review articles

Imaging in Locoregional Management of Breast Cancer

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INTRODUCTION

In the patient with newly diagnosed breast cancer (BC), imaging is used to enable, facilitate, or enhance every aspect of locoregional management. This includes mapping disease extent to guide surgery of the BC, monitoring response of BC to guide neoadjuvant chemotherapy, and guiding management of axillary lymph nodes. In this review, we provide a summary of the evidence regarding the current and future use of imaging to support decision making by the patient and by team members from surgical, radiation, and medical oncology.

IMAGING TO GUIDE IN-BREAST SURGERY

Imaging is used before surgery to improve delineation of the true size of the known cancer (the index cancer), to help the surgeon appropriately define resection margins, to detect additional ipsilateral (multifocal or multicentric) disease, and to detect cancer in the opposite breast. Imaging methods used for this purpose include digital mammography or tomosynthesis, high-resolution (> 10 MHz) ultrasound, and breast magnetic resonance imaging (MRI). Although there is broad consensus that there is no role for positron emission tomography (PET)/computed tomography (CT) for imaging the primary BC, dedicated PET imaging (positron emission mammography, PEM) may be useful in selected patients with suspected multicentric disease.[1-3]

Imaging to Delineate the Size of the Known Cancer

BC surgery has evolved over the past decades from radical to simple mastectomy and quadrantectomy to wide local excision and, now, "no ink on tumor" for women with invasive disease[4]; in women with pure ductal carcinoma in situ (DCIS), the recommended margin is now 2 mm.[5] In parallel, contraindications to breast-conserving surgery (BCS) have been progressively relaxed. Until recently, cancers > 2 cm, cancers with larger (extensive) DCIS component, or multicentric cancers had been considered contraindications for BCS. Today, women with such tumors may be offered BCS as long as resection of all cancer is feasible with adequate cosmetic result.[6-11] This means that surgical treatment of BC should be delivered at a detailed personalized level.[12] With surgeons adjusting their resection margins increasingly closely along the presumed border between healthy and diseased tissue, the role of imaging to provide accurate information on the precise extent of cancer may further increase.

According to a recent meta-analysis on women undergoing BCS in the United States, one (30.1%) out of three women undergo more than one round of surgery, and half of these women end up with "completion mastectomy."[13-15] Re-excisions add to overall costs, may impair the cosmetic result of surgery, are a psychological strain to women, and are an independent driving factor for prophylactic contralateral mastectomies.[16] In their thoughtful editorial, Cody and van Zee[17] called the high rate of re-excisions for positive margins "the other BC epidemic"[17] and explained that even a reduction of the positive margin rate by 10 percentage points would avoid between 10,000 and 20,000 additional surgical procedures in the United States annually. A study from the United Kingdom on surgical outcome of more than 55,000 women who underwent BCS came to the conclusion that "lack of accurate imaging, especially for imaging of DCIS and DCIS components, leads to a consistently high rate of additional surgery."[14]

Indeed, the usual imaging methods used to plan BC surgery (mammography and breast ultrasound) are known to correlate only modestly well with pathologic cancer size.[18] Bosch et al[19] found a correlation coefficient of 0.44 for mammography, and 0.68 for ultrasound, with underestimation of true size being the dominant reason for lack of correlation. Such underestimation of cancer size—and thus positive margins requiring reoperation—is most often due to noncalcified DCIS or DCIS components of no special type (ie, ductal) cancers,[14] and due to invasive cancers with lobular histology (ILC), where the diffuse growth pattern leads to isodensity or isoechogenicity of tumor and normal fibroglandular tissue in mammography and ultrasound, respectively.[20,21]

Breast MRI improves size assessment of BC in general,[22] and of ILC, pure DCIS, and DCIS components in particular (Figs 1 and 2).[22-34] For ILC, the reported correlation coefficients between pathologic and MRI-determined size range from substantial to excellent (0.75-0.98).[22-26] For DCIS components, in a prospective study by Kuhl et al[29] on 593 consecutive

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Accepted on March 26, 2020 and published at ascopubs.org/journal/jco on May 22, 2020: DOI https://doi.org/10.1200/JCO.19.03257

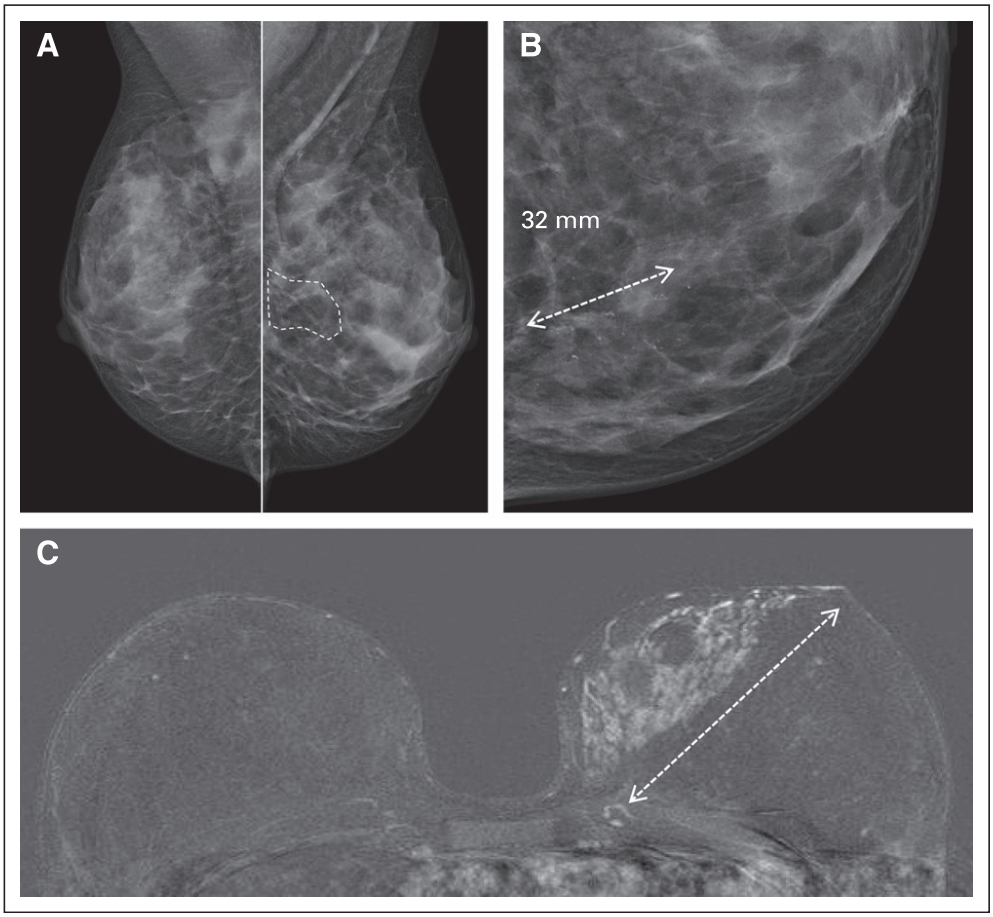

FIG 1. Depicting extent of pure ductal carcinoma in situ (DCIS). A 52-year-old patient had screening-detected calcification-associated DCIS in the posterior part of upper inner quadrant on mammography. Size on mammography was 32 mm in longest diameter. High-resolution ultrasound (12.5 MHz probe; not shown) was negative. Vacuum-assisted biopsy revealed high-grade DCIS. Magnetic resonance imaging (MRI) depicted the large DCIS that affected the entire upper inner quadrant and involved the nipple. Size on MRI was 82 mm. The patient underwent mastectomy that confirmed nipple involvement. Pathologic assessment of the size of the DCIS was 65 mm. Formal analysis would thus indicate MRI had overestimated the size of the DCIS. More likely is that pathology underestimated the size.

women with invasive cancer, the sensitivity advantage of MRI over mammography plus ultrasound for depicting DCIS components was highly significant ($P < .0001$) and increased with increasing relative size and increasing nuclear grade of DCIS components. Accordingly, the larger a DCIS component is in relation to the size of the invasive cancer, and the higher its nuclear grade, the more likely it will be occult on conventional imaging, but detectable by breast MRI. When the DCIS component is as large as, or larger than, the known invasive cancer (but not visible by

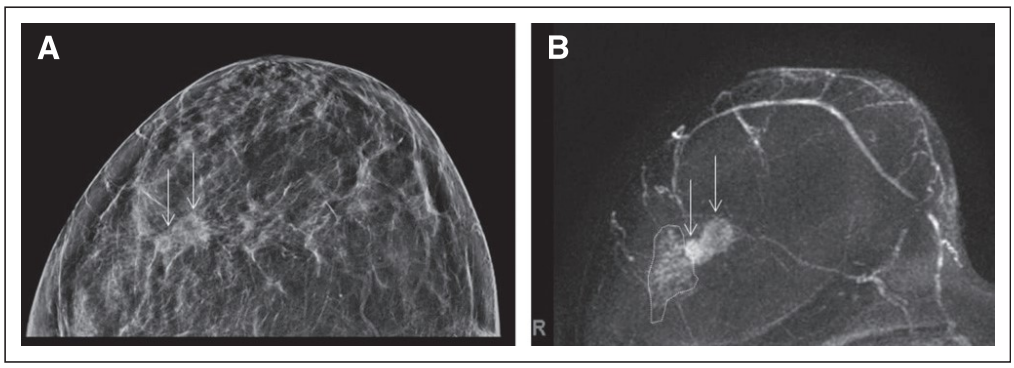

FIG 2. A 62-year-old patient underwent screening mammography and Digital Breast Tomosynthesis (DBT). The breast is nondense (ACR density category A, almost entirely fatty breast). The screening DBT (A) reveals two spiculated masses in the upper outer quadrant (arrows). Ultrasound (not shown) confirms presence of two masses, 8 mm and 14 mm in diameter. Ultrasound-guided core biopsy reveals invasive breast cancer, no special type, luminal B subtype, in both masses. Magnetic resonance imaging (MRI) (B) depicts the two invasive cancers, plus a large segment of non-mass enhancement suggestive of an intraductal component (dotted line) that was occult both on DBT and ultrasound. Surgery after MR-guided bracketing confirmed presence of an extensive DCIS component in addition to the invasive cancer.

usual preoperative imaging), positive margins are predictable, especially when the surgeon adheres to current guidelines and chooses resection margins adapted to the size of the known invasive cancer.[29]

The improved delineation of cancer by breast MRI has been shown to translate into improved surgical treatment outcome[22-29,31-34]; for instance, Mann et al[23] found a 3.7-times lower re-excision rate and a lower mastectomy rate for women who underwent MRI. Similarly, the improved depiction of DCIS components translated into equally low positive-margin rates and mastectomy rates for women with versus without DCIS components (5.0% *v* 3.3% and 10.8% *v* 8.1%), respectively.[29]

Imaging to Identify Additional Ipsilateral Disease

Preoperative imaging may detect cancer in addition to the index cancer. The need to distinguish between multicentric versus multifocal cancer is decreasing with the increasing acceptance to offer BCS for both conditions.[9-11] A prospective study of 166 patients demonstrated that digital breast tomosynthesis (DBT) offered a mild increase of sensitivity for ipsilateral disease from 44% (95% CI, 36% to 52%) for mammography alone to 52% (95% CI, 44% to 60%) with additional DBT, but only in women with nondense breasts.[30]

Across a variety of studies, MRI has consistently been shown to depict additional cancer elsewhere in the same breast with significantly greater sensitivity than ultrasound and mammography.[35-41] In 603 consecutive patients undergoing MRI before BC surgery in a community practice, Hollingsworth et al[36] found multicentric cancer, here defined as cancer ≥ 5 cm away from the index cancer, in 86 (14.3%) of 603 patients using MRI, versus in 43 (7%) of 603 patients using mammography. In another analysis of 2,021 women, MRI detected multicentric cancer (here defined as cancer in a different quadrant) in 4% of patients.[38]

Where reported, the characteristics of the additional cancers found by MRI versus by mammography or ultrasound were similar. Although women with dense breasts were more likely to exhibit additional cancers diagnosed by MRI, one-third of MRI-detected additional ipsilateral cancers were identified in women with nondense breasts.[35,37-41]

An emerging functional breast imaging method to depict additional lesions is PEM. In a prospective multicenter study of 388 patients, Berg et al[41] compared PEM with MRI for surgical planning and found that additional multifocal or multicentric cancers were identified in 82 (21%) of 388 women and had an average size of 0.7 cm. PEM offered a somewhat lower overall sensitivity than MRI but did detect additional lesions that had gone undetected by MRI (one additional pT1b, 11 additional pT1a lesions).[41]

Because local recurrence rates are low in women undergoing BCS even if based only on mammographic staging, sufficient local control of the additional, mammography-occult cancer foci detected by ultrasound, MRI, or PEM is apparently achieved by whole-breast radiotherapy.[42,43] Mastectomy for such ultrasound-, MRI-, or PEM-detected multicentric disease may therefore constitute overtreatment. Still, the 4%-10% rate of additional multicentric cancer matches fairly well with published rates of long-term ipsilateral in-breast recurrence that range between 4% and 14%.[42,43] In a study of 3,781 women undergoing preoperative MRI, multivariate analysis demonstrated that multifocal disease on MRI and HER2-positive subtype were both independently associated with local recurrence, with an odds ratio of 11.9 (95% CI, 1.4 to 102.5) and 12.7 (95% CI, 1.3 to 127.6), respectively.[44] With the Alliance trial A011104/ACRIN 6694 (ClinicalTrials.gov identifier: NCT01805076), a prospective randomized trial of preoperative MRI, we will learn whether long-term local control is further improved if such additional lesions are removed by additional surgery.

In five percent of women with MR-detected multicentric cancer, the additional cancer exhibits more adverse tumor biology than the index cancer.[38] Because personalized systemic therapy depends on tumor biology, it may be prudent to obtain pathology of such additional findings, regardless of whether they require additional treatment or not.

Imaging to Identify Additional BC in the Opposite Breast

Women with BC carry a high risk for contralateral breast cancer (CBC), identified by mammography in between 1% and 4% of women.[45,46] Ultrasound may be used to search for additional CBC. In a recent retrospective analysis, Leblond et al[47] found that ultrasound was positive in 76 of 360 patients with mammographically unilateral cancer; biopsy confirmed cancer in 11 of 76 (positive predictive value, 14.5%), for an additional CBC detection rate of 11 (3.1%) of 360 patients. Of the 11 women with ultrasound-detected CBC, nine were found in women with dense breasts.[47]

MRI has been proposed for the same purpose Because most contemporary MRI protocols use bilateral imaging, CBC screening is included in routine preoperative breast MRI. In a prospective multicenter study of 969 women (ACRIN-6667; ClinicalTrials.gov identifier: NCT00058058), Lehman et al[48] reported MRI to detect mammography-occult invasive CBC in 1.8% of patients; this rate was 2.4% in the series by Hollingsworth et al[36] and 3% in the prospective multicenter study by Berg et al.[41] Accordingly, the invasive cancer detection rate of CBC screening with MRI is higher than that of established high-risk MRI screening indications.[49] The additional CBCs detected by MRI exhibited the same or worse stage than the index cancer in 50% of cases in the series by Hollingsworth et al.[36] Published studies concordantly found that the likelihood with which MRI detected contralateral cancer was independent of mammographic breast density.[36,41,48]

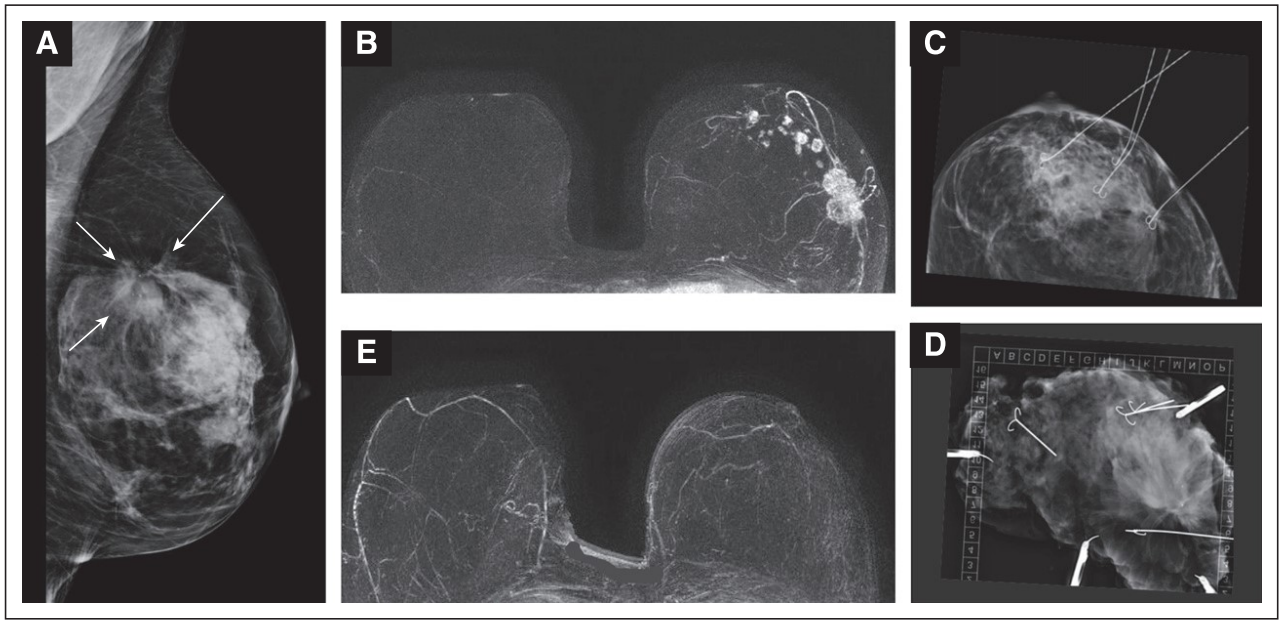

FIG 3. A 63-year-old patient who underwent reduction mammoplasty decades ago presented with a palpable mass in the left upper outer quadrant. (A) Mammography shows large stellate mass. Ultrasound-guided biopsy confirmed luminal B cancer. (B) Magnetic resonance imaging (MRI) demonstrates multifocal/multicentric breast cancer with multiple foci in the upper/outer quadrant, reaching to the upper/inner quadrant, and no evidence of breast cancer on the right. Magnetic resonance (MR)–guided bracketing of the extent was performed. (C, D) Mammography after MR-guided bracketing (C) and specimen radiogram (D) confirm that the vast majority of the cancer foci are mammographically occult. Breast-conserving surgery (BCS) was performed with free margins after a single round of surgery. (E) Follow-up MRI 4 years after BCS and radiotherapy demonstrates absence of local recurrence and absence of contralateral breast cancer.

With improved detection of synchronous CBC with MRI, one would expect to see a reduced incidence of subsequent CBC. There are no prospective studies on this issue; retrospective analyses yield conflicting results. Solin et al[50] reported no reduction of CBC incidence in women undergoing MRI; however, the study had included only 215 women, followed for a median 4.1 years, and thus may not have been adequately powered to detect such differences. Wang et al[51] analyzed SEER data sets of 6,377 women with and 32,594 women without preoperative MRI. They found an increased detection of CBC (12.6% *v* 4.3%) and a reduced rate of subsequent CBC (3.3 *v* 4.5 per 1,000), with a hazard ratio of 0.68 ($P = .02$), yet also a persistently higher 5-year cumulative incidence in the MRI group (7.2% *v* 4.0%), fueling concerns about overdiagnosis.[51] Kim et al[52] demonstrated a significantly reduced cumulative incidence of subsequent CBC in 3,094 women at 45 months follow-up, from 1.4% (95% CI, 0.81% to 2.14%) in the group without MRI down to 0.5% (95% CI, 0.23% to 0.96%) in the group that underwent MRI ($P = .02$).[52]

Guidelines on the Use of Imaging for Breast Surgery

Guidelines for breast surgery are fairly consistent, with broad support for the importance of mammography and ultrasound to guide BC surgery. There are conflicting views and recommendations regarding appropriate use of MRI in the preoperative setting,[1-3] although MRI has been consistently shown to offer the highest diagnostic accuracy for staging the affected breast and for identifying CBC. This paradox is best explained by the fact that published results on the impact of MRI on surgical outcome (reoperation rates) are conflicting; several retrospective studies demonstrated an association of use of pre-operative MRI with an increased mastectomy rate.[53-56]

The COMICE (Comparative Effectiveness of MRI in Breast Cancer) trial—the first randomized study to investigate reoperation rates with versus without MRI—was conducted from 2001-2007 on 1,623 women recruited in 45 different sites throughout the United Kingdom. It did not find reduced reoperation rates in the MRI group.[53] However, at the time the study was done, none of the sites had access to magnetic resonance (MR)–guided biopsy or MR-guided localization/bracketing—methods that today are prerequisites to obtain American College of Radiology accreditation for performing breast MRI.[57] Predictably, if one adds a more sensitive diagnostic test, there will be additional findings. If one then lacks the methods required to nonoperatively obtain histologic verification of these additional findings, one will need additional surgery to confirm or refute the additional diagnoses, which will lead to more, not fewer, surgical procedures. Moreover, without tools for MR-guided lesion localization/bracketing, it is difficult, if not impossible, to translate the MRI information into the operating room, ie, to actually use the information for

improved definition of resection margins (Fig 3). The second randomized trial on the use of MRI for treatment planning, the PreOperative MRI of the Breast (POMB) trial (ClinicalTrials.gov identifier: NCT01859936), enrolled 440 women recruited in three breast centers in Sweden, had these tools available. It did find a significantly reduced reoperation rate which was 5% (11/220) in the MRI-group, versus 15% (33/220) in the no-MRI group ($P < 0.00$), with equal numbers of mastectomies in both groups.[37] A third randomized trial, the IRCIS trial (ClinicalTrials.gov identifier: NCT01112254), enrolled 360 patients with biopsy-proven DCIS, recruited in 10 different hospitals in France from 2010-2014—unfortunately, again, without tools for MR-guided bracketing. Still, a mild reduction of reoperation rates was observed in the MRI arm by 7 percentage points, corresponding to a relative reduction by 26%.[58]

Of note, such studies—those that address the impact of preoperative imaging on surgical outcome (reoperation rates, positive margin rates, mastectomy rates) or oncological outcome (local recurrence-free or overall survival)—have so far only been done for breast MRI but not for any other imaging method (eg, mammography, ultrasound, CT, or other clinical applications of MRI). To appropriately interpret the findings of such research, one should realize that measuring the impact of imaging on surgical or oncological outcome measures is complex. This is because, when therapeutic end points are used to assess diagnostic tests, treatment per se will constitute a strong confounder (Fig 4). Reoperation rates, for instance, vary greatly between surgeons[59-61]: in a cohort of 2,206 consecutive women undergoing BC surgery by 48 different breast surgeons in four different institutions, McCahill et al[59] found that reoperation rates ranged from 0%-70% across surgeons. Because observed rates were not correlated with the respective surgeon's case load or patient-related factors, the broad range was attributable only to variable individual practice styles.[59] Because of the large variations of surgical outcome across surgeons, effects of more accurate imaging will not be able to "shine through," in particular not when multicenter trials pool results across many different surgeons, as the COMICE trial did.

For this reason, the Oxford Centre for Evidence-Based Medicine distinguishes between the types of evidence required to support the use of a new diagnostic test versus a new treatment approach.[62] The Center makes clear that although all diagnostic tests are done to guide treatment or monitor treatment effects, using surgical or medical end points to assess their utility will be misleading. Such outcome measures are therefore reserved for the evaluation of treatment. For new diagnostic tests, diagnostic accuracy is considered the only appropriate outcome measure. This rationale is not new but is consistent with introduction of imaging tests into clinical practice so far: using MRI (not CT imaging or ultrasound) to guide surgery of the knee, or using CT imaging (not chest x-rays) to guide surgery of the lung, or using additional ultrasound (not only mammography) to guide surgery in women with dense breasts are all widely accepted as routine care, justified by improved diagnostic accuracy only, despite the fact that none of the mentioned imaging methods has provided evidence on surgical or medical outcome. There is no reason to make an exception for breast MRI.

Rather, in good accordance with the principles of evidence-based medicine, the use of MRI to improve preoperative mapping of a known invasive cancer or DCIS is supported on a level of evidence grade 1A for diagnostic tests.[62]

Several retrospective studies reported an association of increased mastectomy rates with women's likelihood to undergo MRI,[54-56,63] although others did not observe this.[22-34,37,39,40,64] An association with increased mastectomy rates can in part be attributable to a selection bias: women who had undergone MRI were younger, had denser breasts, and had larger tumors than women in the

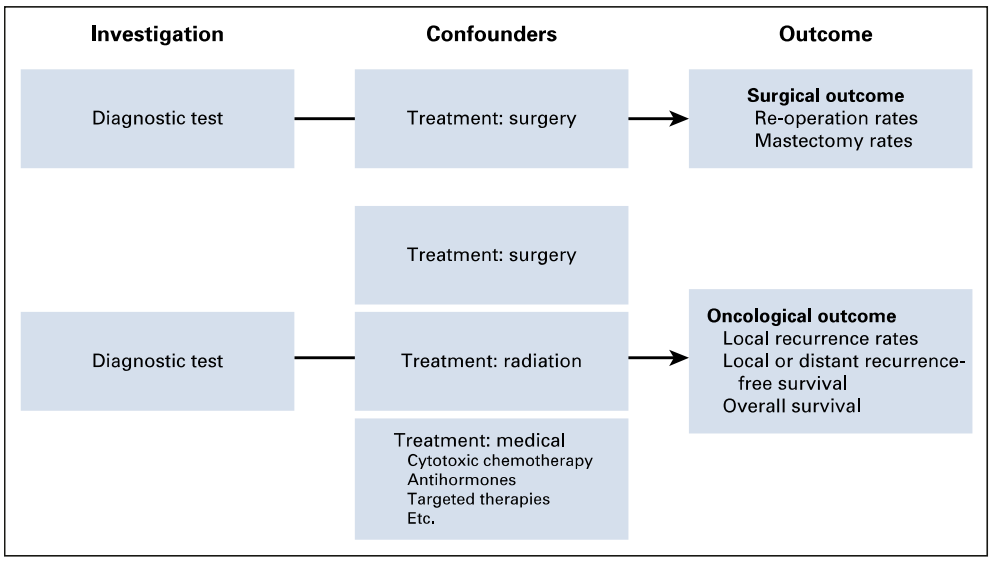

FIG 4. Confounders for diagnostic test.

respective no-MRI cohort.[65] In keeping with this, the ongoing international multicenter trial, MIPA, has already demonstrated that MRI is frequently used to confirm a surgeon's decision to do a mastectomy.[66] Another factor that may explain an association between MRI and mastectomy rate is that, until recently, guidelines required mastectomy for patients with multicentric cancer. Because MRI, just as ultrasound or PEM, will detect multicentric cancer more frequently than mammography alone, it is plausible that women who undergo preoperative ultrasound, MRI, or PEM would more often fulfill the formal criteria for mastectomy. In her landmark commentary, Morrow[67] was the first to correctly point out that, with improved depiction of additional BC manifestations, the number of women who meet the criteria for breast conservation would predictably decrease—predictably with no benefit for the patient; in short, it will lead to overtreatment.

Such overtreatment is avoidable when surgeons and oncologists acknowledge that the recommendation to perform mastectomy for multicentric cancer dates back to the inclusion criteria of Veronesi's[43] and Fisher's[42] randomized trials of BCS and thus refers to multicentric cancer diagnosed by film mammography only. The evidence collected in these BCS trials implies that an appropriate way to manage additional, mammography-occult lesions depicted only by ultrasound, MRI, or PEM is to treat them conservatively or, at most, by additional lumpectomy. In any case, ultrasound-/MRI-, or PEM-only–detected additional cancers should not routinely prompt mastectomy. In agreement with this, surgical oncologists have begun to offer BCS in patients with multicentric disease; German guidelines accept BCS in this situation.[9-11,68] The ACOSOG Z11102 trial (ClinicalTrials.gov Identifier: NCT01556243) supports the feasibility of breast conservation among women with two or three sites of disease, with two-thirds of such patients successfully undergoing BCS. This trial will also provide prospective data on the locoregional outcomes of women with multicentric disease treated with BCS once it matures.[8]

Future Potential to Use Imaging to Guide Local Management of BC

With the increasing understanding of the biologic heterogeneity of BC, systemic treatment is now tailored to its individual biologic aggressiveness. Local treatment, however, has not changed to a similar degree: all women undergo surgery until margins are clear, and if the breast is conserved, they also undergo radiotherapy. Yet only a minority of women who undergo BCS without radiotherapy will exhibit a local recurrence, indicating that for a majority of patients, radiotherapy constitutes overtreatment.[69] One opportunity to use precision imaging is therefore to select women who can safely forgo radiotherapy. A pioneering study that uses MRI to tailor treatment of women with pure DCIS is the ECOG-ACRIN EA4112 trial (ClinicalTrials.gov Identifier: NCT02352883), designed to identify patients who could safely undergo treatment without radiation.[70] First results from examining the impact of preoperative breast MRI and DCIS score on surgical and radiation therapy decision making found that about six in seven women underwent initial wide local excision after MRI, and, of those, only 4% required mastectomy as the final procedure. These data require additional follow-up. In women with pure DCIS who had wide local excision (≥ 2-mm margins) and DCIS scores, nearly half had low scores and were advised that radiotherapy could be avoided. The PROSPECT (Postoperative Radiotherapy Omission in Selected Patients With Early BC) trial[71] is a single-arm phase II trial that pursues a similar objective as E4112 but includes selected patients with low-risk invasive cancer to assess the use of MRI for omission of postoperative radiotherapy. An additional emerging concept to use imaging for improved treatment stratification is to include artificial intelligence–based phenotyping of imaging data to provide complementary prognostic and predictive information beyond immunohistochemical or genomic features.[72]

IMAGING TO GUIDE NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy (NACT), initially deployed to downsize disease to facilitate surgical care, has increasingly been recognized as a useful surrogate for tumor responsiveness, with implications for long-term prognosis.[73,74] Therefore, particularly for triple-negative and HER2-positive BC, NACT is now used even in the earliest stages.

Conventional imaging with mammography and ultrasound relies largely on morphologic changes. Fragmentation of tumors, the development of fibrosis, and the presence of calcifications interfere with accurate detection of response, especially when tumor-bed fibrosis simulates a mass. Calcifications are known to poorly correlate with response and may decrease, remain stable, or even increase during treatment regardless of response.[75] In a retrospective review of nearly 200 patients who had undergone doxorubicin-containing NACT, preoperative mammography and ultrasound had poor correlation with residual pathology tumor size, with correlation coefficients of 0.42 and 0.41, respectively,[76] and 0.66 for the combined use of both methods.[77] Given these limitations, there has been widespread interest in functional imaging approaches. Candidate methods are PET/CT and MRI. Other techniques, such as molecular breast imaging, quantitative ultrasound, and optical imaging are emerging as potential tools, yet clinical data remain sparse in these applications.

In [^{18}F]fluorodeoxyglucose (FDG)-PET/CT, early changes in tumor metabolism may be detectable that may precede any morphologic change. Although studies have shown an association between reduction in standardized uptake value after 1-2 cycles of chemotherapy and pathologic complete response (pCR),[75] overall the sensitivity and diagnostic accuracy reported in the literature are wide ranging.[78] This likely reflects the lack of consensus around crucial elements, such as the optimal cutoff values for

changes in metabolic activity and the optimal timing of FDG PET after initiation of chemotherapy. A meta-analysis of 13 studies offering a head-to-head comparison of PET/CT and MRI concluded that MRI is more suitable for predicting the pathologic response after NAC.[79]

MRI has been extensively studied for response assessment.[80] Marinovich et al[81] presented a meta-analysis on the accuracy with which clinical breast exam (CBE), mammography, ultrasound, and MRI can predict pCR. Results suggested that MRI performance was generally superior to mammography but with a wide range of sensitivities and specificities, ranging from 36%-100% and 25%-100%, attributable in part to variable definitions of pCR and variable interpretation guidelines to diagnose radiologic complete response (rCR) on MRI. A meta-analysis using individual patient data of 300 patients from 8 studies compared the accuracy of CBE, mammography, ultrasound, and MRI to depict the extent of residual disease.[82] Although MRI measurements were consistently superior to other methods, substantial over- and underestimation of residual disease by ± 3.8 cm was observed. Reasons for MRI to underestimate response were presence of residual DCIS but also inflammatory reactions in the former tumor bed.

More recent data from the I-SPY trial (ClinicalTrials.gov Identifier: NCT00043017), with consistent criteria for pCR and rCR, consolidate the superior accuracy of MRI for response assessment, with highest predictive accuracy achieved if the volume—not the longest diameter—of enhancing tissue, the "functional tumor volume" (FTV), is used.[83] The accuracy (area under the curve, AUC) with which FTV can predict pCR was 0.75; accuracy is increased (AUC, 0.84) when a multivariate model included both MR and clinical findings. A similar accuracy is achieved when breast MRI includes diffusion-weighted imaging (AUC, 0.81).[84]

Prevalence of pCR, thus sensitivity of disease to NACT, and thus BC subtype, modulates the accuracy with which imaging predicts pCR/depicts residual disease. The Translational Breast Cancer Research Consortium trial included 746 patients with MRI at baseline and after completion of NACT across eight institutions. With an overall pCR rate of 25%, overall accuracy of MRI for predicting pCR was 74%; the highest negative predictive value (NPV) of MRI to exclude residual disease was observed in the group with highest prevalence of pCR (ie, triple-negative and HER2-positive tumors).[80] With matured MRI procedures, the remaining variability of rCR reflects disease sensitivity to NACT rather than differing MR assessment quality across these subtypes, as De Los Santos et al[80] put it. Independent of subtypes, reduced accuracy of MRI for predicting pCR is also associated with use of taxane-containing versus nontaxane regimens, possibly because of their antiangiogenic effect.[85] Although, accordingly, no imaging modality predicts pCR with an accuracy high enough to consider de-escalation of breast surgery, it is believed that a combined strategy of imaging and image-directed biopsy of the tumor bed may achieve this goal. In a series of 164 patients with clinical complete response (cCR) after NACT, of whom 57% had achieved pCR, the overall NPV of minimally invasive biopsy to exclude residual tumor was only 71%. Improved biopsy technique (9G-11G needles with vacuum assistance *v* 14G core needle) and improved targeting of the tumor bed by biopsy clips were shown to increase the NPV.[86,87] The NRG BR005 study (ClinicalTrials.gov Identifier: NCT03188393) was set up to prospectively assess the accuracy of post-NACT image-guided tumor bed biopsy for determining pCR in women who achieved cCR and rCR at trimodality imaging (mammography, ultrasound, and MRI). Unfortunately, results on 98 patients demonstrated an NPV of only 77.5% (95% CI, 66.8% to 86.1%), well below the targeted NPV of ≥ 90%, indicating that surgery of the tumor bed is still warranted in these women.[88]

IMAGING TO GUIDE MANAGEMENT OF THE AXILLA

Imaging methods to stage the axilla include ultrasound, MRI, and [^{18}F]FDG-PET/CT. High-resolution axillary ultrasound (AUS) is the preferred method for this task and can be combined with AUS-guided biopsy to confirm positive diagnoses. Two meta-analyses, each including 31 different studies on the utility of preoperative AUS ± AUS-guided biopsy, concordantly found pooled sensitivities of 50% (95% CI, 43% to 57%)[89] and 55% (95% CI, 42% to 68%),[90] indicating that AUS identifies axillary involvement in about half of patients with positive nodes.

In view of the ACOSOG-Z11 (ClinicalTrials.gov Identifier: NCT01804309) results obtained in patients with small tumors (cT1-cT2) scheduled for breast conservation, the aim of preoperative axillary imaging has slightly changed. Here, axillary imaging is used mainly to avoid sentinel lymph node biopsy in patients identified to have advanced positive lymph nodes and who may therefore proceed to axillary lymph node dissection directly. Accordingly, the task is to distinguish between negative (N0) or limited disease (N1; ie, 1-3 axillary metastases) versus advanced disease (N2 or N3; ≥ 4 axillary metastases). A single-center study by Schipper et al[91] used AUS in 577 consecutive patients for this purpose. In patients categorized as negative (N0) on AUS, advanced axillary disease (N2-3) was found on pathology in only 4%, for an NPV of 95.5% (93.4%-97.1%); in the subgroup of 278 women fulfilling the ACOSOG-Z11 criteria, NPV of a negative AUS was as high as 97.7% (94.9%-99.0%). In the subgroup of 12 patients where AUS was positive, however, the accuracy to distinguish between limited and advanced stages was insufficient (50%).

In routine breast MRI, axillary as well as parasternal lymph nodes are included in the field of view and can be evaluated. van Nijnatten et al[92] compared the accuracy of such

axillary assessment in routine breast MRI studies with that of dedicated AUS in 377 patients with clinically negative or limited axillary nodes.

They reported an NPV for advanced axillary disease of 99.1%-99.3% for breast MRI, versus 98.5% for AUS and concluded that the accuracy of breast MRI and dedicated AUS is similar; in patients who do undergo preoperative breast MRI, dedicated AUS is likely redundant.

PET/CT is not recommended for routine staging of the axilla but is rather used as a whole-body staging method that might be considered in symptomatic patients or in selected high-risk patients, such as those with inflammatory or locally advanced BC.[93]

Among node-positive patients who undergo NACT, a substantial fraction will achieve pCR in their nodes. As with the breast, there is great interest to identify such women to de-escalate axillary surgery. Ultrasound is the most accurate modality for assessing residual disease in the regional nodes. Hieken et al[94] compared the accuracy of different imaging methods after NACT in 169 women with positive nodes at diagnosis, of whom 65 patients (38%) were pathologically node-negative at surgery. The sensitivity of ultrasound, MRI, and PET/CT for detection of persistent lymph node disease was 70%, 61%, and 63%, respectively. Although ultrasound performed best in this series, its sensitivity remains well below required thresholds to allow omission of axillary surgery post chemotherapy. These findings are also echoed in a secondary analysis from the ACOSOG-Z1071 trial (ClinicalTrials.gov Identifier: NCT00881361)[95]: among the 756 women enrolled in the Z1071 cohort, post-NACT/preoperative ultrasound was available in 611 patients. Although there was a linear association between ultrasound findings and the probability of residual disease, even in women with a completely benign ultrasound (nodal classification type I), 56% percent were pathologically node-positive. Furthermore, unlike in the tumor bed, image-guided biopsy of the nodal basin after NACT does not appear to improve the accuracy for predicting pCR.[96] Therefore, at present, routine omission of axillary surgery after NACT on the basis of imaging findings does not appear to be a feasible goal.

In conclusion, diagnostic imaging methods are tools that can help improve treatment decisions. The impact of these tools on improved patient care depends not only on the diagnostic accuracy of the respective method but also on the expertise of the multidisciplinary team that incorporates the tools into practice. Breast radiologists and surgeons, as well as medical and radiation oncologists, have the opportunity to embrace contemporary imaging in clinical care and treatment trials to support personalized treatment of the diverse spectrum of BC. A number of ongoing and future trials, along with existing evidence on how to appropriately use available methods of precision imaging, will refine the role of imaging in breast cancer to optimize the locoregional management and quality of life in women diagnosed with BC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.03257.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Imaging in Locoregional Management of Breast Cancer

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Research Funding: GE Healthcare (Inst)
Travel, Accommodations, Expenses: GE Healthcare

No other potential conflicts of interest were reported.