, and implant exposure.

Breast Reconstruction Following Lumpectomy: Oncoplastic Approach

The goal of optimizing the cosmetic and oncological outcomes of breast-conserving surgery has been addressed in recent years by the emergence of the field of oncoplastic surgery. The possible cosmetic outcome of lumpectomy should be evaluated prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations in which the resection itself would likely yield an unacceptable cosmetic outcome [106]. The definition of oncoplastic surgery has more recently been expanded to include a wide range of volume displacement or redistribution procedures performed by breast surgeons and general surgeons to optimize breast shape and volume following breast cancer surgery [107]. Oncoplastic volume displacement procedures combine the removal of generous regions of breast tissue with "mastopexy" techniques in

which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect, thereby avoiding the creation of a significant breast deformity. Volume displacement techniques are generally performed in the same operative setting as the breast-conserving lumpectomy and by the same surgeon performing the cancer resection [106–108].

Oncoplastic volume displacement techniques are advantageous because they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the tumor while better preserving the natural shape and appearance of the breast compared to standard breast resections [109].

The limitations of oncoplastic volume displacement techniques include a lack of standardization among centers, restriction to a limited number of facilities, and the potential need for subsequent mastectomy if pathological margins are positive. Patients should be informed of the possibility of positive margins and the potential need for a secondary surgery, which could include re-excision segmental resection or mastectomy with or without nipple loss. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

The primary focus should be on treatment of the tumor, and such treatment should not be compromised when making decisions regarding breast reconstruction.

Adjuvant Systemic Treatment in Invasive Breast Cancer

Chemotherapy

All patients with invasive breast cancer should be evaluated for the need for adjuvant cytotoxic, anti-HER2, and/or endocrine therapy. When indicated, adjuvant cytotoxic chemotherapy should begin 2–8 weeks following surgery. If adjuvant endocrine (either tamoxifen or aromatase inhibitor (AI)) and cytotoxic therapy are indicated, chemotherapy should precede endocrine therapy. For triple-negative disease, adjuvant cytotoxic chemotherapy should begin 2–3 weeks following surgery [12, 32, 34](Figs. 44.8, 44.9, 44.10, 44.11, and 44.12).

Older age is not a contraindication for cytotoxic chemotherapy. Adjuvant treatment should be considered regardless of patient age. The available data are insufficient to make specific recommendations for older age groups [110]. On the other hand, four cycles of docetaxel/cyclophosphamide were found to be superior with regard to DFS and OS compared to standard 4AC, not only in younger patients but also in older women [111]. Hence, third-generation regimens such as dose-dense AC and paclitaxel, AC followed by docetaxel, or the combination of docetaxel/doxorubicin/cyclophosphamide are recommended for patients without major health problems; however, these regimens are associated with a very high risk of recurrence. Currently, it is now recommended not to consider age as an exclusion criterion for cancer treatment as long as survival for a significant period of time is likely and the burden of comorbidity is low. However, one must remember that toxicity of chemotherapy is enhanced at older ages as there are age-related differences in pharmacokinetics of breast cancer treatment as they contain anthracyclines (reduced clearance) and platinum agents (reduced creatinine clearance).

Several gene expression-profiling assays have been developed in an attempt to predict the survival and response to therapies of breast cancer patients. These are based on the identification of prognostic gene signatures using microarrays. Many groups attempted to develop genomic tests based on genomic profiling with the expectation that this might better predict clinical outcomes than the standard pathological and clinical markers [112, 113]. For patients with T1 and T2 hormone receptor-positive, HER-2-negative, and lymph node-negative tumors, in the low-risk range (if OncotypeDx recurrence score <11 according to AJCC eighth edition) regardless of T size, these tumors were placed into the same prognostic group category as T1a–T1bN0M0.

Useful biomarkers and gene expression profiling assays for the decision of adjuvant systemic treatment in early-stage breast cancer are summarized below [12, 34, 113]:

- *ER/PR positive, HER2 negative (node negative)*
  - *Oncotype DX (Genomic Health)*
  - *EndoPredict (Sividon Diagnostics, Germany)*
  - *MammaPrint (Agendia, Irvine, CA): To avoid adjuvant chemotherapy if the patient is at high risk according to MINDACT categorization*
  - *PAM50 ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA)*
  - *Breast Cancer Index (bio Theranostics)*
  - *uPA and PAI-1*
- *ER/PR positive, HER2 negative (1-3 node positive):*
  - *MammaPrint (Agendia, Irvine, CA), Oncotype DX (Genomic Health)*

A prospective, randomized phase III study (MINDACT) has evaluated whether patients with high-risk clinical features and a low-risk gene-expression profile could be spared from chemotherapy safely [114]. Avoidance of chemotherapy on the basis of gene signature results led to a 5-year rate of distant metastatic-free survival (DMFS) (94.7%) that was 1.5 percentage points lower than the rate with chemotherapy achieving the primary objective of the study. The trial included both node-negative and node-positive patients, and

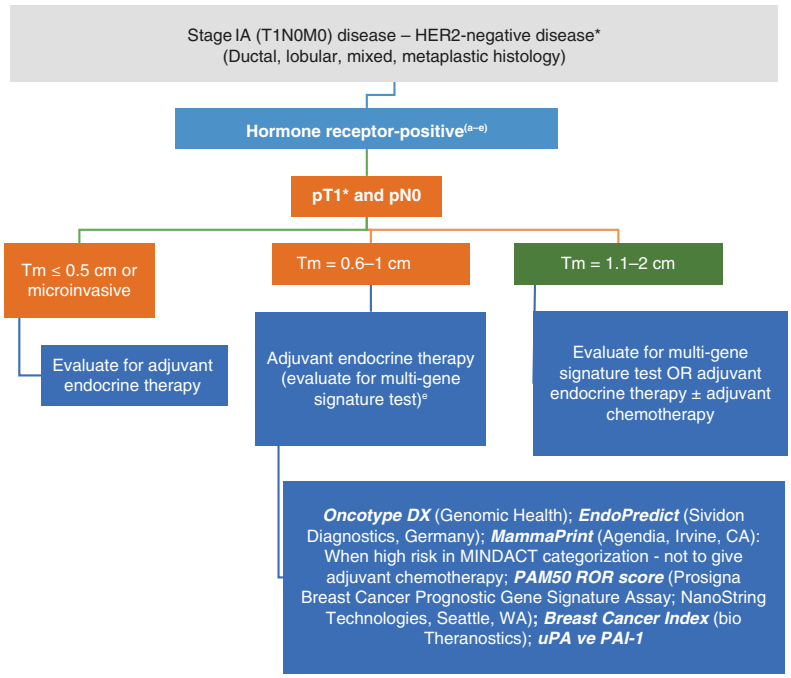

Fig. 44.8 Adjuvant systemic therapy for stage IA – hormone receptor-positive and HER2-negative disease. *In early-stage breast cancer, there are biomarkers that can be used to decide adjuvant systemic treatment administration. In the eighth version of the American Joint Commission of Cancer (AJCC) for breast cancer, prognostic gene signatures will be integrated into the staging scheme as prognostic staging: For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, prognostic gene signatures with a low-risk score regardless of T size place the tumor in the same prognostic category as T1a–T1bN0M0, and the tumor is staged using the AJCC prognostic stage group table as stage I. Based on multigene signature tests, chemotherapy may be omitted for patients with luminal B-like (HER2 negative) disease with a low Oncotype Dx® score, MammaPrint® low-risk status, low PAM50 ROR score, or EndoPredict® low-risk status. The situations in which multigene tests may be particularly helpful can be summarized as follows: tumor size between 1 and 3 cm and ER/PR positive and HER2 negative and node negative or N_{mi} and grade II and Ki-67 between 15% and 35%. In hormone receptor-positive T1cN0 (1–2 cm) tumors, grade III disease with a high Ki-67 value (e.g., above 35%) and PgR <20% may be considered adequate for chemotherapy indication. In cases where multigene tests cannot be performed, the risk factors can be determined using web-based formulas, and an indication for chemotherapy administration can be established. [a]There is no absolute age limit. Rather, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. Treatment should be individualized for patients >70 years. [b]Chemotherapy and endocrine therapy as adjuvant therapy should be given sequentially, with endocrine therapy following chemotherapy. The available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. [c]Fertility preservation (e.g., by ovarian tissue or oocyte conservation) should be offered to women <40 years. For fertility preservation ovarian function suppression with LHRHa during chemotherapy should be offered for these patients. [d]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy. [e]Evaluate for multigene signature test, especially for luminal B-like, high Ki67, or grade III tumors

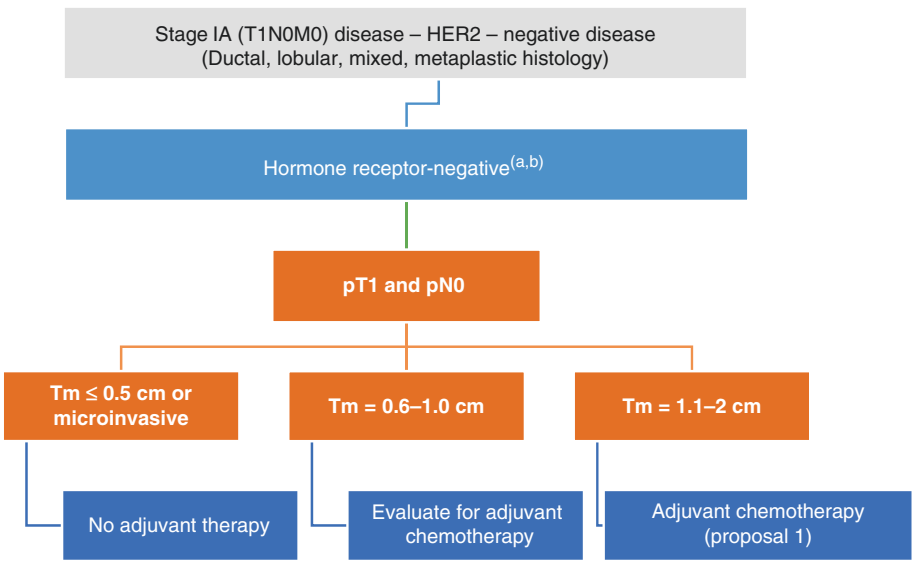

Fig. 44.9 Adjuvant systemic therapy for stage IA – hormone receptor-negative and HER2-negative disease. [a]There is no absolute age limit. Rather, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. Treatment should be individualized for patients >70 years of age. [b]Fertility preservation (e.g., by ovarian tissue or oocyte conservation) should be offered to women <40 years of age. Ovarian function suppression with LHRHa during chemotherapy should be offered for HR-negative disease

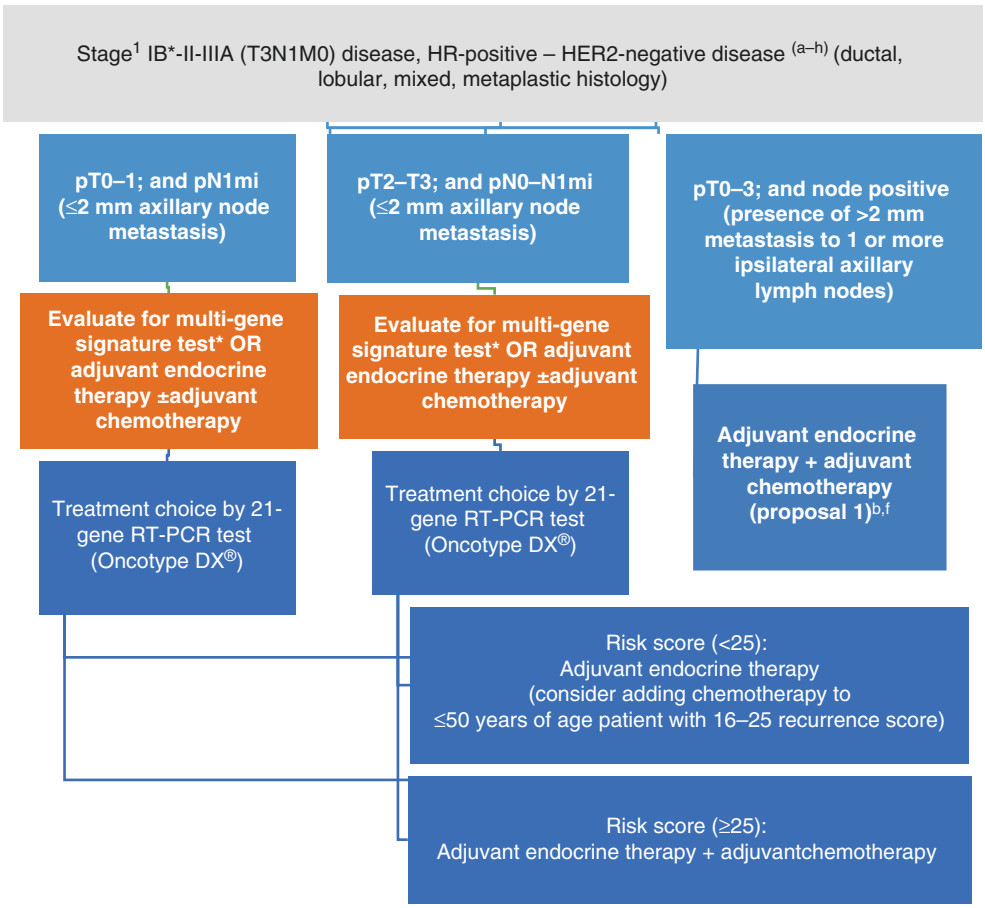

Fig. 44.10 Adjuvant systemic therapy for stages IB, II, IIIA – hormone receptor-positive and HER2-negative disease. *For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, prognostic gene signatures with a low-risk score regardless of T size place the tumor in the same prognostic category as T1a–T1bN0M0, and the tumor is staged using the AJCC prognostic stage group table as stage I (eighth version). [a]There is no absolute age limit. The choice of treatment depends on disease, comorbidities, life expectancy, and patient preferences. In patients over 70 years of age, treatment should be individualized. [b]In patients with luminal A-like tumors and 1–3 positive lymph nodes (with the evaluation of other factors such as grade, age, or multigene signature test results), "adjuvant endocrine therapy alone" may be an option. [c]Factors that are relative indications for the inclusion of adjuvant cytotoxic chemotherapy include the following: histological grade III tumor, four or more positive nodes, high Ki67, extensive lymphovascular invasion, and low hormone receptor staining. [d]The luminal A phenotype is less responsive to chemotherapy. In node-negative disease, chemotherapy should not be added based on the T size. A combination of the biological properties of the tumor (such as Ki67, LVI, grade, and multigene signature) must be used to assess whether to provide chemotherapy. Chemotherapy should be added in high-risk patients based on the involvement of four or more lymph nodes. [e]Based on immunohistochemistry (IHC), in luminal B-like (HER2-negative) tumors, chemotherapy may be omitted in some low-risk patients (based on combinations of certain prognostic factors such as low tumor mass, low grade, low Ki67, an absence of LVI, and older age). [f]Based on multigene signature tests, chemotherapy may be omitted for patients with luminal B-like (HER2-negative) disease with a low-risk score. MammaPrint (Agendia, Irvine, CA): In patients with 1–3 positive lymph nodes, tests can be performed to avoid adjuvant chemotherapy if the patient is at high clinical risk group in the MINDACT categorization (however, the patient should be informed that there may be an additional benefit of chemotherapy with multiple LN positivity). [g]For luminal B-like (HER2-negative) tumors, the regimen, if given, should contain anthracyclines and taxanes. A high-risk group might exist for which dose-dense therapy with G-CSF may also be preferred. [h]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

similar rates of survival without distant metastasis were reported for both groups. An expert panel reviewed the results of the MINDACT study and recommended the MammaPrint assay to be used in patients with one to three positive nodes and a high clinical risk (determined according to Adjuvant! Online) to inform decisions on withholding adjuvant systemic chemotherapy. However, in particular, patients with more than one metastatic lymph node should be informed that a benefit from chemotherapy could not be excluded [113].

The St. Gallen guidelines have recommended gene expression assays for guiding the decision on adjuvant chemotherapy mainly for patients with tumors between 1 and 3 cm, with zero to two or three positive lymph nodes, and an intermediate proliferative fraction [32, 34]. The Panel has not endorsed a particular multigene assay but has suggested that none of

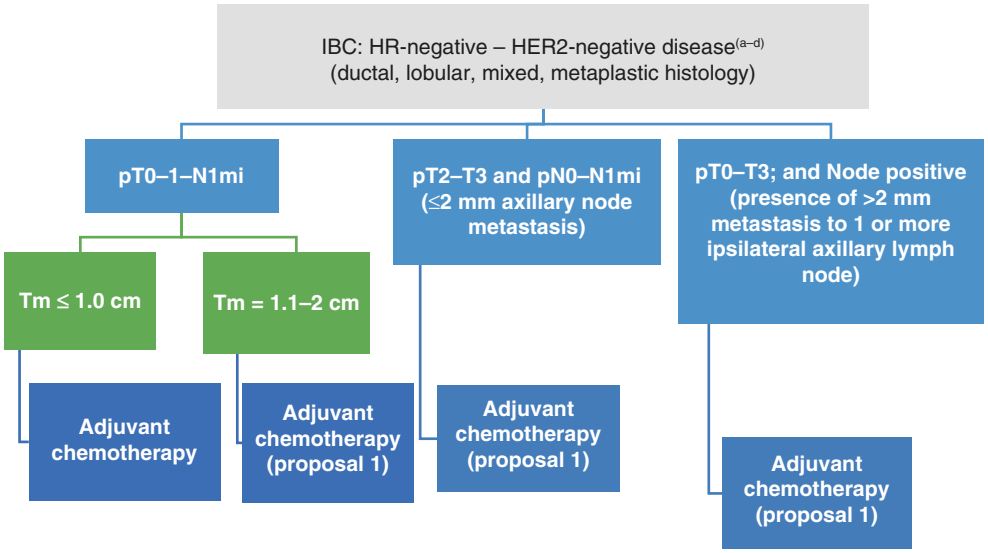

Fig. 44.11 Adjuvant systemic therapy for stages IB, II, IIIA (T3N1M0) – hormone receptor-negative and HER2-negative disease. [a]There is no absolute age limit. Rather, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. For patients >70 years of age, treatment should be individualized. Regardless of the size of the invasive tumor, adjuvant chemotherapy may be recommended in the presence of $N1_{mi}$. [b]Fertility preservation (e.g., by ovarian tissue or oocyte conservation) should be offered to women <40 years. Ovarian function suppression with LHRHa during chemotherapy should be offered for receptor-negative disease. [c]In triple-negative breast cancer (TNBC), the regimen should include anthracyclines and taxanes. Although the data are insufficient, a platinum-based regimen may be considered only when a BRCA mutation has been identified. Anthracyclines followed by taxanes represent an acceptable regimen for BRCA-mutant TNBC. Dose-dense chemotherapy requiring growth factor support may also be an option. Neoadjuvant treatment should be considered in triple-negative patients with stage II and III disease. Treatment with platinum or alkylating agents may be considered in neoadjuvant chemotherapy. A platinum-based regimen may be recommended, particularly when a BRCA mutation is detected. The administration of capecitabine after anthracycline and taxane treatment reduces recurrence in patients with TNBC. Capecitabine reduces the recurrence rate in patients with residual tumors after neoadjuvant therapy. [d]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

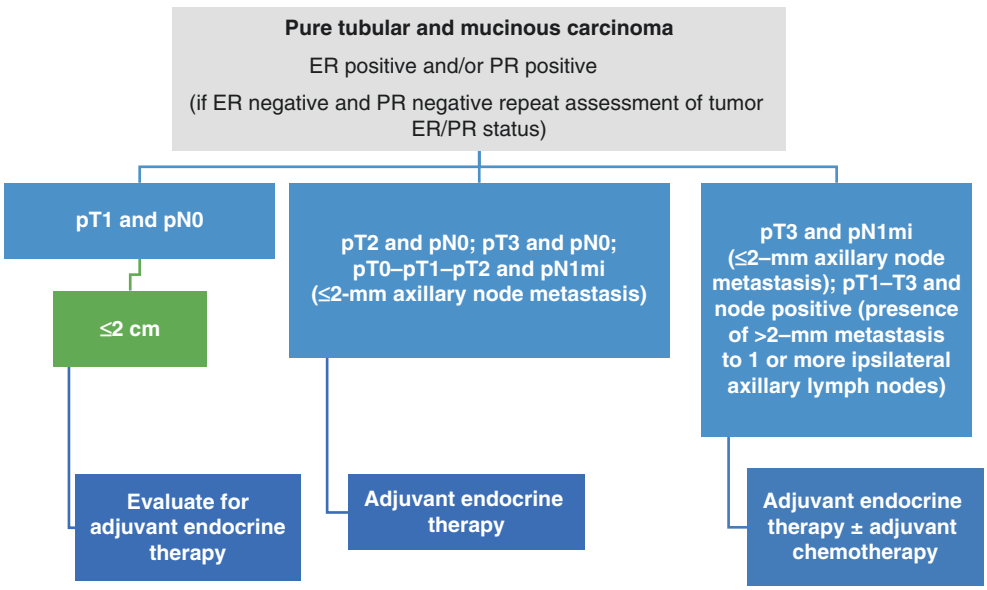

Fig. 44.12 Adjuvant systemic therapy for stages IB, II, IIIA (T3N1M0) – pure tubular and mucinous carcinoma

the tests should be the only factor considered in making a decision to proceed or to avoid chemotherapy. Relying on a retrospective analysis of a prospective study, the NCCN guidelines have additionally recommended OncotypeDx to be considered in select patients with one to three involved lymph nodes to guide the chemotherapy decision [12].

The positivity of any lymph node should not be the sole indication for adjuvant chemotherapy [32, 34]. However,

patients with more than three involved lymph nodes, low hormone receptor positivity, HER2-positive status, triple-negative status, a multigene-based high recurrence score should receive adjuvant chemotherapy. A high Ki67 proliferation index and a histological grade III tumor may be acceptable indications for adjuvant chemotherapy. Lymphovascular invasion without any other poor prognostic factor is not an indication for cytotoxic chemotherapy. In many patients, a high tumor volume (T3) may be an indication for adjuvant chemotherapy.

Breast cancers with a luminal A phenotype are less responsive to chemotherapy. Patients with luminal A breast cancer may, thus, receive less intensive chemotherapy regimens, including four cycles of doxorubicin and cyclophosphamide (AC); six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF); or four cycles of docetaxel and cyclophosphamide (TC) [32, 34, 111, 115].

A luminal B phenotype is an indication for adjuvant chemotherapy in most patients. If adjuvant chemotherapy is provided, patients with luminal B breast cancer should receive chemotherapy regimens containing at least six courses of anthracyclines and taxanes, rather than CMF. Patients with luminal B breast cancer may receive dose-dense chemotherapy.

It was unknown whether the benefit provided by the addition of taxane would obviate the need for anthracyclines. A recent meta-analysis of three adjuvant trials comparing TC for six cycles to different AC and taxane combination regimens did not meet the noninferiority criteria, revealing a 2.5% 4-year invasive disease-free survival advantage for AC and taxane combinations. The difference in survival was evident for basically triple-negative and node-positive breast cancer patients [116].

More recently, an Italian phase III trial randomized node-positive breast cancer patients to four treatment arms that included 5-FU and EC, followed by paclitaxel or EC, and followed by paclitaxel given in 2 or 3 weekly intervals [117]. The study identified a DFS advantage for dose-dense regimens compared with standard interval chemotherapy protocols. Moreover, there was no benefit of adding fluorouracil to sequential EC and paclitaxel.

Unfortunately, trials incorporating agents other than anthracyclines and taxanes in the adjuvant setting have not revealed consistent results. Of those agents, capecitabine has yielded improved outcomes for some subgroups of patients, but the overall benefit was limited. For instance, the phase III FinXX trial integrated capecitabine to sequential docetaxel (T) followed by CEF. Although the interim analysis suggested an increase in recurrence-free survival (RFS) with capecitabine, the final results failed to demonstrate an improvement in RFS for the whole patient group [118]. However, in an exploratory subgroup analysis, capecitabine combined with sequential docetaxel followed by CEX (cyclophosphamide, epirubicin, and capecitabine) was more effective than T + CEF in the subset of patients with TNBC (HR, 0.53; $p = 0.02$).

Recently, a phase III trial evaluated the addition of adjuvant capecitabine for patients with residual breast cancer after neoadjuvant chemotherapy with anthracycline, taxane, or both. At 5 years. The overall survival was longer in the capecitabine group than in the control group (89.2% vs. 83.6%). Among patients with TNBC, the survival benefit was more evident [119]. Due to the positive findings in the FinXX and CREATE-X trials, guidelines recommend considering adjuvant capecitabine combined with anthracyclines and taxanes in the adjuvant setting and for residual cancer after neoadjuvant chemotherapy for the TNBC subtype [32, 34, 120]. Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease at surgery following standard anthracycline- and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine. If clinicians decide to use capecitabine, then the Expert Panel of ASCO preferentially supports the use of adjuvant capecitabine in patients with hormone receptor-negative, HER2-negative breast cancer [120].

A meta-analysis comparing dose-dense regimens with conventional ones has shown that in some trials, dose-dense treatment was associated with improvement in both OS and DFS (HR, 0.83; HR, 0.84, respectively), but modified doses or regimens also provided improvement in DFS and OS (HR, 0.81; HR, 0.85, respectively) [121]. However, the benefit was evident in ER-negative disease rather than ER-positive disease. Thus, dose-dense strategies appear feasible with G-CSF support and have a modest impact on the outcome in an unselected patient cohort; however, emerging data show that specific subtypes such as triple-negative breast cancer may receive more benefit from intensification of CT. A recent meta-analysis showed that the patients who received dose-dense chemotherapy – the same chemotherapy agents at the same dose but administered every 2 weeks instead of every 3 weeks – were 17% and 15% less likely to have disease recurrence and die from breast cancer within 10 years, compared with those who received treatment every 3 weeks. Similarly, patients who received sequential chemotherapy were 14% and 13% less likely to have disease recurrence and die from breast cancer within 10 years, compared with those who received concurrent treatment. There were few additional side effects with the dose-intense schedule compared with standard schedule chemotherapy, and fewer patients who received dose-intense treatment died from non-breast cancer causes than those who received standard treatment [122]. In contrast to other studies, the authors showed that the 15% reduction in recurrence with dose-intense chemotherapy across all trials was similar in ER-positive and ER-negative disease and did not differ significantly by any other patient or tumor characteristics, including age, HER2 status, nodal status, tumor size, and grade.

HER2-Positive Breast Cancer

There is no preferred adjuvant chemotherapy regimen for HER2+ early-stage breast cancer, but taxanes and/or anthracyclines must be part of the adjuvant chemotherapy regimen, i.e., doxorubicin + cyclophosphamide – weekly paclitaxel and trastuzumab (+/− pertuzumab) or docetaxel-carboplatin + trastuzumab +/− pertuzumab (pertuzumab given to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer) can generally be recommended [120, 123]. HER2+ tumors with a diameter of less than 0.5 cm (T1a) may receive chemotherapy plus trastuzumab. HER2+ tumors with a diameter of 0.5–1.0 cm should be considered for adjuvant chemotherapy plus trastuzumab, and those larger than 1 cm (T1c–T4N0M0) require chemotherapy plus anti-HER2 treatment. When chemotherapy is contraindicated, anti-HER2 treatment may be administered either alone or with endocrine therapy [12, 32, 34, 120] (Figs. 44.13, 44.14, 44.15, and 44.16).

Trastuzumab should not be administered with anthracyclines, but should be provided concurrently with taxanes. ER positivity or negativity should not alter the decision regarding adjuvant trastuzumab, if otherwise indicated. The preferred duration of trastuzumab therapy is 1 year [12, 32, 34].

A single arm multicenter trial included breast cancer patients with node-negative tumors up to 3 cm [124]. Patients received weekly treatment with paclitaxel (T) and trastuzumab (H) for 12 weeks, followed by 9 months of trastuzumab monotherapy. The 3-year rate of survival free from invasive disease was 98.7%. The 7-year breast cancer-specific survival (BCSS) was 98.6% and 7-year OS was 95.0%. These data suggest that TH as adjuvant therapy for node-negative HER2+ breast cancer is associated with few recurrences with longer follow-up. Aside from not being supported by randomized data, this regimen might become an option for patients with small (<1–2 cm) node-negative HER2-positive disease in clinical scenarios where there is concern about the potential toxicity from established regimens.

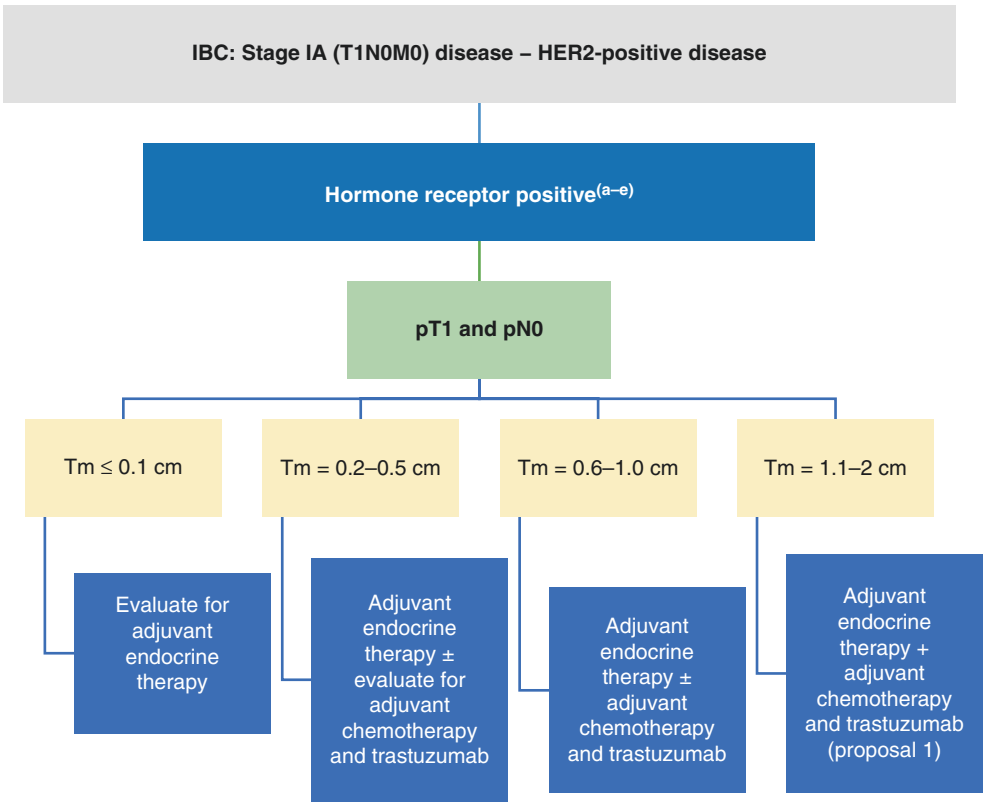

Fig. 44.13 Adjuvant systemic therapy for stage IA (T1N0M0) – hormone receptor-positive and HER2-positive disease. [a]There is no absolute age limit. Instead, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. Treatment should be individualized for patients >70 years of age. [b]Chemotherapy and endocrine therapy as adjuvant therapy should be given sequentially, with endocrine therapy following chemotherapy. The available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. [c]Assuming that HER2 positivity is determined according to the ASCO/CAP guidelines, most patients with T1b disease and all patients with T1c disease require anti-HER2 therapy. The chemotherapy regimen for these patients may contain anthracyclines. If provided in stage I and if the tumor diameter is <1–2 cm, the combination of paclitaxel and trastuzumab is the preferred regimen. Trastuzumab or chemotherapy is not recommended for microinvasive disease (invasive tumor ≤1 mm). [d]Fertility preservation (e.g., by ovarian tissue or oocyte conservation) should be offered to women <40 years of age. [e]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

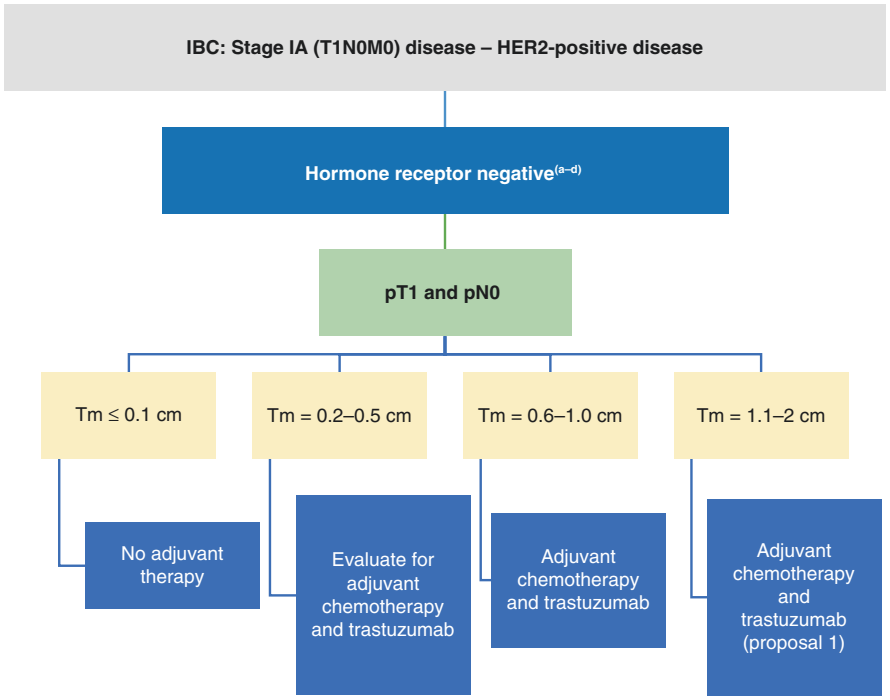

Fig. 44.14 Adjuvant systemic therapy for stage IA (T1N0M0) – hormone receptor-negative and HER2-positive disease. [a]There is no absolute age limit. Instead, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. Treatment should be individualized for patients >70 years of age. [b]Assuming that HER2 positivity is determined according to the ASCO/CAP guidelines, most patients with T1b disease and all patients with T1c disease require anti-HER2 therapy. The chemotherapy regimen for these patients may contain anthracyclines. If provided in stage I and if the tumor diameter is ≤1 cm, the combination of paclitaxel and trastuzumab is the preferred regimen. For patients in stage I with a tumor diameter >1, anthracyclines followed by taxanes and trastuzumab may be preferred, although paclitaxel–trastuzumab may also be an option in select patients. Trastuzumab or chemotherapy is not recommended for microinvasive disease (invasive tumor ≤1 mm). [c]Fertility preservation (e.g., by ovarian tissue or oocyte conservation) should be offered to women <40 years. [d]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

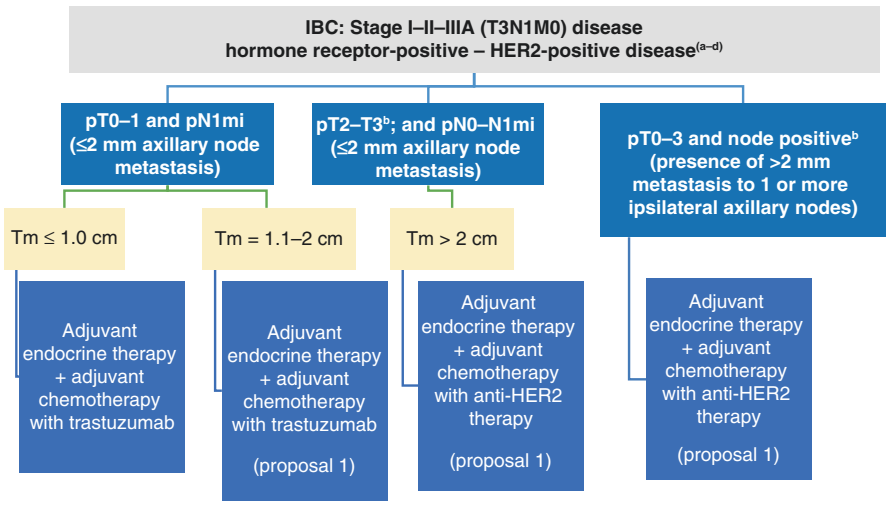

Fig. 44.15 Adjuvant systemic therapy for stages I, II, IIIA – hormone receptor-positive and HER2-positive disease. [a]There is no absolute age limit. Rather, treatment depends on the disease, the presence of comorbidities, the patient's life expectancy, and patient preferences. Treatment should be individualized for patients >70 years of age. [b]Neoadjuvant therapy is recommended in HER2-positive stage II and III patients. Trastuzumab and pertuzumab are recommended in neoadjuvant therapy. Pertuzumab benefit was particularly evident in high-risk patients who were hormone receptor negative and node positive. One-year neratinib use after 1-year administration of trastuzumab reduced the recurrence rate. This benefit was especially evident in ER-positive, Her-2-positive disease. However, diarrhea was an important adverse effect. After 1 year of trastuzumab administration in hormone receptor-positive patients, 1 year of neratinib can be used. [c]In high-risk premenopausal patients, "LHRH-agonist + aromatase inhibitor" may be the preferred adjuvant endocrine therapy. In postmenopausal patients, aromatase inhibitors may be preferred over tamoxifen. [d]The available data suggest that concurrent endocrine therapy with radiation therapy is acceptable

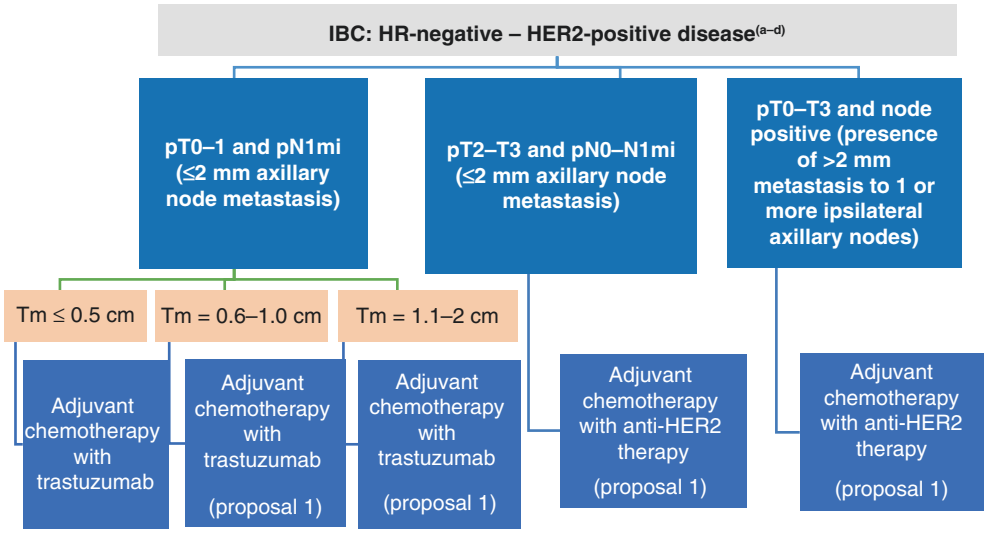

Fig. 44.16 Adjuvant systemic therapy for stages IB, II, IIIA – hormone receptor-negative and HER2-positive disease. [a]There is no absolute age limit. The choice of treatment depends on disease, comorbidities, life expectancy, and patient preferences. Neoadjuvant therapy is recommended in HER2-positive stage II and III patients. Trastuzumab and pertuzumab are recommended in neoadjuvant therapy. For patients >70 years of age, treatment should be individualized. [b]AC – paclitaxel and trastuzumab (+/− pertuzumab); TCH +/− pertuzumab (pertuzumab given to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer) can be recommended. Pertuzumab can be considered as adjuvant therapy in patients with node-positive or locally advanced tumors. [c]In patients with HER2-positive, chemotherapy should always be provided to patients who require anti-HER2 therapy. The chemotherapy regimen for these patients should preferably contain anthracyclines and taxanes. Anti-HER2 therapy should be initiated concurrently with taxane therapy. [d]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

Optimizing Therapy for HER2-Positive and Hormone Receptor-Positive Disease

At least half of HER2-positive breast cancer coexpresses one or both hormone receptors (Figs. 44.13 and 44.15). Analyses from the AC/trastuzumab and AC/T arms of the BCIRG-00651 and B-3153 trials show that the hazard ratios for DFS are very similar for hormone receptor-positive (HR, 0.65 and 0.61 for BCIRG-006 and B-31, respectively) and hormone receptor-negative (HR, 0.64 and 0.62 for BCIRG-006 and B-31, respectively) disease. This also holds true for OS. Similarly, a subset analysis of the HERA study at 11 years of follow-up also demonstrates long-term trastuzumab benefit for all patients regardless of HR status [125]. Although trastuzumab imparts DFS and OS benefit regardless of hormone receptor status, the presence of ER may indicate more indolent, luminal-like tumor behavior. Further evidence supporting the notion that disease behavior differs based on hormone receptor expression comes from neoadjuvant clinical trials, which have consistently shown that pCR rates are lower for hormone receptor-positive, HER2-positive breast cancer than for hormone receptor-negative disease.

However, the longer follow-up in the NeoSphere trial [126] indicates that patients with hormone receptor coexpression have numerically higher PFS than those with tumors lacking hormone receptors (5-year PFS for patients who achieved pCR: 90% if hormone receptor positive, 84% if hormone receptor negative; 5-year PFS for patients who did not achieve pCR: 80% if hormone receptor positive, 72% if hormone receptor negative). Thus, patients with hormone receptor-positive tumors may do better over time. Intriguing biomarker analyses from HERA suggest that although ER-positive tumors with a high level of HER2 amplification (by FISH ratio) derive clear benefit from trastuzumab, those with a low level of HER2 amplification may not receive benefit from trastuzumab-based therapy [127].

Trastuzumab emtansine has also been evaluated in the neoadjuvant and adjuvant settings. The WGS-ADAPT study compared four cycles of T-DM1, either alone or in combination with endocrine therapy, to trastuzumab plus endocrine therapy for patients with hormone receptor-positive, HER2-positive patients [128]. This relatively short course of T-DM1 was associated with an impressive pCR rate (breast and lymph nodes) of 41%, which was considerably higher than that achieved with trastuzumab plus endocrine therapy.

Although neither of these relatively small studies has changed the standard of care, the intriguing results should encourage the investigation of whether less toxic regimens such as these might be beneficial for selected patient populations.

In December 2016 in San Antonio, the results of the NSABP B-52 trial were presented. This study was designed to evaluate whether the addition of an aromatase inhibitor to standard chemotherapy plus HER2-targeted therapy with docetaxel, carboplatin, trastuzumab, and pertuzumab

(TCHP) would improve pCR rates for hormone receptor-positive/HER2-positive breast cancer and to test whether endocrine therapy would be antagonistic in combination with chemotherapy. Although the addition of endocrine therapy to TCHP did not lead to a statistically notable improvement in pCR (41% for TCHP vs. 46% for TCHP plus endocrine therapy), it did not appear to be antagonistic, leaving room for future studies to test less toxic chemotherapy regimens concurrently with hormone therapy approaches.

The preferred duration of adjuvant trastuzumab (+/− pertuzumab) therapy is 1 year. The ExtaNet study suggests that extended anti-HER2 treatment with the dual tyrosine kinase inhibitor, neratinib, reduces recurrence risk, particularly in ER-positive, HER2-positive tumors, but is associated with significant rates of diarrhea [129]. After a median follow-up of 5.2 years, patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (stratified hazard ratio 0.73, $p = 0.0083$). The 5-year invasive disease-free survival was 90.2% (95% CI 88.3–91.8) in the neratinib group and 87.7% (95% CI 85.7–89.4) in the placebo group. Without diarrhea prophylaxis, the most common grade III–IV adverse events in the neratinib group compared with the placebo group were diarrhea (40% grade III and <1% grade IV with neratinib vs. 2% grade III with placebo). Clinicians may use extended adjuvant therapy with neratinib for patients with early-stage, HER2-positive breast cancer. Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used. In summer 2017, The U.S. Food and Drug Administration (FDA) approved 1 year of extended adjuvant neratinib after chemotherapy and a year of trastuzumab for HER2-positive breast cancer. However, we still lack evidence of a substantial benefit for the overall survival or the best surrogate endpoint (distant disease-free survival) for a tolerable schedule. The 1.7% improvement in distant disease-free survival at 5 years in the entire population is not statistically significant. Further, the monetary cost to society is exorbitant, and the subjective tolerability of a year of neratinib therapy using prophylactic loperamide is not clearly established in a large defined population. The Expert Panel of ASCO preferentially favors the use of neratinib treatment for hormone receptor-positive and node-positive patients [120]. There are no data on the added benefit of neratinib treatment for patients who also received pertuzumab in the neoadjuvant or adjuvant setting.

Triple-Negative Breast Cancer

Adjuvant chemotherapy is not recommended for patients with triple-negative invasive breast cancers with a diameter of less than 0.5 cm (T1aN0M0) (Figs. 44.9 and 44.11). Patients with T1b and larger tumors should receive adjuvant cytotoxic therapy. The adjuvant chemotherapy regimen for triple-negative tumors should contain anthracyclines and taxanes [32, 34]. Platinum-based chemotherapy regimens are not standard, and the currently available data are insufficient to recommend these regimens as adjuvant chemotherapy in triple-negative breast cancer patients. Platinum-based chemotherapy regimens may be an option in patients with BRCA mutations. The data for carboplatin and cisplatin in TNBC predominantly emerge from small studies and retrospective analyses in the neoadjuvant or metastatic setting [130]. Although St. Gallen guidelines recommend platinum-based neoadjuvant chemotherapy for TNBC patients, there is no such recommendation for the adjuvant setting. The triple-negative phenotype may be an indication for dose-dense chemotherapy with growth factor support [32, 34, 122, 131].

Integration of targeted agents have also failed to demonstrate survival advantage in the adjuvant setting similar to colon cancer. The BEATRICE trial randomized TNBC patients to receive a minimum of four cycles of chemotherapy either alone or with bevacizumab [132]. After a 56-month median follow-up period, 5-year invasive disease-free survival (IDFS) and OS did not differ between arms. Moreover, biomarker analysis did not indicate a specific subgroup that may benefit from anti-VEGF therapy.

For women desiring fertility preservation and patients with certain comorbidities such as cardiovascular disease and diabetic neuropathy, specific chemotherapy regimens may be preferred. Ovarian function suppression (OFS) with LHRH agonists can be performed during chemotherapy (effective especially in patients with ER-negative tumors) to preserve ovarian function. The intrinsic subtype or BRCA carrier status should not alter the type of adjuvant chemotherapy regimen chosen [32, 34, 133].

Endocrine Therapy

Adjuvant endocrine therapy should be administered to patients with ER+ or PR+ invasive breast cancer regardless of the HER2 status, patient age, or the cytotoxic therapy provided. Endocrine therapy can be initiated either with or after radiotherapy [12] [32, 34, 133] (Figs. 44.17 and 44.18).

Tamoxifen is the standard adjuvant endocrine therapy in women who are premenopausal at the time of diagnosis. OFS might be added to tamoxifen in some patients younger than 35–40 years. Factors supporting the inclusion of OFS include age ≤35 years, premenopausal estrogen levels following adjuvant chemotherapy, grade III disease, four or more involved lymph nodes, and adverse multigene test results [32, 34, 133]. In high-risk premenopausal patients with multiple poor prognostic factors, OFS plus AI may be a treatment option. The adjuvant tamoxifen treatment duration may be prolonged to 10 years in high-risk patients with axillary lymph node involvement, grade III disease or a high

Ki67 proliferation index, and a multigene-based high risk of recurrence score [32, 34, 133–135]. Additionally, after 5 years of tamoxifen, if a patient becomes amenorrheic and if serial blood examinations reveal that follicle-stimulating hormone (FSH) and estradiol are at postmenopausal levels, endocrine therapy may be continued with AIs for an additional 5 years in patients, particularly those with positive lymph nodes, grade III disease, or high Ki67 [32, 34, 133].

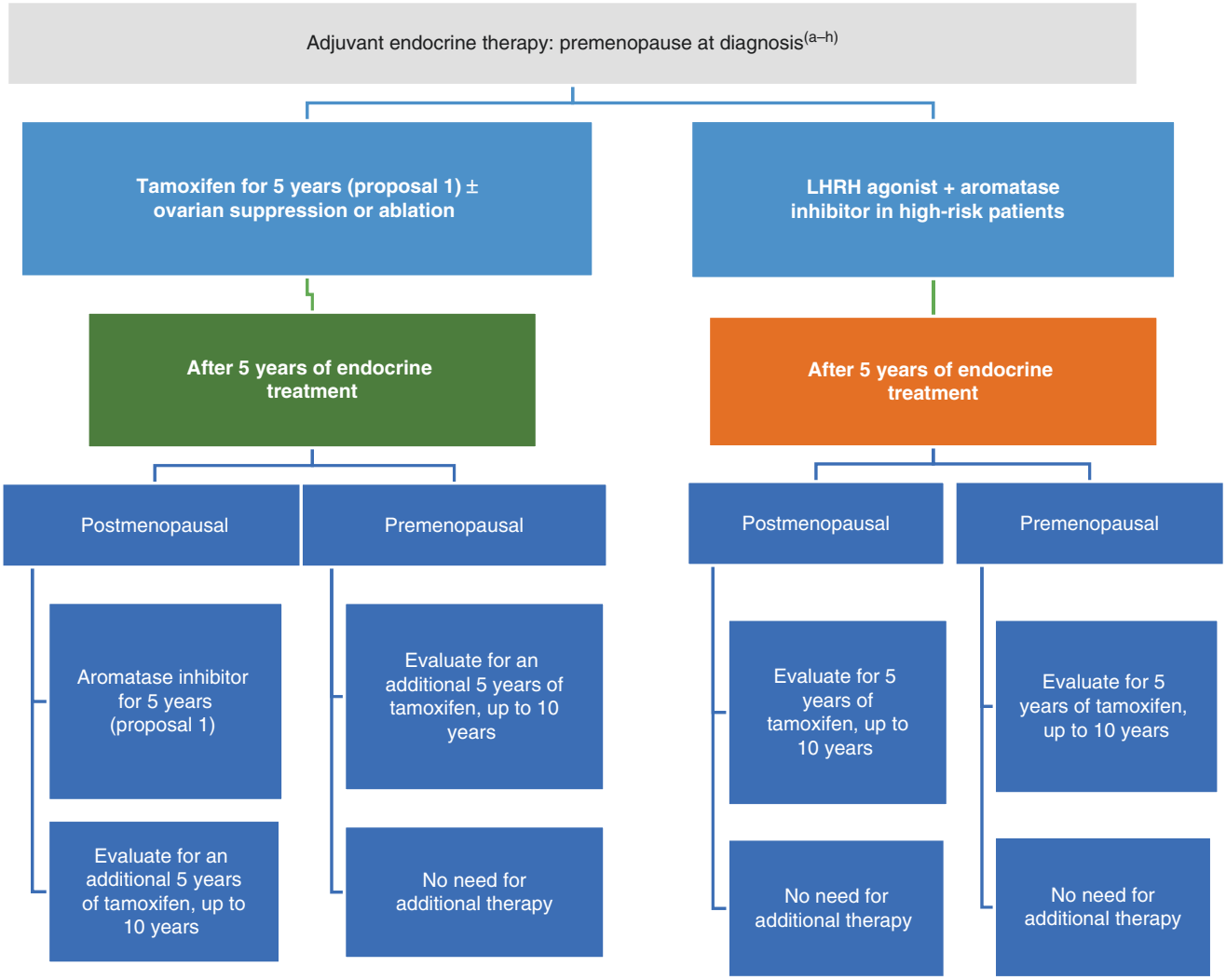

Fig. 44.17 Adjuvant endocrine therapy for premenopausal patients. [a]The following factors are indications for including ovarian function suppression (OFS): age ≤35 years, premenopausal estrogen levels following adjuvant chemotherapy, grade III disease, involvement of four or more nodes, and adverse multigene test results. OFS is not recommended in stage I disease. [b]The optimal duration of OFS (with tamoxifen) may be 5 years. Its use for 5 years should be strongly recommended, especially in high-risk patients. [c]In high-risk premenopausal patients, 5 years of "LHRH-agonist plus aromatase inhibitor (AI)" may be the preferred adjuvant endocrine therapy. Exemestane, letrozole, or anastrozole can be used as an AI. The following factors are indications for the use of OFS plus AI rather than OFS plus tamoxifen: age ≤35 years, grade III disease, high Ki67, node positivity, lobular histology, HER-2 positivity, and adverse multigene test results. Serum estrogen, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels should be measured in the evaluation of menopausal status for the use of an aromatase inhibitor in premenopausal patients who have received chemotherapy. Estradiol levels should be checked at certain intervals. [d]After 5 years of continuous "LHRH-agonist plus AI" adjuvant therapy, we do not (yet) know whether to provide further endocrine treatment. [e]In patients with luminal A-like tumors and 1–3 positive lymph nodes (with the evaluation of other factors such as grade, age, or multigene signature test results), "adjuvant endocrine therapy alone" may be an option. [f]Adjuvant endocrine therapy should be completed in 10 years in stage II and III patients, especially those with moderate to high recurrence risk, but it is not recommended for stage I patients. After 5 years of adjuvant tamoxifen, continued AI (for postmenopausal patients with premenopausal estrogen levels at baseline) or tamoxifen for up to 10 years should be recommended to patients with node-positive disease, grade III disease, or high Ki-67. [g]After 5 years of adjuvant therapy involving a switch from tamoxifen to an AI (therefore assuming postmenopausal status at the 5-year time point and reasonable tolerance to endocrine therapy), patients may continue AI therapy for a cumulative total of 5 years. This subject requires clarification. [h]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

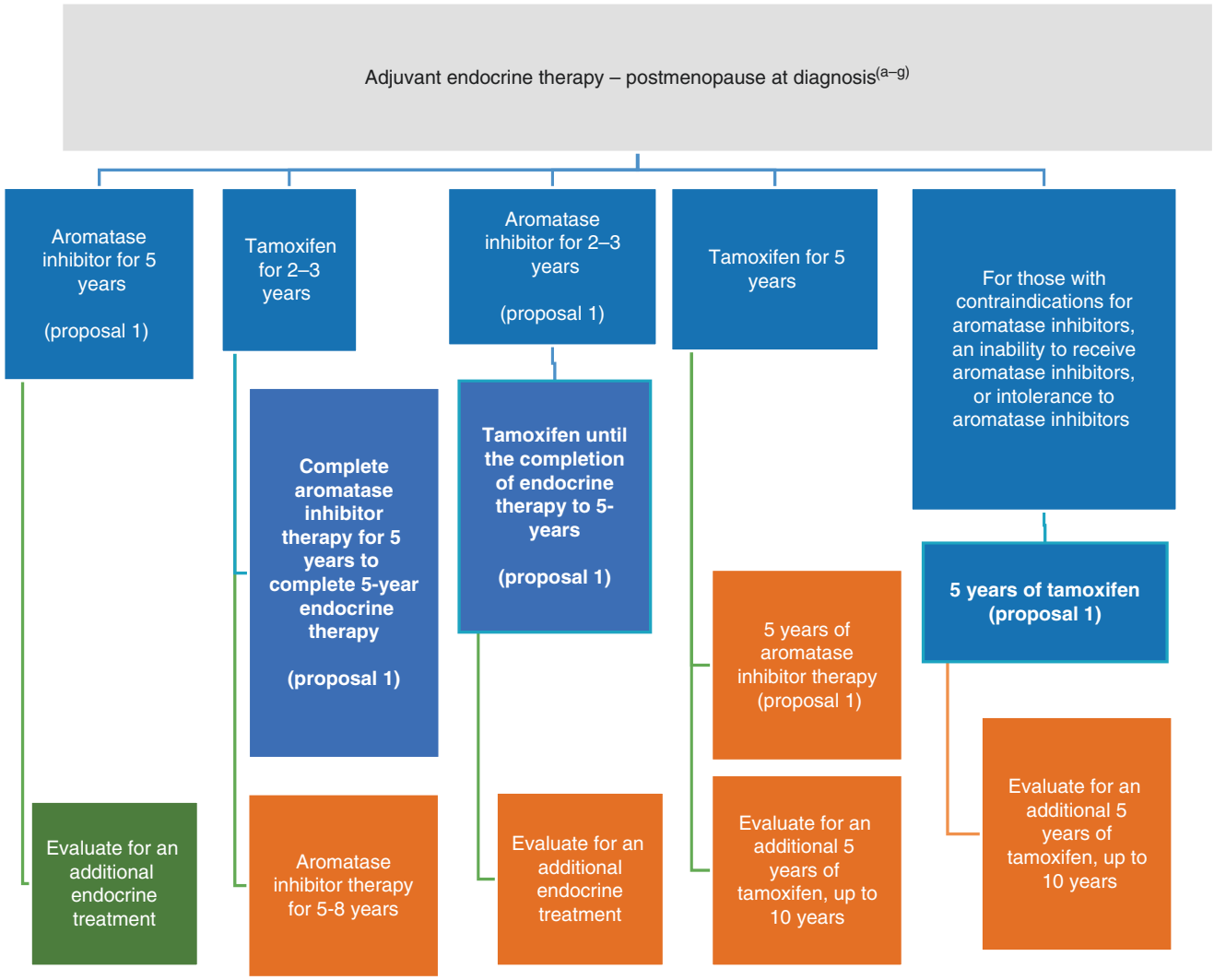

Fig. 44.18 Adjuvant endocrine therapy for postmenopausal patients. [a]In patients with luminal A-like tumors and 1–3 positive lymph nodes (with the evaluation of other factors such as grade, age, or multigene signature test results), "adjuvant endocrine therapy alone" may be an option. [b]Some patients may be adequately treated with tamoxifen alone. In high-risk postmenopausal patients, aromatase inhibitors (AIs) may be preferred over tamoxifen. The following factors argue for the inclusion of an AI at some point: lymph node involvement, grade III disease, high Ki67 proliferation index, or HER2 positivity. If an AI is used, it should be started upfront in patients at higher risk. The upfront AI can be switched to tamoxifen after 2 years in select patients (e.g., those experiencing side effects of the AI). [c]After 5 years of adjuvant tamoxifen, continued AI or tamoxifen (for patients with intolerance to AI therapy) for up to 10 years should be recommended to patients with node-positive disease, grade III disease, or high Ki-67. [d]After 5 years of adjuvant therapy involving a switch from tamoxifen to an AI (therefore assuming postmenopausal status at the 5-year time point and reasonable tolerance to endocrine therapy), patients may continue AI therapy for a cumulative total of 5–8 years (total 10 years). [e]After 5 years of continuous AI adjuvant therapy, extension of treatment with an aromatase inhibitor may be recommended for 3–5 years. In patients with moderate to high risk, adjuvant endocrine treatment should be increased to 10 years (in patients with stage II and III disease); this increase is not recommended for stage I low risk patients. [f]The definition of menopause is important and can include natural menopause (no menses for 12 months before starting chemotherapy or hormone therapy) or menopause with ovarian ablation or suppression. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and serum estradiol (E2) levels should be at postmenopausal levels and should be measured before systemic treatment unless oophorectomy has been performed with hysterectomy in women aged 60 years or younger. [g]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy

In postmenopausal women, both tamoxifen and AIs may be valid endocrine therapy options. Some patients can be adequately treated with tamoxifen alone. Factors supporting the inclusion of an AI at some point include lymph node involvement, grade III disease or high Ki67, and HER2 positivity [32, 34, 133]. All AIs, including letrozole, anastrozole, and exemestane, can be used as adjuvant endocrine therapy in postmenopausal women. An AI provided for a total of 5–10 years, an AI provided for 2–3 years followed by tamoxifen to complete 5–10 years of adjuvant endocrine therapy,

and tamoxifen provided for 2–3 years followed by an AI to complete 5–10 years of endocrine therapy are all options [136–138]. Tamoxifen for 4.5–6 years followed by 5 years of an AI or by tamoxifen for up to 10 years is also an option [134, 138]. Tamoxifen for 2–3 years followed by an AI for up to 5 years is another option.

The recently reported MA.17R trial of randomized women who had already completed 5 years of aromatase inhibitor therapy with or without previous tamoxifen recommended an additional 5 years of letrozole or placebo. DFS was significantly improved in the extended letrozole group, and the quality of life was similar; however, bone fracture rates were higher. The 5-year DFS rate was 95% for the letrozole arm compared with 91% for the placebo arm ($p < 0.01$) [139]. A very similarly designed trial is the randomized, double-blind, placebo-controlled clinical trial, NSABP-B42 [140]. In contrast with the findings of the MA.17R trial, the difference in DFS between control and placebo group did not reach statistical significance. Regarding OS, a significant difference between control and placebo group was also not found ($p = 0.22$). However, patients under extended endocrine therapy were significantly less frequently affected by distant recurrence (HR, 0.72; $p = 0.03$); a risk reduction of 28% was observed. Further, a significantly longer BC-free interval (BCFI), defined as time to recurrence or contralateral BC as first event, could be observed in the letrozole group (HR, 0.71; $p = 0.003$) [140]. The DATA trial presented at San Antonio Breast Cancer Symposium in 2016 was designed to investigate the effect of extended AI therapy after TAM. In this multicenter phase III trial, postmenopausal women with HR-positive early breast cancer who underwent 2–3 years of TAM therapy were randomized to 6 or 3 years of daily anastrozole therapy. The 5-year adapted DFS did not differ significantly (HR, 0.79; $p = 0.07$) [141].

The IDEAL trial is a multicenter phase III trial designed to determine the optimal duration of extended adjuvant letrozole therapy [142]. Patients had to complete 5 years of any commonly used endocrine therapy regimen and then subsequently were randomized to extended adjuvant letrozole therapy, either for 2.5 years or for 5 years. The median follow-up was 6.5 years. No significant difference in 5-year DFS could be found between patients with either 2.5 or 5 years of extended letrozole therapy (HR, 0.96; $p = 0.70$). The 5-year OS did not differ significantly between the two groups (HR, 1.08; $p = 0.59$). The phase III SOLE study included postmenopausal women with HR-positive, N-positive early-stage BC with the purpose to investigate the effect of a new therapy concept of letrozole [143]. The study was designed to assess the role of continuous versus intermittent letrozole intake. After 5 years of adjuvant endocrine therapy, patients were either randomized to 5 years of continuous or to 5 years of intermittent letrozole administration, whereby 3-month treatment-free intervals were followed. After 60 months of follow-up, similar 5 year DFS rates were observed in patients with intermittent and continuous letrozole administration (HR, 1.08; $p = 0.31$).

The current version of the NCCN guidelines recommends the following adjuvant ET options for postmenopausal women with early breast cancer: 5 years of AI as initial adjuvant therapy; 2–3 years of AI followed by tamoxifen to complete 5 years of adjuvant ET; 2–3 years of tamoxifen followed by an AI to complete 5 years or 5 years of AI alone; 5 years of tamoxifen followed by 5 years of AI; or 5 years of AI followed by 3–5 years of AI [12, 32, 34].

Because favorable histology such as tubular carcinoma and mucinous carcinoma are usually hormone receptor positive, the diagnosis of breast cancer with a favorable histology but without hormone receptor positivity should be reevaluated histologically to confirm that the histology or hormone receptor status is correct. Patients with hormone receptor-positive tubular or mucinous carcinoma and a tumor diameter of less than 1 cm should not receive adjuvant endocrine therapy. Patients with a tumor diameter ranging from 1 to 3 cm should be evaluated for adjuvant endocrine therapy. Tamoxifen with or without ovarian ablation therapy or AIs is indicated for primary tumors larger than 2–3 cm with or without axillary lymph node involvement. If lymph node involvement is pathologically confirmed, adjuvant chemotherapy may be administered according to patient and disease characteristics [12, 32].

Preoperative Systemic Therapy

Preoperative systemic therapy (preoperative chemotherapy) is a commonly used therapeutic approach to treat triple-negative breast cancer, HER2-positive breast cancer, and primarily operable or non-operable locally advanced or inflammatory breast cancer. The decision regarding neoadjuvant treatment should be made after discussing the patient's clinical, histological, and imaging characteristics by a multidisciplinary oncology board that includes surgical oncologists, medical oncologists, radiation oncologists, radiologists, and pathologists. Neoadjuvant therapy is most appropriate for patients likely to have a good locoregional response, regardless of tumor size at presentation, including those with HER2-positive or triple-negative breast cancers. Preoperative chemotherapy is a valuable research tool to identify predictive molecular biomarkers and a valid treatment option for patients with early-stage breast cancer. However, the decision to treat a patient with neoadjuvant chemotherapy requires careful clinical judgment and multidisciplinary evaluation by an experienced team.

Neoadjuvant cytotoxic therapy should be discussed as an option in patients with luminal A- and B-like tumors if conservative surgery would not otherwise be feasible. Neoadjuvant endocrine therapy without cytotoxic agents is a

reasonable option for postmenopausal patients with endocrine-responsive disease for a duration of at least 4–8 months or until a maximum response is achieved.

Triple-Negative Breast Cancer

In patients with triple-negative breast cancer (TNBC), the preoperative regimen should include anthracycline plus taxane. The role of carboplatin as neoadjuvant treatment was evaluated in the context of triple-negative breast cancer. The inclusion of carboplatin with anthracycline- and taxane-based chemotherapy improved the rate of pathologic complete response (pCR) in TNBC and translated into disease-free survival benefit though the role for such treatment when patients additionally receive standard alkylator therapy is less clear [144]. In an adaptive randomized trial, the addition of carboplatin and the PARP inhibitor, veliparib, improved the rate of pCR in TNBC [145].

Two randomized trials yielded significantly higher pCR rates with 13–16% increments [144, 146]. A subgroup analysis in the GEPARSIXTO trial revealed that the addition of carboplatin provided benefit irrespective of germline BRCA mutation status [146, 147]. Although germline BRCA status has not been consistently linked with response to platinum-based chemotherapy, there is clinical evidence suggesting that somatic mutations in the BRCA gene or the homologous repair pathway (HRD) may be potentially associated with platin responsiveness. Pooled analysis of six German neoadjuvant studies including triple-negative patients demonstrated that tumors with a high HRD score were more likely to achieve a pCR (53% vs. 18%) irrespective of BRCA status [148]. In contrast, Arun et al. showed that BRCA1 status (OR = 3.16; $p = 0.002$), ER-negativity (OR = 1.96; $p = 0.03$), and concurrent trastuzumab use (OR = 4.18; $p < 0.0001$) were independent significant predictors for a pCR [149]. In their study, at a median follow-up of 3.2 years, 69 patients (22%) experienced a disease recurrence or death. No significant differences were noted in survival outcomes with respect to BRCA status and type of neoadjuvant systemic treatment received. However, among BRCA1 carriers, patients who achieved a pCR had better 5-year RFS ($p = 0.001$) and OS ($p = 0.01$) rates than patients who did not achieve a pCR. In the light of the data showing significantly improved response rates, it would be reasonable to use platin-based regimens in triple-negative patients who otherwise lack effective treatment options.

A phase III study that evaluated the role of nab-Pac in the neoadjuvant setting has been recently reported [150]. In the Gepar-Septo trial, patients were randomized to two arms including standard paclitaxel weekly at 80 mg/m^2 for 12 weeks or nab-Pac weekly at 150 mg/m^2 for 12 weeks followed by four cycles of EC. Patients with Her-2-positive disease received pertuzumab and trastuzumab throughout the treatment period. The use of nab-paclitaxel resulted in a significant benefit in the whole patient group, with an absolute 9% incremental improvement in the pCR rate ($p < 0.001$). A planned subgroup analysis showed a significantly improved pCR rate of 48.2% in the triple-negative subgroup with a hazard ratio of 2.69 ($p < 0.001$). It should be noted that further confirmatory data are required to establish the role of nab-paclitaxel for triple-negative breast cancer.

HER2-Positive Breast Cancer

For patients with HER2-positive disease, the neoadjuvant regimen should include anthracycline plus taxane and an anti-HER2 agent. Trastuzumab ± pertuzumab are the preferred anti-HER2 agents [12, 32, 34].

In Her-2-positive disease, the role of carboplatin as part of a non-anthracycline-based regimen combined with dual blockade (TCH-Lapatinib and TCH-Pertuzumab) was investigated in the phase III TRAIN-II trial. Twenty-seven weeks of this combination was compared to a standard anthracycline- and taxane-based combination with a similar total duration. Overall, the pCR rates were similar in both arms (68% vs. 67%, NS) or in hormone receptor (HR)-positive patients (55% vs. 51%; NS). Nevertheless, the numerically higher pCR rate in HR-negative patients (84% vs. 89%; NS) led to concerns regarding the omission of anthracyclines in this subset [151]. Furthermore, in the phase III Kristine trial, the standard TCHP arm yielded a 56% pCR rate, which was in accordance with previous results utilizing the same regimen, confirming the efficacy of this combination [152]. In conclusion, non-anthracycline-based combinations incorporating carboplatin with taxanes, in addition to pertuzumab-based dual HER2 blockade, have shown favorable pCR rates and should be considered in all patients who are eligible for neoadjuvant treatment, especially for those with cardiac comorbidities. In HR-negative patients, who are considered to harbor high-risk disease, the omission of anthracyclines is still a matter of debate, and the decision should be individualized.

In the Gepar-Septo trial, patients with HER2-positive disease received pertuzumab and trastuzumab throughout the treatment period [150]. A dual HER2-targeted combination of pertuzumab and trastuzumab, together with taxane-epirubicin-cyclophosphamide neoadjuvant chemotherapy, achieved high rates of pCR. Higher rates of pCR were achieved in HER2+ than in HER2− tumors (57.8% vs. 22.0%, $p < 0.0001$), with the highest rate in the HER2+/HR− cohort (71.0%). In HER2+/HR+ tumors, the pCR rate was 52.9%.

The antibody-drug conjugate, ado-trastuzumab emtansine paired with pertuzumab was less effective at achieving pCR than the chemotherapy, trastuzumab-pertuzumab TCHP [152]. In a phase 3 randomized study (KATHERINE), among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone [153]. If residual cancer has been found in a breast and/or axilla after neoadjuvant treatment with AC/EC followed by Taxane-Trastuzumab (without pertuzumab), the

preferred adjuvant systemic therapy would be TDM1 for 91.7% of the panelists in the St Gallen meeting [34]. When neoadjuvant treatment has encompassed Docetaxel-Carboplatin-Trastuzumab-Pertuzumab or AC/EC followed by taxane with trastuzumab and pertuzumab, and there is still residual cancer in tumors > 1 cm and/or an axilla, again, 93.9% of the panelists would recommend TDM1[34].

In the Neo-Sphere trial, women with operable or locally advanced or inflammatory breast cancer were randomized to receive four cycles every 3 weeks of docetaxel, trastuzumab, or docetaxel; trastuzumab and pertuzumab or the doublet of the two monoclonal antibodies; or docetaxel and pertuzumab. Following surgery, patients in the docetaxel-containing arms received adjuvant FEC for three cycles and trastuzumab every 3 weeks for 1 year. The remaining patients received four cycles of docetaxel followed by three cycles of FEC with trastuzumab in the adjuvant setting. The in-breast pCR rate with pertuzumab when added to the conventional trastuzumab and docetaxel combination was 46.8%, which was significantly higher than the 24% pCR rate with the pertuzumab and docetaxel doublet, and 29% with the trastuzumab and docetaxel combination. An updated survival analysis showed a numerically higher 5-year progression-free survival in the dual blockade group than in the standard arm of trastuzumab and docetaxel (86% vs. 81%) [126]. Despite a lack of profound survival benefit with the dual blockade, it seems feasible to utilize the pertuzumab and trastuzumab combination in the neoadjuvant setting, based on evidence that has shown improved outcomes with increased pCR rates.

Clinicians may add 1 year of adjuvant pertuzumab to the trastuzumab-based combination chemotherapy for patients with early-stage, HER2-positive breast cancer [34]. The Expert Panel of ASCO preferentially supports pertuzumab in the node-positive, HER2-positive population in view of the clinically insignificant absolute benefit observed among node-negative patients [120, 123]. The FDA has granted accelerated approval to pertuzumab for its use before surgery when combined with trastuzumab and chemotherapy. Currently, there are insufficient cardiac safety data to recommend concomitant administration of an anthracycline with pertuzumab. In December 2017, the FDA has approved pertuzumab in combination with trastuzumab and chemotherapy as an adjuvant treatment for patients with HER2-positive early breast cancer at high risk for recurrence, based on findings from the APHINITY trial [123]. The phase III double-blind, placebo-controlled APHINITY trial randomized patients with operable HER2+ early (T1–3) breast cancer in a 1:1 ratio to adjuvant treatment with trastuzumab plus chemotherapy (anthracycline or non-anthracycline-containing regimen) with pertuzumab ($n = 2400$) or placebo ($n = 2404$). Patients had undergone mastectomy or lumpectomy. Overall, 63% of the participants had node-positive disease and 36% had HR-negative disease. The pertuzumab arm received 6–8 cycles of chemotherapy with pertuzumab and trastuzumab, followed by pertuzumab and trastuzumab alone every 3 weeks for a total of 1 year of therapy. In this phase III trial, adjuvant treatment with pertuzumab, trastuzumab, and chemotherapy demonstrated a 3-year invasive disease-free survival rate of 94.1% versus 93.2% for those who received trastuzumab plus chemotherapy and placebo. This represented an 18% reduction in the risk of developing invasive disease or death (HR, 0.82; $p = 0.047$). The 4-year invasive DFS rates were 92.3% versus 90.6%. Similar to neoadjuvant trials with pertuzumab, the addition of pertuzumab did not significantly increase cardiotoxicity. Primary cardiac events were reported in 17 patients (0.7%) in the pertuzumab-containing arm versus 8 participants in the standard therapy group (0.3%).

Adjuvant Radiotherapy in Invasive Breast Cancer

Postmastectomy radiotherapy (PMRT) is the standard of care in patients with four or more involved lymph nodes with metastatic disease [23]. However, the benefit of PMRT in patients with one to three involved nodes was more controversial until recently. Although some trials from the 1990s indicated a benefit of PMRT in patients with one to three involved nodes, these studies were criticized for using substandard chemotherapy and having unusually high locoregional recurrence rates without PMRT compared with other studies [24, 25]. A recent meta-analysis provided more evidence of the benefit of PMRT in patients with one to three involved nodes [27]. However, in patients with T1–2 tumors with one to three positive axillary lymph nodes who undergo ALND, the decision to recommend PMRT or not requires a great deal of clinical judgment. The ASTRO panel agreed clinicians making such recommendations for individual patients should consider factors that may decrease the risk of LRF, attenuate the benefit of reduced breast cancer-specific mortality, and/or increase the risk of complications resulting from PMRT [154]. Indirect evidence from the preliminary results of another Canadian randomized trial also indicated the benefit of regional nodal irradiation in patients with less than three involved nodes [155]. PMRT does not provide any benefit in pathologically node-negative patients with negative surgical margins of at least 1 mm [27, 155]. A collective analysis of NSABP trials revealed no benefit of PMRT in T3N0MX patients.

After lumpectomy, whole-breast radiotherapy remains the standard of care [46, 155–157]. A meta-analysis revealed a significant increase in in-breast control and a decrease in breast cancer-specific deaths [158]. Controversial results were obtained for partial-breast irradiation (PBI) in patients with a low local recurrence risk. Two large randomized (intraoperative) PBI trials observed higher in-breast recurrence rates in patients treated with PBI than in those treated

with whole-breast radiotherapy [159, 160]. Several different techniques such as external beam radiotherapy, intracavitary brachytherapy, interstitial brachytherapy, and intraoperative irradiation can be used to deliver PBI. Most likely, not all these techniques will be capable of achieving adequate local control with low side effect rates [161, 162]. The results of large randomized trials are awaited before PBI can be considered standard in some patients [163]. Data are accumulating to consider whether some elderly patients with low-risk disease (T1/T2N0M0), negative surgical margins, and hormone receptor-positive tumors can be followed without any post-lumpectomy radiotherapy [164, 165] (Figs. 44.19 and 44.20).

Techniques, Doses, and Fields

Chest Wall Irradiation

If PMRT is indicated, the chest wall (CW) is always targeted as one of the radiotherapy fields because this is the most common site of locoregional recurrence. In cases with reconstruction, the CW is treated through tangential fields; without reconstruction, the CW can be treated through tangential fields or electron fields. Particularly in cases with a high risk of skin recurrence, the use of bolus material should be considered in at least part of the treatment. CT-based treatment planning should be performed to delineate target volumes and normal tissues to be protected.

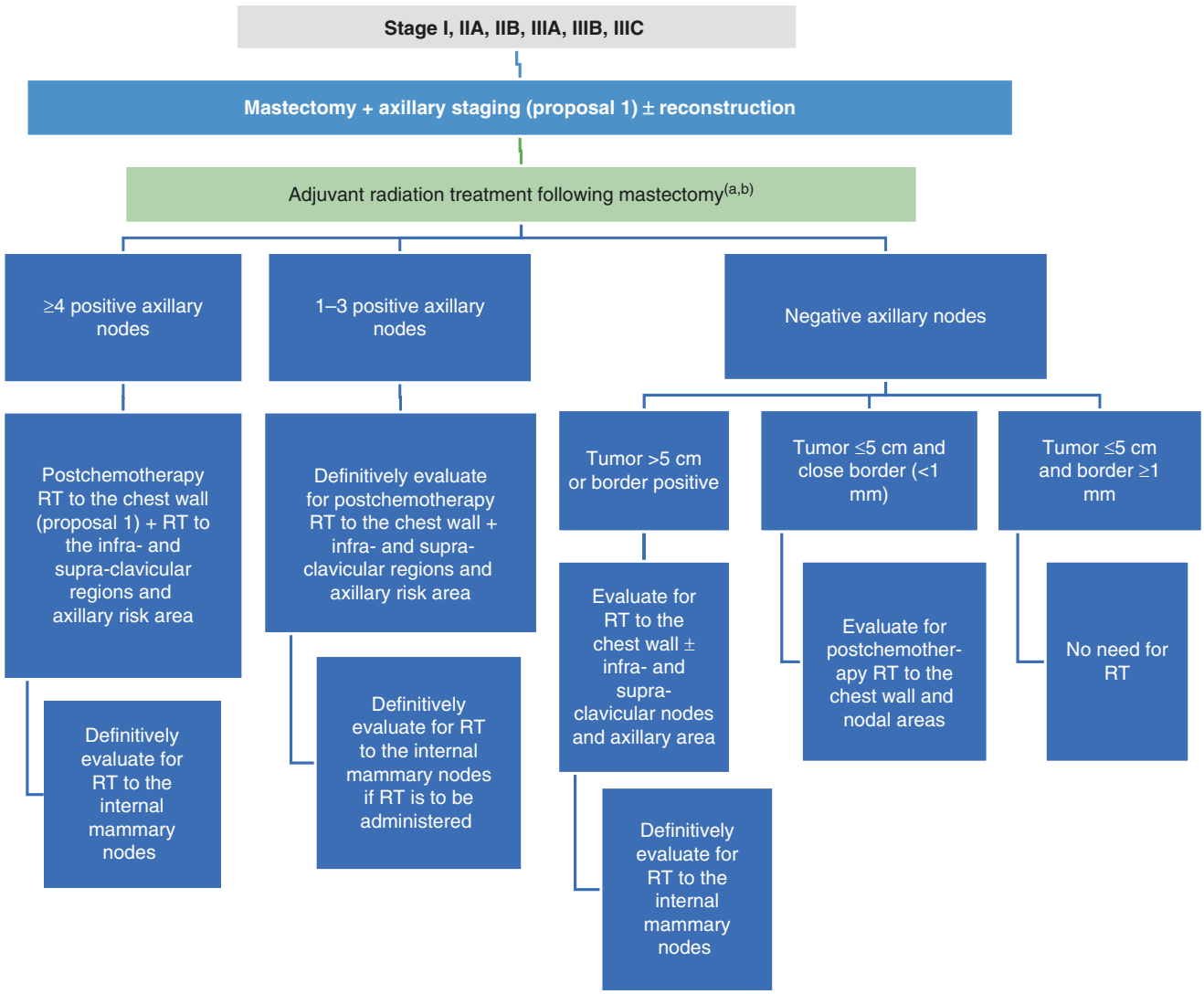

Fig. 44.19 Adjuvant radiotherapy after mastectomy. [a]RT following chemotherapy if chemotherapy is indicated. [b]Postmastectomy RT is standard for patients who meet the following criteria: T size ≥5 cm (node negative); 1–3 nodes with adverse pathology (this is not the sole criterion in patients of young age (<40)); four or more positive axillary LNs; and positive sentinel lymph node biopsy with no axillary dissection. The tumor biology should be considered together with tumor size and stage in the decision for radiotherapy after mastectomy. For pN1 low-risk findings, RT should be performed after having considered the toxicity risks after mastectomy and doing so is more important if the patient is to undergo breast reconstruction. Patients with pT1–pT2, pN1 (1–3) and favorable biological features should be evaluated for omitting radiotherapy after mastectomy

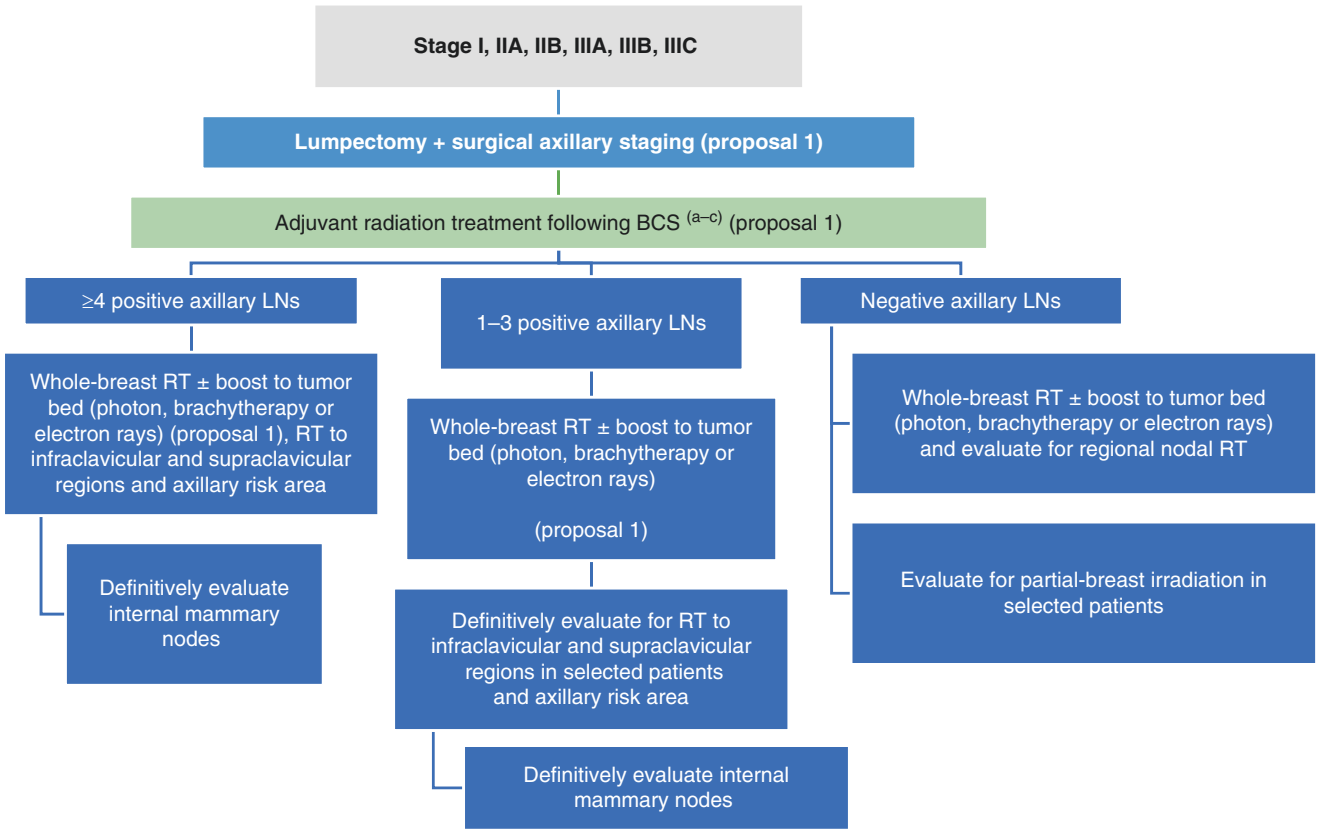

Fig. 44.20 Adjuvant radiotherapy after breast-conserving surgery. [a]RT following chemotherapy if chemotherapy is indicated. [b]Following BCS, hypofractionated whole-breast irradiation may be used in patients without prior chemotherapy or axillary lymph node involvement, in patients 50 years of age or older and in patients <50 years of age. According to the results of a clinical trial that randomized low-risk early-stage breast cancer patients, accelerated partial-breast RT was not inferior to standard whole-breast RT. Partial-breast RT can be performed in ASTRO/ESTRO "eligible" low-risk patients, although there are insufficient data in the literature. Whole-breast RT should be performed in other patients. Boost therapy may not be performed in patients aged 60 years or older, patients with low-grade tumors having favorable tumor biology, and/or patients who will receive adjuvant endocrine therapy. Regional node irradiation (RNI) prolongs disease-free survival in high-risk patients, but the risk of toxicity increases and may lead to complications during reconstruction surgery. RNI is recommended in pN1 (1–3 positive lymph nodes) in the presence of unfavorable clinical features (40 years and younger, unfavorable tumor biology, low or negative estrogen-receptor status, high grade (grade III), diffuse lymphovascular invasion, and positivity of more than three lymph nodes). Axilla-negative patients should be evaluated for RNI for central/medial tumors or >2 cm tumors and the presence of other risk factors (young age or extensive lymphovascular invasion). [c]Studies are underway to evaluate the radiotherapy decision in patients with complete response after neoadjuvant chemotherapy. Patients must be evaluated individually. The decision for radiotherapy is determined according to the disease stage before neoadjuvant chemotherapy, but the disease stage may also be important for management after treatment. When the NSABP B-51 and Alliance A11202 studies are completed, they will provide information about the sufficiency of axillary staging and RT application

The PMRT adjuvant dose is 45.0–50.4 Gy in 25–28 fractions. In inflammatory cases, this dose could be increased to 60 Gy. Special consideration should be given to tolerance doses of the lungs, heart, and left coronary artery. In left-sided cases, breath-holding techniques could be used to better spare the heart. Targets include the ipsilateral CW, mastectomy scars, and, in advanced cases, drainage sites. Several guidelines for target delineation, including the ASTRO and ESTRO atlases, are available (www.guideline.gov, www.astro.org, www.estro.org).

Whole-Breast Irradiation

CT-based treatment planning should be used for target delineation. The most popular technique is tangential fields using forward planning (field-in-field) intensity-modulated radiation therapy (IMRT). The preferred dose homogeneity is ±7%. For left-sided cases, breath-holding techniques are recommended. The classical dose provided to the whole breast is 45–50.4 Gy in 25–28 fractions, with an additional boost dose of 10–16 Gy in 2 Gy fractions to the tumor bed. In patients older than 50 years with T1/T2N0 disease and clear surgical margins, hypofractionated whole-breast irradiation at 42.5 Gy/16 fractions should be considered for both convenience and effectiveness. Revised ASTRO guideline in 2018 did not take into account the age of patients and previous adjuvant chemotherapy administration when considering hypofractionation for whole breast; the recommended doses/fractions were 40 Gy/15 or 42.5/16.

Boost Radiotherapy

Since 65–80% of in-breast recurrence sites is the first tumor localization or its immediate surroundings, two large randomized trials investigated whether boost will provide local control benefit [166, 167]. The Lyon Boost Trial included 1024 patients with stage I–II (<3-cm tumor) breast cancer. After lumpectomy with negative margins + axillary lymph node dissection (ALND) and 50 Gy RT, patients were randomized to receive 10 Gy of electron boost or no boost. At a median follow-up of 5 years, the addition of boost reduced local failures (3.6% vs. 4.5%, $p = 0.04$). Despite a nonsignificant increase in grade I–II telangiectasia (12.4% vs. 5.9%), no difference was observed in self-assessed cosmetic response between the two arms [166].

The second trial, the EORTC Boost Trial, randomized 5518 patients with stage I/II breast cancer to 50 Gy RT vs. 50 Gy + 16 Gy boost following lumpectomy (negative invasive margins, DCIS margins ignored). At the 10-year follow-up, local failure was decreased from 10.2% to 6.2% ($p < 0.0001$) in those with boost, while the largest benefit was observed in patients ≤40 years (local failure decreased from 23.9% to 13%) [167]. Additionally, the updated results of this study with a median follow-up time of 17.2 years detected a significant 20-year risk reduction (from 16.4% to 12%). Again, the most obvious benefit was gained in patients ≤40 years of age (36% vs. 24.4%) at an expense of increased moderate/serious fibrosis rates (30.4% vs. 15%, $p < 0.0001$) [167]. Furthermore, the EORTC 22881 trial demonstrated no difference between three different methods of boost application including photon, electron, and interstitial brachytherapy in terms of local control [168].

Accelerated Partial Breast Irradiation

After BCS, irradiating only the tumor-bearing quadrant of the breast instead of irradiating the whole breast has gained much popularity in the last decade. This kind of breast RT is termed as accelerated partial breast irradiation (APBI). In this technique, the RT period is shortened considerably, and the adjacent normal tissue and organs as well as parts of the breast distant to the tumor bed receive a minimal dose. One disadvantage with this technique, at least in theory, might be that the parts of the breast distant to the tumor bed that harbor occult tumor foci and do not receive therapeutic doses of RT may cause higher rates of in-breast recurrences or new primaries over a longer follow-up.

As a result of increasing interest in this technique, many randomized trials have been conducted to compare APBI with whole-breast RT. Results of some of these randomized trials have been published recently with limited follow-up [159, 160]. Despite a lack of randomized and solid evidence for the safety and efficacy of APBI, the growing popularity of APBI has driven European and American RT societies to publish guidelines that may help to choose patients who are most suitable for APBI applications. Researchers such as Holland, Vaidya, Faverly, Frazier, and Rosen investigated the presence of tumor foci in the other quadrants of the breast on operation specimens when a tumor mass was diagnosed in one site [169–172]. In 60% of the cases, invasive but occult tumor foci were identified in quadrants of the breast other than the quadrant that harbored the index tumor. These findings raised doubts on the efficacy of APBI. The irradiation period in intraoperative APBI is shortened from ten fractions in 5 days to a single fraction, which requires giving a very high dose of RT in a very short time. This kind of ultra-hypofractionation raises questions regarding the safety of the APBI in terms of late sequels and cosmesis [173, 174]. Additionally, radiobiological considerations regarding the use of a single very high dose of irradiation and relating known mathematical models of radiobiological equivalence have raised questions [173].

At this time, according to the updated guidelines published by larger RT societies, it is considered safer to use APBI in those who are ≥50 years of age and have hormone receptor-positive tumors, BRCA ½-negative tumors, no lymphovascular space invasion, T1 or Tis, node-negative disease that is removed surgically with clear margins (≥2 mm) or patients who have tumors ≤2.5 cm in size and low-to-intermediate nuclear graded, screen-detected DCIS with negative margins of ≥3 mm. On the other hand, patients who are aged ≤40 years, or with positive margins, and DCIS ≥3 cm should be accepted as "unsuitable candidates" for APBI. The results of the ongoing RTOG 0413/NSABP B39 trial that compares whole-breast RT and APBI in patients with a <3-cm invasive or noninvasive tumor with 1–3 positive nodes will provide us more accurate data about the safety and efficiency of APBI. The recommended dose regimens are 34 Gy in ten fractions twice daily for brachytherapy or 38.5 Gy in ten fractions twice daily for external beam RT [12].

Hypofractionation

The rationale for hypofractionation has been demonstrated in the study by Yarnold et al. in which the α/β ratios for tumors and late side effects in the breast were found to be 4 Gy and 3.6 Gy, respectively [175]. Four major randomized trials investigated if hypofractionation was as effective and safe as conventional fractionation. Of those, the Canada Ontario Clinical Oncology Group (OCOG) trial emphasized that the 42.5 Gy/16 fr/22 day treatment schedule was similar to the 50 Gy/25 fr/35 day schedule with no boost in terms of 10-year local invasive recurrence rates (6.2% vs. 6.7%) and good cosmetic results (69.8% vs. 71.3%) in 1234 patients staged T1–2N0M0 who received BCS + level I–II ALND with no involved node or margin positivity. Although unconfirmed with other studies, an increase in local recurrence was detected in the high-grade tumor subgroup in the hypofractionation arm (15.5% vs. 4.7%, $p = 0.01$) [176].

Three additional randomized trials from England also compared hypofractionation and conventional fractionation all of

which had no boost treatment. A total of 1410 patients with T1–3N0M0 disease treated with BCS were randomized to three different dose schemas (50 Gy/25 fr vs. 42.9 Gy/13 fr vs. 39 Gy/13 fr) with a total treatment time of 5 weeks in all groups. The 10-year recurrence rates were 12.1%, 9.6%, and 14.8%, respectively, while the difference between 42.9 and 39 Gy was significant ($p = 0.027$) [177]. Furthermore, the other two randomized trials, START-A and START-B included T1–3N0–1M0 patients who were treated with either BCS or modified radical mastectomy (MRM) [177, 178]. Similar to the previous trial, patients were randomized to receive 50 Gy/25 fr vs. 41.6 Gy/13 fr vs. 39 Gy/13 fr all in 5 weeks in START-A, whereas the randomization arms were 50 Gy/25 fr in 5 weeks and 40 Gy/15 fr in 3 weeks in the START-B trial. The three arms were found to be similar in START-A, while a survival benefit in the hypofractionation group was demonstrated in the STAR-B trial (84% vs. 81%, $p = 0.042$) [177, 178].

Lastly, more hypofractionated regimens (28.5 or 30 Gy in 5 one weekly fr vs. 50 Gy/25 fr) were evaluated in the FAST trial, which included 729 patients aged ≥50 years who had early-stage node-negative disease resected with negative margins. The 3-year moderate/marked side effects were more common in 30 Gy (17.3% vs. 9.5%, $p < 0.001$) and 28.5 Gy (11.1% vs. 9.5%, $p = 0.18$) than in 50 Gy/25 fr [179].

Valle et al. compared standard fractionation and hypofractionated irradiation in 8189 patients undergoing BCS with stage T1–T2 and/or N1 breast cancer or DCIS in a recent systematic review and meta-analysis of 13 randomized controlled trials that included a highly selected group of patients who were node-negative, CT-naive, and without high-grade tumor. The local failure ($n = 7$ trials; RR 0.97; 95% CI 0.78–1.19), locoregional failure ($n = 8$ trials; RR 0.86; 95% CI 0.63–1.16), and survival ($n = 4$ trials; RR 1.00; 95% CI 0.85–1.17) were similar. The acute toxicity rate ($n = 5$ trials; RR 0.36; 95% CI 0.21–0.62) was lower in the hypofractionation arm, whereas no difference was detected in late cosmesis (RR 0.95; 95% CI 0.81–1.12). Similar conclusions were reached in two previous meta-analyses [180, 181].

ASTRO guidelines for hypofractionated whole-breast irradiation was recently reported [182]. In previous 2011 guideline for hypofractionation: Age ≥50 years; Stage = T1T2N0; Chemotherapy = none; Dose homogeneity = ±7% in the central axis. In 2018 guideline: Age = Any; Stage = Any stage provided intent to treat the whole breast without an additional field to cover the regional lymph nodes; Chemotherapy = Any chemotherapy; Dose homogeneity = Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation [182]. The ongoing trials will provide more evidence about the use of hypofractionation in DCIS, sequential and integration of additional dose administrations, chest wall, and regional lymphatic RT. Until then, conventional fractionation is the standard treatment regimen in cases in whom dose inhomogeneity >7% exists or regional lymphatic RT.

Regional Lymph Node Irradiation

The axillary LN involvement rate is 10–40% among clinically node-negative patients depending on other prognostic factors [183]. While the involvement probability of level II LN in the absence of level I nodes has been shown to be 1.2%, the risk of level II and other node involvement increased up to 40% in cases of level I node metastasis. Additionally, the second most common relapse site following the chest wall is supraclavicular LN such that the reported recurrence rate of the supra- and infraclavicular region is as high as 14–17% in patients with axillary LN involvement and extracapsular extension. On the other hand, the supraclavicular fossa recurrence rate is approximately 1% in those minimal (1–3 nodes) or without nodal involvement [184, 185]. The predictive factors for supraclavicular LN involvement are higher histologic grade, >4 node involvement, level II or III involvement, and extracapsular extension [184, 186]. While the frequency of supraclavicular lymph node metastasis is 4.4% in those with level I involvement and ≤4 node positivity, it increases to 15.1% in cases of level III involvement [187]. The locoregional recurrence has been found to be 15–20% in patients <50 years of age who have 1–3 positive nodes, grade III, or ER-negative disease even if they received BCS, whole-breast RT, and systemic therapy, which emphasizes the importance of nodal irradiation in this group of patients [188].

The risks factors for in-breast LN involvement were found to be peritumoral vascular invasion, the presence of the primary tumor on histological examination (22.8%), axillary node metastases (21.9%), and >2-cm size of the primary tumor (16%), whereas the only factor affecting mammary internal node metastasis was the peritumoral vascular invasion status in patients with negative axilla (16.4%) [189].

For the question, "Should RNI include both the IMNs and supraclavicular-axillary apical nodes when PMRT is used in patients with T1–2 tumors with one to three positive axillary nodes?": "The ASTRO panel recommends treatment generally be administered to both the IMNs and the supraclavicular-axillary apical nodes in addition to the chest wall or reconstructed breast when PMRT is used for patients with positive axillary lymph nodes [154]. There may be subgroups that will experience limited, if any, benefits from treating both these nodal areas compared with treating only one or perhaps treating only the chest wall or reconstructed breast. There is insufficient evidence at this time to define such subgroups in detail. Additional research is needed to identify them."

Radiotherapy After Neoadjuvant Chemotherapy

No randomized trial data exist to define which women will benefit from PMRT after neoadjuvant chemotherapy. Retrospective data suggest that both the clinical stage at presentation and response to neoadjuvant chemotherapy could be used to indicate RT in these patients [190].

Patients with clinical stage III disease and lymph node involvement at the time of surgery are routinely administered

PMRT. In clinical stage II disease, PMRT is considered for those with lymph node involvement at the time of surgery or features that suggest high-risk disease, such as triple-negative disease, partial response to chemotherapy, low hormone receptor levels, T3 tumor, close surgical margins, diffuse lymphovascular space involvement, or very young age. PMRT could be omitted in patients with low locoregional relapse risk (<10%), defined as older than 40 years of age with estrogen-receptor positivity and pCR after NACT [191].

The results of the ongoing NSABP B-51/RTOG 1304 trial will show if any benefit is gained with PMRT for clinical T1–3N1 disease that became node negative after neoadjuvant chemotherapy [192]. Also, in patients with sentinel lymph node positivity after neoadjuvant chemotherapy, patients are randomly assigned to receive the following: ALND for levels 1–2 and nodal irradiation of the undissected axilla, supraclavicular and internal mammary nodes versus full axilla, and supraclavicular and internal mammary node irradiation without ALND. In this ongoing trial, the Alliance 011202, it will be established whether ALND may be omitted in this group of patients. Until such time, RT should be applied according to prechemotherapy clinical disease stage.

Follow-Up

After primary treatment is completed in patients with early-stage disease, routine follow-up is required for all patients three to four times annually during the first 2–3 years following diagnosis and two times annually during the third to fifth years. No uniform consensus has been reached on monitoring complete blood counts or biochemistry or on scanning other than annual mammography. Physical examination and patient history collection should be routinely performed at all follow-up visits, and the chest, the abdominopelvic region, or any other body part should be scanned if any clinical indication is present. Premenopausal women should be educated regarding contraceptive techniques and should delay pregnancy until adjuvant therapy is completed. Patients on tamoxifen therapy should be referred to a gynecologist at least annually due to the possible risk of endometrial cancer. Bone mineral density should be initially assessed and then periodically evaluated in women who will receive AIs. The evaluation of possible recurrence sites by PET-CT should not be performed as a routine screening method.

Recurrent or Metastatic Disease

For recurrent or advanced breast cancer, less level I evidence is available. The primary aim of treating advanced disease is prolonging disease-specific survival while improving the quality of life. Treatment should be tailored according to disease status and patient priorities as well as to any prior history of disease and to the patients' physical, functional, psychosocial, and spiritual characteristics.

Because elderly patients have several comorbidities that may preclude the initiation of some systemic agents or that may increase the overall toxicity, physicians may not provide a full course of therapy and occasionally may not treat elderly patients appropriately. Age may be an important factor during the treatment decision but should not be the sole guiding criterion in the treatment of breast cancer.

The workup of recurrent or metastatic breast cancer (MBC) patients should include prior medical and breast cancer histories, physical examinations, complete blood counts, blood biochemistry measures comprising liver and renal functions, and chest and abdominopelvic CT. For symptomatic patients with central nervous system-related symptoms, brain MRI may be indicated; for patients with bone-related symptoms, bone scan or PET-CT may be indicated. Symptomatic bones and long, weight-bearing bones can be scanned with X-rays. FDG PET-CT should not be offered to all recurrent or metastatic patients unless the PET-CT results will radically change the treatment decision.

Patients with first disease recurrence and with distant metastasis should undergo a core biopsy of the site of recurrence or metastasis, which may provide new information regarding histology, hormone receptor status, HER2 status, and proliferation/grade [193]. The biopsy should be emphasized, particularly for patients who previously had hormone receptor-negative or HER2-negative breast cancer. If biopsy cannot be performed at the site of metastasis or recurrence, treatment should be planned according to the receptor status of the primary site or to previous pathological findings.

Major determinants of the treatment plan include the number of lesions, extent of visceral involvement, receptor status of the primary lesion, sites of recurrence and metastasis, previous response to anticancer agents, present function of organs, performance status of patients, and social support of patients.

In the absence of any contraindication, treatment with denosumab or a bisphosphonate, including zoledronic acid, ibandronic acid, and pamidronate, must be initiated along with other systemic therapies in patients with bone metastasis [194]. Calcium and vitamin D supplementation should also be added to bisphosphonates or denosumab. Dental examinations and required interventions should be completed before these agents are initiated.

Hormone Receptor-Positive ± HER2-Positive Metastatic or Recurrent Breast Cancer

Premenopausal patients with recurrent or metastatic disease more than 1 year after completing tamoxifen treatment can be treated as "tamoxifen-naive" patients; tamoxifen can be restarted with an LHRH analogue, or an AI can be given with an LHRH analogue or with ovarian ablation therapy [195].

Postmenopausal women with recurrent or metastatic disease more than 1 year after adjuvant AI completion can receive the previous AI, tamoxifen, other selective ER modulators (toremifene), or fulvestrant [196–200]. Other options include switching AIs (e.g., if the previous AI was steroidal, nonsteroidal should be given and vice versa) [201, 202].

Premenopausal patients with recurrent or metastatic disease within 1 year after tamoxifen completion or while receiving tamoxifen therapy should be accepted as "refractory or resistant to tamoxifen," and an AI or fulvestrant should be initiated with an LHRH analogue or ovarian ablation therapy. An AI of a different subgroup than the previously used AI (e.g., if the previous AI was steroidal, a nonsteroidal AI should be given and vice versa), tamoxifen, or another selective ER modulator or downregulator may be a choice for endocrine treatment for postmenopausal women with recurrent or metastatic disease within 1 year following adjuvant AI completion [201, 202].

In phase III of the FALCON (Fulvestrant and Anastrozole Compared in Hormonal Therapy Naive Advanced Breast Cancer) trial, intramuscular fulvestrant 500 mg/month (plus an additional dose at 2 weeks) was significantly more effective in PFS than anastrozole 1 mg/day (particularly in the nonvisceral disease subgroup) (hazard ratio (HR) 0.8; $p = 0.0486$). The median progression-free survival was 16.6 months (95% CI 13.8–21) in the fulvestrant group versus 13.8 months (12–16.6) in the anastrozole group [203]. The objective response rate was found to be similar between the two arms, and the median OS was not yet calculable. The most common adverse events was arthralgia (17% in the fulvestrant group vs. 10% in the anastrozole group). Thus, monotherapy with intramuscular fulvestrant is a well-tolerated agent and a more effective treatment option than the standard-of-care anastrozole for ER+ or HR+/HER2− advanced breast cancer in postmenopausal women not previously treated with endocrine therapy [204].

The combined use of multiple endocrine agents has been studied in several studies in a first-line setting. The Fulvestrant and Anastrozole Combination Trial (FACT) was an open-label randomized phase III clinical trial designed to compare the efficacy of anastrozole alone with that of combined fulvestrant and anastrozole therapy in women who had experienced a first relapse of breast cancer occurring after primary treatment of early disease [205]. The median OS was similar between the two treatment groups. In the SWOG trial, the combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of HR-positive metastatic breast cancer, despite the use of a dose of fulvestrant that was below the current standard [206].

A meta-analysis of these prospective randomized clinical trials was performed to compare the effectiveness of fulvestrant plus anastrozole vs. anastrozole alone as first-line treatment in postmenopausal women with HR+, HER2-negative advanced breast cancer [206]. The combination of the fulvestrant with AI did not improve the time-to-progression, but increased the toxicity. Another more recent meta-analysis also evaluated the effectiveness of fulvestrant plus anastrozole compared to anastrozole alone as first-line treatment of postmenopausal stage IV hormone receptor-positive, HER2-negative breast cancer [207]. The pooled hazard ratio for PFS was 0.88 (95% CI 0.72–1.09), OS was 0.88 (95% CI 0.72–1.08), and the pooled odds ratio for the response rate was 1.13 (95% CI 0.79–1.63). A nonsignificant trend was observed with anastrozole plus fulvestrant being only marginally better than anastrozole alone for the endpoints of PFS, OS, and response rates. The high-dose fulvestrant monotherapy when used for first-line treatment or in patients with limited prior exposure to adjuvant endocrine therapy may delay progression compared with AI. The present evidence is not sufficient to recommend the combination of monthly 250 mg fulvestrant with anastrozole instead of anastrozole or fulvestrant alone to all women with postmenopausal HR+ breast cancer as first-line therapy [207]. However, recently the final survival outcomes of SWOG study was reported. In the final analysis, the addition of fulvestrant to anastrozole was associated with increased long-term survival as compared with anastrozole alone, despite substantial crossover to fulvestrant after progression during therapy with anastrozole alone. The results suggest that the benefit was particularly notable in patients without previous exposure to adjuvant endocrine therapy [208].

First-line and second-line treatment recommendations for hormone receptor-positive and HER2-negative patients are changed after the randomized clinical trials with endocrine treatment combined with CDK4/6 inhibitors (Table 44.1).

First-Line Treatment with Cyclin-Dependent Kinases 4 and 6 Inhibitors

Analysis of the Cancer Genome Atlas revealed the association between deregulated cyclin D, cyclin-dependent kinases 4/6 (CDK4/6) and retinoblastoma (Rb) interaction, and luminal B cancer. Cyclin D activates CDK4/6 and induces Rb phosphorylation and progression of the cell cycle into the S phase and eventually results in endocrine resistance. CDK4/6 inhibitors have been demonstrated to improve the efficacy of endocrine treatment. Palbociclib, ribociclib, and abemaciclib are oral small-molecule inhibitors of CDK4/6 with preclinical and clinical evidence of growth inhibitory activity in HR+ breast cancer cells and synergy with antiestrogens [209]. First-line treatment recommendations for hormone receptor-positive and HER2-negative patients are changed after the randomized clinical

trials with endocrine treatment combined with CDK4/6 inhibitors (Table 44.1).

Palbociclib: Palbociclib in combination with letrozole received US Food and Drug Administration (FDA) accelerated approval as a first-line treatment option for HR+ advanced breast cancer in February 2015 [210]. The approval is based on a randomized, multicenter, open-label phase I/II trial (PALOMA-1) in which 165 patients were randomized to receive palbociclib (125 mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5 mg orally daily) or letrozole alone [211]. A significant improvement in PFS was observed in patients receiving palbociclib plus letrozole (HR, 0.49; 95% confidence interval, 0.32–0.75). The most common adverse reaction in patients receiving palbociclib plus letrozole was neutropenia (grade ¾ toxicity in the combination arm 54% vs. letrozole alone 15%) [210].

Although the increased expression of cyclin D1 and pRb and decreased expression of p16 (a natural CDK4/6 inhibitor) were found to be associated with a response in in vitro preclinical studies, patient selection on the basis of cyclin D1 amplification or p16 loss was not associated with an improved outcome from palbociclib treatment in the PALOMA-1/TRIO-18 trial [211].

Results from the phase III trial, PALOMA-2, comparing letrozole with letrozole plus palbociclib in a first-line setting of HR+, HER2-negative metastatic breast cancer supported the findings of previous trials [212]. At a median follow-up of 23 months, the median PFS in the combination arm was shown to be longer than that of the letrozole alone arm (HR: 0.58, 24.8 months vs. 14.5 months, respectively). A consistent benefit of palbociclib-letrozole was demonstrated across all subgroups. The rate of the clinical benefit response was 84.9% in the palbociclib-letrozole group and 70.3% in the placebo-letrozole group [212].

Ribociclib: LEE011 is another CDK4/6 inhibitor and has been tested in a phase III clinical trial in association with letrozole as first-line treatment of postmenopausal women with HR+ advanced breast cancer (MONALEESA-2) [213]. Patients were randomized to ribociclib (600 mg/day; 3 weeks-on/1 week-off) plus letrozole (2.5 mg/day; continuous) or placebo plus letrozole until progression of disease, unacceptable toxicity, death, or treatment discontinuation. The median PFS was not reached in the combination arm versus 16.4 months in the letrozole arm in patients with de novo advanced breast cancer (HR, 0.45; 95% confidence interval 0.27–0.75). The overall response rate was 41% in the ribociclib and letrozole combination arm versus 28% in the placebo and letrozole arm.

At the MONALEESA-7, a phase II trial, ribociclib was studied in association with nonsteroidal AI/tamoxifen plus goserelin for premenopausal patients [214]. Adding the CDK4/6 inhibitor ribociclib to standard first-line endocrine therapy significantly prolonged survival in premenopausal and perimenopausal women with advanced HR-positive, HER2-negative breast cancer. Median PFS was 23.8 months (95% CI 19.2-not reached) in the ribociclib group compared with 13.0 months (11.0–16.4) in the placebo group (hazard ratio 0.55, 95% CI 0.44–0.69; $p < 0.0001$). This is the first definitive evidence that CDK4/6 inhibitor-based therapy is effective for the first-line treatment of premenopausal and perimenopausal women.

Abemaciclib: Abemaciclib is an orally administered inhibitor of CDK4/6. In the MONARCH-3 trial, abemaciclib in combination with an aromatase inhibitor (letrozole or anastrozole) was compared with aromatase inhibitor monotherapy in endocrine treatment naive first-line HR+ advanced breast cancer patients [215]. The median PFS was significantly prolonged in the abemaciclib arm (HR, 0.54; $p = 0.000021$; median: not reached in the abemaciclib arm, 14.7 months in the placebo arm). In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm ($p = 0.004$). Comparing abemaciclib and placebo, the most frequent grade III or IV adverse events were neutropenia (21.1% vs. 1.2%, respectively), diarrhea (9.5% vs. 1.2%, respectively), and leukopenia (7.6% vs. 0.6%, respectively).

Hormone Receptor-Positive, Endocrine-Sensitive, and HER2-Positive Patients

For patients with HER2-positive and ER-positive/PR-positive breast cancer, clinicians may recommend either standard first-line therapy or, for select patients, endocrine therapy plus HER2-targeted therapy [216] (Fig. 44.21). Although no high-level evidence is available, if endocrine therapy is chosen as the initial systemic therapy instead of chemotherapy for patients with hormone receptor-positive and HER2-positive advanced breast cancer, adding an anti-HER2 agent to the endocrine agent should be considered with the aim of increasing progression-free survival. Patients who have received anti-HER2 therapy with cytotoxic therapy and whose disease has stabilized may be considered for cytotoxic therapy termination and systemic treatment continuation with an anti-HER2 agent plus an endocrine agent. In the absence of any risk factor for subsequent organ failure, chemotherapy with anti-HER2 treatment should be the first option for systemic treatment. The optimal duration of anti-HER2 treatment in the metastatic setting is not known.

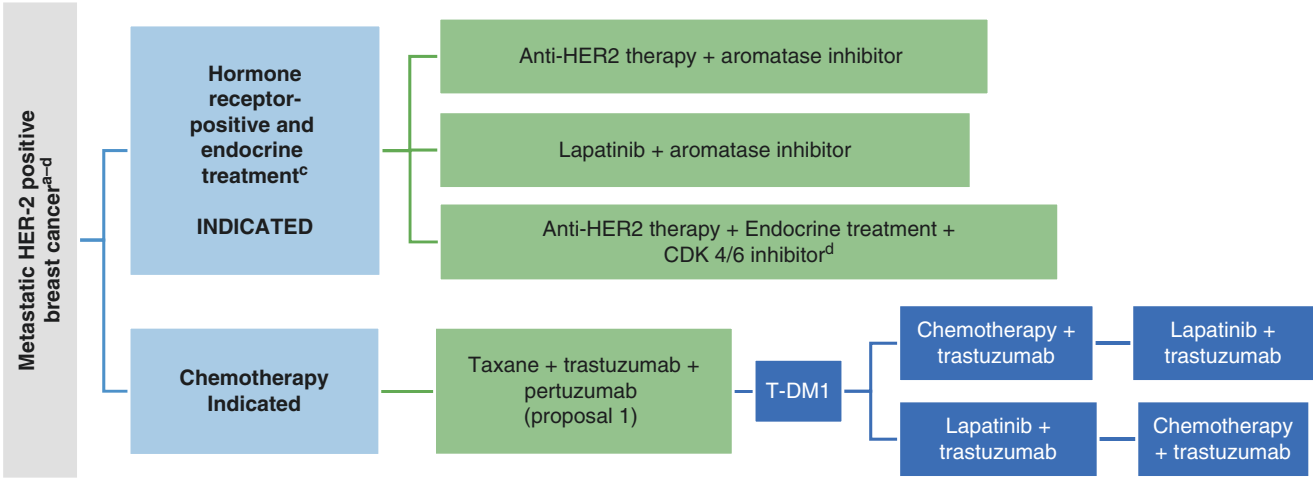

Fig. 44.21 Systemic treatment of recurrent or metastatic HER2-overexpressing breast cancer. [a]Administration of ado-trastuzumab emtansine and pertuzumab was not superior to treatment with chemotherapy + trastuzumab or ado-trastuzumab alone as the first choice treatment in HER2-positive disease. According to the PERTAIN trial, addition of pertuzumab to trastuzumab and endocrine treatment in the first choice prolonged progression-free survival. The addition of pertuzumab in the second choice in patients who did not receive pertuzumab in the first choice provided a minor clinical benefit. [b]T-DM1 may be used as the front line if the patient develops metastasis within 6 months of finishing adjuvant therapy with anti-HER2 treatment. [c]In premenopausal patients, medical or surgical oophorectomy must be performed. [d]Clinical trials are ongoing for anti-HER2 therapy + endocrine treatment + CDK 4/6 inhibitor or anti-HER2 therapy + immunotherapy

Hormone Receptor-Positive and HER2-Negative Endocrine-Refractory Metastatic or Recurrent Breast Cancer

Acquired resistance (defined as recurrence at least 6–12 months after completion of adjuvant therapy or disease progression more than 6 months after endocrine therapy initiated in the metastatic setting) and occasionally primary resistance (recurrence either within adjuvant therapy or within 6–12 months of completion of adjuvant therapy or disease progression less than 6 months after treatment in the metastatic setting) to antiestrogen therapy are inevitable in patients with ER+ MBC. Second-line treatment recommendations for hormone receptor-positive and HER2-negative patients are changed after the randomized clinical trials with endocrine treatment combined with CDK4/6 inhibitors (Table 44.1).

mTOR Inhibitors

The PI3K-Akt-mTOR signaling pathway is a major intracellular signaling pathway that plays a significant role in cell growth and proliferation, and it is implicated in resistance to endocrine therapy [217]. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study demonstrated that inhibiting mTOR with everolimus in combination with exemestane compared with exemestane alone improved PFS in patients with ER-positive MBC previously treated with a nonsteroidal AI [218]. However, the phase III HORIZON trial found that there was no survival benefit when temsirolimus was combined with letrozole in the first-line setting, suggesting that mTOR signaling may have a specific role in acquired resistance to endocrine therapy [219]. While the BOLERO-2 study combination has become a standard of care in patients whose disease has progressed after treatment with a nonsteroidal AI, it is unknown if everolimus has meaningful single-agent activity that could explain results [220, 221].

PI3K Inhibitors

Buparlisib (BKM120) is a pan-PI3K inhibitor with potent activity against mutant PI3Kα [222]. The randomized phase III BELLE-2 trial studied fulvestrant 500 mg plus buparlisib 100 mg daily or placebo in postmenopausal progressive MBC on AIs [223, 224]. In the subset of patients in whom PIK3CA mutation was assessed by circulating tumor DNA at trial entry, buparlisib plus fulvestrant increased PFS in PIK3CA mutant cases compared with fulvestrant alone (HR, 0.56; $p < 0.001$). Serious adverse events were reported in 23% of patients in the buparlisib group compared with 16% of patients in the placebo group. The results from this study show that PI3K inhibition combined with endocrine therapy is effective in postmenopausal women with endocrine-resistant, hormone receptor-positive, and HER2-negative advanced breast cancer [224]. The authors concluded that the use of more selective PI3K inhibitors, such as alpha-specific PI3K inhibitor, was warranted to further improve safety and benefit in this setting. No further studies are being pursued because of the toxicity associated with this combination. Using the same treatment arms as BELLE-2, the phase III BELLE-3 trial enrolled AI-experienced patients with disease progression in the past 30 days on an mTOR inhibitor plus endocrine therapy [225]. Among those with PIK3CA mutations, PFS was 4.7 months in the buparlisib arm versus 1.6 months in the placebo arm.

Cyclin-Dependent Kinases 4 and 6 Inhibitors

A new strategy in treating patients with ER-positive breast cancer is to target CDK4/6, a key pathway involved in the regulation of the G1/S transition of the cell cycle [226]. There is no evidence to recommend a CDK4/6 inhibitor as monotherapy or in combination with other drugs in patients who received another CDK4/6 inhibitor in previous lines. However, CDK4/6 inhibitors are one of the most effective treatment options in patients who are CDK4/6 inhibitor naive and have progressive disease under prior antiestrogen treatment.

Palbociclib: In the phase III PALOMA-3 trial, the combination of fulvestrant plus palbociclib was evaluated in patients with disease progression after at least one line of hormonal therapy and at most one line of chemotherapy but naive to CDK4/6 inhibitors [209, 227]. PFS was significantly longer with palbociclib plus fulvestrant than fulvestrant alone (HR, 0.42; $p < 0.000001$). The most common grade III or IV adverse event in the palbociclib arms was neutropenia (incidence 65%), but treatment was otherwise well tolerated. The US Food and Drug Administration (FDA) approved palbociclib with fulvestrant for second-line treatment of patients with ER+/HER2-negative MBC.

Abemaciclib: Abemaciclib at 150 mg twice daily plus fulvestrant has been approved in the USA for the treatment of HR+, HER2− advanced, or MBC, in combination with fulvestrant in women with disease progression following endocrine therapy, and as monotherapy in adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting based on the findings obtained in the phase III MONARCH 2 trial [228]. PFS was significantly longer with abemaciclib plus fulvestrant than fulvestrant alone (HR, 0.55; $p < 0.001$). In patients with measurable disease, abemaciclib plus fulvestrant achieved an ORR of 48.1% compared with 21.3% in the control arm. The most common adverse events were diarrhea (86.4% vs. 24.7%), neutropenia (46.0% vs. 4.0%), nausea (45.1% vs. 22.9%), and fatigue (39.9% vs. 26.9%) in the abemaciclib versus placebo arms, respectively.

Until recently, there was no sufficient data to guide further lines of ET. In the MONARCH 1 trial, a phase II single-arm open-label study, patients with HR+/HER2− MBC who had progressed on or after prior endocrine therapy and had one or two chemotherapy regimens in the metastatic setting were treated with abemaciclib 200 mg two times daily on a continuous schedule until disease progression or unacceptable toxicity [229]. The objective response rate was 19.7%; clinical benefit rate (CR + PR + SD ≥ 6 months) was 42.4%, median PFS was 6.0 months, and median OS was 17.7 months. In this poor prognosis, heavily pretreated population with refractory HR+/HER2− MBC, continuous dosing of the single-agent abemaciclib was well tolerated and approved by the FDA.

Hormone Receptor-Negative or Endocrine-Refractory and HER2-Positive Metastatic or Recurrent Breast Cancer

All patients with HER2-positive recurrent or MBC and a previous history of adjuvant trastuzumab therapy should be evaluated for further anti-HER2 therapy in the absence of any contraindications. Trastuzumab alone or with chemotherapy (paclitaxel ± carboplatin, docetaxel, vinorelbine, capecitabine) and trastuzumab in combination with pertuzumab and taxane (level I evidence for trastuzumab plus pertuzumab) (docetaxel or paclitaxel) are the preferred regimens in the first-line metastatic setting [230]. In the CLEOPATRA trial, the survival of patients with HER2-positive MBC was significantly improved after first-line therapy with pertuzumab, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel [230]. Compared with the addition of placebo, the addition of pertuzumab to trastuzumab and docetaxel significantly improved the median OS in patients with HER2-positive MBC. In the primary results from the phase III MARIANNE study, HER2-positive, advanced breast cancer, and no prior therapy for advanced disease were randomly assigned to control (trastuzumab plus taxane (HT)), T-DM1 plus placebo (hereafter T-DM1), or T-DM1 plus pertuzumab at standard doses. Neither experimental arm showed PFS superiority to trastuzumab plus taxane. In conclusion, T-DM1 showed non-inferiority, but not superiority, efficacy, and better tolerability than did taxane plus trastuzumab for first-line treatment of HER2-positive, advanced breast cancer [231]. These results suggest that T-DM1 may be an alternative to HT in previously untreated HER2-positive MBC. Lapatinib-containing combination regimens should not be used as first-line systemic therapy in HER2-positive MBC patients.

Pertuzumab-containing regimens may also be preferred in patients who have previously received trastuzumab as a part of adjuvant systemic therapy, but not for recurrent or metastatic disease [230].

Patients whose disease progressed on a trastuzumab-containing regimen may again receive trastuzumab with lapatinib or another cytotoxic agent or may be considered for another anti-HER2 agent such as ado-trastuzumab emtansine or lapatinib with capecitabine [232–234]. In the final descriptive analysis, the median overall survival was longer with ado-trastuzumab emtansine than with control (29.9 months (95% CI 26.3–34.1) vs. 25.9 months (95% CI 22.7–28.3); hazard ratio 0.75 (95% CI 0.64–0.88)). The efficacy and safety of trastuzumab plus capecitabine with or without pertuzumab in patients with HER2-positive MBC who experienced disease progression during or after trastuzumab-based therapy and received a prior taxane were assessed in a

randomized trial [235]. The addition of pertuzumab to trastuzumab and capecitabine did not significantly improve PFS.

Following first-line trastuzumab-based systemic therapy, ado-trastuzumab emtansine should be chosen as the preferred second-line therapy due to its superiority over other anti-HER2 agents, including lapatinib + capecitabine or trastuzumab as a post-progression strategy. The superiority of T-DM1 to capecitabine plus lapatinib in the second-line setting was established in the EMILIA trial [233]. EMILIA was a randomized, phase III study of patients with HER2-positive unresectable, locally advanced or MBC previously treated with trastuzumab and a taxane. Enrolled patients were randomly assigned (1:1) to trastuzumab emtansine or control (capecitabine plus lapatinib) groups. In the final descriptive analysis, the median overall survival was longer with trastuzumab emtansine than with control (HR, 0.75). In the safety population, fewer grade III or worse adverse events occurred with trastuzumab emtansine (48%) than with capecitabine plus lapatinib control treatment (60%). The most frequently reported grade III or worse adverse event in the trastuzumab emtansine group was thrombocytopenia (14%). This descriptive analysis of final overall survival in the EMILIA trial shows that trastuzumab emtansine improved overall survival in patients with previously treated HER2-positive MBC even in the presence of crossover treatment [233].

Patients with progressive disease after two or more HER2-directed regimens for recurrent or MBC have few effective therapeutic options. Th3Resa is a phase III trial to specifically address the efficacy of anti-HER2 therapy in this third-line setting [236]. Eligible patients for the TH3RESA trial were patients with centrally confirmed HER2-positive advanced breast cancer previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and with progression on two or more HER2-directed regimens in the advanced setting. The overall survival was significantly longer with trastuzumab emtansine versus treatment of the physician's choice (HR = 0·68; p = 0·0007). In conclusion, in patients who had progressed on two or more HER2-directed regimens, trastuzumab emtansine treatment resulted in a significant improvement in overall survival versus treatment of the physician's choice [236].

Brain metastasis is a very important problem in HER2-positive MBC. Patients with brain metastases should receive appropriate local therapy and systemic therapy, if indicated. The data strongly support the hypothesis that the best overall treatment improves survival in cases of brain metastases [237, 238]. Other conventional cytotoxic agents that can cross the blood-brain barrier may act with anti-HER2 therapy on CNS metastases, and further research is needed. Local therapies include surgery, whole-brain radiotherapy, and stereotactic radiosurgery. Treatments depend on factors such as patient prognosis, presence of symptoms, resectability, number and size of metastases, prior therapy, and whether metastases are diffuse. Other options include systemic therapy, best supportive care, enrollment in a clinical trial, and/or palliative care. Clinicians should not perform routine magnetic resonance imaging to screen for brain metastases, but rather should have a low threshold for magnetic resonance imaging of the brain because of the high incidence of brain metastases among patients with HER2-positive advanced breast cancer (www.asco.org/breast-cancer-guidelines) [239].

The optimal duration of chemotherapy is at least 4–6 months or until a maximum response is reached, depending on toxicity and the absence of progression. HER2-targeted therapy must continue until progression or unacceptable toxicity occurs [144]. The choice of anti-HER2 agent or agents should be planned according to the prior anti-HER2 therapy, relapse-free survival, and country-specific availability.

Triple-Negative Metastatic or Recurrent Breast Cancer That is at High Risk for a Visceral Crisis

Chemotherapy regimens, either single agent or combination, should be considered for patients with triple-negative metastatic or recurrent breast cancer or who are at high risk for a visceral crisis. No convincing data support the superiority of combination chemotherapy over single-agent chemotherapy. Although combination regimens may increase objective response rates, they also result in increased toxicity without any overall survival advantage.

The preferred single agents are paclitaxel, doxorubicin, pegylated liposomal doxorubicin, capecitabine, gemcitabine, vinorelbine, and eribulin; other single agents provided in this situation include docetaxel, cisplatin, carboplatin, epirubicin, ixabepilone, cyclophosphamide, and albumin-bound paclitaxel. AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide), FEC (fluorouracil and epirubicin and cyclophosphamide), FAC/CAF (fluorouracil and doxorubicin and cyclophosphamide), CMF (cyclophosphamide and methotrexate and fluorouracil), gemcitabine/paclitaxel, gemcitabine/carboplatin, and docetaxel/capecitabine are usually the preferred combination regimens.

Patients who carry a BRCA mutation and have triple-negative or endocrine therapy-resistant MBC should be considered for platinum-based chemotherapy if they have received an anthracycline and a taxane in an adjuvant or metastatic setting. Poly(ADP)-ribose polymerase (PARP) inhibitors may be an option for patients with BRCA mutations. MBC treatment includes olaparib in the OlympiAD trial, which has reached its primary endpoint [240]. In this trial, the researchers randomly assigned patients with inherited BRCA mutations who had MBC that was either ER-positive or triple-negative to receive olaparib tablets or standard chemotherapy (either capecitabine, vinorelbine, or eribulin) until the cancer worsened or the patient developed severe side effects. Tumors shrank in about 60% of patients who received olaparib, compared with 29% of those who received chemotherapy. At a median follow-up of approximately 14 months, patients who received olaparib had a 42%

lower chance of cancer progression than those who received chemotherapy. The median time to progression was 7 months with olaparib and 4.2 months with chemotherapy. Ongoing efforts are focused on molecular diagnostics beyond BRCA testing to predict the benefit from PARP inhibition as well as applying PARP inhibitors in a broader population through combination strategies.

The androgen receptor (AR) has been identified as a possible predictive biomarker for antiandrogen therapy in breast cancer. In a phase II trial, enzalutamide demonstrated clinical activity and was well tolerated in patients with advanced AR-positive TNBC [241]. An androgen-driven diagnostic gene signature was associated with greater clinical benefit, and the phase III ENDEAR trial of paclitaxel plus enzalutamide/placebo and enzalutamide monotherapy has been initiated in diagnostic signature-positive TNBC (NCT02929576).

Promises of Immune Therapies

Immunomodulation appears to be a promising strategy for solid tumors. The immune system can identify tumor antigens through immune surveillance, a process in which antigen-presenting cells present non-self-antigens to T cells, allowing them to recognize and destroy cells expressing such antigens. A hallmark of oncogenesis is that tumor cells can develop mechanisms to evade such immune recognition. Expression of PD-L1 on tumor cells leads to lower activity of CD8+ T cells. Antibodies against PD-1 or PD-L1 are being investigated in clinical trials. The success of immune checkpoint blockade in certain cancers has served as proof-of-concept that immune therapy is a viable therapeutic strategy. Cytotoxic T-lymphocyte antigen (CTLA) inhibitors have shown significant and sustained antitumor activity. Blockade of the programmed cell death 1 (PD-1) and PD-L1 has been found to have antitumor activity in certain cancers. The effects of single-agent checkpoint blockade are modest, with only a small fraction of patients having clinically significant responses; however, recently, a combination checkpoint blockade with CTLA and PD-1 inhibitors has demonstrated synergistic activity with an ORR of 40%, and 31% of patients achieved greater than 80% reduction in their tumors by 12 weeks. These results suggest that combination immune therapy may improve antitumor responses. Several immunotherapies are under development and show promise in the treatment of aggressive breast cancer [242].

High immunogenicity has been described in breast cancer subtypes with a high proliferation index (TNBC, HER2-positive). At the 2018 ESMO annual meeting, Schmid et al. presented the results of the phase III trial in triple-negative MBC [243]. In this phase III trial, patients with untreated metastatic TNBC were randomized to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Atezolizumab plus nab-paclitaxel prolonged progression-free survival in both the intention-to-treat population and the PD-L1-positive subgroup. In the intention-to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; $p = 0.002$); among patients with PD-L1-positive tumors, the median progression-free survival was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; $p < 0.001$). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69–1.02; $p = 0.08$); among patients with PD-L1-positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI, 0.45–0.86).

The success of future immunotherapy strategies will depend on the identification of additional immunogenic antigens that can serve as the best tumor rejection targets. Therapeutic success will depend on developing the best antigen delivery systems and on the elucidation of the entire network of immune signaling pathways that regulate immune responses in the tumor microenvironment.

Surgery for Metastatic Breast Cancer

The primary treatment approach for women with MBC and an intact primary tumor is systemic therapy, with the consideration of surgery following initial systemic treatment in women requiring palliation of symptoms or with impending complications such as skin ulceration, bleeding, fungation, and pain [244]. Generally, such surgery should be performed only if complete local clearance of the tumor may be obtained and if other sites of disease are not immediately life threatening. Alternatively, radiation therapy may be considered as an alternative to surgery. Often, such surgery requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.

Retrospective studies suggest a potential survival benefit from complete excision of the primary tumor in select patients with MBC [245–248]. Substantial selection biases exist in all these studies and are likely to confound the study results [249, 250]. Two recent prospective, randomized studies assessed whether surgery on the primary tumor in the breast is necessary for women who are diagnosed with MBC. The results from both studies presented at the 2013 San Antonio Breast Cancer Symposium were similar and revealed that surgical treatment of primary tumors in women presenting with stage IV disease does not produce an increase in OS in general [251, 252]. However, a survival advantage of primary tumor excision was observed only in patients with solitary bone metastasis in a Turkish study [252].

Randomized clinical trials that address the advantages and disadvantages of local therapy for patients with stage IV disease while eliminating selection biases are necessary. Patient enrollment in such trials is encouraged.

In oligometastatic disease, local ablative therapies such as surgery, radiation therapy, or radiofrequency ablation can be performed for select patients.

Conclusion

We have attempted to provide useful and explicit recommendations for the management of breast cancer, but we must stress that these recommendations are subject to change. Some of the recommendations are controversial and the subject of ongoing clinical trials. Endocrine therapy in hormone receptor-positive, HER2-negative advanced breast cancer is shown in Table 44.1. Systemic chemotherapies and anti-HER2 treatments in the adjuvant/neoadjuvant or in the metastatic setting are shown in Tables 44.2, 44.3, 44.4, 44.5, 44.6, 44.7, 44.8, 44.9, 44.10, 44.11, 44.12, and 44.13. The gold standard for breast cancer care includes an integrated multidisciplinary team approach, comprising pathologists, radiologists, surgical oncologists, medical oncologists, radiation oncologists, oncology nurses, and plastic surgeons.

Drugs and Regimens

Adjuvant and Neoadjuvant Regimens

Table 44.1 Endocrine therapy in hormone receptor-positive, HER2-negative advanced breast cancer (CDK: cyclin-dependent kinase)

Ovarian suppression (GnRH agonist) or ablation in all premenopausal patients			
Endocrine treatment naive		Previous endocrine treatment	
No contraindication to CDK inhibitors	*Contraindication to CDK inhibitors*	*Under endocrine treatment or within 12 months after the end of adjuvant endocrine treatment*	*Disease recurrence at least 1 year after the end of adjuvant endocrine treatment*
CDK inhibitors and aromatase inhibitor	Fulvestrant	CDK inhibitors and aromatase inhibitor	Treat as patients who are endocrine treatment naive
CDK inhibitors and fulvestrant	Aromatase inhibitors	CDK inhibitors and fulvestrant	
Fulvestrant	Tamoxifen	Abemaciclib and tamoxifen	
		Fulvestrant	
		Everolimus and exemestane	
		If an aromatase inhibitor used previously, switch to other (steroidal to nonsteroidal or vice versa)	
		Tamoxifen	
		Progestins	
		Estrogens or androgens	

Table 44.2 Adjuvant or neoadjuvant systemic treatment in HER2-negative breast cancer – preferred

Regimen	Drug	Dosage (mg/m^2)	Frequency of cycles
4× dose-dense AC followed by 4× two weekly paclitaxel			
AC[a]	Doxorubicin	60	Day 1
			Cycled every 14 days
	Cyclophosphamide	600	Day 1
			Cycled every 14 days
Paclitaxel[a]	Paclitaxel	175	Day 1
			Cycled every 14 days
4× dose-dense AC followed by 12× weekly paclitaxel			
AC[a]	Doxorubicin	60	Day 1
			Cycled every 14 days
	Cyclophosphamide	600	Day 1
			Cycled every 14 days
Paclitaxel	Paclitaxel	80	Day 1
			Cycled every 7 days
4-6 × TC			
TC[a]	Docetaxel	75	Day 1
			Cycled every 21 days
	Cyclophosphamide	600	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously
[a]All cycles should be administered with lenograstim or filgrastim support

Table 44.3 Adjuvant or neoadjuvant anthracycline-based systemic treatment in HER2-negative breast cancer – others

Regimen	Drug	Dosage (mg/m^2)	Frequency of cycles
4× dose-dense AC			
AC[a,b]	Doxorubicin	60	Day 1
			Cycled every 14 days
	Cyclophosphamide	600	Day 1
			Cycled every 14 days
4× AC			
AC[a]	Doxorubicin	60	Day 1
			Cycled every 21 days
	Cyclophosphamide	600	Day 1
			Cycled every 21 days
6× FAC			
FAC[a]	5-Fluorouracil	500	Days 1 and 8 or days 1 and 4
			Cycled every 21 days
	Doxorubicin	50	Day 1
			Cycled every 21 days
	Cyclophosphamide	500	Day 1
			Cycled every 21 days
6× CAF			
CAF	5-Fluorouracil[a]	500	Days 1 and 8
			Cycled every 28 days
	Doxorubicin[a]	30	Days 1 and 8
			Cycled every 28 days
	Cyclophosphamide[c]	100	Days 1–14
			Cycled every 28 days
8× EC			
EC[a]	Epirubicin	100	Day 1
			Cycled every 21 days
	Cyclophosphamide	830	Day 1
			Cycled every 21 days
6× CEF			
CEF	Cyclophosphamide[c]	75	Days 1–14
			Cycled every 28 days
	Epirubicin[a]	60	Days 1 and 8
			Cycled every 28 days
	5-Fluorouracil[a]	500	Days 1 and 8
			Cycled every 28 days
6× CMF			
CMF	Cyclophosphamide[c]	100	Once daily on days 1–14
			Cycled every 28 days
	Methotrexate[a]	40	Days 1 and 8
			Cycled every 28 days
	5-Fluorouracil[a]	600	Days 1 and 8
			Cycled every 28 days

[a]The drug(s) recommended must be administered intravenously
[b]All cycles should be administered with lenograstim or filgrastim support
[c]The drug(s) recommended should be administered perorally

Table 44.4 Adjuvant or neoadjuvant anthracycline plus taxane-based systemic treatment in HER2-negative breast cancer – others

Regimen	Drug	Dosage (mg/m^2)	Frequency of cycles
4× AC followed by 4× docetaxel			
AC	Doxorubicin	60	Day 1
			Cycled every 21 days
	Cyclophosphamide	600	Day 1
			Cycled every 21 days
Docetaxel[a]	Docetaxel[a]	100	Day 1
			Cycled every 21 days
4× AC followed by 12× weekly paclitaxel			
AC	Doxorubicin	60	Day 1
			Cycled every 21 days
	Cyclophosphamide	600	Day 1
			Cycled every 21 days
Paclitaxel	Paclitaxel	80	Weekly
3× FEC followed by 3× docetaxel			
FEC[a]	5-Fluorouracil	500	Day 1
			Cycled every 21 days
	Epirubicin	100	Day 1
			Cycled every 21 days
	Cyclophosphamide	500	Day 1
			Cycled every 21 days
Docetaxel[a]	Docetaxel	100	Day 1
			Cycled every 21 days
4× FEC followed by 8× weekly paclitaxel			
FEC[a]	5-Fluorouracil	600	Day 1
			Cycled every 21 days
	Epirubicin	90	Day 1
			Cycled every 21 days
	Cyclophosphamide	600	Day 1
			Cycled every 21 days
Paclitaxel	Paclitaxel	100	Day 1
			Cycled every 7 days
6× FAC followed by 12× weekly paclitaxel			
FAC	5-Fluorouracil	500	Day 1
			Cycled every 21 days
	Doxorubicin	50	Day 1
			Cycled every 21 days
	Cyclophosphamide	500	Day 1
			Cycled every 21 days
Paclitaxel	Paclitaxel	80	Day 1
			Cycled every 7 days
6× TAC			
TAC[a]	Docetaxel	75	Day 1
			Cycled every 21 days
	Doxorubicin	50	Day 1
			Cycled every 21 days
	Cyclophosphamide	500	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously
[a]All cycles should be administered with lenograstim or filgrastim support

Table 44.5 Adjuvant or neoadjuvant systemic treatment with trastuzumab in HER2-positive breast cancer – preferred

Regimen	Drug	Dosage	Frequency of cycles
4× AC followed by 12× weekly paclitaxel plus trastuzumab – trastuzumab for up to 1 year			
AC	Doxorubicin	60 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
Paclitaxel plus trastuzumab	Paclitaxel	80 mg/m^2	Weekly
	Trastuzumab	4 mg/kg on day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After paclitaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
4× dose-dense AC followed by 4× paclitaxel plus trastuzumab – trastuzumab for up to 1 year			
AC[a]	Doxorubicin	60 mg/m^2	Day 1
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 14 days
Paclitaxel plus trastuzumab	Paclitaxel[a]	175 mg/m^2	Day 1
			Cycled every 14 days
	Trastuzumab	4 mg/kg day followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After paclitaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
6× TCH followed by trastuzumab for up to 1 year			
Docetaxel plus	Docetaxel	75 mg/m^2	Day 1
			Cycled every 21 days
Carboplatin plus trastuzumab	Carboplatin	AUC 6	Day 1
			Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After TC ended followed by 6 mg/kg	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously
[a]All cycles should be administered with lenograstim or filgrastim support

Table 44.6 Adjuvant or neoadjuvant systemic treatment with trastuzumab plus pertuzumab in HER2-positive breast cancer – preferred

Regimen	Drug	Dosage	Frequency of cycles
4× AC followed by 12 × paclitaxel plus trastuzumab plus pertuzumab – trastuzumab for up to 1 year			
AC	Doxorubicin	60 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
Paclitaxel plus trastuzumab plus pertuzumab	Paclitaxel	80 mg/m^2	Days 1, 8, and 15
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
Trastuzumab	Trastuzumab	After paclitaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
6× TCH plus pertuzumab followed by trastuzumab for up to 1 year			
Docetaxel plus Carboplatin plus Pertuzumab plus trastuzumab	Docetaxel	75 mg/m^2	Day 1
			Cycled every 21 days
	Carboplatin	AUC 6	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After TC ended followed by 6 mg/kg	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously

Table 44.7 Adjuvant or neoadjuvant cytotoxic therapy with trastuzumab in HER2-positive breast cancer – others

Regimen	Drug	Dosage	Frequency of cycles
4× AC followed by 4× docetaxel plus trastuzumab – trastuzumab for up to 1 year			
AC	Doxorubicin	60 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
Docetaxel[a] plus trastuzumab	Docetaxel	100 mg/m^2	Day 1
			Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After docetaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
4-6 × TC plus trastuzumab – trastuzumab for up to 1 year			
TC[a] plus trastuzumab	Docetaxel	75 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After TC ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
12× weekly paclitaxel plus trastuzumab – trastuzumab for up to 1 year			
Paclitaxel plus trastuzumab	Paclitaxel	80 mg/m^2	Day 1
			Cycled every 7 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Weekly
Trastuzumab	Trastuzumab	After paclitaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously

Table 44.8 Adjuvant or neoadjuvant cytotoxic therapy with trastuzumab plus pertuzumab in HER2-positive breast cancer – others

Regimen	Drug	Dosage	Frequency of cycles
4× AC followed by 4× docetaxel plus trastuzumab plus pertuzumab – trastuzumab for up to 1 year			
AC	Doxorubicin	60 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
Docetaxel plus trastuzumab Plus pertuzumab	Docetaxel	75–100 mg/m^2	Day 1
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
Trastuzumab	Trastuzumab	After docetaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
3× FEC followed by docetaxel plus trastuzumab plus pertuzumab followed by trastuzumab for up to 1 year			
FEC[a]	5-Fluorouracil	500 mg/m^2	Day 1
			Cycled every 21 days
	Epirubicin	100 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	500 mg/m^2	Day 1
			Cycled every 21 days
Docetaxel plus trastuzumab Plus pertuzumab	Docetaxel	75–100 mg/m^2	Day 1
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days

Table 44.8 (continued)

Regimen	Drug	Dosage	Frequency of cycles
Trastuzumab	Trastuzumab	After docetaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
3× FEC followed by paclitaxel plus trastuzumab plus pertuzumab followed by trastuzumab for up to 1 year			
FEC[a]	5-Fluorouracil	500 mg/m^2	Day 1
			Cycled every 21 days
	Epirubicin	100 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	500 mg/m^2	Day 1
			Cycled every 21 days
Paclitaxel plus trastuzumab Plus pertuzumab	Paclitaxel	80 mg/m^2	Days 1, 8, and 15
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
Trastuzumab	Trastuzumab	After paclitaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
4× paclitaxel plus trastuzumab plus pertuzumab followed by 3× FEC followed by trastuzumab for up to 1 year			
Paclitaxel plus trastuzumab Plus pertuzumab	Paclitaxel	80 mg/m^2	Days 1, 8, and 15
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
FEC[a]	5-Fluorouracil	500 mg/m^2	Day 1
			Cycled every 21 days
	Epirubicin	100 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	500 mg/m^2	Day 1
			Cycled every 21 days
Trastuzumab	Trastuzumab	After chemotherapy ended followed by 6 mg/kg	Day 1
			Cycled every 21 days
4× docetaxel plus trastuzumab plus pertuzumab followed by 3× FEC followed by trastuzumab for up to 1 year			
Docetaxel plus trastuzumab Plus pertuzumab	Docetaxel	75–100 mg/m^2	Day 1
			Cycled every 21 days
	Trastuzumab	8 mg/kg day 1 followed by 6 mg/kg	Day 1
			Cycled every 21 days
	Pertuzumab	840 mg day 1 followed by 420 mg	Day 1
			Cycled every 21 days
FEC[a]	5-Fluorouracil	500 mg/m^2	Day 1
			Cycled every 21 days
	Epirubicin	90 mg/m^2	Day 1
			Cycled every 21 days
	Cyclophosphamide	600 mg/m^2	Day 1
			Cycled every 21 days
Trastuzumab	Trastuzumab	After docetaxel ended followed by 6 mg/kg	Day 1
			Cycled every 21 days

All drugs recommended in this table must be administered intravenously
[a]All cycles should be administered with lenograstim or filgrastim support

Metastatic Regimens

Table 44.9 Combined usage of cytotoxic drugs with dual anti-HER2 inhibition for HER2-positive advanced breast cancer

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
Trastuzumab plus pertuzumab with docetaxel	Trastuzumab	8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
	Pertuzumab	840 mg IV day 1 followed by 420 mg	Intravenous	Cycled every 21 days
	Docetaxel	75–100 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
Trastuzumab plus pertuzumab with paclitaxel	Trastuzumab	8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
		4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
	Pertuzumab	840 mg IV day 1 followed by 420 mg	Intravenous	Cycled every 21 days
	Paclitaxel	175 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
	Paclitaxel	80–90 mg/m^2	Intravenous	Day 1
				Cycled every 7 days

Table 44.10 Combined usage of cytotoxic drugs with trastuzumab for HER2-positive advanced breast cancer

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
Trastuzumab plus the following cytotoxic(s)	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
Paclitaxel/carboplatin	Carboplatin	AUC 6	Intravenous	Day 1
				Cycled every 21 days
	Paclitaxel	175 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
Weekly paclitaxel/carboplatin	Carboplatin	AUC 2	Intravenous	Days 1, 8, and 15
				Cycled every 28 days
	Paclitaxel	80 mg/m^2	Intravenous	Days 1, 8, and 15
				Cycled every 28 days
Paclitaxel	Paclitaxel	175 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
	Paclitaxel	80–90 mg/m^2	Intravenous	Day 1
				Cycled every 7 days
Docetaxel	Docetaxel	80–100 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
	Docetaxel	35 mg/m^2	Intravenous	Day 1
				Cycled every week
Vinorelbine	Vinorelbine	25 mg/m^2	Intravenous	Day 1 weekly
				Cycled every 21 days
	Vinorelbine	30–35 mg/m^2	Intravenous	Days 1 and 8
				Cycled every 21 days
Capecitabine	Capecitabine	1000–1250 mg/m^2	Peroral	Twice daily days 1–14
				Cycled every 21 days

Table 44.11 Systemic therapy for previously trastuzumab-treated HER2-positive advanced breast cancer patients

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
T-DM1	Ado-trastuzumab emtansine	3.6 mg/kg	Intravenous	Day 1
				Cycled every 21 days
Lapatinib + capecitabine	Lapatinib PO daily	1250 mg	Peroral	Days 1–21
				Cycled every 21 days
	Capecitabine	1000 mg/m^2	Peroral	Twice daily days 1–14
				Cycled every 21 days
Trastuzumab + capecitabine	Capecitabine	1000–1250 mg/m^2	Peroral	Twice daily days 1–14
				Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days
Trastuzumab + lapatinib (without cytotoxic therapy)	Lapatinib	1000 mg	Peroral	Days 1–21
				Cycled every 21 days
	Trastuzumab	4 mg/kg day 1 followed by 2 mg/kg	Intravenous	Weekly
		8 mg/kg IV day 1 followed by 6 mg/kg	Intravenous	Cycled every 21 days

Table 44.12 First-line single cytotoxic drugs for advanced breast cancer

Drug	Dosage	Route of administration	Frequency of cycles
Anthracyclines			
Doxorubicin	20 mg/m^2	Intravenous	Day 1, cycled weekly
	60 mg/m^2	Intravenous	Day 1, cycled every 21 days
Pegylated liposomal doxorubicin	50 mg/m^2	Intravenous	Day 1, cycled every 28 days
Epirubicin	60–90 mg/m^2	Intravenous	Day 1, cycled every 21 days
Taxanes			
Paclitaxel	80 mg/m^2	Intravenous	Day 1, cycled weekly
	175 mg/m^2	Intravenous	Day 1, cycled every 21 days
Docetaxel	60–100 mg/m^2	Intravenous	Day 1, cycled every 21 days
	35 mg/m^2	Intravenous	Day 1, cycled weekly
Albumin-bound paclitaxel	100 mg/m^2 or 150 mg/m^2	Intravenous	Days 1, 8, and 15, cycled every 28 days
	260 mg/m^2	Intravenous	Day 1, cycled every 21 days
Other microtubule inhibitors			
Vinorelbine	25 mg/m^2	Intravenous	Day 1, cycled weekly
Eribulin (-mesylate)	1.25–1.4 mg/m^2	Intravenous	Days 1 and 8, cycled every 21 days
Ixabepilone	40 mg/m^2	Intravenous	Day 1, cycled every 21 days
Antimetabolites			
Capecitabine	1000–1250 mg/m^2	Peroral	Twice daily from days 1 to 14, cycled every 21 days
Gemcitabine	800–1200 mg/m^2	Intravenous	Days 1, 8, and 15, cycled every 28 days
Platinum compounds			
Cisplatin	75 mg/m^2	Intravenous	Day 1, cycled every 21 days
Carboplatin	AUC 6	Intravenous	Day 1, cycled every 21–28 days
Alkylating agents			
Cyclophosphamide	50 mg	Peroral	Once daily on days 1–21, cycled every 28 days

Table 44.13 Combined usage of cytotoxic drugs for advanced breast cancer

Regimen	Drug	Dosage	Route of administration	Frequency of cycles
CAF	Cyclophosphamide	100 mg/m^2	Peroral	Daily on days 1–14
	Doxorubicin	30 mg/m^2	Intravenous	Days 1 and 8
	5-Fluorouracil	500 mg/m^2	Intravenous	Days 1 and 8
				Cycled every 28 days
FAC	5-Fluorouracil	500 mg/m^2	Intravenous	Days 1 and 8 or days 1 and 4
				Cycled every 28 days
	Doxorubicin	50 mg/m^2	Intravenous	Day 1 or by 72 h continuous infusion
	Cyclophosphamide	500 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
FEC	5-Fluorouracil	500 mg/m^2	Intravenous	Days 1 and 8
				Cycled every 28 days
	Epirubicin	50 mg/m^2	Intravenous	Days 1 and 8
	Cyclophosphamide	400 mg/m^2	Intravenous	Days 1 and 8
AC	Doxorubicin	60 mg/m^2	Intravenous	Day 1
	Cyclophosphamide	600 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
EC	Epirubicin	75 mg/m^2	Intravenous	Day 1
	Cyclophosphamide	600 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
CMF	Cyclophosphamide	100 mg/m^2	Peroral	Once daily on days 1–14
				Cycled every 28 days
	Methotrexate	40 mg/m^2	Intravenous	Days 1 and 8
				Cycled every 28 days
	5-Fluorouracil	600 mg/m^2	Intravenous	Days 1 and 8
				Cycled every 28 days
Docetaxel/capecitabine	Docetaxel	75 mg/m^2	Intravenous	Day 1
				Cycled every 21 days
	Capecitabine	950 mg/m^2	Peroral	Twice daily from days 1–14, cycled every 21 days
GT	Paclitaxel IV day 1	175 mg/m^2	Intravenous	Day 1
	Gemcitabine IV	1250 mg/m^2	Intravenous	Days 1 and 8 (following paclitaxel on day 1)
				Cycled every 21 days
GC	Gemcitabine	1000 mg/m^2	Intravenous	Days 1 and 8
	Carboplatin	AUC 2	Intravenous	Days 1 and 8
				Cycled every 21 days
Paclitaxel/bevacizumab	Paclitaxel	90 mg/m^2	Intravenous	By 1 h days 1, 8, and 15
	Bevacizumab	10 mg/kg	Intravenous	Days 1 and 15
				Cycled every 28 days

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Part IX

Supportive Care in Breast Cancer

Nursing Care and Management

45

Gulbeyaz Can

Roles and Responsibilities of Nurses in Breast Cancer Screening

Breast cancer is the second most common cancer in the world and by far the most frequent cancer among women, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) [1]. Despite being associated with high morbidity and mortality, breast cancer can be diagnosed and treated early. Breast self-examination (BSE), clinical breast examination (CBE), and mammography are the most commonly known and used screening programs worldwide [2, 3]. The primary responsibilities of nurses at breast cancer screening centers are informing the public about cancer and screenings, teaching women how to perform breast self-examination (BSE), and performing age-appropriate cancer screening. Although BSE is not a part of the breast cancer screening recommendations in some Western countries due to the anxiety and unnecessary biopsies associated with BSE, BSE education is important for monitoring changes in breast tissue and for raising awareness. Education about breast cancer and BSE increases awareness of the seriousness of the disease and increases compliance with early diagnostic practices. Because many families in less-developed regions have low income and live in rural areas, many women do not receive mammograms and clinical breast examinations, which prevent the detection of the disease at early stages. Thus, the health education provided by nurses during cancer screening improves awareness about the early diagnosis of breast cancer and increases participation in screening programs [4–6]. However, nurses should understand the society they serve with respect to breast cancer risk factors, and they should determine the risk levels for each patient. To increase women's compliance with screening practices, nurses should know the health beliefs affecting the screening practices and should consider women's beliefs that affect screening practices (predisposition, seriousness, BSE benefits, BSE barriers, confidence, mammography benefits, mammography barriers, and health motivation) when planning breast health education. Nurses should encourage women to participate in screening programs that are appropriate for their age groups and should follow up with patients [3]. If any suspicious lesion is detected at screening, a biopsy should be taken from the suspicious lesion and the obtained material should be sent to a pathology unit for examination.

Nursing Care of Patients Undergoing Breast Biopsy

Many patients experience anxiety when a biopsy decision is made. The reason for the biopsy should be explained to the patient, and the necessary preparations before the procedure should be discussed. If the patient is taking drugs or dietary supplements that increase the risk of bleeding, such as non-steroidal anti-inflammatory drugs or anticoagulants, the patient should be advised to cease taking the drugs to reduce the bleeding risk. Today, many biopsy procedures are performed under mild sedation or local anesthesia, and the patient is sent home as soon as she starts feeding by herself. After the procedure, before the patient is sent home, she should be informed about the potential complications and should be advised to report such complications to a health professional. Slight pain and ecchymosis over the biopsy region are normal, but the patient should be informed about the importance of seeing a health professional if edema, redness, or severe pain develops. The dressing over the biopsy area can be removed after 2 days, but female patients should be advised to wear bras for 3–7 days to limit movement of the breast and to reduce procedure-related tenderness. Paracetamol/acetaminophen can be offered to reduce procedure-related pain. Avoidance of activities requiring intense arm use should be advised. The patient should be sent home after planning the date of the follow-up visit when the pathology results will be available. The roles and

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responsibilities of the nurse will differ according to the result. If the result is negative, the patient is sent home after inspection of the biopsy region; however, if the result is positive, the nurse should provide psychological support to the patient upon the diagnosis of breast cancer and should inform her about the treatment process [7].

Approach to Patients Who Are Newly Diagnosed with Breast Cancer

When confronted with the breast cancer diagnosis, patients experience feelings of fear, shock, sadness, disbelief, or other psychosocial distress. Most patients, with or without psychosocial support, cope successfully with the psychological distress and adjust to their disease. However, some patients experience different psychological distress [8]. Some patients appear anxious and tend to ask an exhaustive number of questions regarding their diagnosis, prognosis, and treatments. This response is unsurprising, as many people still view cancer as a death sentence associated with pain and a lack of dignity. This view is particularly influenced by patients' past experiences and encounters with the disease, e.g., the death of a close relative. In view of the usually overwhelming emotional reactions to the diagnosis, the patient must be given time to absorb the significance of the diagnosis [7, 9].

Younger women worry about their work productivity and career advancement. They face many family concerns related to whether they will be able to have children, whether they will live to see their children grow, and whether their disease will recur and incapacitate them. Middle-aged women worry about their disease in relation to their family and work. They also worry about their aging parents and whether they will be able to care for them in the future. These women are increasingly concerned about their daughters' risk for breast cancer. Older women worry about whether they will have the resources to pay for medications [9, 10].

The need for information varies along with the patients' needs. It is important that the nurse assesses the individual need for information and provides it accordingly. It would be wrong, for example, to overload a patient in denial with an exhaustive amount of information, as this clearly does not allow the patient to utilize her own coping strategy. Equally, it would be wrong to not offer information to a patient who copes through active participation in her treatment [8].

Pathology results, screening results, previous treatments, and medical history can provide information that is an important component in developing an effective individualized treatment plan and can predict a response to a particular therapy and prognosis. Based on the results of these examinations, a nurse should plan the explanations of the disease and treatment process that she will provide to the patient at first meeting. During the explanations, positive survival results that are presented in the pathology report should be emphasized. For example, smaller tumors and negative lymph node status correlated with better prognosis. A smaller number of involved lymph nodes is better than a larger number. Patients with low recurrence risk benefit more from adjuvant chemotherapy. Emphasizing positive survival results during the interview reduces disease-related anxiety and increases compliance with treatment. Breast cancer can be divided into several groups based on histopathologic features: hormone receptor positive (ER and PR positive), triple negative (HER2 negative and ER and PR negative), and HER2 positive. Each subtype has different characteristics associated with different risks of recurrence, and these risks influence treatment choices. A negative hormone receptor status is associated with a less favorable prognosis. According to clinical stage HER2-positive tumors are associated with poorer survival. Additionally, the results of screening tests should also be considered during the patient explanation. Increased values on liver function tests may indicate possible liver metastasis. Increased calcium and alkaline phosphatase levels may indicate possible bone metastasis. Additional metastatic workup, including chest X-ray, bone scans, computed tomography (CT) scans, and positron emission tomography (PET)-CT scans, may indicate possible metastasis. Considering the low survival rates in metastasis, patients should not be given extra hope for recovery; information should focus on the effectiveness of the treatment. Misinforming these patients can adversely affect their trust in health professionals, generate anger toward health professionals, and lead patients to seek nonmedical treatments [7].

A nurse caring for a woman who has just received a diagnosis of breast cancer must be knowledgeable about current treatment options and be able to discuss them with the patient. Patients generally talk with their physician before talking with oncology nurses, and the doctor will have already provided the patient with a preliminary explanation regarding survival and future treatment based on the pathology report and screening test result. The nurse should be aware of the information that has been provided to the patient by the physician. The patient education concerning medications, the extent of treatment, the management of side effects, the possible reactions after treatment, the frequency and duration of treatment, and the treatment goals provided by the nurses must be similar to the physician's explanations. The amount and timing of the information provided are based on the patient's responses, coping ability, and readiness to learn [8].

Nursing Care During Breast Cancer Treatment

Most patients with breast cancer experience a complex course of care during the first year after diagnosis. These patients might undergo one or more procedures for diagnosis, multiple surgical consultations, one or more surgeries

(including reconstruction), and multiple surgical follow-up visits. Most patients will consult radiation oncology and may undergo up to 6 weeks of daily radiation. Virtually all patients will discuss adjuvant (or neoadjuvant) systemic therapy with a medical oncologist. Those undergoing chemotherapy will be treated with 4–16 chemotherapy infusions depending on the regimen. The majority will also be treated with endocrine therapy and will undergo several follow-up visits within the first year [11]. The treatment duration can be longer in patients with advanced-stage breast cancer. Patients may receive numerous chemotherapy treatments to control the disease, and palliative care may need to be planned in patients with metastases.

The specialist breast care nurse must have training and expertise in the management, treatment, and follow-up of patients diagnosed with breast cancer. He or she is an important member of the multidisciplinary breast care team, providing a range of key interventions (e.g., psychosocial support, information, patient advocacy, and acting as a liaison among the various members of the healthcare team):

- Routinely assess and meet the patients' needs for information and support.
- Support the patient emotionally and offer tailored information about emotional coping.
- Prepare the patient for treatment and explain the prevention and management of treatment-related side effects such as lymphedema, neutropenia, fatigue, skin reaction, nausea and vomiting.
- Provide contact with the medical team and other health professionals as required.
- Refer patients to other services as needed, e.g., liaison psychiatry, physiotherapy, algology, and other support services [12].

Nursing Care in Surgical Treatment

The primary treatment approach in breast cancer is surgical excision and pathological examination of the tumor. Although the type of surgical intervention may vary depending on the clinical condition of the patient, risk factors, localization of the tumor, tumor size, clinical stage, and patient choice, the most frequent surgical treatment approaches are breast-conserving surgery and mastectomy. To determine the involvement of lymph nodes, sentinel lymph node biopsy (SLNB) and, if necessary, axillary lymph node dissection (ALND) can be performed during surgery. Although they depend on the type of surgery, the problems most frequently experienced by patients after surgical treatment are pain, infection, reduction in physical mobility, change in body image, and sexual dysfunction. Nurses in charge of patients who undergo surgery are responsible for preparing the patient for surgery, supporting the surgeon during procedures before surgery, monitoring the patient for operation-related complications and initiating appropriate treatment upon doctor request, and improving the quality of life of the patients [13].

Preoperative Patient Preparation

Nurses should ascertain whether the preoperative anesthesia exam and all other examinations are completed before the patient undergoing surgery is admitted to the unit. If there are any missing examinations, they should be completed. The patient should be informed about the procedure and possible postoperative complications. Informing the patient and her family about the procedures before surgery reduces the anxiety of the patient and patient's family and gives them the opportunity to obtain answers to any questions that might have arisen after the interview with the physician. During this explanation, the nurse should explain the purpose and risks of the surgery that is going to be performed (breast-conserving surgery, mastectomy, SLNB (sentinel lymph node biopsy), or ALND (axillary lymph node dissection)). Drains that are likely to be placed during surgery and the site of the surgical incision should be explained to the patient. Nurses should educate the patient and demonstrate the shoulder and arm exercises and the coughing and breathing exercises that are necessary after the operation. If needed, the nurse should refer the patient to liaison psychiatry and ensure that the patient receives psychological support as required [7, 9, 13].

Isosulfan and methylene blue, which are administered to patients during SLNB procedures, are excreted via bile and urine at rates of 90% and 10%, respectively; therefore, it should be explained to patients that there will be blue-green discoloration in their urine and feces for 24 h following biopsy. Some patients may experience allergic rashes against isosulfan blue on their neck, hands, and feet; in rare cases, hypotension may be observed. Following the procedure, the nurse should monitor the patient closely for allergic reactions, should educate the patient and her family about such reactions, and should inform the patient and family about the signs that should be reported to the nurse and physician [13].

Postoperative Patient Follow-Up and Nursing Care

The patient's vital signs and drainage status should be monitored for the first 12 h following the operation. Factors affecting wound healing should be evaluated, and drainage should be reported to the surgeon [13].

After the operation, the patient should lie down in a semi-Fowler's position, and drains should be emptied before they are full. The dressing and bedsheets should be checked for signs of leakage. The patient's arm should be elevated using a pillow, circulation of the arm should be checked, and loss of strength in the fingers, numbness of upper arm, and signs

of swelling should be recorded. Blood pressure measurement, i.v. line placement, and other procedures should not be performed on the affected arm, and the patient should be informed about these precautions. The patient should be told to use the unaffected arm whenever she wants to turn in bed or sit up and to avoid tight clothes that could compress her arm. The presence of pain at the operated area should be evaluated, and if present, analgesics should be administered upon physician request [9, 13].

After mastectomy, the absence of a breast disturbs the patient emotionally and adversely affects self-respect and body image. Patients find it difficult to look at the operated area; it is better if the patient's first examination of the operated area is undertaken with the support of a nurse or another health professional. At that moment, patients should be encouraged to express their feelings. Sharing emotions is normal after breast surgery, and it relaxes the patient. A temporary breast prosthesis inside a bra can be offered at discharge to reduce the patient's embarrassment and increase her self-esteem. The patient can be informed about breast reconstruction and breast prostheses. When the patient and her partner are ready, the partner should also be invited to see the operated area [10, 13].

Discharge Education

The patient and her family should be informed about the postoperative period:

- It should be explained that mild redness, tenderness, and swelling over the operated area is normal.
- The patient should be informed about wound care, asepsis, drain care, signs and symptoms of infection, and frequency of dressing changes before discharge from the hospital. The patient should be educated on the following:
  - Checking the drain area for leakage
  - How to measure the drained volume and how to empty the drain and record it
  - The removal of the drains within approximately 7–10 days, when the drained volume is below 30 ml/24 h
  - The importance of consulting the doctor if there are complaints such as bleeding, fever, and pain at disturbing levels
- Patients should be informed about the possibility of infection and edema at the operated area and should be educated on preventive measures against infection:
  - The patient should be advised to prevent skin damage by wearing gloves when gardening, avoiding exposure to sunlight, wearing a thimble when sewing, using electric shaving machines for axillary cleanup, and avoiding injections.
  - When there is damage to skin, the patient should understand the importance of cleaning the area with soap and water, covering the area, and reporting any warmth or swelling over the area to a physician.
  - The patient should not wear tight accessories and should not lift heavy objects for extended periods.
- The patient should be informed about when the sutures will be removed.
- The patient should be told that numbness can occur over the operated area and arm, and its causes should be explained.
- It should be explained that the patient can use her arm normally after the drains are removed and that if limitations in the range of motion persist, she should elevate her arm for at least for 30 min every day.
- The starting date of additional exercise programs should be planned (generally 1 week later, with retrieval of sutures and drains), and the arm, wrist, and hand exercises that she has to perform (e.g., clenching a rubber ball, clenching and unclenching fingers, touching the shoulder with the hand and wrist movements) should be taught (Fig. 45.1).
  - The patient should be reminded to not abduct her arm as long as the drains are in place, as exercises that begin in the early period increase the risk of seroma formation; she can be told to start all exercises once wound healing is complete and drains are removed.
  - Until drains are retrieved, limited exercises such as hand and wrist extension can be started on postoperative days 1–3.
  - Arm and shoulder movements should start after drains are retrieved. Patients are advised to continue these exercises for 20 min, three times per day, until normal range of motion is obtained with these movements. The number of exercises can be increased in athletic women. Patients should be reminded that they can pause exercises if they experience pain during exercises and that they should continue the exercises for at least a year.
  - Patients should be encouraged to perform daily activities such as eating, combing hair, and washing their face.
  - It should be explained that both arms should be used during exercises to maintain the correct posture, that the patient should not lift objects heavier than 2–3 kg with the affected arm, and that the patient should distribute weight evenly to both arms.
  - It should be explained that the patient may start cycling or trekking as soon as she starts feeling well and that she may start driving once the drain is removed if she is not taking narcotic analgesics and if the range of motion is regained.

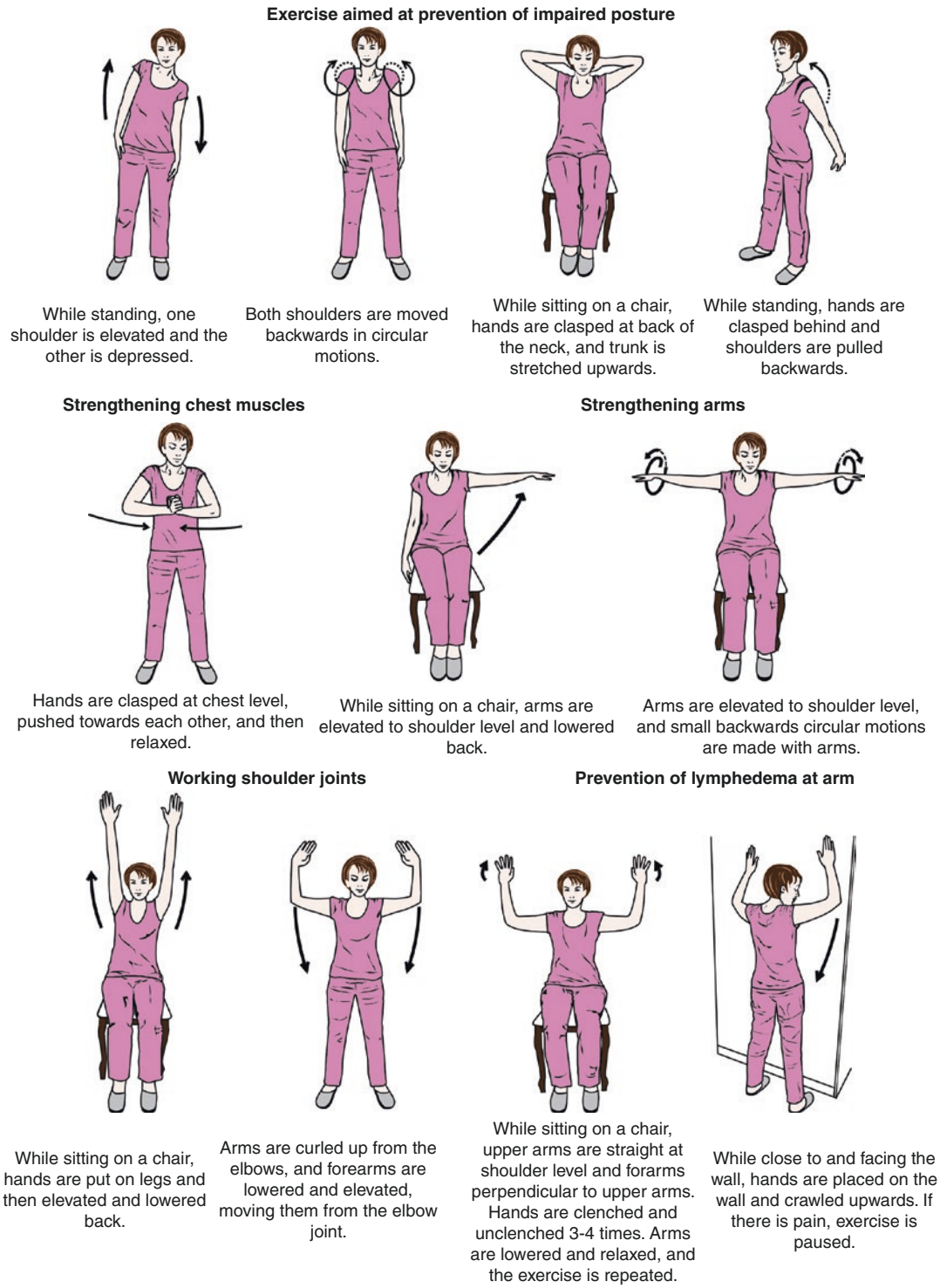

Fig. 45.1 Shoulder and arm exercises after breast surgery

- Lymphedema can develop, especially in patients who undergo axillary dissection, due to the insufficiency of lymphatic drainage and the blockage of the outward motion of fluid and proteins from the interstitial space. Such patients should be informed about how lymphedema occurs, of the signs and symptoms of lymphedema, and of the preventive measures against it (Table 45.1).
- Patients should be informed that there is no harm in resuming sexual activities after discharge.

Table 45.1 Patient education for the prevention of lymphedema

Keep your affected arm above heart level while sitting for extended periods or while driving, lying down, or watching TV
Do not have injections made on the affected arm
Wear gloves when washing dishes or gardening
Protect your hand and arm from burns
Have your blood pressure measured from the unaffected arm
Use lanolin creams to avoid dryness of your hand and arm
In case of cuts and scratches, wash the area and apply antiseptics
Consult your doctor in case of signs or symptoms of infection
Elevate your arm from time to time during the day and while going to bed
Do not use underwire bras or heavy breast prostheses
Do not wear tight or elastic-sleeved clothes that could compress your arm
Do not wear tight watches, bracelets, or rings on your affected side
Do not lift heavy objects with your affected arm
Do not engage in activity that requires strength (rubbing, brushing, pushing, pulling, etc.) using your affected arm
You can have a professional manicure, but care should be taken when cutting cuticles to avoid any injury
Always wear a thimble when sewing to avoid needlestick
Do not stay outdoors for extended periods during hot weather
Avoid hot baths, hot showers, and saunas
Maintain your ideal weight with low-salt, fiber-rich foods
Avoid smoking and drinking alcohol
Partake in a diet rich in easily digestible proteins (fish and chicken)
Use a lymphedema bracelet
After the operation, regularly measure and record your hand circumference at the level of the thumb groove and your arm circumferences 10 cm above and 10 cm below the olecranon. If the measurement values differ by more than 2 cm between arms, consult your doctor for an evaluation of lymphedema

- The importance of prostheses should be explained to patients who undergo mastectomy, both to resolve cosmetic issues and to preserve spinal integrity; patients should be advised to start using prostheses approximately 6–7 weeks after surgery, once the operated area is healed.
- Patients should be advised to avoid creams and deodorants and to not shave their armpit for 2 weeks following surgery.
- Patients should be encouraged to talk about mastectomy, to express their feelings about the loss of a breast, and to communicate with their partners.
- Supporting relatives such as partners, family, and friends of the patients should be identified, and those people should be informed about the importance of the support they will provide to the patients [8, 10, 13, 14].

Monitoring and Management of Possible Complications

Various complications can be observed in patients after breast surgery, including lymphedema, transient edema, lymphangitis, hematoma, seroma, wound infection, and limitations in the range of shoulder and arm movements (frozen shoulder/contracture).

Transient Edema

Following ALND, collateral circulation takes on the function of lymphatic circulation; therefore, some patients may experience transient edema. It should be explained to patients that transient edema is not lymphedema, and they should be advised to keep their arm above heart level until collateral circulation develops.

Lymphangitis

Lymphangitis, which is the infection of lymphatic vessels, causes rash, itchiness, swelling, local heat, pain in the arm, fever, and tremor. Antibiotic treatment should be initiated in those patients upon physician request; body temperature and leukocyte counts should be monitored. The affected arm should be elevated, and no invasive procedures should be performed on this arm.

Hematoma

Hematoma, which is the collection of blood in the operated area, can develop during the first 12 h following either mastectomy or breast-conserving surgeries. Swelling, tenderness, pain, and ecchymosis in the skin can occur at the operated area due to hematoma, and the amount of drained bloody discharge may increase. These signs should be reported to the surgeon, and compression dressings should be applied as required for approximately 12 h [13].

Seroma

Seroma is collection of serous fluid under the breast incision or in the axillary region following mastectomy or BCS. The risk of seroma increases with modified radical mastectomy, greater volumes of drainage during the first 3 days, and being overweight, so such patients should be closely monitored for signs and symptoms of seroma, such as swelling, pain, and dullness at the incision area or axillary region; necessary treatment should be initiated as required, upon physician request [13].

Limitation in Range of Shoulder and Arm Movements

Limitations in the range of shoulder and arm movements can occur due to surgical procedures and radiotherapy. Patients should be advised to practice arm-shoulder exercises regularly and should be referred to physical therapy as required [7, 13].

In conclusion, the surgery specialist nurse should get to know the patient and her family upon the surgery decision, determine the care needs of the patient, and plan individual interventions. Additionally, as a member of a multidisciplinary team, the nurse should take on an active role in the coordination of care and complete preoperative preparations, monitor operation-related complications after surgery, report complications to the doctor at an early stage, and manage such complications. The nurse should educate the patient on an exercise program for the prevention of lymphedema

(Fig. 45.1), drain care, and other preventive measures after surgery, and the nurse should support patients who experience altered body image and refer such patients to liaison psychiatry as required [8–10, 14].

Nursing Care During Radiation Therapy

Although it has been used as a treatment modality for years, many patients experience anxiety concerning radiotherapy. Information regarding the radiotherapy process is important for patients to experience effective therapy. Information facilitates patient participation in treatment decisions, reduces anxiety, and increases compliance with treatment [15]. Moreover, if the need for information is not satisfied, patients may continue to experience treatment-related anxiety and may even misbehave, requiring significantly more time from health professionals [16].

Patient education is one of the main responsibilities of radiotherapy specialist nurses. There are many studies in the nursing field that have evaluated the effect of education on patient satisfaction and the appropriate education content [16]. It is emphasized in these studies that patient education should not be generic but should be specifically planned for breast radiotherapy. Furthermore, patient education should focus on the process and effect of breast radiotherapy, the purpose of therapy, reactions likely to occur during therapy (preventive measures and prevention), examinations that should be performed during treatment, and control visits in general. Although there is not a defined standard with respect to when to inform the patient about radiotherapy, it is important to begin patient education during the first meeting with a health professional and to continue the education process during each weekly control visit to increase its effectiveness. Moreover, it is best that a standard education on the treatment process is planned ahead specifically for each week based on the needs of the patient [16–18].

The education nurse first should explain the purpose of radiation therapy and describe how it will affect the disease of the patient. Subsequently, the following topics must be explained to the patient before treatment:

- To define the area of external radiotherapy, the therapy area will be marked with lines at the first meeting, and these lines should not be erased during the duration of the treatment.
- Therapy will continue every weekday for approximately 6 weeks, and each session will last approximately 1–3 min.
- The patient will be alone in the room during therapy, but she will be closely monitored by a radiotherapist and can talk to the radiotherapist via a closed-circuit system.
- Radiation will pass through her body, and it will not cause any pain.
- Patients should maintain the position directed by the radiotherapist (arm under the head). This position may be uncomfortable, especially during the initial therapy sessions. Therefore, the patient should continue arm exercises and can take analgesics 1 h before the therapy as required.
- The patient will not be radioactive after external radiotherapy.
- Patients should not fast during therapy, and it is best if patients eat a little before therapy.
- Because it can adversely affect the therapy, the patient should not take a multivitamin supplement unless recommended by the physician.
- It is important to attend therapy on time every day.

Patients may experience many physical, psychological, and psychosocial problems during radiotherapy, affecting both themselves and their family relationships. Skin changes, fatigue, pain related to nerve or pectoral muscle inflammation, edema of the breast tissue, and tenderness are the most frequently reported problems. However, every individual is affected at different levels. Some patients continue their daily lives unaffected, whereas others find it difficult because of the symptoms related to the treatment [17].

Today, because there is not a widely accepted standard regarding the prevention and management of skin reactions, patients should be advised to not apply any moisturizing lotion, hot or cold applications, or bandages before therapy unless recommended by the radiotherapist. Patients should be advised to avoid tight, irritating clothes during treatment and to wear comfortable cotton clothes. The patients should be informed about the importance of avoiding skin exposure to direct sunlight and to use sunscreen (30 SPF minimum) when going outdoors. Patients should be advised not to swim in pools and not to visit saunas during therapy [18–20]. For patients experiencing itchiness due to dry desquamation, an appropriate moisturizer and corticosteroid lotion can be recommended to provide comfort for the patient, upon the recommendation of doctor. Dressings can be applied to control wet desquamations with bleeding and discharge. Hyaluronic acid pomades can be initiated upon recommendation of the radiotherapist [18]. Furthermore, because smoking increases the severity of skin reactions, patients should be advised not to smoke during radiotherapy and should be encouraged to quit smoking [21].

In the past, patients were advised to not take baths and to not use deodorants if the axilla was included in the therapy area. However, studies have failed to demonstrate the effectiveness of this approach in the management of skin reactions, and avoiding bathing for the duration of therapy can discomfort patients. Today, it is stated that there is no harm in washing the therapy area with water and soap, and patients are encouraged to wash their skin with soap and water without irritating it and to dry their skin completely with a soft towel applying tapotement [22]. Other than deodorants con-

taining aluminum chlorohydrate, there is no harm in using deodorants during therapy unless skin integrity is damaged. Aluminum chlorohydrate-containing deodorants increase the dose in the skin via the bolus effect, so they are not recommended. However, the utilization of deodorants during therapy is not a well-studied topic [18]. In a study performed in 2009 that included 84 women receiving breast radiotherapy, Theberge et al. reported higher levels of skin reactions in women using deodorants not containing aluminum chlorohydrate than in women not using deodorant [23].

Various studies have stated that the utilization of *Calendula officinalis* can be beneficial for the prevention of skin reactions in patients receiving breast radiotherapy and may be recommended for this purpose [18, 24].

Because the evidence is insufficient to determine the best application in the management of radiation dermatitis today, there is significant diversity in clinical applications. A widely accepted standard preventive method has not yet been established [18, 19]. In Turkey, radiotherapy units follow their own specific skin care protocols.

Another problem that is frequently experienced by patients receiving breast radiotherapy is fatigue. Fatigue related to radiotherapy can adversely affect patients' quality of life both during the treatment period and long after the treatment. Fatigue can be caused by anemia, sleeplessness, poor nutrition, hypothyroidism, depression, previous chemotherapy administration, and pain. The primary approach for management is the treatment of the cause (management of anemia, depression, etc.). Additionally, nonpharmacological approaches that have been shown to be effective in the management of fatigue, such as education, exercise, cognitive behavioral therapies, massage, and Reiki, are also recommended. With respect to education, focused education including the causes of fatigue and coping strategies has been shown to be beneficial [25]. In a recent meta-analysis, 20–30 min of aerobic exercise three times per week and participation in regular exercise programs during the posttreatment period were determined to be beneficial for the management of fatigue in breast patients [26]. As one of the most studied subjects in oncology, the effectiveness of exercise on fatigue has been reported in many studies; quality of life is better and the level of fatigue is lower in breast patients participating in regular exercise programs, and exercise is regarded as a care standard in the management of fatigue, unless there is spinal or bone metastasis [26, 27].

In conclusion, the radiotherapy specialist nurse should get to know the patient and her family from the moment the radiotherapy decision is made and should determine the care needs of the patient and plan the individual interventions. Furthermore, as a member of a multidisciplinary team, the nurse should take an active role in the coordination of the care and provide the patient with a safe care service. Nurses should support patients in returning to their normal lives once treatment is over.

Nursing Care in Systemic Treatment

Treatment protocols that include combinations of various drugs (Adriamycin, paclitaxel, docetaxel, Herceptin, etc.) are used in the treatment of breast cancer depending on the prognostic factors and the patient's response to treatment. Depending on the protocol used, various side effects can develop during treatment, including nausea/vomiting, fatigue, hair loss, weight gain, loss of appetite, joint and muscle pain, and constipation, which can cause the patient to refuse treatment. The purpose of care for these patients is to improve their quality of life by preventing or controlling treatment-related symptoms. Most of the symptoms caused by systemic treatment are multidimensional, complicated, and subjective, reflecting changes in the biopsychosocial functions of the patient. Therefore, symptom management is important for these patients and constitutes an important part of nursing applications in oncology. Cancer patients generally prefer pharmacological approaches (72.5%) for controlling these symptoms. Moreover, fewer patients benefit from nonpharmacological approaches such as resting (38.2%) and sleeping (12.9%) for controlling fatigue, staying hydrated (9%) and maintaining mouth care (15.9%) for dryness of the mouth, and resting (6.5%) and exercising (1.5%) for dealing with psychological symptoms [28]. Although pharmacological approaches are offered to patients, different nonpharmacological approaches can also be recommended for preventing and controlling different symptoms [29].

To control nausea and vomiting, which are observed frequently in Adriamycin-based treatments in breast patients, acupuncture, acupressure, music therapy, progressive muscle relaxation exercises, and diet changes can be suggested. Meals should be prepared in a different environment from the patient, and the patient should be encouraged to eat in small amounts and more frequently, increasing the number of meals from 3 to 5–6. Furthermore, because they are tolerated better than hot food, cold-served foods such as sandwiches, cheese, fat-free toast, and mashed potatoes should be offered; apple juices, cranberry juice, lemonade, and mint tea can be recommended in small sips. Patients are advised to not eat sweet, fat, salty, spicy, and smelly foods because they can increase nausea. Furthermore, because they can decrease appetite, patients should avoid their favorite foods if they experience nausea/vomiting. Based on the emetic effect of the patient's chemotherapy protocol, upon physician request, appropriate antiemetic agents should be recommended for at least 3 days [30, 31]. Although acupressure application in chemotherapy patients has been reported to reduce the intensity of acute nausea, it is not effective for acute vomiting or for late complaints. Nonetheless, the use of an acupressure band can be recommended to some patients who experience high levels of nausea and vomiting [31].

Myelosuppression or a decrease in blood counts is one of the most important side effects during treatment and can lead to a reduction in treatment dosage or postponement of treatment. This side effect is most commonly observed in breast cancer patients receiving doxorubicin, cyclophosphamide, or paclitaxel. Age, previous radiotherapy administration, bone metastases, insufficient renal function, high therapy doses, and long-term therapy can increase the risk for myelosuppression; the selected treatment protocol can also contribute to level of myelosuppression. The most important problem in myelosuppression is neutropenia. In neutropenia, leukocyte counts fall and predispose the patient to infections. These patients should be advised to avoid infected people and to take extra care with their personal hygiene (particularly for the mouth and perineal region) for the following week after therapy. Additionally, the patient should be educated on measuring body temperature, and it should be explained that if her fever rises above 38 °C, she must report it to her physician and follow the physician's recommendations [32].

Fatigue is a multidimensional symptom affecting breast cancer patients in different ways. Fatigue can be caused by decreased hemoglobin levels, pain, depression, or the effects of drugs. Fatigue is especially frequent in patients receiving the taxane group of drugs. Exercise, psychosocial interventions, and other approaches are reported to be effective in the management of fatigue [25]. Most researchers have focused on the effect of exercise on quality of life, physical function, emotional well-being, and fatigue, and studies have examined health-related outcomes, such as cardiovascular fitness, muscular strength, and objective physical functioning [33]. McNeely and colleagues conducted a systematic review and meta-analysis of 14 RCTs involving exercise interventions in 717 breast cancer survivors aged 35–72 years. Pooled data from 156 patients in these trials revealed significant positive effects of exercise on quality of life, cardiorespiratory fitness, and cardiovascular fitness. The pooled data also demonstrated a statistically significant impact on fatigue reduction but only during the survivorship phase [26, 33]. In two studies performed by Yates et al. (2005) and Ream et al. (2006), psychosocial education provided by the nurses decreased the frequency, intensity, and effect of fatigue [34, 35]. Preventive treatment related to the management of fatigue in cancer patients is generally theoretical, and medical approaches focus on the treatment of the symptoms that cause fatigue. For example, patients experiencing fatigue due to pain are given analgesics, patients experiencing fatigue due to anemia are given erythrocyte suspension or Fe^{++}, and patients experiencing fatigue due to depression are given antidepressants and psychostimulants [25].

Although not frequent, oral mucositis is a side effect reported by patients, particularly when leukocyte counts fall 1 week after treatment. For this reason, it is important to review blood counts in patients developing oral mucositis and plan treatment aimed at the cause (e.g., antiseptics, antifungal agents, topical analgesics, or growth factors). Regular application of mouth care protocols and holding ice in the mouth (cryotherapy) for patients receiving bolus 5-fluorouracil can be beneficial for the prevention of this problem [36]. In meta-analyses on this subject, traditional Chinese medicines, cryotherapy, mouth care protocols, and honey are effective for decreasing the prevalence and intensity of oral mucositis [36] but not effective in treating it [36, 37].

Alopecia can be defined as transient or partial hair loss caused by chemotherapy. Although the extent of hair loss depends on the type, dose, and duration of administration of the selected drug, it is generally transient. Methotrexate or 5-fluorouracil causes a small extent of hair loss, whereas complete hair loss is observed in patients receiving doxorubicin, cyclophosphamide, or paclitaxel. Although alopecia is not a side effect that necessitates lowering the treatment dosage, it adversely affects patient quality of life by negatively altering body image, sexual life, and self-respect through effects on individual physical appearance. Hair loss generally begins 2 weeks following treatment, and hair starts to grow again within 8 weeks after treatment is over; it is important to inform the patient of this timeline [38].

Neurotoxicity is a problem during taxane-based treatments. This side effect affects the nervous system, manifesting as paresthesia of the hands and feet and the development of constipation. Paresthesia of the hands and feet is a frequent problem in patients receiving taxane-based treatments. Although this problem is temporary in most patients, some patients can experience symptoms of longer duration, which may require lowering the dose of the administered drug or its discontinuation [39].

For constipation problems, the use of laxatives, a fiber-rich diet, and increased fluid intake can be recommended to the patient [40].

Menopause-like symptoms such as hot flashes or vaginal dryness occur due to the effects of drugs on the hormonal system. The use of water-based lubricants and vaginal dilators during sexual intercourse can be recommended to patients to prevent vaginal dryness. For hot flashes, wearing light clothes, avoidance of synthetic and woolly clothes, reducing smoking, reducing tea and coffee consumption, practicing relaxing exercises, and having a warm shower before bed can be recommended [41].

Nursing Care in the Terminal Period

Upon diagnosis of cancer, the patient is confronted with many questions and problems from diagnosis to treatment and the posttreatment period, such as accepting the diagnosis, dealing with disease- and treatment-related symptoms,

continuing treatment, dealing with social problems, and fulfilling familial responsibilities. However, approaching the terminal phase, problems such as psychological issues, pain, nausea/vomiting, fatigue, dyspnea, anorexia, cachexia, constipation, and delirium constitute the focus of palliative care.

Psychological problems coalesce as the disease advances and disturb the patient's quality of life; the patient and her family can manifest different emotional reactions based on their personalities and previous experiences. Patients should be supported at this stage and during the later stages of the disease to address psychosocial problems and to use their coping skills effectively. Specialists working in liaison psychiatry should be consulted as required, and appropriate treatment modalities such as cognitive behavioral therapies and pharmacological treatment should be initiated. Patients should be encouraged to take active roles in decisions about their treatment and to keep diaries reflecting their mood changes, and they should be encouraged to share their emotions with the people they love [12].

One of the symptoms that are generally difficult to control in the terminal period is pain. Pain is significantly more frequent in patients with bone metastasis. Psychoeducation, supportive psychotherapy, and behavioral cognitive interventions are nonpharmacological approaches shown to be effective in pain control. Additionally, as a part of the multidisciplinary approach, mind-body therapies are recommended for controlling chronic pain and improving quality of life [29, 42]. Listening to music reduces pain levels and the need for opiates, but its benefit is small, and its clinical importance is not clear [43]. For pharmacological treatment of cancer pain, two key concepts, "by the clock" and "ladder method," are very important for the effective management of pain. Whichever drug or method is used for cancer pain, the administration of drugs with certain intervals based on the duration of action should be adopted ("drugs by the clock"). Additionally, the recommendations of the WHO for cancer pain should be considered, and analgesic drugs should be added to treatment step by step, according to their potency. In this approach, non-opioids (paracetamol, aspirin, and nonsteroidal anti-inflammatory drugs) and adjuvant analgesics should be used for mild pain as the first step. In the second step, weak opioids (codeine and tramadol) should be added to the first-step drugs for moderate pain that cannot be controlled with non-opioids. In the third step, strong opioids (morphine and fentanyl) should be initiated for patients experiencing intense pain that is uncontrollable with weak opioids ("ladder method") [42].

Chronic fatigue can be an important problem for many patients. In these patients, fatigue is a multidimensional concept that affects patients differently. The cause of pain can be the disease itself, treatments, nutritional status, drugs, pain, activity level, sleeping problems, infections, or psychosocial problems such as anxiety and depression. Therefore, prevention related to the management of fatigue in cancer patients is generally theoretical, and medical approaches focus on the treatment of symptoms that cause fatigue. For example, patients experiencing fatigue due to pain are given analgesics, and patients experiencing fatigue due to depression are given antidepressants and psychostimulants. Additionally, studies have demonstrated that various approaches, including exercise, psychosocial interventions, decreasing energy consumption, nutrition, and acupuncture, are effective in the management of fatigue [25].

Anorexia and cachexia can also be observed in terminal-phase patient. Their causes can be the local and systemic effects of cancer, chemotherapy and radiotherapy, alterations in the sense of taste, stomatitis, dryness of the mouth, nausea/vomiting, and depression. To manage anorexia and cachexia, nutritional status should be improved with frequent meals in small amounts, and nutritional support should be provided as required. Nutritional balance should be maintained with a high-calorie diet. Progesterone preparations (medroxyprogesterone acetate, etc.), corticosteroids, and prokinetic agents (metoclopramide, etc.) can be used for this purpose. It should be noted that steroids cause a negative nitrogen balance [13].

Utilization of Complementary Approaches in Breast Cancer

After diagnosis, many women with breast cancer want to know, in addition to conventional therapies, what proactive steps they can take to positively impact their prognosis. Most patients make lifestyle changes, and some begin to use different forms of complementary and alternative therapies (CAM), many hoping for a cure. However, complementary methods are not administered to cure such diseases; rather, they may help control symptoms and improve well-being [44]. However, it should be noted that, although studies have demonstrated the safety and efficacy of some CAM approaches, the reliability and effectiveness of most of the methods used by our patients have not yet been proved, results related to their effectiveness are limited, and poorly informed utilization can do more harm than good. Therefore, upon diagnosis, all breast cancer patients should be questioned regarding their use of CAM and informed about CAM utilization by health professionals. Furthermore, because the most correct way for the patient to obtain informed about the interaction of these approaches with her treatment is to discuss the issue with health professionals, one of our primary responsibilities is to guide the patient in this respect to complete a successful course of treatment [45].

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Psychosocial Adaptation During and After Breast Cancer

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Mine Ozkan

Psychosocial Reaction During and After Cancer

From a medical perspective, cancer involves pathophysiological, organic processes; from the patient's point of view, it is a crisis of life, identity, and existence as well as a multidimensional issue that implicates biological, mental, social, environmental, familial, psychosocial, and psychosexual elements. In modern medicine, it is necessary to create solutions for diseases in conceptual and clinical terms by addressing the biological, mental, and social components in concert. We cannot understand the disease and the reactions without understanding the patient as a whole.

In general medical practices, physical diseases are accompanied by organic, mental, psychophysiological, psychopathological, behavioral, and psychosocial morbidity. The psychological-behavioral state is instrumental in the susceptibility to physical diseases, the progression and course of the medical illness, the adaptation of the patient, the response of the patient to treatment, and patient care and survival as a whole. Physical diseases and their complications induce a crisis in the patient and affect the mental state. While providing treatment and care for the patient, it is essential for medical treatment and care to go hand in hand with mental treatment and care in a coordinated and systematic approach [1, 2].

Cancer is a chronic, life-threatening disease that greatly impacts all spheres of life. During the initial phase, the patients experience feelings of disbelief, shock, panic, and a sense of hopelessness. Anger, hostility, and the feeling of losing control over one's life are also common reactions to cancer. Over time, cancer patients and their families and friends face several difficult situations such as making sense of complex medical information, making difficult treatment decisions, dealing with treatment side effects, living with the fear of recurrence, and, for some, facing the unfortunate possibility of impending death, which further disrupts the quality of life [3].

A series of medical, psychical, and psychosocial factors play roles in the adaptation of the cancer patient. These factors are listed below:

- The patient herself—her experiences and opinions regarding medical diseases; the patient's illness; the type, symptoms, signs, and course of the illness; and the organ affected by the illness.
- The age period in which the patient became ill and the level of threat her illness poses to the goals and projects that the patient had at the time (work, family, age period).
- The support systems surrounding the patient and the cultural and social approaches to the illness.

Cancer patients develop various differing emotional, mental, and behavioral reactions regarding their illness during diagnosis, treatment, and the palliative period. Some of these reactions are normal and may even tend toward adaptation. The treatment team must understand such reactions and support them as well. Disordered or maladaptive reactions, however, require psychiatric evaluation and treatment [2].

People react to cancer in numerous ways. In the first stage, the most common reactions are shock and disbelief. Immediate denial of the truth is a defense mechanism against the anxiety, panic, and desperation caused by the truth; these reactions are often very difficult to endure and even impossible for some people to withstand. In a sense, the patient protects herself against unbearable anxiety by refusing to accept the truth and pretending that it does not exist; therefore, it may be more advisable to prepare the patient psychologically by providing her with environmental, social, and emotional support and gently informing her of her condition. Subsequently, anger and depression develop. The patient's inability to express her anger and her feelings of rebellion increases the risk of developing

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depression. Specialists working in oncology services must be aware that such patients might project their anxiety, overreactions, and anger to their families and treatment team. States such as anxiety, not eating or drinking, distractibility, and uneasiness are normal during this period. Feelings of rage and rebellion entailing the question "why me?" can also be experienced.

Bolund has defined the cancer crisis as a four-phase process:

1. State of shock
2. Reaction phase
3. Resistance
4. Adaptation

Due to the catastrophic associations it brings about, a cancer diagnosis creates a reaction of shock in the first phase. The person becomes estranged to her own body and feels that her future investments are threatened. She enters into a life crisis. The most common adaptation style in this phase is denial. Denial is an effort to keep an unendurable truth from entering consciousness and to protect the integrity of the self. Psychological defense reactions such as disaggregation and projection frequently develop. The person appears to be unable to hear what is being said or to comprehend the truth. This state may extend from a few hours to a few days or even to a few weeks, depending on the person. The patient must be given time and positive messages that may inspire hope. Additionally, probabilities and options regarding treatment must be explained to her, and she should receive family support.

Reactions are excessive during the second phase. The person tends to accept the truth and shows emotional reactions to it. The main type of reaction is anxiety. The threat of extinction, the perception of loss, thoughts of separation and death, and the feeling of becoming estranged from one's own body are the main elements of this anxiety. A state of anxiety manifests itself through varying symptoms.

The third phase is the adaptation phase, in which the patient accepts the truth and directs her mental strength to her new life. This is the phase in which the patient learns to live with her illness. Specifying treatment options and presenting a treatment program helps to facilitate acceptance. In this phase, the person starts reinterpreting her life—past, future, and existence. She questions her identity, her purpose in life, her own narcissistic aims, and her life choices. She seeks security and balance.

Elizabeth Kübler Ross has defined the psychological phases of cancer in five phases, starting from the phase specifying how the patient reacts to the cancer diagnosis and continuing on to the processes involving the following reactions:

1. Denial
2. Anger
3. Bargaining
4. Depression
5. Acceptance

Green et al. have designed the Mental Adjustment to Cancer and listed adaptation mechanisms as follows:

1. Fighting spirit
2. Helplessness/hopelessness
3. Anxious preoccupation
4. Fatalism
5. Avoidance and denial

It is the incontestable and fundamental right of every person to learn the truth about one's self. Empathy, understanding, support, and sympathy are essential in conveying the diagnosis to the patient. The patient must be informed in a way that keeps her from losing hope and enables her to accept and continue her treatment. The patient should be told of her situation in a mode, period, and process that she can tolerate. Optionally, this might also be achieved in multiple sessions. Another important factor regarding this issue is that the diagnosis should be explained by the responsible, authorized oncologist or specialist who has been directly involved in the treatment. Liaison psychiatry aids in evaluating the patient and can occasionally be utilized to inform the patient of the diagnosis. It also helps to evaluate and treat the psychopathology that develops afterward.

Interestingly, most patients develop selective denial. In other words, they accept the truth to an extent that they are able to tolerate and adapt without resorting to reactions such as refusing treatment or feeling that treatment is unnecessary. These patients accept the truth up to a degree that they can tolerate. In such cases, it is best to inform the patient of the diagnosis after presenting treatment options and clinical and social support opportunities.

Once it is definitive, the diagnosis must be told with sympathy, directness, and realistic hopefulness. It is best if it is told by including treatment and care options and in a way that enables the patient to understand and that keeps her from denying the situation [1, 2].

Breast Cancer and Psychosocial Responses

Breast cancer is the most common tumor in women and is one of the leading causes of death from cancer. Breast cancer comprises 29% of all cancers observed in women in the USA. Breast cancer comprises 24.9% of all cases of cancer in women in Turkey [4]. The incidence in eastern regions is

20/100,000, whereas in western regions, it is 40–50/100,000 [5]. Although the incidence and prognosis vary geographically, the incidence of breast cancer in Turkey has increased by 1.5% annually [4]. Breast cancer is the most prevalent tumor among women and is one of the main reasons for fatalities from cancer. Unfortunately, the prevalence of breast cancer is increasing every year, and the use of breast self-examination and mammography remains low [3].

Research conducted on breast cancer patients focuses on the following:

- The predispositional role of a premorbid personality in the development of breast cancer
- Stressful life events and breast cancer
- Psychological reactions to breast cancer diagnosis and treatment
- Psychiatric disorders (anxiety, depression, delirium, etc.)
- Lifestyle changes (as a result of problems associated with physical discomfort, marital relations or difficulties experienced in sexual relations, and changes in activity levels)
- The relationship between defense mechanisms, psychological disorders, and personality types
- The impact of organ loss on body image and self-esteem
- Psychiatric disorders in the postsurgical period and the factors affecting them
- Spirituality
- Quality-of-life issues
- Treatment side effects
- The effects of psychological interventions

Breast cancer is a disease that threatens an organ associated with self-respect, sexuality, and femininity. Developments in treatment methods have significantly altered the sociocultural climate for women struggling with breast cancer. The difficulties that women encounter today are different from those that women faced 15–20 years ago. Nevertheless, while the emotional problems they experience today may be different, they are equally challenging [3]. These psychosocial stresses can be summarized as follows:

- Fear of death due to "malignant disease"
- Worries related to uncertainty about the future
- Dread that the illness will reoccur
- Separation anxiety
- The worry that one will lose her self-sufficiency, control over her own body, autonomy, and fundamental functions
- The worry that body parts and organs will be harmed
- Change and deterioration in appearance
- Fears of disfigurement and loss of sexual attractiveness
- Fear of losing love, sympathy, and support
- Feelings of inadequacy and fear of being dependent on others
- Fear of not being able to take care of children
- Fears concerning fertility
- Worry about painful, appearance-altering conditions such as aches and hair loss and worries associated with guilt and punishment
- Confusion about the disease etiology
- Uncertainty about the effects and the effectiveness of treatment regimens
- Fears of recurrence and metastasis [2, 6] that are common among breast cancer patients

A diagnosis of breast cancer can be devastating and can trigger emotional reactions such as chaos, uncertainty, anxiety, hopelessness, and despair. Psychological distress such as depression and difficulty concentrating is common. The breast cancer diagnosis places extraordinary demands on a woman's coping abilities. Women must therefore adapt to being breast cancer patients and redefine their lives and themselves accordingly. Thus, the task for patients is to incorporate the diagnosis (and all that comes with it) into their existing beliefs of meaning in life. They either rework the diagnosis to make it fit existing beliefs or revise their beliefs to better match their experience [6].

Psychosocial Adaptation in Breast Cancer

The term "adjustment to cancer" is used to describe the processes of adaptation that occur during the illness. "Mental adjustment" to cancer has been defined as a person's cognitive and behavioral responses to a cancer diagnosis. The adaptation process requires the patient to accommodate the changes that the cancer introduced into a multitude of dimensions of their lives [7]. To measure the adaptation of these types of changes, the quality of life (QoL) is used as the main instrument. The QoL is considered a multidimensional concept defined as a subjective assessment of physical, functional, emotional, and social well-being [8].

Various models have been proposed to explain the process of adaptation after a personal crisis. According to the transactional theory [9], the process of dealing with a stressor comprises antecedent, mediating, and outcome variables. The outcome is the individual's more-or-less successful adaptation to stress; environmental and personal variables are causal antecedents of the adaptation to stress. The effect of these antecedent variables is mediated by the person's appraisal and coping. Hobfoll's [10] theory of the conservation of resources underscores the importance of personal and coping resources as predictors of positive long-term adaptation. According to social cognitive theory [11], perceived

self-efficacy strongly influences behavior and is positively associated with adjustment.

A woman who receives a diagnosis of breast cancer must adjust to the transition from being healthy to having a life-threatening disease. The patient's coping styles and perception of the illness are crucial factors in this adjustment process. Diagnosis and treatment are commonly affected by psychological stress. Coping styles and social support have an impact on the distress experienced by the patient [8, 12]. Psychological, behavioral, emotional, and physical adjustments are unique for every patient and are related to a number of factors. Factors that contribute to the psychological responses of women to breast cancer can be grouped as follows:

1. Medical factors (stage of cancer at diagnosis and treatments received)
2. Sociocultural context, treatment options, and decision making
3. Psychological and psychosocial factors

The age at the onset of cancer, premorbid emotional balance (personality and coping style), attitudes toward illness, attitudes toward breast cancer in particular, prior psychiatric history, and the existence and accessibility of interpersonal support have been reported to be important variables in psychosocial adjustment [2].

Factors Affecting Psychosocial Adaptation in Breast Cancer

Life Cycle or Age

The life cycle during which breast cancer arises is important because the disease threatens to undermine or altogether curtail the social responsibilities women have at different times in their lives. Studies have consistently shown that younger women (<age 50) report greater psychological morbidity following a breast cancer diagnosis than older women [13–15]. Several investigations have also found that younger women with breast cancer report significantly worse quality of life than older women, particularly in the emotional and social domains [13, 16]. From a developmental perspective, younger women face unique issues such as premature onset of menopause, which may lead to infertility; sudden onset of vasomotor symptoms; long-term consequences of ovarian decline; concern about future pregnancies; changes in relationships with partners and/or children; multiple role demands of parenthood and work; career and work concerns related to productivity, job security, and career interruption; and greater concerns about body image and sexuality [13, 15]. Studies have shown that being married was associated with better adjustment, including better quality of life and possibly even increased survival. Married women have also been found to have less distress and to show better adjustment compared with unmarried women [17].

Coping and Personality

Other variables that affect adjustment are personality and coping styles. Every woman has her own coping style that she uses to adjust to stress. Coping can be defined as constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appreciated as a stressor, according to Lazarus. Coping strategies are classified as "problem-focused coping," behavior directed at solving the problem or situations, and "emotion-focused coping," behavior directed at changing the emotional reactions to the problem or situations. The latter also covers various defensive and avoidance strategies. Coping is independent of the outcome, and defense is regarded as a specific form of coping behavior [18]. The five most significant styles for adjusting to cancer have been summarized as fighting spirit, fatalism, cognitive avoidance, anxious preoccupation, and helplessness/hopelessness [19].

In a longitudinal study of 101 breast cancer patients [20], the latent construct of perceived control, which included measures of fighting spirit, helplessness/hopelessness, and self-efficacy, predicted less psychological distress. In a sample of 55 breast cancer patients, cognitive avoidance was associated with worse psychological adjustment 3 years later [21]. A study of coping patterns and distress showed that women with breast cancer who used emotion-focused engagement coping, i.e., acceptance or emotional expression combined with social support, experienced less distress 3 months later than women with breast cancer who had not used any emotion-focused engagement coping [22]. In a study investigating the correlation between coping responses and psychological adjustment in women with breast cancer, a significant correlation was found between poor adjustment and cognitive avoidance and minimal use of approach-based coping responses [21].

Every individual has a subjective way of perceiving and coping with stress shaped by culture. Women who use more avoidant and passive ways of coping experience higher levels of difficulties adjusting than women who use direct and active coping strategies. Furthermore, women who have a sense of control over the experience take a more active role within their treatment phases. Pessimistic reactions reflect insufficient psychological coping. Therefore, educational level and socioeconomic status are important in ensuring better adjustment. In a study that examined the possible predictors of adjustment to breast cancer, the most consistent predictor of psychological distress at 1 and 4 months after diagnosis was avoidant coping: women who reported more

avoidant coping were more distressed [23]. However, some authors have suggested that avoidant coping facilitates adjustment and decreases emotional distress. For example, in a literature review, it was concluded that avoidant coping could be especially beneficial during active treatment [3].

Several studies have looked at coping strategies employed over time in women with breast cancer. One short-term study found a significant decrease in active behavioral and cognitive coping strategies and no change in the use of avoidance over a 4-month period [23]. Women with early-stage breast cancer were followed for a year and found that some coping strategies such as active coping, planning, denial, and religious coping were used more frequently at the time of diagnosis and rapidly decreased, whereas other coping strategies such as the use of social support, self-distraction, restraint, and suppression of competing activities remained relatively constant or dropped off more slowly. Acceptance was the most frequently employed coping strategy and increased over the year following diagnosis [24]. A longitudinal study that followed up women for up to 5 years found that variability in coping strategies was observed at the times of greatest stress (treatment, recurrence, terminal phase of cancer) and suggested that changes in coping strategies may be linked more to "illness stages" than to any specific length of time since diagnosis [25].

Coping strategies used during the diagnostic phases of breast cancer have been found to be indicators of psychological adjustment after surgery. Active acceptance at diagnosis predicts better adjustment through the first year. Defensive strategies reduce distress at 3 months but increase fear of cancer recurrence at 1 year. Defensive avoidance-oriented coping, which is a helplessness/hopelessness coping style combined with pessimism or passive acceptance and resignation, predicts poor psychological adaptation 1–3 years later [26].

Research suggests that optimism plays an important role in coping and adaptation to breast cancer and is thus included as a covariate. Healthcare professionals should be aware of and respect women's coping strategies and encourage their use to reduce the psychological symptoms. They should also make family members and friends aware of their role in supporting and encouraging coping strategies.

Social Support

Social support is a complex construct that has long been suggested to have direct and buffering effects on well-being and emotional adjustment in cancer. Although the literature on the ameliorative effects of social support in cancer progression appear to be more convincing than in cancer onset [27], conclusive evidence is missing. Interesting and relevant questions include whether social support plays a prognostic role in cancer and whether the quantity or quality of this support is important. The inconsistent findings on social support and cancer progression can be broadly attributed to varying operational definitions of the term social support, the use of its various measures across studies, and the inclusion of various types of cancer and insufficient control for confounding variables in analyses [28].

Social interdependence, having good friends and relationships, and having no other serious family problems were contributing factors. Several researchers have documented the importance of social support when facing breast cancer and have shown that a cancer diagnosis is harder to handle for those with other personal or family problems [29].

It is not possible to separate the experience of the breast cancer patient from the patient's family. The diagnosis of cancer is a traumatic experience for the entire family. The shock due to the diagnosis of cancer can change the relationship and communication between the patient, the family, and the other members. During this period, some patients could form closer relationships with others, whereas other patients could escape from interpersonal relationships. Feelings of fear and uncertainty usually lead to an increase in patients' need for social support. However, during the long intervention period, patients usually have difficulties finding energy to continue their social relationships and may not have the necessary support when they need it most. Supportive family relationships are particularly important to cancer patients due to the fear and uncertainty associated with cancer. Related studies suggest that adjustment to cancer is better in a family environment characterized by cohesiveness, open expression of feelings, and the absence of family conflict. Nevertheless, the fear of cancer, which leads cancer patients to need more support from their families, also may interfere with the amount of support that family members are likely to provide [30].

There is a reciprocal relationship between the partners' reactions and adjustment and the patients' reactions and adjustment. The severity of depressive symptoms experienced by a woman with breast cancer may be influenced by her appraisal of the adequacy of support available from her partner [31]. Quite often, a spouse or significant other is confused about the prospective effects of the illness and thus hides these feelings from the patient.

This type of behavior is more prevalent after mastectomy because the woman experiences a loss. In addition, husbands displayed similar psychological reactions and distress as their spouses did throughout the course of treatment, showing that the experience of breast cancer is a shared experience for couples. Importantly, husbands who had an active role in the decision-making process had better psychological adjustment. In a recent case study in Turkey, husbands of young women with cancer, especially gynecological and breast cancer, perceived the situation as highly traumatic; thus, the marital relationship was negatively affected [32].

Literature on the subject clearly indicates that the partner relationship is unique and that additional social support cannot overcome the negative effect of a distant husband on the female patient's emotional well-being [31].

Children can also experience different fear and anxiety problems according to their development level and can easily be affected during this difficult period. Another anxiety faced by family members is fear of inheriting this illness. Because of the genetic association of breast cancer, family members could have fear and anxiety regarding the risk of having breast cancer.

On one hand, people without cancer could become distant toward people with cancer due to a fear of cancer or death. On the other hand, family and friends could escape from interactions and arguments with the patients because of feelings of shock and uncertainty and feeling uncomfortable for not knowing how to behave. A stigmatizing attitude toward cancer could lead to inconsistent and confused attitudes of the patient and destructive feedback for them. Breast cancer leads to fundamental problems for women's jobs or careers, working environment, and economic status. These problems generally include having no health insurance, being unable to work again, having to change working activities, changing their priorities, and experiencing stigmatization and discrimination about work [33].

Prior Psychiatric History

The risk of anxiety and adjustment difficulties are greater in women with a history of psychiatric illness prior to breast cancer. Adjustment to the diagnosis of breast cancer is also related to a family history of breast cancer. Adjustment is also closely related to the reactions and behaviors of one's social and familial environment. The attitudes of spouses or partners, families, and friends have a great impact on both how a patient perceives the situation and how she copes with the disease [13].

Psychosocial adjustment to cancer varies during the illness, specifically during the treatment time. It is useful for health professionals, nurses, and physicians to know of these changes in patients with cancer to detect and respond to a patient's psychological distress more effectively. The early detection of psychological morbidity may allow for an early intervention, thus reducing distress experienced by the patients.

Psychiatric Morbidity in Breast Cancer Patients

Researchers investigating the impact of breast cancer report high levels of depression and anxiety in breast cancer patients. In a study by Kissane et al. (1998) of women with breast cancer, the prevalence of psychiatric disorders was reported as 45% [34]. One of the most comprehensive reviews on the prevalence of depression in breast cancer patients was conducted by Rowland and Massie [35]. The review included 17 studies, and the percentage of depression in breast cancer patients in these studies changed from 1.5% to 50% depending on the number of patients, the definition of depression, and the evaluation tool used [35]. Some studies have indicated that approximately 20–41% of breast cancer patients confront clinically significant psychological distress [36, 37]. Loscalzo et al. [38] reported that approximately 30% of cancer patients have psychological problems, although only approximately 6% of these patients seek help from family or medical staff. This indicates that medical professionals must be proactively involved in the psychological treatment of breast cancer patients.

Psychological discomfort among breast cancer patients is associated with depressive disorders, anxiety disorders, anger, low self-esteem, and little emotional support [2]. The prevalence of depression in patients with breast cancer is estimated at approximately 10–25%, but there is no definitive meta-analysis of depression prevalence data [39].

We evaluated pre-intervention and post-intervention anxiety, depression, and quality of life in breast cancer patients and found that from the stage of diagnosis, the risk of depression was high and continued throughout the first year. In this study, we analyzed the patients' risk rates of anxiety (33.3%, 35.7%, 28.6%) and depression (40.5%, 42.9%, 44%) in three stages and found that patients were under psychological risk beginning from the stage of diagnosis [40].

In a study including women with breast cancer who were evaluated six times within the first 5 years following diagnosis, it was found that the depression rate (48%) was highest at least 1 year after the diagnosis [37]. In another study, it was found that although the average reported anxiety and depression scores decreased over time, the anxiety rate was 38.4% and the depression rate was 32.3% in the 18th month [41]. Four of every ten women were found to have severe depression and anxiety [42]. Morasso et al. [43] tried to detect depression among 132 breast cancer patients in stages I–III of the disease. Using screening tools for detecting mood disorders, they found a prevalence of psychiatric disorders of approximately 38%, with a classical rate of depression (major episode, adjustment disorder) of approximately 25.9%. Major depressive disorder was found in 8% of patients during the follow-up; 10.6% had adjustment disorders along with depressed mood, and 4.5% had adjustment disorders with mixed anxiety and depressed mood.

Depressive symptoms are typically higher in the period surrounding diagnosis and active treatment and decline over time as patients learn to cope with the disease. Studies have found the depressive symptoms of long-term breast cancer survivors to be comparable to those of the general population [44]. The occurrence of depression in breast cancer patients

is more strongly influenced by the patients' psychosocial environment and personality than by factors associated with the diagnosis and treatment regimen.

The prevalence of depression among women with early-stage breast cancer is twice that observed in the general female population, especially during the first year after diagnosis [37]. One of the most consistent findings is that the rate of depression diagnosis is the third highest in breast cancer, after pancreatic and oropharyngeal cancers [45]. The high rate of depression in patients with breast cancer highlights why it is important to identify it and to then provide appropriate resources and treatment.

To diagnose depression among this specific population, several parameters must be taken into account, such as the diagnostic system used, which means determining the type of criteria that might be more relevant regarding the nosography used, and the time of evaluation, which is an important factor because psychological disturbance changes over time [46]. Moreover, the incidence of depression appears to be dependent on the following parameters: the disease severity and the patient's disability and physical impairment levels, performance status, and past history of depression [47]. Paradoxically, major depression and depressive symptoms are underrated and undertreated in women with breast cancer. One explanation could be that women with breast cancer are generally reluctant to disclose their affective concern. Another reason could be that oncologists are not familiar with screening for depressive symptoms. The failure to diagnose mood disorders can be problematic because depression and its associated symptoms decrease the quality of life, affect compliance with medical therapies, and might reduce survival [48]. In addition to the classical clinical symptomatology of depression, such as sadness, anhedonia, guilt, helplessness, hopelessness, and suicidal ideation, the following risk factors of depression among breast cancer patients must be looked for:

- Past history of psychiatric illness
- The nature of the illness and cancer-related concerns (e.g., pain)
- A lack of confiding relationship
- A personality characterized by neuroticism
- Cognitive attitudes of helplessness/hopelessness
- Racial or ethnic minority status [49]

Greater demands at work or from parenting may make cancer treatment more stressful for younger women. Furthermore, previous psychiatric illness or depression, poorer socioeconomic status, lower levels of social support, and lower levels of education are risk factors for depressive symptoms. In terms of clinical characteristics, several studies on depressive disorder suggest that patients with advanced disease are more likely to report depressive symptoms. In addition, poorer performance status, more severe physical symptoms, and higher disability and physical impairment levels are associated with higher levels of depressive symptoms [50].

The correlation between depression levels with coping styles and cognitive errors in women treated for breast cancer was examined by a study performed at the University of Istanbul. Breast cancer outpatients who had undergone surgery at least 6 months previously, had completed adjuvant cancer treatment, and had not experienced metastasis or recurrent lesions were evaluated. Higher cognitive errors and automatic thought scores were found in the depression group. A fighting spirit was found to be the primary coping style used in the non-depression group, whereas helplessness/hopelessness, anxiousness/preoccupation, and fatalism were the coping styles used most in the depression group. No associations among depression and sociodemographic (except for educational level) and cancer-related variables were detected. However, it was found that automatic thoughts, cognitive errors, education level, fighting spirit, and anxiousness/preoccupation are important indicators of depression in our sample. A causal relationship exists between depression and a patient's cognitive patterns and accompanying anxiety [51].

In another study conducted at our department, the effects of illness perception on depression in patients with breast cancer were evaluated. Depression scores were positively associated with scores of identity and perceived serious consequences and were negatively associated with scores of illness coherence and treatment control. In breast cancer patients, the recognition of the relationship between illness perception and psychiatric factors may provide better recognition of the maladaptive reactions of patients to illness and treatment according to patients' visions [52].

Could depression be a risk factor for breast cancer evolution? In the literature, there are some positive arguments supporting this possibility. First, major depression decreases motivation and reduces compliance with treatments such as chemotherapy. Second, major depression could be an important predictor of late-stage breast cancer diagnosis because patients will delay seeking a medical consultation after finding a lump. Third, considering the two previous points, major depression might have a detrimental effect on the outcome in breast cancer patients. Could depression be considered a possible prognostic factor for breast cancer mortality? The answer to that question remains unclear [49]. Some studies suggest a link between depression and breast cancer mortality. Watson et al. [53] in a prospective study among 578 early breast cancer patients found that depressive symptoms and hopelessness are linked with a significantly reduced chance of survival at 5-year follow-up. Hjerl et al. [54] analyzed data from breast cancer central registers in a study of a retrospective Danish cohort comparing early-

stage and late-stage disease. In this study, they found that breast cancer with depression had a modestly but significantly higher risk of mortality depending on the stage of cancer and the time of depression. When women are confronted with advanced or even palliative or terminal stage cancer, they can experience suicidal ideation or can even attempt suicide to hasten death [55].

Certainly, in terms of suicidality, depression claims lives and represents a considerable risk factor for suicide. The risk for suicide is high among cancer patients compared with the general population. The relative risk for suicide is two times higher in the patient population. Suicide is possible when depression and desperation are comorbid with advanced stages of cancer and with the occurrence of uncontrollable symptoms such as severe pain. Risk factors for cancer patients include a previous history of psychiatric disorders, previous depression, a previous suicide attempt, a recent loss, alcohol or drug abuse, being male, a family history of depression or suicide, inadequate social support, and unemployment. Delirium, dysfunctional judgment, and impulse control disorder could lead to an unpredictable suicide attempt [56]. Although most of the women with breast cancer can adapt well to the situation, being single and having a low socioeconomic status are risk factors for suicide [55].

Anxiety is a normal response to unpleasant stimuli and can promote adaptive responses to new demands. However, it is detrimental when it is excessive and affects one's ability to cope with stress. Many patients diagnosed with breast cancer face extensive uncertainty about the future, concern over potential metastasis, fear of physical suffering, and overwhelming anxiety. Anxiety is one of the most dominant psychological challenges associated with cancer, with rates ranging from 10% to 50%. Research conducted in the USA and the UK has shown that anxiety prevails throughout the spectrum of treatment and recovery for female patients with breast cancer, even among disease-free breast cancer survivors [57]. In another study, moderate-to-severe anxiety was found in 27% of breast cancer patients [58].

A review was conducted of studies discussing the level of anxiety among women with breast cancer who were undergoing cancer treatment(s) and on the factor(s) contributing to anxiety in various treatment modalities between 1990 and 2010. Anxiety appears to be ubiquitous, presenting itself in all treatment types for breast cancer. The anxiety levels in women who underwent chemotherapy were highest, particularly before the first chemotherapy infusion, and were mediated by age and trait anxiety. Radiotherapy regimens did not affect anxiety levels in radiotherapy-treated patients, and most research concluded that anxiety levels were higher among women who underwent mastectomy than those who underwent breast-conserving therapy [57].

Anxiety has also been shown to have a physiological impact, influencing the neuroendocrine and immune systems [59]. Anxiety is negatively correlated with the treatment outcome. It was also reported that anxiety in breast cancer has a detrimental effect on the QoL of female patients, affecting their physical, medical, and sexual QoL indicators [37]. Factors that contribute to anxiety in patients with breast cancer can be broadly classified into physical, psychological, social, and environmental causes. Physical factors include age, treatment side effects, hormonal changes, and issues surrounding fertility. Psychological factors encompass their perception about change in body image and positive and negative feelings about the disease. Social factors include social support, decreased sexual interest, and sexual dysfunction, whereas environmental factors include multiple hospital visits, which adversely affect daily routine and work life, and stress pertaining to the financial situation [15, 60]. When comparing treatment modalities, women receiving radiotherapy or chemotherapy tended to exhibit a higher anxiety score over time compared with those undergoing surgery alone [60]. The level of anxiety is also reported to be higher in patients undergoing chemotherapy compared with radiotherapy, and a higher level of anxiety at the start of chemotherapy has an inverse relationship with the QoL score [61]. Thus, different cancer treatment modalities have a variable impact on the anxiety experienced by patients and should neither be negated nor combined as one single issue to address. Healthcare professionals should pay greater attention to identify signs of anxiety in patients and to design interventions to help alleviate anxiety earlier.

Because breast cancer was acknowledged as a possible traumatic stressor, researchers have documented that dealing with breast cancer could result in poor psychological outcomes such as posttraumatic stress disorder (PTSD) or in positive personal changes and an enhanced appreciation of life, known as posttraumatic growth (PTG). The rate of PTSD in breast cancer patients and survivors was relatively low, varying from 2.4% to 19%. PTSD appears to be related to younger age at diagnosis, lower educational level, and lower socioeconomic status. PTSD was related to disease severity, to perceiving the disease as more stressful and threatening, and to stressful or poor adjustment to the diagnosis. Chemotherapy was also associated with increased symptoms of hyperarousal, which is requisite for identifying PTSD, whereas a longer hospital stay was positively associated with PTSD [62, 63].

Tokgüz et al. [64] reported the prevalence of PTSD in cancer patients as 19%. It is supposed that chemotherapy is a situation that reminds the patient of trauma and could thus lead to continuous problems of traumatic stress; thus, patients receiving chemotherapy require more intense and effective psychological approaches.

The reported prevalence of sleep disorders in cancer patients is approximately 50%; they are found more in women than in men and are also prevalent among breast can-

cer patients [64]. A sleep disorder is usually severe for cancer patients; however, it is often assumed to be a normal reaction for cancer or is not reported by patients. Thus, sleep disorder is a frequent but neglected problem. Studies found that associations exist between poor sleep quality and fatigue, difficulty sleeping and maintaining sleep, perceiving less sleep adequacy, and experiencing restless sleep. Therefore, treating one complaint could affect another. Cancer-related fatigue and sleep disturbances are reported to have a common etiology, and these two situations are related to pain, depression, concentration, and cognitive functional loss [22].

Psychiatric Effects of Breast Cancer Treatment

Surgery

Mastectomy

As in all physical illnesses and surgical procedures, mastectomy is a stressful event that causes psychosocial crises in patients. The psychiatric approach toward mastectomy has created a model for the psychiatric complications brought on by surgical interventions as a whole [1, 2]. Generally, mastectomy has the potential to unleash psychological reactions that are observed in other physical illnesses—concerns over the underlying illness and the narcissistic damage associated with surgical interventions and unique concerns related to the symbolic connection of the breast to femininity and sexuality.

Mastectomy not only creates a heightened sense of loss but also impacts a person's functions, body image and perception, psychological state, and relations with those around her. Moreover, it may engender various concerns and fears, including anxiety over separation from friends and relatives, the loss of love, attention, support, and approval stemming from aesthetic concerns, and the loss of fundamental functions and control over one's body. Feelings of guilt and the fear of punishment due to premorbid lifestyle (smoking and alcohol consumption) may also be observed. Another major worry associated with breast cancer and mastectomy is related to disease recurrence. Various behavioral and emotional reactions such as distress, anxiety, depression, anger, denial, hostility, projection, pathological dependence, angry resistance, and psychological stress may develop in a patient with these types of concerns [20].

Changes in physical appearance greatly impact a woman's quality of life, self-esteem, sexuality, social roles, and relationships. The psychological effects of the surgical treatment of breast cancer on body image and sexuality include embarrassment of exposing one's body, discomfort showing scars, overall bodily changes, lack of sexual interest, problems with sexual relationships, concerns about the resumption of sexual activity and the frequency, and difficulties with becoming sexually aroused [3].

Research on mastectomy has created a model for the psychiatric complications of surgical interventions. The current research indicates that psychiatric morbidity develops after cancer surgeries. Cancer surgery brings anxiety and problems regarding both the surgical intervention and the underlying disease. In other words, the practice of mastectomy has become a significant area of research for understanding the relationship and interaction between cancer, organ loss, and psychopathology [2, 3].

According to the results of a prospective study involving 42 mastectomy cases conducted by Özkan and Turgay in 1992 [65] on the characteristics and prevalence of psychiatric disorders arising post-op and the factors that impact adjustment, mild depression was found to be present in 32% of the patients during the pre-op period, in 52% in the first week and first month post-op, and in 11% 1 year later. Depression was more severe in patients from 20 to 40 years of age, in single individuals, in less educated persons, and in persons who did not know their diagnosis. Anxiety was experienced by 28% of the patients in the pre-op period and 64% of the patients in the early post-op period (the first week after surgery). Anxiety is significantly less common at the first year post-op but is still higher than in the pre-op period. In other words, the highest levels of anxiety and depression are observed in the first week and month post-op, but these levels drop by the end of the first year.

According to the findings from the thesis of Ozkan, which was prepared in 1993 to define the effectiveness of the liaison model in patients who underwent mastectomy at the University Hospital of Istanbul, 26.2% of the patients were found to have depressive disorder in general, and 13.8% were found to have major depression during the period before mastectomy. After the operation, adaptation difficulties were frequently observed in these cases, especially during the first 6 months [2, 3].

Research has indicated that preoperative experiences and coping methods for breast cancer have postoperative impacts [26]. Previous studies of women's experiences of coping in the period between diagnosis and surgery do not provide an in-depth understanding of their experiences. In addition, most studies of women's coping in the preoperative period have been conducted retrospectively. Retrospective investigations have disadvantages such as recall bias and the repression of unpleasant memories, as well as the fact that the outcome of the surgery may color the memories [6].

Acceptance and humor were negatively correlated with distress, whereas denial and emotional expression were positively correlated with distress after surgery and 3 months later. The relationships between coping patterns and distress were also examined. Specifically, participants who used emotion-focused engagement coping presurgery, i.e., accep-

tance or emotional expression combined with social support, experienced less distress 3 months later than participants who did not use any emotion-focused engagement coping. Finally, flexibility, defined as the use of multiple coping strategies, was found to negatively predict distress. These results indicate that the presurgical use of emotion-focused engagement coping can be adaptive and that the adaptiveness of each strategy may vary as the stressor evolves [22].

Anxiety in patients treated by surgery was high; thus, surgery was a physical factor that contributed to anxiety. However, there was no unanimous conclusion on whether the type of surgery served as a moderating factor for anxiety in these patients, as shown by the differing conclusions drawn from the included articles. Nevertheless, all of the included articles illustrated that the level of anxiety preoperatively, if present, was higher in the mastectomy group, although some levels were not statistically significant [57].

For women with breast cancer, recurrence anxiety is reported to be the most common form of anxiety. One year after total mastectomy, relapse anxiety is ranked as number one. The intensity declines over the years; however, the anxiety remains. According to the findings of a study conducted in Turkey, a negative correlation exists between the fear of relapse and the date of surgery. However, according to western sources, in this stage, concerns regarding femininity and sexuality are more emphasized than relapse. As a second important concern, needing someone and being unable to meet their own needs are reported. This type of anxiety was reported by 33% in the study, whereas according to studies in the East and Far East, the rate is much lower, 10–11% [65].

Secondary problems such as pain, sensation loss, and arm swelling are common among mastectomy patients, resulting in further disability in daily life. Several studies have found that lymphedema negatively affects psychosocial well-being, although few of these studies report the specific impact on body image. Lymphedema (potentially exacerbated by weight gain and additional treatment, including radiation therapy) could manifest at a later time and may therefore be more likely to affect body image in the long term [66].

Women weigh multiple factors when deciding which surgical treatment is appropriate and should thus be informed of the potential for greater image concerns associated with more radical surgery. For the majority of women who have a choice regarding the type of breast surgery they receive, awareness that body image might be more compromised by mastectomy than by lumpectomy in the months following surgery may be an important part of the decision-making process. Future research evaluating surgical decision-making in young women and associated body image and psychosocial outcomes is clearly warranted, particularly given the increase in bilateral mastectomies in recent years in this population [66].

Related literature involves studies that compare the effects of radical mastectomy and partial mastectomy on body image, psychosocial adjustment, sex life, and recurrence anxiety. The findings indicate that the body image of women who underwent lumpectomy or partial mastectomies was more positive and that the fear of nudity was less prevalent. The effects of different surgical approaches on psychological adjustment and quality of life have also been extensively examined. A recent meta-analysis of 40 investigations examined postsurgical adjustment in women who underwent partial or radical mastectomy. After controlling for unpublished negative findings, body/self-image was the only factor that significantly differed between the treatment groups, with women who underwent partial mastectomy reporting better body/self-image [67]. Yılmazer et al. [68] conducted a study to compare body image, self-esteem, and social support. The women in the partial mastectomy group had more positive body images. The two groups showed a negligible difference with respect to self-esteem and social support. Furthermore, a negative correlation was found between body image and social support.

Al-Ghazal et al. [69] conducted a study about psychological effects and satisfaction depending on different types of surgery and found that mastectomy has negative effects on body image, self-esteem, and marital adjustment. According to a study of approximately 204 women's problems regarding breast cancer, the main problems were feeling discomfort due to changes in the body and having problems in their relationships with spouses [70]. According to a study by Sertöz et al. [71] which was conducted in Turkey with women with breast cancer, mastectomy has negative effects on body image and self-esteem but not on marital adjustment. Studies comparing different types of surgery and breast cancer reported that mastectomy has negative effects on body image [72].

Several studies have reported that women who had breast-conserving surgery continue to report fewer body image concerns compared with women who underwent more radical surgery in a longer follow-up [69, 70, 72]. Other studies, however, have found no differences between surgical groups in the years following treatment [73]. Both mastectomy and breast-conserving surgery are associated with a poorer body image, which may result in depressive symptoms. However, the type of surgery is not associated with the level of depressive symptoms [49].

With the aim of establishing the demographic, medical, and psychological factors associated with the breast cancer patient's decision-making process and of assessing their satisfaction with the type of surgery received, Noyan et al. [74] assessed patients with breast cancer who had only mastectomy and women who had mastectomy and breast reconstruction surgery. The authors reported that in both groups, women with a low income and less education were more likely to experience decision regret or low satisfaction. Moreover, patients who only underwent total mastectomy had lower self-esteem compared with reconstructive surgery patients and healthy women. According to the authors,

Turkish breast cancer patients may be more concerned with surviving the dreadful cancer diagnosis than the presentation of their feminine form and may therefore be less likely to be interested in breast reconstruction.

One important assumption derived from earlier studies is that a major contributor to psychopathology is the cancer diagnosis itself. Our clinical experience based on liaison with the breast surgery unit and research findings supports this assumption and shows that the primary factors leading to psychopathology in mastectomy patients are related more to the fears and perceptions regarding the underlying illness (cancer) and less to organ loss [1].

Similarly, findings of the thesis studies conducted at the Psychosocial Oncology Department in Istanbul University indicate that in breast cancer patients who had undergone mastectomy, the main basis for distress was the cancer itself; aesthetic concerns and the effects of cancer on the quality of life were secondary. Thus, patients require more information and psychological support regarding their illnesses. It was found that adjustment to mastectomy lasted approximately 6 months and that marital relationships became stronger after the operation. Findings regarding the effects of cancer on sexual life indicated that in addition to the negative effects of the treatment and surgery, misinformation, fear, depression, guilt, and low self-esteem were found to have a significant negative impact on sexual life [3].

The best approach to patients with breast cancer would be to consider psychosocial aspects and the concerns regarding quality of life when deciding on the type of surgery and postoperative treatment modalities. Preoperative psychological preparation and support reduce post-op medical and behavioral complications and hasten psychosocial adjustment. Psychological preparation facilitates the ability of the patient to cope with the difficulties of surgical intervention. This preparation makes it easier for the patient to accept reality and improves her cooperation. It also encourages the patient to assume responsibility and promotes a sense of being in control of her own life. Pre-op psychological preparation and support should be provided with the general knowledge and training of the surgeon. Getting the patient to express her anxieties and fears, providing emotional support and trust, improving her motivation, and promoting a fighting spirit in her are essential to enable the patient to take responsibility, to have the courage to act, and to ameliorate possible catastrophic conditions. Short-term psychotherapy, relaxation, and stress-coping techniques are among the methods used for this purpose [2].

Postmastectomy Reconstructive Surgery

Breast reconstruction is a common option for women undergoing mastectomy. Breast reconstruction can occur at the time of the mastectomy or can be delayed. Reconstruction is cited as the most commonly performed surgery because women have "the psychological desire to feel 'whole' again" and because surgeons want to "restore self-image and self-confidence and improve quality of life" [75].

As presented above, breast cancer and mastectomy experiences are perceived as threats to life, to the wholeness of the body, and to femininity. Although there is a slight increase in the number of women preferring breast reconstruction in Turkey, the number remains low compared with other western countries [74]. However, the exact percentage is unknown because the data on the rate of breast reconstruction are insufficient.

As indicated above, breast cancer and mastectomy are perceived to be as much a threat to physical integrity and to the sense of femininity as they are to life. In recent years, there has been an increase in the number of women undergoing plastic surgery and breast reconstruction. There are many studies demonstrating the favorable impacts of breast reconstruction on the mental health of women who have undergone mastectomies. This intervention plays a major role in attenuating the sense of loss experienced through surgery, and it improves women's psychological, social, and sexual functionality. It has been reported that post-op plastic and breast reconstruction surgeries improve body image [74].

However, it is difficult to show that the use of prostheses enhances a woman's sexual desire and feelings of attractiveness and sexual satisfaction. It appears that the overall emotional adjustment of women, the satisfaction that they obtain from sexual relations, and the quality of their pre-illness sexual life have a much greater impact on post-op sexual adjustment and satisfaction. Some authors have indicated that chemotherapy and radiotherapy have even greater negative effects on sexual desire [35].

Self-esteem is the sum total of the feelings a person has about herself, the importance that she places on those feelings, the judgments that she makes about herself, and how she values herself. Low self-esteem can undermine a person's body image. A person's contentment with her own body is not simply a physical phenomenon; rather, it is a reflection of her psychology.

The use of prostheses enhances a woman's feeling of wholeness and her quality of life. The positive impacts of this type of surgery are multifold:

- Enhances relationships and social interactions
- Improves body image
- Supports mental health
- Improves self-confidence
- Improves mood and satisfaction with body and social functions

Janz et al. [76] reported that body image is the poorest among women who underwent a mastectomy with reconstructive surgery. Collins et al. [77] found that at 6 months post surgery, women who had undergone reconstruction had

worse body images compared with those who only had a mastectomy; however, this difference was no longer apparent 1 year after surgery. In a study by Fobair et al. [78], women who were considering or had already undergone reconstruction had the most body image concerns during the first few months following diagnosis. As the majority of the women included in these prior studies were older than 40, it is important to consider that the divergent findings regarding the impact of reconstruction might reflect differences in body image perceptions in young women versus older women.

Our study aimed to investigate the relationship between body image and psychological problems following mastectomy and the attitudes of Turkish women toward breast reconstruction. It was found that 46.7% of the cases had high depression scores, that 20% had high anxiety scores, and that cases with high depression scores had negative body images. Additionally, 23.3% of the patients were willing to undergo breast reconstruction surgery. For these patients, the psychological effects of breast loss, such as abstention from looking in the mirror, excess mental involvement regarding breast loss, the inability to dress down near a partner, and lessened feelings of femininity and attractiveness, were found to be significant. In patients under 45 years old whose surgeries were performed <2 years prior, the desire to undergo breast reconstruction surgery was high. There were no significant differences between the two groups in terms of depression or anxiety [79].

Adjuvant Therapies

Chemotherapy

The side effects and limitations of adjuvant radiotherapy, chemotherapy, and hormone therapy add to the challenges faced by these women [3]. In general, more complex or toxic treatment regimens are predictors of depressive symptoms. Patients who receive chemotherapy have a higher risk of depressive symptoms, which are associated with the onset of premature menopause, as well as other physical adverse effects of chemotherapy. Some studies indicate that receiving hormonal therapy increases the levels of depressive symptoms, but the results are inconclusive and further research is warranted on this matter [39].

Some studies have suggested that body image may be adversely affected in women undergoing chemotherapy. This is generally attributed to alopecia, a common side effect of many chemotherapeutic regimens [76, 78]. Although chemotherapy itself was not a significant factor, other sequelae often associated with adjuvant treatment were associated with body image, including fatigue, which is consistent with findings from a recent study in which fatigue was negatively correlated with body image [80]. Similarly, weight gain is a well-documented side effect of adjuvant treatment [81]. Although Fobair et al. [78] found that concern with either weight gain or weight loss was associated with poorer body image, most studies in breast cancer survivors have focused exclusively on perceptions of weight gain, which occurs much more commonly than weight loss in this population [82].

Breast cancer treatments potentially confer additional psychiatric risk beyond the risk of depression in a patient with breast cancer. Increased levels of depression are found in perimenopausal patients and in women taking antiestrogen treatments such as tamoxifen; antiestrogens may induce a menopausal state and may contribute to increased levels of depression. Hormonal shifts related to either chemical or surgical menopause may affect mood [83].

Studies identified both age (physical factor) and trait anxiety (psychological factor) as being predictive of anxiety in female patients with breast cancer who were undergoing chemotherapy acutely (when chemotherapy was initiated), chronically (in subsequent chemotherapy infusions), or 2 years after diagnosis, in the form of needle anxiety [84].

In a recently performed systematic review, it was confirmed that anxiety is prevalent in women with breast cancer who are undergoing treatment, especially those being given chemotherapy. Specifically, women of younger age and with higher trait anxiety were more anxious during chemotherapy [57]. Healthcare professionals must thus pay greater attention to younger patients commencing chemotherapy—especially those who exhibit a more anxious personality—and initiate psychiatric help earlier, if necessary.

Central nervous system toxicity caused by chemotherapy or combination radiotherapy and chemotherapy is not fully understood. It can be observed in 3–11% of cases, depending on whether methotrexate is used. Toxic effects can be observed immediately after the treatment or in the future as cognitive and neurological disorders (changes in consciousness, leukoencephalopathy, seizures, cerebral infarction, paralysis, neuropathy, ototoxicity). The initial responses to steroids are euphoria and irritability. Some other effects are feeling good and increased appetite and weight gain, whereas insomnia, restlessness, hyperactivity, muscle weakness, fatigue, and depression can also be observed. With a sudden increase, decrease, or cessation of the steroid dose, hallucinations or delusions can sometimes be observed. Tamoxifen rarely causes depression or delusional disorder. Most chemotherapy agents can cause depression, hallucinations, or delirium [85]. Patients receiving chemotherapy frequently complain about changes in their cognitive functions. This situation can be designated as chemo brain; some examples of complaints include forgetfulness, drowsiness, and the inability to focus on daily tasks [86].

Fitch et al. [87] interviewed 32 cancer survivors (including 15 breast cancer survivors) who had started chemotherapy within the last 6 months and found that the most common cognitive changes reported were problems with memory,

comprehension, and concentration. More recently, Myers [88] interviewed 18 breast cancer survivors who were 6–12 months post-chemotherapy and found that most women reported problems with short-term memory, focusing, word finding, reading, and driving. As part of a larger symptom management survey, Boykoff et al. [89] interviewed breast cancer survivors who were at least 1 year posttreatment and identified cognitive impairment as a side effect of their treatment. Problems with memory, reading, comprehension, and processing speed were described. Cognitive changes in this study were also associated with significant negative outcomes such as decreased quality of life and ability to work.

Cognitive dysfunction in cancer patients is multifactorial and occurs as a result of the interaction between the cancer, the individual (host) factors such as genetic susceptibility and immune reactivity, and the effect of specific treatments. In addition, the real-life impact of cognitive dysfunction on cancer patients is dependent on their pre-illness level of function, the type of work they do, their developmental stage of life (e.g., working parents with small children vs. retired persons), and their overall ability to manage and cope with changing life circumstances [90].

Radiotherapy

A recent study evaluated changes in depressive symptoms from the initiation of radiotherapy (RT) and for 6 months thereafter and investigated whether specific demographic, clinical, symptomatic, and psychological adjustment characteristics predicted the initial levels and trajectories of depressive symptoms. Approximately one-fourth of patients had clinically meaningful levels of depressive symptoms prior to RT, but the trajectory of depressive symptoms improved over time. Women who had less education, children living at home, a higher level of sleep disturbance, worry about disease outcome, less meaning in life, and less support from family and friends had higher levels of depressive symptoms prior to RT [50].

Consistent with previous research [91, 92], women with breast cancer experience higher levels of depressive symptoms prior to and during RT, and these symptoms then decline following the completion of RT. In a recent review, Stiegelis and colleagues [93] summarized findings from several studies that investigated psychological functioning in cancer patients who received RT. Although the results are inconsistent, depressive symptoms were more common during and at the completion of RT than in the period prior to treatment. In addition, psychological functioning improved following the completion of RT.

Previous longitudinal studies were identified that specifically evaluated depressive symptoms in breast cancer patients who underwent RT [91, 92]. Consistent with the review mentioned above, these studies reported higher levels of depressive symptoms during and immediately after RT, followed by a decrease over time. In addition to understanding the trajectories of depressive symptoms during and after RT, it is important to determine patient characteristics associated with higher levels of depressive symptoms. In addition, younger women with breast cancer often require adjuvant treatment, which results in premature menopause and alterations in sexual functioning [15].

Despite the identification of several risk factors, it is difficult to identify a set of predictors that are consistently linked with depressive symptoms in breast cancer patients because of the predictors' potential associations with specific factors such as the treatment type. Most studies that aim to identify predictors of depressive symptoms are cross-sectional and examine different populations of breast cancer patients [94]. Among the studies of depressive symptoms in breast cancer patients receiving RT [92], several predictors associated with demographic, clinical, and treatment characteristics were evaluated. Except for one study [91] in which fatigue was assessed, none of these studies evaluated the impact of physical symptoms on depressive symptoms. In addition, none of these studies examined the impact of physical functioning (e.g., comorbidities and performance status) on patients' levels of depressive symptoms.

Effects on Body Image

Body image is conceptualized as a multifaceted construct, defined as the mental representation of one's body; thoughts and feelings about one's physical appearance, attractiveness, and competence; and one's perceived state of overall health, wholeness, functioning, and sexuality. Body image is a dynamic interaction between this personal expression of being and the social world [95]. One of the most difficult and often persistent challenges facing breast cancer survivors is coping with the various changes to their physical appearance and function resulting from treatment. Side effects from surgery, chemotherapy, and radiotherapy can be significantly disfiguring, including deformation and/or loss of the breast(s), visible scarring, skin changes due to radiotherapy, hair loss due to chemotherapy, and lymphedema. The universal experience of breast cancer survivors is one of profound loss of their body's physical integrity and function, perceived femininity, self-esteem, and confidence [78]. These considerable physical and physiological alterations can dramatically affect a woman's body image. For many breast cancer survivors, dissatisfaction with one's "new" body has detrimental influences on many psychosocial domains. Body image disturbance following treatment has been consistently associated with mental distress, anxiety, reduced physical health, sexual dysfunction, and impaired quality of life [96].

Body image is an important component of a cancer patient's quality of life and plays an important role in adjustment to the

disease. Women with better body image perceptions had higher levels of self-confidence in coping with breast cancer [97]. On the other hand, poorer body image is associated with poorer self-rated health, chronic fatigue, mental distress, and poorer generic and disease-related quality of life [96]. Therefore, body image is an important component of the quality-of-life assessment, but a review of the literature revealed the lack of a suitable scale to measure body image in cancer patients, particularly in the clinical trial setting.

Satisfaction with the body is not only a physical concept but also a psychological experience. In mastectomy applications, body image is one of the important components of the experienced distress and requirement for further adjustment. The formation of body image is a process that starts in infancy and develops throughout life. Self-esteem, however, is the sum of perceptions of how one feels about herself and about values attributed to the self. Body image is one of the main factors of general self-esteem and personality development. The process of body image development is not only related to the general appearance of one's body but also shaped by cognitive functions and environmental messages. Body image involves a sense of wholeness and functionality. Women who consider body image to be a major part of their sense of self-worth, attractiveness, or wholeness are clearly at an increased risk of poor psychosocial adjustment following breast cancer surgery [3].

The lack of change with regard to body image must be considered and compared with studies that have demonstrated improved body image over time, especially in women who have undergone mastectomy, likely due to increased skills in coping with body image impairment. Women with breast reconstruction (BR) and breast-conserving surgery (BCS) scored no differently on the body concern domain of body image. However, women undergoing BR had a significantly worse score on the body stigma domain of body image than women receiving BCS. Women with BR had a better body image score than women who underwent mastectomy. Women who are satisfied with their body shape may still perceive deficiencies because of the stigma of mastectomy and its effect on body image [98].

Effects on Sexuality

Breast cancer patients also often receive chemotherapy, radiotherapy, hormone therapy, or a combination of these treatments. All of the treatments have varying impacts on sexual functioning [70]. Surgery can impact a patient's body image, which may in turn affect sexual functioning. Women receiving breast-conserving surgery or reconstruction report greater satisfaction with their sex lives compared with women receiving mastectomy [99].

Poor adjustment was related to unsatisfactory or unfavorable sexual experiences, a strong emotional attachment to breasts, body image problems, and difficulty in discussing personal problems. Some women who place great importance on their bodies may not be able to tolerate even the idea of damage to or loss of their breast. The risk of these women having problems in adjustment after treatment is also high. Adjustment also depends on the responses of significant others such as spouses or partners, family, and friends [35].

A sizable proportion of women describe mastectomy as a mutilating and disfiguring experience. Approximately one-fourth of these women describe negative effects on sexual adjustment, including a decreased frequency of intercourse, decreased sexual satisfaction, and more difficulty in achieving an orgasm. Research suggests that although sexual issues may not be a patient's main concerns during treatment, they are still important issues. Although any cancer diagnosis can cause sexual problems, breast cancer is a unique case in that the breast, although not directly a sex organ, is observed as a symbol of femininity and plays a role in pleasure and stimulation. Female sexual functioning disorders can be classified into the following categories: sexual desire, sexual arousal, and orgasmic and sexual pain. Avoidance and noncommunication in sexual relationships were the most frequent sexual dysfunctions observed among breast cancer survivors. Sexual problems can be difficult to diagnose. Many women experience sexual problems as a result of a breast cancer diagnosis and its treatment. They can only be identified if sexual functioning is reported using a patient-reported outcome questionnaire [100].

Fatigue, nausea, and alopecia (i.e., hair loss), side effects from chemotherapy and other agents, are often related to reduced sexual desire [101]. Emotionally, a cancer diagnosis can affect sexuality through associated stress, anxiety, depression, body image changes due to surgical scars or damage to sexual organs or other body parts, and feelings of loss of femininity that can arise due to hormonal therapies. In the interpersonal or social realm, changes in a couple's relationship from equal partners to a patient/caregiver relationship create threats to established sexual roles and sexual interest. Moreover, many couples who avoid sexual activity during treatment may find it more challenging to resume sex once the treatment is completed. Although the whole range of cancer types can impact sexuality, breast cancer has a number of unique consequences because of the status of the breast as a signifier of feminine sexuality and its role as a source of erotic pleasure and stimulation. This suggests that clinicians should be particularly sensitive to the consequences of breast cancer for women's sexuality and body image and to the consequences for the women's partners [102].

Quality of Life

Breast cancer thus profoundly disrupts women's emotional equilibrium and quality of life. Health-related quality of life represents the functional effects of an illness and its treatment on the patients and is thus an important indicator of the psychosocial and psychological burden of the illness.

Improvement in the early detection and treatment of breast cancer has led to longer survival of these patients. Breast cancer also affects women's identities; therefore, studying quality of life in women who lose their breasts is vital. In addition, it is believed that women play an important role in families. When a woman develops breast cancer, all of her family members may develop some sort of illness. Thus, the issue of "survivorship" has now become an important topic in breast cancer care that demands the investigation of the long-term effects of a breast cancer diagnosis and its treatment. The time of diagnosis, the initial stages of an adjuvant treatment course, and the months immediately following the end of adjuvant treatment are transition times associated with poor adjustment and decreased quality of life in breast cancer patients [103]. Studies have shown that decreased health-related quality of life as a result of chemotherapy side effects may predict early treatment discontinuation in patients with breast cancer [104]. However, studies on the posttreatment adjustment of breast cancer survivors demonstrated that breast cancer patients might experience a good quality of life [105].

The major concerns were fatigue, aches and pains, sleep problems, psychological distress from cancer diagnosis and treatment, fear of recurrence, family distress, sexuality issues, family burden, and uncertainty, all of which had a negative impact on overall QoL [106]. Helgeson et al. [107] indicated difficulties in physical functioning in disease-free breast cancer survivors. The results showed that they had a high incidence of symptoms related to depression and trait anxiety, resulting in lower QoL. Certain demographic variables, including being of older age at cancer diagnosis, a longer time lapse since diagnosis, being ethnically non-Hispanic white, being more educated, and being employed, predicted lower psychosocial distress. The younger age at diagnosis group showed poorer outcomes in the social aspect, with major concerns regarding changes in self-esteem and appearance. Women who received adjuvant systemic therapy had poorer QoL outcomes in the physical, psychosocial, and sexual aspects compared with women who did not receive systemic adjuvant therapy. Women who had a mastectomy reported more physical concerns compared with women who had breast-conserving therapy. Moreover, the presence of breast-related symptoms such as pain, swelling, and numbness resulted in poor QoL [106].

A study conducted by Uzun et al. [108] that included a sample with a significant proportion of Turkish women examined the quality of life of Turkish women with breast cancer. The findings showed that the educational level, employment status, and degree of pain affected the quality of life to varying degrees. According to the authors, these findings have many implications. The authors stated that patient education should focus on factors that affect quality of life and that supportive interventions should be adapted to the needs of illiterate and literate unemployed surgical patients.

A number of studies have investigated improvements in the psychological status, the QoL following the completion of treatment [105], or the QoL among long-term breast cancer survivors. Some studies have reported certain restrictions in the QoL not only by patients in the first 2 years after initial treatment but also by patients with a survival time longer than 5 years at follow-up [109], whereas gradual improvements in well-being have been observed 5 years after diagnosis. It has been argued that most aspects of health-related QoL during breast cancer treatment or its residual effects vary depending on the type of cancer treatment. However, other studies have indicated that the cognitive variables had a more significant effect on QoL and distress than the type of cancer treatment [110]. Although it was assumed that symptom distress was inversely related to QoL, a previous study performed among a Spanish-speaking population found a significant negative effect of psychological distress on the QoL [111]. Several minor studies have specifically concentrated on longitudinal analysis of the QoL over the illness continuum, whereas other studies have shown that psychological distress impaired the QoL over a 6-month treatment period [112]. Psychological adjustment was a significant predictor of better QoL 1 year after the initial diagnosis of breast cancer [113].

Some studies have described long-term impairment of QoL, impaired functioning, and continuing symptoms, as well as a high percentage of distress in breast cancer survivors [114], whereas others have reported an improving QoL over time [115]. Arndt et al. [114] compared breast cancer patients with reference data from the general population. Three years after diagnosis, breast cancer patients had poorer role functioning and poorer emotional, cognitive, and social functioning, as well as more symptoms of insomnia, fatigue, and dyspnea, especially at younger ages.

We found that patients' physical, psychological, social relationships, general quality of life, and perceived health quality of life decrease to the greatest extent immediately after the operation, whereas the scores of other parts, except the social relationship part, increase later after the operation. However, we reported that the first-year scores were lower compared with the pre-operation scores and that patients were under psychological risk beginning at the time of diagnosis [40]. Schou et al. [116] claimed that breast cancer patients' emotional, cognitive, and social functioning is affected beginning at the time of diagnosis and that their cognitive and social functioning slowly recovers.

The impact of breast cancer diagnosis and its treatment on the quality of life of women with breast cancer was examined longitudinally. Although there were deteriorations in patients' scores for body image and sexual functioning, there were significant improvements for breast symptoms, systematic therapy side effects, and patients' future perspectives. The findings suggest that overall, breast cancer patients perceived benefits from their cancer treatment in the long term. However, patients reported problems with global quality of life, pain, arm symptoms, and body image even 18 months following their treatments. In addition, most of the functional scores did not improve. The results showed that physical functioning was improved 1 year after the completion of breast cancer treatment and later [117]. In our study, patients reported poor social functioning following the completion of breast cancer treatment. Similarly, studies have found that breast cancer survivors suffer from poor social functioning [116].

A 5-year prospective study showed that with the exceptions of body image, sexual functioning, and deterioration in the patient's way of life, the other areas improve over time (within the first 2 years), and there are no fundamental changes observed in the quality-of-life scores in the second, third, and fourth years [72].

Hartl [118] investigated changes in the quality of life (QoL) and body image among breast cancer patients over 2 years and different predictive factors for the QoL 2 years after the primary operation. The overall QoL and most of the functional and symptom scales improved during the 2-year period. The greatest changes in health-related QoL, functioning, and symptoms were observed during the first 6 months. However, cognitive functioning, body image, and the three symptom scales of insomnia, constipation, and diarrhea did not change during the follow-up period. At the time of diagnosis and primary surgery, being confronted with breast cancer as a life-threatening disease has a negative impact on well-being and the QoL. Because most patients are likely to have recovered from the shock of diagnosis, surgery, and hospitalization after 6 months and will have completed radiotherapy and cytotoxic therapy, an improvement in their QoL would be expected. Interestingly, after 12, 18, and 24 months, there were only minor changes in the QoL. The lack of change in cognitive functioning, which is in line with previous studies [116], has been under discussion as a long-lasting neuropsychological effect of chemotherapy.

According to some studies monitoring breast cancer patients' quality of life at different times [72, 115, 118], many aspects of quality of life recover; however, other studies [114] reported that these aspects do not recover in the long term. Studies about this subject generally include the postsurgical treatment period; few studies have evaluated patients' quality of life before the diagnosis.

Risk factors of depression such as fatigue, a past history or recent episode of depression after the onset of breast cancer, and cognitive attitudes of helplessness/hopelessness and resignation might impair the quality of life [49]. During breast cancer diagnosis, the quality of information delivered by doctors and communication about disease concerns and feelings are two important parameters to preserve the quality of life. Many studies have clearly demonstrated that depression and its associated symptoms, such as dysphoria, decrease the quality of life, affect compliance with medical therapies, and reduce survival. This decrease occurs because depression affects interpersonal relationships, occupational performance, stress, and perceptions of health and physical symptoms. Therefore, depression impacts patients' overall quality of life [33, 48]. Two studies [113, 119] found that depression is correlated with lower quality of life. Weitzner et al. [119] studied 60 long-term stage I–III breast cancer survivors (disease-free for 5 years) versus 93 low-risk breast cancer screening patients. In both groups, increased depression is correlated with lower quality of life functioning, except for family functioning.

The quality of life among the breast cancer population requires assessment and subsequent treatment of mood disorders. In a population of 691 older women (>65 years old) with breast cancer, Ganz et al. [113] assessed psychosocial adjustment 15 months after surgery. They showed a decline in mental health scores of the MHI-5 (Mental Health Inventory) and noticed that physical, emotional, and social dimensions impact their quality of life but that cancer-specific psychosocial quality of life improved over time (15 months). The quality of life can be impaired by a number of stressful life events, body image problems, problems with sexual intercourse, financial problems, anxious preoccupations, and, of course, depression. The burden of depression, which has a negative impact, influences the severity and the number of side effects from medical treatment (surgery, chemotherapy, radiotherapy, hormonal therapy) by increasing digestive inconveniences (nausea) and the sense of fatigue and by decreasing cognitive function (difficulty concentrating), all of which can lower the quality of life. However, medical variables such as the tumor stage or sociodemographic data (education, marital status), with the exception of younger age, do not have an adverse impact on the quality of life [120]. Breast cancer treatment can be traumatic for women who can subsequently develop different patterns of depression that might worsen the quality of life [121].

The quality of life and psychological distress during breast cancer treatment were assessed in a longitudinal study. Anxiety symptoms are prevalent at the time of diagnosis, at the beginning of treatment, and in the middle of treatment, whereas women did not report elevated levels of anxiety at the end of treatment. Psychosocial factors were consistently related to the QoL. The women suffering from probable significant distress can be considered as having high anxiety at pretreatment and during treatment, independently of the treatment combination type. This increase in distress could be explained by the uncertainty and fears that patients have during the first stage of cancer treatment. Longitudinal stud-

ies can greatly aid in our understanding of the treatment's impact on the patient's quality of life because occasional changes could be identified. Psychosocial adjustment to breast cancer was dependent on the distinct stages of the illness. The efforts to detect a patient's psychological distress at the early stage of treatment may be the key factor to improve their QoL [8].

A study examined coping strategies over time and the reciprocal relationship between coping strategies and the QoL among younger women with breast cancer within 6 months of diagnosis. Positive cognitive restructuring was the most frequently used strategy. Over time, seeking social support, spirituality, and wishful thinking declined, whereas detachment increased. Prior QoL predicted three subsequent coping strategies (seeking social support, keeping feelings to self, wishful thinking). Coping strategies were minimally associated with the subsequent QoL. Coping strategies and the QoL are dynamic processes. The QoL may predict coping strategies as well as or more than vice versa [13]. Numerous studies have shown a relationship between coping strategies and the QoL among women with breast cancer [23, 120, 121]. Better QoL was associated with the use of more active coping strategies [18, 23, 120, 121]. Despite the unique issues and difficulties experienced by younger women with breast cancer, their coping strategies do not appear to differ from those of the group of all female breast cancer patients [23, 24]. In fact, two studies have shown that coping strategies play a more important role than medical or treatment factors in predicting the QoL [120, 121]. Previous cross-sectional findings suggest that women with breast cancer who use strategies such as positive cognitive restructuring (also known as positive reappraisal), acceptance, emotional processing, or emotional expression have better QoL than those who use more passive coping strategies such as avoidance or minimizing the importance of their cancer [18, 23, 120, 121]. Longitudinal studies have shown similar results. In a short-term 4-month longitudinal study of women with breast cancer, the use of avoidant coping strategies was associated with poorer QoL concurrently but not prospectively [23]. Another study of women with breast cancer found that high use of acceptance within 5 months of treatment was related to better QoL 3 months later. This study also found that emotionally expressive coping was associated with improved QoL, but only for those women who perceived their social context as being highly receptive to their discussion of cancer [122].

Breast Cancer Survivorship

Although the incidence of the most commonly diagnosed cancer in women is on the rise worldwide, breast cancer mortality rates have been stable or have decreased over the past 25 years. Better breast screening procedures have led to the earlier detection of breast cancer, and advances in treatment have also reduced mortality. Europe has geographical variation regarding countries' performance in managing cancer. These differences might be related to the evolving organization of healthcare systems and cultures. Breast cancer is one of the most prevalent tumors in women but also constitutes the largest group of cancer survivors [15]. Despite the increasing 5-year survival rate, survivors remain at high risk for developing psychological problems [123].

We found that the most common symptoms affecting breast cancer survivors were fatigue, insomnia, depression, cognitive dysfunction, reproductive and menopausal symptoms, and lymphedema. Some of these symptoms have even been the objective of randomized controlled trials, but consistent data are missing [124].

Depression substantially impairs the QoL and is associated with poorer adherence to medical regimens. Furthermore, depression may be associated with the progression of cancer or with decreased survival [123]. Dalton et al. [125] have observed an elevated risk of first hospitalization for depression for up to 10 years after breast cancer diagnosis. Furthermore, breast cancer survivors may still experience some specific problems such as lymphedema and sexual dysfunction [101].

The psychological and social problems for cancer survivors include depression, anxiety, distress, fear of recurrence, and impacts on social support/function, family and relationships, and the quality of life. A substantial minority of people surviving cancer experience depression, anxiety, distress, or fear associated with recurrence or follow-up. Receiving treatment for the disease, self-monitoring the symptoms and signs of the disease, attending control appointments, and awaiting laboratory results led people to repeatedly experience the same emotions, including fear and uncertainty. There is some indication that social support is positively associated with better outcomes. The quality of life for cancer survivors appears generally good for most people, but an important minority experiences a reduction in the quality of life, especially those with more advanced disease and reduced social and economic resources. The majority of research knowledge is based on women with breast cancer [126].

One psychosocial factor that is believed to influence body image is the gender role socialization of "standards" regarding physical appearance and behavior. Direct and indirect communications from various influential sources (media, family, and friends/peers) indoctrinate and more importantly, reinforce present-day cultural normative ideals of attractiveness and the roles that women are encouraged to adopt to gain societal approval. Research has shown that an important influential factor is not the bombardment of media messages per se but rather the extent that an individual internalizes the societal ideals, which then become part of one's self-concept [127]. The impact of gender role socialization on body image disturbances in breast cancer survivors, particularly with

respect to adjusting and integrating a "new" body and to changed self-identity and role functioning, has yet to be elucidated.

Women with breast cancer who were more invested in their physical appearance exhibited greater difficulty adjusting after treatment and reported more body dissatisfaction and poorer mental health than those who were less invested [128].

Findings indicate that survivors who demonstrated greater internalization of gender role beliefs, engaged in greater self-surveillance, and reported greater levels of body shame showed greater body image disturbance post treatment. Greater body image disturbance was also significantly associated with poorer quality of life. Increasing awareness of cultural forces shaping gender role expectations and behaviors may be an important element in psychosocial interventions for breast cancer. Psychosocial interventions that help women redefine personal standards of beauty, femininity, and role functioning that are realistic, achievable, and less focused on societal expectations might facilitate flexibility in perceptions and diminish potential negative self-evaluation after treatment, thus promoting adjustment and survivor well-being [95].

The majority of studies show a significant relationship between psychosocial factors and survival, but the actual psychosocial variables related to survival are not consistently measured across studies, and the associations of many of the psychosocial variables with survival/recurrence are not consistent across studies. In particular, more research is likely warranted regarding the role of social support, marriage, minimizing, denial, depression, and emotional constraint on breast cancer survival. Adequately powered multicenter studies using valid assessment tools and meta-analytical approaches may be necessary to show the potential roles of various psychosocial factors in breast cancer outcomes.

Posttraumatic Growth

The adjustment to cancer is not always negative. A healthy adjustment without psychological morbidity may combine with an active psychosocial process to facilitate personal growth [8].

Regarding the effect of cancer on the perception of life, Öner et al. [129] reported optimistic findings. In the study, 80% of the cases reported that cancer had a great impact on their lives, and 48% evaluated the impact as a positive, life-enhancing experience. Patients reported that experiencing cancer has been a power forcing them to see their lives more positively, giving them a chance to restructure their lives and to change their perspective toward people and the world.

The authors reviewed 24 studies published from 1990 to 2010 that measured posttraumatic stress disorder and posttraumatic growth in women with breast cancer in terms of frequency rates, factors associated with posttraumatic stress disorder and posttraumatic growth, and their interrelationships. A relatively small percentage of women experienced posttraumatic stress disorder, whereas the majority reported posttraumatic growth. Age, education, economic status, subjective appraisal of the threat of the disease, treatment, support from significant others, and positive coping strategies were among the most frequently reported factors associated with these phenomena [130].

Breast cancer, due to its severity and traumatic nature, can shatter the patient's core assumptions about the world, and in struggling to rebuild them, he or she may experience positive changes within five aspects (personal strength, new possibilities, relating to others, appreciation of life, and spiritual changes), which constitute PTG [131]. Thus, breast cancer may also be a cathartic and transformative experience for the individual. Clearly, PTG and PTSD represent two different outcomes of the breast cancer experience that have some common parameters, indicating that a relationship exists between them. First, both PTG and PTSD proportionally increase to the level of the perceived threat from the experience. Second, both result from the cognitive struggle of the individual to reconcile the shock from breast cancer diagnosis and treatment with core beliefs about life, justice, and the world. Furthermore, both depend on time passing; according to the stress evaporation theory [132], PTSD diminishes over time, whereas Tedeschi and Calhoun [131] have stated that PTG appears in the weeks, months, or years after trauma. Finally, both PTG and PTSD are connected to social support. According to the social cognitive processing model [133], the existence of an unsupportive social network raises the likelihood of PTSD and simultaneously does not allow growth to occur.

Regardless of their design, studies have concluded that a majority of patients with breast cancer experienced PTG after their diagnosis. For example, in the study by Sears et al. [134], 83% of breast cancer survivors experienced positive changes after their disease, whereas Weiss [135] found that 98% of patients reported PTG.

In 2008, a thesis was conducted at our department and was titled "Post traumatic growth in cancer patients and related factors." The main aim of this study was to address positive transformations that occur after the diagnosis and the experience of cancer in a set period of time. Half of the patients were breast cancer patients. Sociodemographic and illness-related factors and the impact of coping and illness perceptions on posttraumatic growth were evaluated. The results showed that cancer patients in this sample have higher posttraumatic growth levels compared with the mean. The time since diagnosis and the sufficiency of information regarding the illness and treatment variables are correlated with posttraumatic growth. The results for posttraumatic growth and coping revealed a relationship between posttraumatic growth

and confrontive coping, self-controlling, accepting responsibility, escape-avoidance, intentional problem solving, positive reappraisal, and seeking social support. The ways of coping and perceptions of illness were important variables affecting posttraumatic growth.

Parry and Chesler [136] intended to explain the possible positive psychosocial consequences of cancer such as development in their qualitative study. The results showed that coping processes and creating meaning and spiritual-moral development are especially associated with long-term psychosocial well-being.

Principles of Medical Psychotherapy

Psychological treatment undertakings in cancer are systematic efforts that are intended to develop behaviors to cope with cancer via consultancy, training, or psychotherapeutic methods. The main goal of these efforts is to raise morale, increase self-confidence and coping abilities, and decrease distress and mental problems. The principal targets in these undertakings are developing the individual's sense of control as she struggles with a disease; enabling her to bring practical solutions to the problems she faces; ensuring that her emotions and reactions such as anger, rage, and guilt are freely expressed; encouraging her to voice her thoughts about the disease; improving her quality of life by providing psychological and social adaptation; and strengthening her interactions with her family and with others [2].

General Approaches in Psychotherapy

It is essential to encourage the patient to express her feelings about the disease; to support the patient and provide her with security regarding the disease; to reveal the factors that affect her responses by discovering connections between her past and current states; to shed light on emotions, behaviors, and defenses by psychodynamic methods; to examine methods for coping with the uncertainty of the future and existence; and to inquire about sources of distress outside of the disease. Furthermore, investigating the effect of the disease on the family members might encourage the sharing of emotions by bringing the patient and her family together.

A therapist who works in this field must prioritize knowing the medical condition of the patient, evaluating the progression of the disease, and explaining the complications and side effects regarding the medical condition and its treatment to the patient. Understanding psychological problems begins with comprehending how the patient perceives her condition and disease. It is essential to inform the patient without causing her to lose hope, to ensure that she goes through a realistic acceptance process, to explain the treatment possibilities and options to her, and to correct her wrong attitudes and knowledge. The possible catastrophic interpretations that a patient may have must be rectified. The therapist must examine the psychological dynamics of the patient, interpret her defense mechanisms, and aid her in developing more effective positive defense mechanisms. The therapist must also encourage the patient to express her normal psychological and emotional reactions. During periods in which feelings of anxiety and desperation are at their highest, the therapist should apply crisis intervention treatment. It would also help to discuss the patient's current daily problems and to evaluate sources of anxiety regarding family, work, and social environment. In patients who are going through the terminal period, the main subjective experiences of these patients must be discussed, and the focus points in their lives must be addressed during therapy. Bringing together patients who have similar diseases and problems would doubtlessly help the patients to develop empathy. The state of being in a group decreases the feeling of loneliness and facilitates the development of positive defense mechanisms [2].

Psychological Treatment

After the patient has been evaluated, interventions that are in accordance with the aims specified below are planned and applied. The aims of psychological treatment can be summarized as follows:

- Correcting and decreasing psychic morbidity
- Decreasing psychological pain
- Improving the quality of life by providing the patient with psychological and social adaptations
- Resolving psychiatric symptoms such as anxiety, depression, and catastrophic reactions
- Enhancing the fighting spirit and will to live and strengthening the mental-behavioral adaptation to cancer
- Developing and increasing the patient's feeling that she has control over her disease and life and ensuring active participation of the patient in the cancer treatment
- Ensuring that the patient can cope with physical and psychological problems regarding cancer, helping the patient develop effective methods and approaches
- Encouraging the patient to freely express emotions and reactions such as rage, anger, and guilt and to voice her thoughts on the disease
- Enhancing communication between the patient and her family and enhancing other elements of social interaction
- Examining the ways of coping with the uncertainty regarding the future and existence

The interpretations, perceptions, and evaluations of the patient as an individual are crucial elements in her emotional

and behavioral reactions. When the cancer is perceived as a loss of physical strength, role, expectations, and future, the patient will have a depressive reaction. When it is perceived as a threat to life, independence, and autonomy, anxiety and panic disorders are more prevalent. If the patient perceives her disease as an injustice and a consequence of other people's faults, anger and rage come to the forefront. From a medical perspective, the disease is a biomedical and pathophysiological fact. However, for the patient, it goes beyond that and becomes a (bio)psychosocial condition with mental, familial, social, and psychosexual meaning and significance.

The psychiatrist must be in close contact with the specialist who treats the patient to facilitate information exchange and cooperation. We can summarize the methods pertaining to the constituents of this treatment process as follows:

- Biopsychosocial formulation
- Reduction and treatment of symptoms
- Free expression of emotions
- Identification of problem areas
- Examination of perceptual scope
- Examination of wrong, negative, and automatic thoughts, attitudes, views, and interpretations within the perceptual scope
- Informing the patient
- Correction of the cognitive style that causes adjustment disorders and emotional reactions
- Ensuring natural, daily maintenance of life
- Examination of automatic thoughts and cognitive coping methods and reconstruction of perceptual style
- Conducting appropriate and indicated behavior techniques
- Ensuring family communication
- Encouraging new areas of interest and investment
- Improving the quality of life [1, 2]

To care for breast cancer patients with depressive disorders, pharmacological treatment must be combined with psychosocial interventions. Psychosocial interventions improve the well-being of cancer patients by decreasing emotional distress and depression in women diagnosed with breast cancer but do not necessarily impact survival [137]. Many psychotherapeutic interventions for this particular population can be implemented such as individual psychosocial support, adjuvant psychological therapy, cancer support groups, online support for adjuvant psychological treatment, and cognitive-behavioral stress management intervention. All of these psychosocial interventions can be used to treat depression and can also improve the range of coping strategies and, therefore, the quality of life.

Conclusion

A biopsychosocial approach and integrated treatment for cancer patients is very important. A multidisciplinary team and interdisciplinary approach is required for the optimal care of breast cancer patients. The periods of diagnosis, treatment, and recurrence of breast cancer represent a high burden and are highly distressful for the patients. Psychological distress and depression affect the quality of life of the patients, the progression of the disease, and the response to treatment. Thus, the management of distress is one of the vital issues in survivorship.

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Breast Cancer-Related Lymphedema

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Atilla Soran, Ayfer Kamali Polat, and Lisa Groen Mager

Description, Incidence, and Stages of LE

The lymphatic vessels travel parallel to the veins. The lymphatic circulation consists of superficial and deep vessels, which drain the skin and the skeletal muscle. Small superficial lymph vessels are lymph capillaries, which lie nearby blood capillaries in the interstitial space. These lymphatic capillaries form larger vessels called pre-collectors and collectors, which have one-way valves that prevent the backflow of lymph. The lymphatic system has its own circulation of fluid and cells (mainly lymphocytes) from the blood stream, through the interstitial spaces, through the lymph vessels and nodes, and back to the blood stream. The lymphatic system has no single pump; fluid is forwarded via contraction of smooth muscle in the walls of the lymph vessels. Then lymphatic fluid then drains into the lymph nodes, which function as a filtering system. Lymph nodes have an outer fibrous capsule and inner collection of immunologically active cells. Foreign substances like bacteria and toxins are filtered and destroyed in the nodes. The lymph vessels finally open into large ducts—the thoracic duct and right lymphatic duct—and then drain into neck veins [1–4].

The lymphatic system interacts with other circulatory and immune systems in the body. This collective circulation of the lymphatic system is responsible for transporting immune chemicals and cells. For monitoring the body for any cell or substance (microorganisms or toxins, mutated or cancerous cells) that is recognized as foreign by immunosurveillance. This interaction is the main reason people with lymphatic system impairment, such as LE, are predisposed to infection. Additionally, fats and fat-soluble vitamins are absorbed from the digestive system via the lymphatic system and transported to the venous circulation. The lymphatic system also helps maintain fluid balance within the body and macromolecular homeostasis.

LE is blockage of the lymphatic fluid circulation and causes swelling of a part of the body. LE may occur if there is an interruption of the lymphatic system or of failure of normal capillary-lymph exchange. These interruptions of the lymphedema system can occur in instances such as surgery after breast cancer, parasites, bacterial infection, cancer or fibrotic tissue growth after radiation therapy. Accumulation of lymph fluid containing protein and cell debris causes swelling in the affected area of the body. LE is multifactorial and has been described as one of the most significant survivorship problems after breast cancer treatment, causing functional and psychological issues. Women are restricted in their daily productive life activities—their job, housework and hobbies such as gardening and knitting. The debilitating pain, anguish, suffering, and disfiguring swelling of LE can cause physical and emotional distress. Women who develop LE face a lifetime of treatment [2–5]. BCRL symptoms can develop any time after breast cancer treatment. However, BCRL is commonly seen within the first 3 years following the surgical procedure. Initially, lymphedema often may be asymptomatic. Unfortunately, lymphedema is chronic, progressive, and advances slowly. Chronic inflammation, infection, and fibrosis of the skin result in further lymph vessel damage and progression to more severe stages of edema. Minor physical traumas, including cuts, burns, tight jewelry or other injuries to the fingers or hands, may transform a latent condition into active LE requiring treatment [3]. Initial symptoms may be reversible, but over time, LE becomes irreversible and adversely impacts survivors' quality of life. Early detection allows intervention to prevent progression of LE to the more severe stages. Progressive LE is complicated by recurrent infections, non-healing wounds, discomfort or pain, difficulty with daily tasks, and emotional and social distress.

Breast cancer survivors have significant physical, functional, quality-of-life, and economic consequences. In a prospective cohort study, Cormier et al. assessed limb volume

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change (LVC) and quality of life in breast cancer survivors and found that even a small increase in volume was associated with a significant decrease in quality of life [2].

Although it has largely been neglected by healthcare professionals, recently, there have been great improvements in the awareness, clinical diagnosis, and management of BCRL [4–7].

Clinical Definitions of LE

Typically, patients report heaviness or swelling sometime in the past year. The diagnostic criteria for definition of BCRL are based on limb volumes measured in different ways: greater than or equal to 200 mL volume increase as detected by water displacement, volume difference greater than 3% between limbs, or 2 cm in circumferential measurement.

The consensus of the Clinical Resource Efficiency Support Team (CREST) LE group is that a 5% or greater increase in circumferential measurement should be a reference to LE. It is recommended that limbs be measured prior to surgery, radiotherapy, or other possible risks of LE. Measurement changes from the baseline or between limbs may be used to detect LE [6].

Staging of LE

The *International Society of Lymphology* (ISL) has established a staging system for identifying the severity and progression of BCRL. This staging system is based on the amount of swelling and the condition of the skin and tissues at each stage. The system also allows identification of the progression and success of treatments. Currently, there are four stages in the ISL LE staging system [7].

Stage 0 LE (latent or preclinical)
At this stage, there is no apparent swelling or visible evidence of impaired lymph transport. Non-pitting edema may exist and patients may report "heaviness." Although the patient in Stage 0 is at risk of LE, appearance of more severe signs of LE may take months or years. Slower flow may be detected by lymphoscintigraphy. It is also detectable with bioimpedance spectroscopy or perometry, and it is possible to identify changes in the at-risk limb before they become visible. When changes develop, if specialized treatment is started immediately, it may be possible to prevent the development of further stages of LE.

Stage 1 LE (spontaneously reversible, acute phase)
An extracellular accumulation of fluid with high protein content is present at Stage 1 LE. There is visible mild swelling consisting of protein-rich lymph. Volume increase is not more than 20%. Edema is reversible and can be temporarily reduced with elevation of the limb. The swelling makes tissues soft and doughy. Mild pitting edema is present. There is little or no tissue fibrosis. Stage 1 LE is detectable with all techniques. Lymph flow as detected by lymphoscintigraphy is slow and shows initial dermal backflow. Diagnosis can be made by classical measurement techniques. As soon as LE signs are detected, effective treatment should begin. At this stage, LE can often be controlled by prompt treatment so that the condition does not become more severe.

Stage 2 LE (spontaneously irreversible, chronic phase)
Swelling is remarkable and irreversible at Stage 2 LE. Swelling is mild to moderate; volume increase is 20–40%. Excess accumulation of extracellular fluid is seen. There is no reduction of swelling by elevation of the limb. Changes in the tissues are mostly due to *fibrosis,* the formation of fine scar-like structures within the tissues that make the tissues harder. The extracellular fluid compartment is expanded. Thickening of the soft tissues continues progressively. A slight indentation is seen with pressure and pitting becomes more difficult (non-pitting). There is minimal or no decrease with elevation. This stage is too late for prevention; lifelong physiotherapy is needed. Stage 2 LE can usually be improved with intense treatment. Stemmer's sign is positive.

Stage 3 LE (lymphostatic elephantiasis)
Stage 3 LE is also known as lymphostatic elephantiasis. At this stage, the tissues become extremely swollen and thickened due to a blockage in the flow of lymph. Swelling is remarkable and irreversible. There is no reduction of swelling with elevation of the limb; volume increases more than 50%. No pitting is seen with pressure. There are irreversible structural changes and smooth muscle cell atrophy at lymphatic vessels. The tissues become hardened and sclerotic. Fibrosis and fat have replaced most of the fluid accumulated in the tissue. Stemmer's sign is positive. The skin has lost its elasticity and may change color. Hyperkeratosis, lymphangiomata, papillomatosis, and fungal infections can be seen. Stage 3 LE can be prevented from becoming worse with intense therapy, but response to CDT is limited. It is rarely reversed back to the earlier stage. Surgical debulking may be performed to reduce the size of the limb. However, morbidity after this surgery is high, and the hardened skin, hanging folds and deep creases are still present. These areas represent increased risk for fungal infections and open wounds because of the increased risk of breaks in the skin. Acute lymphostasis may progress to chronic fibrosis more than 5 years post treatment and soft tissue contractures may occur.

Stemmer's Sign: *Positive when a thickened skin fold at the dorsum of the fingers or toes cannot be lifted or is difficult to lift. The presence of this sign is an early diagnostic indication*

of LE. The absence of a Stemmer sign does not rule out the possibility of LE.

After a long-standing chronic LE, lymphangiosarcoma may develop, and also it is known as Stewart-Treves syndrome that is a rare, deadly cutaneous angiosarcoma.

Risk Factors of LE

Reports are of varying reliability because detection methods, follow-up, and treatments are not standardized and current knowledge is mostly based on patients' self-reports. BCRL has been the most-studied cause of secondary LE, but LE can occur as a result of other cancers, including melanoma, gynecologic cancer, head and neck cancer, and sarcoma. The average risk of BCRL is 25%. Of the estimated 2.3 million US survivors of breast cancer, affecting LE, approximately 19–33% is following axillary lymph node dissection (ALND), and radiation therapy (RT) and between 3.5% and 24% are following sentinel node (SLN) biopsy and RT. The reported incidence of lymphedema after breast cancer treatment varies from 6% to 63%, depending on the different studies [1–3]. LE incidence ranges from 7% to 77% of patients who undergo ALND. Several cooperative group trials have shown that LE ranges 0–23% with SLN biopsy alone and 21– 51% after axillary radiation therapy and lymph node surgery [8–10]. Five-year cumulative incidence of lymphedema was 42%, and lymphedema first occurred within 2 years of diagnosis in 80% and within 3 years in 89% [9].

Risk factors include:

- Surgery (incision, types of mastectomies, axillary surgery [SLNB, AD], reconstruction surgery)
- Number of lymph nodes removed
- Radiotherapy: Multi-field irradiation
- Tumor-related factors (size, stage, location of tumor)
- Chemotherapy
- Age
- Postoperative seroma and/or infection
- Venous obstruction
- Obesity and higher body mass index
- Delays in the return of shoulder motion
- Sedentary life
- Trauma-infection
- Excessive sun exposure, which may be an inflammatory stimulus to the impaired lymphatic system that results in recurrent LE

Onset of BCRL is commonly seen within the first 3 years following the definitive surgical procedure. Even conservative techniques for breast or axilla do not guarantee a complete elimination of the disorder. Once the condition begins, the possibility of progression to more severe stages of edema increases. Recurrent infections, non-healing wounds, discomfort or pain, difficulty with daily tasks, and emotional and social distress may complicate LE. Most commonly, minor physical traumas, including cuts, burns, tight jewelry, or other injuries to the fingers or hands, may transform a latent condition into active LE.

Due to their lifelong risk of LE, breast cancer survivors must be diligent with daily skin care to prevent and detect cellulitis, as well as prevent LE onset or exacerbation [3].

Diagnosis of BCRL

- Clinical diagnosis: history and physical examination
- Volume measurement: circumferential measurements, water displacement, perometry
- Changes in electrical conductance: bioimpedance spectroscopy
- Changes in biomechanical properties: tonometry
- Soft tissue imaging: US, CT, and MRI
- Vascular imaging; lymph vessel and lymph node imaging; lymphoscintigraphy, lymphangiography, near-infrared fluorescence imaging (NIR), indocyanine green (ICG), NIR-ICG
- Genetic testing
- Blood tests for other conditions that can look like LE
- Differential diagnosis

The diagnosis of BCRL remains a challenge with many women whose BCRL remains undiagnosed until the condition causes significant morbidity. Treatment of LE is based on correct diagnosis and ruling out differential diagnoses. Every condition that causes swelling (edema) is not LE, and LE may coexist with other issues such as chronic venous insufficiency (CVI) or lipedema. Correct diagnosis of LE requires specialized diagnostic testing.

Clinical Diagnosis

History and physical examination:

- History and physical examination is important for all patients with suspected LE and must be performed by experienced healthcare providers. Age at onset, location of swelling, pain and other symptoms, medications, progression and factors associated with swelling, such as cancer, injury, or infection should be reviewed. A family history is important to the diagnosis of inherited forms of LE. The physical examination includes skin and soft tissues in the swollen body part, palpation of lymph nodes,

and evaluating the vascular system. To make a correct diagnosis, diagnostic tests and imaging must be performed with the guidance of findings from the history and physical examination [3, 6, 9, 10]. Self-scored symptoms include swollen appearance or feeling (tightness of ring and bracelets), heaviness, tightness, discomfort, fullness or numbness, redness, tenderness, pain, weakness, and restricted movements. A common technique for assessing BCRL is patient's self-assessment. Patients may also be asked questions regarding hand dominance, social constraints, performance loss at work, body image, anxiety, depression, adaptation problems, and social and sexual issues focusing on quality of life.

Clinical Findings

- Asymmetry of arms.
- Skin folds are lost in the areas of the significance of anatomical structures such as tendons, bone projection, and veins.
- Pitting of the skin with digital compression.
- Skin hypertrophy, skin tension, and stiffness.
- Sensory disturbance and joint stiffness in the hands and feet.
- Recurrent soft tissue infection.
- Chronic fibrosis, soft tissue contractures.

Measures of Volume

Traditional techniques for diagnosis and monitoring of BCRL are circumference-based measurements and the water displacement method. Perometry is now being used; it is capable of detecting as little as a 3% volume difference in limbs.

Circumferential volume measurement: Calculation of limb volume from circumferential measurements is the most widely used and easily accessible method. It is noninvasive and inexpensive. It has sensitivity of 35–91% and has moderate specificity. The limb circumference is measured with a tape at fixed anatomical points with repeated 4-cm measurements. Then these circumferential measurements are entered into a computer program for automatic calculation of limb volume. This technique has been confirmed by some studies including NSABP B-04 trial [11], but it has some limitations such as the fact that there are no standard points of measurement, and thus interobserver variability is a major problem. As another example, McLaughlin et al. [12] performed circumferential measurements at 10 cm above and 5 cm below the olecranon process in both arms preoperatively. Measurements were taken at the same points during follow-up visits. This technique can be accurate if it is done in precisely the same way each time, and is most accurate when the same person takes the measurements each time.

Conical frustum method *is used for volume calculation. It is based on the formula for a truncated cone.* $V = 1/3x\ \pi xhx\ (r_1^2 + r_2^2 + r_1^2 x r_2^2)$. *The frustum of a cone is shaped by removing the apex of a cone by a plane parallel to the base.*

The water displacement method is considered the gold standard for assessing limb volume, especially for hands and feet. The underlying principle is that an object displaces a volume of water equal to its own volume. The body part is plunged into a large cylinder full of water. The difference in water level with and without the body part in place reflects the volume of the body part. This method is effective and accurate when done properly. However, hygiene issues and practicality are limitations of this method and may discourage its use. Additionally, this procedure cannot distinguish LE from other types of edema and changes in muscle, adipose, or extracellular fluid volume, or identify localized areas of swelling. It is not advisable in patients with wounds or infections associated with BCRL [6].

Perometry (optoelectronic volumetry) uses an infrared optical electronic scanner consisting of arrays of optoelectronic sensors to measure limb volume at each 4 mm distance. The calculated volume measures size excluding extracellular fluid. Perometry can measure limb volume quickly and accurately if the body part is given the same position each time and the machine is calibrated properly. Perometry may detect as little as a 3% change in limb volume in breast cancer survivors. Currently, there is no standard cutoff in various volumetric analyses. Although circumferential increases of 2 cm or greater and volume increases of 200 ml have been increasingly used in the literature, these parameters have not been standardized in the clinic. Because this device is relatively large and requires significant space, its usage is limited in clinical settings [6, 13].

Changes in Electrical Conductance [Bioimpedance Spectroscopy (BIS) Multifrequency Bioimpedance Analysis]

BIS measures extracellular fluid based on the impedance to the flow of an imperceptible, low-level electric current. BIS measures impedance to an alternating current over a range of frequencies (4–1000 kHz). BIS is done by passing a small, painless, electrical current through the limb and measuring the resistance (impedance). The machine uses certain current frequencies to determine if more fluid exists as compared to the contralateral limb. It accurately measures extracellular fluid volume differences between the arms to aid in the clinical assessment of unilateral LE. It does this by comparing the difference in resistance to electricity passed through interstitial fluid compared to intracellular fluid. BIS currently is done on the whole limb since the resistance to current flow for standard technique is calculated with regard to the length of the

body part. The higher the water content in the interstitial tissue, the lower the resistance. The device is portable and it is easy to position the patient. BIS measures skin texture and resistance quantitatively. As fluid accumulates in the at-risk arm, the L-Dex value increases. The L-Dex number provides an easy way for clinicians to track extracellular fluid change in the patient's arm over time. An increase of ten L-Dex units from a patient's baseline value represents a change of three standard deviations. BIS has been used for many years for fitness and weight loss purposes in order to assess the total water content of the body and body composition. BIS is now available to measure interstitial fluid as a component of LE diagnosis [3, 6]. Cornish et al. used limb impedance ratios and compared the affected and unaffected limbs, finding that an increase of greater than three standard deviations in the affected arm compared with the contralateral arm was clinically relevant to the early assessment of LE. Further, recent data suggest that BIS represents an improvement in sensitivity over traditional assessment tools with an average detection of 4 months earlier and in some cases up to 10 months earlier [14]. This is important because data from the National Institutes of Health (NIH) has confirmed that management of patients with subclinical BCRL can be done simply and effectively with minimal long-term morbidity, making it imperative to diagnose BCRL at the subclinical stage in order to improve outcomes [15]. An L-Dex measurement greater than 10 and a difference from the baseline or subsequent measurement greater than 10 are considered early-stage (Stage 0) LE.

In their study, Cornish et al. reported the sensitivity and specificity of BIS at 100% and 98%, respectively [14]. Subsequently, Hayes et al. used BIS as the criterion standard to calculate sensitivity and specificity of self-report for assessment of BCRL [14]. There are limitations in detecting non-pitting later-stage edema, at which point, fluid increases have been replaced by adipose tissue and/or fibrotic tissue. Similarly, in patients with chronic BCRL, irreversible tissue changes can develop, and extracellular fluid differences alone no longer represent the true nature of the disease [14–16]. Soran et al. investigated the role of monitoring with BIS on detection and early treatment of subclinical LE in patients who had ALND. In their prospective observational study, the incidence of any LE was 33.8%. It was found that one-third of women needed early intervention and only 4.4% progressed to clinical LE. After a two-year follow-up with early diagnosis and intervention, they reported the reduction rate of clinical LE as 32% [17] (Fig. 47.1).

Changes in Biomechanical Properties of Tissue Dielectric Constant and Tonometry

In addition to increasing limb volume, LE causes inflammation and fibrosis of the skin and subcutaneous tissues, and the affected area skin texture becomes progressively harder. These skin changes are reported as features of tissue texture, edema, inflammation, pitting, enlarged skin folds, or other dermatologic conditions such as wounds or papillomas found by physical examination. Tissue dielectric constant and tonometry are quantitative methods for measuring skin texture and resistance [3]. The tissue dielectric constant measures tissue water content. The test is performed with a device that passes an electrical current of a specific frequency to one location of the skin and measures the reflected wave that returns. The reflected waveform indicates the amount of water present in the tissue [18]. Tonometry measures the amount of force required to indent a certain amount of tissue. It yields a value reflecting the level of dermis compliance, induration, and fibrosis. Compressibility of skin is correlated to the LE volume. However, due to some technical difficulties related to the use of tonometry devices, environmental factors and operator differences, the results obtained may vary [19, 20].

Soft Tissue Imaging

Magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US) can show the presence of extra fluid in the tissues. However, these imaging techniques should be used in conjunction with clinical history, physical examination, and other imaging tests in order to explain the causes of edema. Other conditions such as heart failure or low proteins in the blood from liver disease or malnutrition can cause fluid to build up in the tissues. These imaging modalities are helpful, especially if there is a concern that the LE is related to cancer diagnosis [6]. Ultrasonic skin thickness measurement can be used for monitoring LE [21–25]. Ultrasound scans, particularly high-resolution Doppler, can help differentiate LE from lipedema and may also be helpful in the detection of LE of the head and neck. Magnetic resonance imaging (MRI) of skin can show thickening of the dermis in LE. The subcutaneous tissue may show a honeycomb pattern or a reticular pattern if edema is marked. MRI scans of lower limb LE have been carried out using gadodiamide as a contrast agent given intradermally to facilitate visualization of the lymphatic pathways [26].

A newer technique for improving the clinical assessment of BCRL is dual-energy X-ray absorptiometry (DEXA). DEXA scans measure fat, lean, and bone mineral content in the region of interest extending from the glenohumeral joint to the finger tips. A recent study found that DEXA was superior to circumferential measurements and water displacement with respect to the repeatability of measurements of the affected arm and contralateral arm [27]. Skin viscoelasticity and dual-beam absorptiometry are other techniques used for detection of LE [28, 29].

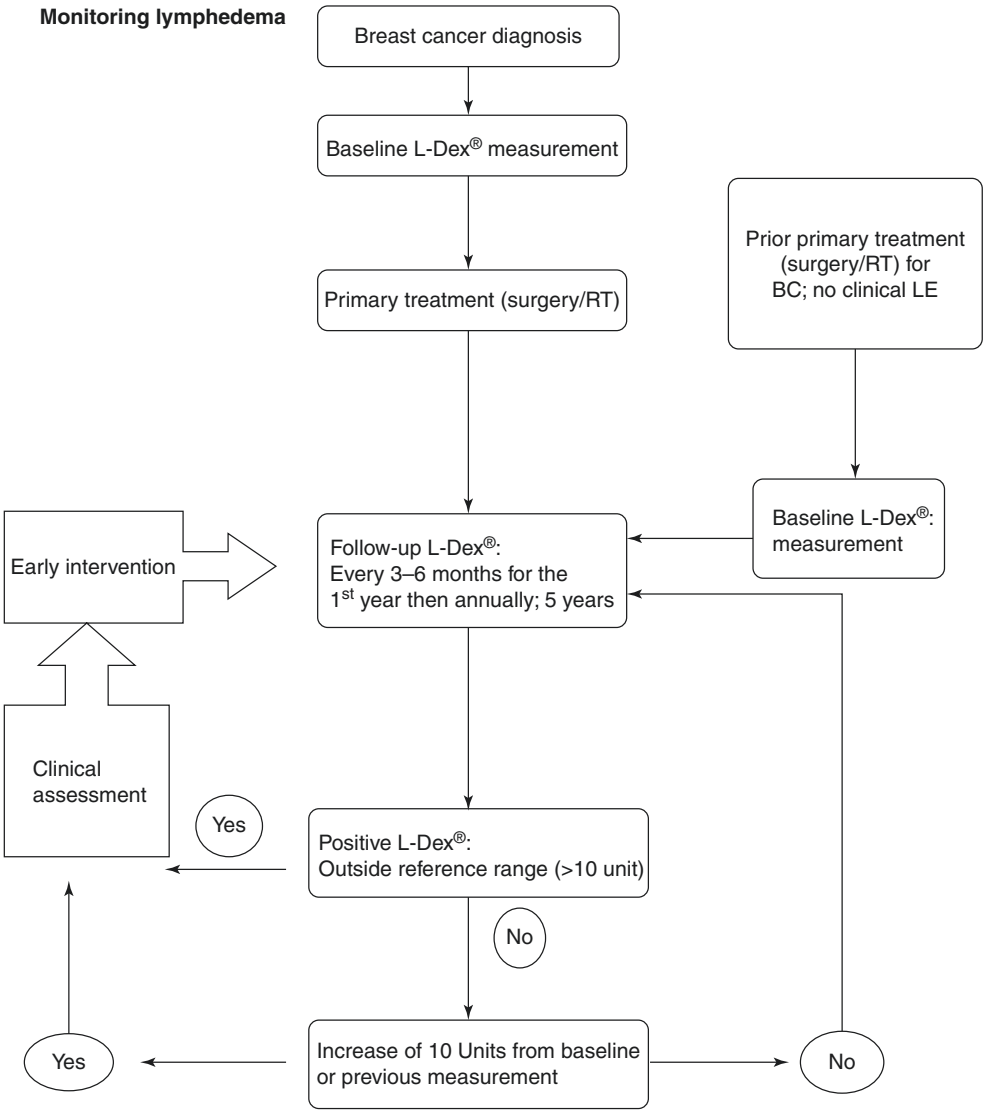

Fig. 47.1 Clinical practice pathways. (With permission Ref. [17])

Vascular Imaging

- Lymph vessel and lymph node imaging; lymphoscintigraphy
- Lymphangiography, MR angiography
- Near infrared florescence imaging (NIR), indocyanine green (ICG), NIR-ICG

Lymphoscintigraphy is beneficial in limb swelling where the diagnosis is unclear [6]. Many studies of lymphoscintigraphy are in the area of BCRL where it can detect early LE with 73% sensitivity and 100% specificity. However, in some patients with LE, lymphoscintigraphy is negative [30–32]. There is no standard protocol, with international differences in colloid used, injection site (dermal or subcutaneous), and exercise protocol. There is debate as to whether lymphoscintigraphy should be quantitative or qualitative and if epifascial as well as subfascial lymphatics should be imaged. Usually, technetium-labeled sulfur colloid is used. Lymphoscintigraphy is accurate for detecting abnormalities of the lymphatic system in the extremities regardless of the cause. It demonstrates slow or absent lymph flow and areas of reflux (backflow). Lymphoscintigraphy can reveal abnormalities of lymph uptake in lymph nodes with some forms of LE. Lymphoscintigraphy can predict response to treatment. Lymphoscintigraphy shows the main, larger lymph vessels and nodes, and the basic architecture of the peripheral lymphatic system. It does not show the deep transport lymph vessels carrying lymph from the nodes back to the blood circulation. Lymphoscintigraphy identifies lymphatic abnormalities at a late stage, after LE has occurred. Lymphoscintigraphy, in combination with other vascular studies, can differentiate venous edema from LE. Lymphoscintigraphy may not be necessary in some

forms of secondary LE where the diagnosis is clear from the history and physical examination or other imaging. The specific tests needed are determined by a specialist in LE. The type of lymphoscintigraphy done for the diagnosis of LE is not available at all radiology departments. Most radiology departments, however, can do a form of lymphoscintigraphy used to identify the sentinel lymph node for cancers such as breast and melanoma. These studies for the sentinel lymph node are different from the lymphoscintigraphy studies done for diagnosis of LE. Before undergoing a lymphoscintigraphy study, the patient should inquire if the radiologist performing and reading the study has a large amount of experience with lymphoscintigraphy studies specifically for the diagnosis of LE.

Lymphangiography, MR Angiography

Lymphangiography involves the direct administration of an iodinated contrast agent into a cannulated lymph vessel for radiography or CT. Lymph vessels architecture, lymph nodes, collateral vessels, and dermal back flow could be clearly visualized from MR (indirect) lymphangiography [33].

Near-infrared florescence imaging (NIR) is a new technique for imaging lymph vessels using a substance known as indocyanine green (ICG). ICG is a green dye that has been used safely in other areas of the body such as the liver and eyes. It can be used in very small amounts to image the lymphatics. The ICG is injected into the skin and immediately imaged with a dynamic (real-time) infrared florescence camera. With NIR-ICG, even very small lymphatic vessels can be seen. Because the study is dynamic, the actual function of the lymphatic vessels can be analyzed. Diseased lymphatics that do not contract (or pulse) normally can be seen with NIR-ICG. NIR-ICG can diagnose LE and find abnormalities at an early stage, possibly before swelling is obvious. Although this technique shows promise for the diagnosis of LE, it is currently available at very few centers, most of which are involved in research [33, 34].

Differential Diagnosis of LE

Although there is no blood test to diagnose LE, other medical conditions such as hypothyroidism (myxedema) or low protein (hypoproteinemia) can cause edema and need to be considered as part of a complete evaluation of swelling. Standard plain X-rays may be ordered for some inherited LEs to evaluate for orthopedic conditions. Edema may be caused by diseases of the cardiovascular system (heart, arteries, veins) such as cardiac failure, chronic venous insufficiency (CVI), or related lipedema. CVI is the most common condition in which the veins of the legs do not efficiently return blood to the heart. Reduced capacity of the venous system caused by damage to the veins increases the workload for the lymphatic system in the affected area. If the problem is primary LE, it is important to evaluate for other vascular abnormalities. Edema secondary to cardiac failure is generally bilateral, symmetrical, and markedly pitting.

Lipedema and LipoLE are also misdiagnosed as LE Lipedema is a bilateral, symmetrical, fatty swelling that consists of adipose tissue deposition. The exact cause of lipedema is not well known. LipoLE is a form of swelling combining lipedema and LE. LipoLE may also present with edema related to CVI and other vascular diseases.

Detailed clinical examination and imaging studies of the heart, veins, or arteries are needed to obtain a complete and accurate diagnosis of edema. The most common cardiovascular studies ordered for the evaluation of complex edemas are echocardiogram, venous ultrasound, and arterial ultrasound with ankle brachial index (ABI). Alternatively, more advanced imaging, such as computed tomography, venograms, or arteriograms, may be recommended.

Early Diagnosis and Monitoring

Traditional measurement procedures such as tape and volume measurements have significant limitations. There are no standard points of measurement; there are interobserver and intermeasurement variabilities, and failure to measure the extracellular space. Using traditional measures, only the clinically apparent LE is feasible and it is unable to detect subclinical disease with relatively low sensitivity compared with newer techniques. Hutson et al. examined the operator variability of traditional measurements and found the variation using circumferential and volume measurements. Recent studies have reported that newer assessment procedures are able to detect BCRL on average 4–10 months earlier than traditional methods [14–17]. Early management has been found to improve outcomes in BCRL. Newer tools provide increased diagnostic accuracy and can directly measure the extracellular volume as well. The most appropriate methods and tools to identify early versus late stages of LE are BIS and perometry, L-Dex monitoring protocol, nomogram integrated care delivery model, components preoperative assessment every 3 months. Every patient with LE should have access to established effective treatment for this condition.

Treatment for LE is most effective when it is diagnosed at the earliest stage, with no irreversible changes such as fibrosis. Early physiotherapy is an effective intervention for prevention of secondary LE after breast cancer surgery and improves quality of life [35]. However, Maria Torres Lacomba et al. reported in 2010 that physiotherapy for every patient of breast cancer surgery may not be feasible in terms of both cost-

effectiveness and patient and physician compliance [36]. A minority of patients develop severe, long-term physical impairments. In this study, among 116 women, 18 (16%) gained benefit; the early physiotherapy group was treated by a physiotherapist with a program including manual lymph drainage, scar tissue mobilization, and progressive active and action-assisted shoulder exercises. This group also received an educational strategy. The control group received the educational strategy only. Of these, 14 (25%) had secondary LE (intervention/control, hazard ratio 0.26, 95% confidence interval 0.09–0.79) and LE occurred four times sooner in control group ($P = 0.01$) [36].

Components of LE Monitoring

Protocol with BIS: An L-Dex measurement greater than 10 and a difference from the baseline or intermeasurement greater than 10 represent Stage 0 LE. This permits early detection and effective early treatment. Preoperative assessment is followed by postsurgical assessments at months 1, 3, 6, 9, and 12. Every three-month surveillance care-baseline and as needed [17, 37]. A five-year study funded by the National Institutes of Health assessed LE (with perometry) in breast cancer patients. 196 patients were assessed preoperatively and then again 1, 3, 6, 9, and 12 months post surgery. Of these, 43 (22%) were identified with sub-clinical LE. Intervention with a compression sleeve resulted in reversal of symptoms in all patients [38].

Prediction of high-risk patients: Cleveland Clinic published a questionnaire study based on formation of a nomogram as a risk prediction assessment tool (http://www.LErisk.com). The 5-year cumulative incidence of LE was 30.3%. Independent risk factors for LE were age, body mass index, ipsilateral arm chemotherapy infusions, level of ALND, location of radiotherapy field, development of postoperative seroma, infection, and early edema. The proposal of the study was that nomograms could help predict the 5-year probability of LE after ALND for breast cancer [39].

Management of BCRL

The current standard management for BCRL consists of physiotherapy based on complete decongestive therapy. The management of LE procedures is listed below.

- Physiotherapy.
  - Complete decongestive therapy (CDT)
  - Manual lymph drainage (MLD)
  - Compression bandaging – LE bandaging (MLLB)
  - Compression garment.
  - Intermittent pneumatic compression therapy (IPT)
  - Modifications and individualization of CDT
  - Exercise (including lymphatic "remedial exercise")
  - Therapist training
  - Patient education, awareness of the signs and symptoms of LE, self-management, and elastic compression garments, lymphedema drainage massage, nocturnal compression bandaging (as needed), skin care with good skin hygiene, and weight management.
- Surgical therapy
  - Debulking
  - Liposuction
  - Vascularized lymph node transfer; tissue transfers (grafts) bring lymph vessels into a congested area
  - Microsurgical lymphatic reconstruction microsurgical and supramicrosurgical lymph vessels and veins, lymph nodes and veins, or lymph vessels to lymph vessels.
- Pharmaceutical approaches, natural supplements, complementary

Physiotherapy

The comprehensive goals for effective management of all patients with BCRL are:

(a) Facilitation of functional independence including musculoskeletal function and correct posture
(b) Infection prevention
(c) Providing limb volume reduction and containment
(d) Improving lymph drainage in affected areas and minimizing fibrosis
(e) Maximizing psychological support
(f) Promoting self-management with education of patients

Complete Decongestive Therapy (CDT)

The goals of CDT are to decrease swelling, increase lymph drainage from the congested areas, reduce skin fibrosis and improve the skin condition, enhance the patient's functional status, relieve discomfort and improve quality of life, reduce the risk of cellulitis and of Stewart-Treves Syndrome, a rare form of angiosarcoma-related LE. Complete decongestive therapy is also referred to as combined, complex, or comprehensive decongestive therapy and multimodal physical therapy [3, 6]. CDT is the "gold standard" of conservative management of LE; it has been shown to be safe and effective [37, 40]. CDT consists of two phases categorized as initial intensive decongestive (Phase I) and maintenance (Phase II). In Phase I, reducing the size of the limb and improving the skin condition are the main goals. Acute management generally occurs in an outpatient clinic setting. On average, it consists of a four-week program of manual lymphatic drainage; short-stretch compression bandaging, exercise,

and proper skin and nail care. Daily treatment is performed up to 5 days per week (up to 6 weeks) by LE therapists skilled in CDT. Phase I should lead directly into Phase II, which is an individualized self-management for long-term maintenance of Phase I reductions. During Phase II, the maintenance of care transfers to the patient who is encouraged to continue lifetime regular checkups or further intensive treatment. The self-management program consist of self-performed lymph drainage (also referred as simple lymphatic drainage), home lymphatic exercises, skin care, and independent application of compression garments or bandages. Phase II maintenance must be monitored and adjusted periodically, just as with treatment for any other chronic medical condition. Compression garments must be replaced every 4–6 months to be effective. Specialized equipment requires maintenance and replacement according to manufacturers' guidelines. Phase II CDT and periodic medical monitoring are essential to the long-term success of LE treatment. These measures may include garments with Velcro, specialized foam construction garments, and pneumatic compression devices. For the therapy to be successful, all the components of CDT must performed in combination. CDT is currently the most effective treatment for LE when performed properly. The literature is conflicting in some points regarding the effectiveness of certain CDT components. Sometimes, CDT may need to be modified in the presence of complex comorbidities or according to the patients' preference, such as for elderly patients living alone who are not able to manage daily visits or intensive treatment as planned. The reasons for modifying the treatment should be clearly explained for each patient's treatment plan. Treatment options are discussed with the patient to formulate an individualized protocol. Many trials confirm the efficacy of CDT. One of the largest studies was performed by Vignes et al. in which they evaluated 537 patients undergoing CDT and found that the mean volume of lymphedema was 1054 ± 633 ml prior to CDT and 647 ± 351 ml after intensive decongestive physiotherapy [41].

Components of CDT

I. Manual lymph drainage (MLD).
II. Compression therapy: multilayer, short-stretch compression bandaging.
III. Therapeutic exercises: regular lymphatic exercise and remedial exercise.
IV. Patient education in LE, self-management, and elastic compression garments, simple lymph drainage, nocturnal bandaging (as appropriate), skin care (good skin hygiene), weight loss.

I. *Manual Lymphatic Drainage (MLD)*

Manual lymph drainage is an essential part of CDT. It is a special manual (hands-on) technique that stimulates superficial lymphatic vessels to remove excess interstitial fluid [3, 6]. MLD is a type of massage, but it is different from the commonly known usual types of muscle or myofascial massage. MLD is the use of specific massage techniques (based on the knowledge of lymphatic anatomy and physiology), which mobilize the skin and stimulate the lymphatic system. MLD is a light skin technique performed by certified LE therapists. MLD improves the lymphatic fluid stream into the venous circulation by using existing lymphovenous anastomoses and lymph vessels/lymph nodes that are properly functioning instead of those from edematous areas with damaged lymphatics. It is mostly effective when combined with compression bandaging, skin care, and exercise. Evidence supporting MLD is not enough in the literature. However, international expert opinion has reached a consensus that MLD is a primary component of CDT, as it is the only technique to move fluid away from the congested areas.

Contraindications for Manual Lymphatic Drainage

In addition to all general contraindications; MLD contraindications include pregnancy, menstruation, recent abdominal surgery; radiation fibrosis/colitis/cystitis; history of DVT in pelvic veins, inflammatory bowel disease, diverticulitis, cirrhosis of liver, abdominal aortic aneurysm, unexplained pain and ileus.

II. *Compression therapy* includes compression bandages, compression garments, gradient compression devices, and pneumatic compression devices to mobilize the lymph fluid.

Multilayer LE Bandaging (MLLB) Compression Bandaging

Compression bandaging is used to create safe and effective compression by applying multiple layers of several materials. Compression bandaging is always a part of Phase I CDT. The components of compression bandaging are a skin protection layer (non-compression); a padding layer (may be foam or layered wool polyester, cotton, or foam under-cast padding); short-stretch compression bandages; tubular bandage lining; and digit bandages. Multiple layers of short-stretch bandages with 50% overlap and 50% stretch to cover the entire limb are recommended. In some patients, it may necessary to use polyurethane foam in various densities and configurations within the bandaging system. Short-stretch bandages have limited stretching capacity when pulled. They can stretch 40–60% from resting length, while long-stretch bandages stretch to greater than 140% of resting length. To achieve an effective compression gradient, short-stretch bandages must be strategically applied with low-to-moderate tension using more layers at the distal ends of the extremities than proximally. Pressure within the short-stretch bandages is low when the patient is resting ("resting pressure"). As

muscles expand within the limited space of the short-stretch bandages, muscle contractions increase interstitial fluid circulation ("working pressure") to help the fluid to move out of congested areas. The cycling between low resting and high working pressures in the interstitial fluid, within the compression bandage, creates an internal pumping action. The short-stretch bandages both increase drainage of congested interstitial fluid into the vascular circulation and also prevent reaccumulation of the fluid into the tissues. They can also reduce areas of fibrosis and reshape the limb.

In the maintenance phase, patients may need to perform nocturnal self-bandaging to supplement compression garments. Incorrect bandaging technique may cause more damage.

Contraindications for Multilayer Bandaging

Absolute contraindication: ardiac edema, peripheral arterial disease, Ankle Brachial Index (ABI <0.5), acute infection.

Relative contraindication: Arterial high blood pressure, cardiac arrhythmia, scleroderma, chronic polyarthritis, Sudeck's atrophy, malignant LE, ABI 0.6–0.8, and specialist consideration.

Compression garments: Following achievement of maximal volume reduction with Phase I CDT, patients should be fitted with a compression garment [3]. Garments may be sleeves, bras, face or neck compression wear, etc. The patient should receive two garments at a time for each affected body part: one to wear and one to wash and dry. Having two garments insures that the patient does not wear a dirty or wet garment which promotes bacterial or fungal infection. Manufacturer instructions must be followed for washing and drying to prolong the life of the garment.

Properly fitted garments are essential for long-term control of LE. Garment style and compression strength should be prescribed according to the patient's ability to manage the garment and maintain the best volume control and skin health. Compression garments are commonly used and deliver 20–60 mm Hg of pressure and can be worn for a few hours a day or all day. Ready-made garments come in a variety of sizes and can be fitted to many individuals. Custom garments are specifically sewn/created per the individual who cannot fit a ready-made garment. They are more expensive than ready-made garments and may be required for patients with irregularly shaped limb(s) or body parts, wounds, lack of sensation, or difficulty with hand dexterity. Custom garments allow for options including special linings to reduce the risk of skin breakdown as well as fastening devices, which may assist the patient in donning and doffing the garment.

Garments should be washed daily to ensure the garment lasts as long as possible and does not lose its compression strength. For optimal results, the garments should be fitted by trained personnel and be replaced every 6 months or when the tension from the elasticity decreases. Most daily garments must be replaced every 4–6 months to maintain compression strength. The efficacy of compression garments is controversial; yet, they continue to be used frequently in patients with early-stage or limited BCRL. Providing correctly fitting garments for each individual patient is essential. Nonfitting garments can be harmful, causing the edema to worsen and further permanent damage. In addition to the day garments used in Phase II, some patients with more severe forms of LE will need night garments or advanced day garments to maintain the reductions obtained in Phase I. These include *Velcro*® brand closure garments and specialized foam compression garments [3–5].

In choosing garments, the clinician should consider:

- Limb shape and size/distribution of swelling.
- Presence of skin folds.
- LE status (stage I–III)-texture of skin.
- Skin sensitivity.
- Overall status of underlying disease, e.g., cancer, arterial disease, diabetes.
- Patient's functional ability.
- Patient's choice regarding material, color, texture, fabric.
- Patient's compliance.
- Some garments have additional attachments including shoulder attachments, separate hand pieces, and waist attachments. In the maintenance phase of treatment reassessment, it is important for a trained clinician to reassess garment choice. Garments should only be assessed by a trained clinician. All patients should be provided with accurate contact details of local LE services in case they require further advice [3, 6].

Vignes et al. reported a total lymphedema-volume reduction as 33%. Intensive phase CDP for 11 days obtained significantly more volume reduction of breast cancer-related lymphedema than 4 days [42].

Data from the NIH have shown that use of compression sleeves in patients with subclinical LE leads to excellent results with minimal morbidity [43].

Absolute contraindication of compression garments: Uncontrolled heart failure, risk of increased cardiac edema and acute deep vein thrombosis (DVT), risk of dislodging the clot, acute ineffective episode (cellulitis, erysipelas), superior vena cava obstruction (SVCO), and acute renal failure.

Relative contraindication: Malignancy – Risk of spread of active cancer.

Intermittent Pneumatic Compression Therapy (IPC)

IPC, also known as compression pump therapy, can be useful in some patients as an adjunct to Phase I CDT or as a necessary component of a successful home program (Phase II CDT) [3, 6]. Intermittent pneumatic compression (IPC) pumps are for daily use for 30 minutes–1 hour and should only be used in conjunction with manual treatments. IPC is contraindicated in patients with congestive heart failure, active infection, or deep venous thrombosis, pneumatic compression devices are contraindicated. Single-chamber pumps are no longer used for LE anymore. Single-chamber pumps can cause fluid to move in both directions which may allow additional fluid to accumulate in the swollen area. Furthermore, the pressure in single-chamber pumps does not stimulate lymphatic flow as well as sequential pumps. Acceptable pumps should have appliances (pump garments) that deliver sequential pressure through multiple chambers in a pattern tailored to each patient, depending on the diagnosis and pattern of LE. LE is a condition involving an quadrant of the body (upper or lower trunk, chest, and abdomen), not only the limb with the edema, and many patients who require IPC will need a pump that treats both the trunk of the body and the edematous limb. Recommended pump pressures generally range from 20 to 60 mmHg, although lower or higher pressures may be indicated. The pressure displayed on the pump may not accurately reflect what is delivered to the skin surface. This is a significant concern because if the pressures applied in therapy are too high, the superficial structures may be harmed. In general, lower pressures are considered to be safer, but the pressure has to be individualized to the patient's diagnosis and skin condition. Typically, a treatment takes 1 hour. IPC is utilized along with standard CDT to maintain control of LE at home, as part of Phase II management. To control edema, a compression garment or short-stretch bandages should be worn between pump treatments and also when IPC therapy is discontinued. It is important to select the proper device and protocol for IPC. The prescription must include the intensity of pressure and pattern of pressure needed, taking into consideration several aspects of the patient's situation. Consider the possible need for programmable pressure to treat fibrotic areas; address treatment of ulcers; and adjust for the patient's level of pain and skin sensitivity. If trunk, chest, or genital swelling is present, the physician must determine whether a pump that provides appliances to treat those areas is necessary or if the patient can manage the trunk swelling through self-MLD or garments. If a pump with only extremity attachments is used, there should be close monitoring to detect an increase in edema or fibrotic tissue, called a fibroscelerotic ring, above the device sleeve. If this occurs, consideration should be given to using a device that treats the trunk in addition to the extremities. Also, the physician or healthcare provider must evaluate the impact of various other medical conditions that are usually considered contraindications for pneumatic compression therapy, including acute infection, severe arterial vascular disease, acute superficial or deep vein phlebitis (inflammation or clot), recurrent cancer in the affected area, or uncompensated congestive heart failure [37, 40–43].

Documented results with IPC are limited and have not been favorable [44]. IPC was compared with manual lymphatic drainage in patients using compression sleeves and found no difference in BCRL and pneumatic compression pump did not contribute to the reduction of LE [45].

Ridner et al. produced a study that provided favorable data about the Flexitouch (Tactile Medical, USA). The Flexitouch system is an advanced, programmable pneumatic compression device that is cleared by the U.S. Food and Drug Administration for home use. This device is designed to emulate the therapeutic techniques of MLD. The Flexitouch system for upper extremities consists of three compressive garments, for trunk, chest, and arm. [46, 47].

Modifications and Individualization of CDT

CDT programs should be individualized based on the presence of other medical conditions and the patient's abilities. Patients with wounds, scars, or musculoskeletal conditions, palliative care patients, or post-radiation fibrosis may require adaptations of CDT. If there is limited mobility of the body part with or near the swelling, the patient may require other therapies, such as scar mobilization or myofascial therapy, in addition to CDT, to have a benefit from CDT.

III. *Therapeutic exercises or remedial exercise refers to exercises* that aid lymph flow through repeated contraction and relaxation of muscles. These exercises should be individualized and should be performed while the edematous arm is bandaged. Ideally, these exercises are initiated by well-trained therapists and then continued at home. Therapeutic exercise and manual lymphatic drainage (MLD) are two treatment options that often represent a bridge between compression sleeves and CDT. Data supports the use of exercise with BCRL. A trial comparing exercise to observation found a nonsignificant decrease in LE volume (101 vs. 7 mL) but statistically significant improvements in tissue resistance and symptomatic heaviness. More recent data has found that active exercise further reduces limb volume along with standard therapy. MLD, while commonly used, has shown limited benefit compared with standard treatments. Analysis of MLD as single treatment applied has found volume reductions of 100–150 mL with reductions in limb heaviness. Recently, some data has

supported MLD with a crossover trial finding that MLD had a trend for decreased arm volumes in 31 patients receiving MLD (10% vs. 4%, $p = 0.053$) [15]. With LE, individualized exercise is beneficial for all patients. Although heavy activity may temporarily increase fluid load, appropriate exercise enables the person with LE to resume activity while minimizing the risk of increased swelling. For people who have LE, compression garments or compression bandages must be worn during exercise (except in aqua therapy) to reduce the buildup of interstitial fluid [37, 43]. Since exercise has been shown to have significant positive effects during and after cancer treatment, safe exercise must be a goal for all cancer-related LE. People with or at risk for LE are encouraged to work with an LE specialist to incorporate an individualized exercise program into their LE management. Remedial exercises are carried out in the intensive phase of treatment in conjunction with multilayer bandages and in the maintenance phase with a compression garment. The aim is to enhance the efficiency of the muscle pump, hence increasing lymph circulation. Patients are given an individually tailored exercise program suited to their particular requirements and abilities.

Summary of CDT Treatment LE

Treatment of LE should be performed only by experienced practitioners after completion of the diagnostic evaluation according to accepted guidelines. The current international standard of care for managing LE is CDT. CDT has been shown to be effective in large numbers of case studies. Limb volume reductions of 50–70% or more improved appearance of the limb, reduced symptoms, and improved quality of life, and fewer infections were demonstrated after CDT treatment. Even people with progressive LE for 30 years or more before starting CDT have been shown to respond. It is recommended that CDT adaptations or other LE treatments should be used as individualized to improve patient adherence and should be applied under the supervision of a healthcare provider (physician, nurse, physician assistant, and therapist) who are experienced on LE management. IPC is a demonstrated effective adjunct to CDT. The main goals must have both reducing and maintaining the volume reduction, preventing medical complications, improving skin condition, reducing infection, and improving patient comfort and adherence and quality of life for all interventions of LE [48]. Therapist Training Therapists providing CDT should have completed at least 135 hours of training as recommended by the Lymphology Association of North America® [43].

Patient Education

LE is a lifelong condition; therefore, patient education in self-management is mandatory. All patients with LE or at risk for LE should be instructed in essential self-care. Risk reduction practices, self-lymph drainage, skin care, signs and symptoms of infection, proper fit and care of garments, and the importance of good nutrition, exercise, and weight control are the important areas of education.

Skin and Nail Care

Good skin care is essential in the management of LE in order to maintain skin integrity against traumas such as cuts and puncture and reduce risk of infection. Meticulous hygiene is mostly important to decrease the amount of fungus and bacteria on the skin. Using a low pH emollients is recommended to keep skin from drying and cracking, which provides entry points for bacteria and fungus. Cuts and abrasions should be monitored for the signs of infection [43]. Skin infections such as cellulitis or erysipelas are a serious infection of the skin that requires antibiotic treatment. For more complex skin conditions such as psoriasis or eczema, the patient should be referred to a local dermatology department to optimize the outcome of their LE treatment [49, 50]. Similarly, patients with complex wounds/ulcers should be assessed.

Weight Loss

LE risk increases with obesity; therefore, weight management is an integral part of LE treatment as well as maintenance of optimal weight in normal weight individuals. An increased body mass index (BMI), especially >30, is noted as a significant risk factor. Patients with a high BMI should be referred to dietetic services. LE treatment is more effective when combined with a weight loss program. LE volume measurements completed in therapy must be correlated with BMI [48, 51, 52].

Exercise for at-risk BCRL patients followed the same 90-minute exercise; these patients had significantly less (70%) development of LE at one-year follow-up.

Comorbidities: Having significant comorbid conditions is generally thought to add to the risk of developing LE. Elevated blood pressure has also been cited as being a risk factor. Cellulitis is both a risk factor and cause of LE.

Surgical Treatment of LE

Even though surgery for LE is not performed with curative intent, it has been used for control of severe conditions in specific circumstances. Surgery may be considered for reducing the weight of the affected limb, improving cosmetic appearance/shape of the limb, minimizing the frequency of inflammatory attacks, or fitting the limb into garments. The risks and benefits of surgical procedures must be balanced according to the personalized needs of the patient and the experience of the surgical team. Surgery is usually performed

if all usual treatment methods have failed. Nonetheless, surgery for LE must be done in conjunction with CDT, and should not be performed alone. Both treatment modalities interfere positively with each other [6, 48, 53–56].

There are several types of LE surgery procedures available:

(a) Excisional operations, including debulking and liposuction
(b) Vascularized lymph node transfer; tissue transfers
(c) Microsurgical lymphatic reconstruction

There are very few surgeons on the whole who perform the above-listed procedures. It is important that patients with lymphedema are treated by qualified physicians. Working with a certified LE therapist for ongoing care after surgery is also important for a successful outcome.

Debulking

Debulking surgery removes the fibrotic connective tissue and any large folds of fatty tissue associated with the LE. Risk associated with debulking include prolonged hospitalization, high morbidity, poor wound healing, nerve damage or loss, significant scarring, risk of destruction of the remaining lymphatic vessels, loss/or decreased limb function, recurrence of swelling, poor cosmetic results, and decrease in quality of life are the potential risks of debulking surgery. Lifelong compression garments are necessary postoperatively for the maintenance of the limb due to the lymphatic scarring from these surgeries and lymphatic insufficiency.

Liposuction

Liposuction surgery of the limb is the circumferential removal of fatty tissue deposits of the affected part by LE. Liposuction performed for LE is similar to, but not identical to, cosmetic liposuction. Tubular suction devices are inserted into many small incisions and fat tissues break up, liquefy, and are removed. Patients with lymphedema require bandaging postoperatively to stop the bleeding. Lifelong compression garments are generally needed to prevent LE recurrence due to the scarring of lymph vessels that may occur after the procedure. The risks of liposuction include bleeding, infection, skin loss, abnormal sensation such as numbness and tingling, and return of LE.

Vascularized Lymph Node Transfer: Tissue Transfers

Tissue transfers (grafts) are performed to relocate lymph vessels into a congested area to remove excess interstitial fluid. There are few studies of the long-term effectiveness of tissue transfers for LE. Published articles are either outdated, performed on animals, or are insufficient to show lymph vessel function in breast reconstruction flaps [53–57].

Microsurgical Lymphatic Reconstruction

Microsurgical and supramicrosurgical techniques have been developed to relocate lymphatic vessels to congested areas in an attempt to improve lymphatic drainage. Surgical procedure is the anastomosis of lymph vessels and veins, lymph nodes and veins, or lymph vessels to lymph vessels. Although there are no long-term studies of the effectiveness of these techniques, there are a number of preliminary studies reporting reductions in limb volume [53–55]. Surgical treatments in general are associated with significant risks and morbidities, but the aspect is promising. However, it is hard to predict how long it will take for LE to reduce postsurgically. Surgical management of LE should be in conjunction with CDT protocol. CDT and adjunctive therapies (advanced garments and IPC) can usually produce excellent management in compliant patients, and surgery is rarely a necessary consideration.

Pharmaceutical Approaches

Pharmacological interventions of BCRL have included benzopyrones, flavonoids, diuretics, hyaluronidase, pantothenic acid, and selenium. Benzopyrones have been used widely in Europe to treat BCRL; however, it is not approved by the US Food and Drug Administration. Casley-Smith et al. reported a randomized, double-blind, placebo-controlled study in which benzo-[alpha]-pyrone was given. Thirty-one patients with BCRL were treated with 400 mg of 5,6-benzo-[alpha]-pyrone (18 patients) or placebo (13 patients) for 6 months There was a significant decrease in the amount of edema in the upper extremities, with reduction of pain, tightness, acute inflammation of those patients given 5,6-benzo-[alpha]-pyrone [58]. However, Loprinzi et al. found no significant difference in arm volumes at 6 and 12 months in 140 patients with BCRL who were treated with 200 mg of oral coumarin twice daily for 6 months [59]. Selenium, a free-radical scavenger, has been shown to be effective in improving radiation-induced secondary LE in the head-and-neck region. Micke et al. confirmed that volume decrease was observed in 83% of patients (10 of 12) after administration of selenium in their study. Although nausea, vomiting, diarrhea, and tachycardia are documented as adverse effects, no toxicities were observed with selenium use in this setting [60]. Diuretics are ineffective for removal of interstitial fluid from the tissues. Excess diuretic use can lead to dehydration, electrolyte imbalance, and tissue damage. However, diuretics may be medically indicated in patients with high blood pressure and heart disease. Therefore, diuretic use must be assessed on a case-by-case basis. Some drugs such as Coumarin and Diosmin have been tried for LE. They have not been found to be effective for LE and have adverse side effects.

Natural Supplements

There is limited evidence on the use of natural supplements for LE. Studies have shown that American horse chestnut may help venous edema but not LE. Selenium has been reported to improve LE in head-and-neck cancer. Bromelain, a substance found in pineapple, has anti-inflammatory, anticoagulant, enzymatic, and diuretic effects. Some have wondered if there might be a benefit for bromelain use with LE, but it has not been studied for use specifically for LE. Due to potential interactions with prescription drugs and other negative side effects, patients should check with their physician or healthcare provider before taking any natural supplement [43].

Complementary and Alternative Treatments

There are some promising treatments that have been reported, but they have not yet been subjected to sufficient research to be recommended as the standard of care. These treatments include cold laser, electrical stimulation, vibratory therapy, oscillation therapy, and aqualymphatic therapy. All of these techniques are done in combination with components of CDT. Mostly, acupuncture has shown benefit for some symptoms of cancer and cancer treatment, including fatigue, hot flashes, muscular or joint pain, neuropathy, and nausea. There are no evidence-based studies on using acupuncture for treating LE or using acupuncture on LE extremities [43]. Cold lasers, known as "low power laser or low level laser therapy (LLLT)," are typically between 5 and 500 mW, use nonthermal mechanisms (photochemical reactions), and can be used to deliver energy to tissues for a wide variety of rehabilitation purposes. Cold laser can be applied either by handheld units (contact or noncontact devices) using spot application to specific anatomical surfaces or by scanning units in which LLLT is applied over a larger region. Nonthermal effects of LLLT include stimulation of adenosine triphosphate production, promotion of ribonucleic acid and collagen production, modulation of inflammatory cytokines, inhibition of bacterial growth, promotion of vasodilatation and endothelial regeneration, stimulation of fibroblast activity, alteration of nerve conduction velocity, and promotion of neural regeneration. LLLT was found to decrease the expression of pro-fibrotic transforming growth factor and type I collagen deposition in the rat tibialis anterior muscle after muscle lesion, suggesting that LLLT may be helpful in preventing tissue fibrosis. This suggests that LLLT may provide benefit to patients with LE by increasing lymphatic flow through encouragement of lymphangiogenesis, stimulation of lymphatic motoricity, and prevention of tissue fibrosis that could potentially further disrupt lymphatic function. Evidence supports that a dose of 1–2 J/cm^2 per point applied to several points covering the fibrotic area can reduce limb volume following BCRL [61–63].

Physical Activity (NCCN General Principles)

- All cancer survivors should be encouraged to avoid inactivity or a sedentary lifestyle and return to daily activities as soon as possible. Patients who are able should be encouraged to engage in physical activity daily.
- Physical activity and exercise recommendations should be tailored to the individual survivor's abilities and preferences.
- General recommendations for cancer survivors: Overall volume of weekly activity should be at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity or the equivalent combination.
- Two to three sessions per week of strength training that include major muscle groups
- Stretch major muscle groups on days exercises are performed [48].

Recent studies in weight lifting, exercise, and weight loss are also showing benefit in the prevention of LE in at-risk patients and in patients with LE. A trial in which 154 breast cancer patients without BCRL were randomly assigned either a progressive weight lifting regimen or no activity found that significantly fewer patients developed BCRL in the lifting group (11% v. 17%, $p = 0.04$). This data has been confirmed by a randomized trial that found no increase in BCRL when patients (with lymphedema) began progressive weight lifting compared with no activity. Breast cancer survivors (at risk for lymphedema) who performed slowly progressive weight lifting twice weekly for 1 year were less likely to experience clinically significant increases in arm swelling than women in the control group. One study of LE onset among survivors at risk for BCRL compared a 1-year trial of slowly progressing weight lifting (the intervention) with no exercise (the control). The weight lifting did not result in increased incidence of LE [64].

Physical Activity and LE (PAL) Trial

The PAL trial was a randomized controlled intervention study involving 295 women who had previously been treated for breast cancer. The trial evaluated the effect of twice-weekly progressive weight lifting during a 12-month period on LE status [65]. Four diagnostic methods were used to evaluate LE outcomes: (i) interlimb volume difference through water displacement, (ii) interlimb size difference through sum of arm circumferences, (iii) interlimb impedance ratio using bioimpedance spectroscopy, and (iv) a validated self-report survey. For the 71 women in the weight-lifting group and the 70 women in the control group defined as having LE according to the PAL trial definition, median time since LE diagnosis was 45 (1, 183) and 56 (2, 170) months, respectively. Approximately 40% of these

women had LE for between 1 and 3 years, whereas around 60% had it for more than 3 years [65]. Progressive weight lifting was shown to be safe for women following breast cancer, even for those at risk or with LE.

Reducing Risk of BCRL

SLNB versus ALND: The incidence of BCRL is less after sentinel lymph node biopsy (SLNB) than after axillary lymph node dissection (ALND). NSABP B-32 trial compared 3-year postsurgical morbidity levels of patients with negative SNLD alone and those with negative SNLD and ANLD, and it has shown that arm volume differences of more than 10% at 36 months and were evident for the ALND (14%) and SLND (8%) groups: $P < 0.05$ [66]. IBCSG 23–01 is a randomized trial of axillary dissection vs. no axillary dissection for patients with clinically node negative breast cancer and micrometastases in the sentinel node, and in this study, BCRL was 13% after ALND, and it was 3% after SLNBc at a median follow-up of 5 years [67]. A retrospective study evaluated rates of lymphedema in mastectomy patients who received SLNB with RT, compared to ALND with or without RT. Six hundred and twenty-seven breast cancer patients who underwent mastectomies between 2005 and 2013 were prospectively screened for lymphedema, median 22.8 months follow-up (range 3.0–86.9). The 2-year cumulative lymphedema incidence was 10.0% (95% CI 2.6–34.4%) for SLNB + RT compared with 19.3% (95% CI 10.8–33.1%) for ALND-no RT, and 30.1% (95% CI 23.7–37.8%) for ALND + RT. The lowest cumulative incidence was 2.19% (95% CI 0.88–5.40%) for SLNB-no RT. By multivariate analysis, factors significantly associated with increased LE risk included RT ($p = 0.0017$), ALND ($p = 0.0001$), and greater number of lymph nodes removed ($p = 0.0006$) [68].

In the EORTC 10981-22023 AMAROS trial from Europe (a randomized, multicenter, open-label, phase 3 non-inferiority trial), patients were randomly assigned by a computer-generated allocation schedule to receive either ALND or axillary RT in case of a positive SLNB.

Information on LE and arm circumference increases were collected from 98% of 1265 patients at baseline, 820 (65%) of 1255 at 1 year, 714 (62%) of 1154 at 3 years, and 614 (69%) of 895 at 5 years. LE was noted significantly more often after ALND than after axillary RTy at every measured time point. An increase in arm circumference by at least 10% was reported in a numerically greater proportion of patients in the ALND group compared with the axillary RT group; however, the difference was only significant at 5 years. LE was significantly more frequently reported in this subgroup compared with patients who were treated with ALND or axillary RT only (13% vs 6%, respectively) [69].

Axillary reverse mapping (ARM) is a new concept The ARM technique has been developed to map and preserve arm lymphatic drainage during ALND and/or SLNB, and minimizing arm LE. The arm and breast lymphatic drainage patterns can be visualized using blue dye or radioisotopes, or with subdermal injection of indocyanine green (ICG) via Photo Dynamic Eye; (Hamamatsu Photonics, Hamamatsu, Japan). This technique allows protection of the lymphatic channels draining the upper extremity during ALND or SLNB via removal of only the breast lymphatics. The hypothesis of ARM procedure is based on mapping the lymphatic pathway both arm and breast and preserve the arm lymphatic drainage during ALND and/or SLNB. However, there are important drawbacks of the ARM procedure; the ARM nodes may be involved with metastatic foci in patients with extensive axillary lymph node metastases, or the SLNB draining of the breast may be the same as the ARM node draining of the upper extremity in a minority of patients. Because the success of ARM in reducing LE has not yet been determined, the ARM procedure is not a standard procedure in surgical management of breast cancer. There are some problems related to practical issues for ARM procedure that remain to be resolved: (a) insufficient identification rates of the ARM nodes and/or lymphatics as well as a persistent blue stain at the site of injection, (b) the ARM nodes may be involved with metastatic foci in patients with axillary lymph node metastases, and (c) the SLNB draining of the breast may be the same as the ARM node draining of the upper extremity in a minority of patients. Therefore, further studies are needed before this technology can be included as a standard procedure in breast cancer surgical management [8, 70].

Challenges and Conclusion

There is significant heterogeneity in the literature regarding incidence, diagnosis, and management of BCRL. Diagnosis and treatment, and level of awareness are not standard among either patients or healthcare providers. There is varying information available regarding the risk factors of lymphedema. Treatment applied in breast cancer, patient records, and follow-up is not standard (the width of surgery: BCT, MRM, oncoplastic, AD, SLNB, RT +/−), and even though there are many reported suggestions in literature, there are no studies on the universal recommendations. Recommendations are based on basic pathophysiological information but no prospective randomized study. During the decision for each procedure of surgical, radiation, and chemotherapeutic, the incidence of BCRL should be foreseen regarding each procedure and their combination. Newer diagnostic techniques, such as DEXA and BIS, showed a significant improvement upon traditional

techniques by providing additional quantitative standardized cutoff values without observer variability, which are increasing the sensitivity the detection of potential subclinical patients, and accurately measuring the extracellular fluid space. Treatment paradigms have evolved over the last decade. There is increasing support in the literature for the use of compression sleeves for subclinical disease, demonstrating excellent outcomes with minimal morbidity, and for CDT being used in more advanced cases of BCRL. Long-term outcomes with treatment strategies are limited. Risk reduction strategies need to incorporate treatment and individual patient risk factors, which increase BCRL. These strategies must include proper surveillance and diagnosis to increase the number of patients diagnosed at early subclinical stage. Awareness is important to reduce the factors that affect lymphedema. Long-term research studies are required to investigate risk factors for lymphedema development in patients undergoing surgical or radiotherapy treatment. Relevant healthcare professionals, particularly within primary care and the specialties of oncology, palliative care, vascular surgery, genetics, and dermatology, and also patients should be aware of the signs and symptoms of LE. After diagnosis, appropriate referral pathways should be constructed to all relevant healthcare professionals in an adequate level of education regarding lymphological disorders and correct treatment.

Conclusion

The main objective is to reduce lymph production and to prevent blockage of lymph flow:

- Subclinical monitoring for early diagnosis and early initiation of therapy and prevention of transition to advanced stages.
- Support the lymph flow: arm and shoulder exercises, massage, elevation, avoid bandages, garments and clothing that are excessively tight.
- Guard against infection: Keep skin moist, avoiding excessive sun and extreme cold, and avoid injury that disrupts the skin integrity.

Current findings:

- Early diagnosis and intervention prevent advanced-stage LE.
- Exercise, massage, elevation, avoidance of tight garments and clothing are important for lymph flow.
- Control in weight: maintain normal healthy weight and perform regular exercise.
- Development of LE affects the general well-being and patient quality of life.
- Exercise does not lead to an increase in LE but improves the quality of life due to the positive functional effect.
- Starting shoulder exercises is more effective at the first 48 h than after 7 days.
- Monitoring for LE with BIS and early physiotherapy: education and increased exercise program.
- Physical therapy programs: manual lymphatic drainage massage produces improvement.
- Scar tissue massage produces improvement.
- Relaxation therapy combined with exercise produces improvement.

Suggestions for preventing BCRL:

- Protection from sunburn.
- Infection prevention (manicures skin incisions).
- Skin care and moisturizing.
- Avoid heavy exercise, as it may increase the blood flow in the arm and therefore the lymph production.
- Tight clothing can disrupt the flow of lymph.
- Any compression garment must be provided by an experienced therapist. Otherwise, it may trigger LE through a tourniquet effect.
- Although there is no consensus regarding the prophylactic use of compression garments, their use for high-risk situations such as air travel is recommended.

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Reproductive Issues in Breast Cancer

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Ercan Bastu and Faruk Buyru

Introduction

Breast cancer is the most common malignancy in women, and on average, more than 25,000 women are diagnosed with breast cancer before reaching the age of 45 years each year in the United States [1]. Generally, cancer can have detrimental effects on the future fertility and pregnancies of women in adolescence or their reproductive years. In addition to the age and family history of the patient, the development of breast cancer is also associated with reproductive issues, which can be characterized as exposure to sex hormones. When a patient is diagnosed with breast cancer during pregnancy, treatment is possible. However, treatment should be administered using a multidisciplinary approach. In the developed world, there is a trend toward delaying childbirth until the later years of reproductive age. Infertility is a risk faced by breast cancer patients undergoing cancer treatment. Hence, preservation of the fertility of breast cancer survivors of reproductive age has become an important factor in quality of life after cancer.

In this chapter, our aim is to present associations between the risk of developing breast cancer and reproductive issues, breast cancer treatment and fetal effects during pregnancy, evidence regarding the effect of breast cancer treatments on fertility, and potential fertility preservation methods.

Reproductive Risk Factors in Breast Cancers

Given recent advances in medical technology, it is now possible to perform molecular testing to subcategorize breast tumors to personalize the cancer treatment regimen according to the specific needs of the patients. Hence, the associations in the chapter will be covered according to the breast tumor subtypes. The subtypes will be evaluated in three main categories: (1) breast tumors that are hormone (estrogen and/or progesterone) receptor positive (HR+); (2) breast tumors that overexpress the human epidermal growth factor receptor 2 protein (HER2+); and (3) breast tumors that lack three markers (estrogen, progesterone, HER2+), which is also referred to as triple-negative breast cancer (TNBC). Evaluating potential associations at the subtype level is vital to advance the understanding of breast cancer's etiology and enable clinicians to establish personalized breast cancer treatment regimens.

Reproductive Risks in HR-Positive Breast Cancers

Parity

According to the currently available literature, the risk of developing HR-positive breast cancers exhibits the strongest association with parity [2–18]. In TNBC, the evidence is not as strong as that observed in HR-positive breast cancers because only few studies have reported a potential association [16, 19, 20]. The literature on HER-positive breast cancers is even more limited. One cohort study documented that women with at least one child exhibited a decreased risk of developing HER-positive breast cancers compared with women with no children [16].

Breastfeeding

Data on the association between the risk of developing HR-positive breast cancers and lactation history are more limited compared with parity. Nevertheless, a few studies indicated a significant, inverse association between the risk of developing HR-positive breast cancers and lactation history [2, 13, 14, 16].

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Menstruation

Menstruation characteristics are associated with the risk of developing HR-positive breast cancer, especially for patients with a younger age at menarche [2, 3, 11–14, 16, 17, 21, 22]. Menopause at an older age is only associated with risk of developing HR-positive breast cancer in a few studies [2, 18, 22].

Hormone Use

Related literature suggests that current hormone usage is associated with an increased risk of developing HR-positive breast cancer [12, 22, 23]. Previous hormone usage does not have a similar strong association; only one study to date has reported a significant association [2].

Reproductive Risks in HER2-Positive Breast Cancers

Current literature on reproductive risks in HER2-positive breast cancers is somewhat limited. One study argued that women who had a single child exhibited a significantly decreased risk of developing HER2-positive breast cancers compared with nulliparous women [16]. The same study suggested that breastfeeding was inversely associated with the risk of developing HER2-positive breast cancers. Another case-control study confirmed this finding [13]. The literature on hormone use and HER2-positive breast cancers is inconclusive [8, 22, 24].

Reproductive Risks in Triple-Negative Breast Cancer

Similar to that of HER2-positive breast cancers, the literature on reproductive risks in TNBCs is limited. Whereas several studies indicated a strong inverse relationship between parity and risk of developing HR-positive breast cancers, only a few studies indicated such a relationship in TNBCs [19, 20]. Breastfeeding was inversely associated with the risk of developing TNBCs [4, 5, 13, 16, 22]. Likewise, age at menarche has an inverse association with the risk of developing HER2-positive breast cancers [13, 18, 19]. Regarding hormone use, only one study documented a significant association with current use and not previous use [22].

Infertility Treatments and Breast Cancer

Some studies have evaluated whether assisted reproductive technology (ART) treatments increase the risk of breast cancer as well as other types of cancers. In one multicenter case-control study, the use of fertility drugs did not increase the risk of developing breast cancer, with the exception of long-term use of human menopausal gonadotropin (hMG) [25]. In a Swedish cohort study on 24,058 women who underwent in vitro fertilization (IVF) of whom 1279 also had a diagnosis of cancer, a reduced risk of developing breast cancer was noted, and this result was even more significant in participants with a history of multiple birth delivery [26]. In a Danish cohort study of 54,362 women who commonly used clomiphene as an ovulation induction agent, a significant association was not noted between developing breast cancer and ovulation-inducing agents [27]. In a meta-analysis that included 22 studies, a significant association between developing breast cancer and ovulation-inducting agents was not documented [28].

Pregnancy During Breast Cancer

Similar to the case with nonpregnant women, breast cancer in pregnant women presents as a palpable mass, changes in skin, and/or bloody nipple discharge. However, these symptoms are occasionally confused with the physiological changes experienced during pregnancy [29, 30]. As more women participate in the workforce and obtain an education, they tend to defer childbearing, especially in developed countries. Because the incidence of several cancers increases with age, facing breast and other cancers during pregnancy has become a more frequent occurrence.

Treatment of Breast Cancer During Pregnancy

Breast cancer treatment strategies during pregnancy depend on several factors, such as the tumor biology and stage, gestational week, and the goals of the mother and the father. Because this condition is a complex issue, counseling is imperative. A multidisciplinary approach to counseling is beneficial. Such a team might include obstetrics, oncological, psychological, and pediatric specialists.

Termination of Pregnancy

When a patient is diagnosed with breast cancer during pregnancy, her choices determine the course of action to continue the pregnancy [31]. The patient and her partner should be well informed regarding potential treatment options, and it should be noted that the termination of pregnancy does not necessarily improve the maternal outcome [32]. However, the continuation or termination of pregnancy is the decision of the patient.

A few studies in the literature have documented that the survival rate is decreased for a patient who chooses preg-

nancy termination compared with a patient who chooses to continue the pregnancy [33, 34]. However, in both studies, the cancer stage was not matched between the termination and continuation groups, thus creating a clear bias. Clinicians are likely more inclined to recommend pregnancy termination to patients with poor prognosis, which might serve as a possible explanation for the bias.

Breast Cancer Surgery During Pregnancy

If breast cancer surgery is chosen as the treatment approach, the use of anesthetic agents is safe for the fetus at any gestational age [35–37]. However, a multidisciplinary approach is beneficial. Such a team should consist of surgeons, obstetricians, pediatricians, and anesthesiologists. Some potential concerns include infections, hypotension, hypoglycemia, thrombosis, or hypoxia because these factors may have detrimental effects on the fetus. It is advisable for surgeons to utilize fetal heart rate monitoring to monitor fetal distress. If the patient feels pain, it can trigger preterm labor. Hence, adequate usage of analgesia is of the utmost importance. Tocometry can be performed postoperatively to evaluate uterine activity that was potentially masked by analgesia [29]. Given the risk of thrombosis, a low molecular weight heparin for thromboprophylaxis should be considered.

In a study that included 67 breast cancer surgeries during pregnancy, only a few complications were documented [38]. If the patient wants breast reconstruction, reconstruction should be considered after the delivery due to physiological changes during and after pregnancy [39].

Lymph node staging appears to be safe during pregnancy [40–43]. The absorbed doses of sulfur colloid into the breast are estimated to be 0.00045 Gy [44], which is considerably less than the fetal threshold of 0.1–0.2 Gy [41, 43]. However, the use of dye may result in an anaphylactic maternal reaction that can cause distress to the fetus; thus, dyes should be not be used during the pregnancy [45]. For lymph node biopsies during pregnancy, technetium-based identification has been used with success [40]. Instead of a 2-day protocol, a low-dose 1-day protocol may be preferred.

Cytotoxic Treatment During Pregnancy

The administration of cytotoxic treatments during pregnancy has varying effects depending on the gestational age of the patient. If treatment is undertaken during the period of fertilization and implantation, it will most likely be an "all-or-nothing" event. Depending on how many omnipotent stem cells survive, a healthy embryo will develop, or a miscarriage will occur. During organogenesis, congenital malformations may occur in the fetus. During the second and third trimesters of pregnancy, fetal anomalies will likely not occur during fetal maturation and growth. However, growth restriction, prematurity, and intrauterine death may occur during these trimesters [46]. The long-term outcome of cytotoxic exposure is not reported in the literature. However, genetic anomalies, carcinogenesis, and neurodevelopmental problems may theoretically occur [42, 46].

Chemotherapy is typically utilized in breast cancer patients, especially in young patients. If the patient is pregnant, the gestational age should be considered along with the timing of surgery and the potential requirement of radiotherapy. It is preferable to utilize chemotherapy after the first trimester. Adjuvant or neoadjuvant therapy may be used. Various clinicians have used weekly epirubicin given its fetal safety [47]. However, epirubicin is not a standard chemotherapy for the treatment of breast cancer. Dose-intensified chemotherapy treatments are beneficial to TNBC patients with increased disease-free rates [48]. TNBC is frequently observed in pregnant women. However, the literature regarding the use of dose-intensified chemotherapy during pregnancy is lacking. Regardless of the treatment used, it is prudent to calculate the drug dosage based on the current weight and constantly modify the dose as the weight of the patient increases during the pregnancy [29].

For the safety of the fetus, chemotherapy is not indicated until week 10 of gestation. The short-term outcomes of such exposure, including congenital malformations, appear to be safe [32, 47, 49–56]. Fetal growth restriction has been documented as a result of chemotherapy exposure due to cancer in general [46]. However, in studies that focused on breast cancer treatment during pregnancy, this growth restriction was not identified [55].

Only a few studies regarding the long-term outcomes of exposure to chemotherapy are available. In one study with a follow-up period of 19 years, no congenital or neurological anomalies were identified [57]. In another study, only 2 of 57 children experienced developmental problems [53]. In a study of 70 children exposed to chemotherapy, their general health was similar to the age-matched population [58]. In this study, prematurity was frequently documented. Hence, iatrogenic preterm delivery should be avoided whenever possible.

Bisphosphonates and Hormonal Agents During Pregnancy

In premenopausal breast cancer patients, the use of bisphosphonates combined with endocrine therapy appears to be effective [59]. However, bisphosphonates have not been utilized in pregnant breast cancer patients to date. In pregnant animal studies, maternal toxicity, skeletal retardation, fetal underdevelopment, and hypocalcemia have been documented [60]. Hence, the use of bisphosphonates is not indicated during pregnancy. The US Food and Drug

Administration (FDA) has rated bisphosphonates as a category C pregnancy risk.

Bisphosphonates can remain in mineralized bone for many years. Thus, if patients use these agents before conception and/or during pregnancy, a teratogenic risk is possible. However, studies on breast cancer patients who received bisphosphonates prior to conception and during pregnancy did not document a significant increase in the risk of forming malformations or changes in fetal bone modeling [61]. If the breast cancer patient uses bisphosphonates during pregnancy, hypocalcemia should be avoided if possible because it can negatively affect uterine contractility.

Any hormonal agents (e.g., selective estrogen receptor modulators) should not be utilized during the pregnancy because they can potentially alter the hormonal environment. According to the available evidence, tamoxifen may cause fetal harm, including ambiguous genitalia, craniofacial malformations, and fetal death [62]. Hence, its usage should be avoided during pregnancy. Similarly, aromatase inhibitors should not be used in premenopausal patients who are pregnant.

Trastuzumab Therapy During Pregnancy

Because HER2 is expressed in the fetal renal epithelium [63], long-term administration of trastuzumab may cause renal failure or fetal death in HER2-positive breast cancer patients [64]. Hence, the use of trastuzumab is not recommended in pregnant HER2-positive breast cancer patients. However, short-term usage of trastuzumab appears to be less toxic because renal function is recovered upon the withdrawal of the drug in the children who survive [29]. More recent breast cancer treatment agents, such as tyrosine and bevacizumab kinase inhibitors, have not been adequately studied in pregnant patient groups. Their usage in the pregnant women with breast cancer may be considered after the results of an adequate number of well-designed studies are available.

Fertility After Breast Cancer

Premenopausal patients with breast cancer who have delayed pregnancy or want more children in the future may want to preserve their ovarian function after breast cancer treatment or be curious as to how treatment will affect their fertility. These concerns are valid because the treatment of breast cancer may increase the risk of infertility in several patients.

Per clinical routine, premenopausal patients who are diagnosed with breast cancer currently receive an adjuvant therapy. This therapy consists of cytotoxic chemotherapy; (surgical, irradiation, and chemical) all describe ovarian suppression, antiestrogen therapy, or a combination of the abovementioned therapies. The use of adjuvant therapy with the abovementioned approaches significantly improves the survival rate of premenopausal breast cancer patients. However, patients must also address toxicity, which can cause early menopause and infertility. For example, cytotoxic chemotherapy agents may have detrimental effects on the germ cells of the ovary, which can lead to premature ovarian failure (POF) in premenopausal patients with breast cancer [65–68]. Hence, the preservation of fertility has become an important aspect of the quality of life after cancer in premenopausal patients who have survived breast cancer. Fertility preservation in cancer survivors of reproductive age has created a new subfield in reproductive medicine [69], which is referred to as “oncofertility” by some researchers.

Fertility Preservation Options in Breast Cancer Patients

For patients who have survived breast cancer or were recently diagnosed with breast cancer, the American Society of Clinical Oncology recommends exploring fertility outcomes and obtaining a referral to an infertility subspecialist [70]. The fertility preservation approach will depend on the age of the patient and the urgency of the adjuvant treatment for the recently diagnosed patient [71, 72].

With the introduction of more effective adjuvant treatments in the field of oncology, more patients with breast cancer are surviving. Hence, the desire to become pregnant after surviving cancer has become a real concern for many premenopausal breast cancer patients. Based on the current clinical routine, various options are available that can preserve fertility in premenopausal breast cancer patients who must address potential POF. These options include ART, such as IVF, in vitro maturation (IVM), and oocyte, ovarian tissue, or embryo cryopreservation [73–93]. Numerous studies have demonstrated up to 60% clinical pregnancy rates and approximately 34% live birth rates after transfer of freeze-thawed embryos in infertility patients with a mean age of 35.1 ± 4.03, which is comparable to outcomes of fresh embryo transfer [103, 104].

In 1992, a patient who was infertile due to radical mastectomy for breast cancer gave birth to a healthy baby via ovarian stimulation and IVF [82]. However, because increased levels of estrogen may trigger dissemination and proliferation of breast cancer cells, several oncologists do not recommend ovarian stimulation protocols for breast cancer survivors [89]. By foregoing ovarian stimulation, natural cycle IVF treatment along with embryo cryopreservation has been the preferred approach in breast cancer patients who have a partner at the time of the treatment. Interestingly, tamoxifen, an agent that is frequently used in breast cancer

patients, has been utilized in infertile patients who are anovulatory as well [84]. However, tamoxifen is not regularly used in ovarian stimulation protocols in IVF. In a study of breast cancer patients, ovarian stimulation with tamoxifen was compared with natural cycle for IVF treatment [85]. The number of embryos achieved in the group that received tamoxifen was significantly increased compared with the group in which the natural cycle was utilized. Ovarian stimulation with tamoxifen increased estradiol levels. However, because tamoxifen has suppressive effects, this agent may reduce the risk of breast cancer. In another study by the same researchers [86], breast cancer patients were divided into three groups: one group received tamoxifen alone, a second group received tamoxifen with a low-dose follicle-stimulating hormone (FSH), and the final group received tamoxifen with low-dose FSH and an aromatase inhibitor (letrozole). The researchers reported that tamoxifen in combination with FSH and/or FSH in combination with letrozole significantly increased the number of embryos. However, the researchers argued that tamoxifen alone might be the preferred protocol because it leads to a lower increase in estrogen levels. In a previous study, the usage of short-term gonadotropins and aromatase inhibitors as ovarian stimulation agents was safe in breast cancer patients prior to administration of adjuvant treatment for breast cancer [86].

If IVF will be utilized after the breast cancer patient has received adjuvant treatment, the safety period remains poorly established [101, 102]. Various studies have documented no significant increase in congenital malformations using IVF after adjuvant therapies in breast cancer survivors [94, 95]. However, until a safety period is well defined, it would be prudent to evaluate all fetuses cytogenetically. The oocyte cryopreservation success rates vary depending on age, the number of oocytes frozen and the freezing protocol. However, embryo cryopreservation before receiving adjuvant treatments appears to be the most preferred fertility preservation approach in premenopausal breast cancer patients. Oocyte and/or oocyte tissue cryopreservation may be an option for breast cancer patients who do not have a partner at the time of treatment or who do not wish to use a sperm donor or cannot use a sperm donor due to legal issues in the country in which she resides. Evidence suggests that embryo and/or oocyte cryopreservation after ovarian stimulation provides the best chance for fertility preservation [96]. Ovarian tissue cryopreservation may be an option for breast cancer patients who do not want to receive ovarian stimulation or have limited time before the initiation of adjuvant treatment because ovarian stimulation typically requires 10–14 days. A live birth was documented after orthotopic autotransplantation of cryopreserved ovarian tissue in one study. The study argued that the transplantation of cryopreserved ovarian tissue should no longer be regarded as an experimental treatment [79, 80]. Particularly in young breast cancer patients who will receive an adjuvant treatment, ovarian tissue cryopreservation is an interesting option. In addition, IVM is also a promising option in such groups because it significantly improves the oocyte outcome [87]. The use of IVM before oocyte or embryo cryopreservation achieved pregnancy rates of 3.8% and 8.1%, respectively, in one study [97]. Another approach to fertility preservation involves the use of ovarian tissue cryopreservation in combination with immature oocyte collection from the tissue, followed by oocyte vitrification via IVM specifically in younger breast cancer patients [74–77]. However, the risk of cryopreserving malignant cells that can be potentially transferred back to the patient during reimplantation is always a concern. Hence, it would be prudent to develop screening using immunohistochemical markers. Leukemia is an example of a cancer with a high risk of malignant cell reimplantation. Hence, it is vital to screen for residual disease before ovarian tissue retransplantation, especially in patients with hematological cancers [78].

Recent advances in the fields of oncology and reproductive medicine have created several options for breast cancer patients who wish to preserve their fertility. However, hurdles must still be overcome. For example, the management of patients with BRCA mutations remains a challenge. Preimplantation genetic diagnosis during IVF treatment can serve as one alternative to prevent the transmittance of the mutation to the offspring in such patients [91]. Moreover, prenatal diagnosis after implantation can be performed. Consequently, a patient may decide to continue the pregnancy if the fetus is not a carrier of the mutation. Of course, there is an ongoing debate on the ethical concerns and wishes of the patients regarding the usage of such methods [98–100].

There are no robust data on the role of ovarian suppression in cancer patients using gonadotropinreleasing hormone (GnRH) analogs to protect the ovaries from chemotherapy-induced damage [106]. The greatest concern regarding the effectiveness of ovarian suppression is that the primordial follicles that constitute the ovarian reserve are quiescent and do not express gonadotropin or GnRH [107, 108]. GnRHa induces a hormonal state similar to the prepubertal stage, and if ovarian suppression were protective, children of prepubertal age would be resistant to the gonadotoxic effects of chemotherapy, which is not the case [109]. Based on these contradictory results and ovarian biological facts, the use of GnRHa for the protection of ovaries from chemotherapy damage remains controversial and cannot be recommended as an effective method of fertility preservation.

A concern related to ovarian stimulation before adjuvant or neoadjuvant chemotherapy is the delay in the initiation of breast cancer treatment. However, some studies have shown that initiation of chemotherapy may be delayed up to 12 weeks after breast surgery without any adverse effect on survival and recurrence rates.

Pregnancy After Breast Cancer

Patients in the decision process for fertility preservation treatments frequently question the safety of pregnancy after completion of cancer treatment. Based on the current evidence, pregnancy after breast cancer is not associated with an increased risk of adverse outcomes. In general, patients are advised to delay pregnancy for at least 2 years after diagnosis, as the risk of recurrence is highest in this time frame [105].

Conclusion

Strong evidence on reproductive risks exists for HR-positive breast cancers. Specifically, plausible data suggest significant associations between HR-positive breast cancers and nulliparity, current hormone use, and age at first birth. The limited data on HER-positive breast cancers do not reveal a strong association with any potential reproductive risk. There is also limited literature available on TNBCs compared with HR-positive breast cancers. The most consistent finding from these studies involves the inverse association between breastfeeding and the risk of developing TNBCs. Because the TNBC subtype is aggressive in nature, there is a definite need for studies to better characterize this subtype.

If breast cancer is detected during pregnancy, termination of pregnancy does not necessarily improve the prognosis of the cancer. Breast cancer during pregnancy must be managed with a multidisciplinary approach that should follow standard protocols for nonpregnant patients as much as possible while considering the safety of the fetus. Several clinicians suggest that the usage of chemotherapy and radiotherapy is safe during pregnancy in breast cancer patients. However, studies that focus on the long-term outcome of children exposed to such treatments are urgently needed to confirm such recommendations. Premature birth will lead to a negative outcome and should be avoided as much as possible in breast cancer patients.

Various ART approaches are available for breast cancer patients who wish to their preserve fertility after cancer treatment. These approaches can be utilized before or after the initiation of adjuvant treatment for breast cancer. Hence, adequate counseling should be provided to premenopausal breast cancer patients prior to cancer treatment. If the patient wishes to preserve her fertility, her chances must be optimized by providing the most suitable ART treatment for her via a multidisciplinary approach.

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Onco-Cardiology for Breast Cancer

49

Ozlem Soran

Introduction

Over the last decade, the breast cancer mortality rate has significantly decreased, and the perception of breast cancer has consequently dramatically changed from a mortal disease to a chronic disease. Similar to all chronic diseases, breast cancer patients face different health challenging problems in addition to cancer-related problems.

Breast cancer is the most often diagnosed cancer and the second leading cause of cancer mortality following lung cancer. Breast cancer is a common health problem in the Western world, comprising approximately one third of all cancers in women [1]. The breast cancer incidence increased approximately 0.2% annually between 1997 and 2000; during the same time, mortality due to breast cancer was reduced by 2.3% per year. Women with early-stage breast cancer are now surviving longer by means of improved outcomes with chemo- and hormone therapy; one disadvantage of this improvement is the risk of adverse cardiovascular effects from breast cancer therapy, also known as cardiotoxicity. The National Cancer Institute generally defines cardiotoxicity as "toxicity that affects the heart" [2]. This definition embraces a variety of side effects affecting both the heart and circulation: valvular injury, dysrhythmias, changes in blood pressure, arterial/venous thrombosis, or impairment in myocardial contraction or relaxation (i.e., systolic and diastolic dysfunction) [3]. In fact, the recognition of cardiotoxicity goes back at least to the classic report by von Hoff and colleagues in the mid-1970s that outlined the relationship between the severity of heart failure and the dosage of doxorubicin. By the mid-1980s, the concept of cardio-oncology or oncologic cardiology became a recognized speciality [4, 5]. From a clinical standpoint, drug-related cardiotoxicity was defined by the Cardiac Review and Evaluation Committee, which supervised trastuzumab clinical trials, as one or more of the following: (a) cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum; (b) symptoms associated with congestive heart failure (CHF); (c) signs associated with CHF (e.g., tachycardia); and (d) reduction in LVEF from baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signs or symptoms of heart failure or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms [6]. Notably, the severity of these cardiovascular toxicities may range from asymptomatic subclinical abnormalities, such as LVEF decline, to life-threatening events, such as acute ischemia [3].

Figure 49.1 summarizes the most common cardiovascular side effects of the chemotherapeutics drugs used in breast cancer treatment (Fig. 49.1). Breast cancer survivors now actually have a higher risk of developing cardiovascular disease than recurrent cancer. Heart failure has become the most common side effect. Many patients who will be cured of their cancer will suffer from heart failure. In fact, the American College of Cardiology and American Heart Association's staging classification for heart failure categorize cardiotoxic chemotherapy as stage A. This classification suggests that exposure to certain chemotherapeutic

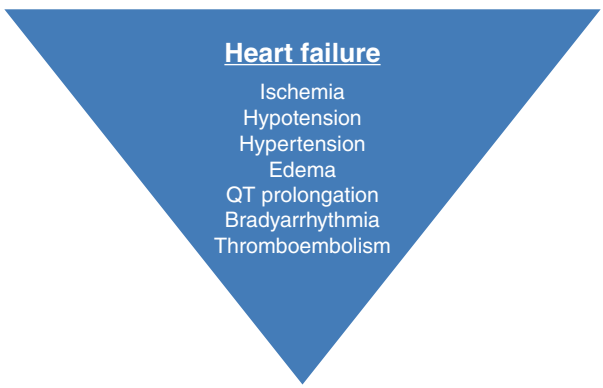

Fig. 49.1 Common cardiovascular manifestations

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drugs is considered a high-risk factor for developing heart failure [7, 8].

Heart failure is a syndrome of epidemic proportions in the USA, affecting more than five million patients. The syndrome is the end result of multiple etiologies, including coronary artery disease, diabetes, hypertension, exposure to chemotherapeutic drugs, family history of cardiomyopathy, previous myocardial infarction (MI), and asymptomatic valvular disease [9, 10]. Heart failure is a clinical syndrome caused by systolic or diastolic left ventricular dysfunction or a combination of both. Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors (ACE-i), and diuretics are the choices of asymptomatic and symptomatic left ventricular dysfunction management. Systolic function is measured via the LVEF, which represents the percentage of blood expelled from the resting left ventricle with each systolic contraction. The normal LVEF is 50% or greater. Diastolic dysfunction is defined as left ventricular dysfunction with normal LVEF, and diastolic heart failure occurs when diastolic dysfunction is accompanied with dyspnea, fatigue, and fluid retention. Left ventricular dysfunction occurs in patients with both decreased and normal ejection. Once heart failure is diagnosed, the survival rate is significantly reduced. Awareness of cardiac sequelae will help oncologists manage patient care and seek cardiac assistance to continue their life-saving treatments [10].

This chapter reviews the cardiotoxic effects of commonly used systemic therapeutic agents in patients with breast cancer and offers advice for effective patient management. Terms "onco-cardiology," "cardio-oncology," and "oncologic cardiology" are used interchangeably throughout the chapter.

Anthracyclines

Anthracycline-based regimens, including epirubicin or doxorubicin, have been the mainstream of breast cancer chemotherapy in both adjuvant and metastatic settings [11]. However, the recognition of cardiac dysfunction as a consequence of these treatments has significantly affected their use [12]. The most common manifestation of anthracycline-induced cardiotoxicity is left ventricular dysfunction.

Although anthracycline-related cardiotoxicity is a well-known adverse effect, its underlying mechanism remains uncharacterized. A well-known hypothesis draws attention to the role of oxygen free radicals that could lead to irreversible damage in cardiomyocytes. However, this hypothesis has been questioned in the last decade because it does not appear to explain the complete mechanism [12]. Recently, a molecular hypothesis suggested that anthracycline impairs DNA repair pathways via interacting with the topoisomerase-II-beta enzyme in myocytes [13].

Anthracycline-related cardiac toxicities are known as type I chemotherapy-related cardiac dysfunction [14]. This type of toxicity causes irreversible damage. A recent meta-analysis revealed a fivefold increased risk of clinical cardiotoxicity, a sixfold increased risk of subclinical cardiotoxicity, and a fivefold increased risk of cardiac death among cancer patients treated with anthracyclines compared with those treated with nonanthracycline-based regimens [15].

Several risk factors have been associated with the increased risk for anthracycline-related cardiac toxicity. One such risk factor is the cumulative dose [16]. For doxorubicin, the estimated percentage of patients with doxorubicin-related heart failure is 5.0% at a cumulative dose of 400 mg/m^2, 26.0% at 550 mg/m^2, and 48.0% at 700 mg/m^2 [17]. Likewise for epirubicin, the risk of cardiotoxicity increased from 1.9% at a dose of 800 mg/m^2 to 4.3% at a dose of 900 mg/m^2 and 15.0% at a dose of 1000 mg/m^2 [18]. These observations have led to the adoption of thresholds regarding the accepted cumulative dose of anthracyclines in treated patients. These thresholds differ for epirubicin and doxorubicin because epirubicin is less cardiotoxic than doxorubicin at equimolar doses. In addition, epirubicin produces lower levels of secondary alcohol metabolites [19]. In the previously mentioned meta-analysis, the authors found that the use of epirubicin significantly decreased the risks of both clinical and subclinical cardiotoxicity [15]. However, recent evidence indicates that anthracycline-related cardiotoxicity may occur even in lower cumulative doses, especially among patients with preexisting cardiovascular risk factors. Therefore, no safe threshold exists. Consequently, in patients receiving anthracycline-based therapy, other classical risk factors for cardiac toxicity should be considered. These risk factors include the following [20]:

1. The age at the time of drug exposure
2. Concomitant administration of other cardiotoxic chemotherapeutic agents (e.g., trastuzumab)
3. Concurrent or prior chest irradiation
4. Preexisting coronary artery disease
5. Preexisting hypertension
6. Preexisting peripheral vascular disease
7. Preexisting diabetes

Because the abovementioned risk factors have been recognized for anthracycline-related cardiotoxicity, a variety of approaches have been suggested to decrease the risk of cardiotoxicity while maintaining efficacy. These following suggestions have been proposed [21, 22]:

1. Alterations in schedules of drug administration
2. Limiting the total cumulative dose
3. Administration of nonanthracycline-based chemotherapy without jeopardizing survival

4. Modifications of the anthracycline molecule (e.g., liposomal anthracyclines)
5. The use of adjunctive cardioprotective treatment with dexrazoxane

Several investigators suggest that bolus administration of anthracyclines may increase the incidence of cardiotoxicity compared with infusional administration. A Cochrane review of five randomized controlled trials found that continuous infusion for 6 h or longer significantly reduced the risk of clinical heart failure (and likely also subclinical cardiac damage) compared with infusions for 1 h or less [21]. No evidence suggests that continuous infusion reduces response rate or survival. Therefore, per the currently available data, the infusional administration of anthracyclines for greater than 6 h may serve as the correct approach to decrease the incidence of cardiotoxicity; however, the need for hospitalization and central venous catheters and its questionable cost-effectiveness limit its clinical use.

The encapsulation of doxorubicin into liposomes significantly reduces its distribution volume, diminishing its diffusion and consequently its toxicity in healthy tissues [23]. In a meta-analysis, liposomal compared with conventional doxorubicin significantly decreased the risk of clinical and subclinical cardiotoxicity [15]. However, all the studies included in the meta-analysis investigated the role of liposomal doxorubicin in patients with metastatic breast cancer, and the role of liposomal doxorubicin in the adjuvant setting is currently unknown and under investigation. Early phase II trials demonstrated that liposomal doxorubicin appears to be a feasible option for elderly patients and can be concurrently administered with trastuzumab as an adjuvant treatment [23, 24]. Several ongoing randomized trials are investigating the efficacy and safety of liposomal doxorubicin in elderly early breast cancer populations. With the use of cross-linked multilamellar liposomes, advances in the liposome formulation have been recently published, and in vivo experiments have demonstrated reduced systemic toxicity and improved anticancer activity compared with currently available liposomal doxorubicin [25]. This new formulation incorporates two different chemotherapeutic agents into the same liposome (doxorubicin and paclitaxel) to reduce the toxicity and increase the synergistic effect. Further studies on this new liposome formulation are warranted [26, 27].

The iron-chelating agent *dexrazoxane* may decrease the cardiotoxic effect of doxorubicin. This drug effectively inhibits the generation of free radicals. Dexrazoxane administered with either doxorubicin or epirubicin significantly reduced the incidence of clinical and subclinical cardiotoxicity in a meta-analysis of six randomized trials, of which only three examined dexrazoxane use in a homogenous breast cancer population that had received initial anthracycline-based therapy. However, a nonsignificant trend toward lower response rates among those who received anthracycline plus dexrazoxane was noted [21]. Dexrazoxane is not recommended for use in early breast cancer because of the lack of clinical data on dexrazoxane in the adjuvant setting and the concerns about potential impact on antitumor efficacy.

Another approach to reduce cardiotoxicity involves the avoidance of anthracycline-based chemotherapy in the adjuvant setting. Recently, the docetaxel–carboplatin–trastuzumab triple combination was proven to be as effective as the anthracycline- and taxane-based standard of care chemotherapies with less cardiac events. This regimen offers a worthwhile alternative in patients with human epidermal growth factor 2 (HER2)-positive early breast cancer [28].

Taxanes

Taxanes were originally identified as the natural product paclitaxel derived from the bark of the Pacific yew tree. Taxane agents include paclitaxel and docetaxel. Docetaxel is a semisynthetic analog of paclitaxel, whereas taxane was originally referred to as taxol. Taxanes prevent the separation of chromosomes during anaphase of cell division [29]. Compared with nontaxane combination chemotherapy, taxane chemotherapy as a first-line or second-line treatment is more effective against breast cancer, especially in patients who had been previously treated with anthracyclines. Taxanes decrease cancer progression (i.e., slows down the development of cancer). However, serious arrhythmias, such as bradycardia, ventricular tachycardia, and MI, have been reported in patients with breast cancer who have undergone taxane therapy [29]. According to a study performed by Arbuck et al., paclitaxel caused acute asymptomatic bradycardia in up to 30% of patients [30]. An early series reported a 5% incidence of serious arrhythmias and MI, including ventricular tachycardia in 5 of 140 patients (3.6%) [31]. However, a larger database found that only 0.1% of patients suffered from serious bradycardias and could not confirm that taxanes increased the frequency of ventricular tachycardia or MI [30]. At high cumulative anthracycline doses, taxanes interfere with the metabolism and excretion of anthracyclines and potentiate anthracycline-induced cardiotoxicity. Excess chemotherapy-related cardiac dysfunction has been noted among patients with cumulative doxorubicin doses that exceed 360 mg/m^2, who also received short paclitaxel infusions shortly after doxorubicin treatment [32].

What Can Be Done to Reduce Cardiotoxicity in the Setting of Taxane Therapy?

Slow infusion of paclitaxel and doxorubicin or increased time (24 h) between doxorubicin and paclitaxel treatments

could potentially decrease cardiotoxicity [33, 34]. When combined with paclitaxel, the cumulative doxorubicin dose should not exceed 360 mg/m^2, and doxorubicin should be administered before paclitaxel [32]. Combination treatments with epirubicin and taxane may be less cardiotoxic [35, 36]. A cumulative epirubicin dose limit of 990 mg/m^2 in combination treatments with paclitaxel has been proposed [36]. In clinical trials, docetaxel is associated with increased cardiotoxicity when combined with doxorubicin or epirubicin. Modern adjuvant regimens of taxanes do not increase anthracycline cardiotoxicity. A trial comparing doxorubicin (75 mg/m^2) followed by CMF with the combination of paclitaxel and doxorubicin (60 mg/m^2) followed by CMF found that the incidences of symptomatic cardiac events at 31 months were similar between arms with (0.3% of patients) and without (0.5%) paclitaxel [37]. In a randomized controlled trial of three cycles of dose-dense epirubicin followed by three cycles of paclitaxel then CMF compared with three cycles of dose-dense epirubicin followed by CMF, no severe cardiotoxicity was observed in either arm [38].

Nanoparticle albumin-bound paclitaxel is a newer paclitaxel formulation that may cause less anthracycline cardiotoxicity [39]. Thus, cardiotoxicity may be minimized by carefully choosing agents and regimens [40].

Trastuzumab

Patients with HER2-positive breast cancer exhibited the worst prognosis among breast cancer patients until 1998, when trastuzumab, a humanized anti-HER2 monoclonal antibody, was first approved for the treatment of HER2-positive metastatic breast cancer. In the adjuvant setting, 1-year treatment with trastuzumab offers substantial benefit in terms of both disease-free and overall survival [41, 42].

In the early pivotal trials in the metastatic setting, cardiac dysfunction was recognized as a potential toxicity of trastuzumab, and the rates of cardiac dysfunction ranged from 8% to the unacceptably high rate of 30% in cases of concomitant administration of trastuzumab with anthracyclines [6]. These findings had a significant impact on the design of adjuvant trials. Treatment schedules with the sequential use of anthracyclines and trastuzumab instead of concomitant administration were followed. Strict cardiac exclusion criteria, such as monitoring cardiac function and interim cardiac safety analyses, were adopted [43]. As a consequence, the cardiotoxicity rates in adjuvant randomized trials were reduced compared with metastatic cases (symptomatic CHF rate ranged from 0.8% to 14.2%) [43]. However, a significantly increased risk for both reduced LVEF and CHF was observed in the trastuzumab-treated arm [44]. In the real-world setting, where cardiac exclusion criteria are not as strict as those applied in randomized controlled trials, the rate of cardiac toxicity is similar to that observed in randomized clinical trials [45, 46].

Although trastuzumab-related cardiotoxicity is a well-known adverse effect, its underlying mechanism remains largely uncharacterized. Preclinical data have suggested an important role for the HER2 signaling pathway in cardiac physiology because both HER receptors and their ligands are expressed in cardiomyocytes [47]. The mechanisms of trastuzumab-induced cardiotoxicity differ from those of anthracyclines. Although anthracycline-induced cardiotoxicity is dose dependent, trastuzumab-induced cardiotoxicity is not. An important characteristic of trastuzumab-induced cardiotoxicity is that cardiac dysfunction is reversible upon therapy withdrawal, and the drug can be safely readministered after the recovery of cardiac function [14]. This type of reversible cardiac toxicity is classified as type II chemotherapy-related cardiac dysfunction [14]. One potential mechanism of cardiotoxicity involves the inactivation of a HER ligand-mediated pathway that leads to cell survival in cases of adverse hemodynamics or other stressors [48]. This proposed mechanism could explain both the increased risk for cardiotoxicity when trastuzumab and anthracyclines are combined (the stress and damage caused by anthracyclines is increased) and the reversibility of cardiotoxicity with trastuzumab withdrawal (the pathway becomes functional again) [48].

Investigators have identified several risk factors for trastuzumab-induced cardiotoxicity. These risk factors are as follows [49–55]:

1. Concomitant administration with anthracyclines
2. Advanced age
3. Antihypertensive medications
4. Borderline cardiac function at baseline
5. A history of heart disease
6. Certain polymorphisms in the HER2 gene

The most critical risk factor for trastuzumab-induced cardiotoxicity is concomitant administration with anthracyclines. The association between cumulative anthracycline doses and trastuzumab-induced cardiotoxicity has been clearly demonstrated [49, 56, 57]. In the neoadjuvant setting, the concomitant administration of anthracyclines and trastuzumab was not correlated with an increased risk for cardiac adverse events compared with sequential administration [58–60]. Due to the absence of any difference in pathologic complete remission with the concurrent administration of trastuzumab and epirubicin, this approach is not recommended as a standard of care [58]. In addition, limited follow-up for cardiac events is reported in these studies, which is an important concern [60].

Some efforts have been made to identify certain polymorphisms in the HER2 gene that could trigger cardiotoxicity.

The I655V polymorphism in the HER2 gene is associated with cardiac toxicity in three different research groups [53–55]. With the help of genome-wide association studies, pharmacogenomics may play a pivotal role in identifying patients who are at high risk for trastuzumab-induced cardiac toxicity.

In addition to trastuzumab, two additional anti-HER2 agents have been developed and approved for the treatment of HER2-positive breast cancer: the tyrosine kinase inhibitor lapatinib is approved in the metastatic setting, and the monoclonal antibody pertuzumab is approved in the neoadjuvant and metastatic setting [56–58]. The combination of two anti-HER2 agents has been evaluated as a new treatment option for patients with HER2-positive breast cancers. Lapatinib in combination with trastuzumab exhibits promising results as neoadjuvant and metastatic treatments, whereas pertuzumab is approved only in combination with trastuzumab for neoadjuvant and metastatic treatments [59, 60]. Both of these agents have cardiotoxicity risk [56–58]. This increased risk for cardiac adverse events is a concern regarding the potential risk when two anti-HER2 agents that both increase cardiac toxicity are combined. However, a recent meta-analysis did not reveal an increased risk for cardiac toxicity with any of the combinations compared with anti-HER2 monotherapy [61]. Randomized trials investigating the role of dual anti-HER2 blockade in the adjuvant setting are needed.

Endocrine Therapy for Postmenopausal Women with Breast Cancer

Cardiovascular disease is a major health problem in many developed countries, with 42.7 million cases in 2005 and 459,000 deaths in 2004 in the USA [62]. In addition, cardiovascular disease constitutes an important health concern in older, postmenopausal women independent of BC [62, 63]. Endocrine treatment remains the mainstay of adjuvant therapy for postmenopausal women with hormone-responsive BC.

Historically, tamoxifen was the standard adjuvant endocrine therapy for postmenopausal women with BC, resulting in a reduction in BC recurrence by 40% and death by 26% after 5 years [64]. In women with estrogen receptor (ER)-positive (or ER unknown) disease, treatment with tamoxifen for 5 years after definitive surgery reduces the annual recurrence rate by 41% and BC mortality by 34%, translating into a 9.2% absolute reduction in patients dying from BC at 15 years [65]. Meta-analysis results revealed that tamoxifen produces lipid-lowering effects; a potential cardioprotective effect of the drug was observed in which the rate of death from serious cardiovascular events, such as MI, was reduced during active treatment [65–68]. However, tamoxifen is associated with some potential and occasionally life-threatening side effects due to its partial estrogen-agonist activity. These side effects include an increased incidence of endometrial cancer and thromboembolic events related to the duration of drug exposure [65, 69, 70]. Cancer Research Network results have demonstrated that third-generation AIs have been replacing tamoxifen as adjuvant endocrine therapy for postmenopausal women with early BC since 2000 [71].

Third-generation AIs are highly selective for the aromatase enzyme and substantially well tolerated. Currently, three third-generation AIs are being used clinically in the USA. All third-generation AIs reduce systemic estrogen levels by 98% [72]. A review of 25 studies reported that AIs demonstrate a significant survival benefit in the treatment of metastatic BC compared with other endocrine therapies [73]. AIs are between 15% and 25% more effective than tamoxifen in reducing the relative risk of recurrence [74–76]. Both anastrozole and letrozole improved 5-year disease-free survival but not overall survival compared with tamoxifen. A meta-analysis of first-line and sequential strategies endorsed the recommendation that AIs should be included in adjuvant therapy for postmenopausal women with endocrine-responsive BC [77–79].

Women with BC live longer due to effective therapies; most may not suffer BC recurrence even though they are all vulnerable to toxicities. Therefore, these women are at increased risk of both cardiovascular disease and the cardiovascular side effects of BC treatments [40, 80]. Cardiovascular disease will remain as a potential cause of death in these patients. In the USA, as many as 2.3 million women live with such risk [80].

The risk of cardiovascular disease increases after menopause and is the greatest cause of morbidity and mortality in postmenopausal women. Estrogen is an independent risk factor for coronary heart disease in symptomatic women [81]. The effects of estrogen in cardiovascular disease are under investigation. However, estrogen contributes to the cardiovascular system via numerous mechanisms, affecting endothelial integrity, inflammation, thrombosis, and lipids [82]. Whether the increasing rate of cardiovascular events observed with AIs compared with tamoxifen results from direct AI cardiac toxicity or is due to the cardioprotective effect of tamoxifen remains under investigation.

Given the incidence of cardiovascular disease that is mostly unrecognized in women and the potential BC therapy-related adverse effects of cardiovascular disease, it is important to assess cardiovascular risk factors in postmenopausal women administered with adjuvant treatment for BC. An updated analysis of the BIG 1–98 trial demonstrated increased rates of cardiac events in the letrozole-treated arm compared with the tamoxifen-treated arm, particularly for women between 65 and 74 years of age [83]. Recent data

suggest that women with early BC are more likely to die of heart disease than recurrent cancer [84].

The Effect of Estrogen on Cardiovascular Disease

Estrogen protects against cardiovascular disease in premenopausal women compared with age-matched men, but these advantages in women disappear with increasing age and decreasing estrogen levels due to menopause [85]. The classical ERs ER-α and ER-β affect the cardiovascular system via intracellular interactions. Estrogen promotes endothelial progenitor cell mobilization, increases mesenchymal stem cell-mediated vascular endothelial growth factor (VEGF) release, and improves endothelial and myocardial function after ischemia [86–88]. A new membrane-bound and G protein-coupled estrogen receptor (GPR30) was recently described. Ischemic reperfusion injury was reduced, and cardiac function was preserved via activation of the GPR30 receptor in the heart. The decreasing effect of estrogen is related to increased methylation of the ER promoter with age in menopausal women. ER expression in the arterial wall diminishes sharply with menopause [89, 90].

Clinical Studies with Tamoxifen and Aromatase Inhibitors

Two approaches are available for the treatment of hormone receptor-positive BC, namely, inhibition of estrogen synthesis or its action. Several prospective studies compared the effects of various AIs (e.g., anastrozole, exemestane, and letrozole) with tamoxifen. These studies examined the effects of these approaches on behalf of their therapeutic effects in postmenopausal women with hormone receptor-positive BC. The third-generation AIs exhibited enhanced efficacy compared with tamoxifen in regard to improvement in disease-free survival and possibly overall survival rate in women with BC [76, 91–93].

Nonsteroidal Aromatase Inhibitors

Anastrozole

Anastrozole, a nonsteroidal AI, binds reversibly to the heme group of the aromatase enzyme. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared the efficacy and safety of the third-generation AIs anastrozole (1 mg) with tamoxifen (20 mg). Both drugs were administered orally every day for 5 years as first-line adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive early BC. This trial compared anastrozole with tamoxifen in 9366 women with newly diagnosed early-stage BC, and 84% of these women were hormone-receptor positive. This trial failed to note significant differences in cardiac events between anastrozole and tamoxifen therapies. However, the trial's definition of cardiovascular events was limited to ischemic heart disease. The event rate was 4.1% and 3.4% in the anastrozole and tamoxifen groups, respectively ($P = 0.1$) [75]. ATAC was the first trial to reveal that an AI is more effective and has fewer serious adverse effects than tamoxifen in adjuvant treatment. The ATAC trial recently published data from 120 months of follow-up [94]. The highest relative reduction in time to recurrence, contralateral BC, and disease-free survival was observed in the anastrozole group compared with the tamoxifen group in the first 2 years of the active treatment. These differences were maintained throughout the follow-up period, including after treatment completion between treatment groups. The absolute reduction of recurrence for the anastrozole group was 2.7% at 5 years and 4.3% at 10 years of follow-up compared with tamoxifen in hormone receptor-positive BC patients [94]. Tamoxifen exhibits a carryover benefit for recurrence in the first 5 years after treatment but not thereafter [65]. The carryover effect for recurrence was more prolonged for anastrozole than tamoxifen in the present study and remained significant for the 10-year follow-up period.

Generally, treatment-related serious adverse events were reduced in the anastrozole group compared with the tamoxifen group (OR 0.84, 95% CI 0.60–1.19; $P = 0.3$), but a similar number of events were noted after completion of treatment (OR 0.84, 95% CI 0.60–1.19; $P = 0.3$) [94]. Of note, the increased fracture rate associated with anastrozole during treatment did not continue after treatment because this short-term effect could be managed with dual-energy x-ray absorptiometry scans and bisphosphonates when needed [75, 95, 96]. Because the study's definition of cardiovascular events was limited to ischemic heart disease, the 68-month follow-up did not provide safety data on all cardiovascular diseases. At the 68-month follow-up, the incidence of ischemic heart disease was not significantly increased with anastrozole compared with tamoxifen (4.1% versus 3.4%, $P = 0.10$) (Table 49.1). Angina pectoris was slightly increased in the anastrozole group compared with the tamoxifen group, but the difference was not significant (2% versus 1.5%, respectively; $P = 0.07$). The MI rate was similar (1%) in both treatment arms both during treatment and after its completion; when only serious events were analyzed at 68 months, there was 34 (0.27) and 33 (0.27) events on treatment, and there was 26 (0.28) and 28 (0.30) off-treatment until 100 months of follow-up. The incidence of both vascular and thrombotic events was significantly reduced with anastrozole versus tamoxifen overall (2.8% versus 4.5%, respectively; $P = 0.0004$), and the incidence of thromboembolic events at 100 months of follow-up was similar to that at 68 months of follow-up [75, 80]. Serious cerebrovascular events were less

common in patients administered with anastrozole during treatment (OR 0.59 (0.32–1.05), $P = 0.056$) but not afterward (OR 1.10 (0.57–2.13), $P = 0.75$) [96]. Additionally, the number of cardiovascular deaths was similar between the anastrozole and tamoxifen groups (49 versus 46 at 68 months of follow-up, 2% versus 2% at 100 months of follow-up, and 2.9% versus 3.0% at 120 months of follow-up, respectively). Fewer cardiovascular deaths were noted in the anastrozole group. This finding has been verified in several studies with AIs [77, 97].

Additionally, trials in which tamoxifen was switched to anastrozole in women with BC have been conducted. In the ARNO-95/ABCSG-8 trials (in which patients were switched to anastrozole after 2–3 years of tamoxifen), the incidence of MI was reduced in both the anastrozole and the tamoxifen groups (Table 49.1). The Italian Tamoxifen Arimidex (ITA) trial compared continued tamoxifen therapy to switching to anastrozole after 2–3 years. Overall, the serious adverse event rate was similar (40 versus 37, respectively; $P = 0.7$); additionally, no difference in cardiovascular event rates was noted between the two arms (14 versus 16, $P = 0.4$ in the preliminary data; 14 versus 17, respectively; $P = 0.6$ at update).

Letrozole

Letrozole is another nonsteroidal AI that binds reversibly to the heme group of the aromatase enzyme and displays a longer half-life at 96 h. The BIG 1–98 trial is the only study with a four-arm design comparing the 5-year sequence of either tamoxifen followed by letrozole or the inverse (letrozole followed by tamoxifen) over 5 years. The BIG 1–98 trial was designed to gather the potential effects of letrozole on cardiac risk. These effects included any cardiac adverse effects, ischemic heart disease, cardiac failure, hypertension, peripheral atherosclerosis, thromboembolic events, and other cardiovascular adverse effects. Specific adverse events were graded according to the Common Toxicity Criteria of the National Cancer Institute (version 2) at each study visit during treatment [98]. All data were collected separately on adverse effects of any grade, especially grade 3–5 effects. The safety data, with a median 30.1 months of follow-up, revealed that the incidence of cardiovascular events was similarly low in both the letrozole and tamoxifen arms, whereas letrozole was associated with significantly more peripheral atherosclerosis and other cardiovascular events of any grade [98]. When all events were reassessed for grade 3–5 adverse effects, tamoxifen resulted in more grade 3–5 thromboembolic events, and letrozole resulted in significantly more grade 3–5 cardiac events of any type, especially cardiac failure (2.4% versus 1.4%, respectively; $P = 0.001$). However, the event rate was relatively low in both arms [98].

The incidence of ischemic heart disease was increased with letrozole compared with tamoxifen, but results did not achieve significance (1.1% versus 0.7%, respectively; $P = 0.06$) [98]. At 51 months of follow-up, no significant differences in cardiac events overall (5.5% versus 5.0%), ischemic heart disease (2.2% versus 1.7%), and cardiac failure (1% versus 0.6%) were noted between the letrozole and tamoxifen monotherapy groups, respectively, even though letrozole is associated with increased cardiac events in each grade compared with tamoxifen [99] (Table 49.2). Although the number of events was minimal in each arm, an increase in the incidence of grade 3–5 cardiac events was noted with letrozole (Fisher exact test, $P < 0.001$) [99]. At a median follow-up of 71 months after randomization, the incidence of any type or grade of cardiac events was similar between women who were treated with one of the regimens that included letrozole and women who were treated with tamoxifen monotherapy (6.1–7.0% and 5.7%, respectively; $P = 0.45$) [97]. The incidence of thromboembolic events was significantly reduced with letrozole compared with tamoxifen before switching tamoxifen to letrozole (1.5% versus 3.5%, $P < 0.001$) or vice versa (1.7% versus 3.9%, $P < 0.001$ at 25.8 months; Table 49.2) [74]. Furthermore, the reduction in thromboembolic events with letrozole remained significant (versus tamoxifen) after switching the monotherapy arms at 51 months and 74 months (2% versus 3.8%, respectively; $P < 0.001$ at 51 months, 2.6% versus 4.3%, respectively; $P < 0.001$ at 74 months of follow-up) [99, 100]. Hence, the reduction in letrozole monotherapy remained significant compared with one of the regimens that included tamoxifen at a median follow-up of 71 months ($P < 0.001$) [97].

Letrozole has a similar incidence of cerebrovascular accidents/transient ischemic attacks (CVA/TIA) as tamoxifen before switching tamoxifen to letrozole or vice versa (Table 49.2) [98]. Additionally, the incidence of CVA/TIA remained similar after 51 months and 74 months of follow-up (1.8% and 1.6%, respectively). Furthermore, similar rates of patients with previous CVA/TIA were assigned to one of the regimens that included tamoxifen and letrozole monotherapy [97].

The MA.17 trial was designed to evaluate the impact of letrozole on lipid parameters compared with placebo in postmenopausal women who were previously subjected to 5 years adjuvant tamoxifen treatment for early-stage BC [101]. The incidence of cardiovascular disease was similar between the letrozole group and the placebo group at 2.5 years of follow-up [101]. MI was noted in <1% of patients for both groups.

Steroidal Aromatase Inhibitors

Exemestane

Exemestane is a third-generation steroidal AI that is orally active and binds irreversibly to the substrate-binding pocket

Table 49.1 Anastrozole: reversible, third-generation nonsteroidal aromatase inhibitor

	ATAC (Arimidex, Tamoxifen, Alone or in Combination)									ITA (The Italian Tamoxifen Anastrozole Trial)			ABCSG8/ARNO 95 (The Austrian Breast and Colorectal Study Group/Arimidex-Nolvadex 95)		
	Tamoxifen for 5 years vs anastrozole for 5 years (tamoxifen + anastrozole arm was discontinued at 47 months)									Tamoxifen for 5 years vs tamoxifen for 2–3 years followed by anastrozole			Tamoxifen for 5 years vs tamoxifen for 2–3 years followed by anastrozole		
Design	First-line adjuvant									Combined adjuvant			Combined adjuvant		
Median follow-up	68 months			100 months			120 months (overall)			64 months			28 months		
	ANA	TAM	*P* value	ANA	TAM	*P* value	ANA	TAM	*P* value	ANA	TAM	*P* value	ANA	TAM	*P* value
Number of patients	3125	3116								223	225		1618	1606	
Median age	64.1 years (+5.7 years)			72 years			+13 months			63 years			62 years		
Disease-free survival	HR: 0.83 (0.73–0.94)		*P* = 0.005	HR: 0.85 (0.76–0.94)		*P* = 0.003	HR: 0.86 (0.78–0.95)		*P* = 0.003	[a]HR: 0.42 (A > T)		*P* = 0.001	HR: 0.42 (A > T)		*P* = 0.0001
Time to distant recurrence	HR: 0.84 (0.70–1.00)		*P* = 0.06	HR: 0.84 (0.72–0.97)		*P* = 0.022	HR: 0.85 (0.73–0.98)		*P* = 0.02						
Time to recurrence	HR: 0.74 (0.64–0.87)		*P* = 0.0002	HR: 0.76 (0.67–0.87)		*P* = 0.0001	HR: 0.79 (0.70–0.89)		*P* = 0.0002	NA			NA		
Overall survival	HR: 0.97 (0.85–1.12)		*P* = 0.7	HR: 0.97 (0.86–1.11)		*P* = 0.7	HR: 0.95 (0.84–1.06)		*P* = 0.4	HR: 0.56 (0.28–1.15)		*P* = 0.1	HR: 0.7 (A > T)		*P* = 0.038
Ischemic cardiovascular events	127 (4.1%)	104 (3.4%)	*P* = 0.10	NA			NA			NA					
Myocardial infarction	37 (1.0%)	34 (1.0%)	*P* = 0.5	60 (1.9%)	61 (1.9%)		NA			NA			3 (<1%)	2 (<1%)	*P* = 1
Angina	71 (2.0%)	51 (1.5%)	*P* = 0.07	NA			NA			NA					
Cerebrovascular events	62 (2.0%)	88 (3.0%)	*P* = 0.03	64	91	*P* = 0.03	NA			NA			2 (<1%)	9 (<1%)	*P* = 0.064
Thromboembolic disease	87 (2.8%)	140 (4.5%)	*P* = 0.0004	NA			NA			NA			3 (<1%)	12 (<1%)	*P* = 0.034
All cardiac events	NA	NA		NA			NA			All cardiovascular disease, A: 7.6%, T: 6.2%		*P* = 0.6	NA		
Cardiovascular deaths	49 (2%)	46 (1%)		67 (2%)	66 (2%)		91 (2.9%)	95 (3.0%)							
Cerebrovascular deaths	14 (<1%)	22 (1%)	*P* = NS	25 (0.8)	29 (0.9)		33 (1.1%)	36 (1.2%)							

ATAC results from ATAC study were obtained from the HR+ group, *NA* not available, *HR* hazard ratio

[a]36 months of follow-up

Table 49.2 Letrozole: reversible, third-generation nonsteroidal aromatase inhibitor

	BIG 1–98												MA.17		
	Adjuvant Endocrine Therapy for Early Breast Cancer Using Letrozole of Tamoxifen (four-arm trial comparing 5 years of monotherapy with tamoxifen or with letrozole with sequences of 2 years of one of these agents followed by 3 years of the other)												Letrozole vs placebo after 5 years of tamoxifen treatment		
Design	First-line adjuvant												Extended adjuvant		
Median follow-up	25.8 months			30.1 months			51 months[a]			74 months[a]			30 months		
	LET	TAM	*P* value	LET	TAM	*P* value	LET	TAM	*P* value	LET	TAM	*P* value	LET	TAM	*P* value
Number of patients	4003	4007		3975	3988		2448	2447		2448	2447		2583	2587	
Median age	61 years			61 years			61 years			61 years			62 years		
Disease-free survival	HR: 0.81 (0.70–0.93)		$P = 0.003$	NA			HR: 0.88 (0.71–0.95)		$P = 0.007$	HR: 0.83 (0.74–0.94)		$P = 0.03$	HR: 0.58 (0.45–0.76)		$P < 0.01$
TTR	HR: 0.72 (0.61–0.86)		$P < 0.001$	NA			231 (0.65)	291 (0.92)	$P = 0.004$	NA			NA		
TTDR	HR: 0.73 (0.60–0.88)		$P = 0.001$	NA			HR: 0.81 (0.67–0.98)		$P = 0.03$	HR: 0.80 (0.67–0.94)		$P = 0.05$	HR: 0.60 (0.43–0.84)		$P = 0.002$
Overall survival	HR: 0.86 (0.70–1.06)		$P = 0.16$	NA			HR: 0.91 (0.75–1.11)		$P = 0.35$	HR: 0.82 (0.70–0.95)		$P = 0.08$	HR: 0.82 (0.57–1.19)		$P = 0.3$
Cardiac events	162 (4.1)	153 (3.8)	$P = 0.61$	191 (4.8)	188 (4.7)	$P = 0.87$	134 (5.5)	122 (5.0)	$P = 0.48$	169 (6.9)	152 (6.2)	$P = 0.36$	NA		
Grade 3–5	85 (2.1)	44 (1.1)	$P < 0.001$	96 (2.4)	57 (1.4)	$P = 0.001$	74 (3.0)	45 (1.8)	$P < 0.001$	93 (3.8)	51 (2.1)		NA		
Ischemic heart disease	57 (1.4)	46 (1.2)	$P = 0.28$	68 (1.7)	60 (1.5)	$P = 0.48$	54 (2.2)	41 (1.7)	$P = 0.21$	69 (2.8)	49 (2.0)	$P = 0.08$	NA		
Myocardial infarction	NA			NA			NA			NA			9 (0.3)	11 (0.4)	NS
Angina	NA			NA			NA			NA			31 (1.2)	23 (0.9)	NS
Cardiac failure	31 (0.8)	14 (0.4)	$P = 0.01$	40 (1.0)	29 (0.7)	$P = 0.19$	24 (1.0)	14 (0.6)	$P = 0.14$	30 (1.2)	25 (1.0)	$P = 0.59$			
Other cardiovascular events	19 (0.5)	8 (0.2)	$P = 0.04$	26 (0.7)	11 (0.3)	$P = 0.01$	19 (0.8)	6 (0.2)	$P = 0.014$	24 (1.0)	13 (0.5)	$P = 0.10$	100 (3.9)	95 (3.7)	NS
CVA/TIA	39 (1.0)	41 (1.0)	$P = 0.91$	47 (1.2)	49 (1.2)	$P = 0.92$	34 (1.4)	35 (1.4)	$P = 0.90$	45 (1.8)	38 (1.6)	$P = 0.51$	17 (0.7)	15 (0.6)	NS
Thromboembolism	61 (1.5)	140 (3.5)	$P < 0.001$	68 (1.7)	154 (3.9)	$P < 0.001$	50 (2.0)	94 (3.8)	$P < 0.001$	63 (2.6)	104 (4.3)	$P < 0.001$	11 (0.4)	6 (0.2)	NS
Cardiac death	13 (0.3)	6 (0.2)		NA			12 (0.5)	7 (0.3)		NA			5*	5*	
Cerebrovascular death	7 (0.2)	1 (0.03)		NA			8 (0.3)	3 (0.1)		NA			2*	1*	

TTDR time to distant recurrence, *TTR* time to recurrence, *NA* not available, *NS* not significant, *HR* hazard ratio

s*Lymph node-negative patients

[a]Results from monotherapy arms

of the aromatase enzyme. Exemestane is indicated as an adjuvant treatment for hormone receptor-positive early-stage BC after 2–3 years of tamoxifen treatment in postmenopausal women. When exemestane is used as a first-line adjuvant treatment in patients who were not previously exposed to AIs, increases in the response rate (from 31% to 46%) and progression-free survival (from 5.8 to 9.9 months) were noted compared with tamoxifen [102]. Three trials are currently evaluating the use of exemestane as an adjuvant treatment in postmenopausal women with early-stage BC, including IES (Intergroup Exemestane Study), TEAM (Tamoxifen, Exemestane, Adjuvant, Multicenter), and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-33 [103].

The IES study has randomized 4724 postmenopausal patients with unilateral invasive, ER-positive (or unknown) BC who were disease-free after 2–3 years of tamoxifen treatment to switch to exemestane (n = 2352) or to continue tamoxifen (n = 2372). With a median follow-up of 55.7 months, exemestane exhibited a 3.3% absolute benefit by the end of the treatment. When ER-negative patients were excluded, the hazard ratio (HR) was 0.75 (0.65–0.87; $P = 0.0001$), and the absolute benefit was 3.5%. Furthermore, a plausible difference in overall survival was noted, reaching significance with an HR of 0.83 (0.69–1.00) [76]. An updated analysis was reported at the 2009 San Antonio Cancer Symposium [104]. These data verified the significant improvement in overall survival with an HR of 0.86 (0.75–0.99, $P = 0.04$), translating into an absolute survival benefit of 2.4% after 8 years of randomization.

The IES trial compared the toxicity profile of exemestane with tamoxifen in patients who previously received adjuvant tamoxifen for 2–3 years before randomization with women with early-stage BC. Cardiac events were defined as ischemic and other events. Results from the trial revealed that the overall rates of ischemic events were 9.9% in the exemestane group and 8.6% in the tamoxifen group. In addition, the MI rates were 1.3% for exemestane and 0.8% for tamoxifen, and the angina rates were 7.1% for exemestane and 6.5% for tamoxifen. Although the overall rates were increased in the exemestane group compared with the tamoxifen group, none of these increases were significant [105]. At 55.7 months of follow-up, the incidence of cardiovascular events did not differ between the exemestane and tamoxifen groups either during treatment (16.5% and 15%, respectively) or posttreatment [76]. The incidence of ischemic cardiovascular disease was comparable between the two arms: 8% for the exemestane group and 6.9% for the tamoxifen group (P = 0.17). Significance was not achieved in terms of MI (1.3% versus 0.8%, respectively; P = 0.08). However, patients in the exemestane arm who experienced an MI had more severe histories of hypertension compared with patients in the tamoxifen arm (71.1% versus 31.6%, respectively). These findings emphasize the importance of blood pressure monitoring for patients administered with adjuvant exemestane [76]. The incidence of venous thromboembolic events was 1.2% in patients who switched to exemestane and 2.3% in patients who remained on tamoxifen ($P = 0.004$), and similar results were observed in the overall study (P = 0.01) (Table 49.3). The incidence of cerebrovascular events occurred in similar proportion between exemestane and tamoxifen in the IES (2.5% versus 2.4%, respectively; P = 0.89). Consequently, the number of cardiovascular deaths was very low in both treatment groups.

The TEAM phase 3 trial was primarily designed to evaluate the efficacy and safety of 5 years of adjuvant exemestane compared with 5 years of tamoxifen in postmenopausal women with early-stage BC. Although results were in favor of the exemestane group during that period, a recent update analyzing 5 years of disease-free survival revealed similar rates between the groups (85.7% versus 85.4%, respectively) randomized to up-front exemestane or sequential treatment with tamoxifen followed by exemestane, and no differences in time to recurrence or overall survival were noted [106]. The incidence of hypertension was increased in the exemestane arm compared with the sequential arm but the difference not significant (4% versus 3%, respectively; $p = 0.38$). The frequency of arrhythmia was 4% versus 3% for the exemestane arm versus the sequential arm, respectively (P = 0.038). The frequency of myocardial ischemia or infarction was 2% versus 1%, respectively ($P = 0.171$); the frequency of cardiac failure was 1% versus <1%, respectively (P = 0.009). Although the overall incidence of cardiovascular events was increased in the exemestane group compared with the sequential arm, none of these results achieved significance. The benefit of AI on tamoxifen in terms of reducing vascular thrombotic events was evident in women with previous exposure to tamoxifen. In the TEAM study, vascular thrombotic events occurred in 2% of patients who switched to exemestane compared with <1% of patients who were exclusively exposed to exemestane ($P = 0.0001$).

Cardiovascular deaths were increased with exemestane compared with sequential treatment; however, this difference was not significant (<1%). Depending on the differences between exemestane monotherapy and sequential treatment in terms of adverse events, the safety of these treatment strategies might play an important role in treatment decisions. It is important to consider the impact of patient age on cardiovascular health because the prevalence of comorbid illness among newly diagnosed BC patients increases with age; the most common comorbid illness is cardiovascular disease. History of hypertension was a significant predictor of ischemic heart disease, CVA/TIA, and thromboembolism. Hypercholesterolemia was associated with any adverse cardiac events, especially ischemic heart disease [85].

Table 49.3 Exemestane: irreversible, third-generation steroidal aromatase inhibitor

	IES (Intergroup Exemestane Study)			TEAM (The Tamoxifen Exemestane Adjuvant Multicenter)		
	Tamoxifen vs exemestane after 2–3 years of tamoxifen (total of 5 years)			Exemestane vs exemestane after 2–3 years of tamoxifen (total of 5 years)		
Design	Combined adjuvant			First-line adjuvant		
Median follow-up	55.7 months			5.1 years		
	TAM–EXE	TAM	*P* value	TAM–EXE	EXE	*P* value
Number of patients	2352	2372		4868	4898	
Median age	<60: 32.4%, 60–69: 42.7%	<60: 32.0%, 60–69: 42.8%		64 years		
Disease-free survival	HR: 0.75 (0.64–0.88)		$P = 0.0003$	HR: 0.97 (0.88–1.08)		$P = 0.60$
TTDR	HR: 0.83 (0.70–0.98)		$P = 0.03$	HR: 0.93 (0.81–1.07)		$P = 0.30$
Overall survival	HR: 0.83 (0.69–0.99)		$P = 0.04$	HR: 1.00 (0.89–1.14)		$P > 0.99$
All cardiac events	483 (20.8)	441 (18.9)	$P = 0.09$	NA		
Cardiac events	NA	NA		NA		
Ischemic heart disease	229 (9.9)	200 (8.6)	$P = 0.12$	NA		
MI or ischemia	31 (1.3)	19 (0.8)	$P = 0.08$	64 (1%)	82 (2%)	$P = 0.171$
Angina	7.1%	6.5%	$P = 0.44$	NA		
Cardiac failure	1.8%	1.8%	$P = 0.94$	26 (<1%)	50 (1%)	
Other cardiovascular events	261 (11.3)	262 (11.2)	$P = 0.96$	73 (2%)	77 (2%)	$P = 0.843$
CVA/TIA	2.5%	2.4%	$P = 0.89$	60 (1%)	87 (2%)	$P = 0.035$
Thromboembolism	45 (1.9)	572 (3.1)	$P = 0.01$			
Venous thrombosis				99 (2%)	47 (<1%)	$P = 0.0001$
Cardiac death	14	13		28 (<1%)	43 (<1%)	$P = 0.11$
Cerebral related				14 (<1%)	19 (<1%)	
Vascular related	17	11		3 (<1%)	4 (<1%)	

IES HR+ group, *TEAM* Phase 3, HR+ group, *MI* myocardial infarction, *NA* not available, *HR* hazard ratio, *TTDR* time to distant recurrence

Comparison of AIs Versus Tamoxifen in Lowering the Incidence of Common Serious Events

Current treatments for BC, which is the most common malignancy among women, involve the adjuvant use of endocrine therapy for hormone receptor-positive BC after surgery (Table 49.4) [107, 108]. AIs are more effective and safer than tamoxifen in adjuvant endocrine strategies for either early or advanced stage hormone receptor-positive BC in postmenopausal women [73, 109–114]. As an endocrine therapy, increasing the use of AIs either sequentially or instead of tamoxifen appears to be beneficial in reducing the incidence of common serious events, such as thromboembolism and stroke, which are increased with tamoxifen treatment. The molecular differences between third-generation AIs affect not only selectivity for aromatase binding but also adverse cardiovascular events via binding to cardiovascular receptors or causing small alterations in serum lipid levels. However, evidence from large clinical trials indicates no major differences with respect to overall cardiovascular safety among AIs [40, 115]. Anastrozole is primarily specific to the aromatase enzyme and has fewer interactions with other enzymes. Hence, anastrozole is emerging as one plausible standard adjuvant treatment for hormone-sensitive early BC [116]. A recently published 10-year analysis of the ATAC trial confirmed the previously reported efficacy and tolerability benefits of anastrozole as an initial adjuvant therapy for hormone-sensitive BC. Treatment-related serious adverse events were reduced in the anastrozole arm compared with the tamoxifen arm ($P < 0.0001$); however, rates were similar in the posttreatment period ($P = 0.3$) [94]. Although deaths without recurrence were increased with anastrozole (10.8% versus 9.8%, respectively; P = NS), cardiovascular deaths were less common with anastrozole compared with tamoxifen (2.9% versus 3.0%, respectively). Additionally, the incidence of cardiovascular deaths may have decreased with anastrozole in the off-treatment period compared with tamoxifen (Table 49.1). Although the median age was 72 years and tamoxifen exerts a cardioprotective effect, the decrease observed with anastrozole is considered remarkable. Regarding the reduction in distant recurrence, the decreased cardiovascular mortality observed with anastrozole might become significantly lower than that observed with tamoxifen in the future. At the 100-month follow-up, fewer CVAs were reported in patients receiving anastrozole ($P = 0.056$) but not in the off-treatment period ($P = 0.75$) [96]. After publishing 74 months of BIG 1–98 follow-up data, the incidence of cardiac and thromboembolic events was proportionately consistent during follow-up. Ischemic heart disease was increased in the letrozole arm compared with the tamoxifen arm, despite overall similar cardiac

Table 49.4 Comparing 5-year follow-up of aromatase inhibitors

	ATAC			BIG 1–98			IES			TEAM		
	Tamoxifen for 5 years vs anastrozole for 5 years (tamoxifen + anastrozole arm was discontinued at 47 months)			Four-arm trial; 5 years tamoxifen vs letrozole or sequences of 2 years of one of these agents followed by 3 years of the other			Tamoxifen vs exemestane after 2–3 years tamoxifen (total of 5 years)			Exemestane vs exemestane after 2–3 years tamoxifen (total of 5 years)		
Median follow-up	68 months			74 months			55.7 months			5.1 years		
	ANA	TAM	*P* value	LET	TAM	*P* value	TAM-EXE	TAM	*P* value	TAM-EXE	EXE	*P* value
Number of patients	3125	3116		2448	2447		2352	2372		4868	4898	
Median age	64.1 years			61 years						64 years		
Disease-free survival	HR: 0.83 (0.73–0.94)		*P* = 0.005	HR: 0.83 (0.74–0.94)		*P* = 0.03	HR: 0.75 (0.64–0.88)		*P* = 0.0003	HR: 0.97 (0.88–1.08)		*P* = 0.60
Time to distant recurrence	HR: 0.84 (0.70–1.00)		*P* = 0.06	HR: 0.80 (0.67–0.94)		*P* = 0.05	HR: 0.83 (0.70–0.98)		*P* = 0.03	HR: 0.93 (0.81–1.07)		*P* = 0.30
Overall survival	HR: 0.97 (0.85–1.12)		*P* = 0.7	HR: 0.82 (0.70–0.95)		*P* = 0.08	HR: 0.83 (0.69–0.99)		*P* = 0.04	HR: 1.00 (0.89–1.14)		*P* > 0.99
All cardiac events	NA						483 (20.8)	441 (18.9)	*P* = 0.09	NA		
Cardiac events	NA			169 (6.9)	152 (6.2)	*P* = 0.36				NA		
Ischemic heart disease				69 (2.8)	49 (2.0)	*P* = 0.08	229 (9.9)	200 (8.6)	*P* = 0.12	NA		
Ischemic CV events	127 (4%)	104 (3%)	*P* = 0.10							NA		
Myocardial infarction	37 (1.0%)	34 (1.0%)	*P* = 0.5				31 (1.3)	19 (0.8)	*P* = 0.08	64 (1%)	82 (2%)	*P* = 0.171
Angina	71 (2.0%)	51 (2%)	*P* = 0.07				7.1%	6.5%	*P* = 0.44	NA		
Cardiac failure				30 (1.2)	25 (1.0)	*P* = 0.59	1.8%	1.8%	*P* = 0.94	26 (<1%)	50 (1%)	
Other CV events				24 (1.0)	13 (0.5)	*P* = 0.10	261 (11.3)	262 (11.2)	*P* = 0.96	73 (2%)	77 (2%)	*P* = 0.843
Thromboembolism	87 (2.8%)	140 (4.5%)	*P* = 0.0004	63 (2.6)	104 (4.3)	*P* < 0.001	45 (1.9)	572 (3.1)	*P* = 0.01			
Cerebrovascular events	62 (2.0%)	88 (3.0%)	*P* = 0.03	45 (1.8)	38 (1.6)	*P* = 0.51	2.5%	2.4%	*P* = 0.89			
Cardiovascular deaths	49 (2%)	46 (1%)								28 (<1%)	43 (<1%)	*P* = 0.11
Cerebrovascular deaths	14 (<1%)	22 (1%)	*P* = NS							14 (<1%) 3 (<1%)	19 (<1%) 4 (<1%)	

NA not available, *NS* not significant, *HR* hazard ratio, *CV* cardiovascular events

events (Table 49.2). An increase in the incidence of grade 3–5 cardiac events with letrozole remained evident with 74 months of follow-up; however, the number of events was minimal in each arm (3.8% versus 2.1% in the tamoxifen arm). In the BIG 1–98 trial, the incidence of heart failure was similar at 74 months of median follow-up between the letrozole and tamoxifen monotherapy groups (1.2% versus 1.0%, respectively); however, the results were significantly different at 25.8 months of follow-up (0.8% versus 0.4%, respectively; $P = 0.01$). The incidence of heart failure was reduced after cessation of letrozole treatment compared with the active treatment period.

In the IES, the frequency MI was very low in both treatment groups at 55.7 months of follow-up even though the patients comprised a population at risk for adverse cardiac events given their age [76]. Most patients who experienced MI in the exemestane group had a history of hypertension (71.1%) compared with the tamoxifen group (31.6%). The importance of blood pressure monitoring should be stressed [76]. Disregarding the other cardiovascular risk factors, advanced age and uncontrolled blood pressure are potentially related to these cardiac events. In the TEAM trial, no significant differences were reported between the exemestane and sequential groups in terms of disease-free survival ($P = 0.60$) and overall survival ($P > 0.99$) at a median 5.1 years of follow-up [64]. Data on disease-free survival were consistent with those from the BIG 1–98 trial, in which tamoxifen followed by letrozole or the reverse sequence versus letrozole alone was not associated with significant differences in efficacy after a median 71 months of follow-up [97]. Cardiac-related deaths were not significantly different in these treatment groups; however, the number of events was increased with exemestane compared with the sequential group ($P = 0.11$). The incidence of cardiac failure was significantly increased in the exemestane monotherapy group compared with the sequential group ($P = 0.009$). This result did not emerge previously in AI monotherapy trials. However, the result may be evident in the next follow-up because approximately 20% of patients were still undergoing the trial treatment. Consequently, treatment compliance appears suboptimum, particularly in the sequence group (47% of patients in the sequence group and 19% of patients in the exemestane group discontinued treatment before 5 years for reasons other than disease-free survival).

The lipid-lowering effect of tamoxifen may explain the increased lipid levels with AIs versus tamoxifen [117, 118]. Whether AIs have long-term detrimental effects on lipids is unknown despite the findings that significantly more patients had hypercholesterolemia in the aromatase group compared with the tamoxifen group in the ATAC and BIG 1–98 trials [74, 75]. Although a steroidal AI (exemestane) was thought to have beneficial effects on lipid metabolism, all third-generation AIs have similar effects on lipids [119]. Additionally, cardiovascular events were similar between the letrozole and placebo groups after 5 years of tamoxifen treatment in the MA.17 trial.

All studies comparing the safety of AIs with tamoxifen have demonstrated an overall decreased risk of thromboembolic events in patients administered with AIs versus tamoxifen; however, postmenopausal women administered with endocrine therapy for BC live longer with their disease and remain at risk for such adverse events [65]. Because AIs carry a risk for cardiovascular events, these patients should be evaluated more carefully than age-matched individuals to minimize cardiovascular events during therapy [85].

Cardiac Monitoring

Several recommendations and guidelines are available for the assessment and monitoring of cardiac toxicity during and after breast cancer treatment [120–125]. These recommendations are mainly based on expert consensus due to the paucity of available high-level evidence.

Two of the basic concepts that are common in all the guidelines include the value of a careful case-by-case baseline evaluation of preexisting risk factors for cardiac adverse events and the need for appropriate and well-structured cardiac monitoring during and after cancer therapy to identify patients with asymptomatic cardiac dysfunction such that breast cancer treatments can be modified and cardiac medication can be initiated.

Table 49.1 presents a summary of recommendations and areas of active research regarding the assessment, monitoring, and treatment of cardiac toxicity due to cancer therapy in patients with early breast cancer.

Baseline Assessment/Evaluation

The purpose of the baseline evaluation is to identify patients at high risk for cardiac toxicity due to cancer therapy. We previously discussed in this chapter several risk factors for cardiac toxicity during anticancer therapy that has been identified. However, it is difficult to incorporate the baseline assessment in an algorithm for cardiac monitoring given the lack of evidence regarding the strength of each risk factor in the estimation of cardiac risk. The only available cardiac risk score has been developed by investigators from the NSABP B-31 trial (trastuzumab versus no trastuzumab in the adjuvant setting) to predict the absolute risk of heart failure in individual patients who received trastuzumab as adjuvant therapy [126]. However, the lack of independent validation of the model limits its clinical use to date.

The baseline evaluation also includes a cardiac imaging test for the evaluation of cardiac structure and function [120–

125]. Some guidelines recognize the practical difficulty of performing baseline imaging evaluation on all breast cancer patients before adjuvant treatment and recommend exclusively evaluating women with risk factors for cardiac toxicities or those who plan to receive high cumulative doses of anthracyclines or at least two therapies that could influence heart function [91]. However, baseline imaging is mandatory for all patients who plan to receive trastuzumab without any exceptions [121, 122].

At present, the most frequently used modality for detecting cardiotoxicity is the measurement of LVEF via either echocardiography or multigated acquisition scanning (MUGA). Echocardiography is generally preferred over MUGA given its widespread availability, the ability to investigate diastolic function, and the absence of radiation exposure [95]. However, echocardiography depends on the expertise and interpretation of echocardiographers, whereas MUGA offers a more objective and reliable calculation of LVEF [127].

The major shortcoming in measuring LVEF is that the technique is insensitive to slight changes in myocardial function [5]. As a consequence, a decrease in LVEF occurs when a critical amount of myocardial damage, which might be irreversible, has already occurred [128, 129]. Moreover, LVEF is a measurement of systolic cardiac function and does not provide any assessment of other measurements, such as diastolic function or valvular structure and function. Novel ultrasound imaging techniques, including tissue Doppler imaging (TDI) and 3D and contrast echocardiography, overcome some of the shortcomings of conventional echocardiography. Contrast and 3D echocardiography offer a more accurate calculation of LVEF compared with standard 2D echocardiography [130, 131]. In addition, 3D echocardiography might provide a tool for earlier identification of subclinical myocardial damages [132]. TDI is a relatively new echocardiographic technique that uses Doppler principles to measure the velocity of myocardial motion, deformation (strain), and the rate of deformation (strain rate). Clinical studies have reported that TDI measurements detect preclinical changes in systolic function that occur prior to conventional changes in LVEF regardless of the cancer therapy (e.g., anthracyclines radiotherapy, trastuzumab) that was responsible for the cardiac toxicity [133–136].

Recently, studies on the general population found that the coronary artery score, as assessed by computed tomography, could serve as an additional marker for the prediction of coronary artery disease [137]. Whether this marker can be used in the baseline assessment of breast cancer patients before adjuvant therapy is unknown. Further studies are necessary to identify the predictive value of these imaging modalities.

Cardiac magnetic resonance imaging is considered the gold standard for LVEF assessment as well as volume and mass measurements. Early studies in cancer patients allow accurate assessments of subclinical or established cardiotoxicity from cancer therapy [138]. However, its lack of availability and high cost limit its routine use. Based on the current data of cost and availability of the method, the authors of a recent review concluded that magnetic resonance imaging is an important complement to the current algorithms of cardiac assessment and monitoring rather than a screening tool for all patients treated with cardiotoxic cancer therapies [138]. In addition to imaging modalities, a new approach based on biochemical cardiac markers (troponins T and I, B-type natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP)) has emerged as a tool for both baseline assessment and monitoring during cancer therapy. In patients treated with anthracyclines, an early elevation of troponin appears to identify patients who are at risk for cardiac toxicity, which allows the individualization of monitoring and the adoption of preventive strategies in selected patients [139, 140]. Similarly, in patients treated with trastuzumab, elevation of troponin during therapy could identify a group of patients who are at high risk for cardiac toxicity and have a reduced likelihood of recovery of cardiac function [141–143]. However, others have failed to detect any clinical value of cardiac troponins during or following cancer therapy [136, 144].

The family of natriuretic peptides (BNP and NT-proBNP) has also been investigated as markers of early cardiac damage during cancer therapy with less reliable and consistent results compared with troponin. Some studies have reported an association between BNP or NT-proBNP elevation and increased risk for cardiac toxicity, whereas others did not identify any correlation [145–150].

A number of barriers in cardiac biomarker studies limit their widespread application as early markers of cancer therapy-induced cardiac toxicity. First, the timing of biomarker assessment varies among studies, which may partially explain the inconsistent results. Thus, the optimal timing remains uncharacterized. Moreover, an optimal assay and a widely acceptable cutoff value are not available. In addition, most of the available studies are small with heterogeneous cancer populations who received multiple types of cancer therapy. As a result, the utility of cardiac biomarkers as diagnostic and predictive tools for cardiac dysfunction in patients with potential cardiotoxic cancer therapy must be clarified using results from larger ongoing studies. Despite these caveats, some guidelines have included the measurements of cardiac biomarkers in their suggested algorithms [121, 122].

Guidelines on Cardiac Monitoring

The same imaging modalities and cardiac biomarkers that were discussed earlier as methods for baseline assessment

and evaluation are also available for cardiac monitoring during cancer therapy. Echocardiography or MUGA for the calculation of LVEF is the backbone of all the current guidelines regarding cardiac monitoring during cancer therapy [120–125].

The ESMO guidelines recommend serial monitoring of cardiac function with echocardiography or MUGA at baseline; 3, 6, and 9 months during treatment (anthracyclines and/or trastuzumab); and 12 and 18 months after the initiation of treatment [89]. The authors also discuss the possibility of using repeated measurements of cardiac biomarkers as an additional monitoring technique [121]. However, they recognize the need for further data by classifying this recommendation as B with a level of evidence III. No recommendations are available regarding the assessment and monitoring of breast cancer patients treated with radiotherapy in the ESMO guidelines [121].

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) use guidelines that are largely similar to the ESMO guidelines concerning time intervals in cardiac monitoring during trastuzumab therapy and the potential value of cardiac biomarkers in the baseline assessment and monitoring [122]. However, some differences are noted in some recommendations. The ASE/EACVI guidelines recommend cardiac monitoring 6 months after completion of trastuzumab therapy only in patients who previously received a type I cardiotoxic agent (i.e., anthracyclines). In addition to cardiac biomarkers, the ASE/EACVI guidelines recommend (with the same grade of recommendation) the use of an additional echocardiographic parameter, namely, global longitudinal strain. The ASE/EACVI guidelines recommend that cardiac monitoring during anthracycline-based chemotherapy is performed at baseline, treatment completion, and 6 months after treatment completion.

The same societies (ASE/EACVI) currently released the first guidelines regarding assessment and cardiac monitoring in adult patients with cancer treated with radiotherapy that will result in a radiation dose to the heart [120]. The authors recommend baseline assessment of cardiovascular risk factors and baseline echocardiography to identify any cardiac abnormalities for all patients before radiotherapy. During follow-up, a yearly history and physical examination with close attention to symptoms and signs of heart disease is recommended. In asymptomatic patients, screening echocardiography is recommended 10 years after treatment (or 5 years in case of high-risk populations, namely, those who received left-side chest radiotherapy or those with at least one risk factor for RIHD) and every 5 years after the initial 10-year echocardiographic screening examination. In high-risk populations, noninvasive stress imaging to screen for coronary artery disease should be considered given the increased risk of coronary events 5–10 years after radiotherapy [27].

Prevention and Management of Cardiac Toxicity in Breast Cancer Survivors

Strategies to Prevent Cardiac Toxicity

The interest in the use of standard cardiovascular medications to prevent cardiac toxicity due to cancer therapy in breast cancer patients is growing. HMG-CoA reductase inhibitors (statins) attenuate doxorubicin-induced cardiomyocyte cell death and radiation-induced cell apoptosis in preclinical studies. One retrospective study (201 patients) and one small randomized trial (40 patients) support the potential role of statins in reducing heart failure and maintaining cardiac function in breast cancer patients treated with anthracyclines [151–154]. No clinical data on the potential protective effect of statins in radiation-induced cardiac toxicity are available. Several studies that investigate the use of statins to prevent cancer therapy-associated cardiac toxicity in breast cancer patients are ongoing, and the results will enlighten their role as cardioprotective agents.

Beta-blockers have also been studied as preventive agents against cardiac toxicity in breast cancer patients. Although the exact mechanism of cardioprotection from beta-blockers remains unclear, several mechanisms have been proposed based on preclinical data, including mitigation of oxidative stress and preservation of β-adrenergic receptor recruitment of β-arrestin, which is an endogenous protective agent [155, 156]. In the only published randomized trial dedicated to breast cancer patients, the administration of nebivolol (n = 27) with anthracycline-based chemotherapy was associated with a reduced risk of LVEF decline at 6 months compared with the placebo arm (n = 18) [157]. Similar data were observed in two additional randomized trials: a small trial with 50 patients treated with anthracycline-based chemotherapy (34 of 50 patients had breast cancer) wherein carvedilol was compared with placebo and a larger trial of 90 patients with hematologic malignancies in which the combination of enalapril and carvedilol was compared with nonintervention [158, 159]. This latter trial (OVERCOME trial) is the first randomized trial to investigate the protective effect of cardiovascular medication in cancer treatment-related cardiotoxicity that presented not only data on surrogate outcomes of cardiac toxicity but also clinically relevant outcomes, such as symptomatic heart failure and death. Interestingly, patients in the intervention group exhibited a reduced incidence of the combined event of death or heart failure compared with the nonintervention group [159]. In contrast with beta-blockers and anthracycline-based cardiotoxicity, limited

clinical evidence regarding the role of beta-blockers in trastuzumab-associated cardiotoxicity is available. Two retrospective studies have found that the combination of beta-blockers and ACE-i lead to an increased possibility of LVEF recovery [160, 161]. As noted for the statins, several randomized trials are ongoing and will hopefully definitively define the role of beta-blockers as cardioprotective agents in anthracycline- and trastuzumab-associated cardiac toxicity.

The third category of cardiovascular medication with potential benefit as a cardioprotective agent for cancer therapy-related cardiotoxicity includes ACE-i/angiotensin II receptor blockers (ARB). Several mechanisms that could mediate this cardioprotective effect have been proposed based on preclinical data: reduction in interstitial fibrosis, attenuation of oxidative stress, and downregulation of the actions of the NRG-1/ErbB system [162–164]. Several small randomized trials have reported that the administration of ACE-i/ARB during anthracycline-based chemotherapy reduces the risk for cardiac dysfunction, as measured by conventional cardiac imaging modalities [165–167]. In addition, in the previously mentioned OVERCOME trial, the combination of beta-blockers and ACE-i reduced the risk of clinically relevant outcomes [159]. The study by Cardinale et al. is unique in its design because the authors used a biomarker (troponin I) to guide treatment [167]. The authors used the elevation of troponin I, which was measured soon after high-dose chemotherapy, to select 114 patients with various malignancies for randomization to placebo versus 20 mg enalapril daily for 1 year. The incidence of a 10% LVEF decline was significantly increased in the control arm (43%) compared with the ACE-i-treated arm (0%) [167]. Only preclinical data are available; no clinical evidence is available on the potential cardioprotective effect of ACE-i/ARB with trastuzumab or radiation therapy [168]. However, this potential cardioprotective effect is an area of active investigation.

In addition to pharmacological interventions, some preclinical data suggest that even nonpharmacological interventions may prevent cardiac toxicity. Aerobic exercise attenuates doxorubicin-induced cardiotoxicity in animal models [169]. However, a small study in patients treated with trastuzumab found that exercise training was not effective in preventing adverse left ventricular remodeling [170]. Whether aerobic exercise is a protective intervention against anthracycline- or trastuzumab-related cardiac toxicity in breast cancer patients must be studied in randomized trials. The only medication that has been approved by the US Food and Drug Administration for the prevention of anthracycline-related cardiotoxicity is dexrazoxane. Its mechanism of action and clinical evidence for its use were described earlier in this chapter.

Management of Cardiac Toxicity

In the general population, the guidelines suggest the use of beta-blockers and ACE-i/ARBs in patients with asymptomatic LVEF decline [171]. A similar treatment strategy, namely, the initiation of appropriate medication promptly after the detection of asymptomatic cardiac dysfunction, should be pursued in patients with cardiac dysfunction due to cancer therapy [121]. However, the evidence behind this treatment strategy for cancer patients is obtained from relatively small prospective studies, and further studies, preferably randomized trials, are still needed [167, 172]. In trastuzumab-treated patients, the evidence that supports the use of ACE-i/ARBs with or without beta-blockers in asymptomatic cardiac dysfunction (LVEF, 40% or between 40% and 50% in some guidelines) is limited to small case series, but this strategy is generally accepted [121, 122, 124]. Two additional parameters that should be considered in trastuzumab-induced cardiac toxicity include the need to withhold trastuzumab according to specific criteria (LVEF 44% or LVEF 45–49% and 10% from baseline) with reevaluation after 3–4 weeks and the fact that the therapeutic target of cardiovascular medications should be achieved faster compared with the general population to readminister trastuzumab [121, 173–175].

In cases of symptomatic heart failure due to cancer therapy, the recommended treatment strategy does not differ from the treatment of heart failure patients in general and includes the routine use of either ACE-i or ARB and beta-blockers with diuretics added for symptomatic congestion. In trastuzumab-induced heart failure, the LVEF should be reevaluated after adequate dose titrations of cardiovascular medication. If the LVEF returns to baseline, trastuzumab can be restarted in combination with cardiovascular medications [121, 173]. If the LVEF remains persistently low or further declines or if heart failure symptoms recur, the treating oncologist should discuss the risks and benefits of discontinuation of trastuzumab with the patient [121, 173]. Patients with radiation-induced heart diseases should be treated as nonradiation-related patients [121].

Recent advancements in curative-intent therapies have led to significant improvements in BC survival, but these advancements have come at the direct expense of increased risks of cardiovascular event or injury. It is important to recognize cardiac toxicity and to attempt to mitigate its onset not only by selecting appropriate patients for adjuvant therapy but also by selecting appropriate therapy based on patient risk factors and risk of recurrence. Increasing awareness and educating patients about cardiac toxicity is crucial. Overall, women with BC exhibit a notably worse cardiovascular risk profile compared with age-matched controls [176, 177]. Adjuvant therapies are selected on the basis of a complex

schema, including patient factors (age, comorbid illness, and patient preference) and tumor factors (grade, size, lymph node involvement, ER, and HER-2) [178].

Women diagnosed with BC are already at risk for cardiovascular disease, and almost all adjuvant therapies are associated with unique and varying degrees of cardiovascular injury. When selecting a treatment regimen, these patients are subjected to a series of sequential cardiovascular injury risks coupled with lifestyle perturbations that leave patients with obvious or subclinical cardiovascular disease. Unfortunately, each of the chemotherapeutic agents used in BC treatment has identically acute and long-term cardiac complications. Ischemic heart disease (e.g., MI, angina pectoris), cardiac failure, hypertension, peripheral atherosclerosis, and thromboembolic events are the major adverse events associated with these agents. The mechanism of chemotherapy-associated cardiac dysfunction or injury remains uncharacterized [85].

Measurement of the LVEF by echocardiography is a frequently used, effective approach to monitor cardiac function and its impairment by chemotherapy. LVEF is one of the most important predictors of prognosis because patients with significantly reduced ejection fractions typically exhibit poorer prognoses. However, current imaging techniques (echocardiography, coronary angiography, etc.) have limited ability to detect early cardiac damage [40]. The use of sensitive monitoring modalities (e.g., magnetic resonance imaging, exercise, or dobutamine stress testing) and biochemical markers (e.g., troponin I, BNP) permits more accurate detection and quantification of subclinical cardiac damage [179]. Increased troponin I levels are a significant predictor of left ventricular dysfunction after chemotherapy among cancer patients [139].

Decreases in physical activity with a diagnosis of BC may trigger increases in body weight and body fat, which may lead to a worse cancer prognosis [180, 181]. A greater decrease in physical activity has been observed among obese BC patients compared with normal weight and overweight patients ($P < 0.05$), suggesting a potential weight gain among already obese women [180, 181]. Furthermore, obesity is significantly associated with an increased recurrence risk in BC patients without any association with age or menopausal status [182, 183]. Results from one weight gain study reported that 84% of 535 BC patients gained weight (mean 1.6 kg) in the first year after diagnosis, and the Women's Healthy Eating and Living (WHEL) study reported that 60% of 1116 women gained weight (mean 2.7 kg) from 1 year before diagnosis to up to 4 years after diagnosis [184, 185]. The effects of weight gain on BC are unclear. Although some studies report an association between weight gain and an earlier disease recurrence, others have failed to produce similar results [184, 186–192]. One study in which 646 patients were followed for a median of 6.6 years found that premenopausal women who gained more than 5.9 kg were 1.5-fold more likely to relapse and 1.6-fold more likely to die from BC than those who were gaining less weight [187]. Although it is unknown whether postdiagnosis weight gain influences the risk for progressive disease, weight gain unfavorably affects risks of cardiovascular disease, hypertension, and diabetes [193–195].

Several strategies have been advised to prevent or reduce cardiac toxicity. One of these strategies involves ACE inhibition, which results in a significant reduction in LV dysfunction in patients with increased troponin I levels soon after chemotherapy [167]. The management of risk factors in patients with BC is crucial. Recommendations for the treatment of these risk factors include either pharmacotherapy or lifestyle modification. Beta-blockers and ACE-i are primarily suggested as initial therapies for hypertension with the subsequent addition of other agents (e.g., thiazides). In cases of hypercholesterolemia, statins are recommended to reduce low-density lipoprotein cholesterol to less than 100 mg/dl. Furthermore, statins are associated with a reduced incidence of thromboembolism in patients with cancer [196]. Additionally, diabetes mellitus management is related to cardiovascular disease given the utility of using biguanides or sulfonylurea for women with type II diabetes to achieve a 7% glycosylated hemoglobin (HbA1c) [197]. Exercise training may be favorable with regard to its demonstrated effects on cardiovascular reserve, individual risk factors, and overall reductions in cardiovascular mortality [198, 199]. A meta-analysis reported that exercise training resulted in a significant increase in exercise capacity among women with early BC, whereas epidemiologic data suggest that greater physical activity after therapy is related to a reduction in all causes of mortality, including BC-specific causes [200].

Of note, data on the adverse cardiovascular effects of AIs must be interpreted with caution in conjunction with baseline cardiovascular disease, LVEF, and cardiac risk factors. All of the safety analyses were conducted via comparisons with tamoxifen, whereas the mechanisms of cardiovascular events have not been clearly elucidated. It is difficult to know how to apply the results of these safety analyses to patients with an elevated risk of cardiovascular disease without analyzing baseline cardiovascular risk factors. Given this weak evidence regarding cardiovascular toxicity and short-term follow-up, no consensus is available regarding the management of cardiovascular toxicity and its consequences [85].

Further research is required to anticipate the relative portion of cardiovascular morbidity and mortality attributable to either lifestyle modification or adjuvant therapy among women with BC.

Conclusion

Exciting new cancer therapies are being discovered; however, to maximize their potential, cardiac toxicities must be identified and addressed up front. Although recent clinical experience has demonstrated significant cardiotoxicity post-trial with cancer therapies, we have also observed the resolution of toxicity using evidence-based cardiology guidelines. For continued success in making cancer history, cardiology and oncology must align their clinical and translational research goals. Cardiologists should also collaborate with oncologists in trial designs.

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Long-Term Complications and Management

50

Megan Wardak and Emilia J. Diego

Introduction

The short-term risk for complications after surgery to the breast and axilla for breast cancer is considered relatively low. Evaluation of over 3000 patients from the prospectively maintained National Surgical Quality Improvement Program (NSQIP) database by El-Tamer et al. demonstrated that the 30-day mortality risk after breast cancer surgery was 0.128% [1]. Likewise, the most common postoperative complication was a wound infection also occurring at a low rate of 4.0% after a mastectomy or 1.6% after a lumpectomy [2]. Some factors known to increase the likelihood of wound complications include a high body mass index and smoking [2]. Nonetheless, because breast and axillary procedures are classified as clean procedures, the incidence of serious wound complications is rare.

It is equally important to understand the long-term complications that may arise after surgical intervention for breast cancer as improvement in treatment results in greater survival rates. Up to 90% of breast cancer survivors will report some physical problem as a result of treatment that may affect their quality of life, and they seek treatment from a provider who may not necessarily recognize the issue or know how to treat it [3]. Some of the more common long-term sequelae may include chronic pain after breast cancer surgery and chronic seromas, all of which will be touched upon in this review. Lymphedema is another sequelae that is complex and discussed as a chapter on its own.

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Chronic Pain

Pain after breast surgery is commonly experienced at the surgical sites as a result of tissue injury, tends to be minimal and is adequately controlled by minimal amounts of oral narcotics in the first few days. Over the course of the following weeks, patients will revert to over-the-counter formulations of analgesics without much issue and can return to their preoperative functionality.

However, there will be a subset of women for whom pain may be persistent, resulting in a diminished quality of life [4]. Specifically, they can impact a breast cancer survivor's mood and mental health, vitality, and ability to work, with personal role limitations due to physical or emotional problems and sleep cycles [5, 6].

The concept of chronic pain after breast cancer surgery, defined as pain that persists 3 months beyond surgical intervention, is often overlooked as the patient may be under the care of multiple providers who may not recognize the symptoms or not fully understand how to treat them [7]. Additionally, the distinction is often difficult to make in this period as patient may still be receiving active treatment for their breast cancer at this point (systemic chemotherapy or radiation).

Though the term postmastectomy pain syndrome has been widely used, because chronic pain can also occur in patients who undergo breast conservation therapy, the more appropriate terminology may be chronic or persistent pain after breast cancer surgery (PPBCS) [8]. It is estimated that 22–64% of patients undergoing breast cancer surgery will experience chronic pain [9–13].

Understanding the etiology of the pain should allow appropriate management. However, the true etiology of PPBCS may be multifactorial and often quite challenging to address [8]. A biopsychosocial model of pain can explain why a similar procedure such as breast cancer surgery can variably impact individuals as a result of a combination of genetic tendencies, physiologic, pharmacologic, and psychological aspects as well as the person's environment [14]. It is

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also this same explanation that makes approaches to pain management inconsistently successful in different individuals.

The higher prevalence of persistent pain in patients after an axillary lymph node dissection versus a sentinel lymph node biopsy supports the concept that nerve injury plays a role in PPBCS given the greater extent of dissection and possible nerve transection with one procedure over the other [5, 13, 15, 16]. Yet, intentional sparing of the intercostobrachial nerve alone does not appear to impact the prevalence of PPBCS lending evidence to the fact that nerve irritation or inflammation also contributes to PPBCS [17, 18].

It is also important to recognize that breast pain and axillary pain are accompanied by varied effects on quality of life and also require different approaches to care [19]. And although it would be expected that PPBCS would be higher in women undergoing a mastectomy with reconstruction versus those without reconstruction, secondary to the greater extent of surgical intervention, a single institution, retrospective series of 310 women undergoing a mastectomy with or without reconstruction reveal no difference in the development of PPBCS [20].

PPBCS is difficult to treat and only a sparse body of literature exists on the topic. There is a larger amount of scientific reports on chronic pain in cancer patients, within which the topic of PPBCS falls. It is recognized that the prevalence of chronic pain is higher in the subpopulation of patients who are diagnosed with breast cancer and for whom these approaches are applicable [21]. Therefore, most strategies for management involve referral to a team of providers well versed in long-term pain, typically with pharmacotherapy as the principal treatment modality [21].

One important point of pain management that is often underscored, is the association between acute pain control and the development of chronic pain [22]. Much as knowledge regarding the entity of PPBCS and long-term management is essential for the cancer surgeon, there is the need for a larger shift of attention to avoiding severe acute postoperative pain with the intention of preventing PPBCS. Opioids have proven for decades to be one of the most powerful analgesics and are extremely effective in acute pain control.

With the growing epidemic of opioid abuse in the United States, coupled with the increasing awareness of multimodality pain management as a more successful strategy to managing acute and chronic pain in those undergoing breast surgery, strategies have shifted toward preventing postoperative pain while also reducing narcotic dependence and narcotic induced postoperative nausea [23, 24]. Many institutions have reported great success with this approach, fashioned after models for enhanced recovery after surgery (ERAS) protocols, that were initially instituted in colorectal surgery [23–26]. As alluded to previously, the goal of ERAS guidelines are to optimize pain control while reducing narcotic use via prescription of a combination of other effective pain medications: non-steroidal anti-inflammatory medications, acetaminophen, anti-convulsants and calcium channel blockers, all inhibiting different pain transmission pathways, with the added benefit of the absence of typical nausea invoking effects [26].

In summary, there is emerging evidence that multimodality pain control is superior to single-agent management of acute pain in breast cancer surgery. Efforts should be directed at the prevention of acute pain as it may later on lead to chronic pain in breast cancer survivors. Although not every case of PPBCS may be prevented by this approach, it must be recognized so that appropriate management can be instituted. This often requires referral to specialists in chronic pain and the employment of a multimodality approach to treatment.

Seroma

A seroma is defined as a collection of fluid that accumulates in dead space, and physically manifests as a swelling in the area of the surgical site. It is considered the most common complication after breast surgery with a reported incidence of 3% to 85% [27]. As a result, it seems more appropriate that it be considered a consequence of the procedure rather than a complication. The pathogenesis has not been fully elucidated, but in a review paper by Agrawal et al., it appears that it is a multifactorial result of an acute inflammatory exudate in response to surgical trauma combined with fibrinolytic activity as well as subsequent leak from blood vessels and lymphatics severed in the process of the procedure [28]. Because a postoperative seroma is a consequence in nearly all patients undergoing a breast procedure, it is a noble cause to employ maneuvers that can decrease the incidence of clinically significant, or symptomatic, seromas that ultimately require intervention and lead to other unintended consequences, such as infections secondary to repeated percutaneous aspirations, or a delay in the initiation of further breast cancer treatment.

It is well established that the extent of surgery is associated with seroma formation and a higher incidence with mastectomy versus breast conservation or axillary lymphadenectomy versus sentinel lymph node biopsy [29–31]. A patient factor that has consistently been found to contribute to likelihood of seroma formation is increased body mass index [32, 33]. Some other factors thought to contribute include age, stage of breast cancer and size or volume of breast removed [33, 34]. In terms of surgical instruments, randomized control trials have demonstrated that the use of electrocautery in dissection contributes to seroma formation as compared to sharp tissue dissection [35, 36]. However, the advantage of reduced blood loss and operative times have led

to continued use of electrocautery in breast surgery despite this consequence. Other devices such as laser scalpel, argon beam coagulator and various vessel-sealing instruments have been investigated in smaller trials but none have proven to be superior in decreasing seroma formation thus far [27, 37–41]. A meta-analysis performed in 2015 of 702 patient undergoing a modified radical mastectomy demonstrate that one instrument emerging as potentially superior to electrocautery in terms of decreasing seroma formation is the harmonic scalpel [42, 43].

Obliteration of the dead space under the skin flaps and axillary space has been recognized as a potential strategy to decrease seroma formation. As early as 1913, Halstead described the technique of flap fixation by suturing the superior flap to the fascia below the first rib and subsequently using a skin graft for the remaining chest wall defect [44]. Since that time, several groups have reported on their experience with quilting sutures and seroma formation. The most commonly reported method involves fixing the skin and subcutaneous tissue of the mastectomy flaps to the underlying pectoralis muscle using absorbable sutures in a continuous or interrupted fashion [45–48]. All four cited studies point to a decrease in seroma formation but also mention that the quilting procedure increases operative time by as much as 20–30 min [22]. In addition, some patients experienced greater postoperative pain requiring a higher amount of postoperative analgesia with concern that it could ultimately translate into chronic postmastectomy pain [46]. Another technique worth mentioning in terms of obliterating dead space was a small study reported by Faisal et al. describing axillary exclusion, in which a few interrupted, absorbable sutures are placed between the pectoralis major and minor muscle to separate the axilla from the mastectomy cavity and placing the drain tip in the mastectomy site, with the finding of decreased seroma formation [49].

External compression dressings are thought to be another method by which the dead space is obliterated. It has been compared against conventional dressings without demonstrating any added benefit in terms of decreased seroma formation while often being reported as uncomfortable for the patient [48, 50]. Therefore, external compression dressings are not routinely used after breast cancer surgery.

Various chemical agents have also been injected into the surgical cavity immediately following the procedure including bovine thrombin, low-thrombin fibrin sealant, sapylin and methylprednisolone, among others, none of which have proven to significantly decrease seroma formation postoperatively [51–54].

Activity limitation or immobilization has been used as a strategy to decrease seroma formation with little benefit. Although a meta-analysis in 2005 demonstrated that delaying arm exercises could decrease seroma formation, more recent evidence reveals contradictory findings and the delay of physiotherapy is therefore not mandated after breast surgery [55–57].

The most common approach used to manage seromas after breast surgery is the placement of a closed suction drain, specifically when performing a total mastectomy or axillary lymph node dissection but not for breast conservation surgery or a sentinel lymph node biopsy [3, 27–30, 32–34, 38, 48]. The purpose of the drain is to facilitate skin and flap apposition and obliterate the dead space. Multiple systematic reviews demonstrate its effectiveness in decreasing seroma formation and number of aspirations needed, albeit sometimes increasing hospital length of stay [30, 33, 34, 38, 58, 59]. However, a recent, single-institution study of over 500 patients comparing drains or no drains postsurgery did not demonstrate a higher symptomatic seroma, aspiration or infection rate, or complications requiring re-admission in those without drains [60]. This is contradictory to most published reports on drains and the authors suggest that more trials be done to confirm these findings.

Timing of drain discontinuation is another nuanced variable in surgical practice, but most drains are typically discontinued on the basis of <20–50 mls output in a 24-hour period [30, 33, 61].

Though the above-described methods can successfully manage the majority of postoperative seromas after breast cancer surgery, a few patients may suffer from seroma that is refractory to conventional drain approach or multiple aspirations and be put at risk for complications such as infections. Additionally, the situation can delay important cancer treatment and potentially jeopardize patient outcomes.

There is a paucity of literature regarding the management of chronic seromas, with majority of reports written on a single-patient experience. Nonetheless, these may serve as valuable tools when the need arises. Surgical resection or "capsulectomy" of a persistent and fibrosed seroma capsule has been described with success by Stanczyk et al. in a 73-year-old after a modified radical mastectomy, several months after her initial procedure [62]. Inspired by pleurodesis, the technique of talc seromadesis involves the reopening of a previous mastectomy incision, instillation of sterile dry talc into the cavity with subsequent drain placement and pressure dressing [63, 64]. Two separate patient reports describe multiple aspirations and significant amounts of seroma fluid re-accumulation over the course of several months after a mastectomy. However, after the talc seromadesis, no recurrence was noted after 5–8 months of follow-up. A third approach that has been reported with good results in over 20 patients involves ultrasound-guided scraping of the fibrous seroma cavity followed by a bi-layered negative pressure dressing for a short duration of time (less than 2 weeks) with no recurrences on follow-up [65].

In summary, seromas post-breast cancer surgery is an expected sequela. Some patient characteristics contribute to

seroma formation but there are variables that cannot be controlled. While closed suction drains remain the mainstay of management, some strategies may be employed to decrease clinically significant seroma formation including obliteration of dead space via quilting or axillary exclusion techniques, and possibly the use of the harmonic scalpel. It is not necessary to delay physiotherapy after surgery as this does not appear to contribute to increased seroma formation. Likewise, compression bandages postoperatively do not decrease seroma formation. Additionally, there are currently no tissue sealant products that have been shown to decrease seroma formation if instilled intraoperatively.

In the rare circumstance that a clinically significant, chronic seroma needs to be addressed, some strategies may include surgical excision of the fibrous capsule, ultrasound-guided scraping of the fibrous capsule and negative pressure dressing, or talc seromadesis.

Suboptimal Cosmetic Outcomes

Since the 1970s, when clinical trials proved breast conservation to be an equivalent approach to mastectomy for locoregional control, there has been a dramatic movement away from breast amputation in favor of breast preserving surgical techniques. This shift has allowed many women to retain the majority of their natural breast, while still receiving treatment for breast cancer. The option of breast-conserving therapy has helped to alleviate some of the fear of having to undergo a major operation for breast cancer treatment [66].

This has in turn led to a focus on improving the cosmetic outcomes and preventing unfavorable results after breast-conserving therapy. The success of breast-conserving therapy is not only based on overall survival but is also dependent on good cosmetic outcomes. The cosmetic outcomes of breast-conserving therapy play a very influential role in the psychosocial aspect and well-being of patients, which includes the patient's physical, mental, and sexual well-being. Poor cosmetic outcomes have been shown to have a negative impact on the quality of life, including self-esteem, body image, feeling feminine, and sexual function [67].

There have been several factors that have been identified to affect the cosmetic outcomes of breast-conserving therapy. These factors include larger breast size, larger tumor size, axillary lymph node dissection, retro areolar location of the tumor, adjuvant chemotherapy administration and whole breast radiation [68, 69]. Poor cosmetic outcomes are viewed as breasts with asymmetry, displacement of the nipple, change in the contour of the breast, changes in the skin and retraction of the scar resulting in a change in the shape of the breast [70].

In addition, there are both patient-related factors and treatment-related factors that play a significant role in producing symmetry after breast-conserving therapy. Patient-related factors that place patients at a higher risk for asymmetry after a breast-conserving operation include age, BMI, tumor location, and tumor size [71]. There is a dichotomy that exists for poor cosmetic outcomes when related to age in women who were treated with breast-conserving therapy, with poorer cosmesis reported in those either less than 40 years or greater than 60 years in age. Women with a body mass index (BMI) of 35 kg/m^2 or greater tend to have higher rates of asymmetry compared to women of lower BMIs [71]. Tumors that are located in the superior lateral aspect of the breast and those that are located in the inferior medial aspect of the breast are associated with higher rates of asymmetrical outcomes [72]. Also, tumors that are larger than 3 cm in size that are resected are more likely to be asymmetrical [72]. Treatment factors that increase the risk of asymmetry include patient that undergo multiple re-excisions (> 2 re-excisions), patients with postoperative seromas, and patients undergoing radiation therapy [71]. The knowledge of these factors can have an influence in the decision for patients and providers to pursue breast-conserving therapy and can help aid in the expectations after breast-conserving therapy and plan for ways to improve cosmetic outcomes.

Breast conserving therapy incorporates multiple disciplines, including surgical oncology, radiation oncology and medical oncology. Each aspect of the multidisciplinary approach has an effect on the cosmetic outcome. The surgical aspect focuses on the resection of the tumor and obtaining adequate resection margins, coupled with radiation therapy to provide locoregional control and decreased rates of local recurrence, from 26% to 7% at 5 years [73]. The combination of surgical resection and radiation has allowed patients to preserve the breast, have a less invasive surgical procedure and achieve survival rates that are similar to a mastectomy [66]. However, the addition of radiation can lead to a poorer cosmetic outcome by reducing the overall size of the breast, creating asymmetry between the two breast, and sometimes thickening of the skin of the breast [72]. The factors that are related to radiation that have an increased risk of producing worse cosmetic outcomes include the use of photon boost, a high boost dose, adjuvant chemotherapy and boost volume [72, 74].

If a poor cosmetic outcome is encountered after breast-conserving therapy, then there are several options for breast reconstruction. Flaps are a great option for breast reconstruction. The decision for the type of flap depends on the location of the defect. For defects that are located on the lateral or superior aspect of the breast, flaps with a pedicle may be used to restore symmetry. For defects that are located medially or inferiorly, a free flap reconstruction would be a better option [75]. In patients with larger tumors located on the lateral and superior aspect of the breast which have been resected using lumpectomy, a rhomboid flap reconstruction technique could facilitate obtaining a more symmetric cosmetic outcome [76]. Other options for reconstruction after a

poor cosmetic outcome include an implant, autologous fat grafting, rotational flap reconstruction and latissimus dorsi flap [75]. Fat grafting has been essential in producing more favorable cosmetic outcomes in breast tissue that has been affected by volume deficits, breast tissue that has been affected by postsurgical scarring, and radiation [71].

As with the other two problems discussed earlier in the chapter, a poor cosmetic outcome can frequently be prevented by proper preoperative assessment and planning by the oncologic surgeon. Oncoplastic breast surgery techniques have gained favor in the last decade, with methods borrowed from plastic surgery that employ breast tissue rearrangement to conceal a defect, particularly when it is anticipated that it will lead to a poor cosmetic outcome [77]. Although this topic is beyond the scope of this chapter, it is worth mentioning that oncoplastic techniques can range from simple re-approximation of breast tissue and elimination of dead space to more complex mobilization of tissue planes. Consideration for contralateral symmetry may also be necessary when larger breast defects are created and this can be done in collaboration with a plastic surgeon, depending upon the comfort level of the oncologic surgeon [77, 78].

In summary, there are patient and tumor factors that need to be considered when offering a woman breast conservation therapy for their cancer treatment. These decisions impact the cosmetic outcome and it is imperative that the oncologic surgeon discusses these consequences with the patient. There are techniques that can be used to prevent inferior cosmetic outcomes, and there are also techniques to rectify them in the event that they occur, some strategies of which have been covered in this text.

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Systemic Treatment Drugs/Regimens and Dose Modifications

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Naziye Ak and Adnan Aydiner

Introduction

Anticancer drugs might have mild, moderate, severe, and life-threatening toxicities in some individuals. Close monitoring of chemotherapy toxicity can be instrumental in ensuring prompt symptom management and quality care. Proper dose selection has great importance for toxicities, particularly when the purpose of treatment is curative, such as in adjuvant treatment of breast cancer. Toxicities can lead to a two-way problem. The profit/loss ratio of treatment should be adequately evaluated, and toxicity may not cause life-threatening conditions. However, decreasing the dosage under the therapeutic range may cause under-dosing in patients, which may compromise cancer outcomes. It is very important to know how to adjust the dose according to toxicity without changing the effectiveness of the drug.

Appropriate dosing for anticancer agents is studied extensively before marketing, with the goal of maximizing efficacy and minimizing toxicity. However, individuals have a highly variable capacity to metabolize and eliminate drugs and/or other medical conditions that lead to variations in drug exposure and susceptibility to toxicities. Other medical conditions, primarily hepatic and renal failures in patients with breast cancer, may require changes in the treatment regimen or dosage. Knowledge about dosage modifications is necessary to avoid undertreating patients. For some toxicities, dose adjustment instead of regimen change may be sufficient, and some toxicities with dose-limiting properties can lead to cessation of treatment.

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Recommendations In Chemotherapy Dose Modifications

Basic Recommendations for Dose Modification in Hematological Toxicity

New Doses of Chemotherapy According to the Maximum Toxicity in the Previous Chemotherapy

Toxicity grade	Dose in the next cycle
ANC[a] <0.5 ($\times 10^9$)/L for 5–7 days or febrile neutropenia	Reduce by 25%[b]
Thrombocyte <25 ($\times 10^9$)/L or bleeding	Reduce by 25%

[a]ANC = Absolute neutrophil count = Neutrophils + number of rod cells
[b]Administering GCSF in curative treatments may not reduce dosage

Chemotherapy is avoided until ANC $\geq 1.5 \times 10^9$/L, platelet $\geq 100 \times 10^9$/L and other toxicities are $\leq$ grade 2. However, if it is necessary to administer chemotherapy despite lower blood laboratory results due to the patient's clinical condition, reducing the doses by 25–50% and administering GCSF (Granulocyte colony-stimulating factor).

Basic Recommendations for Dose Modification in Non-Hematological Toxicity

New doses of chemotherapy according to the maximum toxicity in the previous chemotherapy:

- Toxicity Grade 1: The treatment is continued, and the symptoms are treated. There is no change in dosage.
- Toxicity Grade 2: The treatment is continued, and the symptoms are treated. No dose changes or modifications can be made according to the treatment regimen applied.
- Toxicity Grade 3: Treatment is postponed, and the symptoms are treated; 75% of the previous dose is given.
- Toxicity Grade 4: The treatment is postponed or completely discontinued. If continued, the doses are modified.

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Recommendations in Targeted-Drug Dose Modifications

Everolimus

Everolimus inhibits mTORC1 (mammalian target of rapamycin complex 1), which plays roles in protein synthesis and activation of estrogen receptor (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 2]).

Everolimus is used for postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane.

Dosage 10 mg once daily in combination with either exemestane or fulvestrant.

The most common side effects for everolimus include mucositis, fatigue, diarrhea, gastrointestinal symptoms, rash, hepatotoxicity, anorexia, weight loss, fluid retention and headache.

Dose modifications at toxicity:

1. Thrombocytopenia
   - Thrombocyte count higher than 75,000/microL (Grade 1 thrombocytopenia) does not require dose modification.
   - If the thrombocyte count is 50,000–75,000/microL (Grade 2 thrombocytopenia), hold the drug until symptoms are resolved, and no dose modification is needed.
   - If the thrombocyte count is less than 50,000/microL (Grade 3–4 thrombocytopenia), hold the drug until symptoms are resolved, and then restart at a lower dosage of the drug.
2. Neutropenia
   - Neutrophil count higher than 1000/microL (Grade 1–2 neutropenia) does not require dose modification.
   - If the absolute neutrophil count is between 500 and 1000/microL (Grade 3 neutropenia), hold the drug until a minimum level of 1000/microL, and no dose modification is needed.
   - If the absolute neutrophil count is less than 500/microL (Grade 4 neutropenia), hold the drug until a minimum level of 1000/microL and then restart at a lower dosage of the drug.
3. Febrile neutropenia
   - If Grade 3 febrile neutropenia occurs, hold until recovery, and then restart treatment at a lower dose.
   - Grade 4 febrile neutropenia requires discontinuation of the drug.
4. Non-infectious pneumonitis
   - If the patient has only radiological signs and no or few symptoms, no dose modification is required. Only observe and monitor the patient.
   - If the patient has symptoms that limit instrumental activities and require medical intervention (Grade 2 toxicity), hold the drug until symptoms are resolved, and restart at half of the dosage. If symptoms are not resolved within 4 weeks, stop the drug.
   - If the patient has severe symptoms that limit self-care activities and require oxygen therapy (Grade 3 toxicity), hold the drug until symptoms are resolved, and restart at half of the dosage. At the second event of grade 3 toxicity, stop the drug.
   - If life-threatening respiratory toxicity occurs, stop the drug.
5. Stomatitis
   - Minimal symptoms do not need dose modification, and only the standard approach to mucositis is recommended.
   - Mucositis that does not interfere with oral intake (Grade 2) requires drug cessation until symptoms resolve to grade 1; the drug can then be used at the same dose. If symptoms recur, hold the drug until toxicity resolves to better than grade 1, and restart the drug at a lower dosage.
   - Mucositis that interferes with oral intake (Grade 3) requires drug cessation until symptoms resolve to grade 1, and then restart the drug at a lower dosage.
6. Metabolic events
   - Grade 1 and 2 hyperglycemia and hyperlipidemia do not require dose modification. Only observe and monitor the patient.
   - If hyperglycemia and hyperlipidemia require hospitalization or urgent intervention (Grade 3 and Grade 4), hold the drug until symptoms are resolved to grade 1, and then restart the drug at a lower dosage.

Hepatic Impairment (Table 51.1):

- Mild (Child-Pugh class A): 7.5 mg daily (5 mg daily if 7.5 mg not tolerated).
- Moderate (Child-Pugh class B): 5 mg daily (2.5 mg daily if 5 mg not tolerated).
- Severe (Child-Pugh class C): Use only when benefits outweigh risks at 2.5 mg daily.

Table 51.1 CHILD-PUGH classification [12]

Points	Albumin	Ascites	Bilirubin	Encephalopathy	INR
1	>3.5 g/dL	–	<2 mg/dL	–	<1.7
2	2.8–3.5 g/dL	Slight	2–3 mg/dL	Grade 1–2	1.7–2.3
3	<2.8 g/dL	Moderate	>3 mg/dL	Grade 3–4	>2.3

A score of 5–6 is considered Child-Pugh class A; 7–9 is class B; and 10–15 is class C

INR international normalized ratio

Renal Impairment:
- No dose adjustment is required.

Dosage in the Elderly:
- No dose adjustment is required.

Palbociclib

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, which are involved in cell proliferation. Palbociclib is used in combination with an anti-estrogen agent in advanced estrogen receptor (ER)-positive breast cancer patients (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 3]).

The most common side effects are myelosuppression, infection, fatigue, gastrointestinal symptoms, mucositis, headache, and dermatologic toxicities.

Dosage 125 mg once daily, 21 days for every 28 days in combination with either aromatase inhibitor or fulvestrant.

The recommended dose reduction is to 100 mg daily at the first level; if a second reduction is required, reduce the dose to 75 mg daily. If the 75 mg daily dose is not tolerated, discontinue treatment.

Dose modifications at toxicity:

1. Thrombocytopenia
   - A thrombocyte count higher than 50,000/microL (Grade 1 and Grade 2) does not need dose modification.
   - If the thrombocyte count is 25,000–50,000/microL (Grade 3 thrombocytopenia) at day 1 of the cycle, hold the drug for 1 week. If the thrombocyte count is higher than 50,000/microL, initiate the next cycle at the same dose.
   - If the thrombocyte count is 25,000–50,000/microL (Grade 3 thrombocytopenia) at day 15 of the cycle, complete the cycle at the same dose. If the thrombocyte count is less than 25,000/microL on day 22, hold the treatment until toxicity is resolved to grade 2. After resolution, resume at the next lower dose, 100 or 75.
   - If the thrombocyte count is less than 25,000/microL (Grade 4 thrombocytopenia), hold the drug until the thrombocyte count is higher than 50,000/microL. After resolution, resume at the next lower dose, 100 or 75.
2. Neutropenia
   - A neutrophil count higher than 1000/microL (Grade 1–2 neutropenia) does not need dose modification.
   - If the absolute neutrophil count is between 500 and 1000/microL (Grade 3 neutropenia) at day 1 of the cycle, hold the drug for 1 week; if the neutrophil count is higher than 1000/microL, initiate the next cycle at the same dose.
   - If the absolute neutrophil count is between 500 and 1000/microL (Grade 3 neutropenia) at day 15 of the cycle, complete the cycle at the same dose. If the neutrophil count is less than 500/microL on day 22, hold palbociclib treatment until neutropenia is resolved to grade 2. After resolution, resume at the next lower dose, 100 or 75.
   - If grade 3 neutropenia (500 to 1000/microL) plus fever ≥38.5°C and/or infection at any time, withhold palbociclib treatment until toxicity is resolved. Then, begin at the next lower dose.
   - If the neutrophil count is less than 500/microL (Grade 4 neutropenia) at any time, hold the drug until the neutrophil count is higher than 1000/microL. Then, begin at the next lower dose.

Non-hematologic toxicities:
- Grade 1 or 2 toxicities do not need dose modification.
- If Grade 3 or higher toxicities occur, hold palbociclib until symptoms resolve to lower than grade 1; after resolution, resume at the next lower dose.

Hepatic Impairment:
- No change is needed for mild hepatic impairment.
- The drug has not been studied in patients with moderate and severe hepatic impairment.

Renal Impairment:
- No change is needed for patients with glomerular filtration rate (GFR) >30 mL/dk.
- The drug has not been studied in patients with severe renal impairment.

Dosage in the elderly:
- No overall differences in efficacy and toxicity.

Ribociclib

Ribociclib is a drug with the same mechanism and indication as palbociclib (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 4]).

Dosage 600 mg once daily for 21 days, with 28-day cycles.

The recommended dose reduction is to 400 mg daily at the first level; if a second reduction is required, reduce the dose to 200 mg daily. If the 200 mg daily dose is not tolerated, discontinue treatment.

Dose modifications at toxicity:

1. Neutropenia
   - Neutrophil count higher than 1000/microL (Grade 1–2 neutropenia) does not require dose modification.

- If the absolute neutrophil count is between 500 and 1000/microL (Grade 3 neutropenia), hold ribociclib treatment until neutropenia is resolved to grade 2. After resolution, resume at normal dosage as 600 mg. However, if recurrent grade 3 toxicity occurs, interrupt treatment until recovery, and then resume the drug at the next lower dose level, 400 or 200 mg.
- If grade 3 neutropenia (500 to 1000/microL) plus fever ≥38.5°C and/or infection at any time, withhold ribociclib treatment until toxicity is resolved. Then, begin at the next lower dose.
- If the neutrophil count is less than 500/microL (Grade 4 neutropenia), hold the drug until the neutrophil count is higher than 1000/microL. Then, begin at the next lower dose.

2. QT prolongation
   - If the corrected QT duration is longer than 480 ms, interrupt treatment. When QTc resolves, resume ribociclib at the same dose level. If QTc prolongation recurs, interrupt treatment until QTc resolves, and resume drug at the next lower dose level, 400 or 200 mg.
   - If the corrected QT duration is longer than 500 ms, interrupt treatment. When QTc resolves to less than 481 ms, ribociclib may be resumed at the next lower dose level. If QTc interval prolongation is either more than 500 ms or more than 60 ms, increase from baseline. If this prolongation is associated with life-threatening arrhythmias with or without signs or symptoms of serious arrhythmia, permanently discontinue ribociclib.
3. Hepatobiliary toxicity
   - Grade 1 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation [1 to 3 times upper limit of normal (ULN)] without a total bilirubin increase >2 times ULN does not require dose modification.
   - Grade 2 ALT and/or AST elevation (3 to 5 times ULN) without a total bilirubin increase >2 times ULN requires interruption of the drug until recovery to a minimal baseline. Then, ribociclib can be used at the same dose level. For recurrent grade 2 elevations, ribociclib can be resumed at the next lower dose level after recovery. If baseline AST/ALT level was at grade 2, no dose modification is necessary.
   - Grade 3 ALT and/or AST elevation (5 to 20 times ULN) without a total bilirubin increase >2 times ULN requires interruption of the drug until recovery to a minimal baseline. Then, resume ribociclib at the next lower dose, 400 or 200. For recurrent grade 3 elevations, discontinue ribociclib.
   - If Grade 4 ALT and/or AST elevation (more than 20 times ULN) occurs, stop ribociclib.
   - If combined ALT and/or AST is elevated more than 3 times ULN and total bilirubin increases more than 2 times ULN, discontinue ribociclib.

Hepatic Impairment:
- No change is needed on mild hepatic impairment.
- On moderate or severe impairment (Child-Pugh class B or C), the initial dose is 400 mg.

Renal Impairment:
- No change is needed for patients with GFR >30 mL/dk.
- The drug has not been studied in patients with severe renal impairment.

Dosage in the elderly:
No dosing modification is needed.

Abemaciclib

Abemaciclib is a drug with the same mechanism and indication as palbociclib and ribociclib (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 5]).

Dosage 200 mg twice daily (400 mg/day) as a single agent or 150 mg twice daily (300 mg/day) in combination with an aromatase inhibitor.

The recommended dose reduction for monotherapy is to 150 mg twice daily at the first level; if a second reduction is required, reduce the dose to 100 mg twice daily and then 50 mg twice daily. If a 50 mg twice daily dose is not tolerated, discontinue treatment.

The recommended dose reduction for aromatase inhibitor combined therapy is to 100 mg twice daily at the first level; if a second reduction is required, reduce the dose to 50 mg twice daily. If the 50 mg twice daily dose is not tolerated, discontinue treatment.

Dose modifications at toxicity:

1. Hematologic toxicities
   - No change is needed on Grade 1 and 2 hematologic toxicities.
   - At Grade 3 hematologic toxicity, hold the drug until reaching minimum cell count levels for Grade 2 hematologic toxicities. No dose modification is needed at the next cycle.
   - At Grade 4 or recurrent grade 3 hematologic toxicity, hold the drug until toxicity resolves to the minimum level for grade 2 toxicities, and then resume at the next lower dose.
   - *Note*: If blood cell growth factors are required, withhold the abemaciclib dose for at least 48 h after the last growth factor dose and until toxicity resolves to ≤ grade 2; resume abemaciclib at the next lower dose (unless already reduced due to the toxicity that required the growth factor).
2. Diarrhea
   - Less than 4 loose stools (Grade 1 diarrhea) do not require dose modification.

- Four to six stools and diarrhea that limits instrumental daily activities (Grade 2 diarrhea) and does not resolve to ≤ grade 1 within 24 h requires withholding of abemaciclib until resolution. Then, no dose modification is needed.
- Persistent or recurrent Grade 2 diarrhea (after resumption at the same dose) requires interruption of the drug until toxicity resolves to ≤ grade 1; then resume the drug at the next recommended lower dose.
- Diarrhea of more than seven stools that limits self-care daily activities and/or diarrhea requiring hospitalization or life-threatening toxicity (Grade 3 or 4 diarrhea) require interruption of the drug until toxicity resolves to lower than grade 1 level; then resume abemaciclib at the next lower dose.

3. Hepatobiliary toxicity
   - Grade 1 (ALT, AST elevation up to 3 times ULN) and Grade 2 (ALT, AST elevation 3 to 5 times ULN) hepatocellular toxicities without an increase in total bilirubin of more than 2 times ULN do not require dose adjustment.
   - Persistent or recurrent grade 2 or grade 3 (ALT, AST elevation 5 to 20 times ULN) hepatocellular toxicities without an increase in total bilirubin more than 2 times ULN require interruption of the drug until the toxicity resolves to baseline or grade 1 level; then resume the drug at the next lower dose as recommended above.
   - AST and/or ALT elevation more than 3 times ULN with total bilirubin more than 2 times ULN (in the absence of another reason) and Grade 4 hepatocellular toxicity (ALT, AST elevation more than 20 times ULN) require discontinuation of abemaciclib treatment.

Hepatic Impairment:
- No dose modification is needed for mild and moderate hepatic impairment (Child-Pugh class A or B).
- At severe impairment (Child-Pugh class C), give drug once daily.

Renal Impairment:
- No dose modification is needed for patients with GFR >30 mL/dk.
- The drug has not been studied in patients with severe renal impairment.

Dosage in the elderly:
- No dose modification is needed.

Olaparib

Olaparib is an oral poly (adenosine diphosphate-ribose) polymerase inhibitor that has been approved for metastatic breast cancer (MBC) patients with germline BRCA mutation (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 6]).

Dosing 300 mg twice daily (600 mg/day) in tablet form for breast cancer.

The recommended first dose reduction for tablet form is to 250 mg twice daily (500 mg/day); if a second reduction is required, reduce the dose to 200 mg twice daily (400 mg/day).

Dosing and bioavailability differ; do not substitute the capsules and tablets on a mg-per-mg basis.

Dose modifications at toxicity:

- Pneumonitis requires discontinuation of the drug.
- Secondary acute myeloid leukemia/myelodysplastic syndrome requires discontinuation of the drug.
- If the patient develops severe hematological toxicity or blood transfusion dependence, the drug should be interrupted, and appropriate hematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Hepatic Impairment:
- No change is needed for mild (Child-Pugh class A) hepatic impairment.
- The drug has not been studied in patients with moderate and severe (Child-Pugh classes B and C) hepatic impairment.

Renal Impairment:
- A GFR level greater than 50 mL/minute does not require dose modification.
- A GFR level between 31 and 50 mL/minute requires dose reduction to 200 mg twice daily for tablets.
- The drug has not been studied in patients with severe renal impairment (GFR level lower than 30 mL/minute).

Dosage in the elderly:
- No dose adjustment is required.

Neratinib

Neratinib is an oral pan-HER inhibitor that irreversibly inhibits the tyrosine kinase activity of epidermal growth factor receptor (EGFR or HER-1), HER-2, and HER-4. The drug is approved for HER-2-positive breast cancers in the extended adjuvant setting (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, [1, 7, 8]).

Dosage 240 mg once daily for 1 year.

The recommended neratinib dose reductions for toxicity are first 200 mg once daily and then 160 mg and 120 mg once daily.

If the toxicity does not recover to less than grade 1 level, if toxicities that result in a treatment delay of more than

3 weeks occur, or if patients are unable to tolerate the 120-mg once-daily dose, discontinue neratinib.

Dose modifications at toxicity:

1. Diarrhea
   - Routine antidiarrheal prophylaxis with loperamide is recommended during the first two cycles of therapy; initiate with the first neratinib dose. Titrate to 1 to 2 bowel movements/day.
   - Grade 1, grade 2 (lasting 5 days), or grade 3 diarrhea (lasting 2 days) do not require dose modification. Routine diarrhea management is recommended.
   - If the patient has 4–6 bowel movements daily for more than 5 days, grade 3 diarrhea for more than 2 days (despite optimal antidiarrheal management), or any grade diarrhea with severe complicating features (e.g., dehydration, fever, hypotension, renal failure, or grade 3/4 neutropenia), interruption of the drug is recommended. If diarrhea improves with routine diarrhea management to lower than grade 1 in 1 week or less, resume neratinib at the same dose. If diarrhea improves to lower than grade 1 in more than 1 week, resume neratinib at the next lower dose. For recurrent ≥ grade 2 diarrhea (occurring at the 120 mg once daily dose), permanently discontinue neratinib.
   - If diarrhea has life-threatening consequences, permanently discontinue neratinib.
2. Hepatotoxicity
   - No dose modification is recommended until AST/ALT level elevation up to 5 times ULN.
   - ALT level elevation 5 to 20 times the upper limit of normal value (Grade 3 hepatocellular toxicity) or bilirubin levels between 3 and 10 times ULN (Grade 3) require interruption of neratinib until recovery to below grade 1 toxicity. Resume therapy at the next lower dose level if recovery occurs within 3 weeks.
   - Recurrent grade 3 AST/ALT or bilirubin elevation despite one dose reduction requires discontinuation of the drug permanently.
   - ALT levels greater than 20 times ULN (Grade 4) or bilirubin levels greater than 10 times ULN (Grade 4 hepatic toxicity) require discontinuation of the drug permanently.

Hepatic Impairment:

- No dose modification is required for mild and moderate hepatic impairment (Child-Pugh class A or B).
- Dosage at severe impairment (Child-Pugh class C) is 80 mg once daily.

Renal Impairment:
No dose modification is recommended.

Dosage in the Elderly:
No dose modification is recommended.

Lapatinib

Lapatinib is a small-molecule tyrosine kinase inhibitor that dually targets HER-1 and HER-2. Lapatinib enters the cell and binds to the intracellular domain of the tyrosine kinase receptor, completely blocking the autophosphorylation site and halting the downstream cascade.

Dosage Oral 1250 mg once daily in combination with capecitabine, 1500 mg once daily in combination with letrozole, and 1000 mg once daily in combination with trastuzumab [9–11].

Dose modifications at toxicity:

1. Cardiac toxicity
   - Left ventricular ejection fraction (LVEF) level decreased to more than lower level of normal: Hold the drug for at least 2 weeks.
   - LVEF recovers to normal value and patient is asymptomatic: Lapatinib may be restarted at 1000 mg once daily (for capecitabine combined regimen) or 1250 mg once daily (for letrozole combined regimen).
2. Dermatologic toxicity
   - Erythema multiform, Stevens-Johnson syndrome, or toxic epidermal necrolysis: Discontinue the drug.
3. Diarrhea
   - Grade 3 diarrhea or grade 1 or grade 2 diarrhea with complicating features requires interruption of the drug until toxicity resolves to ≤ grade 1. Then, resume the drug at the recommended lower dose (1250 mg once daily or 1000 mg once daily).
   - Diarrhea requiring hospitalization or life-threatening toxicity (Grade 4 diarrhea): Discontinue the drug permanently.
4. Pulmonary toxicity
   - Patient has severe symptoms that limit self-care activities and requires oxygen therapy (Grade 3 toxicity): Discontinue the drug.

Renal Impairment:

- No dose modification is needed.

Hepatic Impairment:

- Mild or moderate pre-existing impairment (Child-Pugh class A or B) requires no dosage adjustments.
- Severe preexisting impairment (Child-Pugh class C): Although there are no clinical data associated with the adjustments, dose reduction to 750 mg (capecitabine combined form) or 1000 mg (letrozole combined form) is reasonable.
- Severe hepatotoxicity during treatment requires discontinuation of the drug permanently.

Dosage in the Elderly:

- No dose modification is needed.

Ado-Trastuzumab Emtansine (T-DM1)

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of trastuzumab and the microtubule inhibitor DM1 that can be used in advanced HER-2-positive breast cancer patients [13, 14].

Dosage 3.6 mg/kg iv, every 21 days.

The recommended dose reduction is to 3 mg/kg at the first level; if a second reduction is required, reduce the dose to 2.4 mg/kg. If 2.4 mg/kg is not tolerated, discontinue treatment. After a dose reduction, continue at that dose. If one cycle is missed or delayed, administer at the dose and rates most recently tolerated, and then continue at that schedule.

The most common side effects are fatigue, musculoskeletal symptoms, headache, hypopotassemia, skin rash, increased serum transaminases, and decreased platelet count.

Dose modifications at toxicity:

1. Hematologic toxicities
   - A thrombocyte count higher than 50,000/microL (Grade 1 and Grade 2) does not need dose modification.
   - If the thrombocyte count is 25,000–50,000/microL (Grade 3 thrombocytopenia), withhold the drug until the platelet count recovers to a minimum of 75,000/mm^3; initiate the next cycle at the same dose.
   - If the thrombocyte count is lower than 25,000/microL (Grade 4 thrombocytopenia), withhold the drug until the platelet count recovers to a minimum of 75,000/mm^3, and then resume treatment with one dose level reduction.
2. Hepatobiliary toxicity
   - Grade 1 and Grade 2 ALT and/or AST elevation (1 to 5 times ULN) without a total bilirubin increase >2 times ULN do not need dose modification. Grade 1 and 2 hyperbilirubinemia (lower than 3 times ULN) require discontinuation of the drug until bilirubin recovers to lower than grade 1 level; then resume the drug at the same dose level.
   - Grade 3 ALT and/or AST elevations (>5 to ≤20 times ULN) without a total bilirubin increase >2 times ULN and grade 3 hyperbilirubinemia (>3 to ≤10 times ULN) require interruption of the drug until recovery; then resume the drug at the next lower dose level.
   - Concomitant increase in transaminase levels more than 3 times ULN and total bilirubin levels more than 2 times ULN or grade 4 ALT and/or AST elevations (>20 times ULN) or grade 4 hyperbilirubinemia (>10 times ULN) or idiopathic non-cirrhotic portal hypertension require that treatment be stopped permanently.
3. Infusion-related reaction
   - For mild reactions, slow the infusion rate, or interrupt infusion.
   - For life-threatening infusion reactions, stop treatment permanently.
4. Peripheral neuropathy
   - Neuropathy that limits self-care daily living activities and/or has life-threatening consequences requires interruption of the drug until neuropathy resolves to a minimal level of grade 2.
5. Pulmonary toxicity
   - Interstitial lung disease or pneumonitis requires permanent cessation of treatment.

Hepatic Impairment:

- No change is needed for mild and moderate (Child-Pugh class A or B) hepatic impairment. The drug has not been studied in patients with severe (Child-Pugh class C) hepatic impairment.

Renal Impairment:

- No change is needed for patients with GFR >30 mL/min, and the drug has not been studied in patients with severe renal impairment.

Dosage in the Elderly:
No overall differences in efficacy and toxicity.

Cardiotoxicity of Trastuzumab, Pertuzumab, and T-DM1

The single most important contraindication to HER2-targeted therapy is decreased left ventricular ejection fraction (LVEF) and/or clinical evidence of congestive heart failure (CHF) arising from low LVEF. The University of Texas M.D. Anderson Cancer Center evaluated the cardiac safety of long-term trastuzumab therapy in patients with HER2-overexpressing MBC [15]. The median cumulative time of trastuzumab administration was 21.3 months. The median follow-up was 32.6 months (range, 11.8–79.0 months). Among the patients, 28% experienced a cardiac event (CE): 15.6% with grade 2 cardiac toxicity and 19 patients (10.9%) with grade 3 cardiac toxicity. With trastuzumab discontinuation and appropriate therapy, all but three patients had improved left ventricular ejection fraction (LVEF) or diminished symptoms of congestive heart failure. Baseline LVEF was significantly associated with CEs (hazard ratio, 0.94; $P = 0.001$). The risk of CE among patients receiving concomitant taxanes was higher early in the follow-up period and subsequently declined. This toxicity was reversible in the majority of patients. Additional treatment with trastuzumab can be considered after the recovery of cardiac function among patients who experience CE (Tables 51.2–51.4) [16–18].

Patients receiving HER2-directed therapy require regular cardiac function monitoring via an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan. We typically follow

Table 51.2 Dosage dose modification of trastuzumab based on asymptomatic left ventricular ejection fraction decrease from baseline

Relationship of left ventricular ejection fraction (LVEF) to the lower limit of normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	≤10 percentage points	10–15 percentage points	≥15 percentage points
Within a facility's normal limits	Continue	Continue	Hold and repeat MUGA/ECHO after 4 weeks[a]
<6% below LLN	Continue[a]	Hold and repeat MUGA/ECHO after 4 weeks [a,b]	Hold and repeat MUGA/ECHO after 4 weeks[b,c]
≥6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks[c]	Hold and repeat MUGA/ECHO after 4 weeks[b,c]	Hold and repeat MUGA/ECHO after 4 weeks[b,c]

[a]Consider cardiac assessment. Cardiotoxicity associated with trastuzumab typically responds to appropriate medical therapy but may be severe and lead to cardiac failure [16]
[b]After 2 holds, consider permanent trastuzumab discontinuation
[c]Refer to cardiologist

Table 51.3 Dosage dose modification of trastuzumab and pertuzumab combination based on asymptomatic left ventricular ejection fraction decrease from baseline

Left ventricular ejection fraction	Trastuzumab and pertuzumab		
	Action	LVEF at reassessment	Dose
<40% AND asymptomatic	Pause and repeat MUGA in 3 weeks	>45% OR 40–45% AND <10% ↓ from baseline	Restart
40–50%[a] AND ≥10% points below baseline AND asymptomatic		<40% OR 40–50%[a] AND ≥10% points below baseline OR symptomatic	Discontinue
Symptomatic	Consider discontinuing	Not applicable	Not applicable

[a]In the CLEOPATRA trial [17], trastuzumab and pertuzumab treatments were paused if LVEF was 40–45% and ≥10% below baseline and asymptomatic. At LVEF reassessment, pertuzumab and trastuzumab may be restarted if LVEF "≥46%" or "40–45% and <10% ↓ from baseline"; otherwise, discontinue

the recommendations for cardiac monitoring presented on the drug label (every 3 months) for the first year of therapy, and if there has been no evidence of cardiac toxicity after 1 year of treatment, we decrease the frequency of monitoring to every 6 months for patients remaining on treatment.

Dose modifications of trastuzumab, pertuzumab, and T-DM1 based on asymptomatic left ventricular ejection fraction decrease from baseline are shown in Tables 51.2–51.4 [16–18].

Table 51.4 Dosage modification of T-DM1 based on asymptomatic left ventricular ejection fraction decrease from baseline [18]

Criteria	Left ventricular ejection fraction (LVEF)	Action	Action at LVEF reassessment
1	> 45%	Continue and follow routine monitoring guidelines	Follow actions based on criteria
2	40–45% AND <10% below Baseline and asymptomatic	Continue and repeat LVEF in 3 weeks	Discontinue permanently if no recovery. If improved to criterion # 1 (for # 2, 3 or 4) or # 2 (for # 3 or 4), treatment may be restarted; monitor closely
3	40–45% AND ≥10% below baseline, and asymptomatic	Pause and repeat LVEF in 3 weeks	
4	<40% and asymptomatic		
5	Symptomatic or confirmed congestive heart failure	Discontinue	Not applicable

Preoperative/Adjuvant Therapy Regimens

Regimens for HER2-Negative Diseases

- *Dose dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel*
- *Dose dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks*
- *AC followed by weekly paclitaxel*
- *AC followed by docetaxel every 3 weeks*
- *TAC (docetaxel/doxorubicin/cyclophosphamide)*
- *FEC (fluorouracil/epirubicin/cyclophosphamide)*
- *TC (docetaxel and cyclophosphamide)*
- *Dose dense AC (doxorubicin/cyclophosphamide)*
- *AC (doxorubicin/cyclophosphamide) every 3 weeks*
- *EC (epirubicin/cyclophosphamide)*
- *CMF (cyclophosphamide/methotrexate/fluorouracil)*

Dosing Schedules

- *Dose dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel.*
- Cyclophosphamide 600 mg/m^2 IV D1.
- Doxorubicin 60 mg/m^2 IV D1.
- Cycled every 14 days for four cycles, all cycles are with granulocyte colony-stimulating factor (GCSF) support.
- Followed by:
- Paclitaxel 80 mg/m^2 D1, 1 h IV infusion weekly for 12 weeks.

- *Dose dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1

- Cycled every 14 days for four cycles, all cycles are with GCSF support.
- Followed by:
- Paclitaxel 175 mg/m^2 IV D1, 3 h IV infusion
- Cycled every 14 days for four cycles, all cycles are with GCSF support.

- *AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel*
- Cyclophosphamide 600 mg/m^2 IV D1
- Doxorubicin 60 mg/m^2 IV D1
- Cycled every 21 days for four cycles.
- Followed by:
- Paclitaxel 80 mg/m^2 D1, 1 h IV infusion weekly for 12 weeks

- *AC (doxorubicin/cyclophosphamide) followed by docetaxel*
- Cyclophosphamide 600 mg/m^2 IV D1
- Doxorubicin 60 mg/m^2 IV D1
- Cycled every 21 days for four cycles.
- Followed by:
- Docetaxel 100 mg/m^2 IV D1
- Cycled every 21 days for four cycles, all cycles are with GCSF support.

- *TAC (docetaxel/doxorubicin/cyclophosphamide)*
- Docetaxel 75 mg/m^2 IV D1
- Doxorubicin 50 mg/m^2 IV D1
- Cyclophosphamide 500 mg/m^2 IV D1
- Cycled every 21 days for six cycles, all cycles are with GCSF support.

- *FEC (fluorouracil/epirubicin/cyclophosphamide)*
- Fluorouracil 500 mg/m^2 IV D1
- Epirubicin 100 mg/m^2 IV D1
- Cyclophosphamide 500 mg/m^2 IV D1
- Cycled every 21 days for six cycles, with GCSF support.

- *TC (docetaxel/cyclophosphamide)*
- Docetaxel 75 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days for four cycles, all cycles are with GCSF support.

- *Dose dense AC (doxorubicin/cyclophosphamide)*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 14 days for four cycles, all cycles are with GCSF support.

- *AC (doxorubicin/cyclophosphamide)*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days for four cycles.

- *EC (Epirubicin/cyclophosphamide)*
- Epirubicin 100 mg/m^2 IV D1
- Cyclophosphamide 830 mg/m^2 IV D1
- Cycled every 21 days for eight cycles.

- *CMF (cyclophosphamide/methotrexate/fluorouracil)*
- Cyclophosphamide 100 mg/m^2 PO, D1–14
- Methotrexate 40 mg/m^2 IV D1, D8
- 5- fluorouracil 600 mg/m^2 IV D1, D8
- Cycled every 28 days for six cycles.

Regimens for HER2-Positive Disease

- *AC (doxorubicin/cyclophosphamide) followed by paclitaxel + trastuzumab.*
- *Dose dense AC followed by paclitaxel trastuzumab*
- *AC followed by weekly paclitaxel + trastuzumab + pertuzumab*
- *TCH (Docetaxel + carboplatin + trastuzumab)*
- *TCHP (Docetaxel + carboplatin + trastuzumab) + pertuzumab*
- *AC followed by docetaxel + trastuzumab*
- *AC followed by docetaxel + trastuzumab + pertuzumab*
- *Docetaxel + cyclophosphamide + trastuzumab*
- *Paclitaxel + trastuzumab*

Dosing Regimens

- *AC followed by paclitaxel + trastuzumab*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days for four cycles.
- Followed by:
- Paclitaxel 80 mg/m^2 D1, 1 h IV infusion weekly for 12 weeks
- With:
- Trastuzumab 8 mg/kg IV with first dose of paclitaxel
- Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 year of treatment
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *Dose dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel trastuzumab*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 14 days for four cycles, all cycles are with GCSF support.
- Followed by:
- Paclitaxel 175 mg/m^2 D1, 3 h IV infusion
- Cycled every 14 days for four cycles, all cycles are with GCSF support.
- With:
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

- Followed by:
- Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment
- As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel and given to complete 1 year of trastuzumab treatment.
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment.

- *AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel + trastuzumab + pertuzumab*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days for four cycles.
- Followed by:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV, every 21 days to complete 1 year of treatment
- Trastuzumab 8 mg/kg day 1 followed by 6 mg/kg IV, every 21 days to complete 1 year of treatment
- Paclitaxel 80 mg/m^2 D1, 1 h IV infusion weekly for 12 weeks
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *TCH (Docetaxel + carboplatin + trastuzumab)*
- Docetaxel 75 mg/m^2 IV D1
- Carboplatin area under the curve (AUC) 6 IV D1
- Cycled every 21 days for six cycles.
- Trastuzumab 4 mg/kg IV wk. 1.
- Followed by:
- Trastuzumab 2 mg/kg IV weekly for 17 weeks
- Followed by:
- Trastuzumab 6 mg/kg IV cycled every 21 days to complete 1 year of trastuzumab treatment
- or
- Trastuzumab 8 mg/kg IV wk. 1.
- Followed by:
- Trastuzumab 6 mg/kg IV cycled every 21 days to complete 1 year of trastuzumab treatment
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *TCH (Docetaxel + carboplatin + trastuzumab) + pertuzumab*
- Docetaxel 75 mg/m^2 IV D1.
- Carboplatin AUC 6 IV D1.
- Cycled every 21 days for six cycles.
- and
- Pertuzumab 840 mg IV D1
- Trastuzumab 8 mg/kg IV D1
- Followed by:
- Trastuzumab 6 mg/kg IV D1
- Pertuzumab 420 mg IV D1
- Cycled every 21 days to complete 1 year of therapy.
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *AC followed by docetaxel + trastuzumab*
- Cyclophosphamide 600 mg/m^2 IV D1
- Doxorubicin 60 mg/m^2 IV D1
- Cycled every 21 days for 4 cycles.
- Followed by:
- Docetaxel 100 mg/m^2 IV D1, all cycles are with GCSF support
- Cycled every 21 days for 4 cycles.
- With:
- Trastuzumab 8 mg/kg IV wk. 1.
- Followed by:
- Trastuzumab 6 mg/kg IV cycled every 21 days to complete 1 year of trastuzumab therapy
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *AC followed by docetaxel + trastuzumab + pertuzumab*
- Cyclophosphamide 600 mg/m^2 IV D1
- Doxorubicin 60 mg/m^2 IV D1
- Cycled every 21 days for 4 cycles.
- Followed by:
- Pertuzumab 840 mg IV D1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m^2 IV D1, with GCSF support
- Cycled every 21 days for 4 cycles
- Followed by:
- Trastuzumab 6 mg/kg IV D1
- Pertuzumab 420 mg IV D1
- Cycled every 21 days to complete 1 year of trastuzumab and pertuzumab therapy.
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *Docetaxel + cyclophosphamide + trastuzumab*
- Docetaxel 75 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days for 4 cycles, all cycles are with GCSF support.
- With:
- Trastuzumab 8 mg/kg IV wk. 1.
- Followed by:
- Trastuzumab 6 mg/kg IV cycled every 21 days to complete 1 year of trastuzumab therapy.
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

- *Paclitaxel + trastuzumab*
- Paclitaxel 80 mg/m^2 D1, 1 h IV infusion weekly for 12 weeks

- With:
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel
- Followed by:
- Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment
- As an alternative trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel and given to complete 1 year of trastuzumab treatment.
- *Evaluate left ventricular ejection fraction prior to and every 3 months during treatment

Systemic Endocrine Therapy for Hormone-Positive Recurrent or Stage IV Disease

HER2-Negative Disease

Premenopausal

- Tamoxifen
- Ovarian ablation or suppression plus endocrine therapy as for postmenopausal women

Postmenopausal

Non-steroidal aromatase inhibitor (anastrozole, letrozole)

- Fulvestrant (proposal 1)
- Tamoxifen or toremifene
- Steroidal aromatase inactivator (exemestane)
- Palbociclib + aromatase inhibitor (proposal 1)
- Palbociclib + fulvestrant (proposal 1)
- Ribociclib + aromatase inhibitor (proposal 1)
- Ribociclib + fulvestrant (proposal 1)
- Ribociclib + tamoxifen (proposal 1)
- Abemaciclib + aromatase inhibitor (proposal 1)
- Abemaciclib + fulvestrant (proposal 1)
- Abemaciclib + tamoxifen
- Exemestane + everolimus
- Everolimus + fulvestrant
- Everolimus + tamoxifen
- Megestrol acetate
- Abemaciclib

HER2-Positive Disease

Premenopausal

- Tamoxifen +/− trastuzumab (+/− pertuzumab) or
- Ovarian ablation or suppression plus therapy as for postmenopausal women

Postmenopausal

- Aromatase inhibitor + trastuzumab (+/− pertuzumab)
- Aromatase inhibitor + lapatinib + trastuzumab
- Aromatase inhibitor + lapatinib
- Fulvestrant + trastuzumab (+/− pertuzumab)
- Tamoxifen + trastuzumab (+/− pertuzumab)

Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer

Regimens for HER2-Negative Disease

Single Agent

- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel
- Vinorelbine
- Capecitabine
- Gemcitabine
- Docetaxel
- Eribulin
- Albumin-bound paclitaxel
- Carboplatin
- Cisplatin
- Epirubicin
- Ixabepilone
- Cyclophosphamide
- Olaparib (option for HER2-negative, BRCA1/2-positive tumors)

Dosing Regimens

- *Doxorubicin* 60–75 mg/m^2 IV D1 cycled every 21 days or 20 mg/m^2 IV D1, weekly
- *Liposomal doxorubicin* 50 mg/m^2 IV D1 cycled every 28 days or 30 mg/m^2 IV D1 cycled every 21 days
- *Paclitaxel* 80 mg/m^2 D1, IV D1 weekly or 175 mg/m^2 IV D1 cycled every 21 days
- *Vinorelbine* 25 mg/m^2 IV D1, weekly cycled every 21 days
- *Capecitabine* 850–1250 mg/m^2 PO, twice-daily D1–14 cycled every 21 days
- *Gemcitabine* 800–1200 mg/m^2 IV D1, 8, 15 cycled every 28 days
- *Docetaxel* 60–100 mg/m^2 D1 cycled every 21 days or *docetaxel* 35 mg/m^2 D1, weekly for 6 weeks followed by a 2-week rest, then repeat
- *Eribulin* 1.25–1.4 mg/m^2 IV D1, 8 cycled every 21 days
- *Albumin-bound paclitaxel* 100–125 mg/m^2 IV D1, 8, 15 cycled every 28 days or 260 mg/m^2 IV D1, cycled every 21 days
- *Carboplatin* AUC 5–6 on D1, cycled every 21–28 days
- *Cisplatin* 75 mg/m^2 IV D1 cycled every 21 days
- *Epirubicin* 60–90 mg/m^2 IV D1 cycled every 21 days
- *Ixabepilone* 40 mg/m^2 IV D1 cycled every 21 days
- *Cyclophosphamide* 50 mg PO daily on days 1–21 cycled every 28 days
- *Olaparib* tablet 300 mg PO twice daily cycled every 28 days

Chemotherapy Combinations

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- Docetaxel/capecitabine
- Gemcitabine/paclitaxel
- Paclitaxel/carboplatin (especially for triple negative tumors)
- Gemcitabine/carboplatin (especially for triple negative tumors)
- Gemcitabine/cisplatin (especially for triple negative tumors)
- Paclitaxel/bevacizumab
- CMF (cyclophosphamide/methotrexate/fluorouracil)

Dosing Regimens

- *AC (doxorubicin/cyclophosphamide)*
- Doxorubicin 60 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days.

- *EC (epirubicin/cyclophosphamide)*
- Epirubicin 75 mg/m^2 IV D1
- Cyclophosphamide 600 mg/m^2 IV D1
- Cycled every 21 days.

- *Docetaxel/capecitabine*
- Docetaxel 75 mg/m^2 IV D1
- Capecitabine 950 mg/m^2 PO, twice-daily D1–14
- Cycled every 21 days.

- *GT (gemcitabine/paclitaxel)*
- Paclitaxel 175 mg/m^2 IV D1
- Gemcitabine 1250 mg/m^2 IV D1, 8 (following paclitaxel on day 1)
- Cycled every 21 days.

- *Paclitaxel/carboplatin*
- Paclitaxel 80 mg/m^2 D1, 8, 15
- Carboplatin AUC 5–6 IV D1
- Cycled every 21–28 days.

- *Gemcitabine/carboplatin*
- Gemcitabine 1000 mg/m^2 IV D1, 8
- Carboplatin AUC 2 IV D1, 8
- Cycled every 21 days.

- *Gemcitabine/cisplatin*
- Gemcitabine 1000 mg/m^2 IV D1, 8
- Cisplatin 60–75 mg/m^2 IV D1
- Cycled every 21 days.

- *Paclitaxel/bevacizumab*
- Paclitaxel 90 mg/m^2 IV D1, 8, 15
- Bevacizumab 10 mg/kg IV D1, 15
- Cycled every 28 days.

- *CMF (cyclophosphamide/methotrexate/fluorouracil)*
- Cyclophosphamide 100 mg/m^2 PO, D1–14
- Methotrexate 40 mg/m^2 IV D1, 8
- 5-fluorouracil 600 mg/m^2 IV D1, 8
- Cycled every 28 days.

Regimens for HER2-Positive Disease

- Pertuzumab + trastuzumab + docetaxel
- Pertuzumab + trastuzumab + paclitaxel
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel +/− carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib
- Trastuzumab + other agents
- Lapatinib + capecitabine

Dosing Regimens

- *Pertuzumab + trastuzumab + docetaxel*
- Pertuzumab 840 mg IV D1 followed by 420 mg IV D1
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV D1
- Docetaxel 75–100 mg/m^2 IV D1 with GCSF support
- Cycled every 21 days.

- *Pertuzumab + trastuzumab + paclitaxel*
- Pertuzumab 840 mg IV D1 followed by 420 mg IV cycled every 21 days.
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV day 1 followed by trastuzumab 2 mg/kg IV weekly.
- Paclitaxel 80 mg/m^2 IV D1 weekly or 175 mg/m^2 IV D1 cycled every 21 days.

- *Ado-trastuzumab emtansine (T-DM1)*
- 3.6 mg/kg IV D1, cycled every 21 days.

- *Trastuzumab + paclitaxel/carboplatin*
- Carboplatin AUC 5–6 IV D1
- Paclitaxel 175 mg/m^2 IV D1
- Cycled every 21 days.
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV day 1 followed by trastuzumab 2 mg/kg IV weekly.

- *Weekly paclitaxel/carboplatin + trastuzumab*
- Paclitaxel 80 mg/m^2 IV D1, 8, 15
- Carboplatin AUC 2 IV D1, 8, 15
- Cycled every 28 days.
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Trastuzumab + paclitaxel*
- Paclitaxel 175 mg/m^2 IV D1 cycled every 21 days or 80–90 mg/m^2 IV weekly.
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Trastuzumab + docetaxel*
- Docetaxel 80–100 mg/m^2 IV D1 cycled every 21 days with GCSF support, or 35 mg/m^2 IV weekly.
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Trastuzumab + vinorelbine*
- Vinorelbine 25 mg/m^2 IV D1 weekly or 30–35 mg/m^2 IV D1, 8 cycled every 21 days
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV, cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Trastuzumab + Capecitabine*
- Capecitabine 1000–1250 mg/m^2 PO, twice-daily D1–14 cycled every 21 days.
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Trastuzumab + Lapatinib*
- Lapatinib 1000 mg PO daily
- Trastuzumab 8 mg/kg IV D1 followed by 6 mg/kg IV cycled every 21 days or 4 mg/kg IV D1 followed by trastuzumab 2 mg/kg IV weekly.

- *Lapatinib + Capecitabine*
- Lapatinib 1250 mg PO daily
- Capecitabine 1000 mg/m^2 PO, twice-daily D1–14, cycled every 21 days.

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