Breast Cancer Staging: Updates in the *AJCC Cancer Staging Manual*, 8th Edition, and Current Challenges for Radiologists, From the *AJR* Special Series on Cancer Staging

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The standardization of the AJCC TNM staging system for breast cancer allows physicians to evaluate patients with breast cancer using standard language and criteria, assess treatment response, and compare patient outcomes. Previous editions of the *AJCC Cancer Staging Manual* relied on the anatomic TNM method of staging that incorporates imaging and uses population-level survival data to predict patient outcomes. Recent advances in therapy based on biomarker status and multigene panels have improved treatment strategies. In the newest edition of the *AJCC Cancer Staging Manual* (8th edition, adopted on January 1, 2018), breast cancer staging integrates anatomic staging with tumor grade, biomarker data regarding hormone receptor status, oncogene expression, and gene expression profiling to assign a prognostic stage. This article reviews the 8th edition of the AJCC breast cancer staging system with a focus on anatomic staging and the challenges that anatomic staging poses for radiologists. We highlight key imaging findings that impact patient treatment and discuss the role of imaging in evaluating response to neoadjuvant therapy. Finally, we discuss biomarkers and multigene panels and how these impact prognostic stage. The review will help radiologists identify critical findings that affect breast cancer staging and understand ongoing limitations of imaging in staging.

The standardization of the TNM staging system by the AJCC has allowed physicians to evaluate patients with breast cancer using a universal language, facilitating effective communication regarding appropriate treatment planning. Since the publication of the first edition of the *AJCC Cancer Staging Manual* in 1977, advances in diagnosis and treatment have necessitated periodic updates to the staging manual [1, 2].

Breast cancer treatment is at the forefront in the age of personalized medicine, which incorporates patient- and tumor-specific factors into the prognostic and treatment decisions for each patient. The previous edition (7th) of the AJCC manual staged cancer according to anatomic information (TNM). The current breast cancer expert panel concluded that, whereas the TNM staging system provides important insight into a patient's prognosis, the addition of biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2, also known as ERBB2) as well as gene expression profiling refines the prognostic information and leads to better selection of treatment options. Therefore, the addition of this information warranted modification of the TNM staging system for breast cancer in the 8th edition of the *AJCC Cancer Staging Manual*, which was adopted January 1, 2018 [3, 4].

Although breast cancer treatment has evolved, the TNM staging system remains relevant. In lower- and middle-income countries that do not have access to biomarker analysis, the TNM system remains the only staging system. Furthermore, the TNM staging system ensures that physicians worldwide communicate in a standard language that reflects the tumor burden and allows investigators to compare patients treated during different time periods since the inception of the staging system in 1959 [2, 4].

Imaging is the foundation of anatomic staging in breast cancer. This article reviews the 8th edition of the AJCC TNM staging system for breast cancer, with a focus on preoperative anatomic staging. We discuss anatomic TNM staging and the major changes in the 8th edition as it applies to imaging. For each subsection of the TNM staging system, we review the role of individual imaging modalities with a focus on mammography, ultrasound, and MRI. We discuss the challenges that radiologists face in the imaging evaluation of a pa-

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tient with breast cancer and what imaging information is critical to provide to referring clinicians to optimize patient care. We discuss imaging in the neoadjuvant setting. Finally, we discuss prognostic staging because radiologists, as part of multidisciplinary teams, need to understand both the anatomic and the prognostic staging systems that guide patient care.

Staging System Basics

The AJCC breast cancer staging system should be used for invasive carcinoma and ductal carcinoma in situ (DCIS). It is not intended for staging of breast lymphoma, breast sarcoma, or phyllodes tumors.

The breast cancer staging system in the AJCC 8th edition [3] consists of two staging tables: the anatomic and the prognostic categories. The anatomic stage is based on the anatomic extent of cancer as defined by the TNM categories. Anatomic staging includes the primary tumor size (T), the nodal status (N), and distant metastasis (M) according to clinical and/or pathologic assessment and was the basis of the 7th edition of the AJCC staging system.

For determination of anatomic stage, the National Comprehensive Cancer Network (NCCN) [5] advises performing a history and physical examination, bilateral mammography and ultrasound as warranted, pathology evaluation, and assessment of hormone receptors. Breast MRI is deemed optional, with tumors that are mammographically occult warranting special consideration. Imaging studies are deemed elements of staging when performed within 4 months of the diagnosis or upon completion of surgery, whichever gives the longer interval, provided that the patient's disease has not progressed [5].

The AJCC 8th edition staging system contains four categories of anatomic TNM classification. The first category is clinical staging, designated by the prefix "c," based on clinical examination, diagnostic imaging, and core biopsy or aspiration samples obtained before treatment. The second category is pathologic staging, designated by the prefix "p," based on surgical specimens, including sentinel lymph node biopsy (SLNB) specimens. The third category is posttherapy staging, designated by the prefix "yp," and applies to patients who have been treated with neoadjuvant therapy including neoadjuvant chemotherapy (NAC), radiation, or hormonal therapy. Finally, the last category, restaging, applies in the event of tumor recurrence.

The anatomic staging system provides quantitative classification categories for primary tumors (Tis to T4), the regional lymph node status (N0 to N3), and distant metastases (M0 or M1), and these categories are combined to determine the overall anatomic stage (stage 0 to stage IV) [3]. Overall anatomic stage has historically been associated with outcome measures, including overall survival [4, 6].

In addition to anatomic TNM stage, prognostic stage is determined by tumor grade, biomarker status (ER, PR, HER2), and genomic panels. Every patient is assigned a clinical prognostic stage because it sets a baseline and therefore guides initial treatment. The clinical prognostic stage is intended to provide a comparison for all patients regardless of sequence of therapy (initial surgery with adjuvant therapy vs NAC) [3]. The pathologic prognostic stage is assigned to patients who undergo surgery as the initial treatment and excludes patients who receive NAC.

HIGHLIGHTS

- *Thorough anatomic staging of breast cancer using mammography, ultrasound, and MRI (when appropriate) is critical in guiding patient treatment decisions.*
- *In the AJCC Cancer Staging Manual, 8th edition, breast cancer staging now integrates biomarker data with anatomic staging (TNM) to assign a final prognostic stage.*
- *Imaging has a significant role in evaluating response to neoadjuvant therapy.*

Tumor

The T category is determined by tumor size and locoregional invasion [3]. The AJCC 8th edition staging system clarifies that the T category is based on the size of the invasive component of the largest mass (in the setting of multiple masses) in the largest dimension. Small satellite nodules are not added to tumor size. Multiple cancers are documented with the "m" modifier. Although tumor volume (as measured in three dimensions) does not affect stage, volumetric assessments are helpful when evaluating response to treatment in patients undergoing NAC [6, 7].

The updated staging system does not account for multifocal or multicentric disease (Fig. 1). The T category of multicentric disease is determined by the largest mass and may be the same as for a unifocal malignancy even though disease is much more extensive. It is critical that radiologists provide tumor measurements of the largest mass and describe the location and size of other masses because this information impacts surgical management (lumpectomy vs mastectomy) and may determine whether the patient receives NAC [8]. It is also important to describe findings such as associated calcifications to estimate the extent of disease, which may include DCIS associated with an invasive component. Other findings, such as extension of disease to the skin, nipple, or chest wall (or a combination of these), should also be reported [3].

The categories range from Tis to T4. Tis is designated for DCIS and Paget disease (without underlying DCIS) without an invasive component. One change to the AJCC 8th edition staging system is that lobular carcinoma in situ (LCIS) is not classified as category Tis and is now deemed benign. However, LCIS confers a higher-than-average risk of future breast cancer. Nonclassical LCIS variants, including pleomorphic LCIS and LCIS with necrosis, signet ring cells, or apocrine features, tend to have high-grade cytology and an unfavorable biomarker profile. Current evidence suggests these lesions should be treated with complete surgical excision, similar to DCIS [9].

In the setting of DCIS, an estimation of disease extent may alter surgical management (mastectomy vs lumpectomy) and determine whether the patient requires an SLNB (Fig. 2). The American Society of Clinical Oncology clinical practice guideline recommends SLNB for women with DCIS who are planning to undergo a mastectomy or who have a large DCIS tumor size (> 5 cm) [10]. Therefore, reporting the extent of calcifications is critical. The ex-

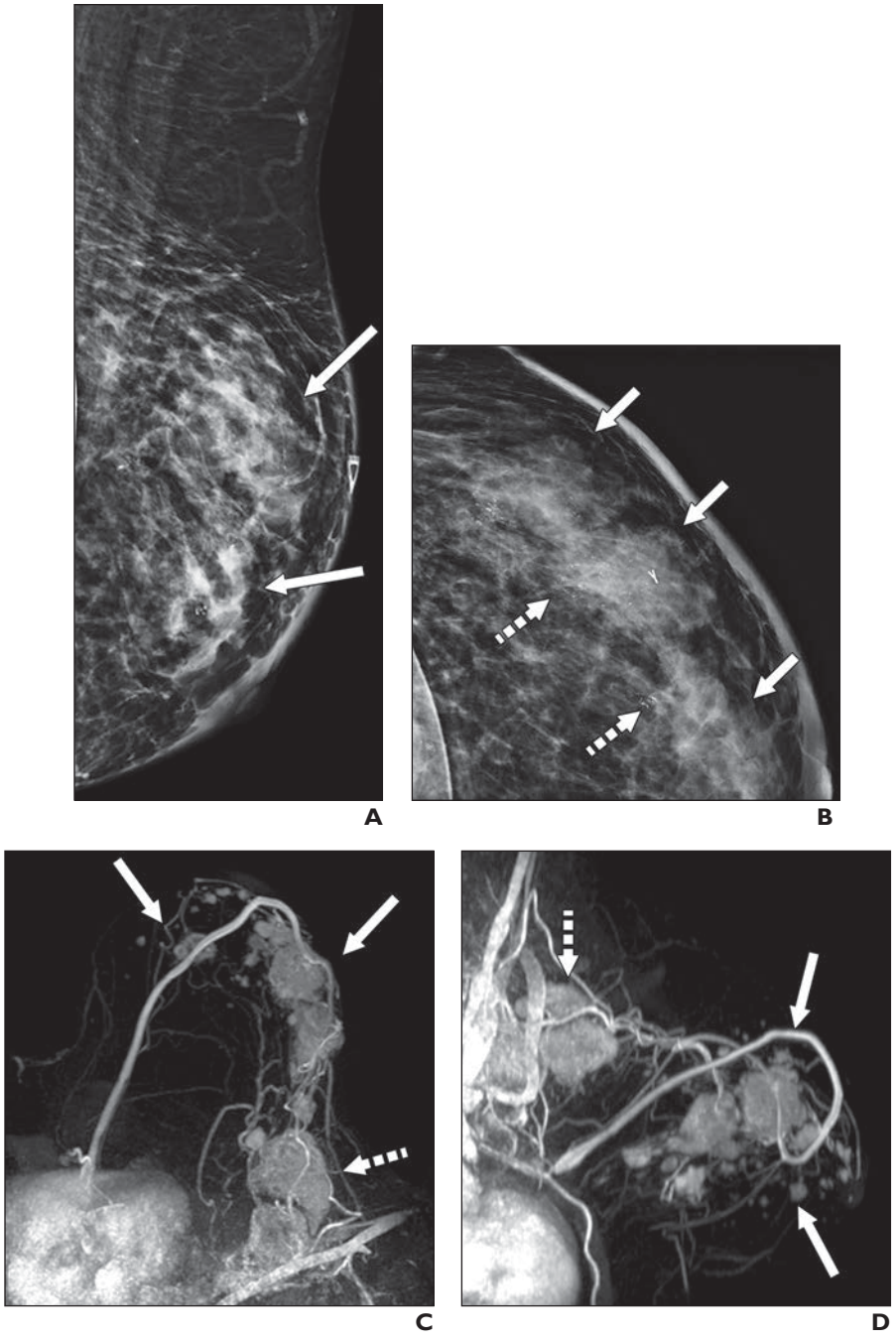


Fig. 1—51-year-old woman with multicentric left invasive ductal carcinoma.
A and **B,** Full-field mediolateral oblique implant-displaced mammogram obtained before biopsy (**A**) and magnified craniocaudal implant-displaced mammogram obtained after biopsy (**B**) show conglomerate of obscured masses (*solid arrows*) with associated pleomorphic calcifications (*dashed arrows*, **B**) occupying entire upper-outer quadrant of left breast with associated skin thickening. Biopsy clip in **B** is seen at site of index mass at 1 o'clock position.
C and **D,** Axial (**C**) and sagittal (**D**) contrast-enhanced maximum-intensity-projection MRI reconstructions show multiple masses (*solid arrows*) in lateral and medial breast, consistent with multicentric disease with skin involvement (not shown). Images also show matted axillary lymphadenopathy (*dashed arrows*), which was proven by biopsy to represent nodal metastatic disease and supraclavicular nodal metastases (not shown). Patient's anatomic stage was IIIC (cT4bcN3c[f]cM0) and clinical prognostic stage was IIIC (cT4bcN3ccM0, grade 3, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] negative).

tent of disease, especially in relation to the nipple, can determine whether the patient is a candidate for nipple-sparing mastectomy. Contraindications for nipple-sparing mastectomy include microcalcifications close to the subareolar region (< 2 cm) [11], Paget disease, and bloody nipple discharge (Figs. 3 and 4).

The subcategories of T1 disease are T1mi (microinvasive; tumor ≤ 1 mm in greatest dimension), T1a (> 1 mm but ≤ 5 mm), T1b (> 5 mm but ≤ 10 mm), and T1c (> 10 mm but ≤ 20 mm). Another change in the AJCC 8th edition staging system is that a tumor measuring more than 1 mm and less than 2 mm is rounded to 2 mm. With T2 disease, tumor size is larger than 20 mm and no greater than 50 mm. With T3 disease, tumor size is greater than 50 mm.

The subcategories of T4 disease are T4a, T4b, T4c, and T4d (Fig. 5). Category T4a is defined by chest wall extension, where the chest wall consists of the ribs and the intercostal and serratus anterior muscles. Involvement of the pectoralis major or minor muscles alone is not considered chest wall involvement and does not affect the T category [6]. MRI is excellent for evaluating pectoralis muscle involvement and chest wall invasion [12] (Figs. 6 and 7). Involvement of the pectoralis muscle may manifest as enhancement of the muscle (Fig. 6) with loss of the fat plane between the

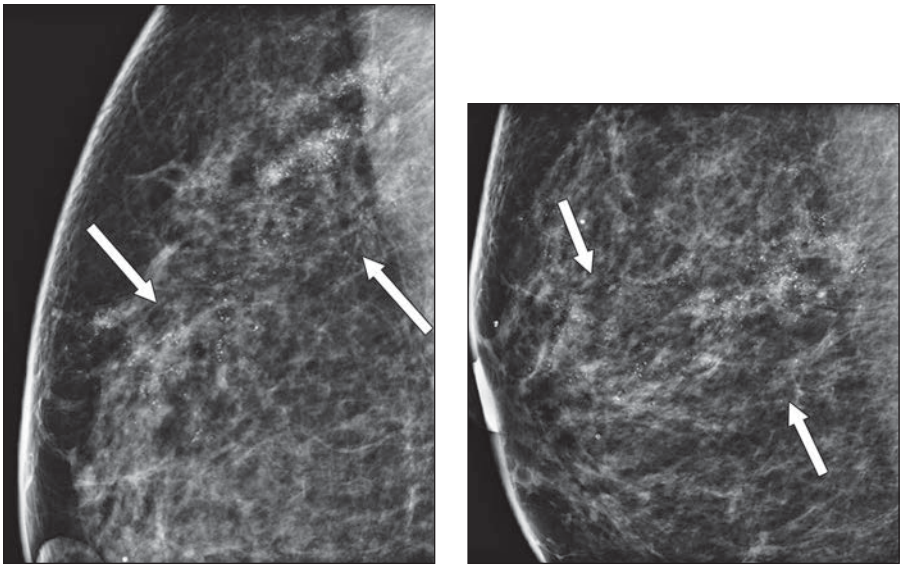


Fig. 2—68-year-old woman with newly diagnosed ductal carcinoma in situ of right breast.
A and **B,** Magnified exaggerated craniocaudal (**A**) and lateral medial (**B**) mammograms of right breast show segmental pleomorphic calcifications (*arrows*) measuring 8 cm in maximal dimension. Patient underwent skin-sparing mastectomy of right breast and sentinel lymph node biopsy. Her anatomic stage was 0 (cTiscN0cM0) and clinical and pathologic prognostic stage was 0 (pTispN0cM0, grade 2, estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor 2 [also known as ERBB2] not assessed).

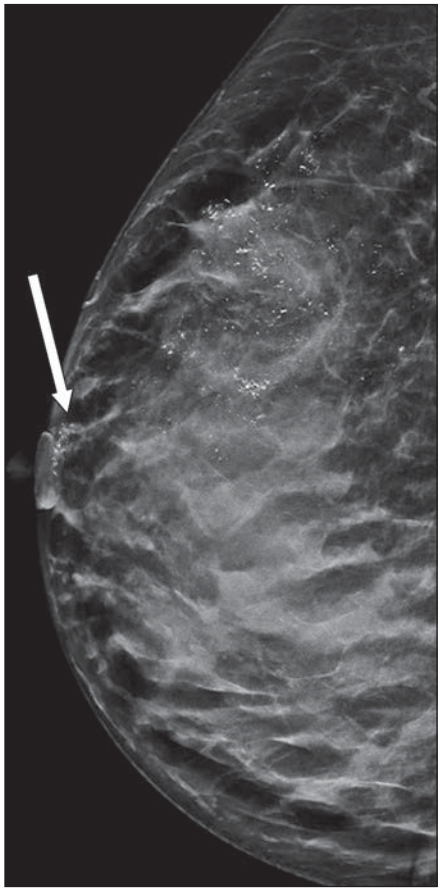


Fig. 3—38-year-old woman with multicentric right invasive ductal carcinoma and ductal carcinoma in situ whose anatomic stage was IIIA (cT3cN1[f]cM0). Patient was treated with neoadjuvant chemotherapy and underwent total mastectomy and axillary lymph node dissection. Full-field synthesized 2D (C-View, Version 1, Hologic) lateral medial mammogram of right breast shows calcifications extending to base of nipple (*arrow*) in segmental distribution, which excluded patient from undergoing skin-sparing mastectomy. Patient's clinical prognostic stage was IIIA (cT3N1[f]cM0, grade 3, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] positive).

muscle and the tumor on MRI. Loss of the fat plane without muscle enhancement is not definitive for muscle involvement [12, 13] (Fig. 8). Although pectoralis muscle involvement does not affect clinical stage, reporting this finding is critical because it may impact surgical decision making (whether the surgeon resects the muscle) and radiation therapy planning. Furthermore, chest wall involvement may require more extensive surgery, including thoracic surgery.

Category T4b involves macroscopic skin changes that include a combination of ulceration, satellite skin nodules, and edema. The AJCC 8th edition staging system states that satellite tumor nodules involving the skin must be separate from the primary tumor and macroscopically identified to be considered T4b. Skin and dermal nodules identified on microscopic examination and in the absence of skin ulceration or skin edema (peau d'orange) do not meet T4b criteria [4]. Tumors categorized as T4c meet the criteria for both T4a and T4b (Fig. 7).

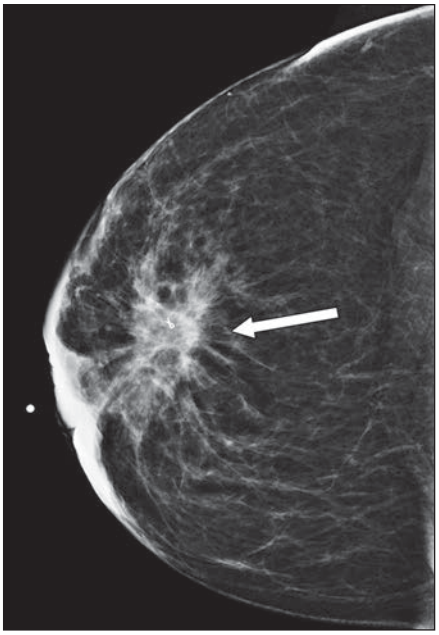
Category T4d is inflammatory breast cancer, which is a clinical and pathologic entity requiring features of diffuse erythema and edema (peau d'orange) involving at least one-third of the breast and progressing rapidly over weeks to months [4, 14] (Fig. 9).

Imaging Tumor Size

Digital breast tomosynthesis (DBT) has been well documented in the screening setting to be superior to full-field digital mammography (FFDM) in improving cancer detection rate and decreasing recall rates [15]. However, the performance of DBT combined with FFDM in the staging of patients with breast cancer has been studied less. Although DBT combined with FFDM shows better diagnostic performance and sensitivity than FFDM alone in the diagnostic setting, breast cancers without distinct masses or without calcifications are still difficult to detect [16]. Fontaine et al. [17] found that the additional value of DBT in breast cancer staging (in detecting additional ipsilateral disease or contralateral lesions) was limited to women with nondense breasts.

Most DCIS lesions found at mammography present as microcalcifications, with approximately 75% presenting only as calcifications [18, 19]. Ultrasound does have a role in the workup of DCIS given its variable appearance. Ultrasound is also useful in evaluating for an associated mass, which may indicate invasion [20].

Whole-breast ultrasound is critical in staging to assess tumor size and in evaluating for additional disease that is mammographically occult, especially in patients with dense breasts



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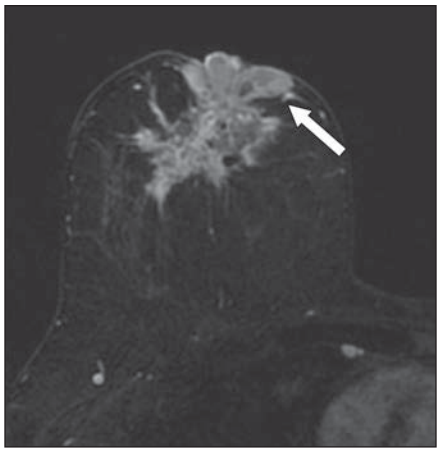
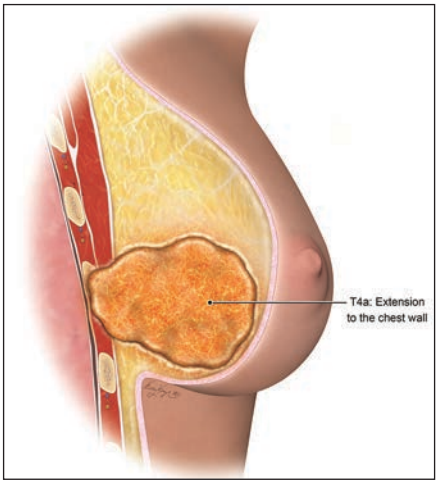


B

Fig. 4—56-year-old woman who presented with right nipple thickening and retraction, areolar scaling, and palpable mass. Skin punch biopsy results showed adenocarcinoma involving epidermis, consistent with Paget disease. Ultrasound biopsy (not shown) of retroareolar mass showed invasive lobular carcinoma.
A, Full-field craniocaudal mammogram shows irregular mass (*arrow*) with biopsy clip in retroareolar region and associated nipple retraction and skin thickening.
B, Contrast-enhanced axial subtraction MRI shows irregular heterogeneously enhancing retroareolar mass with enhancement of nipple-areola complex (*arrow*). Patient's anatomic stage was IIIA (cT3cN1[f] cM0) and clinical prognostic stage was IIIA (cT3cN1cM0, grade 2, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] negative).



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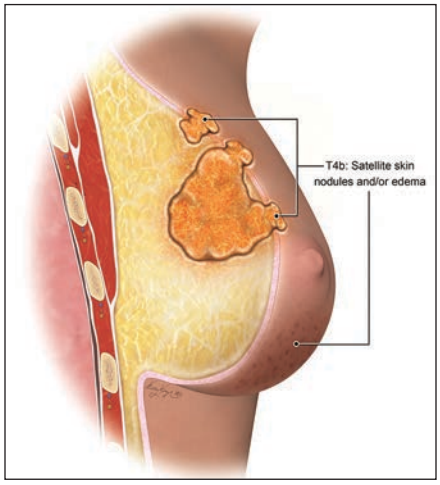

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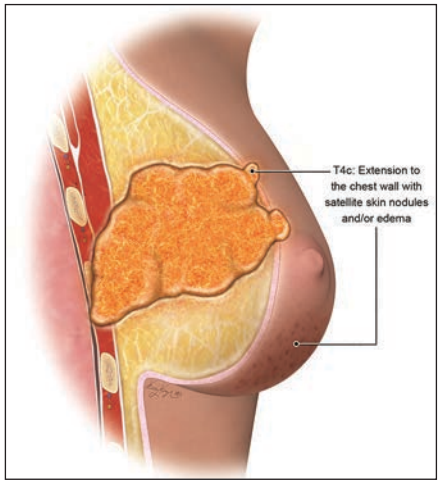

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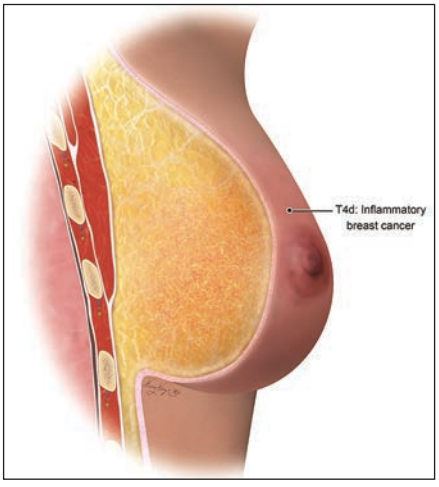


D

Fig. 5—Illustrations of category T4 tumors. (© 2020 The University of Texas MD Anderson Cancer Center, used with permission)
A, Illustration shows category T4a tumor, which can be any size and extends to chest wall (not including pectoralis muscle adherence or invasion).
B, Illustration shows category T4b tumor, which is characterized by macroscopic skin changes, including some combination of ulceration, satellite nodules, and edema, and does not meet criteria for inflammatory breast cancer.
C, Illustration shows category T4c tumor, which meets criteria for both categories T4a and T4b.
D, Illustration shows category T4d tumor. These tumors represent inflammatory breast cancer, which requires features of diffuse erythema and edema (peau d'orange) involving at least one-third of breast and progresses rapidly over weeks to months.

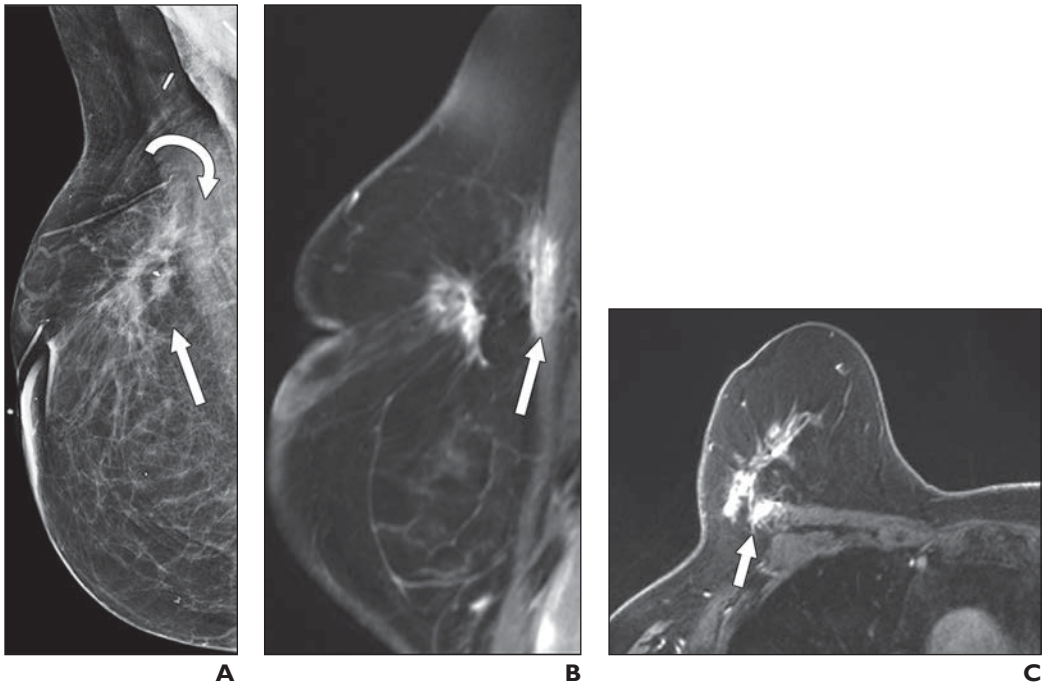


Fig. 6—77-year-old woman with new right invasive lobular carcinoma possibly extending to pectoralis major muscle. Patient had remote history of screen-detected right breast cancer 27 years prior (type and biomarkers unknown, negative lymph nodes according to patient) treated with lumpectomy, axillary lymph node dissection, and radiation therapy.
A, Right mediolateral oblique full-field mammogram shows 4.5-cm region (*straight arrow*) encompassing architectural distortion and biopsy clip at site of new invasive lobular carcinoma and possible extension to pectoralis major muscle (*curved arrow*).
B and **C,** Sagittal (**B**) and axial (**C**) contrast-enhanced MR images show enhancement of pectoralis major muscle (*arrow*), confirming muscle involvement. Patient's anatomic stage was IIA (cT2cN0cM0) and clinical prognostic stage was IB (cT2cN0cM0, grade 2, estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor 2 [also known as ERBB2] negative).

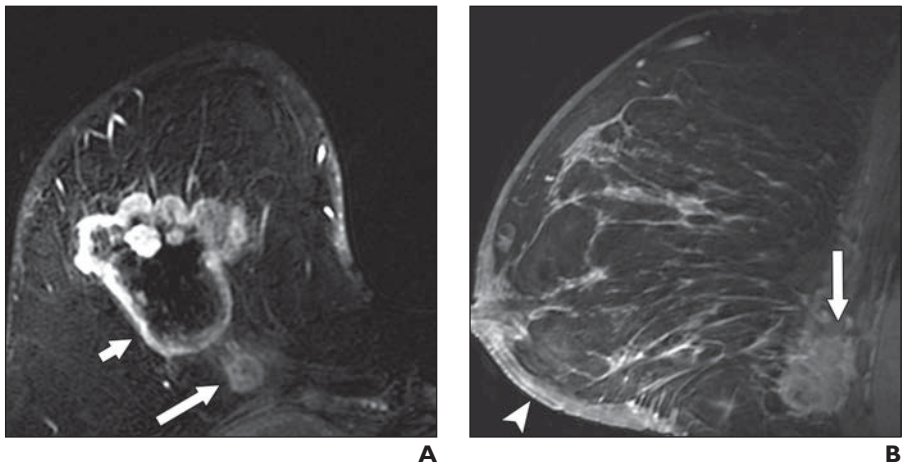


Fig. 7—37-year-old woman with locally advanced invasive ductal carcinoma of right breast with chest wall invasion and skin involvement.
A and **B,** Axial (**A**) and sagittal (**B**) contrast-enhanced MR images of right breast show rim-enhancing necrotic mass (*short arrow*, **A**) occupying much of breast with chest wall extension involving pectoralis and intercostal muscles (*long arrow*). Skin edema (*arrowhead*, **B**) is also seen. Patient's anatomic stage was IIIC (cT4ccN0cM0) and clinical prognostic stage was IIIC (cT4ccN0cM0, grade 3, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] negative).

[21]. The detection of additional malignant lesions may lead to a wider surgical excision or alter surgical management (mastectomy vs lumpectomy) [22, 23].

The routine use of contrast-enhanced MRI for preoperative staging continues to be controversial given that the impact of MRI on survival is still unknown [8]. Currently, evidence that preoperative MRI improves overall or disease-free survival is lacking [24]. Furthermore, numerous studies have found that MRI overestimates tumor size when compared with final pathology [25]. In the initial staging setting, MRI could result in overstaging.

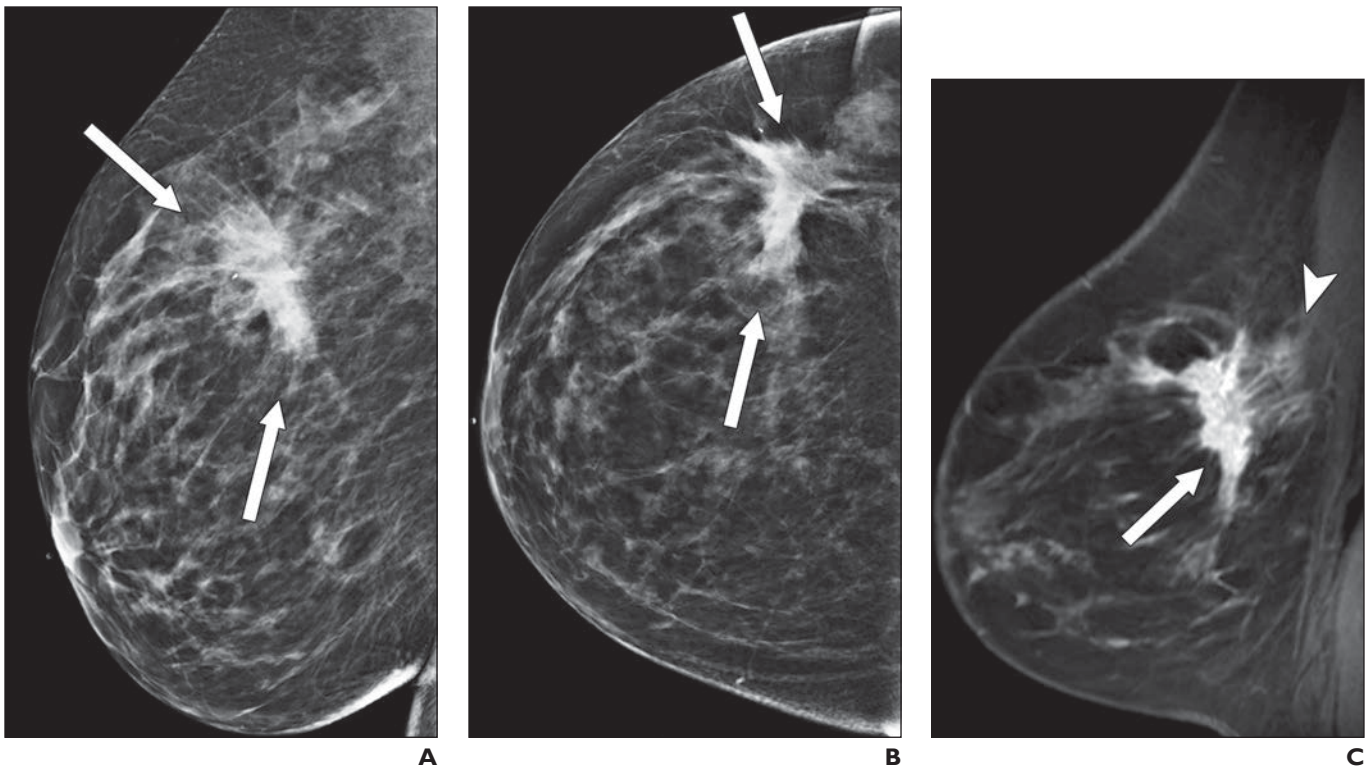
MRI may be appropriate in certain circumstances. MRI has shown value in staging invasive lobular cancer, a subtype that is typically underestimated by mammography and ultrasound. MRI may be helpful in reducing reexcision rates in invasive lobular cancer, which range from 11% to 18% [26] (Fig. 8). MRI is also useful in showing multicentricity [25] and involvement of the pectoralis muscle and chest wall [12, 13] (Figs. 1, 6, and 7).

There is no consensus regarding which imaging modality best predicts tumor size. Mammography is less accurate in dense breasts yet is superior in showing microcalcifications. Ultrasound is highly operator-dependent, inexpensive, and helpful in showing mammographically occult disease, especially in dense breasts. MRI, though highly sensitive, lacks specificity and often overestimates tumor size [25, 27]. When tumor measurements are discrepant between imaging modalities, the MRI measurements are typically used [3].

As MRI has low specificity in distinguishing benign from malignant enhancement, obtaining a tissue sample from a lesion showing suspicious enhancement is critical and could alter patient stage and/or clinical management [28].

Regional Lymph Nodes

The expert panel did not recommend any major changes to the clinical nodal staging classification in the AJCC 8th edition staging



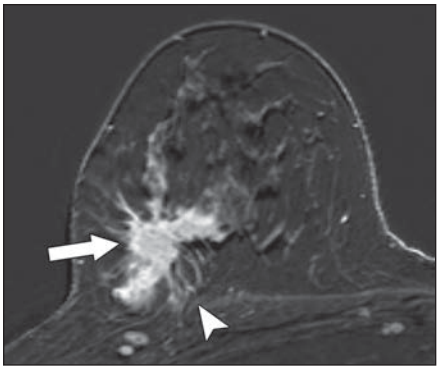


Fig. 8—53-year-old woman with right breast invasive lobular carcinoma.
A and **B,** Right mediolateral oblique (**A**) and craniocaudal (**B**) full-field digital mammograms show irregular mass (*arrows*) at 11-o'clock position 9 cm from nipple with biopsy clip at anterior lateral aspect of mass. On mammography and ultrasound (not shown), mass measured 4.3 cm in maximal dimension.
C and **D,** Sagittal (**C**) and axial (**D**) contrast-enhanced MR images show mass (*arrow*) measuring 6.7 cm in maximal dimension with spiculations extending to pectoralis major muscle and blurring of retromammary fat without muscle enhancement (*arrowhead*). Patient underwent right skin-sparing mastectomy and axillary lymph node dissection (three of 23 positive nodes). Her anatomic stage was IIB (cT3cN0cM0). Invasive lobular carcinoma measured 7 cm on final pathology, indicating that size was better estimated on MRI than on mammography and ultrasound. Patient's clinical and pathologic prognostic stage was IB (pT3pN1[sn]cM0, grade 2, estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor 2 [also known as ERBB2] negative). Pectoralis major muscle was not affected by tumor.

system [3, 4]. However, they did clarify that category cNx is only to be used when lymph nodes are removed and cannot be examined by imaging or physical examination. A cN0 category is assigned when evaluation of the lymph nodes is possible and no regional lymph node metastases are detected by physical examination or imaging [3]. The clinical nodal category is based on imaging or clinical evaluation of the nodal basins [3], whereas the pathologic category is based on the number of involved lymph nodes on surgical pathology. The abbreviations (sn) and (f) are suffixes added to the N category if metastases are confirmed with SLNB or with fine-needle aspiration and core biopsy, respectively [3].

Staging of axillary lymph nodes is determined by the lymph node's location in relation to the pectoralis minor muscle. Level I axillary lymph nodes are located lateral to the pectoralis minor muscle, level II axillary lymph nodes are between the pectoralis minor muscle's medial and lateral margins and encompass interpectoral (Rotter) lymph nodes, and level III axillary lymph nodes lie medial to the pectoralis minor muscle's medial margin (Fig. 10).

Category cN1 disease encompasses metastases to movable ipsilateral level I and/or level II nodes. Category cN2 disease includes metastases to fixed or matted ipsilateral level I and/or level II nodes or to ipsilateral internal mammary (IM) nodes in the absence of axillary metastases. Category cN3 disease includes ipsilateral level III node metastases with or without level I or level II nodes (Fig. 11), ipsilateral IM metastases with level I or level II metastases, or ipsilateral supraclavicular (SC) lymph node metastases. Metastatic intramammary lymph nodes are equivalent to level I for staging purposes.

Cervical lymph nodes and contralateral axillary, SC, and IM metastases are considered distant metastases (M1).

When multiple suspicious lymph nodes are present in different nodal basins, the nodal level that should be sampled first is the one that would have the greatest effect on stage. For example,

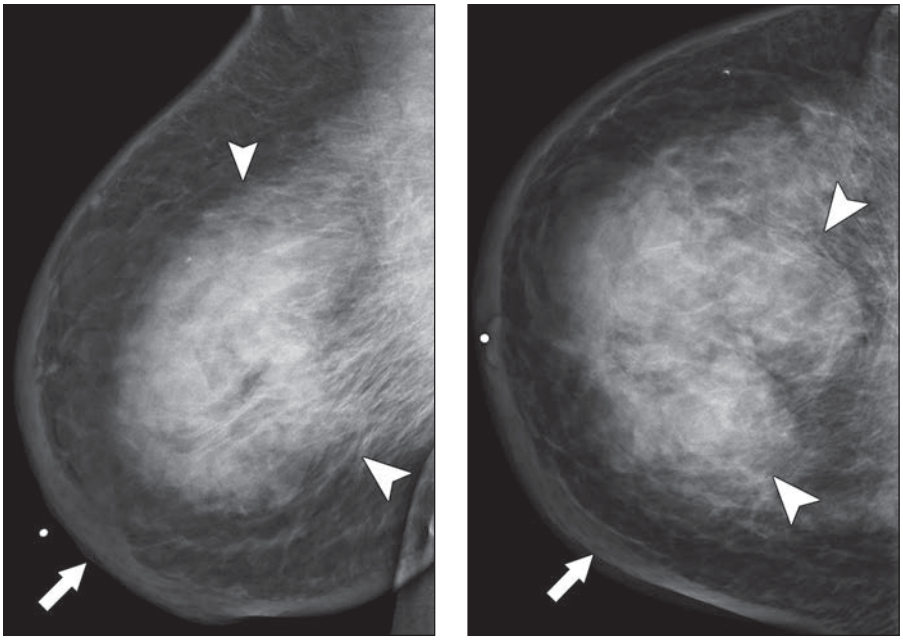


Fig. 9—45-year-old woman with inflammatory right breast cancer. Patient presented with peau d'orange and rapid onset of breast hardening and redness. **A** and **B,** Mediolateral oblique (**A**) and craniocaudal (**B**) full-field digital mammograms of right breast show diffuse skin thickening (*arrow*), edema, and multiple obscured masses (*arrowheads*) occupying majority of breast. Patient's anatomic stage was IIIC (cT4dcN3ccM0) and clinical prognostic stage was IIIC (cT4dcN3ccM0, grade 3, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] negative).

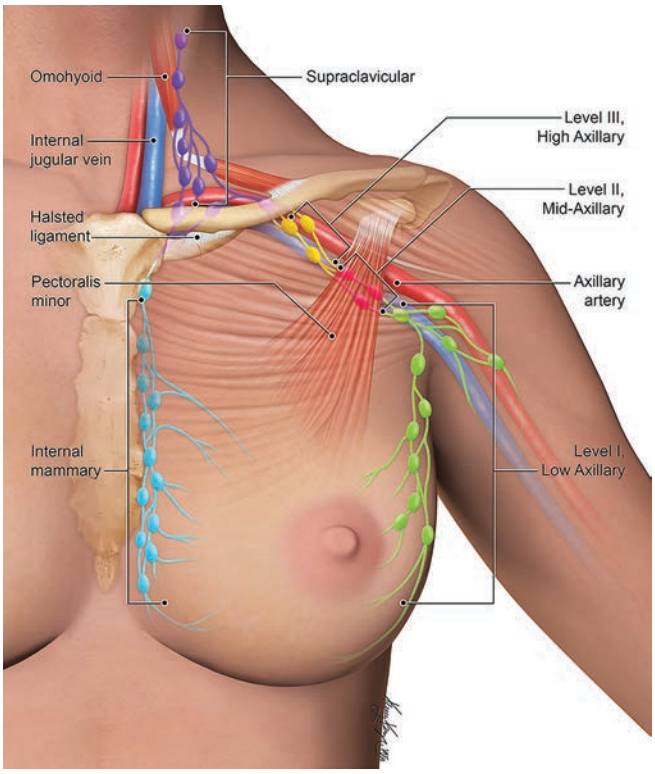


Fig. 10—Illustration shows regional nodal staging. Level I axillary lymph nodes (low axillary) lie lateral to lateral border of pectoralis minor muscle, level II axillary lymph nodes (midaxillary) lie between medial and lateral borders of pectoralis minor muscle, and level III axillary lymph nodes (high axillary or infraclavicular) lie medial to medial border of pectoralis minor muscle. Internal mammary lymph nodes lie in intercostal spaces along sternum in endothoracic fascia. Supraclavicular lymph nodes lie within supraclavicular fossa, triangle defined by omohyoid muscle and tendon (lateral and superior borders), internal jugular vein (medial border), and clavicle and subclavian vein (lower border). (© 2020 The University of Texas MD Anderson Cancer Center, used with permission)

if suspicious level III and level I nodes are present, the level III node should be biopsied first. If the biopsy of a level III node shows benign results, then the abnormal level I node should be sampled [29].

Imaging Regional Lymph Nodes

Ultrasound remains the modality of choice for evaluating the axillary lymph nodes. However, ultrasound is operator-dependent. Axillary and IM lymph nodes are well evaluated by breast MRI, chest CT, or FDG PET/CT. SC nodes can be evaluated with ultrasound or cross-sectional imaging.

Historically, patients with biopsy-proven metastatic axillary lymph nodes underwent axillary lymph node dissection (ALND), a procedure with significant morbidity. However, in 2010, the American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized trial found that ALND may not be necessary in patients who are clinically node negative and are undergoing breast conservation with one or two positive sentinel lymph nodes. The study found no difference in local recurrence between the ALND group and SLNB group [30, 31].

Given the shift in surgical management, the use of axillary nodal ultrasound has become controversial. The concern is that, when mildly abnormal axillary nodes are imaged and sampled in a patient who meets the criteria for SLNB as established in the Z0011 trial, a positive biopsy would commit the patient to ALND. However, studies have found that patients with a positive axillary ultrasound finding and subsequent positive biopsy results are more likely to have more axillary nodes involved on pathology at the time of surgery [32–34]. Furthermore, Verheuvel et al. [35] found that patients with axillary disease on ultrasound were more likely to have involvement of level III nodes and a decrease in overall and disease-free survival.

NAC is used to downstage not only the breast malignancy but also the axilla. Targeted axillary dissection has emerged to help treat

patients with limited nodal involvement who show evidence of response to treatment. The ACOSOG Z1071 trial investigated SLNB performed after NAC in patients with stage II, stage IIIA, and stage IIIB disease who had biopsy-proven axillary metastases before NAC. This study found that when the clipped biopsy-proven metastatic node (that showed response to NAC) and at least two sentinel nodes are excised, the false-negative rate of SLNB was 6.8% [36, 37]. Therefore, it is reasonable to consider SLNB in patients with cN1 or cN2 disease at presentation and good clinical response to NAC [38].

Complete evaluation of the axilla and regional nodal basins during initial staging is critical to determine which patients may be candidates for targeted axillary dissection before NAC and therefore require placement of a biopsy clip in biopsy-proven metastatic axillary lymph nodes. In patients with proven or suspected metastatic level I or II lymph nodes, imaging studies to evaluate level III, IM, and SC lymph nodes should be considered when determining whether the patient is a candidate for targeted axillary dissection [6, 8, 23]. In addition, the presence of IM, SC, and level III lymph node metastases alters radiation therapy planning (Fig. 11).

Metastases

The M category is classified as M0 (no distant metastases) or M1 (metastatic disease present). The most common sites of metastases in breast cancer are bone, lung, brain, and liver [6]. The AJCC 8th edition staging system clarifies that pM0 is not a valid category [3, 4]. A benign biopsy of a suspicious lesion does not guarantee absence of metastatic disease elsewhere. Only cM0, cM1, and pM1 are used. Category cM0 is defined as no clinical or imaging evidence of distant metastases. Category cM1 is defined as distant metastases on the basis of clinical or imaging findings. Category pM1 is defined as distant metastases on the basis of pathologic proof.

Imaging of Metastases

NCCN guidelines state that routine systemic staging is not indicated for early breast cancer (T0–3N1M0 or T1–3N0–1M0) in the absence of signs and symptoms of metastatic disease [5]. Additional studies are guided by patient symptoms.

For patients with clinical stage IIIA disease or those considering NAC for T2M0 or higher or N1M0 or higher disease, studies to consider include chest CT, abdominopelvic CT or MRI, bone scan, and FDG PET/CT. When used in addition to other imaging studies, FDG PET/CT is helpful in identifying undetected regional nodal disease and/or distant metastases. Systemic imaging is also recommended in recurrent disease, stage IV (M1) disease, or inflammatory breast cancer.

Imaging Neoadjuvant Response

Traditionally, NAC has been administered for locally advanced breast cancers (clinical category T3N1–3M0) and inflammatory breast cancer because it can reduce both breast tumor and locoregional nodal recurrence. Currently, NAC is used at earlier stages to potentially change a patient's treatment from mastectomy to lumpectomy [39]. Furthermore, NAC may reduce the extent of axillary surgery, converting an ALND to a targeted axillary dissection. In HER2 and triple-negative subtypes, pathologic response can predict long-term progression-free and overall survival rates [40, 41].

After a patient receives NAC, the prefix "y" is used in assigning a TNM category. The use of NAC does not change the anatomic (pretreatment) stage. Clinical (posttreatment) T category is determined by the size and extent of disease on physical examination and imaging, and the ycT category is determined by measuring the largest residual mass [3].

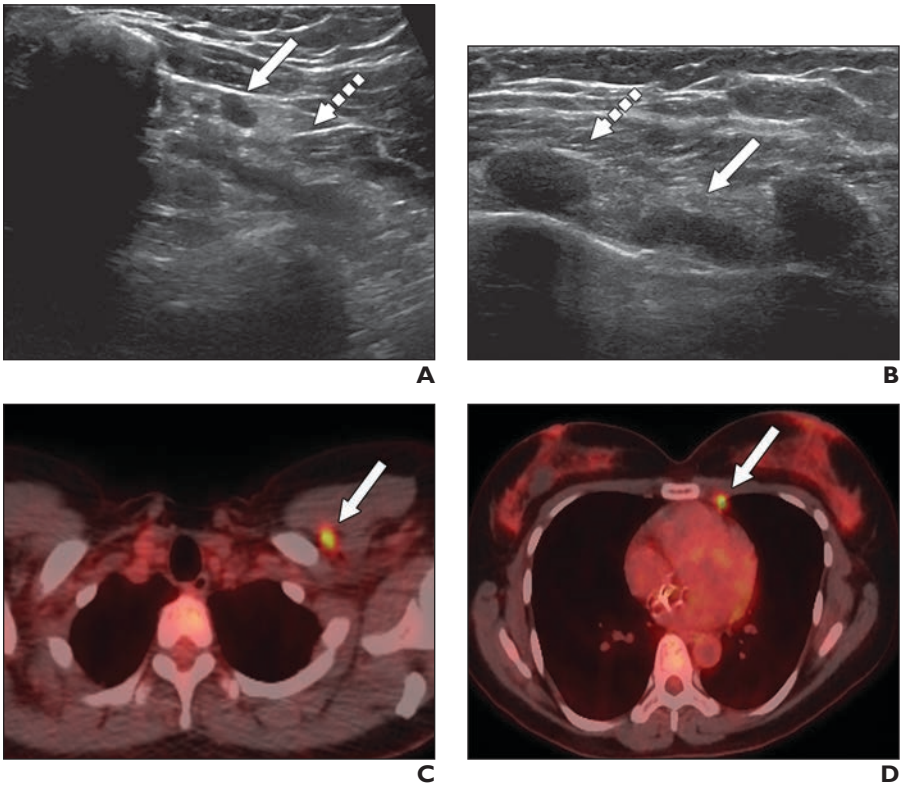


Fig. 11—46-year-old woman with left breast invasive ductal carcinoma.
A, Transverse ultrasound shows abnormal axillary level III lymph node (*solid arrow*) medial to medial border of pectoralis minor muscle (*dashed arrow*). Fine-needle aspiration confirmed metastatic disease.
B, Longitudinal ultrasound of chest wall shows abnormal lymph node (*solid arrow*) between third and fourth costal cartilages (*dashed arrow*).
C, FDG PET/CT shows FDG-avid biopsy-proven metastatic axillary level III lymph node (*arrow*) medial to pectoralis minor muscle, corresponding to lymph node in **A**.
D, FDG PET/CT shows FDG-avid internal mammary lymph node in third space (*arrow*). Patient's anatomic stage was IIIC (cT2cN3b[f]cM0) and clinical prognostic stage was IIIC (cT2cN3bcM0, grade 3, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2 [also known as ERBB2] negative).

There is no standard consensus regarding imaging assessment of NAC response. Although mammography is superior to physical examination, it can overestimate residual disease in lesions with architectural distortion or indistinct margins and in lesions that show no change in calcifications [39, 42]. The presence of calcifications does not correlate with viable tumor [41]. Ultrasound is a better predictor for pathologic tumor response and response in regional nodal metastases. However, though more accurate than mammography alone, ultrasound underestimates viable tumor given the difficulty in distinguishing posttreatment fibrosis from viable tumor on imaging [43].

MRI is the most accurate modality for assessment of tumor response to NAC, with a reported PPV (for correctly predicting the presence of residual disease on final surgical pathology) of 93% and NPV of 64% [39]. The American College of Radiology Imaging Network 6657 and Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis trial, which involved 216 women with tumors measuring 3 cm or greater treated with NAC, showed that tumor volume calculations were superior to measurements of the longest dimension for predicting response [7]. However, factors such as tumor molecular subtype and the chemotherapy regimen affect the accuracy of MRI in assessing NAC response.

Emerging technologies, such as functional and molecular imaging and use of advanced MRI techniques and/or radionuclide imaging to assess physiologic changes, may play a role in assessing response in combination with anatomic imaging. However, these methods are currently investigational [39].

After completion of NAC, the same imaging modalities used in pretreatment staging should be performed for evaluating response, and tumor size in three dimensions should be compared [39]. Other details to report are more qualitative, such as change in density of a mass on mammography, change in echogenicity and margin features on ultrasound, and normalization of nodal morphology.

Prognostic Staging

The most significant change in the AJCC 8th edition staging system is that the final prognostic stage is determined by tumor grade, biomarker status (ER, PR, and HER2), genomic panels, and anatomic TNM stage.

Grade

Tumor grade is defined by the Scarff-Bloom-Richardson histologic grading system, which was standardized by the Nottingham group and used by the College of American Pathologists [6]. The morphologic features of gland characteristics, pleomorphism, and mitotic counts are each given a score ranging from one to three, and these scores are then summed to determine grade [44, 45]. Grade 1 (score between 3 and 5) represents a well differentiated tumor, grade 2 (score 6 or 7) represents a moderately differentiated tumor, and grade 3 (score 8 or 9) represents a poorly differentiated tumor. Tumor grade is an important prognostic factor, independent of tumor size and number of positive lymph nodes [46].

ER, PR, and HER2 Expression and Molecular Subtypes

The AJCC 8th edition staging system stipulates that the ER and PR receptor status and HER2 expression status of all invasive carcinomas should be determined whenever possible. Endocrine therapies such as tamoxifen are known to slow progression of ER-positive and PR-positive tumors [6]. Furthermore, advances in breast cancer genomics have allowed prognostic profiling based on the expression of combinations of thousands of genes in tumor cells. The main subgroups, according to hormone receptor status and gene expression patterns, are the luminal A–like, luminal B–like, HER2-enriched, and basal-like (triple-negative) subtypes (Table 1).

Multigene Panel Testing

The AJCC 8th edition staging system also incorporates multigene panel testing in assigning prognostic subgroups. At the time of publication of the revised AJCC staging manual, Oncotype DX Breast Recurrence Score (Genomic Health) was the most validated panel and was therefore incorporated into the 8th edition prognostic staging system [3]. However, other multigene panels are available. The expert panel did not advocate one

TABLE 1: Clinically Defined Treatment-Oriented Subtypes of Breast Cancer

Subtype	Hormone Receptor Status, Histologic Grade, and Prognosis
Luminal A–like	High hormone receptor, low proliferation High ER and PR expression; usually HER2 negative Usually low grade and low proliferation rate (low Ki-67, low mitotic count), generally histologic grade 1 or 2 [52, 53] Favorable prognosis, 5-year survival rate > 80% [53]
Luminal B–like	Low hormone receptor, high proliferation Lower ER and PR expression; usually HER2 negative but approximately 30% of cases will be HER2 positive High proliferation rate (high Ki-67, high mitotic count) Generally, histologic grade 3 Less favorable prognosis compared with luminal A–like [54]
HER2-enriched	HER2 positive (ER and PR negative or positive) Generally histologic grade 3 Targeted therapy for HER2 positive cancers (such as trastuzumab) has improved prognosis [51]
Basal-like	Most commonly triple negative (ER, PR, and HER2 negative) Defined by absence of ER, PR, and HER2 markers and overexpression of oncogenes that favor cell proliferation and carcinogenesis Generally histologic grade 3 Unfavorable prognosis [55, 56]

Note—ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2 (also known as ERBB2), negative = no expression by tumor, Ki-67 = marker for cellular proliferation, positive = expression by tumor.

TABLE 2: Examples of Different Anatomic Stages and Prognostic Stages Using Biomarkers and Oncotype DX Breast Recurrence Score (Genomic Health)

T	N	M	Histologic Grade	ER	PR	HER2	Oncotype DX Score < 11[a]	Anatomic Stage (AJCC 7th Edition) [57]	Clinical Prognostic Stage (AJCC 8th Edition) [3]
1	0	0	1	Negative	Negative	Negative	NA	IA	IB
2	0	0	3	Positive	Negative	Negative	NA	IIA	IIB
2	0	0	Any	Positive	Positive	Negative	Yes	IIA	IA
3	1	0	1	Positive	Positive	Positive	NA	IIIA	IIA

Note—ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2 (also known as ERBB2), negative = no expression by tumor, NA = not applicable, positive = expression by tumor.
[a]If applicable.

specific vendor and acknowledged that further modifications of the staging system will be necessary as additional data validating these panels are obtained [4]. Currently, Oncotype DX is used to predict the average 10-year distant recurrence risk in patients receiving endocrine therapy alone for T1–2N0M0 (ER-positive, PR-positive, HER2-negative) disease. Oncotype DX is used to assess the additional benefit of adjuvant chemotherapy with respect to endocrine therapy. For low-risk disease (score less than 11), the model does not predict any additional benefits from chemotherapy [47, 48]. The AJCC 8th edition staging system incorporates the Oncotype DX score, if available, in the prognostic staging of this subset of patients.

Prognostic Staging Versus Anatomic Staging

In two previous studies, data from two large cohorts from the MD Anderson Cancer Center and the California Cancer Registry were analyzed and incorporated into prognostic staging. The MD Anderson study evaluated 3327 patients treated between 2007 and 2013 and found that disease-specific survival was more precise using a staging system that incorporated tumor grade, ER status, and HER2 status compared with anatomic staging alone [49]. These findings were validated using a cohort of 67,944 patients from the California Cancer Registry [50].

The integration of new biomarkers into the AJCC 8th edition staging system may result in upstaging or downstaging (Table 2), depending on the tumor biology, which can result in a prognostic stage different from the anatomic stage. Patients with triple-negative tumors, regardless of grade, have survival rates comparable with those of patients with disease one anatomic stage higher [4] and are generally upstaged in their prognostic stage (for example, anatomic stage IA and prognostic stage IIA). Similarly, patients with grade 3 tumors that are HER2-negative and positive for either ER or PR also have survival rates comparable with those of patients with disease one anatomic stage higher [6, 9]. Conversely, a patient with a T3N0M0 cancer of any grade that is ER positive, PR positive, and HER2 positive would be considered to have anatomic stage IIB and prognostic stage IB disease, and therefore, the patient's disease would be downstaged. HER2 expression is generally a downstaging factor given the success of anti-HER2 therapy [4, 51] (Fig. 8).

The new prognostic staging system also incorporates multigene panel testing in a subset of patients with hormone receptor–positive, HER2-negative, and lymph node–negative disease [4]. For example, a patient with a T2N0M0 tumor and Oncotype DX score less than 11 has an anatomic stage of IIA but a prognostic stage of IB.

The AJCC 8th edition staging system includes multiple prognostic stage tables that incorporate the clinical anatomic stage (TNM), tumor grade, biomarkers, and multigene panel (when appropriate) [3]. The prognostic staging system presumes that patients receive appropriate systemic treatment, hormonal therapy, and chemotherapy.

Conclusion

The AJCC 8th edition staging system now includes two staging systems: the anatomic staging system (TNM) and the prognostic staging system. The prognostic stage includes the anatomic stage and grade, biomarkers, and multigene panels. Radiologists play a critical role in anatomic staging and the triage of patients with breast cancer for appropriate treatment. With the increased use of NAC, radiologists also play a role in evaluating response to neoadjuvant treatment. Radiologists should strive to identify the key findings that affect stage and understand where imaging and each modality may fall short in staging patients with breast cancer.

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