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Paradigm Shifts in Breast Care Delivery: Impact of Imaging in a Multidisciplinary Environment

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Abstract

The practice of breast imaging in a collaborative multidisciplinary environment adds significant value to outcomes in women's healthcare. In this article, we describe multidisciplinary considerations in breast cancer screening and early detection, the impact of imaging and histopathologic findings in the diagnostic evaluation and management of breast abnormalities, and the contribution of imaging to surgical and radiation therapy planning for the breast cancer patient.

Keywords

Breast cancer; Atypia; Lobular neoplasia; Ultrasound; biopsy; Nodal metastases

BREAST CANCER SCREENING AND EARLY DETECTION CONSIDERATIONS

The current paradigm for breast cancer screening allows a woman to schedule a screening mammogram without a clinician order. The value of this self-referral model is that it reduces barriers for a woman to obtain a screening mammogram. The downside of this practice is that risk reduction and screening recommendations for women at increased risk may or may not occur. Many breast imaging facilities are now routinely assessing breast cancer risk

when women are seen for their annual mammogram. This information provides the opportunity for collaborative care between the breast imager and the cancer prevention specialist (CPS), who may be a primary care physician or medical oncologist, in the management of women at increased or high risk. Communication of this risk as well as providing guidance regarding the available supplemental screening modalities, such as breast MRI, to CPSs helps to ensure the appropriate screening of the high-risk woman. Breast imagers are likely to have the greatest knowledge and understanding of current supplemental high-risk screening recommendations (1). Based on the outcome of the breast cancer risk assessment performed in the screening mammography setting, additional opportunities exist to inform the CPS of the need for possible genetic counseling and/or risk reduction therapy (e.g., selective estrogen receptor modulators [tamoxifen, raloxifene] and aromatase inhibitors [exemestane, anastrozole] (2–5).

DIAGNOSTIC EVALUATION AND MANAGEMENT OF BREAST ABNORMALITIES

The evaluation of suspicious breast lesions using image-guided needle biopsy is an established practice for routine patient care in most breast centers. Radiological-histopathological correlation ensures accurate sampling of an imaging abnormality in the breast to guide appropriate clinical management. However, as percutaneous needle biopsy has become more prevalent, histologic diagnoses are made with less breast tissue. While the majority of lesions are benign on biopsy, it is imperative that there is a determination of clinical, radiographic, and pathologic concordance. Ideally, the radiologist would provide a differential diagnosis that would allow the clinician to determine concordance when pathology is available (e.g., imaging findings are suggestive of a fibroadenoma and biopsy confirms such). When findings are discordant, communication between the clinician, the radiologist, and, possibly, the pathologist, is imperative to reconcile the discordance. Ultimately, discussion at a multidisciplinary clinical management conference may be necessary to determine management recommendations. Effective communication and collaboration between the multidisciplinary breast care team allows for the delivery of optimal treatment by providing opportunities to share best practices around areas of controversy for which standard of care has not yet been established, or where evolving knowledge initiates novel ideas that could be tested in clinical practice (6). Rigorous validation of findings in well-designed prospective studies provides evidence that can lead to meaningful changes in routine clinical practice and that is ultimately beneficial to patients.

HISTOPATHOLOGIC CONSIDERATIONS

Active collaboration between multidisciplinary groups is currently making a significant difference in the management of patients with a biopsy proven diagnosis of lesions associated with an increased risk of developing invasive breast cancer. Histopathological diagnoses of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS), fall under the category of high risk breast lesions (7, 8). Lobular neoplasia encompasses ALH and LCIS, currently regarded risk factors and non-obligatory precursors of breast neoplasia (9, 10). These lesions are clinically,

morphologically, and biologically heterogeneous and are associated with varying levels of increased risk for the development of invasive breast cancer.

Ductal carcinoma in situ (DCIS) is traditionally regarded and treated as breast cancer, with surgery as the first line of treatment (11). While it is recognized that breast cancer comprises a broad spectrum of biologic behavior, recent data has generated controversy around current strategies for the detection and treatment of DCIS. Narod et al reported that the long term bilateral risk of developing breast cancer after a diagnosis of DCIS was 5.9% and 6.2%, for ipsilateral and contralateral invasive breast cancer, respectively (12). These findings have led to several interesting suggestions (13). First, the majority of DCIS may be considered a potential risk factor (such as atypia) for invasive breast cancer. Second, low and intermediate grade DCIS may not meet threshold targets for screening and early detection. Third, radiation therapy should not be routinely administered after breast conservation surgery for non-high-risk DCIS in light of the lack of association with mortality reduction. Current understanding of the biologic characteristics of high risk DCIS include large size, high grade, hormone-negative, HER2-positive disease, women of very young age, and African American women. In this regard, it is interesting to note that two randomized trials in Europe and one in the United States have or will shortly commence evaluating patients with a diagnosis of low and intermediate grade DCIS with observation alone versus standard surgical excision and adjuvant therapies (14–16).

The management of other high risk lesions such as ADH, ALH, and LCIS, which are associated with a relative risk of breast cancer development in either breast of 4, and 4, and 10, respectively, is more controversial, specifically regarding the need for subsequent surgical excision of the imaging abnormality (17). Historically, women with high-risk proliferative breast lesions (atypical hyperplasia [ALH], or LCIS) on needle biopsy have been referred for surgical excision due to the possibility of a co-existing, occult carcinoma at the site of the residual imaging abnormality (18–22). While this topic remains controversial, recent reports suggest that not all women with ALH or LCIS on needle biopsy require surgical excision to rule out a higher grade lesion (23–28). A recent study reports that breast core biopsies with a diagnosis of lobular carcinoma in situ should be excised in view of a higher upgrade rate of 8.4% to 9.3%, while surveillance may be reasonable for a diagnosis of atypical lobular hyperplasia with an upgrade rate of 2.4% to 3.5% (29). While MRI may be considered prior to excision of patients diagnosed with LCIS, the reported negative predictive value of 88% in the largest series to date (28, 30) is too low to obviate the need for excision. Multidisciplinary review in a clinical management conference provides value in appropriate management recommendations (23, 24).

Similarly, lesions such as radial scar, papilloma, and mucocoele-like lesions may demonstrate heterogeneity in morphological findings that range in spectrum from benign, to higher grade lesions including atypia, and carcinoma. Flat epithelial atypia (FEA), a commonly encountered lesion in stereotactic biopsies performed for grouped calcifications, has an uncertain risk level and is another histopathologic lesion where the management is variable in different practices (31).

Most of the controversy regarding the management of patients following a core biopsy diagnosis of high risk lesions other than DCIS relates to the need for subsequent surgical excision of the lesion (32, 33). There are no currently understood clinic-pathological or molecular alterations that can help identify women with high risk breast lesions who will progress to invasive carcinoma. Management strategies including active surveillance, chemoprevention, and bilateral prophylactic mastectomy, are currently not personalized for individual patients but are based on determination of the population-level risks following models such as Gail, IBIS, Claus, BRCAPRO, Tyrer-Cuzick (34–36).

At The University of Texas MD Anderson Cancer Center, a multidisciplinary approach is employed to provide management recommendations for patients with discordant, indeterminate or high-risk proliferative breast lesions. The weekly multidisciplinary conference includes breast specialists from the departments of Radiology, Pathology, Cancer Chemoprevention, and Surgery and allows for the integration of clinical, radiologic and pathologic data (23). The patients' clinical history, radiological and pathological findings are reviewed in depth. Review and discussion of each case takes into consideration the variables listed in Table 1 and leads to personalized management recommendations (23, 24).

For example, the finding of focal ADH on pathological evaluation (<3 terminal ductal lobular units [TDLU]) accompanied by near complete removal of the calcifications of concern (> 90% of calcifications removed with the stereotactic biopsy) may result in a recommendation of imaging follow-up together with risk assessment and counseling regarding breast cancer risk-reduction options (24, 28, 37). In contrast, the finding of extensive disease (high risk lesions) on pathologic review and limited sampling (< 50% of targeted lesion) raises concern about the possibility of co-existing, higher-grade lesions. For this reason, surgical excision may be recommended. A mass lesion, as opposed to calcifications, with an associated high-risk proliferative breast lesion is more worrisome and may require excision, especially those involving an atypical papillary lesion (38, 39). For lesions including radial scar, papilloma and mucocoele-like lesion that have been sampled with a large-gauge vacuum assisted device revealing no atypia at histopathology, the probability of finding a higher grade lesion at excision is markedly reduced; such patients may be followed without the need for surgery (40, 41). Additionally, vacuum assisted biopsy devices have been employed for the percutaneous acquisition of additional large volume tissue samples in lieu of surgery when an initial 14-gauge limited core biopsy sample exhibits these lesions without atypia (40, 41).

Notably, a significant number of final recommendations from the multidisciplinary conference do not involve surgical excision in patients where excision would have otherwise been the standard management recommendation. A single and uniform approach does not seem reasonable for the management of patients with a CNB diagnosis of high risk breast lesions. While risk reducing medical agents are currently available to reduce breast cancer risk in these patients, the immediate need for surgical excision or active surveillance can be individualized based on a multidisciplinary approach (42). This multidisciplinary conference provides personalized recommendations based on a critical review of clinical, radiologic and pathologic data. Prospective validation of our approach is currently underway so that eventually more patients universally can benefit from this strategy.

SURGICAL CONSIDERATIONS FOR THE BREAST CANCER PATIENT

Preoperative Staging of Breast Cancer with Imaging

Multidisciplinary collaboration has led to meaningful changes in surgical paradigms for the breast cancer patient. Breast and nodal imaging of breast cancer is critical in the selection of appropriate surgical management. In the initial loco-regional staging of biopsy proven breast cancer, additional indeterminate and suspicious breast lesions identified by ultrasound can be managed by performing on-site ultrasound-guided fine needle aspiration biopsy (FNAB) or core biopsy (CB). Core biopsy is widely adopted, more commonly available in clinical practice, and has the advantage of being able to differentiate invasive from in situ disease. The advantage of FNAB in adequately resourced breast imaging centers is ability to provide on site assessment of the cytological specimen, which contributes towards the initial staging evaluation of breast cancer patients. The overall sensitivity of FNA biopsy of the breast is variable, and is as high as 93% (43). Active partnership between the radiologist and the pathologist enables accurate delineation and confirmation of additional sites of disease in the breast and influences the selection of breast conservation surgery versus mastectomy.

The role and utilization of breast MRI in the staging of a patient with newly diagnosed breast cancer is practiced in many facilities with appropriate resources. Breast MRI remains a powerful tool for the identification of cancer foci that are occult by mammography, ultrasound, and clinical examination. A meta-analysis performed of 19 studies involving 2,610 patients revealed additional disease foci identified by MRI in a median of 16% (range, 11–24%) of breast cancer patients (44). The detection of additional tumor foci with MRI did not provide clear benefit to patient outcomes, given that 10 year ipsilateral breast tumor recurrence rates in women who underwent breast conservation surgery followed by adjuvant therapy without prior MRI were between 3–7% (45). Additionally, there is currently inadequate data to demonstrate that MRI improves candidate selection for breast conservation surgery or improves patient outcomes by increasing the negative margin rate at initial surgery. The Comparative Effectiveness of MRI in Breast Cancer (COMICE), and the Mammography of Nonpalpable Breast Tumors (MONET), trials did not significantly reduce reoperation rates, including margin re-excision and conversion to mastectomy rates (46, 47). The identification of contralateral breast cancer in women diagnosed with breast cancer has been reported in 2 prospective studies; contralateral breast cancer was detected in 4% and 3% of patients, when MRI was performed within 6 months and 12 months, respectively, from the time of cancer diagnosis (48, 49). These numbers are significantly higher than the reported 1% per year rates of clinical contralateral breast cancer in all subgroups of patients, excluding the 20–29 year group with estrogen receptor-negative cancers. These findings suggest that many of these “occult” cancers detected by MRI would not have become clinically significant as a function of their biology, or would have been adequately treated with adjuvant systemic therapy administered for treatment of the primary breast cancer.

Preoperative Imaging Evaluation of Regional Lymph Nodes

The preoperative evaluation of loco-regional lymph nodes in the initial staging of breast cancer patients can be performed using FNA or core biopsy (50). In patients with early stage breast cancer, confirmation of positive axillary lymph node status by ultrasound-guided FNA

biopsy or core biopsy generally indicates higher tumor nodal burden; and complete axillary dissection rather than sentinel lymph node biopsy is more suitable (51, 52). In contrast to core biopsy, ultrasound-guided FNA biopsy allows sampling of multiple lymph nodes including the supraclavicular or infraclavicular lymph node chains, which may potentially upstage patients with locally advanced breast cancer (53, 54).

More recently, there has been a dramatic shift in the use of ultrasound for the evaluation of the axilla and other nodal draining regions to facilitate preoperative systemic therapy and surgical planning related to axillary lymph node dissection. The presence of axillary nodal metastases has significant impact on loco-regional and systemic treatment decisions. Historically, all node positive patients underwent complete axillary lymph node dissection; however, this paradigm has shifted in the past few years.

Z0011 Trial

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was a prospective, randomized, multicenter trial involving women with early stage (T1-2N0) breast cancers, 1 or 2 positive sentinel nodes, who underwent breast conservation therapy with whole breast irradiation (55). This trial reported no difference in overall survival, disease-free survival, and local recurrence rates for women who had completion axillary lymph node dissection versus sentinel node biopsy alone. Data reported post Z0011 confirmed a new paradigm whereby surgeons would omit axillary lymph node dissection in patients with 1 to 2 positive sentinel lymph nodes in women with early stage breast cancer scheduled for whole breast irradiation (56–58). Subsequently, surgeons in some institutions also elected to omit preoperative imaging of the axilla for women with early stage breast cancer (59).

Targeted Axillary Dissection

There has been interest in expanding the role of sentinel lymph node biopsy to include removal of the index biopsy-proven (ultrasound-guidance) metastatic node in patients who receive neoadjuvant chemotherapy. This new paradigm may provide a way to restage the axilla after receiving neoadjuvant chemotherapy in hopes of sparing women who convert to node negative status from the morbidity of complete nodal dissection. Sentinel lymph node dissection alone may not accomplish this goal as many reports in the literature have shown the false negative rate for this procedure to exceed the threshold for best clinical practice. Emerging novel techniques, such as Targeted Axillary Dissection (TAD), may allow for reliable nodal staging after chemotherapy to limit morbidity (60–62). In this procedure, patients undergo ultrasound of the axilla with ultrasound-guided FNA biopsy of an index abnormal axillary node, followed by placement of a metallic marker [Figures 1A, 1B]. Following neoadjuvant chemotherapy, an I125-radioactive seed is placed in this clipped lymph node [Figures 1C, 1D] under ultrasound guidance to ensure removal at the time of surgery (62–64). Routine intraoperative lymphatic mapping is performed along with removal of this radioactive seed using an intraoperative Geiger counter [Figure 1E]. Work conducted at MD Anderson has demonstrated that approximately 25% of lymphatic mapping performed will fail to identify the lymph node that had the documented metastases (60). Utilizing this new technique of TAD to combine sentinel lymph node dissection with seed

localized removal of clipped metastatic lymph nodes, the false negative rate for staging the axilla is below 5%, and provides an acceptable standard for staging of the axilla among node-positive patients receiving neoadjuvant chemotherapy (63). Alternate methods of localizing clipped metastatic axillary nodes include hook wires and electromagnetic wave markers (62, 65). Based on this early work, the National Comprehensive Cancer Network (NCCN) guidelines changed in 2015 to reflect this new procedure as a potential safe way to limit axillary surgery even among women who initially present with node positive breast cancer (66). Approximately 40% of women who receive neoadjuvant chemotherapy will have complete eradication of axillary node metastases. These women who presented with nodal metastases and routinely underwent complete axillary lymph node dissection in the past may thus be spared this potentially morbid surgery (67–69). This advance represents a significant paradigm shift in the management of the axilla and epitomizes value-driven breast healthcare as it improves outcome and the quality of life of patients based on interdisciplinary research driven clinical excellence.

RADIATION THERAPY CONSIDERATIONS FOR THE BREAST CANCER PATIENT

Imaging assessment of the regional lymph nodal basins yields substantial benefit to the evaluation by the radiation oncologist, particularly in the management of locally advanced breast cancer. Accurate nodal imaging guides the radiation oncologist in determining which nodal chains to target with radiation, and what radiation dose to administer. Imaging assessment is particularly important for the infraclavicular, supraclavicular, and internal mammary nodal basins, as these areas are not typically resected, and no pathologic data are available to determine disease involvement in these regions [Figures 2A, 2B]. Ultrasound forms the cornerstone to the assessment of the unresected nodal basins at our institution. The singular value of ultrasound in assessing the extent of disease in these regions and thereby guiding radiation treatment planning, is underscored by the observation that ultrasound frequently identifies small volume nodal disease which does not meet size criteria for malignant adenopathy on CT and/or is not FDG-avid on PET/CT. An additional benefit of ultrasound, as opposed to cross-sectional imaging, is the ability to perform ultrasound-guided FNA biopsy in real time to establish a pathologic diagnosis. When extra-axillary nodal disease is identified by ultrasound, the radiation oncologist uses this information to ensure that the entirety of the involved nodal basin is treated with radiation up to 45 Gy in 25 fractions. This is followed by an adequate radiation boost, typically 9 Gy in 5 fractions if the node resolved during chemotherapy, or 14.4 Gy in 8 fractions if residual nodal disease is identified on ultrasound at the completion of chemotherapy.

A recent study by our group reported the utility of regional lymph node ultrasound evaluation in 865 patients presenting with clinical stage III breast cancer. Ultrasound identified extra-axillary nodal metastases in 37% (n=325) of such patients, thereby leading to changes in these patients' radiation treatment plans (70). Of those patients with extra-axillary disease, approximately 85% had infraclavicular involvement, 40% had supraclavicular involvement, and 30% had internal mammary involvement. The majority of these nodal metastases were pathologically confirmed by ultrasound-guided FNA biopsy

prior to commencing radiation therapy. Thoughtful radiation to include appropriate targeting and dosing of these involved nodal basins is highly effective, with recent series from our group documenting durable control of the involved nodal basin in greater than 90% of treated patients (71, 72).

For patients with inflammatory breast cancer, FDG-PET confers additional benefit beyond conventional cross-sectional imaging and ultrasound. For example, our group reported in a case series of 62 patients that FDG-PET identified additional sites of disease in 44% of patients, most commonly distant/contralateral nodal regions, bone, and mediastinum. This finding led to changes in the post-mastectomy radiation treatment plan in 18% of patients, including adjustment of fields, changes in dosing and addition of fields (73). Based on this experience, we strongly favor FDG-PET staging at baseline for patients with inflammatory breast cancer and consider using FDG-PET to assess response to both chemotherapy and radiation.

CONCLUSION

The multidisciplinary delivery of breast care for women that incorporates screening, the diagnosis of borderline and high risk lesions, and the management of the breast cancer patient, adds considerable value to outcomes in healthcare. Breast imaging significantly impacts multidisciplinary considerations in breast cancer screening and early detection, the discussion around histopathologic findings in the diagnostic evaluation and management of breast abnormalities, and the surgical and radiation therapy planning for the breast cancer patient.

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A.

B.

C.

D.

E.

Fig. 1.

27-year-old woman with biopsy-proven invasive ductal right breast cancer metastatic to right axilla.

A. Baseline ultrasound right axilla demonstrates markedly hypoechoic node (arrow) with clip in situ (short arrow) that was placed at time of needle biopsy.

B. Follow-up ultrasound right axilla 6 months later after completion of neoadjuvant chemotherapy shows interval decrease in size of hypoechoic node (arrow), and clip (short arrow).

C. Ultrasound right axilla during I125 radioactive seed placement shows radioactive seed within node (arrow), and shaft of introducer (short arrow).

D. Right MLO mammogram demonstrates radioactive seed (long arrow) and marker clip (short arrow).

E. Specimen radiography of right axillary content at surgery confirms removal of seed (long arrow) and clip (short arrow).

A.

B.

Fig. 2.

64-year-old woman diagnosed with grade 3 invasive mammary (ductal and lobular features) carcinoma.

A. Ultrasound of left axilla shows 2 contiguous markedly hypoechoic left axillary nodes (arrows), suspicious for metastases.

B. Ultrasound left supraclavicular nodal region demonstrates multiple small hypoechoic nodes (arrows). Ultrasound-guided needle biopsy confirmed metastatic carcinoma. Radiation therapy was administered to left breast via medial and lateral approach; left supraclavicular fossa and axillary apex were treated via AP oblique photon field.

Table 1

Clinical, radiologic and pathologic variables considered in the multidisciplinary management of women with ADH, ALH or LCIS

<u>Clinical</u>	
•	Finding on clinical exam
–	Yes/No
•	Association of clinical finding with imaging abnormality
–	Yes/No
<u>Radiologic</u>	
•	Imaging finding
–	Architectural distortion
–	Asymmetry
–	Calcifications
–	Enhancing lesion
–	Mass
–	None
•	Biopsy features
–	Type
♦	Stereotactic biopsy
♦	Ultrasound-guided FNA
♦	Ultrasound-guided core needle biopsy
♦	Vacuum-assisted ultrasound-guided core needle biopsy
♦	MRI-guided core needle biopsy
–	Sampling
♦	Stereotactic biopsy
•	<50% of lesion removed
•	>50% of lesion removed
•	>90% of lesion removed
♦	Ultrasound or MRI-guided biopsies
•	Lesion removed: Yes/No
<u>Pathologic</u>	
•	Extent of lesion on pathology
–	Focal (<3 lobules)
–	Extensive (>2 lobules)
•	Association of lesion with radiographic abnormality
–	Associated with targeted lesion
–	Incidental to targeted lesion

Note: Table 1 is adapted and expanded from Appendix I in “Multidisciplinary considerations in the management of high-risk breast lesions,” by Krishnamurthy S, Bevers T, Kuerer H, Yang WT, AJR Am J Roentgenol 2012; 198:W132–W140 (23)