Regional Lymph Node Staging in Breast Cancer: The Increasing Role of Imaging and Ultrasound-Guided Axillary Lymph Node Fine Needle Aspiration

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KEYWORDS

• Breast cancer • Staging • Axilla • Ultrasound
• Fine needle aspiration • Biopsy

Axillary lymph node staging is a crucial component of breast cancer management, with the radiologist playing an increasing role. Historically, axillary lymph node staging was performed entirely through axillary lymph node dissection without using imaging or percutaneous diagnosis. However, more recently, less morbid techniques have been developed that require imaging guidance and necessitate that radiologists have an understanding of the anatomy, imaging appearance, and significance of abnormalities in the regional lymph node system of the breast. This article reviews the clinical significance and surgical staging of axillary metastatic involvement in breast cancer and then focuses on the use of axillary ultrasound and ultrasound-guided fine needle aspiration (USFNA) as a preoperative staging method. A brief discussion of internal mammary lymph node evaluation is also included.

SIGNIFICANCE AND ANATOMY OF AXILLARY LYMPH NODE METASTASIS IN BREAST CANCER

Once breast cancer is diagnosed, lymph node status is the most powerful indicator of long-term survival.[1] Although other features, such as tumor size, histologic grade, and hormone and Her2/neu receptor status, have predictive value, the status of the lymph nodes reflects the actual interaction of tumor aggressiveness and host resistance.[2] The number of lymph nodes involved, the extent of lymph node involvement within the individual nodes, and the location of involved lymph nodes also have prognostic significance. For instance, gross involvement of the lymph node by metastatic disease and extranodal extension of disease have a worse prognosis than microscopic metastatic disease. In addition, information on lymph node involvement not only is important for prognosis but also is used in treatment decision making.

The primary lymphatic drainage of the breast is to the axillary lymph nodes. Various names have been given to the groups of lymph nodes that constitute the axillary lymph node chain, although surgeons typically classify axillary nodes by their location relative to the pectoralis minor muscle. Level I nodes are lateral or inferior to the pectoralis minor, level II nodes are posterior to the pectoralis minor, and level III nodes are medial to the pectoralis minor (**Fig. 1**). Although involved level III nodes

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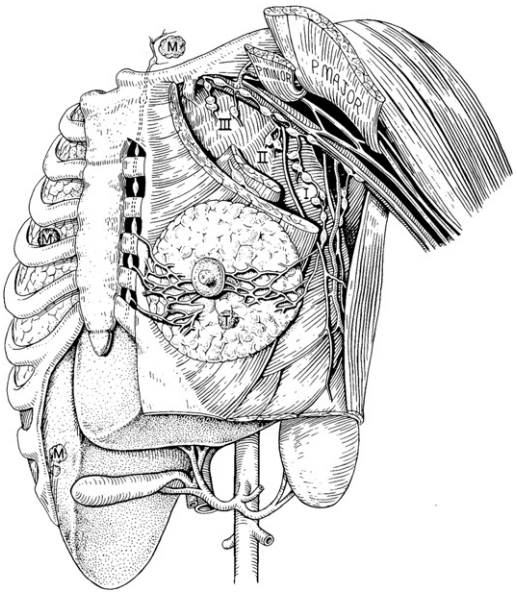

Fig. 1. Lymphatic drainage of the breast with roman numerals identifying axillary lymph node groups. Level I nodes are located lateral or inferior to the pectoralis minor, level II nodes are located deep to the muscle, and level III nodes are located medial to the muscle. M, metastatic supraclavicular node; T, primary tumor. *Reprinted from* Bland KI, Copeland EM, editors. The breast: comprehensive management of benign and malignant diseases. 4th edition. Philadelphia: Saunders Elsevier; 2009. p. 33; with permission.

are rarely present without involved level I or II nodes,[3,4] metastatic disease can "skip" to level II nodes without involving level I nodes in up to 25% of cases.[5] Most axillary metastases affect level I and II axillary lymph nodes, and contemporary axillary dissection involves removing level I and II nodes only.[6]

AXILLARY LYMPH NODE DISSECTION

Physical examination and mammography are unreliable in determining whether axillary lymph nodes are metastatic.[7,8] Axillary lymph node dissection (ALND) has been a standard part of breast cancer treatment since the advent of the radical mastectomy. Although it renders the most complete staging information and provides excellent local control of the axilla involved with metastatic disease, ALND is associated with significant morbidity, including lymphedema, decreased range of motion in the shoulder, and paresthesias. With earlier detection of breast cancer leading to fewer positive axillae, ALND has become a less-than-ideal modality for initial staging of the axilla. Sentinel lymph node biopsy (SLNB), in which the first (sentinel) lymph node to drain the breast is identified and resected, was developed as an alternative to ALND for breast cancer in the 1990s after the technique was used successfully in melanoma.[9] SLNB is a less-invasive surgical technique, associated with less morbidity than ALND.

LYMPHOSCINTIGRAPHY

Injection of blue dye or a radioisotope into the breast maps the lymphatic drainage, and the sentinel lymph node is identified either through visual inspection, in the case of dye, or with a gamma camera or handheld gamma probe, in the case of Technetium-99m sulfur colloid injection. Although some surgeons will use blue dye alone to minimize expense, the lymphoscintigraphy procedure offers several advantages. The gamma camera's wide field of view of the entire chest allows visualization of both axillary and internal mammary nodal regions, and shows the three-dimensional distribution of lymph nodes. In addition, lymphoscintigraphy can alert the surgeon to surface contamination or dilated lymphatic channels, which may be mistaken for lymph nodes by the intraoperative handheld gamma probe.[10] Surgeons may use both dye and radiotracer to increase the success rate of finding the sentinel node.[11] Numerous technical considerations and protocols exist for injection and imaging during lymphoscintigraphy, which are reviewed elsewhere.[10]

SENTINEL LYMPH NODE BIOPSY

SLNB has become standard of care for clinicians experienced with the technique. SLNB is a technically challenging procedure, and the accuracy is related to the experience of the surgeon, both in total number and monthly number of cases performed.[12,13] In experienced hands, SLNB accurately predicts the status of the remainder of the axilla in greater than 95% of cases.[14–16] When SLNB is positive for metastatic disease, complete ALND is then performed for more detailed staging and to provide local control.

Although fewer lymph nodes are removed in SLNB than in ALND, the nodes removed are those most likely to be involved with tumor and are examined more rigorously by pathology with serial sectioning and immunohistochemistry. Removal of "hot" nodes downstream from the first sentinel node has been shown to decrease the false-negative rate of SLNB.[17–19]

The sentinel node may be examined intraoperatively with touch preparation, cytology smear, or

frozen section, and an axillary dissection performed if evidence of metastatic disease is present. However, the sensitivity of these techniques is poor for micrometastases and, because of the concern about destroying tissue through intraoperative evaluation, many surgeons prefer to wait for definitive pathologic evaluation of the sentinel node and return the patient to the operating room for ALND if needed.[9]

The time-consuming, challenging nature of SLNB is a disadvantage, as is the need for a second surgery if the lymph nodes contain metastatic disease on permanent section. In addition, the procedure may be unsuccessful because of failure to visualize a sentinel node. Lack of radiotracer uptake and nonvisualization of the sentinel node may be from replacement of the node by tumor.[20] In addition, SLNB has a higher false-negative rate in patients who have undergone neoadjuvant chemotherapy.[21] Therefore, patients undergoing neoadjuvant chemotherapy often undergo SLNB before chemotherapy and will have to return to the operating room for breast surgery after chemotherapy. Given the disadvantages, an easier method that replaces SLNB is valuable.

AXILLARY ULTRASOUND

Although CT, MRI, and nuclear medicine techniques visualize the axillary lymph nodes, ultrasound is the most advantageous technique and has been the most used to characterize lymph nodes and detect axillary lymph node metastases.[7,22–25] Before SLNB, no real indication existed for routine ultrasound evaluation of the axilla for patients with breast cancer because these patients would undergo ALND for both diagnosis and treatment of metastatic disease in one operation. The advent of SLNB has resulted in the increased use of axillary ultrasound and the development of USFNA for preoperative diagnosis of metastatic disease to minimize the number of operative procedures.[26–28] In addition, patients identified as having nodal disease preoperatively may be considered for enrollment in neoadjuvant chemotherapy protocols.[29]

A high-frequency (7.5 MHz and above) transducer provides the spatial resolution needed to identify and characterize lymph nodes adequately. The most important lymph node to at identify is the one most likely to be the sentinel node. Therefore, attention should be focused on the lower axilla near or just behind the lateral edge of the pectoralis major.[30]

Normal lymph nodes are oval in shape, typically having a long to short axis ratio of greater than 2, and have a wide echogenic fatty hilum and a thin cortex (**Fig. 2**A).[24] When normal lymph nodes are largely fatty replaced, the central echogenic hilum will actually become paradoxically hypoechoic because of the presence of relatively few vessels and mostly homogenous fat cells (see **Fig. 2**B).[31] One pitfall of axillary ultrasound is mistaking a large hypoechoic fatty hilum for a thickened hypoechoic cortex.

Size is not a useful criterion for distinguishing normal from abnormal axillary lymph nodes.[32,33] Reactive or fatty lymph nodes may be large enough to even be palpable and mistaken for metastatic disease. However, specific cortical and hilar morphologic changes seen on ultrasound have been shown to be predictive of malignancy, although different criteria have been used at different institutions to determine level of suspicion. As ultrasound of the axilla becomes more widely adopted, the criteria that are most useful in detecting metastatic disease are becoming more clearly defined.

The principal feature used in assessing axillary lymph nodes is the presence of cortical thickening, including cortical thickening that narrows or obliterates the fatty hilum.

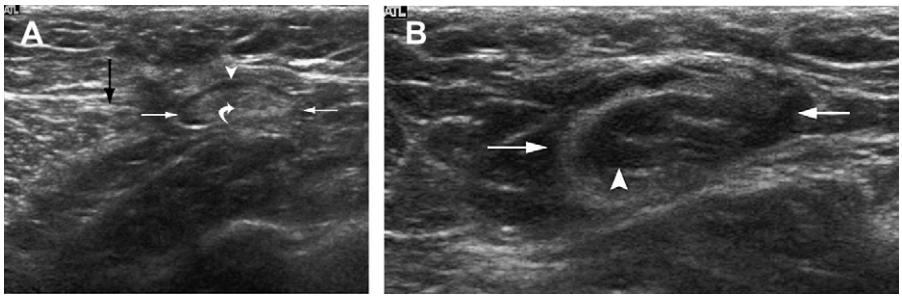

Fig. 2. Normal appearance of axillary lymph nodes on ultrasound. (*A*) This lymph node (*white arrows*), located adjacent to the pectoralis major muscle (*black arrow*) has a wide echogenic hilum (*curved arrow*) and a thin cortex (*arrowhead*). (*B*) A largely fatty-replaced lymph node (*arrows*) with a paradoxically hypoechoic hilum (*arrowhead*).

Although the normal vascular supply of a lymph node enters the hilum, the lymphatic channels enter through the cortex. When enough metastatic cells are deposited, the cortex becomes thicker. As the cortex is replaced and expanded by metastatic disease, the hilum becomes compressed and eventually absent. Therefore, the earliest changes seen on ultrasound will be focal thickening of the cortex, with the lymph node retaining a normal hilum (**Fig. 3**). Further involvement of the cortex will thicken the cortex more diffusely (**Fig. 4**). As the cortex enlarges, changes may occur in shape from outward bulging of the cortex, with the lymph node taking on a more lobulated appearance. Distortion, compression, or absence of the hilum is seen with large metastatic deposits from inward bulging of the involved cortex (**Fig. 5**). Decreased echogenicity of the cortex is also a feature of malignancy,[33] and completely replaced lymph nodes will be round and markedly hypoechoic, or even anechoic (**Fig. 6**). A round, anechoic lymph node may be mistaken for a cyst. This pitfall can be avoided by recognizing the typical lymph node location and using color Doppler to detect vascularity.

The presence of blood flow in a lymph node seen with color Doppler is not useful as a criterion to distinguish benign from malignant nodes, because both normal and abnormal nodes have hilar flow.[34,35] However, malignant lymph nodes are more likely to have nonhilar blood flow, in which the blood flow enters the cortex directly. This altered blood flow is presumably caused by engorgement of preexisting vessels as a consequence of hilar flow obstruction from metastatic disease.[36]

USFNA FOR PREOPERATIVE DIAGNOSIS OF NODAL DISEASE

Although ultrasound is sensitive for detecting metastatic disease to the axilla, overlap occurs in the appearance of metastatic disease and normal or hyperplastic lymph nodes, limiting specificity. Adding fine needle aspiration to ultrasound allows a specific diagnosis of metastatic disease to be made that changes patient management. When metastatic disease to the axilla is diagnosed using USFNA as the initial staging procedure, the patient is spared SLNB and proceeds directly to ALND or neoadjuvant chemotherapy.[30,32,33,37–39]

The sensitivity of USFNA reported in the literature varies widely depending on patient selection criteria and the criteria for determining if a lymph node is abnormal. Reports of sensitivity range from 21% to 86%.[32,39] The wide range of sensitivities reflects the fact that USFNA is most sensitive in patients with more extensive lymph node involvement and less sensitive for the detection of small metastatic deposits (<5 mm) and micrometastases (<2 mm).[32,33] Patients with large primary tumors are more likely to have more extensive nodal disease that will alter the morphology of the lymph node and be more easily detected with

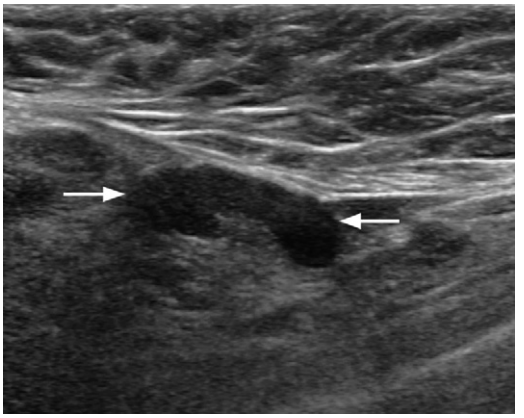

Fig. 4. Ultrasound image of a metastatic axillary lymph node (*arrows*) with diffuse cortical thickening.

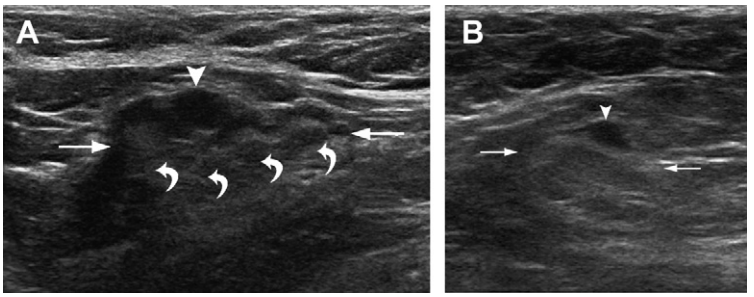

Fig. 3. Focal cortical thickening on ultrasound. (*A*) A metastatic lymph node (*arrows*) with suspicious cortical thickening (*arrowhead*). The large fatty hilum (*curved arrows*) is retained. (*B*) A metastatic lymph node (*arrows*) with one small focal area of cortical thickening (*arrowhead*).

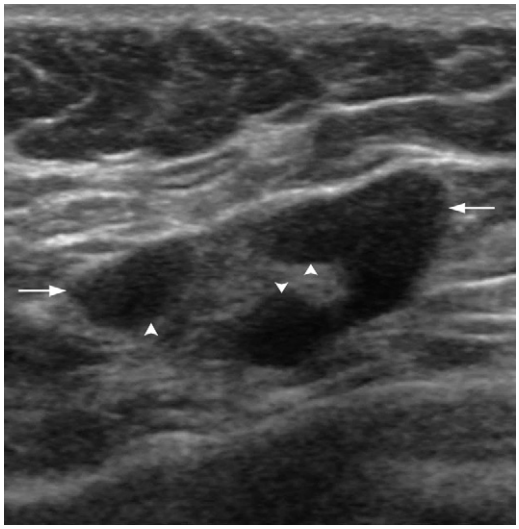

Fig. 5. Ultrasound image of a metastatic axillary lymph node (*arrows*) with distortion of the fatty hilum from focal cortical thickening in multiple areas (*arrowheads*).

ultrasound, and therefore USFNA will be more sensitive in this population. Koelliker and colleagues[33] reported a sensitivity of USFNA ranging from 56% in T1 tumors to 100% in T4 tumors. Similarly, the reported sensitivity of USFNA will vary depending on selection criteria based on the appearance of the axillary lymph nodes. When selecting only patients with abnormal-appearing lymph nodes, the sensitivity of the procedure to detect nodal disease has been in a more narrow range of 82% to 89%.[32,38,40,41] Most of the false-negative USFNA procedures in this population will be in patients with metastatic deposits smaller than 5 mm and only one lymph node involved.[32] Expanding on their previous work as reported by Koelliker and colleagues,[33] in which USFNA was performed on all patients presenting for axillary ultrasound regardless of tumor size or lymph node appearance, the author's practice has been investigating the utility of USFNA in patients as a function of lymph node appearance and has found it to have a sensitivity of 11% for normal-appearing nodes, 44% for indeterminate nodes, and 93% for suspicious nodes (Martha B. Mainiero, MD, unpublished data).

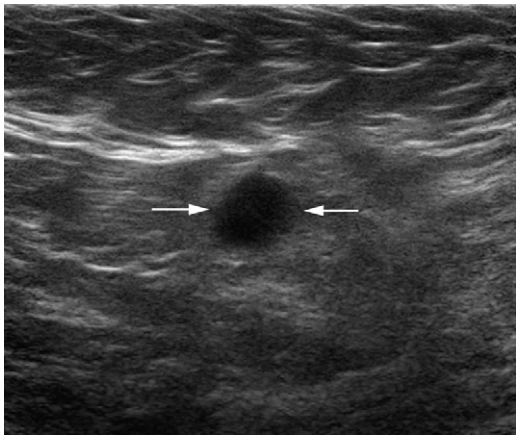

Fig. 6. Ultrasound image of a hypoechoic metastatic axillary lymph node (*arrows*) with a round shape and completely absent hilum.

Core needle biopsy (CNB) of axillary lymph nodes can be used as an alternative to fine needle aspiration.[42–46] Care must be taken to avoid the major vessels and nerves, and a biopsy device with a controllable needle action is safest, because the cutting cannula traverses tissue that has already been passed through by the needle.[45] The range of sensitivity of CNB for metastatic disease in the axilla ranges from 53% to 94%.[45,46] Unlike in the breast, in which a wide range of benign and malignant conditions require histology for diagnosis, the diagnosis of metastatic disease in the axilla can be made through identifying carcinoma cells on cytology without the need for histologic evaluation. Fine needle aspiration is less costly and less invasive than core biopsy, and core biopsy has the same problem as fine needle aspiration, with false-negatives in cases of small metastatic deposits.[42,45] In a comparison of fine needle aspiration and CNB of axillary nodes by Rao and colleagues,[40] in which the decision to perform fine needle aspiration or CNB was based on equipment availability and operator preference, the sensitivity of fine needle aspiration was 75% and the sensitivity of CNB was 82%. The author's practice concluded that given the consideration of cost, fine needle aspiration may allow equivalent sensitivity at lower cost. However, institutions without adequate cytology support or expertise may prefer to use ultrasound-guided core biopsy instead of fine needle aspiration.[45]

INDICATIONS FOR USFNA

Whether axillary ultrasound and USFNA should be performed on all patients with newly diagnosed breast cancer or only those at high risk for nodal disease is not firmly established. Because ultrasound and USFNA are not as sensitive as SLNB, patients will still need surgery when imaging or cytology results are negative. Patients who are most likely to be spared SLNB are, therefore, most likely to have a positive result on USFNA,

either based on the high likelihood of having nodal disease because of characteristics of the primary tumor or because of the suspicious appearance of lymph nodes on ultrasound. Therefore, some authors suggest that the procedure can replace SLNB as the initial staging procedure in larger tumors only.[28]

In patients with smaller tumors or normal-appearing nodes, the technique will be less sensitive, but has been used to spare some patients SLNB, because USFNA is so much less time-consuming and invasive than SLNB.[33] Some authors recommend that USFNA should be part of the preoperative staging of all primary breast cancers.[37,41] The exact cutoff of what is an acceptable sensitivity to make the procedure worthwhile is still controversial and may require a cost-effective analysis.

Axillary ultrasound and USFNA are clearly indicated in patients with locally advanced disease. In a series of 27 axillae in 26 patients with a median primary tumor size of 4 cm, Oruwari and colleagues[47] reported a sensitivity of 100% and concluded that the technique is particularly useful in this population and should be used more frequently. Positive USFNA procedures in that series included two patients with normal-appearing lymph nodes. Patients with large primary tumors should have axillary ultrasound, and may benefit from USFNA even when lymph nodes appear normal because of the high prevalence of nodal disease. In addition, patients with large primary tumors are likely to be treated with neoadjuvant chemotherapy, and USFNA is particularly useful to establish a diagnosis of metastatic disease before chemotherapy is initiated.

USFNA is also indicated in patients with suspicious lymph nodes found on ultrasound. However, studies have used different criteria to determine whether a lymph node is suspicious enough to warrant fine needle aspiration.[30,32,33,38,42] Each ultrasound criterion has a different sensitivity and specificity for predicting nodal disease. Absence of a fatty hilum has been shown to be the most specific predictor of malignancy, but is not sensitive because it is a late finding.[33,45,48] Therefore, some measure of cortical thickening, either objective or subjective, must be used to determine whether USFNA is indicated if one hopes to detect most positive axillae preoperatively.

Based on an in vitro sonographic study, Bedi and colleagues[31] concluded that asymmetric focal hypoechoic cortical lobulation or a completely hypoechoic node (without a fatty hilum) should serve as guidelines for universal performance of USFNA. However, the appearance of the cortex is a subjective feature, and in practice, measuring the thickness of the cortex has been shown to provide the best compromise of sensitivity and specificity.

Deurloo and colleagues[30] evaluated multiple nodal features, including cortex appearance and thickness, and found that the area under the receiver operating characteristic curve was highest (0.87) for maximum cortex thickness, and that a cutoff of 2.95 mm was the best indicator of when to perform USFNA. In a larger study also evaluating multiple nodal features, Choi and colleagues[48] found that a cortical thickness of greater than 3 mm was the best indicator to predict metastasis, with a higher sensitivity and specificity than eccentric or irregular nodular cortex. Abe and colleagues[45] reported a better sensitivity and specificity using 4 mm rather than 3 mm as the threshold.

The author's practice has found that using either a cortical thickness threshold of 3 mm or the presence of focal cortical thickening to be useful criteria for determining indication of USFNA. They previously reported the use of USFNA in patients with a wide range of primary tumor sizes and recommended further evaluation of the technique in a larger number of patients with smaller

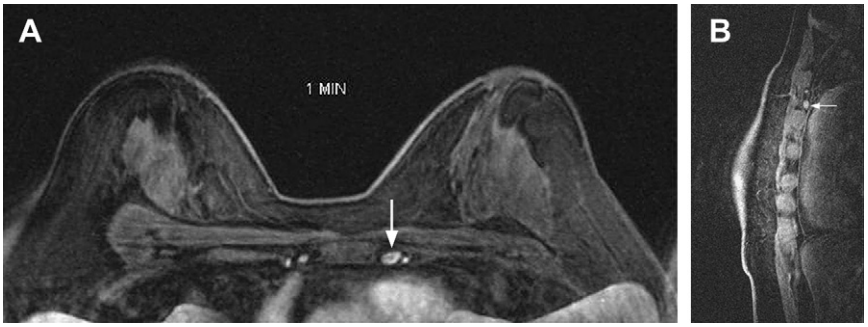

Fig. 7. Axial (*A*) and sagittal (*B*) MR images showing the parasternal location of a metastatic 7-mm internal mammary lymph node (*arrow*), immediately adjacent to the internal mammary vessels.

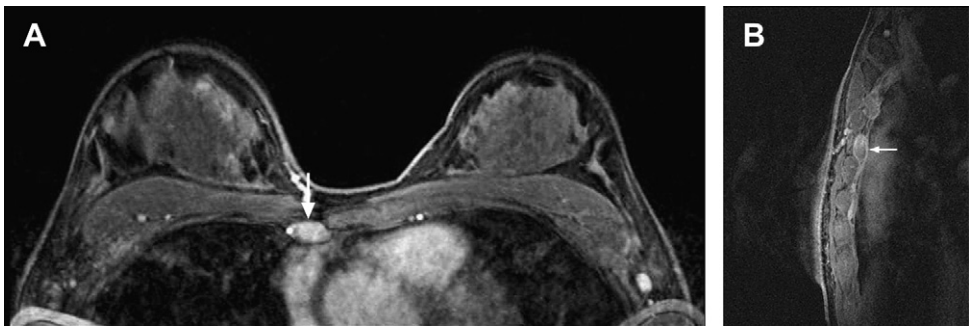

Fig. 8. Axial (*A*) and sagittal (*B*) T1-weighted MR images with fat saturation showing a metastatic 1.4-cm internal mammary lymph node (*arrows*).

tumors.[33] As they gained further experience, they have found that the low prevalence of metastatic disease in patients with invasive cancers smaller than 1 cm limits the utility of the procedure in this population, because the lymph nodes are rarely abnormal in this population. In patients with tumors 1 cm or larger, axillary ultrasound is worthwhile to assess the appearance of the axillary nodes, with USFNA indicated when lymph nodes meet selected criteria. In addition, the author's practice will perform USFNA of normal-appearing lymph nodes in patients with large tumors at very high risk for nodal disease.

INTERNAL MAMMARY LYMPH NODES

The internal mammary lymph node chain is another route of systemic dissemination in breast carcinoma, and the status of internal mammary nodes is also predictive of survival. The internal mammary nodes reside immediately adjacent, either medial or lateral, to the internal mammary artery and vein, parallel to the sternum and deep to costal cartilage (**Fig. 7**). The nodes most frequently involved in breast cancer are in the second to third intercostals spaces.[49] Abnormal internal mammary nodes can be seen on parasternal ultrasound, CT, and MRI.[49–51] Normal internal mammary nodes are very small and not visible on CT,[49] although they can often be seen on MR.[50] Kinoshita and colleagues[50] found that using a size criterion of 5 mm on MRI or greater had a 93.3% sensitivity and 89.3% specificity for predicting internal mammary node metastasis (**Fig. 8**).

Although most breast cancers that drain to the internal mammary nodes are located in the medial breast, tumor size and axillary nodal status are the most significant predictors of internal mammary nodal disease. Isolated involvement of internal mammary lymph nodes is low, with the rate of internal mammary metastases in patients with a negative axilla reported to be 1% to 10%, with most series reporting less than 5%.[52]

SLNB of internal mammary drainage identified on lymphoscintigraphy is not routine but has been used to change management in patients with internal mammary node metastases.[53,54] When abnormal internal mammary nodes are identified through imaging, treatment regimens, particularly the radiation field, may be altered. In addition, if abnormal internal mammary nodes are detected through imaging, evaluation for more distant metastatic disease may be indicated, because internal mammary lymph node involvement is a poor prognostic sign.

SUMMARY

The status of axillary lymph nodes is a key prognostic indicator in patients with breast cancer and helps guide patient management. SLNB is increasingly being used as a less-morbid alternative to axillary lymph node dissection; however, when results are positive, axillary dissection is typically performed for complete staging and local control. Axillary ultrasound and USFNA are useful for detecting axillary nodal metastasis preoperatively and sparing patients SLNB, because patients with positive cytology on USFNA can proceed directly to axillary dissection or neoadjuvant chemotherapy. Internal mammary nodes are not routinely evaluated, but when the appearance of these nodes is abnormal on imaging, further treatment or metastatic evaluation may be necessary.

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