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

Variant 1: **Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	9	Mammography or DBT is most often combined with other modalities (US and/or MRI). See references [6,10,26,27].	☢ ☢
Digital breast tomosynthesis diagnostic	9	DBT is equivalent to mammography and is most often combined with US.	☢ ☢
US breast	9	Use this procedure if cancer is mammographically occult. This procedure is often performed in conjunction with mammography/DBT. See references [26-29].	O
MRI breast without and with IV contrast	9	This procedure is good for evaluation of multicentric/multifocal disease, especially in dense breasts. In order to evaluate response to neoadjuvant chemotherapy, a pretreatment MRI must be performed as a baseline for comparison. See references [1,20,27,30,31,33,37].	O
Tc-99m sestamibi MBI	2	See references [38-42].	☢ ☢ ☢
MRI breast without IV contrast	1		O
FDG-PET/CT whole body	1	The primary benefit of this procedure is evaluating systemic disease.	☢ ☢ ☢ ☢
FDG-PEM	1		☢ ☢ ☢ ☢
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**			***Relative Radiation Level**

Variant 2: **Imaging of the breast after initiation or completion of neoadjuvant chemotherapy. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
MRI breast without and with IV contrast	9	This procedure requires a prechemotherapy MRI to be performed. See references 1,20,30,34,35,43,56-91].	O
US breast	8	This is a reliable modality to determine tumor size, especially if the residual tumor is >7 mm. This procedure is most helpful when documented on US prior to neoadjuvant therapy. See references [7,27,49-55].	O
Mammography diagnostic	7	This procedure is used for masses well seen on pretreatment mammogram. Mammography and DBT are better than clinical breast examination for evaluation of residual disease, but assessing response may be challenging post chemotherapy because changes in many tumors can be variable. See references [27,43-48].	☢☢
Digital breast tomosynthesis diagnostic	7	This procedure is an alternative to mammography.	☢☢
Tc-99m sestamibi MBI	2	See references [3,92-103].	☢☢☢
MRI breast without IV contrast	1		O
FDG-PET/CT whole body	1	Because of their relatively low specificity, PET and PET/CT should be used only in combination with other imaging modalities. This procedure is especially helpful if metastatic disease is seen on baseline PET or if progression of local disease is present. This procedure is not routinely done for the initial evaluation of the breast. See references [95-104].	☢☢☢☢
FDG-PEM	1		☢☢☢☢
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**			***Relative Radiation Level**

Variant 3: **Known breast cancer. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
US breast	9	This procedure is the modality of choice for imaging of the axilla. However, it does not replace surgical staging. See references [2,105,106].	O
MRI breast without and with IV contrast	5	MRI provides better visualization of level III and interpectoral nodes. If suspicious, they are typically biopsied under US. See reference [109].	O
FDG-PET/CT whole body	3	This procedure may provide better visualization of level III and interpectoral nodes. Its main benefit is systemic disease evaluation. See references [110-113].	☢☢☢☢
Mammography diagnostic	1	This procedure is part of the preliminary workup and is not routinely done for evaluation of the axilla.	☢☢
Digital breast tomosynthesis diagnostic	1	This procedure is part of the preliminary workup and is not routinely done for evaluation of the axilla.	☢☢
MRI breast without IV contrast	1		O
Image-guided fine needle aspiration breast	1	This procedure is not an initial imaging examination. See references [114-116].	Varies
Image-guided core biopsy breast	1	This procedure is not an initial imaging examination. See references [114-116].	Varies
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

Variant 4: **Known breast cancer. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
US breast	8	This procedure may be useful for detection of residual axillary nodal disease. See references [23-25].	O
MRI breast without and with IV contrast	4	This procedure may provide better visualization of level 3 and interpectoral nodes. See references [25,109].	O
Mammography diagnostic	2	Routine imaging of the axilla may not be indicated after neoadjuvant chemotherapy.	☢☢
Digital breast tomosynthesis diagnostic	2		☢☢
FDG-PET/CT whole body	2	See references [25,11].	☢☢☢☢
MRI breast without IV contrast	1		O
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

Variant 5: **Known breast cancer with clinical suspicion of metastatic disease. Staging or assessment of response to neoadjuvant chemotherapy. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
Tc-99m bone scan whole body	9		☢☢☢
FDG-PET/CT whole body	9	This procedure may be preferable to conventional CT chest, abdomen, and pelvis imaging in specific settings. It is an alternative to CT and bone scan to be done routinely if greater than stage IIIA disease is present. It is superior in detecting internal mammary and mediastinal lymphadenopathy; it is not useful for invasive lobular carcinoma or low-grade malignancy. See references [39,40,122-127].	☢☢☢☢
CT chest abdomen pelvis with IV contrast	8	This procedure is generally indicated if there is clinical suggestion of distant metastasis.	☢☢☢☢
CT chest abdomen pelvis without and with IV contrast	7	This procedure is generally not needed to do both without and with contrast for staging.	☢☢☢☢
CT chest abdomen pelvis without IV contrast	1	See reference [121].	☢☢☢☢
MRI chest abdomen pelvis without and with IV contrast	1		O
MRI chest abdomen pelvis without IV contrast	1		O
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**			***Relative Radiation Level**

MONITORING RESPONSE TO NEOADJUVANT SYSTEMIC THERAPY FOR BREAST CANCER

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Summary of Literature Review

Introduction/Background

Patients with locally advanced invasive breast cancers (defined as a breast cancer typically >5 cm with regional and/or metastatic involvement or those that involve the skin or chest wall) are often treated with neoadjuvant chemotherapy prior to definitive surgical intervention. Other indications where neoadjuvant therapy is considered include T2 tumors (2–5 cm) where excision by lumpectomy might result in substantial cosmetic defect, triple-negative tumors 2 to 5 cm in size even if node negative, and 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 survival and disease progression for women receiving neoadjuvant versus adjuvant chemotherapy are not substantially different, women who do receive neoadjuvant therapy are less likely to undergo mastectomy and more likely to be treated with breast conservation.

In addition, women who demonstrate a complete pathologic response to neoadjuvant chemotherapy carry improved disease-free survival [1,3]. Therefore, imaging plays a vital role in managing women with locally advanced breast cancer 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 prior to, during, and following completion of initial therapy including the axilla and potential distant metastatic sites.

Overview of Imaging Modalities

Accurate assessment of tumor burden is critical in determining the best management for women presenting with locally advanced breast cancer. Assessment of tumor size and response to treatment can vary depending on the modality used, the measurement technique (such as single longest diameter, 3-D measurements, or calculated tumor volume), and varied response of different tumor subtypes to neoadjuvant chemotherapy (such as concentric shrinkage or tumor fragmentation). Most practices define response per the Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST 1, which defines complete response (CR) as disappearance of the tumor in its entirety following treatment, partial response (PR) as at least a 30% decrease in the longest diameter of the tumor as compared to the pretreatment measurement, progression of disease as at least a 20% increase in the longest diameter as compared to the baseline measurement, and stable disease as no change in tumor size that would qualify as PR or progression of disease based on the tumor's longest diameter [4]. Pathologic CR represents a surrogate end point for treatment.

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 [5]. Although mammography and ultrasound (US) are reliable tools to determine tumor size at diagnosis [6-10], changes within the tumor secondary to neoadjuvant chemotherapy may be difficult to evaluate. Digital breast tomosynthesis (DBT) can

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address some of the limitations encountered with standard mammographic views. In addition to planar images, DBT allows for creation and viewing of thin-section reconstructed images that may decrease the lesion-masking effect of overlapping normal tissue and reveal the true nature of potential false-positive findings. Some authors found the advantages of DBT to be especially pronounced in women under age 50 years [11,12], in those with dense breasts [11,13], and with lesion types including spiculated masses [14] and asymmetries [15]. DBT can be useful in the diagnostic setting as well, improving lesion characterization [16-19] in noncalcified lesions when compared to conventional mammographic workup. Overall, conventional tools, such as clinical breast examination, mammography, DBT, and US, have limitations in monitoring treatment response.

Therefore, functional imaging techniques, such as magnetic resonance imaging (MRI) and molecular breast imaging (MBI), that permit evaluation of residual viable tumor following neoadjuvant chemotherapy by detecting changes in tumor vascularity and metabolism are useful tools in evaluating the patient during and after completion of chemotherapy [20]. In particular, 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 at times overestimate as well as underestimate the amount of residual tumor after completion of neoadjuvant chemotherapy. On the other hand, MBI represents a diverse, metabolically based approach ranging from technetium Tc-99m sestamibi to positron emission tomography (PET)/positron emission mammography (PEM), with growing evidence of the pros and cons of these tools in the neoadjuvant setting. As none of the current imaging modalities is entirely accurate in determining pathologic CR, surgical excision of the area of biopsy-proven malignancy following completion of neoadjuvant chemotherapy remains indicated. However, the key role of imaging is to guide management because a lack of response on imaging often leads to modifications in the chemotherapeutic regimen [21].

Furthermore, as nearly 70% of women with locally advanced breast cancers are likely to have metastatic disease at diagnosis, imaging of the axilla is essential [22]. Assessment of the axilla prior to and following neoadjuvant therapy with US can help guide management because preoperative identification of pathologic axillary lymphadenopathy may lead to full axillary node dissection rather than sentinel lymph node biopsy at the time of definitive surgery, although this is somewhat controversial given more recent ongoing trials. US serves as the primary modality for evaluation of the axilla, although the axilla can be seen on cross-sectional studies including computed tomography (CT) and MRI. Image-guided fine-needle aspiration (FNA) and core-needle biopsy offer minimally invasive options to obtain histopathologic proof of axillary nodal involvement, although a negative biopsy does not reliably exclude metastatic disease. If performed, some centers place a clip in the biopsied axillary node so that it is surgically excised after completion of the neoadjuvant therapy. Therefore, patients often undergo sentinel node biopsy, and sometimes full axillary dissection, to determine axillary status, most commonly prior to initiation of any chemotherapy, although a recent study of patients after completion of neoadjuvant chemotherapy showed similar accuracy [23]. No imaging test can reliably detect residual nodal disease after neoadjuvant chemotherapy (reported sensitivities of 69.8%, 61.0%, and 63.2% for US, MRI, and PET/CT, respectively). Therefore, surgical intervention (either sentinel node biopsy or full axillary dissection) is necessary after completion of neoadjuvant treatment, provided the patient demonstrated a PR or CR warranting surgery and did not undergo axillary dissection prior to treatment [24,25]. Sentinel lymph node biopsy after completion of neoadjuvant chemotherapy is associated with a 20.8% false-negative rate, especially if 2 or fewer nodes are removed or the initial tumor was <2.5 cm in size since sentinel lymph node biopsy after completion of neoadjuvant chemotherapy is associated with a 12.6% to 20.8% false-negative rate, especially if 2 or fewer nodes are removed or the initial tumor was <2.5 cm in size [24,26].

Finally, staging of patients prior to and after treatment typically entails a combination of CT of the chest, abdomen, and pelvis and bone scan or PET/CT, most often depending upon institutional preferences.

Discussion of Procedures by Variant

Variant 1: Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy. Initial imaging examination.

Mammography and digital breast tomosynthesis diagnostic

Mammography is one of the 2 main modalities for assessing primary tumor size at diagnosis, being most accurate for ductal malignancies and low-grade malignancies and less accurate for invasive lobular cancers and higher-grade lesions [6-10,27]. DBT can be useful in the diagnostic setting, improving lesion characterization [16-19] in noncalcified lesions when compared to conventional mammographic workup. Because of the presence of dense tissue in up to 50% of women, obscured margins may limit evaluation of the extent of disease [28]. Therefore,

mammography or DBT is most often combined with other modalities, such as physical examination, US, and/or MRI, to guide clinical management.

Ultrasound breast

US is the second main modality used to assess primary tumor size prior to neoadjuvant chemotherapy and 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 for low-grade malignancies and those of ductal subtype [27,29]. However, as US is operator dependent, its accuracy is variable [28]. In a small study of 69 patients, the presence of a single feeding vessel and overall hypovascularity correlated with improved treatment response [30], although typically tumors with more neovascularity are those which are most responsive to neoadjuvant treatment.

Magnetic resonance imaging breast

Dynamic contrast-enhanced MRI is a sensitive tool to determine extent of disease, especially in young women (age <50 years), with sensitivity approaching 90% and specificity ranging between 50% and 97% [1,31]. In order to accurately evaluate for response to neoadjuvant chemotherapy, a pretreatment MRI must be obtained to serve as a baseline for comparison. Ideally, for premenopausal patients, this study should be performed in the first half of the menstrual cycle in order to minimize the background parenchymal enhancement because moderate and marked background enhancement lowers the sensitivity to accurately determine the disease extent [32]. However, in reality, most centers do not delay imaging in a newly diagnosed patient, recognizing that false positives may be increased. MRI is particularly useful in the assessment of multifocal and multicentric disease as this is more often underestimated on both mammography and US [28]. In fact, multifocal and multicentric disease is detected in up to 16% of women [33]. 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 more commonly reveal a scattered cell pattern on post-treatment 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 post-treatment imaging [34]. In addition, several studies have also shown that MRI is more accurate than mammography and US in defining disease extent for invasive lobular cancer [31,35,36]. MRI can reliably assess the chest wall because pectoral or intercostal muscle enhancement correlates well with pectoral muscle or chest wall invasion, respectively [37]. Finally, several studies have shown that up to 3.1% of women have unsuspected contralateral disease at the time of initial diagnosis and MRI has been proven effective in detecting such contralateral disease [38].

Molecular breast imaging

A few institutions routinely image newly diagnosed breast cancer with MBI using Tc-99m sestamibi, showing similar sensitivity and specificity to breast MRI when employing dedicated breast devices [39]. However, there are insufficient data to support its routine use at this time.

FDG-PET and PEM

PET imaging is limited by the spatial resolution of the scanners and by the relatively low fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) uptake of both invasive lobular cancers and low-grade malignancies [40,41]. Therefore, PET imaging is not routinely used for pretreatment imaging for disease within the breast. There are several studies demonstrating that PEM outperforms PET and PET/CT in detecting and determining the extent of primary breast lesions based on a study of 178 women [42]. A study by Berg et al [43] showed that PEM is less sensitive than MRI but had better specificity. At present, there are insufficient data to support its routine use.

Variant 2: Imaging of the breast after initiation or completion of neoadjuvant chemotherapy. Initial imaging examination.

Mammography and digital breast tomosynthesis diagnostic

Although most patients do undergo mammography or DBT and US following treatment, it is well known that the changes in many tumors related to necrosis, fragmentation, and fibrosis make it difficult for mammography, DBT, and US to accurately determine residual tumor burden [44,45]. However, a study by Huber et al showed that if >50% of the margin of the primary lesion is mammographically visible on pretreatment mammography, post-treatment mammographic imaging is a reliable tool for determining lesion size [28,46]. In a study of 56 women who underwent neoadjuvant chemotherapy, mammography was better than clinical breast examination but not reliable in predicting residual disease, with a sensitivity of 79% and specificity of 77% [47]. In addition, the extent of calcifications on mammography following chemotherapy does not correlate well with residual tumor

burden and therefore is not a reliable marker of remaining viable tumor, overestimating residual disease in up to 40% of patients [48,49]. Also, 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 least likely to have residual malignant calcifications following therapy, suggesting that different tumor subtypes may warrant different surgical approaches [48].

Ultrasound breast

US is a reliable modality to determine tumor size, especially if the residual tumor measures >7 mm [50,51]. A decrease in tumor vascularity does appear to correlate with response [28]. In 2 recent studies, US predicted residual tumor size accurately in 59.6% to 80% of patients, as compared to 31.7% to 71%% for mammography [23,52]. In a study by Keune et al [53] the absence of residual disease on both mammography and US correlated with a pathologic CR in 80% of patients. Although pretreatment tumor stiffness as determined by shear-wave elastography has shown strong correlation with response to therapy, there are insufficient data to support its routine use at this time [54,55]. In addition, there are 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 [56].

Magnetic resonance imaging breast

Multiple studies have shown that dynamic contrast-enhanced MRI is the optimal imaging tool to determine disease response, with a sensitivity approaching 90%, a specificity of 60% to 100%, and an accuracy of approximately 91% [20,31,35,36,44,57-60], and 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 [61,62]. However, there is a lack of consensus in the literature on the optimal imaging interval to assess response to therapy. In a study of 216 patients with stage I and II breast cancer, volumetric tumor measurements more accurately predicted pathologic response than clinical assessment [63]. Evaluation of tumor response on 3-D maximum-intensity projection images in a study of 38 patients showed strong correlation with histopathologic response, whereas only moderate correlation was seen with sonography [64]. Another study of 54 patients showed that change in the largest diameter was predictive of tumor response, with a <25% change associated with substantial residual disease [65]. A >45% reduction in tumor size early in treatment was linked with pathologic CR [66]. A small study of 21 patients revealed that responders have reduction in tumor volume and decreases in the choline peak on magnetic resonance spectroscopy as compared to nonresponders [67]. In several studies, kinetic changes detectable on MRI correlate with response to therapy and occur prior to changes in tumor volume, although there is no established cutoff of enhancement, which has been associated with partial versus complete response [68-70]. A more recent study in 21 patients linked at least a 64% decrease in voxels with washout kinetics after 1 cycle of chemotherapy to a higher likelihood of achieving a pathologic CR [71].

In 3 recent studies, the routine use of diffusion-weighted imaging allowed early differentiation between responders and nonresponders by at least a 20% increase in apparent diffusion coefficient, thereby allowing for tailoring of chemotherapy [72-76]. A separate study revealed that a low apparent diffusion coefficient prior to treatment predicted response [77]. In addition, based on a study of 78 patients, the addition of diffusion-weighted imaging to dynamic contrast-enhanced MRI results in improved diagnostic performance in predicting residual disease following chemotherapy [78]. The ability of MRI to evaluate disease response is also variable based on tumor subtype, being more effective for invasive lobular carcinoma, triple-negative tumors, and HER2/neu-positive tumors and less accurate for luminal subtypes (ER and/or PR positive, HER2/neu positive or negative), with an overall accuracy of approximately 75% [79-87].

A recent study of 208 patients suggested that patients who can safely consider breast conservation therapy after neoadjuvant therapy have tumors <3 cm in maximal size on pretreatment MRI, show reduction in tumor size on post-treatment MRI, and more often have HER2/neu-positive or triple-negative tumors [61,88]. When the tumor presents as diffuse nonmass enhancement on the pretreatment MRI or is of low nuclear grade, MRI is less helpful in assessing for response to therapy [89]. In addition, tumors presenting initially as nonmass enhancement more likely presented as scattered foci within an area of fibrosis on post-treatment MRI, making prediction of residual disease challenging [34,90]. 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 underestimation [91,92].

Molecular breast imaging
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 following chemotherapy did not correlate with treatment response [93]. A small study of 62 patients also showed that high uptake after chemotherapy predicts poor survival [94]. At present, there are insufficient data to support the routine use of MBI in patients undergoing neoadjuvant chemotherapy. In one study of 122 patients, breast-specific gamma imaging had a sensitivity of 74% and a specificity of 72.2% for detection of residual tumor following chemotherapy, but it underestimated the amount of residual disease for tumors of luminal subtype [95].

FDG-PET and PEM
Given the relatively low spatial resolution of PET scanners despite their high sensitivity, in a recent study by Bassa et al [96], PET was able to accurately predict residual disease in only 75% of cases, as compared to 88% for US. In 2 small studies of <50 patients, a decrease in maximum standardized uptake value of at least 50% to 60% was able to differentiate between responders and nonresponders, with a sensitivity of 86% and specificity of 91% [3,97]. However, most studies suggest that because of their relatively low specificity, PET and PET/CT should be used only in combination with other imaging modalities [98,99]. However, PET imaging may be helpful for certain tumor subtypes. Three recent studies showed that PET/CT can reliably detect early response and predict residual disease in HER2/neu-positive tumors [100-102], and a <42% decrease in radioisotope uptake in triple-negative tumors correlates with poor response and outcome [103]. In addition, lobular cancers are less FDG avid, making assessment challenging [104,105]. At present, there are no data investigating whether PEM may be useful in the neoadjuvant setting.

Variant 3: Known breast cancer. Axillary evaluation prior to neoadjuvant chemotherapy. Initial imaging examination.

Mammography and digital breast tomosynthesis diagnostic
Mammography and DBT do not completely visualize the axilla, although at times pathologically enlarged nodes may be seen as dense enlarged nodes on the mediolateral projection.

Ultrasound breast
US is the modality of choice for imaging of the axilla as it permits visualization of level I and II nodes routinely. By identifying pathologic-appearing nodes, US-guided FNA or core biopsy can confirm metastatic disease, thereby obviating the need for pretreatment sentinel node biopsy because the completion of axillary node dissection is typically performed following completion of therapy [2,106]. However, as axillary US has false-negative rates of up to 20%, surgical staging of the axilla prior to neoadjuvant therapy is important in order to determine the most appropriate management [107-109].

Magnetic resonance imaging breast
The axilla is often visualized, permitting identification of pathologic lymphadenopathy. However, MRI is typically not obtained solely for this purpose and several studies have shown that it is only moderately sensitive for detection of nodal metastasis [110]. However, MRI does provide reasonable assessment of level III nodes and the internal mammary lymph node chain.

FDG-PET/CT
In several studies, including a multicenter study of 360 patients, PET had a sensitivity of 43% to 79% and specificity of 66% to 93% for the detection of nodal disease, possibly related to differences in tumor size in the different patient populations [111,112]. 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 [113]. In addition, in node-positive tumors, this modality can be used to monitor response and possibly lead to sentinel node biopsy upon completion of chemotherapy rather than full axillary dissection [114].

Fine-needle aspiration and core biopsy breast
US-guided FNA, frequently performed with 22-gauge or 25-gauge needles, or US-guided core biopsy using a 14- to 18-gauge device permits sampling of abnormal-appearing nodes and provides an accurate means to assess for axillary involvement in clinically node-negative patients, with a sensitivity of 71%, specificity of 99%, negative predictive value of 84%, and positive predictive value of 97% [115-117]. FNA requires the availability of skilled cytopathologists. False-negative rates are low, being <2% in experienced hands.

Sentinel lymph node biopsy
Sentinel lymph node biopsy performed prior to initiation of chemotherapy is more accurate than after administration of chemotherapy [118] and should be considered if FNA/core biopsy is nondiagnostic.

Variant 4: Known breast cancer. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated. Initial imaging examination.

Mammography and digital breast tomosynthesis diagnostic
The axilla is incompletely visualized on the mediolateral projection, thereby limiting the utility of these modalities to reliably detect residual disease.

Ultrasound breast
Based on several studies, US has a 69.8% sensitivity for detection of residual nodal disease after neoadjuvant chemotherapy [25]. A study of 150 patients with node-positive disease showed that normalized nodal morphology after completion of neoadjuvant chemotherapy correlated with higher pathologic response rates [24].

Magnetic resonance imaging breast
MRI of the axilla is only 61.0% sensitive for detection of residual disease after neoadjuvant chemotherapy [25,110]; therefore, sentinel node biopsy or full axillary node dissection (if pretreatment evaluation revealed metastasis) remains warranted.

FDG-PET/CT
Although a few studies have suggested that PET can reliably predict the response of axillary nodes early in treatment, a majority of studies show that PET imaging has only 63.2% sensitivity for detection of residual disease after neoadjuvant chemotherapy [25,119]. Therefore, it is not routinely employed to evaluate the axilla following completion of neoadjuvant therapy.

Fine-needle aspiration and core biopsy breast
There is no evidence to support FNA or core biopsy of the axillary lymph nodes after completion of neoadjuvant chemotherapy.

Sentinel node biopsy/axillary node dissection
After completion of neoadjuvant chemotherapy and provided the patient is eligible for surgery, patients who have not previously had axillary assessment typically undergo axillary node dissection rather than sentinel node biopsy, especially as imaging and percutaneous biopsy or FNA are unable to accurately exclude metastatic involvement [25,120]. The Z1071 study showed that in a cohort of 663 patients, the false-negative rate of sentinel node biopsy after neoadjuvant therapy was 12.6% [26]. Therefore, at some centers, patients with documented involvement of axillary nodes prior to neoadjuvant treatment with clinically negative nodes after treatment may undergo sentinel node biopsy rather than axillary dissection. However, in some cases, if there is response, no axillary surgery is performed.

Variant 5: Known breast cancer with clinical suspicion of metastatic disease. Staging or assessment of response to neoadjuvant systemic therapy. Initial imaging examination.

Computed tomography chest, abdomen, and pelvis
CT of the chest, abdomen, and pelvis is commonly used to stage patients with newly diagnosed, locally advanced breast cancer or recurrent cancer [121].

Bone scan
Bone scan represents one of the standard imaging tests to stage a patient with newly diagnosed breast cancer, allowing assessment of bony metastasis.

FDG-PET/CT
PET/CT combines cross-sectional imaging with tumor metabolism and has been shown to be more sensitive than conventional staging with CT and bone scan but is less specific (ie, higher false-positive rates) [122]. When combined with PEM, this technique permits simultaneous evaluation of the primary breast lesion and distant metastatic disease, but PEM is not widely available. However, PET/CT has diminished ability to detect bone metastases. A recent study suggests that PET/CT staging is more useful for stage IIIB and operable IIIA tumors and specific tumor subtypes including invasive ductal cancers, ER-negative and triple-negative tumors, high-grade malignancies, and those with p53 mutations [123-125]. PET imaging also appears to have utility in assessing early response to therapy, with a recent study in 47 women showing that a >50% to 60% reduction in

FDG uptake after 1 cycle of therapy correlated with a pathologic CR [126]. PET staging is not as useful for low-grade malignancies or invasive lobular cancer because of the overall low isotope uptake [40,41]. Staging with PET/CT detects distant metastasis with a sensitivity of 50% to 100% and a specificity of 50% to 97% in women with advanced breast cancers, some of which were occult on conventional CT imaging, and in 1 study by Groheux led to changes in clinical stage for 52% of women [127]. Given that 8% to 14% of women with locally advanced breast cancer have distant metastatic disease at diagnosis (that is, beyond the axillary nodes), PET/CT may be preferred over conventional CT imaging. In addition, in a few studies, it has been shown to be superior in detecting internal mammary and mediastinal lymphadenopathy [127].

Magnetic resonance imaging chest, abdomen, and pelvis
MRI is not routinely used for staging and monitoring for progression or recurrence of disease outside the breast.

Summary of Recommendations

- The appropriate initial imaging examinations to determine disease extent or tumor size in the breast for a woman who is a candidate for neoadjuvant therapy include mammography, DBT, US, and MRI.
- MRI is the most sensitive and specific test to determine response after completion of neoadjuvant chemotherapy, but it is critical to obtain a pretreatment MRI for comparison. Mammography, DBT, and US may be used as well to monitor response if the index lesion was well defined and tumor extent was fully characterized by those modalities in the pretreatment setting. In general, they are less accurate than MRI.
- Axillary US serves as the best modality to assess axillary involvement at the time of initial cancer diagnosis, although MRI provides better evaluation of the chest wall and level II and III nodes.
- Even after completion of neoadjuvant therapy, axillary US remains the best imaging examination for assessing residual lymphadenopathy.
- For staging or assessment of response to therapy in patients with locally advanced breast cancer and suspected metastatic disease, either whole-body PET/CT or bone scan combined with contrast-enhanced abdominal CT remains the standard, with the choice primarily varying by institutional preferences.

Summary of Evidence

Of the 128 references cited in the *ACR Appropriateness Criteria® Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer* document, 1 reference is categorized as therapeutic of good quality. Additionally, 124 references are categorized as diagnostic references, including 7 well-designed studies, 43 good-quality studies, and 50 quality studies that may have design limitations. There are 24 references that may not be useful as primary evidence. There are 3 references that are meta-analysis studies.

The 128 references cited in the *ACR Appropriateness Criteria® Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer* document were published from 1984 to 2017.

Although there are references that report on studies with design limitations, 51 well-designed or good-quality studies provide good evidence.

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, both because of 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 to 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 [128].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	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".		

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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