

**American College of Radiology  
ACR Appropriateness Criteria®  
Imaging of Invasive Breast Cancer**

**Variant 1:** Newly diagnosed. Clinical stage I-IIA (early stage) breast cancer at presentation. Evaluation for locoregional disease (includes invasive ductal carcinoma [IDC], or invasive lobular carcinoma [ILC], or not otherwise specified [NOS]).

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
MRI breast without and with IV contrast	Usually Appropriate	○
US axilla	May Be Appropriate	○
Mammography with IV contrast	May Be Appropriate	☼☼
MRI breast without IV contrast	Usually Not Appropriate	○
Bone scan whole body	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:** Newly diagnosed. Clinical stage I-IIA (early stage) breast cancer at presentation. Evaluation for distant disease (includes IDC, or ILC, or NOS).

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Not Appropriate	○
US breast	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
Mammography with IV contrast	Usually Not Appropriate	☼☼
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Bone scan whole body	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:****Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for locoregional disease (includes IDC, or ILC, or NOS).**

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Appropriate	○
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
MRI breast without and with IV contrast	Usually Appropriate	○
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
Mammography with IV contrast	May Be Appropriate	☼☼
MRI breast without IV contrast	Usually Not Appropriate	○
Bone scan whole body	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 4:****Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for distant disease. IDC or ILC that is ER+/HER2-.**

Procedure	Appropriateness Category	Relative Radiation Level
Bone scan whole body	Usually Appropriate	☼☼☼
CT chest abdomen pelvis with IV contrast	Usually Appropriate	☼☼☼☼
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
US axilla	Usually Not Appropriate	○
US breast	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
Mammography with IV contrast	Usually Not Appropriate	☼☼
MRI breast without and 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 5:**

**Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for distant disease. IDC or ILC that is HER2+ or triple negative (ER, PR, and HER2-).**

Procedure	Appropriateness Category	Relative Radiation Level
Bone scan whole body	Usually Appropriate	☼☼☼
CT chest abdomen pelvis with IV contrast	Usually Appropriate	☼☼☼☼
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
US axilla	Usually Not Appropriate	○
US breast	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
Mammography with IV contrast	Usually Not Appropriate	☼☼
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
MRI head without and with IV contrast	Usually Not Appropriate	○
MRI head without IV contrast	Usually Not Appropriate	○
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	☼☼☼☼
CT chest abdomen pelvis without IV contrast	Usually Not Appropriate	☼☼☼☼

**Variant 6:**

**Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for local recurrence in patient with history of BCT.**

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

**Variant 7:** Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for local recurrence in patient with history of mastectomy.

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

**Variant 8:** Suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory value in patient with history of BCT. Regardless of clinical stage at time of original presentation.

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

**Variant 9:** Suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory value in patient with history of mastectomy. Regardless of clinical stage at time of original presentation.

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

**Variant 10:**

**Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for distant metastatic disease.**

Procedure	Appropriateness Category	Relative Radiation Level
US axilla	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
MRI head without and with IV contrast	Usually Not Appropriate	○
MRI head without IV contrast	Usually Not Appropriate	○
Bone scan whole body	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 11:**

**Suspected distant recurrence of breast cancer based on symptoms, physical examination, or laboratory value. Regardless of clinical stage at time of original presentation.**

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

# IMAGING OF INVASIVE BREAST CANCER

Expert Panel on Breast Imaging: Elizabeth S. McDonald, MD, PhD<sup>a</sup>; John R. Scheel, MD, PhD, MPH<sup>b</sup>; Alana A. Lewin, MD<sup>c</sup>; Susan P. Weinstein, MD<sup>d</sup>; Katerina Dodelzon, MD<sup>e</sup>; Basak E. Dogan, MD<sup>f</sup>; Amy Fitzpatrick, MD<sup>g</sup>; Cherie M. Kuzmiak, DO<sup>h</sup>; Mary S. Newell, MD<sup>i</sup>; Lisa V. Paulis, MD<sup>j</sup>; Melissa Pilewskie, MD<sup>k</sup>; Lonie R. Salkowski, MD, PhD, MS<sup>l</sup>; H. Colleen Silva, MD<sup>m</sup>; Richard E. Sharpe Jr., MD, MBA<sup>n</sup>; Jennifer M. Specht, MD<sup>o</sup>; Gary A. Ulaner, MD, PhD<sup>p</sup>; Priscilla J. Slanetz, MD, MPH<sup>q</sup>.

## Summary of Literature Review

### **Introduction/Background**

In 2022, the American Cancer Society estimates more than 287,000 women in the United States will be diagnosed with and >43,000 will die from invasive breast cancer [1]. Invasive breast cancer is defined as a proliferation of cells in the breast milk ducts (ductal) or glands that make milk (lobular) that has spread outside of these components into the surrounding tissue. The American Joint Commission on Cancer (AJCC) categorizes invasive breast cancer anatomic stage based on tumor size, lymph node status (locoregional spread), and spread to distant sites (metastatic disease). Stage I/IIA cancers are <2 cm and involve ≤3 axillary lymph nodes or are 2 to 5 cm without axillary lymph node spread. Stage IIB include tumors that are >5 cm or 2 to 5 cm with 1 to 3 involved axillary nodes, and stage III tumors are any size with >3 involved axillary lymph nodes or direct extension to the skin or chest wall or >5 cm with 1 to 3 involved nodes. Locoregional spread refers to involvement of the draining regional lymph node basins. Although this usually refers to the ipsilateral axilla, regional spread can also be to the infraclavicular (level III axillary), supraclavicular, and internal mammary/parasternal nodal basins [2]. Contralateral lymph node involvement is classified as distant (stage IV) disease in the absence of synchronous contralateral breast malignancy [2]. Any clavicular nodal metastasis is classified as N3, whereas metastases to the internal mammary nodes are classified as N2 [3]. Stage IV disease has spread beyond the breast and locoregional lymph nodes to involve other areas in the body, such as the lungs, liver, bone or brain. In 2018, tumor grade, hormone receptor (estrogen [ER] and progesterone [PR]) status, and human epidermal growth factor (HER2) were added to improve prognostication, along with multigene panel results for earlier stage ER-positive tumors. Although AJCC anatomic staging is still used, validated prognostic biomarkers, as described above, now augment anatomic extent in a refined AJCC clinical prognostic stage to allow for more informed shared clinical decisions [4]. The difference between early (I/II) and later stage (III) is critical to management and prognosis because early stage carries a 93% to 98% 10-year survival, compared with a 70% to 88% 5-year survival for later stage [5]. It is important to note that in the United States, breast cancer mortality is 40% higher among Black women than among non-Hispanic White women (27.7 versus 20.0 deaths per 100,000 women from 2014 through 2018) [6,7]. The reasons for survival disparities are multifactorial, including access to care, social determinants of health, cancer genomics, and allostatic load. Lack of historical availability of diverse translational models of disease for drug development may also play a role. Correct staging in all women and men is critical because stage determines treatment, with recommendations ranging from lumpectomy and no chemotherapy to mastectomy with years of chemotherapy, immunotherapy, and hormonal treatment. The goal of this document is to formulate evidence-based guidelines that allow for correct staging, while avoiding unnecessary imaging that can lead to additional cost and testing without patient benefit.

Despite current American Society of Clinical Oncology (ASCO) Choosing Wisely<sup>®</sup> recommendations, inappropriate use of advanced imaging for staging occurs in 15% to 42% of women with early stage breast cancer [8,9] and results in follow-up imaging, biopsies, and delays in care without improvement in outcomes [9]. This document evaluates the evidence for imaging to determine extent of disease in the setting of newly diagnosed early-

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and later-stage breast cancer prior to treatment. Additionally, we investigate the use of surveillance imaging after completion of treatment, both in the asymptomatic and symptomatic settings. In the post-treatment setting, we differentiate recommended imaging algorithms by symptomatology, because routine screening of asymptomatic patients after treatment for metastatic disease does not provide survival benefit, but early detection of nonmetastatic recurrence does improve overall outcomes [10].

### **Special Imaging Considerations**

Although still investigational, whole body diffusion weighted imaging and whole body fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) PET/MRI may show improved staging compared with whole body FDG-PET/CT in patients with later-stage disease [11-15]. Further studies are warranted to support their use in routine practice.

Breast-specific gamma imaging (BSGI) or molecular breast imaging (MBI) have been evaluated in the setting of newly diagnosed disease. One of the largest studies by Sumkin et al [16] compared MRI, contrast-enhanced mammography (CEM), and MBI in 99 patients, and all modalities had similar cancer detection rates. In that study, MBI was effective for local staging with a similar visualization of index cancers and a higher specificity for additional malignancy than MRI. BSGI also showed a similar high sensitivity as MRI (88.8% versus 90.1%, respectively) and a higher specificity (92.3% versus 39.4%), respectively, in a different study [17]. BSGI/MBI may provide an alternative to MRI for preoperative estimation of total tumor size and extent of disease, although further study is warranted [18]. The use of  $^{16}\alpha$ - $^{18}\text{F}$ -fluoro- $^{17}\beta$ -estradiol noninvasively characterizes ER ligand-binding function of breast cancer lesions and can be used for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer [19].

### **Discussion of Procedures by Variant**

**Variant 1: Newly diagnosed. Clinical stage I-IIA (early stage) breast cancer at presentation. Evaluation for locoregional disease (includes invasive ductal carcinoma [IDC], or invasive lobular carcinoma [ILC], or not otherwise specified [NOS]).**

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

There is no evidence to support the use of Tc-99m bone scan whole body to evaluate for locoregional disease.

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

Few studies have evaluated the use of CT chest, abdomen, and pelvis with intravenous (IV) contrast to determine locoregional disease. A study investigating the use of CT at evaluating locoregional disease, stages I to III, adding CT to mammogram, ultrasound (US) and physical examination correctly changed the surgical approach in 13.1% of patients, based on final pathology. However, CT failed to show any disease (false-negative) in 10.8% and had a low sensitivity for detecting multicentric and multifocal tumors [20].

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR–Society of Advanced Body Imaging (SABI)–Society for Pediatric Radiology (SPR) practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast to evaluate for locoregional disease.

#### **Digital Breast Tomosynthesis Diagnostic**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). However, mammography is limited by breast density. In a prospective study of 111 consecutive women with newly diagnosed breast cancer, sensitivity of 2-D mammography for malignancy decreased from 100% in breasts that are almost entirely fatty to 45% in extremely dense breasts [22]. In addition, 2-D mammography was more sensitive than US in detecting ductal carcinoma in situ (DCIS) and less sensitive in detecting ILC.

Digital breast tomosynthesis (DBT) shows a higher overall sensitivity, compared with 2-D mammography, with a similar specificity. Overall sensitivity for DBT was 88.2% compared with 78.3% for 2-D mammography [23]. DBT also has a higher sensitivity for detecting multifocal, multicentric, and contralateral breast cancer [24,25]. The improved diagnostic performance of DBT over 2-D mammography in breast cancer staging was limited to women with nondense breasts in 1 study [24], but not others [25].

The correlation between mammographic size and pathologic size is variable. Some studies show mammographic size to be superior to US [26], whereas others show it to be inferior in the case of invasive lobular histology [27]. At least some of this variation may be related to tumor subtype. Mammography shows a higher correlation with pathologic size for DCIS and HER2/neu-negative invasive cancers and a lower correlation for hormone receptor–negative and HER2/neu-positive invasive cancers compared with US [27]. The accuracy of DBT in assessing tumor size was 70.4% compared with 60.2% on 2-D mammography [28]. However, The Screening with Tomosynthesis Or standard Mammography-2 (STORM-2) trial showed that DBT tended to overestimate tumor size in women with dense breasts, compared with those with nondense breasts; this was more likely to impact management in women with larger tumors [29]. Despite the limitations of mammography in women with dense breasts, breast density was not a predictor of positive margins or conversion to mastectomy [30].

However, 2-D mammography is limited in detecting and measuring the size of ILC, which often presents as architectural distortion and uncommonly has associated calcifications [31]. Multiple studies have shown DBT to be superior to digital mammography (DM) alone in ILC detection, with the differential performance between DM/DBT and DM greatest in ILC when compared with IDC [32]. Therefore, it follows that DBT is also more accurate than DM in evaluating extent of disease for this subtype, which is commonly multicentric, multifocal, and sometimes bilateral. Still, DBT can underestimate the true pathologic extent of ILC [33], so MRI may be warranted in this subtype, as discussed below. In a retrospective study of 904 women with breast cancer (n = 97 ILC) imaged with mammography ± US, 38.8% of women with ILC undergoing breast-conserving surgery required re-excision compared with 22.3% with IDC [34].

Due to patient positioning constraints, 2-D mammography and DBT have limited value for evaluating the axilla. In a single-institution retrospective study of 3,944 patients with breast cancer, mammography improved the sensitivity over US alone for distinguishing N0 to N1 from N2 and N3, but at a lower specificity [35]. After the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial supported the omission of axillary lymph node dissection in women with <3 positive sentinel lymph nodes undergoing breast-conserving surgery and radiation therapy, some providers now request that radiologists not image the axilla in the setting of clinically node-negative disease [36]. Even when neoadjuvant chemotherapy is planned, radiologists should be thoughtful about whether to image the axilla, discussing risks and benefits with surgical colleagues, because it is not universally recommended [37].

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

FDG-PET/CT has limited sensitivity for subcentimeter lesions. For this reason, it is seldom used for determining locoregional extent in the breast. Nevertheless, some studies have evaluated the use of PET/CT for detecting the primary tumor and estimating tumor size. From these studies, the overall sensitivity for detecting the primary tumor was 77% to 94% [38-40]. The sensitivity of PET/CT is lower (59%) when the tumor is ≤1 cm [41]. PET/CT is inferior at estimating T stage compared with MRI (T-stage accuracy is 68% with PET/CT versus 82% with MRI,  $P < .05$ ). Specificity ranged from 94% to 100% [38,39]. Additionally, PET/CT failed to identify additional lesions in up to 57% of patients with multicentric or multifocal disease [40].

PET/CT has the potential to have greater sensitivity than US for axillary staging because it uses a functional measurement instead of an anatomic determination (eg, cortical thickness, loss of fatty hilum) as criteria for determining suspicion for metastatic disease [42]. Surgical studies show that 21% to 33% of T1 and 45% to 60% T2 tumors with normal appearing lymph nodes have metastatic disease on pathological examination [43]. Thus, studies have queried whether a functional measurement might be better. One study retrospectively evaluated PET/CT in 826 consecutive patients with breast cancer and showed a sensitivity and specificity of 74.7% and 83.4%, respectively, for identifying metastatic disease. Studies show a negative predictive value (NPV) from 87% to 88% [39,44]. Other studies show the sensitivity and specificity for detecting lymph node metastasis as 79% and 100%, respectively [38]. However, Sohn et al [45] showed a higher sensitivity for US plus fine-needle aspiration (FNA) at determining lymph node status than PET/CT (83% versus 80%, respectively). Despite extensive scientific investigation, given the results above and the Z0011 trial, the role of PET/CT in determining locoregional extent is likely nominal.

### **Mammography Diagnostic**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). However, mammography is limited by breast density. In a prospective study of 111 consecutive women with newly diagnosed breast cancer, the sensitivity of 2-D mammography for malignancy decreased from 100% in breasts that are almost



entirely fatty to 45% in extremely dense breasts [22]. In addition, 2-D mammography was more sensitive than US in detecting DCIS and less sensitive in detecting ILC.

DBT shows a higher overall sensitivity, compared with 2-D mammography, with similar specificity. Overall sensitivity for DBT was 88.2% compared with 78.3% [23]. DBT has a higher sensitivity for detecting multifocal, multicentric, and contralateral breast cancer [24,25]. The improved diagnostic performance of DBT over 2-D mammography in breast cancer staging was limited to women with nondense breasts in 1 study [24], but not others [25].

The correlation between mammographic size and pathologic size is variable. Some studies demonstrate the assessment of size with mammography to be superior to US [26], whereas others show it to be inferior [46]. At least some of this variation may be related to tumor subtype. Mammography shows a higher correlation with pathologic size for DCIS and HER2/neu-negative invasive cancers and a lower correlation for hormone receptor–negative and HER2/neu-positive invasive cancers compared with US [27]. The accuracy of DBT in assessing tumor size was 70.4% compared with 60.2% on 2-D mammography [28]. However, the STORM-2 trial showed that DBT tended to overestimate tumor size in women with dense breasts, compared with those with nondense breasts; this difference was more likely to impact management in women with larger tumors [29]. Despite the limitations of mammography in women with dense breasts, breast density was not a predictor of positive margins or conversion to mastectomy [30].

However, 2-D mammography is limited in detecting and measuring the size of ILC, which often presents as architectural distortion and uncommonly has associated calcifications [31]. Multiple studies have shown DBT to be superior to DM alone in ILC detection, with the differential performance between DM/DBT and DM greatest in ILC when compared with IDC [32]. Therefore, it follows that DBT is also more accurate than DM in evaluating the extent of disease for this subtype, which is commonly multicentric, multifocal, and sometimes bilateral. Still, DBT can underestimate the true pathologic extent of ILC [33], so MRI may be warranted in this subtype, as discussed below. Supporting this, in a retrospective study of 904 women with breast cancer (n = 97 ILC), imaged with mammography ± US, 38.8% of women with ILC undergoing breast-conserving surgery required re-excision compared with 22.3% with IDC [34].

Due to patient positioning constraints, 2-D mammography and DBT have limited value for evaluating the axilla. In a single-institution retrospective study of 3,944 patients with breast cancer, mammography improved the sensitivity over US alone for distinguishing N0 to N1 from N2 and N3, but at a lower specificity [35]. After the ACOSOG Z0011 trial supported the omission of axillary lymph node dissection in women with <3 positive sentinel lymph nodes undergoing breast-conserving surgery and radiation therapy, some providers may request that radiologists not image the axilla in the setting of clinically node-negative disease [36]. Radiologists can be thoughtful about whether to image the axilla, discussing risks and benefits with surgical colleagues, because it is not universally recommended [37].

### **Mammography With IV Contrast**

Several retrospective studies have compared the sensitivity and specificity of CEM with conventional 2-D and 3-D mammography, US, and MRI. Overall, CEM and MRI are superior to DM and DM/DBT imaging [47]. The sensitivities between CEM and MRI are comparable, with some studies showing improved sensitivities with CEM [48] and some showing MRI to be superior [49,50]. Overall sensitivities ranged from 92% to 100% [16,49,51-53], including CEM detecting 92.3% of satellite masses and up to 100% of contralateral cancers [28]. CEM and MRI show similar abilities to estimate tumor size ( $r = 0.72-0.89$  versus  $0.65-0.84$ ), but studies have shown an improved positive predictive value (PPV) of CEM (52%-93%) compared with MRI (28-60%) [16,49,53]. Despite increased specificity over MR, limitations of contrast mammography in determining disease extent include evaluation of the axilla and other nodal groups as well as chest wall involvement [47], and there is evidence against using CEM to determine disease extent in lobular cancer, due to lower conspicuity [54].

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

MRI breast is useful for detecting additional cancers in the ipsilateral or contralateral breast [16,55], particularly in women with dense breasts [23,56,57]. A meta-analysis of 22 studies investigated MRI screening of the contralateral breast in women with newly diagnosed breast cancer. This meta-analysis reported contralateral malignancies that were detected by MRI in 131 of 3,253 women. Thus, the summary estimate for incremental cancer detection rate was 4.1%. In studies in which pathologic tumor stage was reported, all but 2 tumors were in situ or stage I, and of those 2 tumors, 1 was node-negative ILC (42 mm). Summary estimates were as follows: MRI-directed additional

biopsy in 9.3% of women (95% confidence interval [CI], 5.8%-14.7%) with PPV for malignancy of 47.9% (95% CI, 31.8%-64.6%). Where reported, 35.1% of MRI-detected cancers were DCIS (mean size = 6.9 mm) and 64.9% were invasive cancers (mean size = 9.3 mm) [58].

MRI can accurately assess tumor size for preoperative planning [50,59-61]. In a study involving 343 tumors, size measurements of cancers on breast MRI were within 5 mm of pathological size in 88% of patients [60]. Still, other studies using mastectomy specimens have shown that MRI underestimates primary tumor size in 21% and overestimates primary tumor size in 24% of cases [62]. MRI also overestimated the number of invasive lesions by 19% and underestimated the number of invasive lesions in 28% in the same study [62]. These data underscore the importance of using biopsy to pathologically confirm MRI findings instead of relying on them to alter surgical planning, especially when the MRI finding is nonmass enhancement [63].

In addition to tumor size assessment, some studies show a reduction in re-excision after preoperative MRI [64-68]. For example, in a study of 991 women, preoperative MRI changed the surgical procedure in 25% (157/626) of cases. In 81% (127/157), MRI benefited some patients, as otherwise occult carcinomas were removed (n = 122) and further biopsy prevented (n = 5) [67]. In this trial, the rate of mastectomy did not differ between patients undergoing preoperative MRI and those who did not. A recent multinational observational study at 27 centers also found that subjects receiving MR as part of routine clinical care had a significantly lower reoperation rate after breast conservation (8.5% versus 11.7%,  $P < .001$ ) [69]. However, other large multicenter studies, such as the comparative effectiveness of MRI in breast cancer (COMICE) trial, showed the addition of MRI to conventional imaging was not significantly associated with a reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the non-MRI group (odds ratio [OR], 0.96; 95% CI, 0.75-1.24;  $P = .77$ ) [70]. Although the findings are important, limitations from the COMICE trial are also noted, such as its inclusion of patients from several small centers where technical factors and varying degree of experience among interpreting radiologists could have influenced the MRI results. It is also not clear that the data from the MRI was incorporated into surgical planning, and nearly 7% of the group assigned to MRI did not actually have an MR interpreted (analyzed by intention to treat). When all breast cancer subtypes were included, a meta-analysis of 19 studies did not find evidence that MRI impacted the rates of re-excision, reoperation, or positive margins, but MRI was significantly associated with increased odds of receiving contralateral prophylactic mastectomy (OR, 1.91; 95% CI, 1.25-2.91;  $P = .003$ ) [71]. This analysis of 85,975 women also showed that preoperative MRI was associated with increased odds of receiving mastectomy (OR, 1.39; 95% CI, 1.23-1.57;  $P < .001$ ) [71]. Still, it is unknown whether some of the studies included in that meta-analysis had a bias in randomization (ie, women who were preplanned for mastectomies were more likely to have been referred rather than randomized to the preoperative MRI arm). As an example of this, in the multicenter international prospective analysis cited above [69], mastectomy was already planned based on conventional imaging in 22.4% (MRI group) versus 14.4% (no MRI group) ( $P < .001$ ).

The data are different for ILC histological subtypes. For ILC, there is strong evidence that MRI improves surgical outcomes [72-81]. In a study with 70 cases of ILC, preoperative MRI reduced re-excision rates, particularly in young women with dense breasts [82]. In another study with 369 women, preoperative breast MRI was also associated with a reduction in repeat surgery (OR, 0.140;  $P < .001$ ), without increasing mastectomy rates [76].

Although MR does lead to increased cancer detection, there is limited evidence that preoperative MRI improves survival or decreases recurrence, including data from multicenter analyses [61,68,83-85]. In 3,180 affected breasts in 3,169 women (median age, 56.2 years), 8-year disease-free survival did not differ between the MRI (97%) and the non-MRI (95%) groups ( $P = .87$ ), and the multivariable model showed no significant effect of MRI on disease-free survival: hazard ratio (HR) for MRI (versus non-MRI) was 0.88 (95% CI, 0.52-1.51;  $P = .65$ ); age, margin status, and tumor grade were associated with disease-free survival (all  $P < .05$ ) [85]. Of the 31,756 patients included in a survival cohort (70% non-MRI and 30% MRI), breast MRI was not significantly associated with overall survival (HR, 0.91; 95% CI, 0.74-1.11,  $P = .35$ ) or with disease-free survival (HR, 1.16; 95% CI, 0.81-1.67), even among the different histological subtypes. The lack of survival benefit extends also to patients with ILC, despite improved surgical outcomes in this population as described above [83]. One recent study did show lower recurrences (locoregional, distant and contralateral) in women who received a preoperative MRI, with a nonsignificant trend toward MR improving disease-free survival ( $P = .057$ ) [86], and another study of 1,199 subjects did show improved overall survival in the group who received MRI [87].

Given these data, benefits of preoperative MRI for additional cancer detection or delineating extent of disease should be balanced with the possibility of a false-positive diagnosis leading to additional biopsy, unnecessary additional imaging, and potential delays in definitive treatment. Due to additional cancer detection on a per-patient

level, MRI is considered optional, despite a lack of definitive data supporting classical improved outcomes and continued controversy regarding potential harms. Considering the evidence above, MRI-detected suspicious masses >2 cm from the index malignancy or nonmass enhancement significantly larger than expected from mammographic/sonographic findings should be sampled before using MRI findings to alter surgical planning or change treatment recommendations.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating extent of disease.

### **US Axilla**

This section was previously described in the ACR Appropriateness Criteria® topic on “[Imaging of the Axilla](#)” [88]. The Z0011 trial showed that in women with tumor size <5 cm and no clinically palpable nodes, ≤2 positive axillary nodal macrometastases on sentinel lymph node biopsy can avoid axillary nodal dissection without compromising survival [89].

US is the most established noninvasive imaging test for assessing the axilla following a clinically or imaging detected suspicious lymph node. US features associated with a higher likelihood of malignancy include short-axis lymph node size >1 cm, cortical thickness of >0.3 cm, and an absence of a fatty hilum [90-93]. There is a wide range of reported sensitivity and specificity for axillary US, and none of these imaging features are specific enough to avoid the need for histologic sampling. The sensitivity ranges from 26.4% to 94%, and the specificity ranges from 53% to 98% [94-97]. Axillary US alone has a relatively low NPV to rule out metastatic disease [36,98]. A meta-analysis of 21 studies showed that US combined with needle biopsy improved the sensitivity from 61% to 79% [99-101]. 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 [102]. Axillary US and an MRI performed similarly (sensitivity of 99.1% versus 97.4% and specificity 15.4% versus 15.4%, respectively) in evaluating axillary lymph nodes. Despite this performance, approximately 14% of women with breast cancer and negative imaging for axillary metastasis ultimately have metastatic disease on sentinel lymph node biopsy [103].

### **US Breast**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). The sensitivity of US for detecting cancer ranges from 79% to 94% [22,25,104,105]. The addition of DBT to US improved sensitivity for detecting both primary breast cancer and multicentric and multifocal disease, from 82.6% (nondense) and 91.6% (dense) with US alone to 97.7% with combined DBT and US [106]. However, DBT and mammography have limited added value over US alone for initial evaluation in women <40 years of age [105]. Although bilateral US use in women with primary breast cancer to evaluate for multicentric and multifocal disease shows a lower sensitivity than MRI (85.1% versus 71.1%), US showed higher accuracy and specificity than MRI (67.6% versus 39.3% and 69.2% versus 60.2%, respectively), suggesting that bilateral US may be an acceptable alternative to MRI for locoregional staging [57]. When compared with DM alone, supplemental US more accurately depicted the extent of disease needing wider excision in 17 of 96 (18%) breasts for which conservation was anticipated, corresponding to 17 of 30 (57%) breasts with mammographically occult disease [22]. Based on mammography/clinical examination, 2% to 3% of patients have synchronous bilateral cancer [107]. This risk for bilateral synchronous cancer is increased in patients less than 55 years of age or in those diagnosed with invasive lobular subtypes [108]. In 1 series with 9% contralateral synchronous malignancy, mammography detected 60%, US detected 80%, and MRI detected 90% (with the remainder detected on follow-up imaging) [22].

In addition to its role in the initial diagnostic workup, US is important in the secondary evaluation of a suspicious finding on MRI in the setting of evaluation of disease extent. US sensitivity and NPV are higher than those of DBT [109]. Compared with DBT, US showed a lower specificity (98.1% versus 78.9%) and similar PPV (66.7% versus 52.2%). However, a meta-analysis of second-look US following a suspicious finding on MRI showed heterogeneity in US performance, with the detection rate ranging from 22.6% to 82.1% (pooled detection rate 57.5%) and an 87.8% pooled NPV [110]. Therefore, a negative US is insufficient to obviate the need for an MRI biopsy in this setting.

There is no evidence supporting US as an accurate method for determining disease extent of those diagnosed with ILC subtype. Conventional imaging with mammography and/or US can significantly underestimate the extent of ILC [26,111-114]. For example, US specifically underestimated ILC tumor size by 27% (95% CI, 17%-37%) in a

study [113], and a different study showed that the greatest discrepancy between tumor size and pathologic size using US measurements was for the ILC subtype [26].

### **Variant 2: Newly diagnosed. Clinical stage I-IIA (early stage) breast cancer at presentation. Evaluation for distant disease (includes IDC, or ILC, or NOS).**

It has long been recognized that steroid receptor expression reflects intrinsic biologic diversity in breast cancer with treatment and survival implications, also determining patterns of metastatic spread. Historically, bone is the most likely site of breast cancer metastases (51%), followed by liver/soft tissue (19%), pleura (16%), lung (14%), and brain (4%) [115]. The higher percentage of bone metastases from breast cancer appears to be driven primarily by the majority of primary tumors expressing ER and/or PR. In 1 large multidecade study, 82% of patients with breast cancer who developed bone metastases had either ER and PR or ER positivity in the primary tumor [115].

A landmark study 2 decades ago transformed our field by discovering 5 distinct composite molecular portraits using quantitative analysis of breast cancer gene expression patterns; luminal A, luminal B, HER2-enriched, basal-like, and normal-like, providing a new type of disease characterization [116]. The molecular subtypes were linked to pattern and type of metastatic spread, as well as disease-specific survival [117,118]. For example, luminal cancers have a propensity to give rise first to bone metastases, HER2-enriched cancers to liver and lung metastases, and basal type cancers to liver and brain metastases [119,120]. These molecular subtypes share similarities with ER/PR expression and HER2 gene amplification but are not synonymous. Luminal subtypes more commonly have ER expression, HER2-enriched cancers more commonly exhibit HER2 expression, and triple-negative breast cancers are most often the basal breast cancer subtype. Although luminal subtypes have significantly better overall and relapse-free survival [118], they carry a long-term risk of recurrence, especially to bone, whereas basal and HER2 subtypes have a higher rate of recurrence in the first 4 years [121], which can be considered when planning frequency and type of surveillance imaging.

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

Bone is the most common site for breast cancer metastasis; up to 70% of women with stage IV disease have bone metastasis, with the predilection for bone metastases not applying to basal-like tumors [117]. Up to 13.6% of women diagnosed with early stage breast cancer will develop bone metastasis within 15 years of diagnosis [122], even if the parent tumor is low grade [123]. Tc-99m bone scans detect early bone metastasis because of the new bone formation occurring at these sites [124] and have a 98% sensitivity for detecting early bone metastasis in symptomatic patients. However, bone scan is not helpful for asymptomatic women with newly diagnosed early stage breast cancer due to the low prevalence of metastasis (<1%) at initial diagnosis [125]. Whole body bone scans are performed in up to 35% of women with newly diagnosed breast cancer despite National Comprehensive Cancer Network (NCCN) guidelines recommending against routine staging in asymptomatic women with early stage breast cancer [125,126]. The unnecessary use of this imaging test and the further evaluation of false-positive findings can result in treatment delay [127]. There is no evidence to use whole body bone scan in the evaluation of distant disease in stage I to IIA breast cancer.

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

National and international guidelines (American Board of Internal Medicine [ABIM]/ASCO, European Society for Medical Oncology [ESMO], and Spanish Society of Medical Oncology [SEOM]) discourage the use of imaging for staging in asymptomatic patients with newly diagnosed early stage breast cancer [128-130].

NCCN guidelines recommend chest, abdomen, and pelvic CT as an additional test prior to preoperative systemic therapy in clinical stage I to IIA if the tumor is >2 cm, >1 cm and immunohistochemical subtype is triple negative, or HER2+ or any size/subtype with known axillary nodal spread [126]. However, this test is often used in the staging evaluation of low-risk cancers, outside these guidelines, despite a lack of evidence suggesting that it improves detection of metastatic disease or increases survival. There is a lack of evidence demonstrating a benefit for the use of CT in asymptomatic individuals with clinical stage I or II disease outside the guidelines above. A survey of NCCN member institutions found that 11% of patients with stage I and 36.2% of patients with stage II received a staging CT of the chest. This resulted in 27% of patients diagnosed with pulmonary nodules requiring a mean 2.34 additional CTs (range 0-16) for follow-up. Of pulmonary nodules detected in asymptomatic women with early stage breast cancer, only 2% of these patients were ultimately diagnosed with pulmonary metastasis [131,132].

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR-SABI-SPR practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast in identifying distant disease.

### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT to evaluate distant disease.

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

According to the ABIM/ASCO, ESMO, and SEOM guidelines, there is insufficient evidence to routinely use FDG-PET/CT to evaluate for distant disease in asymptomatic women with early stage breast cancer [128-130].

NCCN guidelines recommend chest, abdomen, and pelvic CT as an additional test prior to preoperative systemic therapy to evaluate for distant disease if the tumor size is >2 cm (T2) or there are positive lymph nodes, or the tumor size is >1 cm (T1c) and HER2+, or there is triple-negative disease [126]. Although not definitive, and not currently recommended in the guidelines above, there is evidence that PET/CT may be useful in early stage breast cancer [133]. A recent study of 196 subjects [134] tested the utility of PET/CT in breast cancer and found the overall yield of unsuspected distant metastases was 14% (n = 27), including 0% for stage IIA, 13% for stage IIB (10/79), 22% for stage IIIA (9/41), 17% for stage IIIB (5/30), and 37% for stage IIIC (3/8). In another study of 303 patients, PET/CT demonstrated unknown metastatic disease in 4.9% (15/303), 0.8% in stage IIA, and 9.8% in stage IIB [135]. Finally, Groheux et al [136] performed a prospective study of 254 women with breast cancer, and PET/CT found unsuspected metastatic disease in 2.3% of stage IIA and 10.7% in stage IIB [128]. The performance of PET/CT was independent of cancer subtype, as shown in other studies on stage IIB disease [137]. Finally, a recent meta-analysis of 4,276 patients (29 studies) also found 11% (95% CI, 3%-22%) of patients with stage I and 20% (95% CI, 16%-24%) of patients with stage II breast cancer changed disease stage or management plan (including up or downstaging) with PET/CT [13]. Thus, there is some evidence to consider this test, even in early breast cancer, if the immunohistochemical subtype is HER2+/TN or the disease is locally advanced as described above.

### **Mammography Diagnostic**

There is no evidence to support the use of diagnostic mammography to evaluate distant disease.

### **Mammography With IV Contrast**

There is no evidence to support the use of diagnostic mammography with IV contrast to evaluate distant disease.

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

There is no evidence to support the use of MRI breast to evaluate distant disease.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating extent of disease.

### **US Axilla**

There is no evidence to support the use of US axilla to evaluate distant disease.

### **US Breast**

There is no evidence to support the use of US breast to evaluate distant disease.

### **Variant 3: Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for locoregional disease (includes IDC, or ILC, or NOS).**

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

There is no evidence to support the use of bone scan whole body for determining locoregional disease.

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

Few studies have evaluated the use of CT to determine locoregional disease in breast cancer and so there is limited supporting evidence for this indication. In a study using CT to determine the size of the in-breast malignancy, surgical treatment was changed in 42 of 297 (14.1%) patients. The same study showed that CT failed to show the extent of disease in 10.8% of patients and overestimated the extent of disease in 1% of tumors. Notably, MRI was not included as a comparator [20]. An additional study looking at later stage (at least 2 cm) or higher risk (triple

negative or other biomarkers of risk such as high Ki67 or HER2+) found that CT predicted the N stage correctly in 64 of 80 patients (80%, 95% CI,70.0%-87.3%), with a sensitivity of 61.5% (CI,45.9%-75.1%) and a specificity of 97.6% (CI, 87.4%-99.6%). Despite the higher specificity of CT, MRI has better performance to detect multicentric/multifocal disease and estimate final pathologic size.

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR-SABI-SPR practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast for determining locoregional disease and guiding surgical management in late-stage disease.

### **Digital Breast Tomosynthesis Diagnostic**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). However, mammography is limited by breast density. In a prospective study of 111 consecutive women with newly diagnosed breast cancer, sensitivity of 2-D mammography for malignancy decreased from 100% in breasts that are almost entirely fatty to 45% in extremely dense breasts [22]. In addition, 2-D mammography was more sensitive than US in detecting DCIS and less sensitive at detecting ILC.

DBT shows higher overall sensitivity, compared with 2-D mammography, with similar specificity. Overall sensitivity for DBT was 88.2% compared with 78.3% for 2-D mammography [23]. DBT also has a higher sensitivity for detecting multifocal, multicentric, and contralateral breast cancer [24,25]. The improved diagnostic performance of DBT over 2-D mammography was limited to women with nondense breasts in 1 study [24], but not others [25].

The correlation between mammographic size and pathologic size is variable. Some studies demonstrate that the assessment of size with mammography to be superior to US [26], whereas others show it to be inferior [46]. At least some of this variation may be related to tumor subtype. Mammography shows a higher correlation with pathologic size for DCIS and HER2/neu-negative invasive cancers and a lower correlation for hormone receptor–negative and HER2/neu-positive invasive cancers compared with US [27]. The accuracy for DBT for assessing tumor size was 70.4% compared with 60.2% on 2-D mammography [28]. However, the STORM-2 trial showed that DBT tended to overestimate tumor size in women with dense breasts, compared with those with nondense breasts; this difference was more likely to impact management in women with larger tumors [29]. Despite the limitations of mammography in women with dense breasts, breast density was not a predictor of positive margins or conversion to mastectomy [30].

However, 2-D mammography is limited in detecting and measuring the size of ILC, which often presents as architectural distortion and uncommonly has associated calcifications [31]. Multiple studies have shown DBT to be superior to DM alone in ILC detection, with the differential performance between DM/DBT and DM greatest in ILC when compared with patients diagnosed with IDC [32]. Therefore, it follows that DBT is also more accurate than DM in evaluating extent of disease for this cancer subtype, which is commonly multicentric, multifocal, and sometimes bilateral. Still, DBT can underestimate the true pathologic extent of ILC [33], so MRI may be warranted in this subtype, as discussed below. Supporting this, in a retrospective study of 904 women with breast cancer (n = 97 ILC) imaged with mammography ± US, 38.8% of women with ILC undergoing breast-conserving surgery required re-excision compared with 22.3% with IDC [34].

Due to patient positioning constraints, 2-D mammography and DBT have limited value for evaluating the axilla. In a single-institution retrospective study of 3,944 patients with breast cancer, mammography improved the sensitivity over US alone for distinguishing N0 to N1 from N2 and N3, but at a lower specificity [35]. After the ACOSOG Z0011 trial supported the omission of axillary lymph node dissection in women with <3 positive sentinel lymph nodes undergoing breast-conserving surgery and radiation therapy, some providers may request that radiologists not image the axilla in the setting of clinically node-negative disease [36]. Although axillary US is not recommended for every patient [37], axillary abnormality visible on mammography is still considered an appropriate indication for sonographic axillary evaluation. Also, when neoadjuvant chemotherapy is planned, the NCCN recommends consideration of axillary US, with marker placement if a biopsy is performed, in addition to mammography [126].

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

FDG-PET/CT is helpful in evaluating locoregional disease in patients with stage IIB to III breast cancer. Locoregional spread refers to disease spread to the draining regional lymph node basins. Although this usually refers to the ipsilateral axilla, regional spread can also be to the infraclavicular (level III axillary), supraclavicular, and internal mammary/parasternal nodal basins [2]. Contralateral lymph node involvement is classified as distant (stage IV) disease in the absence of synchronous contralateral breast malignancy [2]. When used to evaluate locoregional extent of disease, there was a change in stage or management in 20% of stage II and 34% of stage III disease [13-15,138,139]. NCCN guidelines recommend PET/CT as an optional additional test prior to preoperative systemic therapy if the tumor size is  $\geq 2$  cm, or there are positive lymph nodes, or the tumor size is  $>1$  cm with HER2+ or triple-negative disease [126].

### **Mammography Diagnostic**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). However, mammography is limited by breast density. In a prospective study of 111 consecutive women with newly diagnosed breast cancer, the sensitivity of 2-D mammography for malignancy decreased from 100% in breasts that are almost entirely fatty to 45% in extremely dense breasts [22]. In addition, 2-D mammography was more sensitive in detecting DCIS and less sensitive, compared with US, in detecting ILC.

DBT shows higher overall sensitivity, compared with 2-D mammography, with similar specificity. Overall sensitivity for DBT was 88.2% compared with 78.3% [23]. DBT has higher sensitivity for detecting multifocal, multicentric, and contralateral breast cancer than 2-D mammography alone [24,25]. The improved diagnostic performance of DBT over 2-D mammography in breast cancer staging was limited to women with nondense breasts in 1 study [24], but not others [25].

The correlation between mammographic size and pathologic size is variable. Some studies demonstrate that the assessment of size with mammography to be superior to US [26], whereas others show it to be inferior [46]. At least some of this variation may be related to tumor subtype. Mammography shows a higher correlation with pathologic size for DCIS and HER2/neu-negative invasive cancers and a lower correlation for hormone receptor–negative and HER2/neu-positive invasive cancers compared with US [27]. The accuracy of DBT for assessing tumor size was 70.4% compared with 60.2% on 2-D mammography [28]. However, the STORM-2 trial showed that DBT tended to overestimate tumor size in women with dense breasts, compared with those with nondense breasts; this was more likely to impact management in women with larger tumors [29]. Despite the limitations of mammography in women with dense breasts, breast density was not a predictor of positive margins or conversion to mastectomy [30].

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### **Mammography With IV Contrast**

Several retrospective studies have compared the sensitivity and specificity of CEM with conventional 2-D and 3-D mammography, US, and MRI. Overall, CEM and MRI are superior to DM and DM/DBT imaging [47]. The sensitivities between CEM and MRI are comparable, with some studies showing improved sensitivities with CEM

[48], and some showing MRI to be superior [49,50]. Overall sensitivities ranged from 92% to 100% [16,49,51-53], including CEM detecting 92.3% of satellite masses and up to 100% of contralateral cancers [28]. CEM and MRI show similar abilities to estimate tumor size ( $r$ , 0.72-0.89 versus 0.65-0.84), but studies have shown improved PPV of CEM (52%-93%) compared with MRI (28-60%) [16,49,53]. Despite increased specificity over MR, limitations of contrast mammography in determining disease extent include evaluation of the axilla and other nodal groups as well as chest wall involvement [47], and there is evidence against using CEM to determine disease extent in lobular cancer, due to lower conspicuity [54].

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

MRI breast is useful for detecting additional cancers in the ipsilateral and contralateral breast [16,55], particularly in women with dense breasts [23,56,57]. A meta-analysis of 22 studies investigated MRI screening of the contralateral breast in women with newly diagnosed breast cancer. The study reported contralateral malignancies that were detected by MRI in 131 of 3,253 women. Thus, the summary estimate for incremental cancer detection rate was 4.1%. In studies in which pathologic tumor stage was reported, all but 2 tumors were in situ or stage I, and of those 2 tumors, 1 was a node-negative ILC (42 mm). Summary estimates were as follows: MRI-directed additional biopsy in 9.3% of women (95% CI, 5.8%-14.7%) with PPV for malignancy of 47.9% (95% CI, 31.8%-64.6%). Where reported, 35.1% of MRI-detected cancers were DCIS (mean size = 6.9 mm) and 64.9% were invasive cancers (mean size = 9.3 mm) [58].

MRI can accurately assess tumor size for preoperative planning [50,59-61]. In a study involving 343 tumors, size measurements of cancers on breast MRI were within 5 mm of pathological size in 88% of patients [60]. Still, other studies using mastectomy specimens have shown that MRI underestimates primary tumor size in 21% and overestimates primary tumor size in 24% of cases. MRI also overestimated the number of invasive lesions by 19% and underestimated the number of invasive lesions in 28% in the same study [62]. These data underscore the importance of using biopsy to pathologically confirm MRI findings before using them to alter surgical planning, especially when the MRI finding is nonmass enhancement [63].

In addition to tumor size assessment, some studies show a reduction in re-excision after preoperative MRI [64-68]. For example, in a study of 991 women, preoperative MRI changed the surgical procedure in 25% (157/626) of cases. In 81% (127/157), MRI was beneficial for the patients, as otherwise occult carcinomas were removed ( $n = 122$ ) or further biopsy could be prevented ( $n = 5$ ) [67]. In this trial, the rate of mastectomy did not differ between patients undergoing preoperative MRI and those who did not. A recent multinational observational study at 27 centers also found that subjects receiving MR as part of routine clinical care had a significantly lower reoperation rate after breast conservation (8.5% versus 11.7%,  $P < .001$ ) [69]. However, other large multicenter studies, such as the COMICE trial, showed the addition of MRI to conventional imaging was not significantly associated with a reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the non-MRI group, (OR, 0.96; 95% CI, 0.75-1.24;  $P = .77$ ) [70]. Although the findings are important, limitations from the COMICE trial are also noted, such as its inclusion of patients from several small centers where technical factors and varying degree of experience among interpreting radiologists could have influenced the MRI results. It is also not clear that the data from the MRI were incorporated into surgical planning, and nearly 7% of the group assigned to MRI did not actually have an MR interpreted (analyzed by intention to treat). When all breast cancer subtypes were included, a meta-analysis of 19 studies did not find evidence that MRI positively impacted the rates of re-excision, reoperation, or positive margins, and MRI was significantly associated with increased odds of receiving contralateral prophylactic mastectomy (OR, 1.91; 95% CI, 1.25-2.91;  $P = .003$ ) [71]. Primary analysis of 85,975 women also showed that preoperative MRI was associated with increased odds of receiving mastectomy (OR, 1.39; 95% CI, 1.23-1.57;  $P < .001$ ) [71].

Still, it is unknown whether some of the studies included in that meta-analysis had a bias in randomization (ie, women who were preplanned for mastectomies were more likely to have been referred rather than randomized to the preoperative MRI arm). As an example of this, in the multicenter international prospective analysis cited above [69], mastectomy was already planned based on conventional imaging in 22.4% (MRI group) versus 14.4% (no MRI group)  $P < .001$ .

The data are different for ILC histological subtypes. For ILC, there is strong evidence that MRI improves surgical outcomes [72-81]. In a study with 70 cases of ILC, preoperative MRI reduced re-excision rates, particularly in young women with dense breasts [82]. In another study with 369 women, preoperative breast MRI was also associated with a reduction in repeat surgery (OR, 0.140;  $P < .001$ ), without increasing mastectomy rates [76].



Still, there is no evidence that preoperative MRI leads to improved survival or decreased recurrence, including data from multicenter analyses [61,68,83-85]. In 3,180 affected breasts in 3,169 women (median age, 56.2 years), 8-year disease-free survival did not differ between the MRI (97%) and the non-MRI (95%) groups ( $P = .87$ ), and the multivariable model showed no significant effect of MRI on disease-free survival: HR for MRI (versus non-MRI) was 0.88 (95% CI, 0.52-1.51;  $P = .65$ ); age, margin status, and tumor grade were associated with disease-free survival (all  $P < .05$ ) [85]. Of the 31,756 patients included in a survival cohort (70% non-MRI and 30% MRI), breast MRI was not significantly associated with overall survival (HR, 0.91; 95% CI, 0.74-1.11,  $P = .35$ ) or with disease-free survival (HR, 1.16; 95% CI, 0.81-1.67), even among the different histological subtypes. The lack of survival benefit extends also to patients with ILC, despite improved surgical outcomes in this population as described above [83].

Given these data, benefits of preoperative MRI for additional cancer detection or delineating extent of disease should be balanced with the possibility of a false-positive diagnosis leading to additional biopsy or unnecessary additional imaging.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating extent of disease.

### **US Axilla**

This section was previously described in the ACR Appropriateness Criteria® topic on “[Imaging of the Axilla](#)” [88]. The Z0011 trial showed that in women with tumor size <5 cm and no clinically palpable nodes,  $\leq 2$  positive axillary nodal macrometastases on sentinel lymph node biopsy can avoid axillary nodal dissection without compromising survival [89].

US is the most established noninvasive imaging test for assessing the axilla following a clinically or imaging detected suspicious lymph node. US features associated with a higher likelihood of malignancy include short-axis lymph node size >1 cm, cortical thickness of >0.3 cm, and absence of a fatty hilum [90-93]. There is a wide range of reported sensitivity and specificity for axillary US, and none of these imaging features are specific enough to avoid the need for histologic sampling. The sensitivity ranges from 26.4% to 94%, and the specificity ranges from 53% to 98% [94-97]. Although axillary US alone has a relatively low NPV to rule out metastatic disease [36,98], axillary imaging is significantly more likely to identify metastatic disease in patients with pN2-3 disease compared with low volume burden (ie, those eligible for axillary preservation according to the Z0011 trial). Therefore, detection of nodal disease can help identify patients who would benefit from neoadjuvant systemic therapy to help downstage and de-escalate their axillary surgery and avoid axillary lymph node dissection. However, imaging is less sensitive in detecting invasive lobular cancer metastasis compared with ductal type [140]. A meta-analysis of 21 studies showed that US combined with needle biopsy improved the sensitivity from 61% to 79% [99-101]. 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 [102]. Axillary US and an MRI performed similarly at evaluating axillary lymph nodes in an additional study [103]. In a meta-analysis of 9,232 cases of preoperative axillary staging procedures in 9,212 patients with breast cancer, preoperative axillary US-guided biopsy was able to identify approximately 50% of women with axillary involvement, but the false-negative rate was 25% [141]. An additional meta-analysis reported similar findings [100]. The NCCN does recommend consideration of axillary US, with marker placement if biopsy is performed, prior to preoperative systemic therapy [126].

### **US Breast**

Diagnostic mammography and US together can assess for extent of disease and tumor size. These imaging tests are usually already completed as part of the diagnostic workup (prior to pathological diagnosis). The sensitivity of US for detecting cancer ranges from 79% to 94% [22,25,104,105]. The addition of DBT to US improved sensitivity for detecting both primary breast cancer and multicentric and multifocal disease, from 82.6% (nondense) and 91.6% (dense) with US alone to 97.7% with combined DBT and US [106]. However, DBT and mammography have limited added value over US alone for initial evaluation in women <40 years of age [105]. Although bilateral US use in women with primary breast cancer to evaluate for multicentric and multifocal disease shows lower sensitivity to MRI (85.1% versus 71.1%), US showed higher accuracy and specificity than MRI (67.6% versus 39.3% and 69.2% versus 60.2%, respectively), suggesting that bilateral US may be an acceptable alternative to MRI for locoregional staging [57]. When compared with DM alone, supplemental US more accurately depicted extent of disease needing wider excision in 17 of 96 (18%) breasts for which conservation was anticipated, corresponding to 17 of 30 (57%) breasts with mammographically occult disease [22]. Based on mammography/clinical examination, 2% to 3% of

patients have synchronous bilateral cancer [107]. This risk of synchronous bilateral malignancy is increased for patients less than 55 years of age or those with diagnosis of invasive lobular subtype [108]. In 1 series with 9% contralateral synchronous malignancy, mammography detected 60%, US detected 80%, and MRI detected 90% (with the remainder detected on follow-up imaging) [22].

In addition to its role in the initial diagnostic workup, US is important in the secondary evaluation of a suspicious finding on MRI in the setting of evaluation for disease extent. US sensitivity and NPV are higher than DBT [109]. Compared with DBT, US showed a lower specificity (98.1% versus 78.9%) and a similar PPV (66.7% versus 52.2%). However, a meta-analysis of second-look US following a suspicious finding on MRI showed heterogeneity in US performance, with the detection rate ranging from 22.6% to 82.1% (pooled detection rate 57.5%) and an 87.8% pooled NPV [110]. Therefore, a negative US is insufficient to obviate the need for an MRI biopsy in this setting.

There is no evidence supporting US as an accurate method for determining disease extent in those diagnosed with the ILC subtype. Conventional imaging with mammography and/or US can significantly underestimate the span of ILC [26,111-114]. For example, US specifically underestimated ILC tumor size by 27% (95% CI, 17%-37%) in a study [113], and a different study showed that the greatest discrepancy between tumor size and pathologic size using US measurements was for those with the ILC subtype [26].

#### **VARIANT 4: Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for distant disease. IDC or ILC that is ER+/HER2-.**

It has long been recognized that steroid receptor expression reflects intrinsic biologic diversity in breast cancer with treatment and survival implications, also determining patterns of metastatic spread. The specific response patterns and outcomes associated with ER/PR/HER2 status occur despite the known limitation of pathologic sampling and receptor expression heterogeneity [142]. Historically, bone is the most likely site of breast cancer metastases (51%), followed by liver/soft tissue (19%), pleura (16%), lung (14%), and brain (4%) [115]. The higher percentage of bone metastases from breast cancer appears to be driven primarily by the majority of primary tumors expressing ER and/or PR. In 1 large multidecade study, 82% of patients with breast cancer who developed bone metastases had either ER and PR or ER positivity in the primary tumor [115].

A landmark study 2 decades ago transformed our field by discovering 5 distinct composite molecular portraits using quantitative analysis of breast cancer gene expression patterns; luminal A, luminal B, HER2-enriched, basal-like, and normal-like, providing a new type of disease characterization [116]. The molecular subtypes were linked to pattern and type of metastatic spread, as well as disease-specific survival [117,118]. For example, luminal cancers have a propensity to give rise first to bone metastases, HER2-enriched cancers to liver and lung metastases, and basal type cancers to liver and brain metastases [119,120]. These molecular subtypes share similarities with ER/PR expression and HER2 gene amplification but are not synonymous. Luminal subtypes more commonly have ER expression, HER2-enriched cancers more commonly exhibit HER2 expression, and triple-negative breast cancers are most often the basal breast cancer subtype. Although luminal subtypes have significantly better overall and relapse-free survival [118], they carry a long-term risk of recurrence, especially to bone, whereas basal and HER2 subtypes have a higher rate of recurrence in the first 4 years [121], which can be considered when planning frequency and type of surveillance imaging.

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

Bone is the most common site for breast cancer metastasis; up to 70% of women with stage IV disease have bone metastasis, with the predilection for bone metastases not applying to basal-like tumors [117]. Up to 13.6% of women diagnosed with early stage breast cancer will develop bone metastasis within 15 years of diagnosis [122], even if the parent tumor is low grade [123]. Tc-99m bone scans detect early bone metastasis because of the new bone formation occurring at these sites [124] and have a 98% sensitivity for detecting early bone metastasis in symptomatic patients.

The sensitivity of whole body bone scans for detecting bone metastases in patients with late-stage breast cancer ranges from 62% to 100%, regardless of tumor subtype [143]. Studies using bone scans to stage women with late-stage disease have shown the prevalence of osseous metastases ranging from 4.7% to 45% [144]. A study by Chu et al [145] on 256 women with N2/N3 disease showed a metastatic workup for asymptomatic patients was only indicated with T3 or T4 primary lesions. For patients with T0, T1, and T2 diseases, the incidence of stage IV disease was 0%, 0%, and 6%, respectively. The incidence increased with higher T stage; 22% for T3 and 36% for T4 tumors.

Several studies comparing bone scan performance with CT and PET have been performed in women presenting with late-stage disease [144]. Some studies have shown up to 17.1% of women with extrasosseous metastasis on CT had negative or inconclusive bone scans. One of the benefits of whole body bone scans is the detection of metastasis in the peripheral skeleton, areas not included by CT chest, abdomen, and pelvis with IV contrast. However, the presence of peripheral metastasis almost always (>99%) occurs in the context of extrasosseous or central osseous metastasis, and detection of additional peripheral metastases does not typically result in a change in management [144,146].

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

Correctly identifying the stage of breast cancer prior to surgery has important prognostic implications, because survival decreases as stage increases [145]. In a study of 1,329 patients with breast cancer, metastatic disease of any type was identified by imaging between 15% to 16% and 22% to 36% based on N2/3 and T3/4 status, respectively [145]. NCCN guidelines recommend chest, abdomen, and pelvic CT as an additional test prior to preoperative systemic therapy to evaluate for distant disease if the tumor size is >2 cm (T2) or there are positive lymph nodes, or the tumor size is >1 cm (T1c) and HER2+, or there is triple-negative disease [126]. In asymptomatic women with late-stage breast cancer, metastatic disease to the thorax is identified in 5% to 9% of patients [17,132,147]. The false-positive rate requiring additional imaging studies for further evaluation or follow-up ranged from 10% to 33% [17,132,148].

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR-SABI-SPR practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast. Chest CT without IV contrast is often used to evaluate for metastatic disease to the lung. In asymptomatic women with late-stage breast cancer, metastatic disease to the thorax is identified in 5% to 9% of patients [17,132,147]. The false-positive rate requiring additional imaging studies for further evaluation or follow-up ranged from 10% to 33% [17,132,148].

#### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT to evaluate for distant disease.

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

There is a large body of evidence that FDG-PET/CT is useful to detect metastatic disease in stage IIB to III breast cancer [136-139,149-158]. This is important because patients with locoregional breast malignancy have 5-year survival rates of 76% to 99%, but for patients with distant metastases, 5-year survival rates decrease to 20% to 28% [159]. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT in identifying metastatic disease in this population are 100%, 96%, 80%, 100%, and 97%, respectively [41]. The false-positive rate of PET/CT was 19%. In comparison with CT and other modalities, 80% of patients with distant disease had the metastases exclusively identified on PET/CT [41]. Groheux et al [136] investigated 254 patients and found previously unknown metastases in 1 of 44 (2%) women with stage IIA breast cancer, 6 of 56 (11%) women with stage IIB cancer, 11 of 63 (18%) women with stage IIIA cancer, 27 of 74 (37%) women with stage IIIB cancer, and 8 of 17 (47%) women with stage IIIC cancer. PET/CT has especially high yields in patients newly diagnosed at <40 years of age, revealing distant metastases in 17% of asymptomatic stage IIB [155]. PET/CT modified staging between 14% and 28% of patients with late-stage disease, regardless of tumor receptor status [138,139]. In a study of 163 women, PET/CT and whole body bone scan demonstrated concordance in identifying osseous metastases in 81% of cases. Also, PET/CT had the added benefit of detecting extrasosseous metastasis in 62% of patients with osseous metastasis. Of those patients with extrasosseous metastases, 6% had equivocal and 42% had negative bone scans [160]. The sensitivity and specificity for PET/CT in the detection of distant metastases is higher than conventional imaging, with a 97% sensitivity and 91% specificity versus an 86% sensitivity and 67% specificity ( $P = .009$  and  $P < .001$ , respectively) [161]. However, PET/CT has limited sensitivity for ILC [162]. NCCN guidelines recommend FDG-PET/CT as an optional additional test prior to preoperative systemic therapy to evaluate for distant disease if the tumor size is >2 cm (T2) or there are positive lymph nodes, or the tumor size is >1 cm (T1c) and HER2+, or there is triple-negative disease [126].

#### **Mammography Diagnostic**

There is no evidence to support the use of diagnostic mammography to evaluate for distant disease.

### **Mammography With IV Contrast**

There is no evidence to support the use of mammography with IV contrast to evaluate distant disease.

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

There is no evidence to support the use of MRI breast without and with IV contrast to evaluate for distant disease.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating extent of disease.

### **US Axilla**

There is no evidence to support the use of US axilla to evaluate for distant disease.

### **US Breast**

There is no evidence to support the use of US breast to evaluate for distant disease.

### **Variant 5: Newly diagnosed. Clinical stage IIB-III (late stage) breast cancer at presentation. Evaluation for distant disease. IDC or ILC that is HER2+ or triple negative (ER, PR, and HER2-).**

It has long been recognized that steroid receptor expression reflects intrinsic biologic diversity in breast cancer with treatment and survival implications, also determining patterns of metastatic spread. The specific response patterns and outcomes associated with ER/PR/HER2 status occur despite the known limitation of pathologic sampling and receptor expression heterogeneity [142]. Historically, bone is the most likely site of breast cancer metastases (51%), followed by liver/soft tissue (19%), pleura (16%), lung (14%), and brain (4%) [115]. The higher percentage of bone metastases from breast cancer appears to be driven primarily by the majority of primary tumors expressing ER and/or PR. In 1 large multidecade study, 82% of patients with breast cancer who developed bone metastases had either ER and PR or ER positivity in the primary tumor [115].

A landmark study 2 decades ago transformed our field by discovering 5 distinct composite molecular portraits using quantitative analysis of breast cancer gene expression patterns; luminal A, luminal B, HER2-enriched, basal-like, and normal-like, providing a new type of disease characterization [116]. The molecular subtypes were linked to pattern and type of metastatic spread, as well as disease-specific survival [117,118]. For example, luminal cancers have a propensity to give rise first to bone metastases, HER2-enriched cancers to liver and lung metastases, and basal type cancers to liver and brain metastases [119,120]. These molecular subtypes share similarities with ER/PR expression and HER2 gene amplification but are not synonymous. Luminal subtypes more commonly have ER expression, HER2-enriched cancers more commonly exhibit HER2 expression, and triple-negative breast cancers are most often the basal breast cancer subtype. Although luminal subtypes have significantly better overall and relapse-free survival [118], they carry a long-term risk of recurrence, especially to bone, where basal and HER2 subtypes have a higher rate of recurrence in the first 4 years [121], which can be considered when planning frequency and type of surveillance imaging.

### **Bone Scan Whole Body**

Bone is the most common site for breast cancer metastasis; up to 70% of women with stage IV disease have bone metastasis, with the predilection for bone metastases not applying to basal-like tumors [117]. Up to 13.6% of women diagnosed with early stage breast cancer will develop bone metastasis within 15 years of diagnosis [122], even if the parent tumor is low grade [123]. Tc-99m bone scans detect early bone metastasis because of the new bone formation occurring at these sites [124] and have a 98% sensitivity for detecting early bone metastasis in symptomatic patients.

The sensitivity of whole body bone scans for detecting bone metastases in patients with late-stage breast cancer ranges from 62% to 100%, regardless of tumor subtype [143]. Studies using bone scans to stage women with late-stage disease have shown the prevalence of osseous metastases ranging from 4.7% to 45% [144]. A study by Chu et al [145] on 256 women with N2/N3 disease showed a metastatic workup for asymptomatic patients was only indicated with T3 or T4 primary lesions. For patients with T0, T1, and T2 diseases, the incidence of stage IV disease was 0%, 0%, and 6%, respectively. The incidence increased with higher T stage; 22% for T3 and 36% for T4 tumors.

Several studies comparing bone scan performance with CT and PET have been performed in women presenting with late-stage disease [144]. Some studies have shown up to 17.1% of women with extrasosseous metastasis on CT had negative or inconclusive bone scans [144]. One of the benefits of whole body bone scans is the detection of metastasis in the peripheral skeleton, areas not included by CT chest, abdomen, and pelvis with IV contrast.

However, the presence of peripheral metastasis almost always (>99%) occurs in the context of extraosseous or central osseous metastasis, and detection of additional peripheral metastases does not typically result in a change in management [144,146].

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

Correctly identifying the stage of breast cancer prior to surgery has important prognostic implications, because survival decreases as stage increases [145]. In a study of 1,329 patients with breast cancer, metastatic disease of any type was identified by imaging between 15% to 16% and 22% to 36% based on N2/3 and T3/4 status, respectively [145]. NCCN guidelines recommend chest, abdomen, and pelvic CT as an additional test prior to preoperative systemic therapy to evaluate for distant disease if the tumor size is >2 cm (T2) or there are positive lymph nodes, or >1 cm (T1c) and HER2+, or triple-negative disease [126]. In asymptomatic women with late-stage breast cancer, metastatic disease to the thorax is identified in 5% to 9% of patients [17,132,147]. The false-positive rate requiring additional imaging studies for further evaluation or follow-up ranged from 10% to 33% [17,132,148].

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR-SABI-SPR practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast. Chest CT without IV contrast is often used to evaluate for metastatic disease to the lung. In asymptomatic women with late-stage breast cancer, metastatic disease to the thorax is identified in 5% to 9% of patients [17,132,147]. The false-positive rate requiring additional imaging studies for further evaluation or follow-up ranged from 10% to 33% [17,132,148].

### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT to evaluate for distant disease.

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

NCCN guidelines recommend PET/CT as an optional additional test prior to preoperative systemic therapy if the tumor size is greater than T2, or there are positive lymph nodes, any HER2+, or triple-negative disease [126].

There is a large body of evidence that FDG-PET/CT is useful to detect metastatic disease in stage IIB to III breast cancer [136-139,149-158]. This is important because patients with locoregional breast malignancy have 5-year survival rates of 76% to 99%, but for patients with distant metastases, 5-year survival rates decrease to 20% to 28% [159]. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT in identifying metastatic disease in this population are 100%, 96%, 80%, 100%, and 97%, respectively [41]. The false-positive rate of PET/CT was 19%. In comparison with CT and other modalities, 80% of patients with distant disease had the metastases exclusively identified on PET/CT [41]. Groheux et al [136] investigated 254 patients and found previously unknown metastases in 1 of 44 (2%) women with stage IIA breast cancer, 6 of 56 (11%) women with stage IIB cancer, 11 of 63 (18%) women with stage IIIA cancer, 27 of 74 (37%) women with stage IIIB cancer, and 8 of 17 (47%) women with stage IIIC cancer. PET/CT has especially high yields in the case of patients newly diagnosed at <40 years of age, revealing distant metastases in 17% of asymptomatic patients with stage IIB breast cancer <40 years of age [155]. PET/CT modified staging between 14% and 28% of patients with late-stage disease, regardless of tumor receptor status [138,139]. In a study of 163 women, PET/CT and whole body bone scan demonstrated concordance in identifying osseous metastases in 81% of cases. Also, PET/CT had the added benefit of detecting extraosseous metastasis in 62% of patients with osseous metastasis. Of those patients with extraosseous metastases, 6% had equivocal and 42% had negative bone scans [160]. The sensitivity and specificity for PET/CT in the detection of distant metastases is higher than conventional imaging, with a 97% sensitivity and 91% specificity versus an 86% sensitivity and 67% specificity, respectively ( $P = .009$  and  $P < .001$ , respectively) [161]. However, PET/CT has limited sensitivity for ILC [162]. NCCN guidelines recommend PET/CT as an optional additional test prior to preoperative systemic therapy to evaluate for distant disease if the tumor size is >2 cm (T2) or there are positive lymph nodes, or tumor size is >1 cm (T1c) and HER2+, or there is triple-negative disease [126], because these subtypes tend to be more aggressive with earlier spread to extraosseous locations compared with other molecular subtypes as described above.

### **Mammography Diagnostic**

There is no evidence to support the use of diagnostic mammography to evaluate for distant disease.

### **Mammography With IV Contrast**

There is no evidence to support the use of mammography with IV contrast to evaluate for distant disease.

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

There is no evidence to support the use of MRI breast without and with IV contrast to evaluate for distant disease.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating the extent of disease.

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

The cumulative incidence of brain metastasis across all stages and subtypes of breast cancer ranges from 5.1% to 9.1% [163,164]. However, the incidence increases to 14.2% in patients with other metastases [163]. In a single study of 968 patients with brain metastasis, Martin et al [165] found a higher incidence proportion among hormone receptor–negative, HER2+ (1.1%), and triple-negative (0.7%) subtypes. In patients with known metastasis to any extracranial site, the incidence increased to 11.5% and 11.4%, respectively. The incidence of brain metastases was also higher among Black women, possibly due to later stage at diagnosis (OR, 1.27; 95% CI, 1.06-1.53;  $P = .01$ ). Currently, the NCCN and ASCO do not recommend routine screening for brain metastasis using MRI because there is no evidence of improved survival [126,166].

### **MRI Head Without IV Contrast**

There is no evidence to support the use of MRI head without IV contrast to evaluate for distant disease.

### **US Axilla**

There is no evidence to support the use of US axilla to evaluate for distant disease.

### **US Breast**

There is no evidence to support the use of US breast to evaluate for distant disease.

### **Variant 6: Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for local recurrence in patient with history of BCT.**

Breast-conserving treatment (BCT) of lumpectomy followed by whole-breast radiation is the most common treatment following a diagnosis of stage I and II breast cancer. Long-term studies show no significant difference in survival rates of patients treated with BCT versus mastectomy. Locoregional recurrence typically occurs 3 to 6 years post-treatment, at an average annual rate of 1% to 2.5% per year [167,168]. More recent studies indicate the risk of developing locoregional recurrence in patients with early stage disease treated with breast-conserving surgery, whole-breast radiation, and appropriate systemic treatments is approximately 0.5% per year [169]. In 1 meta-analysis, the 10-year local recurrence rate in patients after neoadjuvant chemotherapy and breast conservation was 6.5% and locoregional disease recurrence was 10.3%. Factors found to be associated with a higher risk of local recurrence were ER-negative disease, axillary spread, especially in >3 nodes or clinically palpable disease, and a lack of pathologic complete response [170]. Studies have shown that early detection of recurrence (prior to clinical detection) improves long-term survival by approximately 17% to 28% [171]. Therefore, imaging surveillance remains important in this patient population.

### **Digital Breast Tomosynthesis Diagnostic**

The most widely accepted guidelines regarding the surveillance of asymptomatic women with a history of breast cancer come from 2 national organizations: ASCO and NCCN [172,173]. Both organizations state that routine surveillance with an annual mammogram can detect an in-breast recurrence or a new primary breast cancer in women with an average risk for recurrence.

However, there is institutional variation on the frequency (every 6 months versus annual) and time period (1-5 years post-BCT) for surveillance after BCT. There is also variation on whether to include women in the screening versus diagnostic patient populations, in which women in the diagnostic population wait for possible additional imaging needed to reach a final assessment prior to leaving the imaging facility. The sensitivity of mammography is decreased due to post-treatment changes from surgery and radiation therapy, and some institutions prefer closer follow-up after BCT to assess changes due to radiation and surgery and potentially detect local recurrences earlier than on annual follow-up imaging. A single-institution study of 2,329 women following BCT showed that a 6-month interval for surveillance detected a higher proportion of local recurrences at an earlier stage compared with annual surveillance [174]. In a single-institution study of 789 asymptomatic women after BCT, 1.2% had cancer diagnosed at the 6-month timepoint following treatment ( $n = 169$ ), and 0.6% had cancer detected in women who

underwent routine mammographic screening a year after treatment (n = 620) [175]. However, earlier diagnosis did not result in a difference in local and distant disease-free survival. In summary, there is insufficient evidence demonstrating superior outcomes with diagnostic versus screening mammography for breast cancer surveillance. Expert consensus is to perform an annual diagnostic examination for the first 3 years, followed by routine annual screening, due to the increased complexity of interpretation from postsurgical and postradiation changes [176] and the increased risk of recurrence in the first 3 years following treatment [177-180].

There have been multiple studies evaluating the performance of DM versus DBT for surveillance. Chikarmane et al [181] compared tomosynthesis with 2-D mammography in women with a personal history of breast cancer treated with lumpectomy and mastectomy. They reported a significant decrease in recall rate (7.9% versus 10.1%, respectively) and increased sensitivity (92.3% versus 90.0%, respectively) with tomosynthesis with no significant difference in the cancer detection rate (6.1 versus 6.0 per 1,000 women screened, respectively) or PPV (12.0% versus 6.4%, respectively). These changes in interpretive performance were similar regardless of whether the women underwent breast-conserving surgery or mastectomy.

There is evidence that mammography alone may not be sufficient for surveillance in this population. In a large study involving 32,331 women with a history of breast cancer undergoing 117,971 surveillance mammographic examinations (112,269 digital mammographic examinations and 5,702 DBT examinations), surveillance mammography performance in the detection of interval cancers was inferior to established screening mammography benchmarks [182]. The main limitation of this study was the relative low proportion of DBT examinations, because DBT does detect more cancer than DM alone [183]. Women <50 years of age at primary breast cancer diagnosis appear to be at highest risk of a missed interval cancer using surveillance mammography [184]. These data suggest a need for evolving evidence-based surveillance recommendations on supplemental screening.

### **Digital Breast Tomosynthesis Screening**

The most widely accepted guidelines regarding the surveillance of asymptomatic women with a history of breast cancer come from 2 national organizations: ASCO and NCCN [172,173]. Both organizations state that routine surveillance with an annual mammogram can detect an in-breast recurrence or a new primary breast cancer in women with an average risk for recurrence.

However, there is institutional variation on the frequency (every 6 months versus annual) and time period (1-5 years post-BCT) for surveillance after BCT. There is also variation on whether to include women in the screening versus diagnostic patient populations, in which women in the diagnostic population wait for possible additional imaging needed to reach a final assessment prior to leaving the imaging facility, whereas women in the screening population could leave after their standard views are performed. The sensitivity of mammography is decreased due to post-treatment changes from surgery and radiation therapy, and some institutions prefer closer follow-up after BCT to assess changes due to radiation and surgery and potentially detect local recurrences earlier than on annual follow-up imaging. A single-institution study of 2,329 women following BCT showed that a 6-month interval for surveillance detected a higher proportion of local recurrences at an earlier stage, compared with annual surveillance [174]. In a single-institution study of 789 asymptomatic women after BCT, 1.2% had cancer diagnosed at the 6-month timepoint following treatment (n = 169) and 0.6% had cancer detected in women who underwent routine mammographic screening a year after treatment (n = 620) [175]. However, earlier diagnosis did not result in a difference in local and distant disease-free survival. In summary, there is insufficient evidence demonstrating superior outcomes with diagnostic versus screening mammography for breast cancer surveillance. Expert consensus is to perform an annual diagnostic examination for the first 3 years, followed by routine annual screening, due to the increased complexity of interpretation from postsurgical and post radiation changes [176] and the increased risk of recurrence in the first 3 years following treatment [177-180].

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

There is no literature to support the use of FDG-PET/CT to evaluate local recurrence of breast cancer.

### **Mammography Diagnostic**

The most widely accepted guidelines regarding the surveillance of asymptomatic women with a history of breast cancer come from 2 national organizations: ASCO and NCCN [172,173]. Both organizations state that routine surveillance with an annual mammogram can detect an in-breast recurrence or a new primary breast cancer in women with an average risk for recurrence.

However, there is institutional variation on the frequency (every 6 months versus annual) and time period (1-5 years post-BCT) for surveillance after BCT. There is also variation on whether to include women in the screening versus

diagnostic patient populations, in which women in the diagnostic population wait for possible additional imaging needed to reach a final assessment prior to leaving the imaging facility. The sensitivity of mammography is decreased due to post-treatment changes from surgery and radiation therapy, and some institutions prefer closer follow-up after BCT to assess changes due to radiation and surgery and potentially detect local recurrences earlier than annual follow-up. A single-institution study of 2,329 women following BCT showed that a 6-month interval for surveillance detected a higher proportion of local recurrences at an earlier stage compared with annual surveillance [174]. In a single-institution study of 789 asymptomatic women after BCT, 1.2% had cancer diagnosed at the 6-month timepoint following treatment (n = 169), and 0.6% had cancer detected in women who underwent routine mammographic screening a year after treatment (n = 620) [175]. However, earlier diagnosis did not result in a difference in local and distant disease-free survival. In summary, there is insufficient evidence demonstrating superior outcomes with diagnostic versus screening mammography for breast cancer surveillance. Expert consensus is to perform an annual diagnostic examination for the first 3 years, followed by routine annual screening, due to the increased complexity of interpretation from postsurgical and postradiation changes [176] and the increased risk of recurrence in the first 3 years following treatment [177-180].

There is evidence that mammography alone may not be sufficient for surveillance in this population. In a large study involving 32,331 women with a history of breast cancer undergoing 117,971 surveillance mammographic examinations (112,269 digital mammographic examinations and 5,702 DBT examinations), surveillance mammography performance in the detection of interval cancers was inferior to established screening mammography benchmarks [182], with the main limitation of this study being the relative low proportion of DBT examinations because DBT does detect more cancer than DM alone [183]. Women <50 years of age at primary breast cancer diagnosis appear to be at highest risk of a missed interval cancer using surveillance mammography [184]. These data suggest a need for evolving evidence-based surveillance recommendations on supplemental screening.

### **Mammography Screening**

The most widely accepted guidelines regarding the surveillance of asymptomatic women with a history of breast cancer come from 2 national organizations: ASCO and NCCN [172,173]. Both organizations state that routine surveillance with an annual mammogram can detect an in-breast recurrence or a new primary breast cancer in women with an average risk for recurrence.

However, there is institutional variation on the frequency (every 6 months versus annual) and time period (1-5 years post-BCT) for surveillance after BCT. There is also variation on whether to include women in the screening versus diagnostic patient populations, in which women in the diagnostic population wait for possible additional imaging needed to reach a final assessment prior to leaving the imaging facility, whereas women in the screening population could leave after their standard views are performed. The sensitivity of mammography is decreased due to post-treatment changes from surgery and radiation therapy, and some institutions prefer closer follow-up after BCT to assess changes due to radiation and surgery and potentially detect local recurrences earlier than on annual follow-up imaging. A single-institution study of 2,329 women following BCT showed that a 6-month interval for surveillance detected a higher proportion of local recurrences at an earlier stage compared with annual surveillance [174]. In a single-institution study of 789 asymptomatic women after BCT, 1.2% had cancer diagnosed at the 6-month timepoint following treatment (n = 169), and 0.6% had cancer detected in women who underwent routine mammographic screening a year after treatment (n = 620) [175]. However, earlier diagnosis did not result in a difference in local and distant disease-free survival. In summary, there is insufficient evidence demonstrating superior outcomes with diagnostic versus screening mammography for breast cancer surveillance. Expert consensus is to perform an annual diagnostic examination for the first 3 years, followed by routine annual screening, due to the increased complexity of interpretation from postsurgical and postradiation changes [176] and the increased risk of recurrence in the first 3 years following treatment [177-180].

### **Mammography With IV Contrast**

A large study (n = 858) comparing the use of mammography with IV contrast to 2-D mammography showed an increase in the sensitivity of cancer detection from 50% to 87.5% with minimal changes to the specificity (97.1% versus 93.7%, respectively) and PPV (25.0% versus 20.9%, respectively) [185]. This study cohort included a large portion of women with a personal history of breast cancer (40.2%) and women with dense breasts (77.5%), although no information is given about the time since breast cancer diagnosis or stage at presentation in the surveillance population.



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

For most breast cancer survivors, there is insufficient evidence for or against the use of breast MRI to detect disease recurrence in women of average risk. However, the ACR recommends annual surveillance with breast MRI in women with a personal history of breast cancer and dense breast tissue, or those diagnosed before age 50 [186]. This ACR recommendation is partially due to data showing that women with a personal history of premenopausal breast cancer benefited from MRI screening [187].

Data from the Breast Cancer Surveillance Consortium (BCSC) showed that, compared with mammography, MRI identified more cancers (10.8 versus 8.2 per 1,000 women screened) at the expense of a higher biopsy rate (10.1% versus 4.0%). However, multivariate models showed no difference in interval cancer detection rate or sensitivity (61.4% versus 70.3%, respectively) [188]. Wernli et al [188] also found that surveillance breast MRI leads to higher biopsy rate (OR, 2.2; 95% CI, 1.9-2.7;  $P < .001$ ) and cancer detection rate (OR, 1.7; 95% CI, 1.1-2.7;  $P = .03$ ) than mammography alone. However, there were no differences in sensitivity (OR, 1.1; 95% CI, 0.4-2.9;  $P = .84$ ) or interval cancer rate (OR, 1.1; 95% CI, 0.6-2.2;  $P = .70$ ) compared with mammography. Single-institutional studies at academic centers evaluating MRI for surveillance report sensitivities between 75% to 100% [189-193]. The cancer detection rate ranges from 1% to 2.9% for women whose only risk factor is a personal history of breast cancer [190-192]. However, this increases to 5.4% in patients with a personal history of breast cancer and dense breasts [194]. Another study from the BCSC group showed that women with a personal history of breast cancer undergoing MRI had a 2-fold increase in biopsy rate per 1,000 screening episodes (57.1% versus 23.6%) and lower cancer yield (267.6 versus 404.6 per 1,000 episodes with biopsy) than following mammography [195]. Most recently, a meta-analysis from 2000-2019 evaluating MRI as a screening modality in 8,338 women with a history of breast cancer (12,335 MRI examinations) found insufficient data to recommend for or against MRI as a surveillance examination in addition to mammographic screening [196]. Cancer detection rates of a second breast cancer by MRI were 8 to 20 per 1,000 examinations, but the sensitivity range was from 61% to 100%, with BI-RADS benchmark for MRI screening of at least 80%. Thus, clinical performance benchmarks have not been met in this population. Still, with the exception of the study on the BCSC cohort, other studies did not account for patient characteristics that could increase risk, such as premenopausal status, breast density, mutation status, or family history, through adjustment, stratification, or descriptive analysis.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating extent of disease.

### **US Breast**

There is limited evidence to support the use of US breast for surveillance in women with history of BCT. A single study in Asian patients with a personal history of breast cancer treated with breast-conserving surgery or mastectomy showed diagnostic performances for the sensitivity, specificity, PPV, and accuracy of US of 95.8%, 97.8%, 27.1%, and 97.9% after BCS and 42.9%, 97.5%, 9.4%, and 97.2% after mastectomy [197]. There is additional evidence that whole breast US, as an adjunct to screening mammography in all women with dense breasts, detects additional 0.3 to 7.7 cancers per 1,000 at the expense of 11.7 to 106.6 biopsies per 1,000 women [198]. Although useful as a general supplemental screening tool, these limited data do not support US breast as supplemental screening after breast cancer conservation, with more data needed to determine how postoperative changes and fat necrosis specific to this population might impact specificity and sensitivity.

### **Variant 7: Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for local recurrence in patient with history of mastectomy.**

Minimal residual breast tissue remains after all forms of mastectomy [199]. Although locoregional recurrence is typically detected clinically, some are incidentally detected by imaging, during the screening examination of the native contralateral breast. For these reasons, ASCO recommends frequent clinical surveillance with physical examination and history every 3 to 12 months for the first 5 years after mastectomy, followed by annual clinical breast examination in subsequent years [173].

### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT to evaluate for recurrence after mastectomy in an asymptomatic patient.

### **Digital Breast Tomosynthesis Screening**

There is no evidence to support the use of screening DBT to evaluate for recurrence after mastectomy.

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no role for imaging to screen for locoregional recurrences with FDG-PET/CT skull base to mid-thigh. ASCO, NCCN, and ESMO all recommend against the routine use of imaging to screen for distant disease recurrence [172,173,200].

### **Mammography Diagnostic**

There is no evidence to support the use of diagnostic mammography to evaluate for recurrence after mastectomy in asymptomatic women.

### **Mammography Screening**

There is no evidence to support the use of screening mammography to evaluate for recurrence after mastectomy.

### **Mammography With IV Contrast**

There is no evidence to support the use of CEM to evaluate for recurrence after mastectomy in asymptomatic women.

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

High-risk women with mastectomies may benefit from MRI surveillance of their remaining breast. In a small study evaluating MRI in women with a unilateral mastectomy, the cancer detection rate was 10 per 1,000 in the asymptomatic mastectomy side, and these cancers would have otherwise been undetected until symptomatic because screening mammography is not performed after mastectomy. In this population, surveillance MR had a sensitivity of 66.7%, a specificity of 99.2%, a PPV of 57.1%, and an NPV of 99.5%. Larger studies are needed to assess the utility of surveillance MR in the setting of mastectomy [201].

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

There is no evidence to support the use of noncontrast breast MRI in surveillance.

### **US Breast**

There is limited evidence to support the use of US breast for surveillance in the women with history of mastectomy.

### **Variant 8: Suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory value in patient with history of BCT. Regardless of clinical stage at time of original presentation.**

#### **Digital Breast Tomosynthesis Diagnostic**

Mammography can assist in monitoring women with a history of breast cancer and evaluating for suspicion of local recurrence. Diagnostic DBT improves lesion characterization in noncalcified lesions when compared with conventional mammographic workup [202]. The performance of DM versus DBT has not been determined for symptomatic imaging specifically in the post-BCT population.

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

There is no evidence to support the use of FDG-PET/CT to evaluate for locoregional recurrence after BCT.

### **Mammography Diagnostic**

Mammography can assist in monitoring women with a history of breast cancer and evaluating for suspicion of local recurrence. Diagnostic DBT improves lesion characterization in noncalcified lesions when compared with conventional mammographic workup [202]. The performance of DM versus DBT has not been determined for symptomatic imaging specifically in the post-BCT population.

### **Mammography With IV Contrast**

There are limited data on the use of CEM in breast cancer surveillance. Sorin et al [203] did show a high incremental cancer detection rate (13.1 cancers per 1,000 women) when mammography with IV contrast replaced DM in patients with a personal history of breast cancer or with an intermediate lifetime risk. US (targeted and whole breast) increased the number of women needing biopsy from 80 to 134 without detecting additional malignancy.

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

Although MRI does have greater sensitivity for malignancy than diagnostic mammogram alone, this use serves to detect asymptomatic disease. If there is a finding on the mammogram or US, then workup may be performed based on the most suspicious finding identified during the standard diagnostic workup. A mammographic finding can be sampled using tomosynthesis or stereotactic biopsy, and a sonographic finding can be sampled using US-guided biopsy. If mammogram and US are unrevealing, MRI is not useful as a problem-solving test, and, therefore, further management should be based upon the clinical symptoms. For example, evidence does not support the use of MRI

in cases of a palpable breast mass without corresponding suspicious finding on mammography or US. In a study, 2 of 82 patients were subsequently diagnosed with malignancy with PPV of 25% [204], and in another, 3 of 167 women with PPV of 13% [205]. Finally, a third study starting with 22,004 women with palpable abnormalities demonstrated 9,334 with negative mammogram and/or US. Thirty-one of these patients underwent subsequent MRI, with 8 subsequent biopsies and no malignancies found [206].

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

There is no role for noncontrast MRI in the setting of suspected local recurrence based on signs and symptoms.

#### **US Breast**

In the setting of symptoms suggesting a local recurrence such as a palpable mass or focal pain, US is used after diagnostic mammography for a full evaluation, as per the ACR Appropriateness Criteria® topics on “[Palpable Breast Masses](#)” [207] and “[Breast Pain](#)” [208].

US breast may be helpful to further evaluate women with suspected recurrence unless the findings on mammography corresponding to the physical examination finding are classic for a benign etiology (eg, fat necrosis).

**Variant 9: Suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory value in patient with history of mastectomy. Regardless of clinical stage at time of original presentation.**

#### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT to evaluate suspected local recurrence in the setting of mastectomy unless the local recurrence suspected is in the axillary region or the patient has a history of breast reconstruction.

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

There is no evidence to support the use of FDG-PET/CT to evaluate suspected local recurrence in the setting of mastectomy.

#### **Mammography Diagnostic**

There is no evidence to support the use of mammography to evaluate suspected local recurrence in the setting of mastectomy unless the local recurrence suspected is in the axillary region or the patient has a history of breast reconstruction.

#### **Mammography With IV Contrast**

There is no evidence to support the use of mammography with IV contrast to evaluate suspected local recurrence in the setting of mastectomy unless the local recurrence suspected is in the axillary region or the patient has a history of breast reconstruction.

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

Although breast MR has been evaluated in the setting of asymptomatic screening after mastectomy, there is insufficient evidence to support the use of MR as a problem-solving tool after a negative mammogram (axillary finding/reconstructed breast) and/or US. Therefore, management should be based on clinical suspicion rather than additional imaging.

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

There is no evidence to support the use of noncontrast breast MRI in evaluating disease suspected recurrence.

#### **US Breast**

In the setting of symptoms suggesting a local recurrence such as a palpable mass or focal pain, US is used after diagnostic mammography (if indicated) for a full evaluation, as per the ACR Appropriateness Criteria® topics on “[Palpable Breast Masses](#)” [207] and “[Breast Pain](#)” [208].

**Variant 10: Surveillance. Regardless of clinical stage of breast cancer at time of original presentation. Evaluation for distant metastatic disease.**

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no evidence to support the use of bone scan whole body for surveillance of distant metastatic disease. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no evidence to support the use of CT chest, abdomen, and pelvis for surveillance of distant metastatic disease. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no evidence to support the use of CT chest, abdomen, and pelvis for surveillance of distant metastatic disease. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no evidence to support the use of CT chest, abdomen, and pelvis for surveillance of distant metastatic disease. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

### **Digital Breast Tomosynthesis Diagnostic**

There is no evidence to support the use of DBT in asymptomatic women for surveillance of distant metastatic disease.

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

In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no evidence to support the use of FDG-PET/CT for surveillance of distant metastatic disease. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

### **Mammography Diagnostic**

There is no evidence to support the use of mammography to evaluate suspected distant metastatic disease unless the recurrence suspected is in the axillary region.

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

There is no evidence supporting the use of MRI head without and with IV contrast in asymptomatic women for surveillance. In asymptomatic patients with a history of breast cancer who received treatment for curative intent, there is no role for imaging to screen for distant recurrences. The ASCO, NCCN, ESMO, and ESO all recommend against the routine use of imaging to screen for distant disease recurrence [126,128,209,210].

### **MRI Head Without IV Contrast**

There is no evidence supporting the use of MRI head without IV contrast in asymptomatic women for surveillance.

### **US Axilla**

There is no evidence supporting the use of US axilla in asymptomatic women for surveillance of distant metastatic disease.

## **Variant 11: Suspected distant recurrence of breast cancer based on symptoms, physical examination, or laboratory value. Regardless of clinical stage at time of original presentation.**

### **Bone Scan Whole Body**

In the setting of suspected distant recurrence, bone scan along with chest, abdomen, and pelvis CT is recommended by the NCCN [126].

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

In the setting of suspected distant recurrence, bone scan plus chest, abdomen, and pelvis CT is recommended by the NCCN [172].

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

The majority of clinical questions for abdominal and/or pelvic CT can be appropriately answered with a single-phase study as detailed in the ACR-SABI-SPR practice parameter for the performance of CT of the abdomen and CT of the pelvis [21].

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

There is no evidence to support the use of CT chest, abdomen, and pelvis without IV contrast to evaluate for distant recurrence.

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

In symptomatic patients with a history of breast cancer who received treatment for curative intent, PET/CT can be used to evaluate for recurrence according to NCCN guidelines [126].

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

The cumulative incidence of secondary breast cancer brain metastases among a US-based population of patients with primary breast cancer was 9.1% (95% CI, 8.5%-9.8%) and the prevalence was 11.7% (95% CI, 11.0%-12.4%) in a study including any patient with a breast cancer diagnosis [164]. In a single study of 968 patients with brain metastasis, Martin et al [165] found a higher incidence among hormone receptor–negative, HER2+ (1.1%), and triple-negative (0.7%) subtypes. In patients with known metastasis to any extracranial site, the incidence increased to 11.5% and 11.4%, respectively. The incidence of brain metastases was also higher among Black women, possibly due to later stage at diagnosis (OR, 1.27; 95% CI, 1.06-1.53;  $P = .01$ ). In the setting of symptoms concerning for brain metastases (headache, nausea, vomiting), a CT head with IV contrast or MRI head with and without IV contrast may be helpful, as detailed in the ACR Appropriateness Criteria® topic on “[Headache](#)” [211].

### **MRI Head Without IV Contrast**

There is no evidence supporting the use of MRI head without IV contrast in symptomatic women for the detection of distant disease.

### **Summary of Recommendations**

- **Variante 1:** US breast, DBT diagnostic, mammography diagnostic, and MRI breast without and with IV contrast are usually appropriate for a newly diagnosed patient with clinical stage I to IIA (early stage) breast cancer at presentation getting an evaluation for locoregional disease (includes IDC or ILC, or NOS). These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient’s care).
- **Variante 2:** Imaging is usually not appropriate for a newly diagnosed patient with clinical stage I to IIA (early stage) breast cancer at presentation to evaluate for distant disease (includes IDC, or ILC, or NOS).
- **Variante 3:** US axilla, US breast, DBT diagnostic, mammography diagnostic, MRI breast without and with IV contrast, and FDG-PET/CT skull base to mid-thigh are usually appropriate for a newly diagnosed patient with clinical stage IIB to III (later stage) breast cancer at presentation to evaluate for locoregional disease (includes IDC, or ILC, or NOS). These procedures can be complementary, each providing unique clinical information to effectively manage the patient’s care.
- **Variante 4:** Bone scan whole body, CT chest abdomen pelvis with IV contrast, and FDG-PET/CT skull base to mid-thigh are usually appropriate for a newly diagnosed patient with clinical stage IIB to III (later stage) breast cancer at presentation to evaluate for distant disease with IDC or ILC that is ER+/HER2-negative. These procedures can be complementary, each providing unique clinical information to effectively manage the patient’s care.
- **Variante 5:** Bone scan whole body, CT chest abdomen pelvis with IV contrast, and FDG-PET/CT skull base to mid-thigh are usually appropriate for a newly diagnosed patient with clinical stage IIB to III (later stage) breast cancer at presentation to evaluate for distant disease with IDC or ILC that is HER2+ or triple-negative (ER, PR, and HER2-negative). These procedures can be complementary, each providing unique clinical information to effectively manage the patient’s care.
- **Variante 6:** DBT diagnostic, DBT screening, mammography diagnostic, or mammography screening are usually appropriate for a patient with a history of breast cancer, regardless of clinical stage at time of original presentation to evaluate for local recurrence and screen for de novo disease. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).
- **Variante 7:** MRI breast without and with IV contrast may be appropriate as a routine screening tool for the contralateral breast in a patient with a history of breast cancer who has undergone a mastectomy.

- **Variation 8:** US breast, DBT diagnostic, and mammography diagnostic are usually appropriate to evaluate a patient with suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory values. 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).
- **Variation 9:** US breast is usually appropriate for a patient with suspected local recurrence of breast cancer based on symptoms, physical examination, or laboratory value that has a history of mastectomy regardless of location or history of reconstruction.
- **Variation 10:** Imaging is usually not appropriate to evaluate for distant disease in an asymptomatic patient with a history of breast cancer.
- **Variation 11:** MRI head without and with IV contrast, bone scan whole body, CT chest abdomen pelvis with IV contrast, and FDG-PET/CT skull base to mid-thigh are usually appropriate for a patient with suspected distant recurrence of breast cancer based on symptoms, physical examination, or laboratory value regardless of clinical stage at time of original presentation. These procedures can be complementary, each providing unique clinical information to effectively manage the patient’s care.

### Supporting Documents

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

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

### Appropriateness Category Names and Definitions

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

### Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for

pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document [212].

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
☼	<0.1 mSv	<0.03 mSv
☼☼	0.1-1 mSv	0.03-0.3 mSv
☼☼☼	1-10 mSv	0.3-3 mSv
☼☼☼☼	10-30 mSv	3-10 mSv
☼☼☼☼☼	30-100 mSv	10-30 mSv

\*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies.”

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