American College of Radiology
ACR Appropriateness Criteria®
Imaging of the Axilla

Variant: 1 Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	May Be Appropriate	☢☢
Mammography diagnostic	May Be Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 2 Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.

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

Variant: 3 Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 4 Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive.

Initial imaging of the axilla following diagnostic mammography or DBT.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate (Disagreement)	O
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

<u>Variant: 5</u> Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	May Be Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

<u>Variant: 6</u> Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate	O
CT chest abdomen pelvis with IV contrast	May Be Appropriate	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	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	☢☢☢☢

<u>Variant: 7</u> Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☢☢
Mammography diagnostic	Usually Not Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O

Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 8 Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	May Be Appropriate (Disagreement)	O
MRI breast without and with IV contrast	May Be Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☢☢
Mammography diagnostic	Usually Not Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 9 Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☢☢
Mammography diagnostic	Usually Not Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 10 Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	May Be Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate	O
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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: 11 Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.

Procedure	Appropriateness Category	Relative Radiation Level
US-guided core biopsy axillary node	Usually Appropriate	O
US-guided fine needle aspiration biopsy axillary node	Usually Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate (Disagreement)	O
MRI breast without IV contrast	Usually Not Appropriate	O
Sestamibi MBI	Usually Not Appropriate	☢☢☢
CT chest abdomen pelvis with 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	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

Variant: 12 Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Appropriate	☢☢
Mammography diagnostic	Usually Appropriate	☢☢
US-guided core biopsy axillary node	May Be Appropriate (Disagreement)	O
US-guided fine needle aspiration biopsy axillary node	May Be Appropriate	O

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Summary of Literature Review

Introduction/Background

Unilateral or bilateral palpable or clinically suspicious axillary mass(es) have a broad differential diagnosis, including inflammatory, infectious, vascular, and malignant etiologies [1]. In most cases, an axillary mass confirmed on imaging is either normal tissue or of lymphoid or mammary origin. With the increased use of ultrasound (US) as a screening tool and as more advanced cross-sectional imaging detects incidental nonpalpable and clinically occult axillary findings, further evaluation with biopsy is often necessary to obtain a definitive diagnosis.

If metastatic nodal disease is confirmed at biopsy, the most common cause is ipsilateral breast cancer. Historically, axillary lymph node dissection (ALND) was the standard of care for nearly all

breast cancer patients. The results of several impactful clinical trials have changed the guidelines on axillary management. Sentinel lymph node (SLN) dissection is now preferred. The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial and American College of Surgeons Oncology Group (ACOSOG) Z0011 trial have redefined the role of ALND [2]. In the NSABP trial, 2,804 clinically node-negative women were randomized to SLN biopsy (SLNB) alone or SLNB with ALND [3]. No statistically significant difference in overall survival was seen between the two arms, but the SLNB alone group had lower postoperative morbidity. The International Breast Cancer Study Group Trial 23-01 (IBCSG 23-01) compared SLNB alone versus ALND for 933 patients with tumors <5 cm and nodal micrometastases (0.2 mm–2.0 mm) [4]. There was no difference in overall survival or disease-free survival after 5 years of follow-up [4]. For the Z0011 trial, 891 women with T1 or T2 invasive primary breast cancer and no palpable axillary adenopathy and with one or 2 positive SLNs were randomized to SLNB versus ALND [5]. The 10-year overall survival for Z1011 patients treated with SLNB alone was noninferior to those treated with ALND [4]. Therefore, SLNB became a safe alternative to ALND for women with one or two positive SLNs. SLNB has replaced ALND as the standard nodal staging procedure for clinically node-negative patients and even for some node positive patients with limited nodal tumor burden.

The clinically negative axilla is defined having no palpable nodes on physical examination [6]. If the clinical physical examination or imaging test(s) reveal a suspicious finding, then further investigation may involve US and breast MRI. If positive, percutaneous biopsy is often performed. The National Comprehensive Cancer Network (NCCN) guidelines do refer to the use of axillary US or MRI with possible biopsy to determine if there is ipsilateral axillary lymph node involvement in operable breast cancer patients prior to preoperative systemic therapy [7]. Several imaging modalities (mammography, tomosynthesis, US, CT, fluorine-18-2-fluoro-2-deoxy-D-glucose [FDG]-PET/CT, MRI) can visualize the axillary nodes and evaluate the size and morphology. In 2014, the American Society of Breast Surgeons published a consensus guideline on the management of the axilla in which SLNB has replaced ALND for clinically node-negative invasive breast cancer patients [6]. It is desirable to identify those patients who can safely receive SLNB and those who we can potentially omit SLNB. However, there is no standard radiologic imaging test for this purpose.

In patients undergoing neoadjuvant chemotherapy (NAC), SLNB or targeted ALND remains an option in patients with clinical node-negative or small-volume nodal disease. Targeted ALND consists of removing the biopsy-proven metastatic node (which usually has a biopsy marker placed and is often called a "clipped node”) in addition to the SLNs and any pre-NAC positive nodes [8]. SLNB is preferred over ALND in order to reduce morbidity, notably lymphedema. Several multicenter trials reported a decrease in the false negative rate (FNR) of SLNB when a dual tracer is used or when three or more SLNs including the clipped node are removed at surgery [9-13]. SLNB after NAC has a sentinel node identification rate between 87.6% and 92.7% and FNR between 12.6% and 14.2% with no immunohistochemistry (IHC) and 8.4% and 8.7% with IHC [9-11]. The utilization of imaging to assess nodal disease extent is now recommended based on recent surgical consensus guidelines [6]. Yet, the modality and timing of the imaging test remains controversial. Clinical trials that include imaging often utilize US, with CT or FDG-PET/CT being utilized in some practices [14,15].

Special Imaging Considerations

There are a few publications reporting on the utilization of elastography, contrast-enhanced US, photoacoustic imaging, and MRI with magnetic nanoparticles [16-18]. These advanced imaging

methods are still investigational and not recommended for routine clinical use.

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 in which each procedure provides unique clinical information to effectively manage the patient's care).

Discussion of Procedures by Variant

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla.

A palpable axillary lump has a wide differential diagnosis, ranging from nonmalignant etiologies to primary breast malignancy or metastatic disease from a nonbreast malignancy or lymphoma. There are many nonmalignant etiologies and vascular lesions that may present as a unilateral palpable axillary lump, including nerve sheath tumors, infection, inflammatory disease, and autoimmune disease [19]. The risk of cancer in women with no personal history of breast cancer is low but increases with age [20]. In a study of 171 women who underwent biopsy for an abnormal node detected on axillary US, only 7% were found to be malignant [20]. According to NCCN guidelines, a diagnostic mammogram and/or digital breast tomosynthesis (DBT) complement axillary US by evaluating the breast for underlying lesions in the setting of patients presenting with axillary lymphadenopathy [7,21]. Based on the clinical presentation, medical history, risk factors, and patient's age, imaging most often entails a combination of different imaging modalities followed by surgical consultation or follow-up (see the ACR Appropriateness Criteria® topic on "Palpable Breast Masses" [22]).

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla.
A. CT Chest, Abdomen, and Pelvis

If a chest wall lesion or an axillary mass invading the chest wall is suspected, CT chest can determine if there is any adjacent bony involvement or any chest wall or pleural space involvement [23]. An axillary mass may also be an incidental imaging finding detected on a CT examination that includes the chest. In such situations, further investigation with axillary US and possible US-guided biopsy may be helpful.

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla.
B. Digital Breast Tomosynthesis Diagnostic

There is insufficient data to support the use of DBT as the single initial imaging test for an axillary palpable mass, even though a portion or all of the axillary mass may be visible on DBT. If there is a personal history of breast cancer or clinical suspicion of axillary tail breast carcinoma, DBT, as an adjunct test to axillary US, can provide a global assessment of the ipsilateral breast and also assess for other suspicious findings such as microcalcifications associated with the palpable axillary mass.

DBT allows better characterization of lesions and addresses some of the limitations associated with standard 2-D mammography [24-27].

If the unilateral axillary mass is suspicious for metastatic adenopathy from a primary breast cancer or occult breast cancer, the reported data from multicenter trials for DBT use in this population, in addition to digital mammography, was associated with an increased primary breast cancer detection rate compared with digital mammogram alone [28]. DBT, in addition to digital mammography, demonstrated best performance gains in women ages 40 to 49 years [29].

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla. C. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT is not beneficial for assessing an axillary mass of unknown etiology as the initial imaging assessment because of its low yield to detect an occult primary malignancy without first confirming that the unilateral axillary mass is of malignant etiology [30,31]. Less than 1% of breast cancers initially present as axillary adenopathy [32,33]. If FDG-PET/CT incidentally detects an FDG-avid lymph node, then axillary US is helpful to characterize the nodal morphology and guide biopsy, if warranted.

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla. D. Mammography Diagnostic

There is insufficient data to support the use of mammography as the initial imaging test for an axillary palpable mass, even though pathologically enlarged nodes may be seen as dense enlarged nodes or masses on the mediolateral or mediolateral-oblique projection of a mammogram. However, if there is a personal history of breast cancer or clinical suspicion of axillary tail breast carcinoma or metastatic adenopathy from a breast primary, then mammography as an adjunct test to axillary US can provide global assessment of the ipsilateral breast and identify other suspicious findings such as microcalcifications associated with the palpable mass.

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla. E. MRI Breast

MRI of the breast is not routinely performed as the initial imaging assessment for a unilateral palpable axillary mass. MRI may be helpful in defining disease extent and characterizing the breast primary if axillary US reveals adenopathy of unknown primary malignancy and the mammogram is negative for a primary breast malignancy [34,35]. MRI can also help characterize the axillary mass by determining any adjacent vascular involvement, chest wall involvement, and involvement of other axillary structures.

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla. F. Sestamibi MBI

There is no relevant literature to support the use of Tc-99m sestamibi molecular breast imaging (MBI) for assessing a unilateral palpable axillary mass.

Variant 1: Female. New palpable, unilateral, axillary lump. Initial imaging of the axilla. G. US Axilla

Multiple studies support the use of US to characterize findings in the axilla [36,37]. The most common etiology, besides normal tissue, is adenopathy from benign or malignant disease, typically of lymphatic or mammary origin. In addition, accessory breast tissue and both benign and cancerous lesions within accessory tissue can be seen [36]. If a suspicious US finding or mass is identified, US-guided biopsy can be performed for definitive diagnosis, even if the malignancy rate

may be low in a woman with palpable axillary mass and no other signs of malignancy [37].

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.

Bilateral palpable axillary lumps have a wide differential ranging from benign reactive lymphadenopathy due to infectious and inflammatory processes to metastases from primary breast cancer and nonmammary malignancies, most commonly lymphoma and leukemia. Axillary US can help differentiate benign from malignant etiologies when interpretation is made in conjunction with the clinical history and laboratory result. However, the choice of imaging modalities may vary based on the patient's age, clinical presentation or situation, and patient's risk factors for breast cancer.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
A. CT Chest, Abdomen, and Pelvis

There is no relevant literature to support the use of CT with or without intravenous (IV) contrast as an initial imaging test for palpable axillary mass. If systemic disease or nonmammary malignancy, such as lymphoma, is in the differential diagnosis, CT chest may be helpful to determine other areas of lymphadenopathy, as well as to assess for local bony, chest wall, or intrathoracic involvement.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
B. Digital Breast Tomosynthesis Diagnostic

There is insufficient data to support the use of DBT as the initial imaging test for evaluating bilateral palpable axillary masses even though a portion of the axillary region can be visualized on DBT. DBT can provide global assessment of the breasts as well as assess for microcalcifications associated with the axillary mass(es). NCCN guidelines suggest that a diagnostic mammogram and/or DBT may complement axillary US by evaluating the breast for underlying lesions in the setting of patients presenting with axillary lymphadenopathy [7,21,32].

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
C. FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT as the initial imaging test for bilateral axillary adenopathy even though FDG-PET/CT can detect the axillary lymphadenopathy as well as other lymphadenopathy in the neck, chest, abdomen, and pelvis. In one series of breast cancer patients, FDG-PET/CT was significantly more accurate than US (75% versus 62%) for the detection of axillary lymph node metastases, but there was no difference in sensitivity (54% versus 38%) [38]. Incidental axillary FDG uptake on PET/CT may require further evaluation with mammography, DBT, and US, followed by possible image-guided biopsy.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
D. Mammography Diagnostic

There is insufficient data to support the use of mammography as the initial imaging test for evaluating bilateral palpable axillary masses, even though a portion of the axillary region can be visualized on mammography. NCCN guidelines also suggest that a diagnostic mammogram and/or DBT may complement axillary US by providing a global evaluation of the breast for underlying lesions in the setting of patients presenting with axillary lymphadenopathy [7,21]. However, the choice of the imaging modality varies based on the patient's age, clinical presentation or situation, and patient's risk factors for breast cancer.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
E. MRI Breast

MRI of the breast is not routinely performed as the initial imaging assessment for bilateral palpable axillary masses. If digital mammography or DBT is negative for a primary breast malignancy in a patient with suspicious axillary lymphadenopathy, MRI can often identify the breast primary [34,35]. In a meta-analysis of 9 retrospective studies, MRI detected an occult breast cancer in more than two-thirds of patients [39]. MRI can also help further characterize the axillary mass(es) by determining involvement of adjacent vessels, the chest wall, and other axillary structures.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
F. Sestamibi MBI

There is no relevant literature to support the use of Tc-99m sestamibi MBI as the initial imaging of patients presenting with bilateral palpable axillary masses.

Variant 2: Female. New palpable, bilateral, axillary lump. Initial imaging of the axilla.
G. US Axilla

The differential diagnosis of bilateral axillary masses is broad and includes normal variants (eg, accessory breast, ectopic breast tissue, lactational changes), infectious or nonmalignant etiologies (eg, reactive adenopathy from mastitis, granulomas, lipomas), and malignancies (eg, lymphoma, leukemia, metastatic breast cancer). Axillary US can determine if the mass is solid or cystic. Management of the finding varies depending on the sonographic appearance. For example, lipomas require no further evaluation, whereas enlarged lymph nodes may require biopsy unless clinical history provides a reasonable explanation [20,37]. Mammography is also often performed to detect a primary breast carcinoma as the cause of the axillary adenopathy [40,41]. Initial imaging with an US of the axilla's is appropriate in the setting of a new palpable, bilateral, axillary lump.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.

Regional nodal staging is an important prognostic factor in guiding the treatment of breast cancer, which has undergone significant change over the last decade [42,43]. Historically, ALND was the standard of care for staging the nodal region and providing local control of breast cancer that has metastasized to regional nodes. The result of the Z0011 trial changed the approach to axillary disease management [5]. The Z0011 trial recruited 891 women with T1 or T2 invasive primary breast cancer and no palpable axillary adenopathy [5]. These women were randomized to SLNB versus ALND. The 10-year overall survival for Z0011 patients treated with SLNB alone was noninferior to those treated with ALND [4]. Therefore, SLNB became a safe alternative to ALND for clinically node-negative breast cancer patients, with a less invasive approach and less morbidity. In 2014, the American Society of Breast Surgeons published consensus guideline on the management of the axilla in which SLNB has replaced ALND for clinically node-negative invasive breast cancer patients [6]. It is desirable to identify those patients who can safely receive SLNB and those who we can potentially omit SLNB. However, there is no standard radiologic imaging test for this purpose and this remains an area of controversy.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
A. CT Chest, Abdomen, and Pelvis

Studies have shown that the use of advanced imaging modalities such as CT and FDG-PET/CT for staging asymptomatic women with early stage breast cancer has low yield for occult disease [44-46]. The 2020 NCCN Guidelines for Invasive Breast Cancer also suggest the use of CT with IV contrast only when there is elevated liver function tests, pulmonary or abdominal symptoms, or

abnormal physical examination [7]. CT chest can visualize and assess the level I, II, and III regions of the axilla. The predictive accuracy of CT is not high enough to replace SLNB. In a single center study involving 297 newly diagnosed breast cancer patients, these patients were randomized to receive CT versus no CT prior to axillary surgery. This trial reported that there was no reduction on the axillary nodal reoperation rate with the addition of CT [47]. In another single center study of 1,917 breast cancer patients with clinical T1 and T2 invasive carcinoma, the investigators concluded that preoperative imaging with US, CT, or FDG-PET/CT was able to predict patients with more than three metastatic axillary nodes or high tumor burden per these investigators' definition. If patients had abnormal appearing nodes on preoperative chest CT, then these patients could proceed directly to ALND and avoid intraoperative SLNB, which would reduce operation times and costs.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
B. FDG-PET/CT Skull Base to Mid-Thigh

According to the breast cancer guidelines, such as NCCN, European Society for Medical Oncology, Spanish Society of Medical Oncology, and National Institute for Health and Care Excellence, FDG-PET/CT is not routinely performed for staging of early-stage breast cancer in the absence of symptoms (see the ACR Appropriateness Criteria® topic on "Stage I Breast Cancer: Initial Workup and Surveillance for Local Recurrence and Distant Metastases in Asymptomatic Women" [46] for further guidance). FDG-PET/CT is commonly performed when there are equivocal or suspicious findings on standard staging studies and for staging locally advanced breast cancer or metastatic disease from breast cancer [7,48]. The rationale is that FDG-PET/CT cannot replace SLNB even though this imaging test can visualize the entire axillary region and can detect distant metastases. A meta-analysis of 25 studies compared the accuracy of FDG-PET/CT with SLNB and reported that the performance of FDG-PET/CT was inferior to SLNB despite its high specificity of 94% in axillary lymph node assessment (95% confidence interval [CI], 91%–96 %) [49]. The use of FDG-PET in assessing axillary lymph node status in a newly diagnosed breast cancer of ≤2 cm is not supported by current data in patients who do not have clinical node positive disease.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
C. MRI Breast

Dynamic contrast-enhanced MRI is a sensitive tool for assessing disease extent within the breast, with sensitivity approaching 90% and specificity ranging between 50% and 97% [50,51]. This high sensitivity does not extrapolate to the axillary assessment. Although the axilla is often visualized on a breast MRI examination, there is little literature specifically addressing the utilization of breast MRI as the initial imaging test for the axilla in patients with tumor size of ≤2 cm and clinically node negative. The NCCN guidelines refer to the use of axillary US or MRI with possible biopsy to determine if there is ipsilateral axillary lymph node involvement in operable breast cancer patients prior to preoperative systemic therapy [7,48]. If the ipsilateral axillary node evaluation is negative, then SLNB can be performed. If the ipsilateral axillary node biopsy is positive, then axillary restaging after preoperative systemic therapy is recommended. One publication reported the results of 6 studies that evaluated the accuracy of MRI on histological positive nodes. Contrast-enhanced MRI was more accurate than unenhanced MRI with FNR of 12% to 19% and negative predicative value (NPV) of 97% to 99% [52]. MRI can also detect more node-negative breast cancers than mammography [53]. In summary, the current data suggest that MRI can be helpful for nodal staging in patients with newly diagnosed breast cancer.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative.

Initial imaging of the axilla following diagnostic mammography or DBT.
D. Sestamibi MBI

There is no relevant literature to support the use of Tc-99m sestamibi MBI for staging of the axilla in breast cancer patients.

Variant 3: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-negative.
Initial imaging of the axilla following diagnostic mammography or DBT.
E. US Axilla

Axillary US is often performed in early-stage breast cancer patients since the Z0011 trial showed that early-stage cancer and low nodal burden minimizes surgical morbidity because patients can undergo SLNB rather than ALND without compromising survival [5].

However, there are currently differences in opinion on the use of preoperative axillary US and controversy regarding its routine use in staging clinically node-negative breast cancer patients. One point of view is that a positive axillary US with biopsy proven nodal involvement may commit the patients to ALND who could have received SLN surgery if the Z0011 inclusion criteria were met. The Z0011 inclusion criteria involve histologically confirmed invasive breast carcinoma of ≤5 cm clinically with no palpable adenopathy and an SLN-containing breast cancer on frozen section, touch preparation, or hematoxylin-eosin staining on permanent section, with <3 positive nodes on SLNB [5].

The other point of view supporting preoperative axillary US argues that the finding of an abnormal axillary node on axillary US followed by percutaneous biopsy confirmation would help to identify those patients with higher tumor burden [54,55], who would benefit from proceeding directly to ALND. This approach avoids the need for a second surgery. One study supporting the utilization of preoperative axillary US from a single center reported that only 3% to 5% of patients had an abnormal axillary US yet met the Z0011 criteria (ie, ALND was not necessary in these patients with preoperative abnormal axillary US). Other studies also supporting the use of preoperative axillary US even in patients who meet Z0011 criteria argue that axillary US can help identify patients with unsuspected extensive nodal disease, thereby removing them from consideration for unindicated SLNB [56-58]. Patients with negative preoperative axillary US and SLNB had fewer positive nodes, smaller nodal metastases, and lower extranodal extension on final pathology [58].

US-guided biopsy of any suspicious axillary node either via fine-needle aspiration (FNA) or core biopsy is commonly performed when preoperative axillary US is done. The sensitivity of US-guided biopsy is variable with a wide range of 52% to 90%, whereas the specificity is higher, ranging from 98% to 100% [59-63].

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive.
Initial imaging of the axilla following diagnostic mammography or DBT.

Prior to the ACOSOG Z0011 era, women who had metastatic sentinel node involvement received ALND. The result of the Z0011 trial changed the surgical management of the axilla for patients undergoing breast conservation surgery with 2 or fewer positive SLNs [5]. At median follow-up of 9.3 years, there was no differences in survival between those who received ALND versus those who did not receive ALND [5]. The results of the Z0011 trial was further supported by the IBCSG 23-01 trial, which demonstrated that there were no differences in disease-free survival between the ALND and no ALND (SLNB alone) in patients with tumors ≤5 cm, and one or more micrometastases (≤2 mm) in the SLNs [64]. If axillary radiation is given in mastectomy or breast conserving surgery

patients with 1 or 2 positive SLNs, ALND can be omitted provided that the patients receive axillary radiation therapy [65]. In summary, both studies showed that in patients with pT1/pT2 tumors and limited metastatic SLNs (<3), the use of SLNB alone compared with ALND was not associated with a significant increase in recurrence rate. Current guidelines therefore recommend omission of ALND if Z0011 criteria are fulfilled [6,66].

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT.
A. CT Chest, Abdomen, and Pelvis

Even in women with clinical node-positive disease, contrast-enhanced CT is not routinely performed and is not a part of the initial staging assessment if the patient does not have any signs or symptoms of disease outside the breast. When adenopathy is seen on CT, the Hounsfield unit of the metastatic lymph node is likely higher than nonmetastatic nodes.

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT.
B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT is a valuable modality with potential to impact clinical management of patients with newly diagnosed locally advanced disease, monitoring treatment response in patients with known metastatic breast cancer, and for detection of recurrent disease. FDG-PET/CT is not suggested for routine systemic staging in T0 to T3, N0 to 1, M0 breast cancer patients without signs or symptoms of metastatic disease. A meta-analysis of 25 studies demonstrates the inferiority of FDG-PET/CT to SLNB for evaluation of the axilla [49].

FDG-PET/CT has high specificity of 90% to 100% for detecting lymph node metastases but variable sensitivity ranging from 48% to 87% [67-71]. FDG uptake by an axillary node does not always represent a true positive metastatic node [72]. Single-center studies proposed certain imaging features that may be predictive of axillary metastases or predicts recurrent risk, such as higher maximum standardized uptake value (SUV_{max}) of the primary breast tumor, higher SUV_{max} of the axillary nodes, and axillary node-to-primary tumor SUV_{max} ratio [73-76]. However, other investigators reported that no FDG-PET/CT features were associated with any predictive factors for axillary metastases [77,78]. The tumor size within the metastatic node was associated with positive FDG-PET/CT finding in one retrospective study of 156 breast cancer patients [78]. In summary, FDG-PET/CT is usually not appropriate as the initial imaging of the axilla following diagnostic mammography or DBT in women newly diagnosed breast cancer, ≤2 cm, with clinical node-positive disease.

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT.
C. MRI Breast

Dynamic contrast-enhanced MRI is useful for staging prior to systemic therapy and for restaging of the axilla after systemic therapy if the preoperative axillary staging was positive [7,48]. However, most of the data focuses on the tumor within the breast and not the axillary nodes. Current standard MRI of the breast has some technical challenges that do not allow simultaneous optimal imaging of both the breast and axilla, with approximately 30% of the MRI examination excluding the axilla because of technical challenges or incomplete axillary visualization in a retrospective study of 803 newly diagnosed breast cancer patients [79]. When comparing contrast-enhanced breast MRI with noncontrast breast MRI, contrast-enhanced breast MRI is more accurate than

noncontrast MRI, based on a summary of 6 studies evaluating the accuracy of MRI in detecting pathologically proven positive axillary nodes [52]. In a meta-analysis of 21 eligible studies evaluating the efficacy of MRI versus FDG-PET/CT, the pooled sensitivity of MRI was significantly better (82% versus 64%, respectively), and the pooled specificity of MRI was similar (93%) [69]. A negative MRI does not exclude metastatic nodal disease on final histopathology, but a positive MRI finding suggests high tumor burden (>3 abnormal nodes) [15,69,79]. Based on the review of the literature, there was disagreement for the role of breast MRI in this clinical scenario.

Diffusion-weighted imaging (DWI) is a noninvasive imaging technique that does not require contrast injection, measuring the mobility of water molecules and may complement contrast-enhanced MRI. In a meta-analysis of 13 studies from a literature search of 159 articles, the apparent diffusion coefficient value of metastatic nodes are lower than nonmetastatic nodes with pooled sensitivity of 86% and specificity of 86% using a b-value of 800 [80].

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT.
D. Sestamibi MBI

There is no relevant literature supporting the routine use of Tc-99m sestamibi MBI for staging of the axilla in breast cancer patients.

Variant 4: Female. Newly diagnosed breast cancer, 2 cm or less, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT.
E. US Axilla

US is the most established noninvasive imaging test for assessing the axilla. Benign lymph nodes can often be differentiated from malignant nodes based on size, morphology, and vascularity, although there is a wide range of reported sensitivity and specificity for axillary US. The reported sensitivity can range from 26.4% to 94% and specificity from 53% to 98% [58,81,82]. Axillary US alone has a relatively low NPV and sensitivity to be useful as a predictor of axillary nodal burden [83,84]. When combined with needle biopsy, however, the sensitivity improves from 61% to 79% in a meta-analysis of 21 studies [54,62,85]. US-guided core needle biopsy was superior to US-guided FNA in a meta-analysis of 1,353 patients with newly diagnosed invasive breast carcinoma, with a reported sensitivity of 88% for core biopsy and 74% for FNA [86].

US features associated with a higher likelihood of malignancy include short-axis lymph node size >1 cm, cortical thickness of >0.3cm, and absence of a fatty hilum [87-90]. However, these imaging features are not specific enough to avoid the need for histologic sampling.

Since the Z0011 trial, there continues to be variability in incorporating axillary US into practice. Those in favor of performing axillary US routinely argue that >3 abnormal nodes or a positive axillary lymph node on needle biopsy warrant ALND rather than SLNB because these patients tend to have a high nodal tumor burden [58,91]. Those not in favor of performing axillary US recommend proceeding with SLNB, even if the preoperative US identify malignant-appearing lymph node(s) because the specificity of US is relatively low.

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.

Lymph node staging is crucial in the management of breast cancer, and several multicenter trials have impacted the approach to axillary lymph node treatment in breast cancer patients. For

patients with clinically node-negative disease, SLNB is an oncologically safe approach with less morbidity than ALND. The prospective IBCSG 23-01 trial of 934 patients randomized to completion of ALND (n = 465) or no ALND (n = 469), with median follow-up of 9.7 years, revealed that omitting ALND was safe, even if the sentinel nodes contained micrometastases [64]. The NSABP B-32 trial of 5,611 women randomized to SLNB alone versus axillary lymph node biopsy and ALND with follow-up of 8 years reported no statistical differences in overall survival, disease-free survival, and regional control with less postoperative morbidity in the SLNB alone group [2,3]. The Z0011 trial recruited 891 women with T1 or T2 invasive primary breast cancer and no palpable axillary adenopathy [5]. These women were randomized to SLNB versus ALND. The 10-year overall survival for patients treated with SLNB alone was noninferior to those treated with ALND. The Z0011 trial, with median follow-up of 9.3 years, also demonstrated no differences in survival between those who received ALND versus no ALND [5]. The After Mapping of the Axilla: Radiotherapy Or Surgery trial from the European Organization for Research and Treatment of Cancer with median follow-up of 10 years also showed no significant differences at 10 years for axillary recurrence or overall survival between the 2 groups [66].

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
A. CT Chest, Abdomen, and Pelvis

Contrast-enhanced and noncontrast-enhanced CT studies are not typically performed for early-stage breast cancer in asymptomatic patients because asymptomatic distant disease is rare. Contrast-enhanced CT can be used if the primary breast cancer is >2 cm, there is clinical node-positive disease, the tumor demonstrates biologically aggressive features on histopathology, or patients present with clinical symptoms such as elevated liver function tests [7,92]. However, findings on CT do not influence the approach for axillary surgery, reduce the number of axillary surgeries, or reduce the reoperation rate [14,47].

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT is not routinely performed for pretreatment imaging of the axilla and is not useful in staging newly diagnosed breast cancer [7]. Given that nodal metastases are often subcentimeter in size, FDG-PET/CT has poor sensitivity for axillary nodal metastases as compared with SLNB [93]. FDG-PET/CT is more helpful in detecting clinically occult extra-axillary locoregional nodes, such as supraclavicular or internal mammary nodes. FDG-PET/CT identification of unsuspected regional nodal or distant metastases can be useful in locally advanced breast cancer or inflammatory breast cancer and can substantially change the patient's stage [94,95].

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
C. MRI Breast

Dynamic contrast-enhanced MRI is not routinely performed [7,92] for staging prior to systemic therapy and for restaging of the axilla after systemic therapy if preoperative axillary staging was negative [7,48]. Current breast MRI protocols do not adequately image the breast and entire axilla in up to 30% of cases based on a retrospective study of 803 newly diagnosed breast cancer patients [79]. However, contrast-enhanced breast MRI is more accurate than noncontrast imaging with a FNR of 12% to 19% and NPV of 97% to 99% based on 6 studies designed to evaluate the accuracy of MRI in patients with histologically positive nodes [52]. In a meta-analysis of 21 eligible

studies evaluating the efficacy of MRI versus FDG-PET/CT, the pooled sensitivity of MRI was significantly better (82% versus 64%, respectively), and the pooled specificity was similar (93%) [69]. A negative MRI does not exclude metastatic nodal disease on final histopathology, but a positive MRI finding suggests high tumor burden (>3 abnormal nodes) [15,69,79].

DWI is a noninvasive imaging technique that does not require contrast injection, measures the mobility of water molecules, and may complement contrast-enhanced MRI. In a meta-analysis of 13 studies from a literature search of 159 articles, the apparent diffusion coefficient value of metastatic nodes is lower than nonmetastatic nodes with pooled sensitivity of 86% and specificity of 86% using a b-value of 800 [80].

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
D. Sestamibi MBI

There is no relevant literature supporting the routine use of sestamibi MBI for staging of the axilla in breast cancer patients.

Variant 5: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-negative. Initial imaging of the axilla following diagnostic mammography or DBT.
E. US Axilla

SLNB is currently the standard of care for axillary staging in early clinically node-negative breast cancer. However, if axillary node involvement is proven by percutaneous biopsy of a suspicious node detected by axillary US or another imaging modality, which more often may be the case for women with a known breast cancer ≥2 cm, this would lead to ALND rather than SLNB [6,92,96].

However, there are currently differences in opinion on the use of preoperative axillary US and controversy regarding its routine use in staging clinically node-negative breast cancer patients. One point of view is that a positive axillary US with biopsy-proven nodal involvement may commit the patients to ALND who could have received SLN surgery if the Z0011 inclusion criteria were met. The Z0011 inclusion criteria involve histologically confirmed invasive breast carcinoma of ≤5 cm clinically with no palpable adenopathy and one or two SLNs containing breast cancer on frozen section, touch preparation, or hematoxylin-eosin staining on permanent section, with <3 positive nodes on SLNB [5].

The other point of view supporting preoperative axillary US argues that the finding of an abnormal axillary node on axillary US followed by percutaneous biopsy confirmation would help to identify those patients with higher tumor burden [54,55], and these patients would benefit from proceeding directly to ALND. This approach avoids the need for a second surgery. One study, supporting the utilization of preoperative axillary US from a single center, reported that only 3% to 5% of patients had an abnormal axillary US and met the Z0011 criteria (ie, ALND was not necessary in these patients with preoperative abnormal axillary US). Other studies also supporting the addition of preoperative axillary US to the management of patients who met Z0011 criteria argue that axillary US can help identify patients with more extensive nodal disease who meet the Z0011 criteria [56-58]. Patients with negative preoperative axillary US and SLN had fewer positive nodes, smaller nodal metastases, and lower extranodal extension on final pathology [58].

US-guided biopsy of any suspicious axillary node either via FNA or core biopsy is commonly performed when preoperative axillary US is done. The sensitivity of US-guided biopsy is variable

with a wide range of 52% to 90%, whereas the specificity is higher, ranging from 98% to 100% [59-63].

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

Nodal status remains a significant predictor of breast cancer outcome. Even though physical examination is not sensitive or specific, historically clinicians would record the size of the palpable node(s) and presence or absence of nodal matting. Axillary US can be used to confirm clinical suspicion and guide percutaneous biopsy. ALND or SLNB is performed in patients with biopsy-proven axillary metastases on US-guided biopsy. Recent trials randomizing patients to SLNB alone have shown that this approach appears safe for patients with low axillary nodal tumor burden [3,5,64]. If the axilla is initially clinically positive but has a clinical complete response after NAC treatment, SLNB may be performed if the clipped node is removed, a dual tracer is used, and more than two sentinel nodes are removed [50] (see the ACR Appropriateness Criteria® topic on "Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer" [97].

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

A. CT Chest, Abdomen, and Pelvis

Contrast-enhanced CT is not routinely used to stage the axilla, even in patients with clinically positive axillary findings. While CT chest can visualize and assess the level I, II, and III regions of the axilla, the predictive accuracy of CT is not high enough to replace SLNB [50,51,95]. When adenopathy is seen on CT, the Hounsfield unit of the metastatic lymph node is likely higher than nonmetastatic nodes. Contrast-enhanced CT may be used if the primary breast cancer is >2 cm, there is clinical node-positive disease, the tumor demonstrates biologically aggressive features on histopathology, or patients present with clinical symptoms such as elevated liver function tests [7,92]. However, findings on CT do not influence the approach for axillary surgery, reduce the number of axillary surgeries, or reduce the reoperation rate [14,47]. For locally advanced breast cancer (>5 cm in size, involving skin or underlying chest wall) and local recurrence, CT may be helpful [7]. For inflammatory breast cancer, the incidence of nodal metastases at presentation is high, up to 79.8% in a SEER registry of 761 patients and 5-year survival is worse for lymph node-positive patients (49%) than node-negative patients (66%) [98]. If there is clinical suspicion of inflammatory breast cancer, contrast-enhanced CT may be helpful for staging [7].

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT may be useful in the staging of newly diagnosed advanced breast cancer given a higher likelihood of extra-axillary metastatic disease or distant disease [94,95]. It has been proposed that if a primary breast tumor is >2 cm and has a high SUV_{max}, there is a higher probability of axillary nodal metastases [73,99]. In addition to assisting in the staging of advanced breast cancer, FDG-PET/CT may be beneficial in staging patients with T1 stage breast cancer, particularly those with triple negative or human epidermal growth factor receptor 2 (HER2) positive breast cancer with clinical node positive disease because there is a higher prevalence of nodal disease and distant metastases [71]. In order to assess response to neoadjuvant therapy,

comparing pretreatment nodal FDG uptake to subsequent midtreatment or post-treatment FDG uptake is essential and also can be used to identify those at a higher risk of recurrence [100-102].

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

C. MRI Breast

Dynamic contrast-enhanced MRI may be useful for staging prior to systemic therapy and for restaging of the axilla after systemic therapy if the preoperative axillary staging was positive [7,48]. However, most of the data focuses on the tumor within the breast and not of the axillary nodes. Current breast MRI protocols do not adequately image the entire axilla (level I, II, III) in up to 30% of cases based on a retrospective study of 803 newly diagnosed breast cancer patients [79]. However, contrast-enhanced breast MRI is more accurate than noncontrast imaging with a FNR of 12% to 19% and NPV of 97% to 99% based on 6 studies designed to evaluate the accuracy of MRI in patients with histologically positive nodes [52]. In a meta-analysis of 21 eligible studies evaluating the efficacy of MRI versus FDG-PET/CT, the pooled sensitivity of MRI was significantly better (82% versus 64%, respectively), and the pooled specificity of MRI was similar (93%) [69]. A negative MRI does not exclude metastatic nodal disease on final histopathology, but a positive MRI finding suggests high tumor burden (>3 abnormal nodes) [15,69,79].

DWI is a noninvasive imaging technique that does not require contrast injection, measures the mobility of water molecules, and may complement contrast-enhanced MRI. In a meta-analysis of 13 studies from a literature search of 159 articles, apparent diffusion coefficient value of metastatic nodes are lower than nonmetastatic nodes with pooled sensitivity of 86% and specificity of 86% using a b-value of 800 [80]. There is insufficient data to support the use of DWI for detecting metastatic disease in axillary nodes at this time.

In summary, although current breast MRI protocols do not consistently image the entire axilla in patients with newly diagnosed breast cancer over 2 cm in size and clinical node-positive, breast MRI can be beneficial for evaluation of tumor within the breast and may be helpful for the axilla in some circumstances.

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

D. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for staging of the axilla in clinically node-positive breast cancer patients.

Variant 6: Female. Newly diagnosed breast cancer, greater than 2 cm, with clinical node-positive. Initial imaging of the axilla following diagnostic mammography or DBT (prior to treatment).

E. US Axilla

Axillary US is typically performed for assessing nodal disease in patients with newly diagnosed breast carcinoma and palpable adenopathy [7,92]. In a retrospective series of 1,287 breast cancer patients who had preoperative axillary US-FNA followed by SLNB or ALND, the group with axillary US-FNA had a higher number of metastatic axillary lymph nodes than those with micro- or macrometastatic nodal disease on SLNB. This suggests that patients with US visible nodal disease,

confirmed by axillary US-FNA, have more extensive nodal involvement [60]. Positive axillary US, confirmed with biopsy, helps to identify patients with higher tumor burden [54,55], and as such, these patients can proceed directly to ALND. However, axillary US is not able to detect all metastatic nodes and therefore cannot replace SLNB or ALND [58]. It is well known that negative axillary US with or without biopsy does not rule out nodal disease [58]. The sensitivity of US-guided biopsy also has variable sensitivity ranging from 52% to 90%, whereas the specificity is higher, ranging from 98% to 100% [59-63]. For many cases, axillary US can differentiate patients with high lymph node tumor burden from patients with low lymph node tumor burden, suggesting that those with positive axillary nodes on percutaneous biopsy should have ALND rather than SLNB, especially because the Z0011 criteria do not apply to patients with clinically palpable adenopathy. Axillary US features favoring nodal metastases include cortical thickness of >0.3 cm and absence of a fatty hilum, a finding with a high positive predictive value (PPV) of 90% to 93% [103-105].

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.

The NSABP B-04 and King's/Cambridge trials showed that treatment of the axilla with surgery or radiation therapy in patients with clinically node-negative breast cancer substantially reduces the risk of axillary recurrence [106,107] (see the ACR Appropriateness Criteria® topic on "Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer" [97].

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
A. CT Chest, Abdomen, and Pelvis

CT allows assessment of the axillary level II and III nodal regions that are not always well visualized on US. However, there are no data to support the routine use of CT for assessing a new palpable axillary lump in breast cancer patients at midtreatment of NAC and very limited data on the use of CT for assessing nodal response. One retrospective study reviewed the pretreatment breast MRI, FDG-PET/CT, and CT imaging on 348 breast cancer patients who received NAC followed by surgery and reported that patients with higher radiological nodal stage on imaging were more likely to have node-positivity upon surgery, larger nodal metastases, and more frequent extranodal extension [108].

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
B. Digital Breast Tomosynthesis Diagnostic

DBT allows visualization of axillary level I nodal regions but does not fully assess the axilla. Although not typically used for axillary evaluation, DBT may be helpful in evaluating for progression of the primary breast malignancy.

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
C. FDG-PET/CT Skull Base to Mid-Thigh

There is no relevant literature to support the use of FDG-PET/CT for assessing a new palpable axillary mass during midtreatment of NAC.

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
D. Mammography Diagnostic

Similar to DBT, mammography does not visualize the entire axilla and is not useful for assessing an axillary lump. Mammography may be performed to determine if there is also progression of the primary breast carcinoma.

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
E. MRI Breast

There is no evidence to support the use of breast MRI as the initial imaging test for assessing a new palpable axillary lump during NAC treatment. However, breast MRI may be helpful in assessing response of the primary breast tumor and associated axillary adenopathy.

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
F. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for assessing a new palpable axillary lump during midtreatment of NAC.

Variant 7: Female. Breast cancer, greater than 2 cm in size, at mid-treatment of neoadjuvant chemotherapy, with initial clinical node-negative disease but now presenting with new palpable axillary lump. Imaging of the axilla at mid-treatment.
G. US Axilla

Despite the limited literature addressing the use of axillary US for assessing a new palpable axillary lump during midtreatment, axillary US may be useful in this scenario because of its noninvasive nature. If the axillary US finding is uncertain, biopsy can be performed [86]. A small single-center study looking at the role of midtreatment axillary US in 159 patients of mixed breast cancer subtypes observed that US performed better for residual axillary nodal tumor burden than for residual index breast cancer and provided more consistent results across different cancer subtypes [109].

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

NAC is used to treat operable large tumors, nonoperable locally advanced tumors, and inflammatory breast cancers prior to definitive surgical management. If there is pathological response to NAC and the patient is clinically node-negative, SLNB is preferred over ALND in order to minimize morbidity. In a study of 925 patients treated with NAC, 5-year overall survival was superior for patients with pathologic complete remission of cytological proven axillary lymph node metastases (93%) compared with those without complete response (72%) [110].

Clinically node-negative breast cancer patients treated with NAC can undergo SLNB compared with those who undergo upfront surgery because they have similar locoregional recurrence, disease-free survival, and overall survival rates [111]. In a study of 3,746 patients with clinically node-negative breast cancer, the FNR of SLNB after NAC (5.9%–12%) was similar between those

receiving SLNB after NAC and upfront surgery [111]. If the axilla is initially clinically positive but has a clinical complete response after NAC treatment, then SLNB may be performed if the clipped node is removed, a dual tracer is used, and more than 2 sentinel nodes are removed [7]. Otherwise ALND should be performed.

The prognostic significance of response to NAC can vary between the primary breast tumor and the axilla and based on tumor receptor subtypes (eg, triple negative versus HER2 positive cancers) [112]. Those patients with initial node-positive breast cancer who achieve complete pathological response after NAC have similar prognoses as to those with clinical node-negativity [112]. Even though no imaging will replace SLNB or ALND for staging, the ability to assess response during or after NAC helps to predict outcomes and aids with treatment planning.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.
A. CT Chest, Abdomen, and Pelvis

There is no relevant literature to support the use of contrast-enhanced or noncontrast-enhanced CT to image the axilla after completion of NAC.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.
B. Digital Breast Tomosynthesis Diagnostic

There are no data to support the use of DBT to image the axilla after completion of NAC in patients with initial clinical node-negative disease and no new clinical concern or palpable axillary lump. For assessment of the primary breast tumor, one prospective study of 51 stage II and III breast cancer patients reported that MRI and DBT outperformed mammography and whole-breast US in the prediction of pathologic complete response [113]. However, this study cannot be extrapolated to axillary nodal disease.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.
C. FDG-PET/CT Skull Base to Mid-Thigh

There are limited data to support the use of FDG-PET/CT for assessing response of nodal disease from breast cancer following completion of NAC. Most studies report changes in size and SUV measurements of the index breast carcinoma or distant metastases. Four meta-analyses of FDG-PET/CT in detecting residual breast disease reported a pooled sensitivity of 81% to 84% and a specificity of 66% to 79% [114-118]. FDG-PET/CT is limited by the lack of consensus for standard criteria to measure response of the index tumor or nodal disease, and SUV measurements underestimating the amount of residual disease when the residual tumor size is small. In one meta-analysis, 4 of 19 studies reported a pooled sensitivity of 92% and an NPV of 88% in predicting regional lymph node response but the specificity was inconclusive [118]. Even though there is suggestion that the early changes in SUV may correlate with NAC response, a negative FDG-PET/CT does not guarantee that the final pathology is also negative, especially if the residual tumor is of low to moderate grade [119,120]. A recent report from the National Cancer Database of 33,162 patients concluded that a breast-only response from a node-only response or both breast and nodal response had different prognoses, which also varied with tumor subtypes [112]. Given the limited data, FDG-PET/CT is not currently performed post-NAC to restage the axilla.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

D. Mammography Diagnostic

Mammography can reliably be used to assess response of a primary breast malignancy to NAC. However, it is less useful in assessing axillary nodal response to therapy given that the axilla is incompletely visualized.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

E. MRI Breast

The role of breast MRI in detecting residual tumor within the axillary lymph nodes remains questionable [121]. Based on a 26-study meta-analysis, MRI has moderate sensitivity (77%) and specificity (90%) for detecting residual disease after NAC [122,123]. Most of the literature confirms the superiority of MRI in detecting residual tumor within the breast after NAC compared with mammography, US, and physical examination [124]. However, it is not proven that preoperative MRI is associated with improved surgical outcomes or lower recurrence rates [125]. A meta-analysis of 44 studies reported MRI sensitivity for detecting residual disease in the breast was 92% and a specificity of 90% [124]. MRI also demonstrates higher accuracy in triple negative tumors and HER2-positive tumors [126-128]. The performance of MRI for the primary breast lesion cannot be extrapolated into MRI performance of the axillary nodal disease [112]. Therefore, MRI is not used routinely for predicting response of axillary nodal disease.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

F. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for assessing response after treatment with NAC.

Variant 8: Female. Breast cancer, greater than 2 cm in size, clinical node-negative. Imaging of the axilla after completion of neoadjuvant chemotherapy.

G. US Axilla

The role of axillary US to assess the axilla after NAC remains controversial [7]. Most of the data from multicenter trials involve patients with initial clinical node-positive disease [129,130]. These studies, evaluating SLNB after NAC, report that the accuracy rates of SLNB are acceptable. With the variable sensitivity and specificity of axillary US, even in combination with percutaneous biopsy, axillary US is not able to replace SLNB. Therefore, axillary US may not assess axillary response after chemotherapy.

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.

NAC is used to treat operable large tumors, nonoperable locally advanced tumors, and inflammatory breast cancers prior to definitive surgical management. Information on the residual disease or positive axillary nodes after NAC is beneficial for the determination of the axillary surgical management and for the need of radiation therapy [7]. The guidelines define low tumor burden in the axilla as nodal disease that is image-detected disease not apparent on clinical examination; however, the imaging test is not specified in the guidelines. If there is pathological response to NAC and the patient is clinically node-negative, SLNB is preferred over ALND in order to minimize morbidity. In a study of 925 patients treated with NAC, 5-year overall survival was superior for patients with pathologic complete remission of the cytological proven axillary lymph node metastases (93%) compared with those without complete response (72%) [110].

Clinically node-negative breast cancer patients treated with NAC can undergo SLNB compared with those who undergo upfront surgery because they have similar locoregional recurrences, disease-free survival, and overall survival rates [111]. In a study of 3,746 patients with clinically node-negative breast cancer, the FNR of SLNB after NAC (5.9%–12%) was similar between those receiving SLNB after NAC and upfront surgery [111]. If the axilla is initially clinically positive but has a clinical complete response after treatment, SLNB may be performed if the clipped node is removed, a dual tracer is used, and more than 2 sentinel nodes are removed [7]. Otherwise ALND should be performed.

For clinically node-positive breast cancer, several multicenter trials have demonstrated similar findings with good detection rate and FNR ranging from 7.3% to 12.6%, which improved with the dual tracer method and if >3 SLNs were removed. The ACOSOG Z1071 multicenter trial evaluating the effectiveness of SLNB after NAC reported a detection rate of 93% and the FNR of 13% [11]. The FNR drops to 11% when mapping was performed with both blue dye and a radioisotope (dual tracer) and further decreased to 9% when ≥3 SLNs were removed [11]. The Sentinel Node Biopsy Following Neoadjuvant Chemotherapy trial reported an FNR of 8% but isolated tumor cells were considered positive. The use of a dual tracer was also found to lower FNRs [9]. The SENTinel NeoAdjuvant study consisting of initially clinically node-positive patients who converted to ycN0 after NAC reported overall FNR of 14.2%, which decreased to 8.6% if a dual tracer was used, and further decreased to 7% if ≥3 SLNs were removed [12]. If the clipped node was in the resected nodal tissue, FNR further dropped to 7% [10]. Based on one prospective single-center study of 85 patients, patients with T1/T2 disease and ≤3 level I or II axillary nodes on pretreatment US can undergo targeted ALND after NAC instead of full ALND given a reported FNR of 2% as a targeted ALND consists of removing the biopsy proven metastatic node in addition to the SLNs and any pre-NAC positive nodes [8].

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
A. CT Chest, Abdomen, and Pelvis

There are no relevant data to support the use of contrast-enhanced or noncontrast-enhanced CT to image the axilla after completion of NAC.

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
B. Digital Breast Tomosynthesis Diagnostic

There are no data to support the use of DBT to image the axilla after completion of NAC in patients with initial clinical node-positive disease pre-NAC and who have no clinical suspicion of disease progression or new axillary nodal disease. When comparing mammography to DBT, one prospective study of 51 stage II and III breast cancer patients reported that MRI and DBT outperformed mammography and whole-breast US in the prediction of pathologic complete response [113]. Unfortunately, this cannot be extrapolated to axillary nodal disease because DBT does not completely visualize the entire axilla. DBT may be useful in selected cases after NAC because it may identify response within a clipped node and provide a means for image guided localization [131].

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
C. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT is widely used to assess response to therapy, despite the lack of consensus on the criteria for determining response. The reported pooled sensitivity for FDG-PET/CT is 71% to 88% and specificity is 69% to 79.3% [117,120,132,133]. Most of the studies do not specifically report on response of the regional lymph nodes. In one meta-analysis of four studies involving 920 patients, the sensitivity of FDG-PET/CT for regional lymph node response assessment is 92% [118]. In another meta-analysis of 987 abstracts, only four were eligible for analysis, yielding a PPV between 40% and 100% [134].

The timing of FDG-PET/CT is critical and varies between studies, with some investigators demonstrating FDG-PET/CT has more accuracy during NAC (after first or second cycles of chemotherapy) than after NAC, whereas MRI performed better at the end of NAC [118,133]. MRI had higher sensitivity in predicting the pathologic response after NAC in 13 studies involving 575 patients, and FDG-PET/CT had a higher specificity in these same 13 studies involving 618 patients [132]. Currently, there is lack of consensus that early response detected by imaging tests translates into improved overall outcomes. A negative FDG-PET/CT during or after NAC does not necessarily correlate with final pathological node-negative disease, as demonstrated in one series of 206 patients [119].

SUV values may underestimate or overestimate response when the residual tumor is small. Some investigators have reported SUV_{max} <2.5 as negative [120], whereas others demonstrated that the change in SUV before and after NAC or change between the pre-NAC FDG-PET/CT examination and the examination performed after the first or second cycle of NAC were better predictors of response [134-136]. Despite the research, there is no accurate noninvasive test to replace SLNB or ALND at this time. However, one benefit of using FDG-PET/CT is that this examination can also evaluate other sites of metastases in a single study [102]. A search for a noninvasive restaging technique for identifying patients with axillary complete response is ongoing.

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
D. Mammography Diagnostic

Mammography can reliably be used to assess response of a primary breast malignancy to NAC. However, it is less useful in assessing axillary nodal response to therapy given that the axilla is incompletely visualized.

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
E. MRI Breast

In patients who have had axillary nodal metastatic disease diagnosed prior to NAC for breast cancer, there is little consensus on how to image the axilla subsequently. MRI has some limitations in evaluating the axilla and is unlikely to be the sole imaging test for estimating residual tumor burden preoperatively [121]. However, a combination of tests with axillary US, MRI, or FDG-PET/CT may be the future direction for clinical trials trying to answer such questions (https://clinicaltrials.gov/ct2/show/NCT03188393). At least one study suggests that measurements at 360 seconds after contrast administration provides the most accurate measurements of size, compared with the earlier phase or the later phase of the dynamic series [137].

Most of the literature focuses on the evaluation of response of the primary breast tumor after NAC and MRI superiority to mammogram, US, and physical examination in this setting [124].

The performance of MRI for the primary breast lesion cannot be extrapolated to MRI performance of the axillary nodal disease [112]. Therefore, MRI is not used routinely for predicting response of axillary nodal disease.

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
F. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for assessing response after treatment with NAC

Variant 9: Female. Breast cancer, greater than 2 cm in size, clinical node-positive. Imaging of the axilla after completion of neoadjuvant chemotherapy and prior to surgery.
G. US Axilla

Because of its noninvasive nature, axillary US may evaluate for residual axillary nodal disease despite its PPV of 60% to 81%, NPV of 43% to 74%, and specificity of 37% to 92% [138]. However, the sensitivity of US (71%) for prediction of residual nodal metastatic disease was higher than that of clinical examination and MRI/PET in most studies [139]. Limited data have suggested that the sensitivity of axillary US is higher for some subtypes such as triple negative breast cancer (69%) and HER2 positive breast cancer (71%) [140,141].

In the Z1071 prospective trial consisting of clinical T0-T4, N1-N2, and M0 of 611 patients, the post-NAC US features predictive of residual nodal disease included continued loss of the fatty hilum, cortical thickness of ≥0.3 cm, and a decrease in lymph node size [87]. However, a normal axillary US does not exclude pathological nodal disease [142]. The absence of a fatty hilum can be an indication for performing a biopsy [88,143]. A clip placed at the time of biopsy prior to NAC can help to reduce the FNR of SLNB [8,10]. However, the clipped node is not the SLN in 23% of cases based on a single-center prospective study [8]. The detection rate after radioactive seed placement was 97% [138].

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.

In a patient with a history of breast cancer, recurrent disease can occur within the ipsilateral breast after breast conserving surgery (ie, in-breast recurrent disease), within the ipsilateral chest wall after mastectomy, or within the ipsilateral axilla. Patients may also develop a new second primary breast cancer within the ipsilateral breast or in the contralateral breast, or develop distant metastatic disease; these latter scenarios are not within the scope of this document. Therefore, patients presenting with recurrent disease fall into 3 main groups: post–breast-conserving surgery, postmastectomy, and localized axillary recurrent disease. For patient's status post–breast-conservation surgery (BCS), imaging to detect the local recurrence can be challenging because of background postsurgical and/or postradiation changes, and, if detected, treatment involves mastectomy. For patient's status postmastectomy, chest wall recurrence without nodal recurrence is the most common presentation [144,145]. Invasion into the ribs, sternum, or other thoracic structures is considered to have poor prognosis; however, carefully selected patients may have resection with excellent outcomes [146]. Postmastectomy radiation therapy is beneficial in reducing locoregional recurrent disease and breast cancer mortality in patients with original node-positive disease but not in patients with original node-negative disease, based on a meta-analysis of 3,786 women postmastectomy radiation therapy and axillary dissection [144]. For those

presenting with localized axillary recurrence, both ipsilateral and contralateral presentations have been reported [145].

Advances in the systemic therapies and radiation therapy have lowered the risks of isolated locoregional recurrences. Locoregional recurrent disease accounts for less than 10% to 15% of all recurrences [147]. Individual risk for recurrent disease is difficult to predict given variable settings, patient populations, and treatments. Systematic literature review on isolated local breast cancer recurrence reports the median annual incidence rates of 0.6% (range: 0.4%–1.1%) [148]. The risk of recurrence is related to the biology of the cancer (high grade, lymphovascular invasion, and nonluminal tumor type), tumor burden (size >5 cm), surgical margins, and lymph node involvement at initial diagnosis [7,92,149-151]. Per the European Society of Medical Oncology guidelines, the annual hazard of recurrence peaks in the second year after diagnosis and remains at 2% to 5% in the 5th to 20th years [91]. Patients with node-positive disease at initial diagnosis of breast cancer are at higher risk for recurrence than patients with node-negative disease [150,152]. The likelihood of local recurrent disease for original node-negative breast cancer is 6.7% versus 11% for original node-positive disease at 5 years [153].

This discussion is based on the understanding that patients post-BCS or postmastectomy with reconstruction have likely already undergone a diagnostic mammogram or DBT to evaluate for or rule out in-breast recurrent disease. Therefore, the possible next imaging test or initial imaging test for the axilla are discussed below for each modality.

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.
A. CT Chest, Abdomen, and Pelvis

There are no data to support the utilization of CT for axillary node assessment in the setting of newly diagnosed in-breast recurrent disease or as the initial imaging test for the axilla. However, CT can be performed concurrently at the time of the locally recurrent breast cancer diagnosis to rule out distant metastatic disease and for pretreatment planning. CT allows visualization of any chest wall involvement as well as the relationship of the recurrent disease to regional vital structures such as axillary artery and vein [7,92,154].

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.
B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET/CT may be ordered concurrently at the time of the locally recurrent breast cancer diagnosis to rule out distant metastatic disease and for pretreatment planning. PET/CT is helpful in identifying unsuspected regional nodal disease or distant metastases in certain situations such as in patients with locally advanced breast cancer and inflammatory breast cancer [7]. In a meta-analysis of 26 studies involving 1,752 patients with suspected recurrent breast cancer, the pooled sensitivity for FDG-PET/CT was 90% and specificity was 81%; FDG-PET/CT is more accurate than PET alone [155]. The authors noted that the studies were heterogeneous, and therefore the analysis had limitations. In-breast recurrent disease versus chest wall or nodal recurrent disease was not specified [155].

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.
C. MRI Breast

Breast MRI is a highly sensitive imaging modality for assessing disease within the breast [156,157]. There are no data to support breast MRI as the initial imaging test of the axilla in patients with newly diagnosed locally recurrent breast cancer to evaluate for additional nodal disease. The MRI may be ordered after the mammogram or DBT to evaluate additional recurrent disease or disease extent within the breast not completely seen on mammogram or DBT [158]. An observational cohort study of 13,266 women and a single-center study of 1,521 women reported higher cancer detection rate with MRI compared with mammography [156,157].

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.
D. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for imaging the axilla in patients with newly diagnosed recurrent disease.

Variant 10: Female. Newly diagnosed locally recurrent breast cancer. Initial imaging of the axilla following diagnostic mammography or DBT.
E. US Axilla

US can be used to evaluate the axilla in patients with newly diagnosed recurrent breast cancer after BCS, after mastectomy, or with suspicion of recurrent nodal disease in the axilla. Diagnostic mammogram and/or DBT to evaluate for in-breast recurrent disease has also been shown to be helpful [154]. Axillary US can also provide guidance for percutaneous biopsy of any suspicious nodes because it influences potential surgical approach (SLNB versus full ALND).

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.
A. CT Chest, Abdomen, and Pelvis

CT is not frequently used to assess abnormal axillary nodes detected on US or mammography; however, it is often used to evaluate a biopsy-proven nonbreast malignant axillary node. One study with 297 patients from two centers found no change in the number of second axillary surgeries between patients who received a CT scan of their axilla versus those who did not [47]. There are little data to support the use of contrast- or noncontrast-enhanced CT for this indication if there is no clinical suspicion of additional systemic disease.

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.
B. FDG-PET/CT Skull Base to Mid-Thigh

Less than 1% of breast cancers initially present as axillary adenopathy [32,33]. Historically, mammography, US, and breast MRI have helped to identify the primary malignancy in patients with pathologic axillary adenopathy from unknown primary. However, mammography and US have relatively low sensitivity for detecting the primary breast lesion [31,159]. The addition of breast MRI has improved sensitivity [160] because MRI is able to detect the primary breast lesion in 36% to 86% of cases [39]. Although PET/CT can be helpful in identifying the site of an unknown primary, for breast cancer, there are little data to support its routine use.

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.
C. MRI Breast

Once the suspicious axillary node has been documented as metastatic nodal disease, then breast MRI can detect a mammographic or sonographic occult breast lesion with high sensitivity for detecting an in-breast lesion or confirm no breast primary [34,35]. In a meta-analysis of 8 retrospective studies involving 220 patients, MRI detects an occult breast cancer in 72% of cases with a pooled sensitivity of 90% and a specificity of 31% [39]. MRI can also help further characterize the axillary mass by evaluating its relationship to adjacent vessels, the chest wall, and other axillary structures. In a meta-analysis of 26 studies looking at the diagnostic performance of MRI in detecting metastatic nodal disease, the pooled sensitivity and specificity in patients with breast cancer is 77% and 90%, respectively [123].

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.

D. Sestamibi MBI

There is no relevant literature supporting the use of Tc-99m sestamibi MBI for imaging the axilla in patients with suspicious axillary nodes detected on mammography and US.

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.

E. US-Guided Core Biopsy Axillary Node

US-guided biopsy (either core needle biopsy or FNA) may provide a diagnosis for morphologically abnormal lymph nodes detected on imaging. In a meta-analysis of 1,353 patients from 6 studies, US-guided core needle biopsy was superior to US-guided FNA in diagnosing axillary nodal metastases with reported pooled sensitivity of 88% versus 74%, respectively. Both US-guided core needle biopsy and FNA had a high specificity of 100% [86]. Complications such as pain, hematoma, and bruising were higher with core needle biopsy than FNA.

Variant 11: Female. Suspicious axillary node on mammography or ultrasound. Next imaging study.

F. US-Guided Fine Needle Aspiration Biopsy Axillary Node

US-guided FNA biopsy is a reliable procedure associated with minimal complications. In a meta-analysis of 31 studies, US-guided FNA improved the median sensitivity of US from 61% to 79% and specificity from 82.0% to 100% [62]. In another publication of 3,781 breast cancer patients, the sensitivity and specificity of axillary US alone were 59% and 89%, respectively. The specificity improved to 100% when axillary US was combined with FNA. FNA resulted in sensitivity, specificity, PPV, NPV, and accuracy of 52%, 100%, 100%, 74.8%, and 80%, respectively [63]. The decision to perform FNA or core biopsy of a suspicious axillary node is not standardized and depends on provider choice and patient factors.

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.

A. Digital Breast Tomosynthesis Diagnostic

When a suspicious lymph node is identified on imaging, correlation with clinical history and physical examination is essential to guide management. If a breast primary is of concern, mammography and DBTcan assist in identifying the breast primary. At least one study has shown that DBT is superior to full-field digital mammography for detection of subtle architectural distortion [161].

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.
B. Mammography Diagnostic

When a suspicious lymph node is identified on imaging, other than mammography or DBT, correlation with clinical history and physical examination is essential to guide further imaging. If a breast primary is of concern, mammography and/or DBT may assist in identifying a primary breast malignancy. Mammography is not optimal for evaluating the axilla. Valente et al [162] found that mammography has a high FNR in the detection of axillary metastatic lymphadenopathy.

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.
C. US Axilla

If mammogram or DBT identifies a primary breast malignancy, then axillary US after mammogram and/or DBT may evaluate the nodal size, nodal cortical, and hilar morphology. The sensitivity and specificity for axillary US for differentiating benign from malignant nodes is variable, with reported sensitivity ranging from 26% to 94% and specificity from 53% to 98% [58]. Axillary US alone has relatively low NPV and sensitivity and therefore is not a reliable predictor of axillary nodal burden [83,84]. When combined with needle biopsy, however, the sensitivity improves from 61% to 79% in a meta-analysis of 21 studies [54,62,85].

Some US features that are more likely to be associated with malignancy include short-axis diameter >1 cm, cortical thickness >0.3 cm, and absence of a fatty hilum [87-90]. The absence of a fatty hilum has the highest PPV (90% to 93%) for malignancy [103,104]. A suspicious node on US warrants percutaneous biopsy because a positive axillary US helps to identify those patients at risk for higher tumor burden [54,55]. However, a negative axillary US with or without biopsy does not rule out nodal disease [58].

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.
D. US-Guided Core Biopsy Axillary Node

Based on a meta-analysis of 1,353 patients with newly diagnosed breast cancer, US-guided core needle biopsy is superior to US-guided FNA with a reported sensitivity of 88% for core biopsy and 74% for FNA [86]. The overall sensitivity of US-guided biopsy ranges from 52% to 90%, whereas the specificity ranges from 98% to 100% [59-63].

Variant 12: Female. Suspicious axillary node on any other imaging modality (excluding mammography and ultrasound). Next imaging study.
E. US-Guided Fine Needle Aspiration Biopsy Axillary Node

US-guided FNA of an axillary node is a well-tolerated low-risk procedure that can accurately confirm metastatic disease in a suspicious lymph node. Although a recent meta-analysis of 1,353 patients showed that US-guided core needle biopsy is superior to US-guided FNA [86], FNA does have a role in diagnosing patients with suspicious lymphadenopathy, especially if a patient is unable to discontinue anticoagulants. On-site cytopathologist is not a common practice even though immediate pathology assessment for inadequate sampling is very beneficial because inadequate sampling rates can occur in 5% to 10% of cases [163-165].

Summary of Recommendations

- **Variant 1**: US axilla is usually appropriate for the initial imaging of the axilla in a female patient with a new palpable, unilateral, axillary lump.
- **Variant 2**: US axilla is usually appropriate for the initial imaging of the axilla in a female patient with a new palpable, bilateral, axillary lump.
- **Variant 3**: US axilla may be appropriate for the initial imaging of the axilla in a female patient with newly diagnosed breast cancer with a tumor size of ≤2 cm in which the patient is clinical node-negative and has already had a diagnostic mammography or DBT.
- **Variant 4**: US axilla is usually appropriate for the initial imaging of the axilla in a female patient with newly diagnosed breast cancer with a tumor size of ≤2 cm in which the patient is clinical node-positive and has already had a diagnostic mammography or DBT. The panel did not agree on recommending MRI breast without and with IV contrast as the initial imaging test of the axilla for this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this modality in the clinical scenario. Imaging with this procedure in this patient population is controversial but may be appropriate.
- **Variant 5**: US axilla or MRI breast without and with IV contrast may be appropriate for the initial imaging of the axilla in a female patient with newly diagnosed breast cancer with a tumor size >2 cm in which the patient is clinical node-negative and has already had a diagnostic mammography or DBT.
- **Variant 6**: US axilla is usually appropriate for the initial imaging of the axilla in a female patient with newly diagnosed breast cancer with a tumor size >2 cm in which the patient is clinical node-positive and has already had a diagnostic mammography or DBT that was performed prior to treatment.
- **Variant 7**: US axilla is usually appropriate for the initial imaging of the axilla at midtreatment of NAC in a female patient with breast cancer with a tumor size >2 cm in which the patient initially had clinical node-negative disease but is now presenting with a new palpable axillary lump.
- **Variant 8**: MRI breast without and with IV contrast may be appropriate for imaging of the axilla in a female patient with breast cancer with a tumor size >2 cm in which the patient is clinical node-negative and has completed NAC. The panel did not agree on recommending US axilla for this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this modality for the clinical scenario. Imaging with this procedure in this patient population is controversial but may be appropriate.
- **Variant 9**: US axilla is usually appropriate for imaging of the axilla prior to surgery in a female patient with breast cancer with a tumor size >2 cm in which the patient is clinical node-positive and has completed NAC.
- **Variant 10**: US axilla, or MRI of the breast without and with IV contrast, or FDG-PET/CT of the skull base to mid-thigh may be appropriate for the initial imaging of the axilla in a female patient with newly diagnosed locally recurrent breast cancer. In this scenario, diagnostic mammography or DBT has already been performed on the patient.
- **Variant 11**: US-guided core biopsy of the axillary node or US-guided FNA biopsy of the axillary node is usually appropriate for a next imaging study in a female patient with a suspicious axillary node identified through mammography or US. The biopsy procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). The panel did not agree on recommending MRI of the breast without and with IV contrast for this clinical scenario. There

is insufficient medical literature to conclude whether or not these patients would benefit from this modality for the clinical scenario. Imaging with this procedure in this patient population is controversial but may be appropriate.

- **Variant 12**: US axilla, or diagnostic DBT, or diagnostic mammography is usually appropriate for a next imaging study in a female patient with a suspicious axillary node identified on any other imaging modality (excluding mammography and US). 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). The panel did not agree on recommending US-guided core biopsy of the axillary node for this clinical scenario. There is insufficient medical literature to conclude whether or not these patients would benefit from this modality for the clinical scenario. Imaging with this procedure in this patient population is controversial but may be appropriate.

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, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

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 [166].

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."		

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Disclaimer

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.

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