

**American College of Radiology  
ACR Appropriateness Criteria®  
Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer**

**Variant 1:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	⊗⊗
Mammography diagnostic	Usually Appropriate	⊗⊗
MRI breast without and with IV contrast	Usually Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	⊗⊗⊗
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⊗⊗⊗⊗

**Variant 2:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Imaging of the breast after initiation or completion of neoadjuvant chemotherapy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	⊗⊗
Mammography diagnostic	Usually Appropriate	⊗⊗
MRI breast without and with IV contrast	Usually Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	⊗⊗⊗
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⊗⊗⊗⊗

**Variant 3:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-negative. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	○
US-guided core biopsy axillary node	Usually Not Appropriate	○
US-guided fine needle aspiration biopsy axillary node	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	⊗⊗
Mammography diagnostic	Usually Not Appropriate	⊗⊗
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⊗⊗⊗⊗

**Variant 4:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-positive. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	○
MRI breast without and with IV contrast	May Be Appropriate	○
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	⚠⚠⚠⚠
US-guided core biopsy axillary node	Usually Not Appropriate	○
US-guided fine needle aspiration biopsy axillary node	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	⚠⚠
Mammography diagnostic	Usually Not Appropriate	⚠⚠
MRI breast without IV contrast	Usually Not Appropriate	○

**Variant 5:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-negative. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Not Appropriate	○
US-guided core biopsy axillary node	Usually Not Appropriate	○
US-guided fine needle aspiration biopsy axillary node	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	⚠⚠
Mammography diagnostic	Usually Not Appropriate	⚠⚠
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⚠⚠⚠⚠

**Variant 6:** Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer with clinical suspicion of metastatic disease. Staging or assessment of response to neoadjuvant chemotherapy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Bone scan whole body	Usually Appropriate	⚠⚠⚠
CT chest abdomen pelvis with IV contrast	Usually Appropriate	⚠⚠⚠⚠
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	⚠⚠⚠⚠
MRI chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	○
MRI chest abdomen pelvis without IV contrast	Usually Not Appropriate	○
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	⚠⚠⚠⚠
CT chest abdomen pelvis without IV contrast	Usually Not Appropriate	⚠⚠⚠⚠

**Variant 7:**

**Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known axillary lymph node-positive breast cancer on prior mammography, US, or MRI. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla previously evaluated. Next imaging study.**

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	○
US breast	Usually Not Appropriate	○
US-guided core biopsy axillary node	Usually Not Appropriate	○
US-guided fine needle aspiration biopsy axillary node	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☢☢
Mammography diagnostic	Usually Not Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

**Variant 8:**

**Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Axillary imaging suspicious for metastatic disease on mammography, US, or MRI during initial evaluation. Next imaging study.**

Procedure	Appropriateness Category	Relative Radiation Level
US-guided core biopsy axillary node	Usually Appropriate	○
US-guided fine needle aspiration biopsy axillary node	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☢☢
Mammography diagnostic	Usually Not Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○

# MONITORING RESPONSE TO NEOADJUVANT SYSTEMIC THERAPY FOR BREAST CANCER

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## **Summary of Literature Review**

### **Introduction/Background**

Neoadjuvant chemotherapy (NAC) is often given before definitive surgical intervention for locally advanced breast cancer, which is defined as a tumor >5 cm with regional and/or metastatic lymph nodes, skin, or chest wall involvement. NAC is also indicated in T2 tumors (2-5 cm) in which lumpectomy might result in substantial cosmetic defect, triple-negative tumors 2 to 5 cm in size even if node-negative, and human epidermal growth factor receptor 2 (HER2)/neu-positive tumors 2 to 5 cm in size even if node-negative. The primary aims of this approach are to 1) reduce tumor burden, thereby permitting breast conservation rather than mastectomy; 2) promptly treat possible metastatic disease, whether or not it is detectable on preoperative staging; and 3) potentially tailor future chemotherapeutic decisions by monitoring in vivo tumor response [1,2]. Although the overall and disease-free survival for women receiving neoadjuvant versus adjuvant chemotherapy are not substantially different, women who do receive neoadjuvant therapy are less likely to undergo mastectomy and are more likely to be treated with breast conservation [1].

Imaging plays a vital role in managing patients undergoing NAC as treatment decisions rely heavily on accurate assessment of response to therapy. Beyond assessing the primary lesion, imaging is used to stage and monitor patients before, during, and after completion of initial therapy, including the axilla and potential distant metastatic sites. Accurate assessment of tumor burden is critical in determining the best management. Imaging plays an important role as clinical breast examination is challenging for primary tumors that are <2 cm in size, have an irregular shape or ill-defined margins, and show necrosis, fibrosis, or fragmentation with treatment [3]. Axillary imaging is increasingly used before, during, and after therapy to monitor response to treatment and help guide surgical management [4]. Most practices define response per Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST 1, which defines complete response (CR) as disappearance of the tumor in its entirety, partial response (PR) as at least 30% decrease in the longest diameter of the tumor compared with pretreatment baseline, progression of disease as at least 20% increase in longest diameter, and stable disease as no change in the tumor size that would qualify as PR or progression of disease on the basis of longest diameter [5]. Pathologic complete response (pCR) is defined as a surgical specimen free of carcinoma following therapy and represents a surrogate endpoint for treatment with pCR predicting improved disease-free survival [1,6].

Although there is a paucity of published data in men and transgender patients diagnosed with breast cancer, in practice, these patients are managed similarly to women.

### **Special Imaging Considerations**

There are several single-institution studies that demonstrate contrast-enhanced mammography has comparable sensitivity and specificity to contrast-enhanced MRI in evaluating for residual disease after NAC [7-10]. Therefore, although not widely used in clinical practice, this may be an option for patients who are unable to undergo MRI [7-10].

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## Initial Imaging Definition

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

## Discussion of Procedures by Variant

**Variant 1: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy. Initial imaging.**

### Digital Breast Tomosynthesis Diagnostic

Mammography, ultrasound (US), and MRI are complementary modalities for assessing primary tumor size before treatment because they are reliable tools to determine tumor size at diagnosis [1,11-15]. Mammography and US are the two main modalities for assessing primary tumor size before treatment because they are reliable tools to determine tumor size at diagnosis [11-15]. Mammography is most accurate for ductal and low-grade malignancies and less accurate for invasive lobular cancers and higher-grade lesions [11-16].

Digital breast tomosynthesis (DBT) addresses some of the limitations encountered with standard mammographic views. In addition to planar images, DBT creates thin-section reconstructed images, which decreases the lesion-masking effect of overlapping normal tissue. In the screening setting, some authors found the advantages of DBT to be especially pronounced in patients <50 years of age [17,18], in patients with dense breasts [17,19], and with lesion types including spiculated masses, [20] asymmetries [21], and architectural distortion [22]. DBT is also useful in the diagnostic setting, improving lesion characterization [22-25] in noncalcified lesions compared with conventional mammography.

A prospective study of 166 patients with breast cancer compared digital mammography (DM) to combined DM plus DBT for accuracy of local tumor staging. They demonstrated better accuracy of DM plus DBT for detecting additional ipsilateral and contralateral disease in patients with nondense breasts [26]. A retrospective study of 222 cancers demonstrated that pathologic response to NAC was less likely with the baseline mammographic finding of spiculation [27].

Because of the presence of dense tissue in up to 50% of patients, obscured margins may limit evaluation of the extent of disease [28]. Therefore, mammography or DBT is most often combined with other modalities, such as US or MRI, to guide clinical management.

### FDG-PET/CT Skull Base to Mid-Thigh

Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT has a low sensitivity for detection of primary breast cancer because of the low spatial resolution of the scanners and the relatively low FDG uptake of both invasive lobular cancers and low-grade malignancies [29,30]. As a result, this modality is not routinely used for pretreatment imaging of the primary breast tumor.

### Mammography Diagnostic

Mammography, US, and MRI are complementary modalities for assessing primary tumor size before treatment because they are reliable tools to determine tumor size at diagnosis [1,11-15]. Mammography is most accurate for ductal and low-grade malignancies and less accurate for invasive lobular cancers and higher-grade lesions [11-16].

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Because of the presence of dense tissue in up to 50% of patients, obscured margins may limit evaluation of the extent of disease [28]. Therefore, mammography or DBT is most often combined with other modalities, such as US or MRI, to guide clinical management.

### **MRI Breast Without and With IV Contrast**

MRI is complementary to mammography and US for assessing tumor size before treatment. MRI permits evaluation of a viable tumor before and after NAC by detecting changes in tumor vascularity [31]. There is substantial evidence to support the routine use of contrast-enhanced MRI to stage, monitor early response, and assess for residual and recurrent disease given the overall high sensitivity and relatively high specificity of this technique [1].

Dynamic contrast-enhanced MRI is a sensitive tool to determine extent of disease in the breast, especially in young patients (<50 years of age), with sensitivity approaching 90% and specificity ranging between 50% and 97% [1,32]. To accurately evaluate for response to NAC, a pretreatment MRI must be obtained to serve as a baseline for comparison. MRI is particularly useful in the assessment of multifocal and multicentric disease, which is often underestimated on both mammography and US [28]. In fact, multifocal and multicentric disease are detected in up to 16% of patients on staging MRI according to a study by Houssami et al [33].

A prospective study of 216 patients demonstrated that size determination on MRI was superior to clinical examination in predicting pathologic response both before, during, and after completion of NAC [31]. The enhancement pattern on the pretreatment MRI also indicates how reliable this technique will be in evaluating response. Nonmass enhancement on the pretreatment MRI has been shown to reveal a scattered cell pattern more commonly on posttreatment imaging, thereby making assessment of residual disease more difficult [34]. However, when a mass with well-defined margins is seen, MRI can more accurately predict the amount of residual disease on posttreatment imaging [34]. In addition, several studies have shown that MRI is more accurate than mammography and US in defining disease extent for invasive lobular cancer [32,35,36]. MRI can reliably assess the chest wall because pectoral or intercostal muscle enhancement correlates well with invasion [37]. Finally, several studies have shown that up to 3% of patients have unsuspected contralateral disease at the time of initial diagnosis and MRI has been proven effective in detecting such contralateral disease [38].

### **MRI Breast Without IV Contrast**

A small study of 71 patients with MRI before and after treatment found no significant difference in lesion size interpretation on unenhanced versus enhanced MRI sequences [39].

However, there is insufficient literature to support the use of MRI without intravenous (IV) contrast in initial imaging evaluation of tumor size and extent in the breast before NAC.

### **Sestamibi MBI**

A few institutions routinely image newly diagnosed breast cancer with molecular breast imaging (MBI) using Tc-99m sestamibi, which is also sometimes referred to as scintimammography. This functional imaging technique reflects cell metabolism by accumulating in active mitochondrial cells.

A prospective study of 90 patients found the longest dimension of the cancer measured on MRI was within 1 cm of that on MBI in 72% of cases and concluded that MBI may be an option for patients with contraindication to MRI [40,41].

However, there is insufficient literature to support the routine use of sestamibi MBI in initial imaging evaluation of tumor size and extent in the breast before NAC.

### **US Breast**

Mammography, US, and MRI are complementary modalities for assessing primary tumor size before treatment because they are reliable tools to determine tumor size at diagnosis [1,11-15]. US is more accurate in measuring tumor size than clinical breast examination or mammography. It is most often performed in conjunction with mammography and is more accurate in assessing tumor size [16,42].

**Variant 2: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Imaging of the breast after initiation or completion of neoadjuvant chemotherapy. Initial imaging.**

### **Digital Breast Tomosynthesis Diagnostic**

Although mammography, DBT, and US are reliable for determining tumor size at diagnosis [11-15], changes within the tumor secondary to NAC may be difficult to evaluate after treatment is initiated. It is well known that tumoral changes related to necrosis, fragmentation, and fibrosis make it difficult for mammography, DBT, and US to accurately determine residual tumor burden [43,44].

In a retrospective study of 445 patients who underwent NAC, mammography was 94% sensitive and 50% specific for predicting residual disease in the breast. In cases presenting as mass lesions, 95% of masses decreased in mammographic size with treatment. However, there was correlation between mammographic size and surgical pathology in only 60% of cases [45]. One study found that if >50% of the margin of the primary lesion was mammographically visible at baseline, posttreatment mammographic imaging was a reliable tool for determining lesion size [28,46]. In a study of 56 patients, mammography was 79% sensitive and 77% specific in predicting residual disease after therapy, performing better than clinical breast examination [47].

The extent of calcifications on mammography after therapy does not correlate well with residual tumor burden and is overestimated in up to 45% of patients [48-50]. Therefore, it is not a reliable marker of remaining viable tumor. In a study including 139 patients with baseline mammographic calcifications, residual calcifications were present on all posttreatment mammograms [45]. Estrogen receptor (ER)-positive tumors are more likely than ER-negative tumors to have residual malignant calcifications on mammography after treatment, whereas triple-negative tumors are the least likely to have residual malignant calcifications after therapy, suggesting that different tumor subtypes may warrant different approaches [48,51].

There is no relevant literature specifically comparing the performance of DBT to mammography after initiation or completion of NAC.

### **FDG-PET/CT Skull Base to Mid-Thigh**

Because of its relatively low specificity, PET/CT is not routinely used for posttreatment imaging of the primary breast tumor and is typically only used in combination with other imaging modalities to monitor treatment response [52-54]. Two meta-analyses found posttreatment PET/CT sensitivities of 77% to 84% and specificities of 66% to 78% for predicting response to therapy [52,54]. In a study by Bassa et al [55], PET was able to accurately predict residual disease in only 75% of cases, compared with 88% for US. However, PET may have use in assessing early response to therapy, with a study in 47 patients showing that a >50% to 60% reduction in FDG uptake after one cycle of therapy correlated with a pCR [56].

PET imaging may be more helpful for certain tumor subtypes. Three studies showed that PET/CT can reliably detect early response and predict residual disease in HER2/neu-positive tumors [57-59], and a <42% decrease in radioisotope uptake in triple-negative tumors correlates with poor response and outcome [60]. Lobular cancers are less FDG avid, making assessment challenging [61,62].

### **Mammography Diagnostic**

Although mammography and US are reliable for determining tumor size at diagnosis [11-15], changes within the tumor, secondary to NAC, may be difficult to evaluate after treatment is initiated. It is well known that tumoral changes related to necrosis, fragmentation, and fibrosis make it difficult for mammography, DBT, and US to accurately determine residual tumor burden [43,44].

In a retrospective study of 445 patients who underwent NAC, mammography was 94% sensitive and 50% specific for predicting residual disease in the breast. In cases presenting as mass lesions, most masses (95%) decreased in mammographic size with treatment. However, there was correlation between mammographic size and surgical pathology in only 60% of cases [45]. One study found that if >50% of the margin of the primary lesion was mammographically visible at baseline, posttreatment mammographic imaging was a reliable tool for determining lesion size [28,46]. In a study of 56 patients, mammography was 79% sensitive and 77% specific in predicting residual disease after therapy, performing better than clinical breast examination [47].

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There is no relevant literature specifically comparing the performance of DBT to mammography after initiation of completion of NAC.

### **MRI Breast Without and With IV Contrast**

MRI is a functional imaging technique that permits evaluation of a viable tumor before and after NAC by detecting changes in tumor vascularity [31]. There is substantial evidence to support the routine use of MRI to stage, monitor early response, and assess for residual and recurrent disease, given the overall high sensitivity and relatively high specificity of this technique [1]. However, MRI can overestimate as well as underestimate the amount of residual tumor after completion of therapy.

Multiple studies show that dynamic contrast-enhanced MRI is the optimal imaging tool to determine disease response, with sensitivity approaching 90%, specificity ranging from 60 to 100%, and an accuracy of approximately 91% [31,32,35,36,43,63-66]. MRI is particularly helpful in patients with documented multifocal and multicentric tumors on the pretreatment study, despite the fact that MRI underestimates disease extent in up to 18% of cases [67,68]. However, there is a lack of consensus in the literature on the optimal imaging interval to assess response to therapy.

Tumor measurements on MRI more accurately predict residual tumor and pathologic response than clinical assessment, a finding corroborated in several studies [69-71], with volume measurements performing better than tumor diameter early in treatment after the first cycle of chemotherapy [31]. In a prospective clinical trial of 138 patients, longest diameter on posttreatment MRI was superior to both mammography and clinical breast examination in detecting residual disease. MRI tumor volume was also shown to predict recurrence free survival in a trial of 162 patients [72]. The ability of MRI to evaluate disease response is variable on the basis of tumor subtype, being more effective for invasive lobular carcinoma, triple-negative, and HER2/neu-positive tumors and less accurate for luminal subtypes (ER and/or progesterone receptor positive, HER2/neu-positive or negative), with an overall accuracy of approximately 75% [73-81].

A study of 208 patients suggested that patients who can safely consider breast conservation therapy after NAC have tumors <3 cm in maximal size on pretreatment MRI, reduction in tumor size on posttreatment MRI, and more often have HER2/neu-positive or triple-negative tumors [67,82]. When the tumor presents as diffuse nonmass enhancement on the pretreatment MRI or is of low nuclear grade, MRI is less helpful in assessing response to therapy [83]. In addition, tumors presenting initially as nonmass enhancement more likely presented as scattered foci within an area of fibrosis on posttreatment MRI, making prediction of residual disease challenging [34,84]. Finally, there is some evidence that certain chemotherapeutic agents, such as ER modulators, antiangiogenic agents, and taxane-based therapies, may alter perfusion to the breasts, limiting the ability of MRI to accurately predict residual tumor after chemotherapy, most often leading to disease underestimation [85,86].

Studies demonstrate that adding diffusion-weighted imaging helps predict response for some tumor subtypes. In a retrospective study of 354 patients, adding diffusion-weighted imaging to tumor volume helped predict response in hormone receptor positive and triple negative breast cancers [87]. A prospective randomized trial of 272 patients with tumor size  $\geq 2.5$  cm demonstrated that a change in the apparent diffusion coefficient at midtreatment MRI predicted response [88]. Three studies showed the routine use of diffusion-weighted imaging allowed early differentiation between responders and nonresponders, thereby allowing for tailoring of chemotherapy [89-93]. A separate study revealed that a low apparent diffusion coefficient before treatment predicted response [94].

### **MRI Breast Without IV Contrast**

A small study of 71 patients with MRI before and after treatment found no significant difference in lesion size interpretation on unenhanced versus enhanced MRI sequences [39].

However, there is insufficient literature to support the use of MRI without IV contrast of the breast in initial imaging evaluation of tumor size and extent in the breast after initiation or completion of chemotherapy.

### **Sestamibi MBI**

In a study of 20 patients who underwent imaging with Tc-99m sestamibi, reduction in tumor size correlated reliably with size on MRI, but tumor to background ratio after chemotherapy did not correlate with treatment response [95].



A small study of 62 patients also showed that high uptake after chemotherapy predicts poor survival [96]. In one study of 122 patients, breast-specific gamma imaging had sensitivity of 74% and specificity of 72% for detection of residual tumor after chemotherapy, but it underestimated the amount of residual disease for tumors of luminal subtype [97]. In a small study of 49 patients with locally advanced breast cancer, MBI did not accurately predict response to therapy [98].

In a prospective study of 90 patients, posttreatment MBI had a higher false-negative rate than MRI (41% versus 18%) for predicting pathologic response [41]. A retrospective study of 114 patients demonstrated that posttreatment MBI had a lower sensitivity than MRI for detecting residual tumor (70% versus 83%). However, MBI was more specific than MRI in determining CR (90% versus 60%) [99].

At present, there is insufficient literature to support the routine use of Sestamibi MBI in imaging of the breast after initiation or completion of NAC.

### **US Breast**

US is a reliable modality for determining tumor size, especially if the residual tumor measures >7 mm [100,101]. A decrease in tumor vascularity does appear to correlate with response [28]. In 2 studies, US predicted residual tumor size accurately in 60% to 80% of patients, compared with 32% to 71% for mammography [102,103]. In a study by Keune et al [104], the absence of residual disease on both mammography and US correlated with a pCR in 80% of patients.

Although pretreatment tumor stiffness as determined by shear-wave elastography has shown strong correlation with response to therapy, there is insufficient data to support its routine use at this time [105,106]. In addition, there is insufficient data to support the routine use of contrast-enhanced US, although some early research suggests that changes in the time-intensity curves may reliably predict response to therapy [107,108].

**Variant 3: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-negative. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging.**

### **Digital Breast Tomosynthesis Diagnostic**

There is no relevant literature to support the use of DBT in the initial imaging evaluation of the axilla before NAC.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **FDG-PET/CT Skull Base to Mid-Thigh**

FDG-PET/CT is not routinely used for initial imaging of the clinically node-negative axilla before NAC because of its low sensitivity and specificity for detecting nodal disease [4].

In several studies on detection of nodal disease, including a multicenter study of 360 patients, PET had disparate sensitivities (43%-79%) and specificities (66%-93%), possibly related to differences in tumor size in patient populations [109,110]. Given these limitations, surgical sampling of the axillary nodes remains the standard of care. However, when an FDG-avid axillary node is seen on a pretreatment PET/CT scan, this is highly predictive of metastasis [111].

### **Mammography Diagnostic**

There is no relevant literature to support the use of diagnostic mammography in initial imaging evaluation of the axilla before NAC.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **MRI Breast Without and With IV Contrast**

There is robust evidence to support MRI for determining the extent of disease in the breast, both before and after NAC [1,4,31,32,35,36,43,63-66]. Although the axillary lymph nodes are included on MRI, it is only moderately sensitive for the detection of axillary nodal metastasis before and after therapy [4,112,113]. Therefore, MRI is not typically obtained solely for the purpose of staging the clinically node-negative axilla before NAC [4].

Although breast MRI can identify stage I–III and internal mammary lymph nodes, it is only moderately sensitive for detection of nodal metastases [113]. In a prospective trial of stage I–III breast cancer patients undergoing NAC, MRI was only 65% sensitive for predicting metastases before therapy [113]. A prospective study of 45 patients found pretreatment MRI to be 97% sensitive and 50% specific in predicting axillary lymph biopsy results [114].

### **MRI Breast Without IV Contrast**

There is no relevant literature to support the use of MRI breast without IV contrast in initial imaging evaluation of the axilla before NAC.

### **US Axilla**

Current National Comprehensive Cancer Network practice guidelines recommend considering axillary US and possible biopsy before starting NAC, even in clinically node-negative patients [115,116]. Assessment of the axilla before and after NAC with US can help guide surgical management. US permits routine visualization of stage I and II nodes. By identifying subclinical metastases in clinically node-negative patients, US-guided fine-needle aspiration (FNA) or core needle biopsy (CNB) may select patients who require axillary lymph node dissection [116]. However, a study of 402 patients with a clinically negative axilla demonstrated that half of patients with abnormal lymph nodes on pretreatment imaging did not require axillary lymph node dissection [116]. Therefore, pretreatment imaging of the axilla in clinically node-negative patients remains controversial [4].

### **US-Guided Core Biopsy Axillary Node**

There is no evidence to support US-guided sampling as the initial imaging test for axillary lymph node evaluation.

However, US-guided axillary lymph node sampling is typically the next study performed when axillary imaging is suspicious for metastatic disease. Overall, US-guided biopsy offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy, because the completion of axillary surgery is typically performed after therapy [2,117].

### **US-Guided Fine Needle Aspiration Biopsy Axillary Node**

There is no evidence to support US-guided sampling as the initial imaging test for axillary lymph node evaluation.

However, US-guided axillary lymph node sampling is typically the next study performed when axillary imaging is suspicious for metastatic disease. Overall, US-guided FNA offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy, because the completion of axillary surgery is typically performed after therapy [2,117].

**Variant 4: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-positive. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging.**

### **Digital Breast Tomosynthesis Diagnostic**

There is no relevant literature to support the use of DBT in the initial imaging evaluation of the axilla before NAC.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **FDG-PET/CT Skull Base to Mid-Thigh**

FDG-PET/CT may be useful for staging and restaging clinically node-positive patients undergoing NAC [4]. In node-positive patients, the decrease in standardized uptake value from pre- to posttreatment scans can be used to monitor response and help predict pCR [116]. This possibly may lead to less aggressive axillary surgery upon completion of chemotherapy rather than complete lymph node dissection [118].

In several studies on detection of nodal disease, including a multicenter study of 360 patients, PET had disparate sensitivities (43%-79%) and specificities (66%-93%), possibly related to differences in tumor size in patient populations [109,110]. Given these limitations, surgical sampling of the axillary nodes remains the standard of care. However, when an FDG-avid axillary node is seen on a pretreatment PET/CT scan, this is highly predictive of metastasis [111].

### **Mammography Diagnostic**

There is no relevant literature to support the use of diagnostic mammography in initial imaging evaluation of the axilla before NAC.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **MRI Breast Without and With IV Contrast**

MRI does not always include the entire axilla and is not routinely used solely for evaluation of axillary lymph nodes. However, contrast-enhanced MRI may be useful for monitoring the breast and axillary response in clinically node-positive patients [4].

MRI is only moderately sensitive for detection of axillary nodal metastasis before and after therapy [4,112,113]. Although breast MRI does not always include the entire axilla, it often images stage I–III and internal mammary lymph nodes. In a prospective trial of stage I–III breast cancer patients undergoing NAC, MRI was only 65% sensitive for predicting metastases before therapy [113]. A prospective study of 45 patients found pretreatment MRI to be 97% sensitive and 50% specific in predicting axillary lymph biopsy results [114].

### **MRI Breast Without IV Contrast**

There is no relevant literature to support the use of MRI breast without IV contrast in initial imaging evaluation of the axilla before NAC.

### **US Axilla**

Axillary US is routinely performed for pretreatment evaluation of a clinically positive axilla [4]. Current National Comprehensive Cancer Network practice guidelines recommend axillary US and possible biopsy before starting systemic therapy [115]. US-guided FNA or CNB can confirm and mark metastatic disease. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy because the completion of axillary surgery is typically performed after therapy [2,117]. Placing a biopsy clip to mark the metastatic lymph node before therapy can also help guide the type of axillary restaging surgery following NAC [119].

### **US-Guided Core Biopsy Axillary Node**

There is no evidence to support US-guided sampling as the initial imaging test for axillary lymph node evaluation.

However, US-guided axillary lymph node sampling is typically the next study performed when axillary imaging is suspicious for metastatic disease. Overall, US-guided biopsy offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy, because the completion of axillary surgery is typically performed after therapy [2,117].

### **US-Guided Fine Needle Aspiration Biopsy Axillary Node**

There is no evidence to support US-guided sampling as the initial imaging test for axillary lymph node evaluation.

However, US-guided axillary lymph node sampling is typically the next study performed when axillary imaging is suspicious for metastatic disease. Overall, US-guided FNA offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy, because the completion of axillary surgery is typically performed after therapy [2,117].

**Variant 5: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer, clinically node-negative. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated. Initial imaging.**

### **Digital Breast Tomosynthesis Diagnostic**

There is no relevant literature to support the use of DBT in initial imaging of the axilla after NAC [4].

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **FDG-PET/CT Skull Base to Mid-Thigh**

PET/CT is not routinely used for evaluation of the axilla after NAC as data are limited [4]. In several studies on detection of nodal disease, including a multicenter study of 360 patients, PET had disparate sensitivities (43%-79%) and specificities (66%-93%), possibly related to differences in tumor size in patient populations [109,110]. Given these limitations, this modality is not particularly useful to evaluate the axilla, and surgical sampling of the axillary nodes remains the standard of care. However, when an FDG-avid axillary node is seen on a pretreatment PET/CT scan, this is highly predictive of metastasis [111]. In addition, in node-positive tumors, PET/CT can be used to monitor response and possibly lead to sentinel node biopsy upon completion of chemotherapy rather than full axillary dissection [118].

### **Mammography Diagnostic**

There is no relevant literature to support the use of diagnostic mammography in initial imaging of the axilla after NAC [4].

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **MRI Breast Without and With IV Contrast**

The current literature evaluates performance of posttreatment MRI evaluation of the axilla only in the setting of baseline pretreatment imaging and/or clinically node-positive patients, as described below. These data cannot necessarily be extrapolated to initial imaging after completion of therapy in the absence of pretreatment axillary evaluation.

MRI of the axilla is only 38% to 61% sensitive for detection of residual disease after NAC [112,113]; therefore, surgical sampling is the standard of care [114,120-122]. In a retrospective study of 135 clinically node-positive patients after NAC, MRI had a low negative predictive value (NPV) of 26% for predicting axillary disease when a positive MRI was defined by node >1 cm, cortex >3 mm, loss of hilum, or irregular contour [121]. In a retrospective study of 269 node-positive patients, posttreatment MRI was only 38% sensitive, 76% specific, and 58% accurate in predicting the pathology of the sentinel lymph node (SLN). In a prospective study of 45 patients, 35 of whom were node-positive, there was no association between posttreatment axillary MRI and surgical pathology; MRI had a high false negative rate (46%), low sensitivity (55%), and specificity (63%) [114].

### **MRI Breast Without IV Contrast**

There is no relevant literature to support the use of MRI breast without IV contrast in initial imaging of the axilla after NAC.

### **US Axilla**

US is not typically performed for initial evaluation of the axilla after initiation of NAC, and the current literature does not specifically evaluate this scenario. The literature on posttreatment axillary US predicting residual nodal disease evaluates patients with established node-positive disease before therapy, as described below. These data cannot necessarily be extrapolated to initial imaging after therapy in the absence of pretreatment axillary evaluation. No imaging test can reliably detect residual nodal disease after NAC, and therefore surgical sampling is the standard of care.

In established node-positive patients after therapy, axillary US only demonstrates moderate sensitivity (53%-86%) and specificity (78%) for detecting residual disease with an NPV ranging from 46% to 90% [112,123,124]. Therefore, surgical sampling of axillary lymph nodes after therapy remains the standard of care.

In a retrospective study of 408 clinically node-positive breast cancer patients treated with NAC, the strongest predictor for residual axillary disease was preoperative US showing axillary lymphadenopathy, defined as axial cortical thickness >3.5 mm or loss of the hilum [125]. The prospective clinical Z1071 trial included 611 patients with US after NAC; US features associated with residual disease included increased cortical thickness (mean 3.5 mm), absent hilum, and longer lymph node diameter [126].

### **US-Guided Core Biopsy Axillary Node**

There is no relevant literature to support the use of US-guided core biopsy of axillary nodes in initial imaging of the axilla after completion of NAC.

### **US-Guided Fine Needle Aspiration Biopsy Axillary Node**

There is no relevant literature to support the use of US-guided FNA of axillary nodes in initial imaging of the axilla after completion of NAC.

**Variant 6: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer with clinical suspicion of metastatic disease. Staging or assessment of response to neoadjuvant chemotherapy. Initial imaging.**

#### **Bone Scan Whole Body**

Staging of patients before and after treatment typically entails either 1) FDG-PET/CT skull base to mid-thigh only or 2) bone scan in conjunction with CT chest, abdomen, and pelvis with IV contrast, depending upon institutional preference. There is no evidence to support performing all 3 studies.

Bone scan represents one of the standard imaging tests to stage a patient with newly diagnosed breast cancer, allowing assessment of bony metastasis. PET/CT combines cross-sectional imaging with tumor metabolism and has been shown to be more sensitive and accurate than conventional staging with combined CT and bone scan [127].

#### **CT Chest, Abdomen, and Pelvis With IV Contrast**

Staging of patients before and after treatment typically entails either 1) FDG-PET/CT skull base to mid-thigh only or 2) bone scan in conjunction with CT chest, abdomen, and pelvis with IV contrast, depending upon institutional preference. There is no evidence to support performing all 3 studies. CT with IV contrast is commonly used to stage patients with newly diagnosed, locally advanced, or recurrent breast cancer [128]. PET/CT combines cross-sectional imaging with tumor metabolism and has been shown to be more sensitive and accurate than conventional staging with combined CT and bone scan [127].

#### **CT Chest, Abdomen, and Pelvis Without and With IV Contrast**

There is no relevant literature to support the use of CT chest, abdomen, and pelvis without and with IV contrast in the initial evaluation of metastatic disease.

#### **CT Chest, Abdomen, and Pelvis Without IV Contrast**

There is no relevant literature to support the use of CT chest, abdomen, and pelvis without IV contrast in the initial evaluation of metastatic disease.

#### **FDG-PET/CT Skull Base to Mid-Thigh**

Staging of patients before and after treatment typically entails either 1) FDG-PET/CT skull base to mid-thigh only or 2) bone scan in conjunction with CT chest, abdomen, and pelvis with IV contrast, depending upon institutional preference. There is no evidence to support performing all 3 studies. PET/CT combines cross-sectional imaging with tumor metabolism and has been shown to be more sensitive and accurate than conventional staging with combined CT and bone scan [127].

Staging with PET/CT detects distant metastases with a sensitivity of 50% to 100% and a specificity of 50% to 97% in patients with advanced breast cancers, some of which were occult on conventional CT imaging. In one study by Lee et al, the detection of distant metastases occult on conventional CT imaging led to changes in clinical stage for 52% of women [129]. Given that 8% to 14% of women with locally advanced breast cancer have distant metastatic disease at diagnosis (beyond the axillary nodes), FDG-PET/CT skull base to mid-thigh may be preferred over conventional CT imaging [130]. In addition, several studies have shown FDG-PET/CT to be superior in detecting internal mammary and mediastinal lymphadenopathy [129] but inferior to contrast-enhanced chest CT at detecting pulmonary metastases [130].

Multiple studies show that PET/CT staging is more useful for stage IIIB and operable stage IIIA tumors and specific tumor subtypes including invasive ductal cancers, ER-negative and triple-negative tumors, high-grade malignancies, and those with p53 mutations [131-133]. PET/CT staging is not as useful for low-grade malignancies or invasive lobular cancers because of the overall low isotope uptake [134].

#### **MRI Chest, Abdomen, Pelvis Without and With IV Contrast**

There is no relevant literature to support the use of MRI chest, abdomen, and pelvis without and with IV contrast in the initial evaluation of metastatic disease.

### **MRI Chest, Abdomen, Pelvis Without IV Contrast**

There is no relevant literature to support the use of MRI chest, abdomen, and pelvis without IV contrast in the initial evaluation of metastatic disease.

**Variant 7: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known axillary lymph node-positive breast cancer on prior mammography, US, or MRI. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla previously evaluated. Next imaging study.**

### **Digital Breast Tomosynthesis Diagnostic**

Although many patients undergo mammography or DBT after NAC, there is no specific evidence supporting its use in the imaging of known axillary lymph node-positive breast cancer after completion of therapy. The axilla is incompletely visualized on the mediolateral and lateral projections, thereby limiting the use of these modalities to reliably detect residual disease.

### **FDG-PET/CT Skull Base to Mid-Thigh**

PET/CT is not routinely used to evaluate the axilla after completion of NAC. Although a few studies suggest that PET can reliably predict the response of axillary nodes early in treatment, a majority of studies show that PET has low sensitivity (63%) for detection of residual disease after NAC [112,135]. No imaging test can reliably detect residual nodal disease after NAC, and therefore surgical sampling is the standard of care.

### **Mammography Diagnostic**

Although many patients undergo mammography or DBT after NAC, there is no specific evidence supporting its use in the imaging of known axillary lymph node-positive breast cancer after completion of therapy [4]. The axilla is incompletely visualized on the mediolateral and lateral projections, thereby limiting the use of these modalities to reliably detect residual disease.

### **MRI Breast Without and With IV Contrast**

MRI is not routinely used for evaluation of the axilla after completion of NAC because it is only 38% to 61% sensitive for detecting residual axillary disease [112-114,120-122]. No imaging test can reliably detect residual nodal disease after NAC, and therefore surgical sampling is the standard of care.

Use of MRI for restaging the axilla in clinically node-positive patients is questionable [4]. In a retrospective study of 135 clinically node-positive patients who underwent NAC, MRI evaluation of the axilla after treatment had a low NPV (26%) and therefore could not predict residual axillary disease when a positive MRI of the axilla was defined as node >1 cm, cortex >3 mm, loss of hilum, or irregular contour [121]. In a retrospective study of 269 node-positive patients, postchemotherapy MRI was only 38% sensitive, 76% specific, and 58% accurate in predicting the pathology result of the SLN. In a prospective study of 45 patients, 35 of whom were node-positive, there was no association between posttreatment axillary MRI findings and surgical pathology; MRI had a high false negative rate (46%), low sensitivity (55%), and specificity (63%) [114].

### **MRI Breast Without IV Contrast**

There is no relevant literature to support the use of MRI breast without IV contrast in the imaging of known axillary lymph node-positive breast cancer after completion of NAC.

### **US Axilla**

If the axilla is imaged after NAC, US is the most useful imaging modality, although it only demonstrates moderate sensitivity (53%-86%) and specificity (78%) for detecting residual disease [112,124]. Therefore, surgical sampling of axillary lymph nodes after therapy remains the standard of care. US permits image-guided localization of the clipped metastatic axillary lymph node if the patient is undergoing sentinel node biopsy with surgical excision of the clipped node.

The axilla is most commonly imaged after NAC in patients with a clinically positive axilla before therapy [4]. In a retrospective study of 408 clinically node-positive breast cancer patients treated with NAC, the strongest predictor of residual axillary disease was posttreatment US showing axillary lymphadenopathy, defined as axial cortical thickness >3.5 mm or loss of the hilum [125]. The prospective clinical Z1071 trial included 611 patients with US after NAC, 238 of whom had axillary CR. US features associated with residual disease included increased cortical thickness (mean 3.5 mm), absent hilum, and longer lymph node diameter [126].

## **US Breast**

There is no relevant literature to support the use of breast US alone in the evaluation of known axillary lymph node-positive disease after completion of NAC. However, some studies have shown a correlation between pCR in the breast and the axilla [136].

### **US-Guided Core Biopsy Axillary Node**

There is no relevant literature to support the use of US-guided core biopsy of the axillary node in imaging of known axillary lymph node-positive breast cancer after completion of NAC. No imaging test can reliably detect residual nodal disease after NAC; therefore, surgical intervention (either sentinel node biopsy or axillary dissection) is necessary after completion of treatment, provided the patient demonstrated a PR or CR warranting surgery and did not undergo axillary surgery before treatment [112,137].

Some centers place a clip in the biopsied positive axillary node before treatment so that it can be surgically excised along with the sentinel node(s) after completion of the NAC; this procedure is sometimes referred to as targeted axillary dissection [138]. US-guided localization of the clipped lymph node can be performed preoperatively [139]. Excising the clipped lymph node and SLN(s) decreases the false-negative rate of SLN biopsy (SLNB) [140]. In a study of 31 patients, 11 patients had residual axillary disease, and, in all cases, the clipped lymph node was positive [141]. In a prospective study of 23 patients with clipped axillary metastases before NAC, the surgeon retrieved the clipped node in 22 cases, and the SLN was retrieved in only 19. The clipped node was the SLN in only 14 cases (61%). The NPV was 100% for removal of clipped and sentinel node but only 85% for SLN removal alone [119].

### **US-Guided Fine Needle Aspiration Biopsy Axillary Node**

There is no relevant literature to support the use of US-guided FNA of the axillary node in imaging of known axillary lymph node-positive breast cancer after completion of NAC. No imaging test can reliably detect residual nodal disease after NAC; therefore, surgical intervention (either sentinel node biopsy or axillary dissection) is necessary after completion of neoadjuvant treatment, provided the patient demonstrated a PR or CR warranting surgery and did not undergo axillary surgery before treatment [112,137].

Some centers place a clip in the biopsied positive axillary node before treatment so that it can be surgically excised along with the sentinel node(s) after completion of the NAC; this procedure is sometimes referred to as targeted axillary dissection [138]. US-guided localization of the clipped lymph node can be performed preoperatively [139]. Excising the clipped lymph node and SLN(s) decreases the false-negative rate of SLNB [140]. In a study of 31 patients, 11 patients had residual axillary disease, and, in all cases, the clipped lymph node was positive [141]. In a prospective study of 23 patients with clipped axillary metastases before NAC, the surgeon retrieved the clipped node in 22 cases, and the SLN was retrieved in only 19. The clipped node was the SLN in only 14 cases (61%). The NPV was 100% for removal of clipped and sentinel node but only 85% for SLN removal alone [119].

**Variant 8: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Known breast cancer. Axillary imaging suspicious for metastatic disease on mammography, US, or MRI during initial evaluation. Next imaging study.**

### **Digital Breast Tomosynthesis Diagnostic**

There is no relevant literature to support the use of DBT in further evaluation of axillary imaging suspicious for metastatic disease.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **Mammography Diagnostic**

There is no relevant literature to support the use of diagnostic mammography in further evaluation of axillary imaging suspicious for metastatic disease.

Mammography or DBT is performed for initial diagnosis of the primary breast cancer. This procedure incompletely images the axilla, although pathologically enlarged stage I and II nodes may be included on the lateral and mediolateral oblique projections.

### **MRI Breast Without and With IV Contrast**

There is no relevant literature to support the use of MRI breast with IV contrast in the further evaluation of axillary imaging suspicious for metastatic disease.

There is robust evidence to support MRI for determining extent of disease in the breast, both before and after NAC [1,4,31,32,35,36,43,63-66]. Although the axillary lymph nodes are included on MRI, it is only moderately sensitive for detection of axillary nodal metastasis before and after therapy [4,112,113].

### **MRI Breast Without IV Contrast**

There is no relevant literature to support the use of MRI breast without IV contrast in the further evaluation of imaging suspicious for metastatic disease.

### **US-Guided Core Biopsy Axillary Node**

US-guided axillary lymph node sampling is the most useful next study performed when axillary imaging is suspicious for metastatic disease [4]. Sampling of abnormal-appearing nodes by CNB is typically performed using a 14- to 18-gauge device. Some centers place a clip in the biopsied node to facilitate future image-guided localization of the lymph node at surgical excision after completion of NAC.

US-guided CNB has proven high specificity, with a moderate to high sensitivity in the detection of metastatic lymph nodes. Houssami et al [33] published a meta-analysis of 2,874 FNA and CNB procedures and found a pooled sensitivity of 80%, a specificity of 98%, and a positive predictive value of 97%. Another meta-analysis of 1,353 patients undergoing axillary lymph node biopsy to detect metastases showed that both CNB and FNA procedures performed well, with sensitivities of 74% and 88%, respectively, and a specificity of 100% for both procedures. Complication rates with US-guided biopsies were low, although slightly higher for CNB when compared with FNA (7% versus 1%, respectively), and most commonly included pain, hematoma, and bruising [142].

Some centers place a clip in the biopsied positive axillary node before treatment so that it can be surgically excised along with the sentinel node(s) after completion of the NAC; this procedure is sometimes referred to as targeted axillary dissection [138]. US-guided localization of the clipped lymph node can be performed preoperatively [139]. Excising the clipped lymph node and SLNs decreases the false-negative rate of SLNB [26]. In a study of 31 patients, 11 patients had residual axillary disease, and, in all cases, the clipped lymph node was positive [141]. In a prospective study of 23 patients with clipped axillary metastases before NAC, the surgeon retrieved the clipped node in 22 cases, and the SLN was retrieved in only 19. The clipped node was the SLN in only 14 cases (61%). The NPV was 100% for removal of clipped and sentinel nodes but only 85% for SLN removal alone [119].

Overall, US-guided biopsy offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy because the completion of axillary surgery is typically performed after therapy [2,117].

### **US-Guided Fine Needle Aspiration Biopsy Axillary Node**

US-guided axillary lymph node sampling is the most useful next study performed when axillary imaging is suspicious for metastatic disease [4]. Sampling of abnormal-appearing lymph nodes by US-guided FNA is frequently performed with a 22- or 25-gauge needle and also requires the availability of skilled cytopathologists. False-negative rates are low (<2%) in experienced hands but may occur, especially with smaller metastatic deposits [143]. Some centers place a clip in the biopsied node to facilitate future image-guided localization of the lymph node at surgical excision after completion of NAC.

US-guided axillary FNA has proven high specificity, with a moderate to high sensitivity in the detection of metastatic lymph nodes. A retrospective study of 65 patients compared US-guided FNA results to final surgical pathology in patients with radiographically suspicious lymph nodes and demonstrated high sensitivity, specificity, and positive predictive value (89%, 100% and 100%, respectively) for FNA [144]. A larger meta-analysis of 1,353 patients undergoing axillary lymph node biopsy to detect metastases showed that both FNA and CNB performed well, with sensitivities of 74% and 88%, respectively, and a specificity of 100% for both procedures. Complication rates for FNA were lower than CNB (1% versus 7%, respectively) and were most commonly pain, hematoma, and bruising [142]. Additionally, one prospective study of combined axillary US and FNA in 315 patients with sonographically positive lymph nodes again demonstrated high sensitivity (81%), specificity (100%), and positive predictive value (100%). However, the NPV was low (50%), supporting the need for definitive surgical sampling [145].

Some centers place a clip in the biopsied positive axillary node before treatment so that it can be surgically excised along with the sentinel node(s) after completion of the NAC; this procedure is sometimes referred to as targeted



axillary dissection [138]. US-guided localization of the clipped lymph node can be performed preoperatively [139]. Excising the clipped lymph node and SLNs decreases the false-negative rate of SLNB [26]. In a study of 31 patients, 11 patients had residual axillary disease, and, in all cases, the clipped lymph node was positive [141]. In a prospective study of 23 patients with clipped axillary metastases before NAC, the surgeon retrieved the clipped node in 22 cases, and the SLN was retrieved in only 19. The clipped node was the SLN in only 14 cases (61%). The NPV was 100% for removal of clipped and sentinel node but only 85% for SLN removal alone [119].

Overall, US-guided biopsy offers a minimally invasive option to obtain histopathologic proof of axillary nodal involvement for suspicious findings, although a negative biopsy does not reliably exclude metastatic disease, and therefore surgical pathology remains the reference standard. When US-guided biopsy confirms metastatic disease in pathologic-appearing nodes, it can obviate the need for pretreatment sentinel node biopsy because the completion of axillary surgery is typically performed after completion of therapy [2,117].

### Summary of Recommendations

- **Variant 1:** US breast, DBT diagnostic, mammography diagnostic, and MRI breast without and with IV contrast are usually appropriate for the initial imaging of patients with known breast cancer for initial determination of tumor size and extent within the breast before NAC. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously in which each procedure provides unique clinical information to effectively manage the patient's care).
- **Variant 2:** US breast, DBT, mammography diagnostic, and MRI breast without and with IV contrast are usually appropriate for the initial imaging of patients with known breast cancer for imaging of the breast after initiation or completion of NAC. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously in which each procedure provides unique clinical information to effectively manage the patient's care).
- **Variant 3:** US axilla is usually appropriate for the initial imaging of patients with known breast cancer, clinically node-negative, for axillary evaluation before NAC.
- **Variant 4:** US axilla is usually appropriate for the initial imaging of patients with known breast cancer, clinically node-positive, for axillary evaluation before NAC.
- **Variant 5:** Imaging is usually not appropriate for the initial imaging of patients with known breast cancer, clinically node-negative, for axillary evaluation after completion of NAC when the axilla was not previously evaluated.
- **Variant 6:** Bone scan whole body in conjunction with CT chest abdomen pelvis with IV contrast is usually appropriate for the initial imaging of patients with known breast cancer with clinical suspicion of metastatic disease for staging or assessment of response to NAC. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously in which each procedure provides unique clinical information to effectively manage the patient's care). FDG-PET/CT is an equivalent alternative to these procedures for this clinical scenario (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 7:** US axilla is usually appropriate as the next imaging study for patient with known axillary lymph node-positive breast cancer on prior mammography, US, or MRI for axillary evaluation after completion of NAC when the axilla was previously evaluated.
- **Variant 8:** US-guided core biopsy axillary node or US-guided FNA biopsy axillary node are usually appropriate as the next imaging study for patients with known breast cancer in which axillary imaging was suspicious for metastatic disease on mammography, US, or MRI during initial evaluation. These are equivalent procedures for this clinical scenario (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

### Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

### Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

### Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document [146].

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."		

## References

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.