Imaging the Axilla

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Abstract

The presence of axillary lymph node metastases remains one of the most important prognostic factors in breast cancer. Axillary ultrasound is used routinely in clinical practice, with both morphological features and cortical thickness prompting selective needle biopsy of lymph nodes. Ultrasound and axillary core needle biopsy have a positive impact on the management of patients with breast cancer, as preoperative identification of axillary metastases allows the patient to proceed directly to full axillary lymph node dissection, avoiding unnecessary sentinel lymph node biopsy. The performance characteristics of axillary US vary widely in the literature, and its clinical utility has been called into question with the advent of the American College of Surgeons Oncology Group Z0011 trial. Subsequently, focus has been on imaging to improve discrimination between limited and advanced nodal disease as well as improved targeting of the sentinel lymph node. The timing of sentinel lymph node biopsy and the use of imaging in the setting of neoadjuvant chemotherapy have also been a subject of much debate. While US is the most widely used

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technique for axillary assessment, multimodality imaging techniques including MRI and PET-CT have been investigated to provide nodal staging information.

1 Indications for Axillary Imaging and Clinical Relevance

The presence of axillary node metastases remains one of the most important prognostic factors in breast cancer, and for determining the need for systemic chemotherapy and radiation therapy (Kleer and Sabel 2010). Approximately 30–40% of newly diagnosed breast cancer patients will have nodal metastases (Siesling et al. 2003). The AJCC TNM staging system (eighth edition) includes both clinical and pathological staging (Amin et al. 2017). Clinical nodal staging is based on the findings on both clinical examination and imaging, while pathological nodal staging is defined according to node assessment at sentinel lymph node (SLN) surgery or complete axillary lymph node dissection (ALND). Clinically detected nodes are defined as nodes that have suspicious characteristics on clinical examination or imaging. Pathologic lymph node staging is dependent on the size of the metastasis, the total number of positive nodes, and the anatomic location of the involved nodes. The pathologic node staging criteria are based on the number of nodes identified histologically as containing metastases. One to three positive nodes are considered pN1, four to nine positive nodes are considered pN2, and ten or more positive nodes are considered pN3.

Historically, ALND has been used for the evaluation and treatment of axillary metastases (Banerjee et al. 2004; Benson et al. 2007). However, ALND is associated with noteworthy morbidity, including postoperative seroma, paresthesia, and lymphoedema (Fleissig et al. 2005; Lucci et al. 2007; Ahmed et al. 2008; Liu et al. 2009). Subsequently, sentinel lymph node biopsy (SLNB), involving intramammary injection of a radiolabeled colloid (Tc-99 sulfur colloid) with or without the addition of a blue dye (lymphazurin or methylene blue) followed by an open surgical biopsy of axillary nodes demonstrating radioactive or blue dye uptake, emerged as a safe and accurate minimally invasive alternative for clinically node-negative patients. SLNB was shown to have a low false-negative rate, high negative predictive value, and importantly considerably less morbidity (Veronesi et al. 2003). In 2005, a panel from the American Society of Clinical Oncology (ASCO) published guidelines recommending SLNB as an initial alternative for ALND with early-stage breast cancer, and only patients who were detected as lymph node positive at SLNB required complete axillary dissection (Lyman et al. 2005).

The benefit of preoperative identification of axillary metastases means that the patient, if node positive, can proceed directly to ALND at the time of tumor excision, thereby sparing a second operation and general anesthetic, as well as the small risk of complications from SLNB.

While multiple imaging modalities have been used to determine axillary status preoperatively (Hyun et al. 2016), it is only axillary ultrasound with selective needle biopsy of morphologically abnormal nodes which is used routinely in clinical practice (NICE 2009; ACBS 2011), given its relatively high sensitivity and specificity compared to physical examination of the axilla as well as its ease of use. The strategy for identifying axillary metastases with US prior to surgery varies among countries and institutions, ranging from imaging only patients with suspicious clinical findings of the axilla to specific protocols imaging patients with invasive tumors larger than a certain size. It is routine practice in the UK to perform axillary US in all patients with suspected breast cancer on initial imaging (NICE 2009).

2 Anatomy and Ultrasound Examination Technique

Axillary ultrasound should be performed using a high-resolution, linear array, high-frequency transducer of at least 10 MHz, with the frequency suitably adjusted based on patient body habitus and imaging findings. The patient should lie in a supine oblique position, with their hand held behind their head and with the arm abducted and externally rotated. Nodes should be imaged in orthogonal planes with grayscale US. If color Doppler US is used, it is recommended to use low-wall filter settings and low-velocity settings to detect abnormal cortical blood flow (Dialani et al. 2015).

Anatomically, the axilla has a three-dimensional shape resembling a pyramid, with borders consisting of four sides, and a base with an opening at the apex. The size and shape of the axilla varies with arm abduction, and it contains structures including the axillary artery and vein, brachial plexus, and axillary lymph nodes. The axilla is divided into three levels by the pectoralis minor muscle. Level I is bounded by the axillary vessels and the lateral border of pectoralis minor, with level I lymph nodes lying lateral and inferior to pectoralis minor (Fig. 1). Lymph nodes lying beneath pectoralis minor are classified as level II, and those deep and medial to the medial border of pectoralis minor are level III (infraclavicular). Drainage generally proceeds in a stepwise fashion from level I to II to III, and finally into the thorax (Moore 1985). Nodal metastases to level III carry a worse prognosis than metastases to level I and level II axillary nodes. Metastases to the internal mammary nodes usually occur after a tumor has metastasized to the axilla, although isolated metastases to the internal mammary nodes occur in up to 5% of breast cancers and often come from deep or medially situated lesions. The presence of internal mammary node metastases does have prognostic significance and carries a small risk of local recurrence (Chen et al. 2010).

A set routine is recommended when performing ultrasound of the axilla so that lymph nodes are not overlooked (Britton et al. 2009a, b). A thorough examination of level I should be performed, with emphasis placed on scanning inferiorly through the axillary tail, with the reason being the majority of sentinel lymph nodes lying low in the axilla at a distance from the axillary vessels, with more than three-quarters of the SLNs being the lowest identifiable node (Britton et al. 2010). High rates of ultrasound targeting of the SLN have been demonstrated by tightly focused US technique examining the axilla 2 cm above to 3 cm below the lowest axillary hair follicles (Nathanson et al. 2007). The examination should start in the axillary tail with the probe moved cranially along the lateral border of the pectoralis muscles to the level of the axillary vessels. Then further similar sweeps can be performed moving further laterally until teres major and subscapularis muscles are seen at the lateral edge (Fig. 2). The lateral thoracic and thoracodorsal arteries may be seen along each margin, although lymph nodes are often found in isolation within the axillary fat (Fig. 3). Occasionally, the hilar vessels to a particular node can be seen and traced back to their artery of origin. Only if morphologically abnormal nodes are seen in level I should level II and III be scanned to determine the likely extent of lymph node involvement. This practice varies between institutions, with some centers advocating examination of

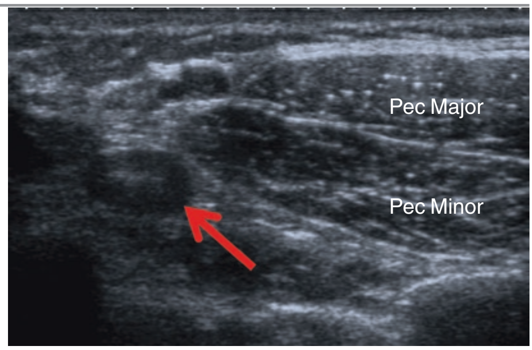

Fig. 1 US of level 1 lymph node (arrow) lying lateral to pectoralis minor

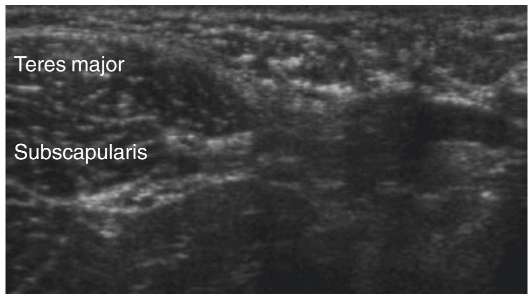

Fig. 2 US of the lateral border of the axilla demonstrating teres major and subscapularis muscles

Fig. 3 US of normal lymph node lying in axillary fat

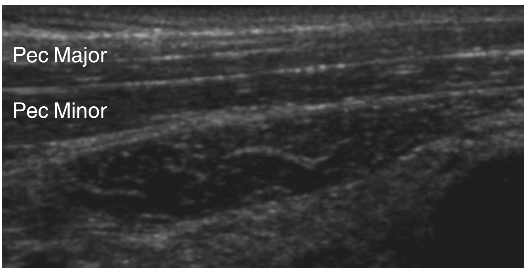

Fig. 4 US appearances of level II of the axilla demonstrating pectoralis major and minor muscles

level II, the fat behind pectoralis minor muscle, in patients whose cancer is located superiorly in the breast and where lymph node spread may bypass level I (Fig. 4). Some institutions also scan the supraclavicular area and along the margin of the sternum, following the course of the internal mammary artery if abnormal nodes are found in level I.

3 US Features of Morphologically Normal and Abnormal Lymph Nodes

The normal axillary lymph node should be oval with a smooth, well-defined margin and a uniformly thin hypoechoic cortex. The echogenic hilum should comprise most of the lymph node (Fig. 5). US findings which should prompt lymph node biopsy due to suspicion of metastatic involvement include both morphological features and cortical thickness. Overall size of the node has been shown to have a very poor diagnostic accuracy for predicting metastasis; however, in some centers, the ratio of longitudinal length to transverse length of <2 is used as a criterion for biopsy (Feu et al. 1997). When considering the morphological appearances of abnormal lymph nodes, it is helpful to consider the fashion in which metastatic deposits spread to the lymph nodes. One model suggests that tumor cells enter the lymph nodes through afferent lymphatics and are deposited in the subcapsular sinusoids, proliferating in the medullary sinusoids and then into the efferent lymphatics. As deposits spread in the nodal parenchyma, they replace the normal nodal architecture as they proliferate (Ching et al. 2010). As the metastatic deposits get bigger, they can obliterate the normal histological features of large parts of the node, and then eventually replace the entire lymph node. Finally, extra-nodal spread of the tumor into the adjacent axillary fat can occur, and the node is ultimately replaced by an irregular mass.

It is not surprising therefore that diffuse cortical thickening and eccentric cortical thickening, or a focal cortical budge, are considered the earliest detectable changes (Figs. 6 and 7). It is important to note that normal lymph nodes often have a lobulated shape because of concurrent constrictions and bulges of both the cortex and fatty hilum. A true abnormal cortical bulge is seen as focal thickening of the cortex that does not follow the margin of the echogenic hilum and should be distinctly hypoechoic (Fig. 8). Findings seen in cases with more advanced nodal involvement, such as effacement of the fatty hilum or a rounded hypoechoic mass, have a higher positive predictive value in patients with invasive breast cancer (Fig. 9). Replacement of the entire node by an ill-defined mass is highly suspicious for malignant involvement (Fig. 10). Color Doppler may also be useful in the assessment of abnormal lymph nodes, with metastatic deposits leading to distortion of the intranodal angioarchitecture and engorgement of the peripheral vascularity. This is hypothesized to result in non-hilar blood flow demonstrated at color Doppler as peripheral vascular flow at the cortex of the node with no detectable connection to the hilum. Various authors have published odds ratios for biopsy cri-

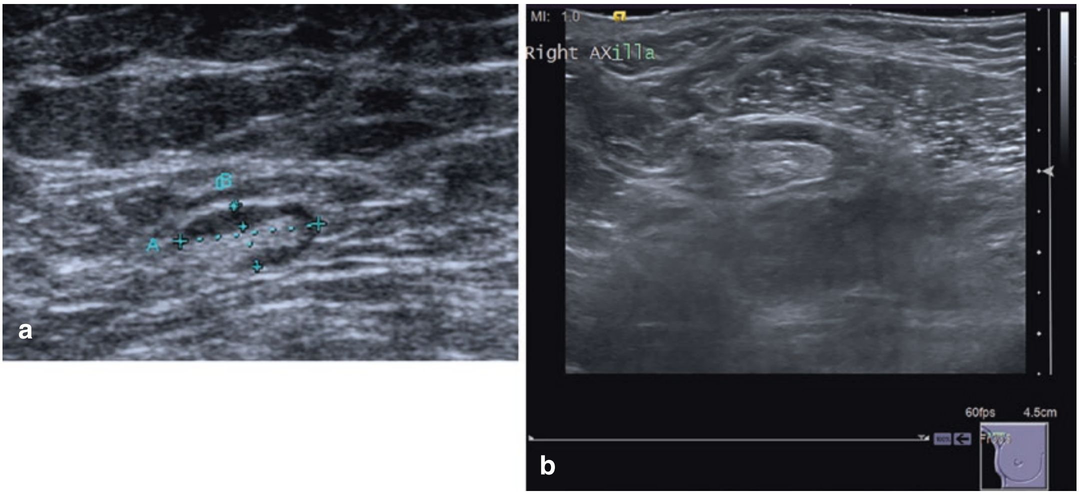

Fig. 5 (**a**, **b**) US appearances of morphologically normal lymph nodes with a uniform smooth hypoechoic cortex and fatty hilum

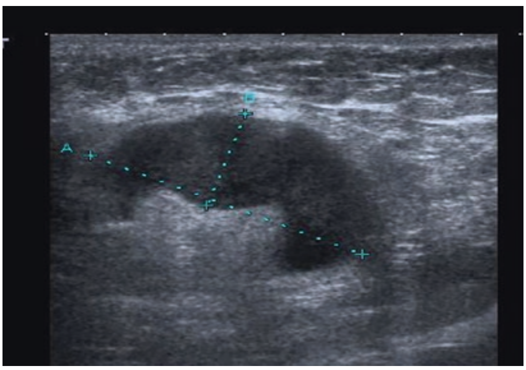

Fig. 6 Diffuse cortical thickening in a metastatic axillary lymph node

teria (Britton et al. 2009a, b; Abe et al. 2009; Mainiero et al. 2010), but it is important to note that these are not pathognomonic of malignancy and biopsy confirmation is required.

Diffuse cortical thickening can also be seen with metastatic involvement of nodes; however, this finding is nonspecific and is often associated with reactive nodes (Fig. 11). There is a significant correlation between increasing cortical thickness of nodes and presence of malignancy, and investigators have suggested multiple cutoff values for cortical thickness, with inevitable trade-off in sensitivity and specificity (Bedi et al. 2008; Choi et al. 2009; Saffar et al. 2015). Work done by Duerloo demonstrated that a diffusely thickened cortex of 4 mm or greater was 80% sensitive and 80% specific for malignancy, but if the cutoff was lowered to 2 mm, sensitivity increased to 95% but specificity dropped to 44% (Deurloo et al. 2003). Submitting of a greater proportion of patients to biopsy to see if this improves sensitivity was performed by Britton et al., with 87% of patients undergoing lymph node biopsy resulting in only a modest increment in sensitivity to 53% but with a substantial increase in biopsies. All centers will use their own cutoff criteria, but consideration should be given to the fact that the highest needle biopsy sensitivities will be achieved in patient groups with high likelihood of metastatic disease. Patients who present with a palpable lump, multifocal or multicentric malignancy, central cancers, and cancers >20 mm are more likely to have axillary nodal involvement than asymptomatic screen-detected patients with small <20 mm tumors.

Other techniques such as US elastography have shown potential for preoperative axillary staging in breast cancer (Taylor et al. 2011; Wojcinski et al. 2012), with significantly harder cortex seen in metastatic lymph nodes. The highest sensitivity and specificity of 73% and 99.3%, respectively, in these studies were achieved with a combination of conventional US and elastogra-

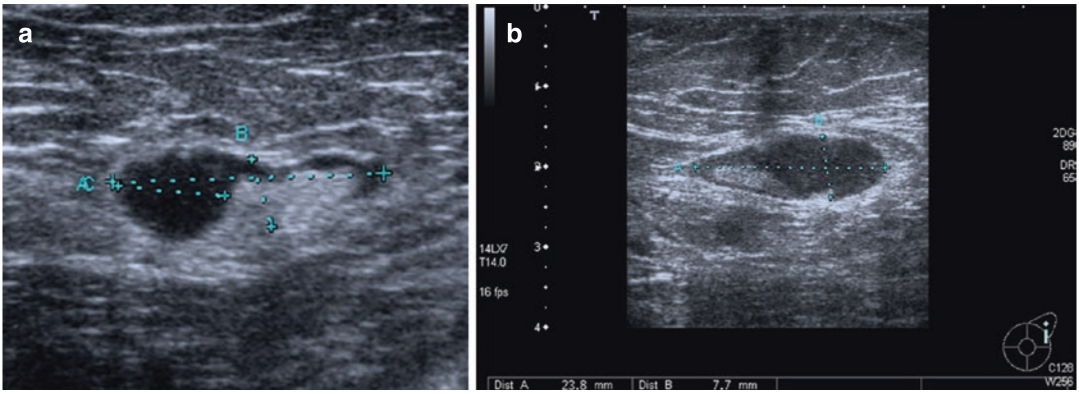

Fig. 7 (**a**, **b**) US appearances of a focal cortical bulge in metastatic axillary lymph nodes

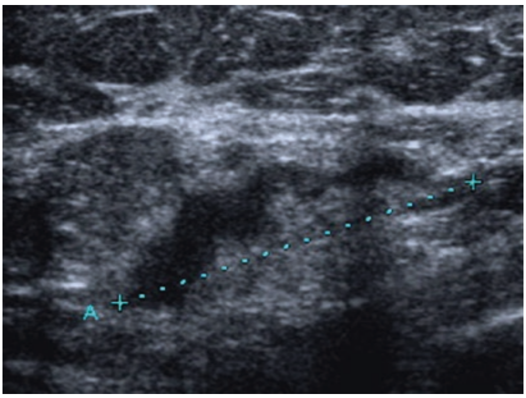

Fig. 8 Multiple cortical bulges in a metastatic axillary lymph node

phy, suggesting that elastography may be a useful adjunct to conventional US to improve diagnostic performance.

4 US-Guided Biopsy Technique of Axillary Lymph Nodes

If US evaluation of the axilla reveals a suspicious finding, percutaneous procedures including ultrasound-guided fine needle aspiration (FNA) or ultrasound-guided core needle biopsy (CNB) should be performed to substantiate clinical decision-making. FNA is preferred by some centers, usually using a 22–25 G needle with three passes and with aspirates sent to cytology. However, FNA is operator dependent, requires access to reliable cytology, and has a relatively high false-negative rate of 12–23% (Krishnamurthy et al. 2002). CNB is now widely used as an alternative because it has been shown in several studies to be more sensitive than FNA (90–94%), with no reported false positives and equivalent low rate of morbidity, with multiple studies reporting no significant complications (Rautiainen et al. 2013). The latter is of importance as concerns have been raised regarding vascular or nerve damage with CNB. Although most SLNs are located low in the axilla in axillary fat, for those that are located near axillary vessels potential complications can be avoided by continuous US monitoring, clear operator understanding of axillary anatomy, and operator experience (Fig. 12). Furthermore, most spring-loaded biopsy devices offer the option of a "no-throw" technique, with an open bowl advanced through the lymph node and a cutting cannula then released over the open bowl, which may be desirable in situations with vessels located nearby to the targeted lymph node. Either FNA or CNB of the axilla provides good accuracy in this clinical context, and it may be more relevant to consider each center's expertise in breast cytology or core needle histology in deciding on the type of percutaneous procedure to perform.

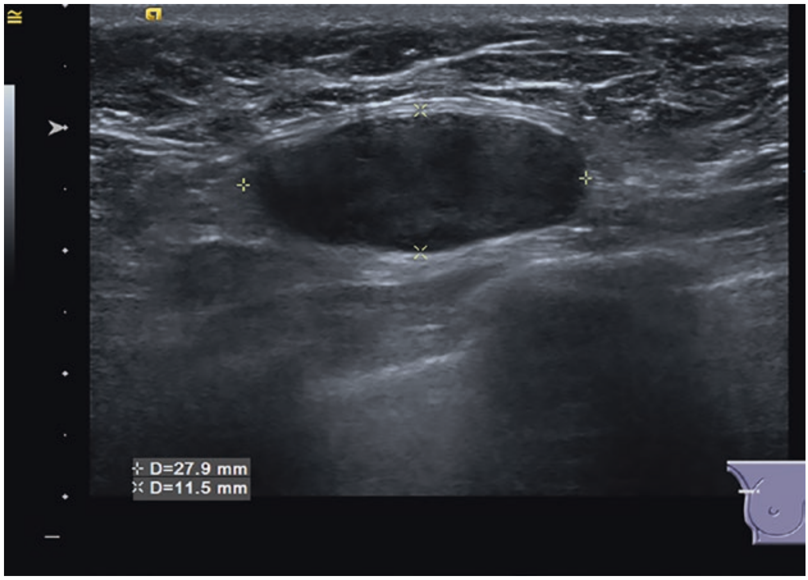

Fig. 9 Enlarged metastatic lymph node with absent fatty hilum

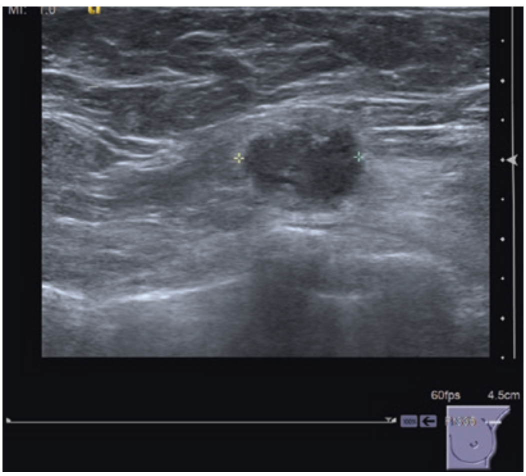

Fig. 10 Complete replacement of metastatic lymph node by a hypoechoic ill-defined mass

5 Clinical Utility of Axillary US

Ultrasound and axillary core needle biopsy have a positive impact on the management of patients with breast cancer, as preoperative identification of axillary metastases allows the surgeon to proceed directly to full axillary lymph node dissection and avoid an unnecessary sentinel lymph node biopsy. A meta-analysis performed by Houssami estimated the clinical utility of axillary US and biopsy as triaging 19.8% of patients directly to ALND (Houssami et al. 2011). However, the performance characteristics of axillary US vary widely in the literature. The underlying prevalence of axillary metastases within the study population will influence results, as will inclusion of only patients undergoing ultrasound-guided biopsy as opposed to all patients undergoing US imaging. In addition, criteria for classifying axillary lymph nodes as positive or negative have not been clearly defined. Three large meta-analyses looking at diagnostic accuracy report a pooled estimate for sensitivity of axillary US and biopsy of approximately 50% (Diepstraten et al. 2014; Houssami and Turner 2014; Van Wely et al. 2015). There is better utility in women who have higher underlying nodal risk, e.g., larger tumors.

When considering why we are not able to detect more axillary nodes which are involved with metastatic disease, the answer is likely threefold. Most metastases are too small to be seen on conventional axillary grayscale US,

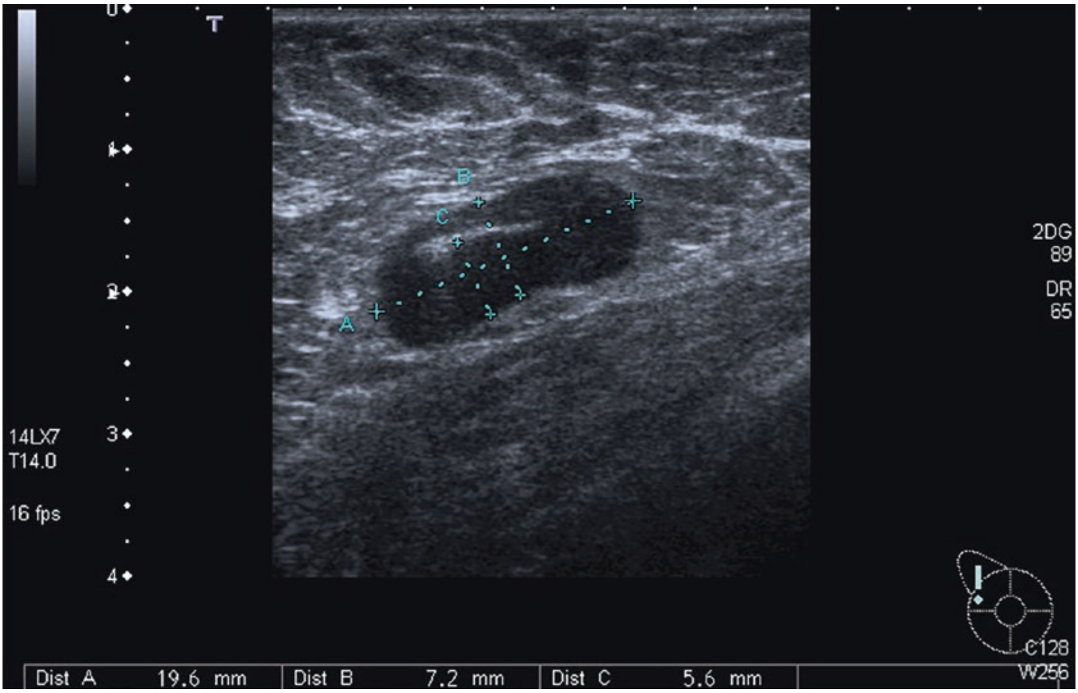

Fig. 11 Axillary lymph node with diffusely thickened cortex of 6 mm, which could represent either metastatic involvement or a reactive node

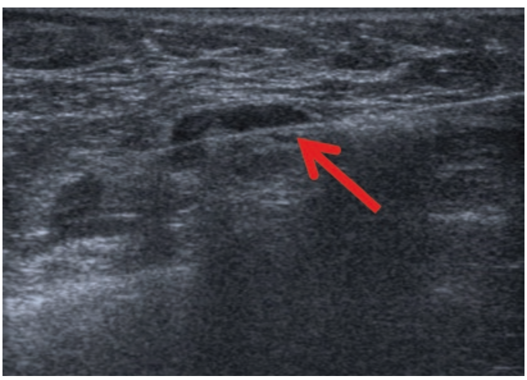

Fig. 12 US of axillary lymph node undergoing percutaneous core biopsy, with the needle seen to pass through the cortex (arrow)

given that micrometastases at less than 2 mm will cause no apparent nodal morphological change. One in four women with a negative/normal axillary US will still be proven to have axillary metastases at subsequent SLNB (Diepstraten et al. 2014). Secondly, we are only able to identify the sentinel node using US in 64–78% of cases (Britton et al. 2009a, b), and finally even using core needle biopsy as opposed to FNA we are only able to sample part of the node.

More "intelligent" targeting of the SLN using a gamma probe, fluorescence imaging, and ultrasound-guided contrast agents such as microbubbles has been investigated. The use of contrast-enhanced US (CEUS) to localize the SLN has shown it to be both safe and feasible. In comparison to traditional isotope SLNB, the sensitivity of CEUS to detect the SLN correctly was shown in studies to be 89%. In clinically node-negative patients, the sensitivity of CEUS-guided biopsy was 61–66.7% (Sever et al. 2012; Suvi et al. 2015).

However, the clinical utility of preoperative axillary US was called into question with the advent of the American College of Surgeons Oncology Group Z0011 trial, a large prospective randomized control trial in which SLNB-positive patients with small tumors were randomized to ALND versus no further surgery. They reported that ALND was not associated with any survival benefit and that both groups had an extremely low regional recurrence rate (0.9% for SNB alone and 0.5% for ALND), confirming that ALND provided minimal benefit while exposing a substantial number of patients to long-term morbidity, specifically lymphedema (Giuliano et al. 2011).

A number of concerns were raised regarding the trial, including a high proportion of patients with low burden of axillary disease, failure to meet accrual targets, and lack of detail on radiation therapy. The POSNOC trial in the UK (Goyal and Dodwell 2015) is currently underway and designed to overcome some of the limitations of Z0011 with respect to patient selection and statistical power.

However, the results of the Z0011 trial led to a significant change in surgical practice (Gainer et al. 2012), with the majority of surgeons in the USA now omitting completion ALND in patients who fulfill Z0011 criteria (stage T1 or T2 tumor, one or two positive SLNs only, undergoing breast conservation treatment and planned for whole-breast irradiation). The changing algorithm of axillary surgical treatment means that ultrasound-guided biopsy will have less utility if surgeons omit ALND for minimal nodal metastatic disease. Positive findings on preoperative axillary US and biopsy identifying nodal involvement would commit patients to ALND who may have not required this if they fulfilled Z0011 criteria.

The focus has therefore shifted from trying to improve identification of any nodal metastatic disease to discriminating between limited and advanced nodal disease, given that this has the greatest impact on patient management of the axilla post-Z0011. While axillary US alone is inadequate for excluding axillary metastases given its false-negative rate of 25% (Diepstraten et al. 2014), preoperative negative axillary US can exclude 96% of stage N2 and N3 axillary metastases (Neal et al. 2010; Schipper et al. 2013a, b). Characteristics associated with false negatives in this study included invasive lobular carcinoma, larger tumor size, and multifocality of the primary tumor. The prospective randomized controlled multicenter SOUND (Sentinel node versus Observation after axillary UltrasouND) trial is currently underway to compare SLN surgery to observation when axillary US is negative in patients with small breast cancers (Gentilini and Veronesi 2012).

Conversely, when at least two abnormal lymph nodes are identified on axillary US, pN2 or higher disease is highly likely (PPV 82%) and is even more likely when the tumor is larger than 10 mm (Abe et al. 2013). A correlation between increasing number of abnormal nodes identified on axillary US and mean number of abnormal nodes on final histology has been demonstrated (Van Wely et al. 2015). Therefore, when multiple nodes are seen on US, it is unlikely that these patients will fulfill Z0011 criteria and have only two lymph nodes positive on final histology, and therefore these patients will still benefit from preoperative biopsy and triaging to ALND.

However, a more usual scenario in both symptomatic and screen-detected breast cancer patients is the identification on axillary US of just one abnormal node. This poses a greater diagnostic dilemma, as biopsy proving metastatic involvement will commit the patient to ALND when they may have had no more than two nodes in total involved. Furthermore, in the Z0011 trial, the patients did not require axillary imaging, and final nodal number was determined on SLNB. The question therefore arises if women who are detected as lymph node positive on axillary US are more likely to have more extensive nodal disease burden than those detected by SLNB. Studies by Caudle et al. and Verheuvel et al. compared node-positive patients identified by axillary US and needle biopsy to women with negative axillary imaging found to have a positive node with SLNB (Caudle et al. 2014; Verheuvel et al. 2016). While women identified as being node positive by US and needle biopsy were at higher risk for heavy nodal disease burden, 37–52% had only 1–2 total positive LNs and were therefore potentially Z0011 “eligible.” Furthermore, while survival was expectedly worse in the needle biopsy cohort reported by Verheuvel et al. that presented with more advanced-stage disease, there was no difference in regional recurrence, with only one isolated regional relapse in each group. Other studies (Cools-Lartigue et al. 2013; Schipper et al. 2013a, b) have demonstrated similar findings. Various authors have attempted to clarify the degree of "overtreatment" of patients who undergo routine axillary US and biopsy, with estimations of 38% (Farrell et al. 2015), 47% (Pilewskie et al. 2016a, b), and 53% (Wallis et al. 2017). On this basis, it is debated as to whether women presenting with small T1 or T2 breast cancer should undergo preoperative axillary biopsy if only one abnormal node is identified on axillary US and instead proceed to SLNB, with some centers such as Memorial Sloan Kettering Cancer Center abandoning all preoperative axillary imaging to avoid direct triage to ALND (Pilewskie et al. 2016a, b).

6 Neoadjuvant Chemotherapy and Imaging of Axillary Lymph Nodes

Neoadjuvant chemotherapy (NAC) has been shown to be as effective as adjuvant treatment, and to decrease disease burden to allow less extensive surgery. Furthermore, it also affects axillary nodes achieving pathological complete response (pCR) in up to 40–60% of previously node-positive patients with new anti-Her2 therapies. The extent of persistent axillary disease following NAC is a prognostic marker for locoregional recurrence and survival (Kuerer et al. 1999). Historically, ALND was always performed after NAC, but as neoadjuvant chemotherapy is increasingly offered in early-stage and clinically node-negative breast cancer usually to improve breast conservation outcomes, the timing of SLNB in the setting of NAC has been a subject of much debate.

There are advantages and disadvantages to performing SLNB either prior to or post-NAC. The strongest argument for SLNB before NAC is that knowing the pathological status of the axilla before NAC may influence subsequent radiotherapy. However, several studies have suggested that accurate staging after NAC is a more meaningful predictor of locoregional recurrence than accurate staging before NAC. The main indication for performing SLNB after NAC is to take advantage of the pCR resulting in more conservative axillary surgery. However, the concern has been whether performing SLNB post-NAC results in an unacceptably high false-negative rate (FNR). Various studies have documented the FNR to be higher than the generally accepted 10% cutoff (Fu et al. 2014). Three prospective studies ACOSOG Z0171, SENTINA, and SN FNAC (Boughey et al. 2013; Kuehn et al. 2013; Boileau et al. 2015) aimed to address this issue, and the conclusions were that by using dual-tracer mapping and immunohistochemistry and removing ≥3 SLNs at surgery, the FNR could be lowered to less than 10%. Importantly for radiologists, it has also been shown that post-NAC assessment of the axilla with US can lower the FNR. A secondary analysis of Z1071 trial assessed axillary US as a selection criterion to stratify women for risk of residual axillary involvement following NAC, with the goal of identifying those who could be safely spared a full ALND in the setting of negative SLNB. An abnormal axillary US after neoadjuvant chemotherapy was also associated with more positive nodes (75.4%) compared with patients with a normal axillary US (63.9%). A key point is that if combined, normal axillary US following NAC and SLNB had a FNR of 9.8%, under the 10% threshold for clinical care (Boughey et al. 2015).

Also of importance to radiologists is that preoperative clip placement in the positive axillary node at the time of US-guided biopsy, allowing documentation of its excision at the SLNB procedure, also results in reduced FNR. The MD Anderson researchers developed targeted axillary dissection (TAD), which includes placing a clip at the time of the axillary node biopsy, and after NAC and before surgery a I^{125} seed was placed in the clip node to guide the surgical excision of this node. Initial reports show that the seeds do not interfere with the radioisotope for the axillary surgery, and in 80% the node that had the clip was the SLN (Caudle et al. 2015). Other groups have tried other techniques for marking and removing the axillary nodes, including wire placement and black carbon tattooing (Choy et al. 2015). With more patients undergoing NAC for breast cancer and improvements in pCR, there is increasing importance of research to improve prediction of pCR and to determine which patients can feasibly be spared ALND and its associated morbidity.

7 Multimodality Imaging of Axillary Lymph Nodes

While US is the most widely used technique for the assessment of axillary lymph nodes given its high specificity and ease of use, given the shift towards less aggressive management of the axilla, imaging techniques that may have sufficient negative predictive value to omit surgical staging of the axilla by SLNB have been investigated. Breast MRI, as well as CT and whole-body PET/CT, is often obtained in newly diagnosed breast cancer patients for clinical staging and can be used to provide regional nodal staging information.

Breast MRI often includes the axillary region in the field of view (FOV), with the additional benefit that both axillae can be compared easily (Fig. 13). However, examination of the axillary region is technically challenging since respiratory motion can cause artifacts from the adjacent thoracic wall, and pulsation artifact from the heart may obscure the axillary region due to the phase-encoding direction often being from left to right (Hieken et al. 2013). The use of additional coils to the standard breast MRI coil or performing a separate dedicated axillary MRI can overcome this (Baltzer et al. 2011; Schipper et al. 2013a, b). Although this requires an additional MRI examination, it does have the advantage of facilitating the use of a dedicated lymph node contrast agent, for example gadofosveset or ultrasmall superparamagnetic iron oxide (USPIO).

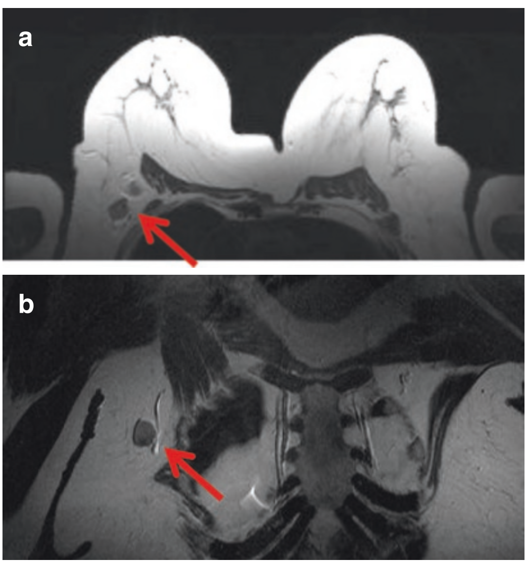

Fig. 13 (**a**) Axial T2W breast MRI demonstrating morphologically abnormal enlarged right axillary node (arrow). This is also clearly demonstrated on the coronal view (**b**)

On MRI, the nodal cortex demonstrates decreased signal intensity with T1W and intermediate to increased signal with T2W (Fig. 14). Usually at least one nonfat-sat sequence is performed where the hilar fat is shown to demonstrate increased signal. As with US, features that are seen with metastatic involvement of lymph nodes include cortical irregularity, loss of fatty hilum, and round shape (Luciani et al. 2004) (Fig. 15). Similar to US, a short-axis threshold of 4 mm yielded the best predictive value for metastatic nodal involvement with a sensitivity and specificity of 78.6% and 62.3%, respectively (Luciani et al. 2004). Two MRI-specific imaging features that have been reported to have potential diagnostic utility are perifocal edema, presence of areas with marked T2 prolongation in the fat surrounding a lymph node (Baltzer et al. 2011), and comet-tail sign, an imaging finding first described in breast lesions and hypothesized to represent infiltration or angiogenesis (Arslan et al. 2016).

Regarding the addition of diffusion-weighted imaging, while some authors have demonstrated high reproducibility and reliability of measurements of ADCs and shown metastatic nodes to have mean ADC lower than that of benign nodes (Fornasa et al. 2012), DWI has not yet convincingly been shown to improve diagnostic performance (Scaranelo et al. 2012; Schipper et al. 2015).

Lymph nodes enhance rapidly on dynamic enhanced contrast sequences, and a type 3 curve is usually seen and is not useful for predicting metastatic involvement (Fig. 16). However, nodes

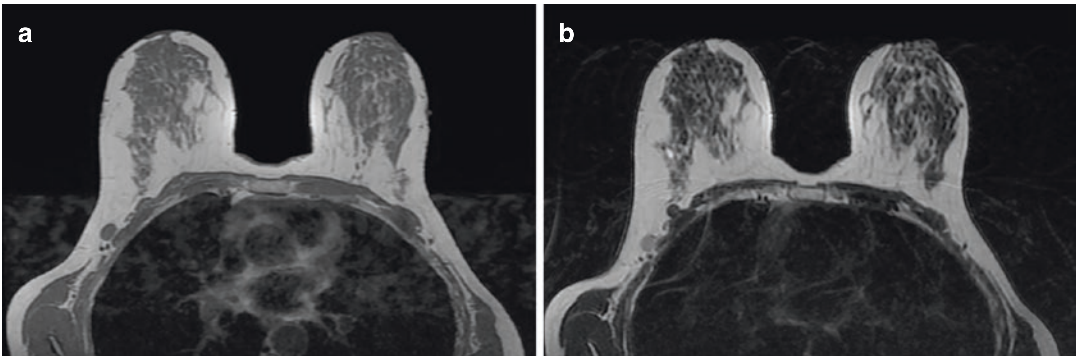

Fig. 14 Axial T1w (**a**) and T2W (**b**) breast MRI demonstrating decreased signal intensity of abnormal right-sided axillary node on T1W imaging and intermediate signal on T2W imaging

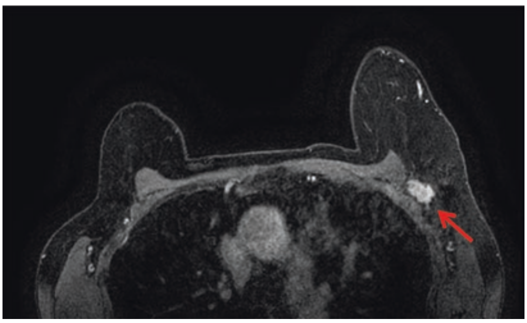

Fig. 15 T1W fat-sat post-IV gadolinium breast MRI demonstrating an enhancing enlarged and irregular left-sided axillary lymph node (arrow) with metastatic involvement

with less intense enhancement have been shown to have a high negative predictive value for metastatic involvement (Murray et al. 2002). The presence of rim enhancement, defined as signal intensity that is higher at the periphery of a node than at its center on DCE MR images at delayed imaging, has also been reported to have a high positive predictive value for the detection of metastases (Baltzer et al. 2011).

Diagnostic performance of unenhanced axillary MR imaging for nodal staging in patients with breast cancer has shown a negative predictive value (NPV) of 86–91% (Scaranelo et al. 2012; Schipper et al. 2015). As the NPV of enhanced MRI is not close enough to that of SLNB to substitute, lymph node-specific contrast agents have been investigated to improve the diagnostic performance of MRI.

After intravenous injection of superparamagnetic iron oxide USPIO, normal nodes accumulate iron-containing nanoparticles, which reduce the nodal signal due to susceptibility effects, while metastatic nodes that do not accumulate the nanoparticles maintain a high signal intensity in T2- or T2*-weighted images. USPIO-enhanced MRI has shown superior sensitivity compared to normal MRI (Will et al. 2006) and high diagnostic accuracy for identifying axillary lymph node metastases in patients with early-stage breast cancer. However, this conclusion is based on limited articles, and additional studies are required to further validate these findings.

18F-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography/computed tomography (PET/CT) has proven useful in the evaluation of distant metastatic disease. Despite lower sensitivity, specificity of PET/CT in the detection of lymph node metastases is high, ranging from 95% to 100%. Lymph node morphology as well as increased FDG avidity can be assessed on PET/CT. Previous authors have reported high specificity for metastasis for all visually FDG-avid lymph nodes, and it can be used to identify internal mammary chain and supraclavicular metastases, which may be incompletely included or difficult to evaluate by MRI (Aukema et al. 2010) (Fig. 17).

A pitfall of PET/CT is its relatively high false-negative rate due to its inability to detect small metastatic deposits (Challa et al. 2013). While comparisons of diagnostic performance of MRI

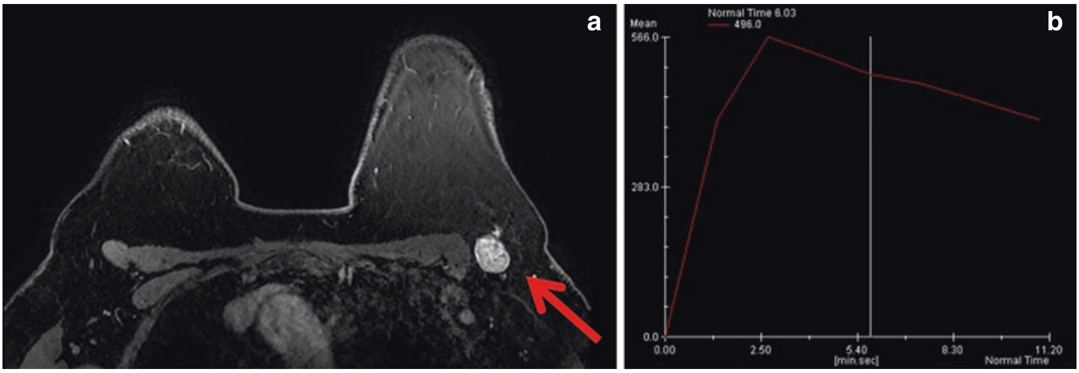

Fig. 16 (**a**, **b**) T1W fat-sat post-IV gadolinium breast MRI demonstrating an enhancing left-sided axillary lymph node (arrow) with a type 3 curve. The abnormal enlarged morphology of the lymph node indicates suspicion for metastatic involvement, rather than enhancement curve

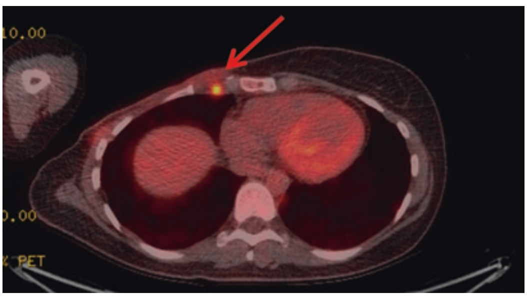

Fig. 17 FDG PET/CT demonstrating tracer uptake within the right internal mammary region (arrow) in a metastatic node. No morphologic abnormality was appreciated on conventional CT

versus PET/CT have suggested that MRI has a higher sensitivity than PET/CT for axillary lymph node metastatic diagnosis (Liang et al. 2017), it is possible that a combination of USPIO-enhanced MRI and FDG PET may provide high enough sensitivity, specificity, PPV, and NPV to be clinically useful in identifying patients who should undergo direct ALND.

8 Summary

The movement to reduce surgical treatment of the axilla in breast cancer patients is continuing. It is now established that ALND is overtreatment in a significant subset of patients with early breast cancer. As surgical staging of the axilla continues to evolve, so too must the role of axillary imaging. While there are significant limitations to US assessment of the axilla, it is important to remember that axillary US and biopsy have the ideal characteristics of an accurate triage test in axillary staging given its consistently high specificity and PPV, as well as its ease of use. Advances in ultrasound technology and newer generation microbubble agents may potentially allow improved accuracy in the preoperative axillary staging setting and may identify patients who are likely to have no or limited axillary disease and therefore be spared ALND and potentially any surgical intervention. Implementation of parameters from imaging techniques and tumor biology into nomograms predicting the probability of lymph node metastasis is another approach to improve preoperative assessment (Qiu et al. 2016). This, along with the accurate identification of axillary status after NAC, remains the great challenge for axillary imaging and patient care, and where future research should be directed.

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