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Editors

Breast Disease

Management and Therapies,
Volume 2

Second Edition

 Springer

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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 ≥ 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 phylloides, 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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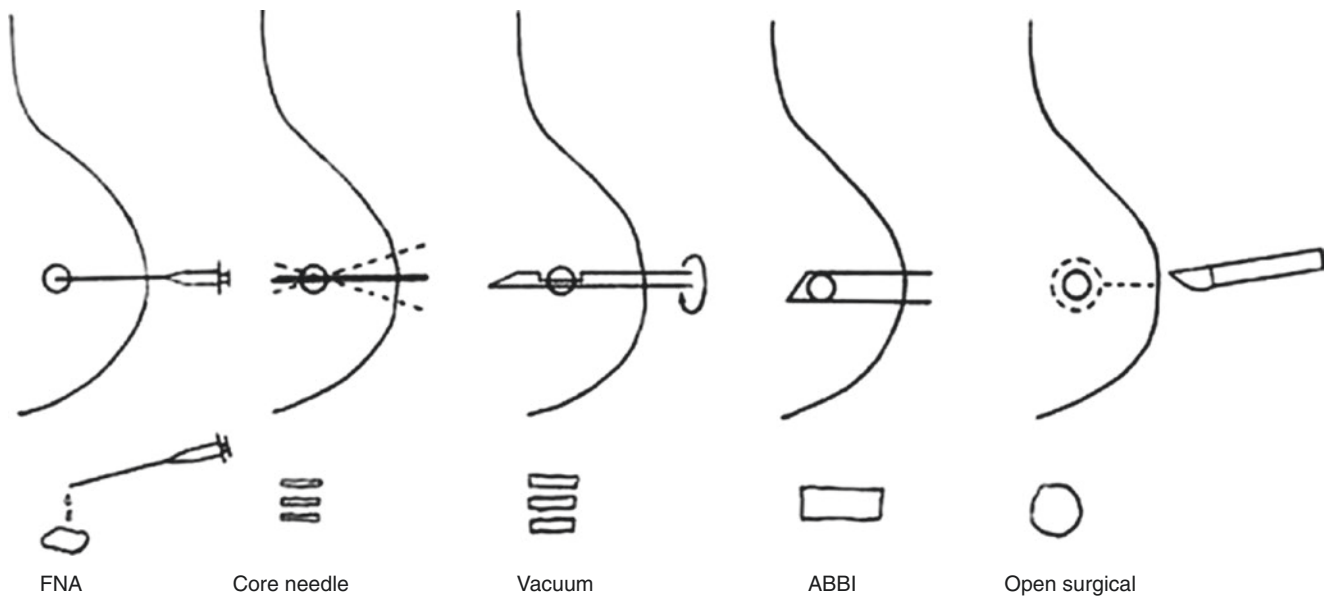


Fig. 1.1 Different types of biopsies. (Reproduced with kind permission from Imaginis, Copyright 2000, [Imaginis.com](http://www.imaginis.com))

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,

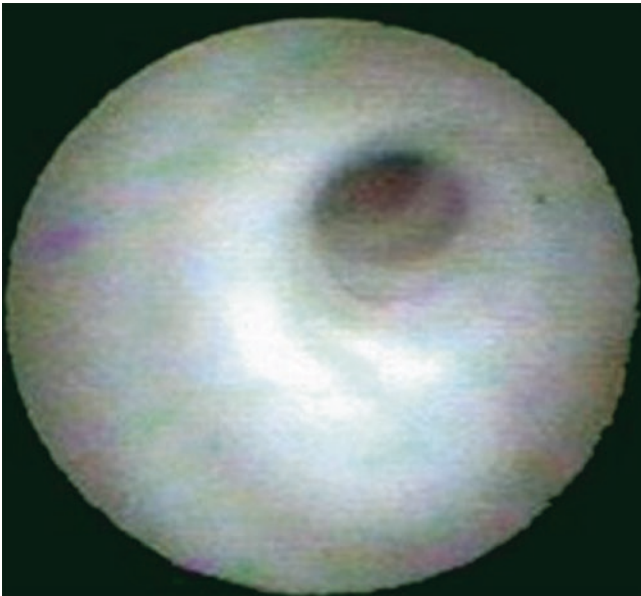


Fig. 1.2 Clean duct

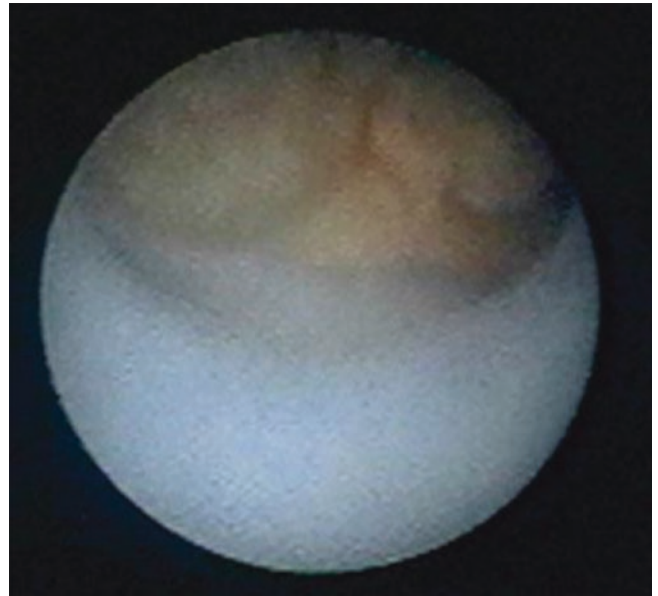


Fig. 1.4 Papilloma

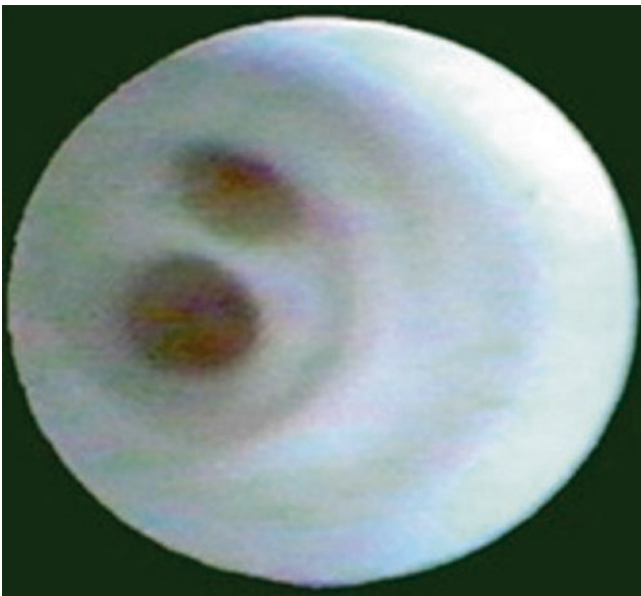


Fig. 1.3 Bifurcation

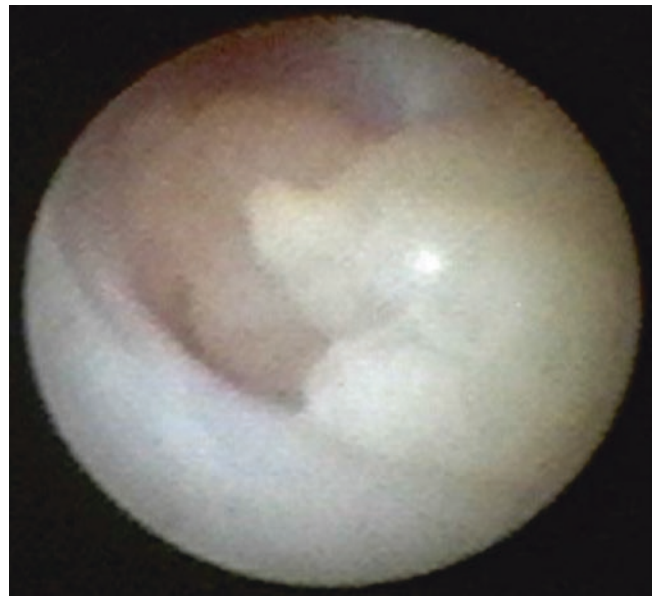


Fig. 1.5 Papillomas

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].

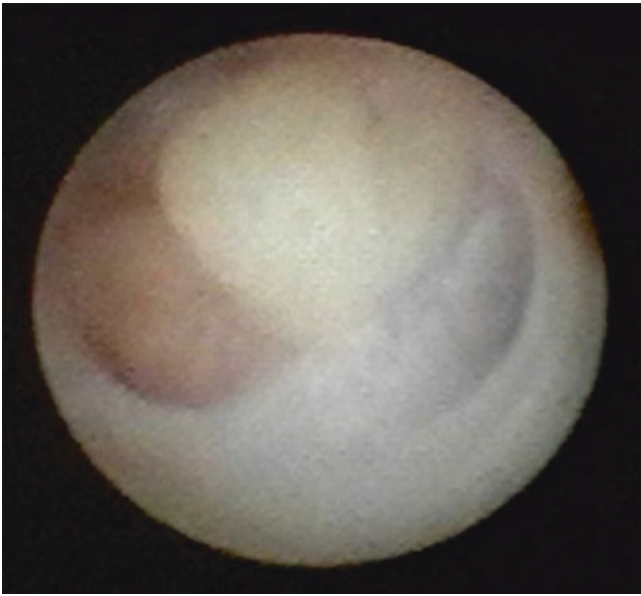


Fig. 1.6 Papillomas



Fig. 1.8 Low-grade DCIS

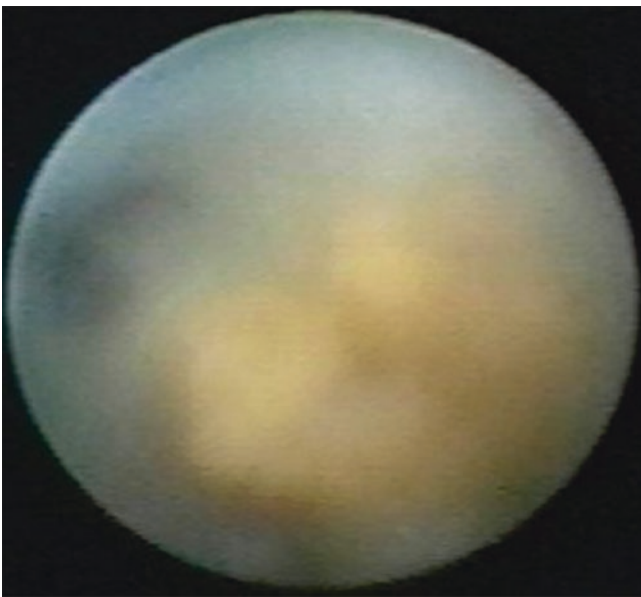


Fig. 1.7 DCIS

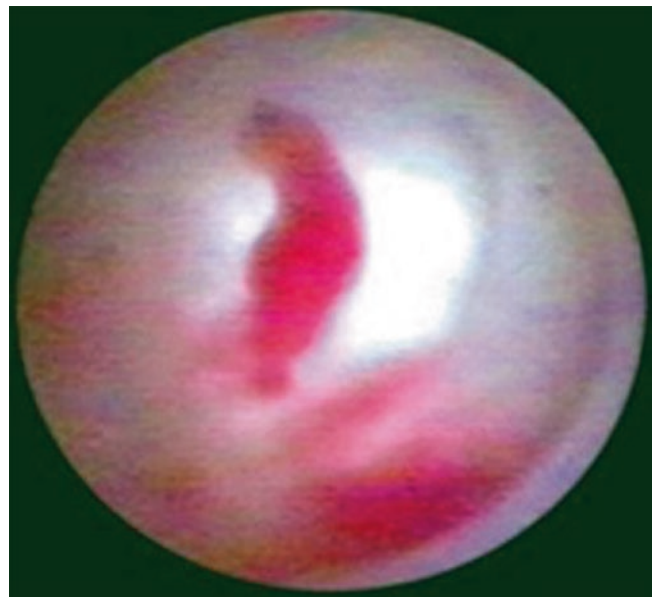


Fig. 1.9 High-grade DCIS

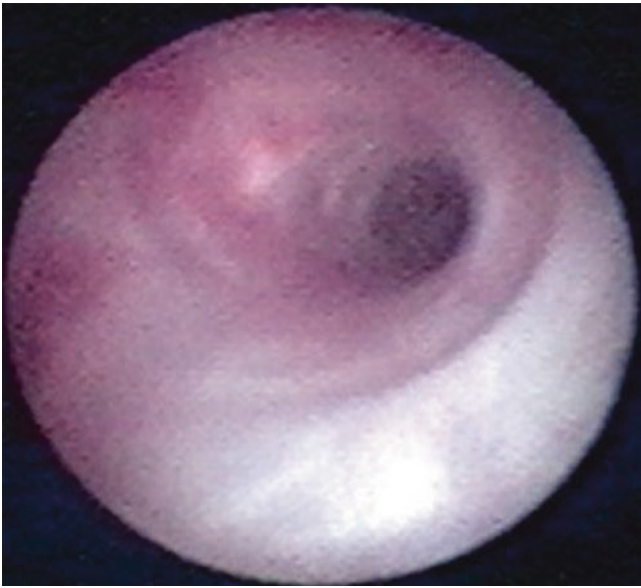


Fig. 1.10 DCIS

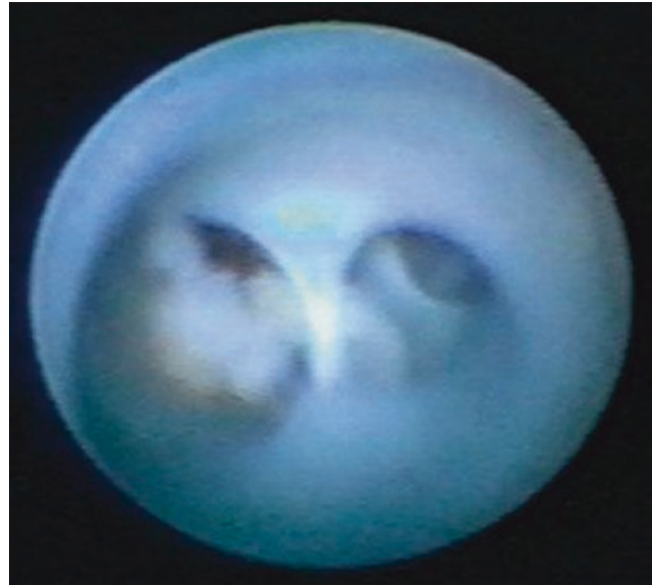


Fig. 1.12 High-grade DCIS

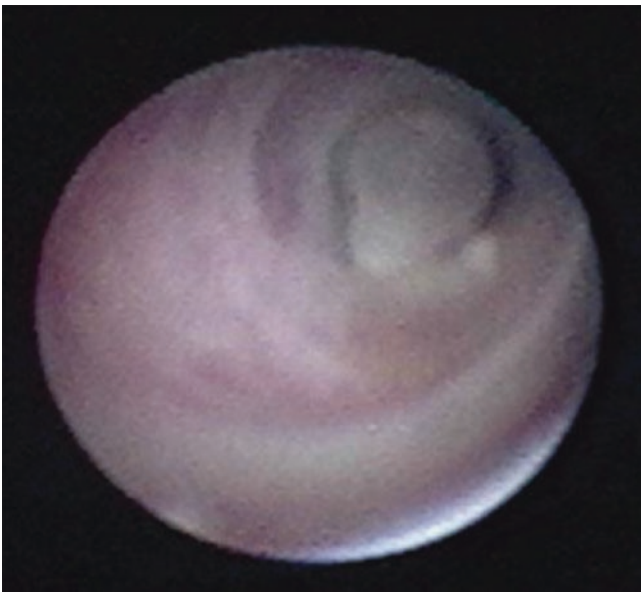


Fig. 1.11 DCIS

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 CO₂ 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 pro-

ducing 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 post-operative (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

Deniz Eren Böler and Neslihan Cabioğlu

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 health-care 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 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.

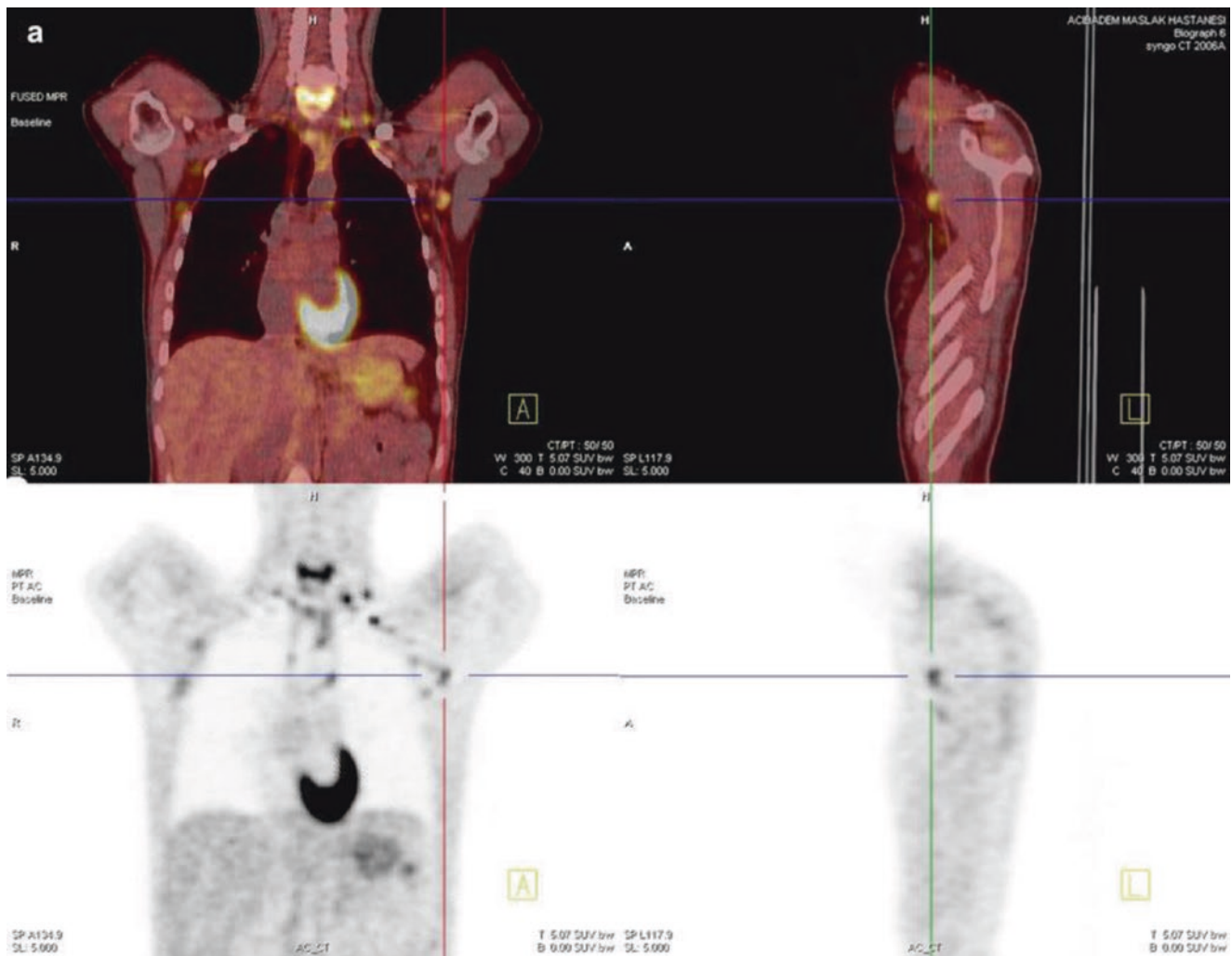


Fig. 2.1 (a) FDG PET/CT of a patient with increased SUV in the left axillary lymph nodes suspicious for metastases. (b) FDG PET/CT of a patient with increased SUV in the right axillary lymph nodes and the right pulmonary nodule suspicious for metastases. (c) FDG PET/CT of

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

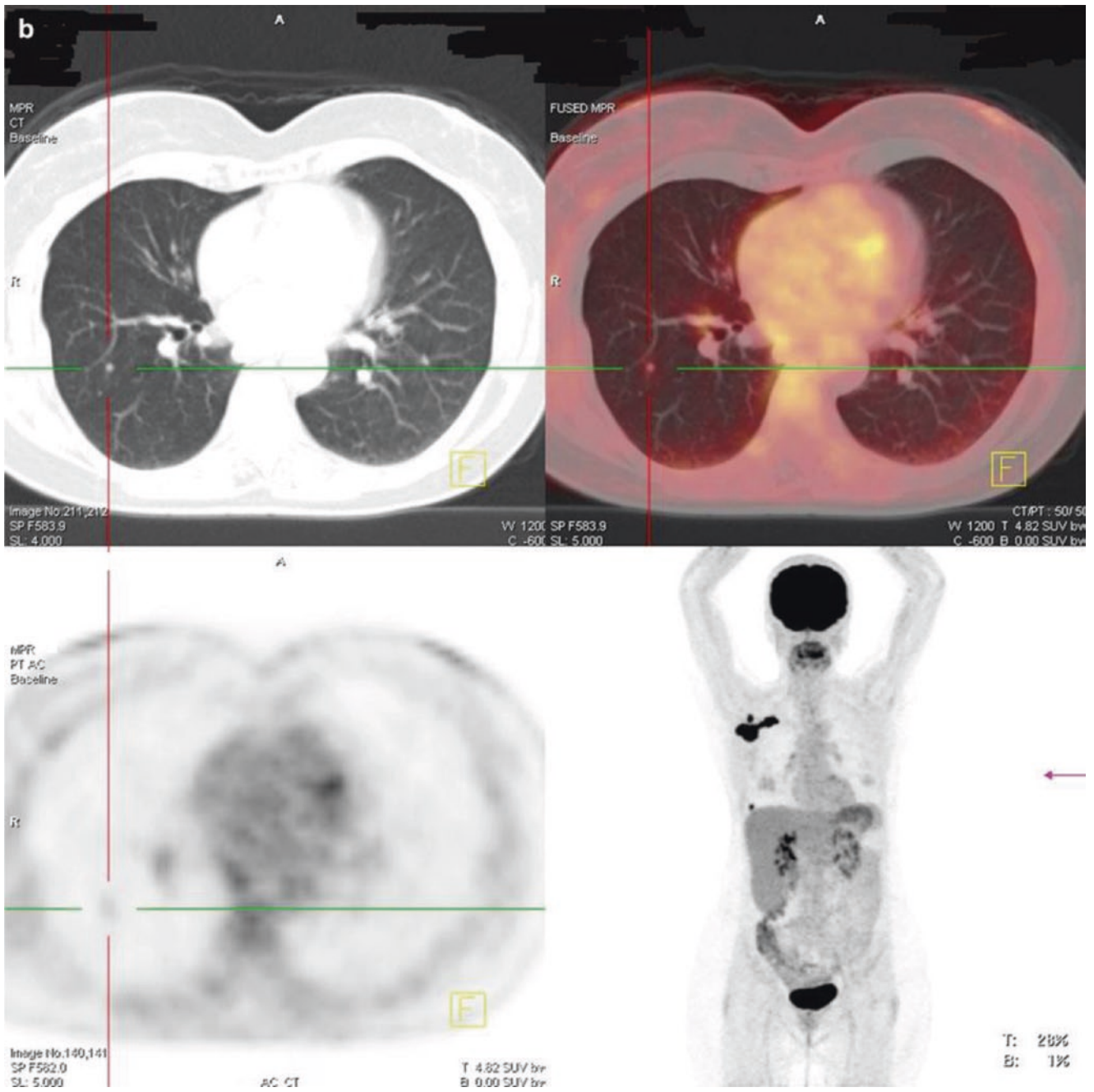


Fig. 2.1 (continued)

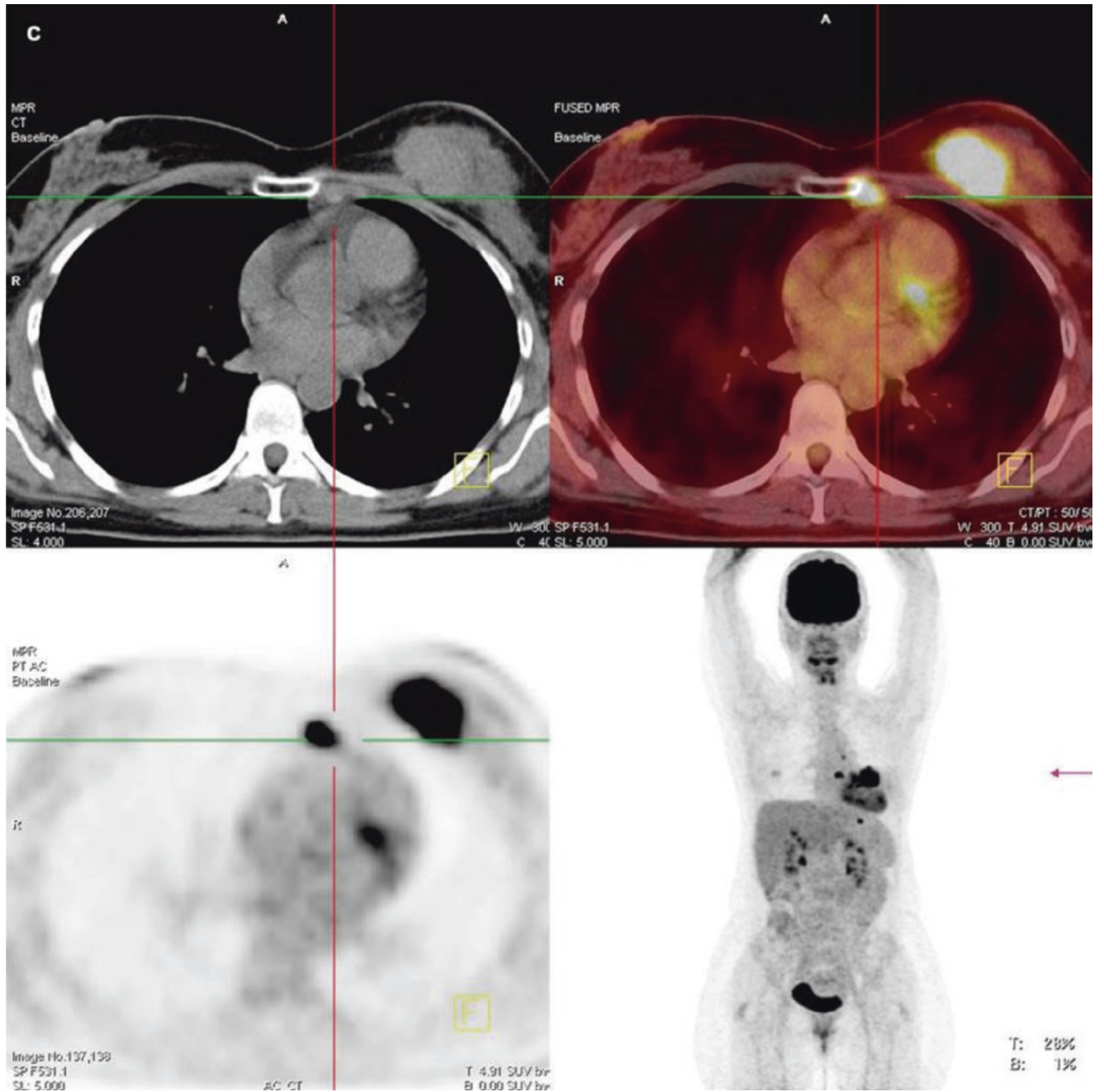


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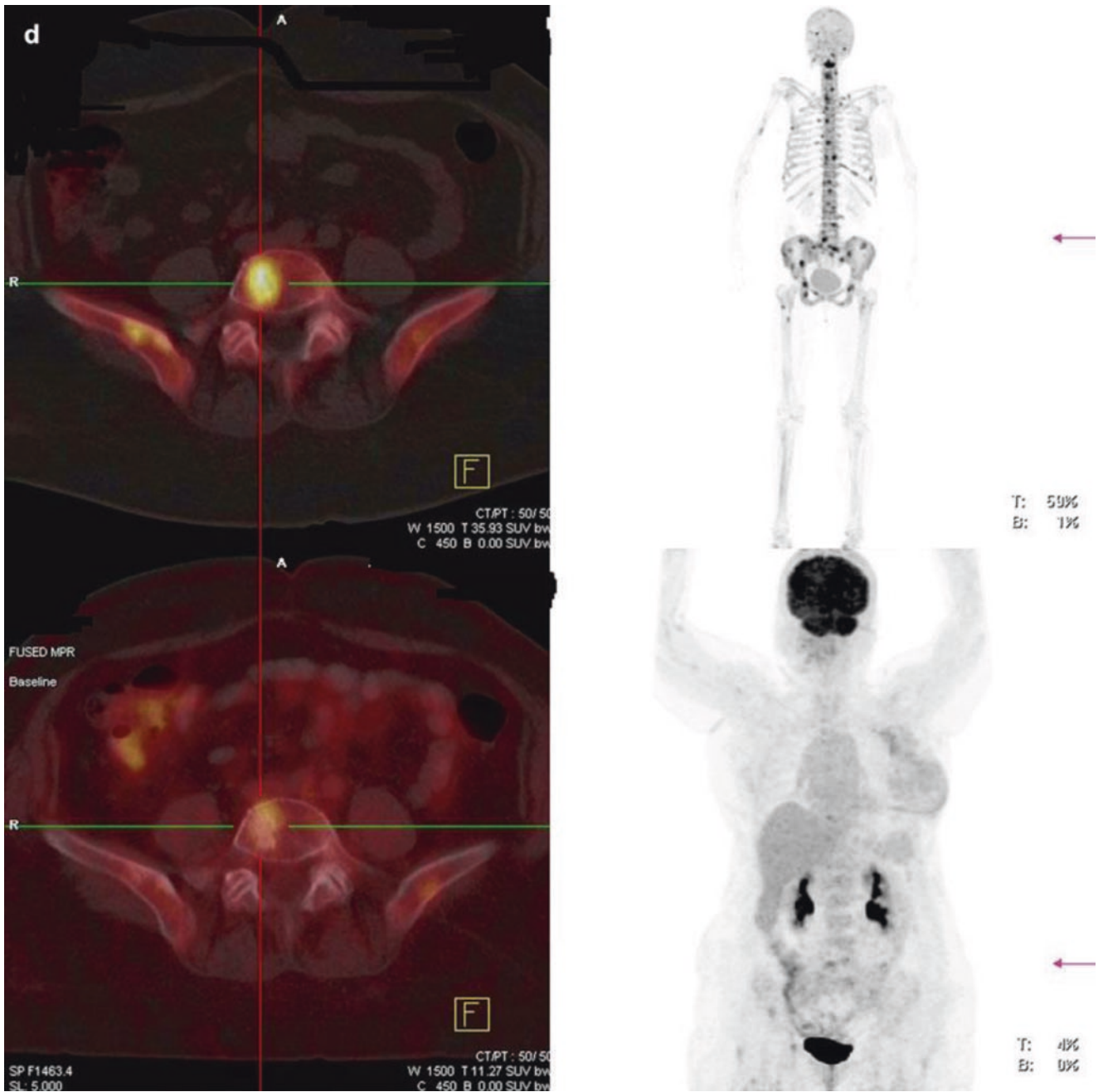


Fig. 2.1 (continued)

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.