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Review

Evolving imaging techniques for staging axillary lymph nodes in breast cancer

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The presence and extent of axillary nodal metastases at the time of breast cancer diagnosis is a critical factor in disease prognosis and plays a central role in deciding the best treatment for patients. Accurate assessment of the axilla is therefore an essential component in staging breast cancer. Over the years, axillary staging has evolved from surgical axillary lymph node dissection (ALND), with its numerous associated long-term complications, to the much less-radical surgical sentinel lymph node excision biopsy (SLNB), the current reference standard. In parallel, radiological staging of the axilla has become increasingly more useful as our knowledge and techniques have improved. Preoperative axillary ultrasound is used widely to stage patients with breast cancer, providing an evaluation of node morphology and allowing targeted biopsy of abnormal nodes. This is important in helping stratify which patients should proceed directly to ALND and which should undergo SLNB first. Grey-scale ultrasound on its own is not perfect and can over- and underestimate axillary disease. Newer ultrasound techniques such as elastography may help to improve diagnostic confidence when visually assessing axillary nodes; for example, in more accurately assessing the extent of axillary disease burden or in differentiating benign reactive nodes from malignant nodes in equivocal cases. The use of intradermal "microbubbles" has shown great promise in being able to locate and biopsy the sentinel lymph node under ultrasound guidance, and raises the possibility that in the future such techniques may obviate the need for surgical SLNB in select patient populations.

Introduction

The presence and extent of axillary nodal metastases at the time of breast cancer diagnosis is a critical factor in disease prognosis and plays a central role in deciding the best treatment for the patient.[1] Accurate assessment of the axilla is therefore an essential component in staging breast cancer. Historically, the axilla was staged surgically by axillary lymph node dissection (ALND), a radical procedure whereby all axillary nodes are excised, allowing each node to be individually assessed by the pathologist for evidence of metastases. Although effective at assessing axillary

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disease burden, it can be associated with significant long-term morbidity, including ipsilateral arm lymphoedema and paraesthesia, in addition to shorter-term post-operative complications such as wound infections and seromas.[2] As well as living with these complications, for the many women that are subsequently found not to have metastatic nodes, this procedure would arguably have been unnecessary.

Routine staging by ALND has since been superseded by surgical sentinel lymph node (SLN) excision biopsy (SLNB), which is a much smaller operation and aims to excise only the sentinel axillary node. Because the SLN is, by definition, the first node in the lymphatic chain draining the breast, it is the first node in which breast cancer metastases should be detectable. Prior to the surgical procedure, a radiotracer (technetium-99m sulphur colloid) and blue dye are injected subdermally into the periareolar upper outer quadrant region,[3] whereupon they enter the lymphatics and drain into the SLN. The surgeon identifies the position of the SLN first using a handheld gamma camera to detect radioactivity prior to making an incision, and then using a combination of the gamma camera and visual inspection of the stained blue node(s) once the incision is made (Fig 1).

SLNB has been shown to accurately reflect the status of the axillary basin draining the primary breast cancer[4] and has become the widely accepted standard for initial surgical staging of the axilla; if the SLN does not contain metastases it implies the remainder of the axilla is also deemed disease-free and there is no benefit from undergoing subsequent ALND.[5] After 10 years of follow-up, the risk of local recurrence in patients with a negative SLNB is low (1.6 %).[6]

The accepted complications of wound infection, seroma, arm lymphoedema, and paraesthesia[2] are much less for SLNB than ALND. For example, 6% of patients undergoing SLNB had lymphoedema >12 months post-surgery, compared to 19% following both SLNB and ALND, 9% of those undergoing SLNB had paraesthesia at 12 months compared to 39% undergoing both SLNB and ALND.[2] There are also intra-operative complications, such as the small, but serious, risk of anaphylaxis following injection of the blue dye,[7] as well as a small risk of breast tattooing, which can last for at least a year.[8] Technetium-99m lymphoscintigraphy is also not without its problems. Although it may indicate the position of the SLN, by the time of surgery the small size of the radioactive colloid means that the isotope may have passed through the SLN and entered other regional lymph nodes.[9] There are also important considerations related to obtaining, handling and disposing of radioactive material. Finally, a meta-analysis of 69 studies found surgical SLNB to have a median false-negative rate of 7%.[10] Until recently, conventional surgical treatment of the axilla dictated that all patients with SLN metastases required a completion ALND to excise the remainder of potentially malignant lymph nodes. The publication of the ACOSOG Z0011 trial in which patients with SLN metastases were randomised to either ALND or no further surgery changed practice and ushered in the concept of axillary conservation.[11] Despite the fact that 27.3% of patients in the ALND arm had further lymph node metastases, there were no statistical differences in local and regional recurrences between the groups.[12] These results emphasise the key role that modern adjuvant therapy plays in achieving loco-regional disease control.

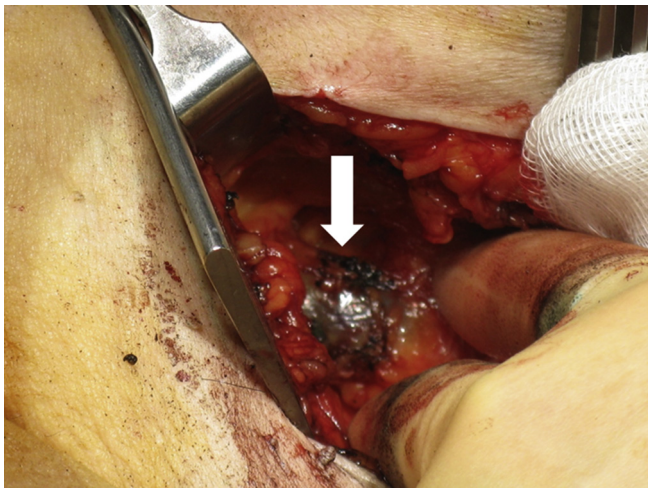

Figure 1 Intraoperative identification of the axillary SLN stained with blue dye (white arrow).

As current medical and surgical approaches to managing the axilla strive to become less invasive, state of the art imaging techniques now play an increasingly important role in staging the axilla, providing as much preoperative information as possible. By developing approaches that optimise the sensitivity and negative predictive value (NPV) of imaging tests, radiologists are beginning to guide the operative management of the patient, minimising the number and extent of surgical procedures the patient undergoes. Identifying high-volume metastatic axillary nodes preoperatively would enable the patient to proceed directly to ALND obviating a two-stage surgical procedure. Alternatively, if axillary metastases can be excluded, this would spare the patient axillary surgery and the potential complications and associated morbidity. Accurate diagnosis and quantification of axillary disease in an outpatient setting could lead to individualised patient-appropriate treatment plans where only affected nodes are excised or monitored, or non-surgical treatment regimens are informed by accurate outpatient staging and review.

Surgical management of the axilla is highly controversial, with both clinicians and patients concerned about “over-treatment” resulting from diagnosis of axillary disease, or conversely, “under-treatment” where high-volume axillary metastases are missed and not excised. Furthermore, some studies have suggested that preoperative diagnosis of axillary disease is not as critical as initially thought in the management of the axilla. The purpose of this review is to discuss the current status of radiological assessment of the axilla, and, in the light of recent clinical trials on management of the axilla, the directions we may be headed over the coming years.

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Current and emerging radiological approaches to assessing the axilla

Grey-scale ultrasound

Ultrasound remains one of the key imaging tools in breast departments and plays a role in the assessment of virtually all breast cancers. As well as determining the size and imaging characteristics of breast tumours, it facilitates accurate ultrasound-guided biopsies to confirm the diagnosis. In addition to assessing the breast itself, all patients with confirmed or suspected breast cancer should undergo grey-scale ultrasound assessment of the ipsilateral axilla.[13]

The main purpose of axillary ultrasound is to provide a visual assessment of the axillary lymph nodes in an attempt to identify and estimate the extent of disease in the axillary nodes. There are several well described features that help aid detection. Morphologically normal lymph nodes are typically oval in shape with a smooth contour, a uniformly thin hypoechoic cortex, and an echogenic fatty hilum (Fig 2). Because the bulk of the normal lymph node is made up of the fatty hilum, this can make normal nodes appear inconspicuous against the surrounding axillary fat, particularly when the cortex is pencil-thin, so even with careful assessment they may be overlooked. Nevertheless, these hyper-reflective nodes with little or no visible cortex are almost always benign.[14]

When metastases enter nodes, they do so through the afferent lymphatic chain via the subcapsular sinus around the cortex.[14,15] As a consequence, thickening of the cortex of nodes should be regarded as suspicious for metastatic invasion (Figs 3 and 4). It is generally accepted that a cortical thickness of <3 mm is normal, but thresholds may vary between different institutes, depending on local experience.

Different patterns of cortical thickening can be observed. Diffuse cortical thickening, for example, is relatively non-specific and seen in reactive as well as metastatic nodes, although should be regarded with suspicion in the context of breast cancer (Fig 3). Focal/eccentric cortical bulging or lobulation is generally a more specific indicator of malignancy (Fig 4). Compared with a smooth cortex, a unilobulate cortex indicates a higher risk of malignancy, and a multilobulate cortex higher still.[16] Based on an *in vitro/ex vivo* study assessing nodes freshly excised from axillary clearance

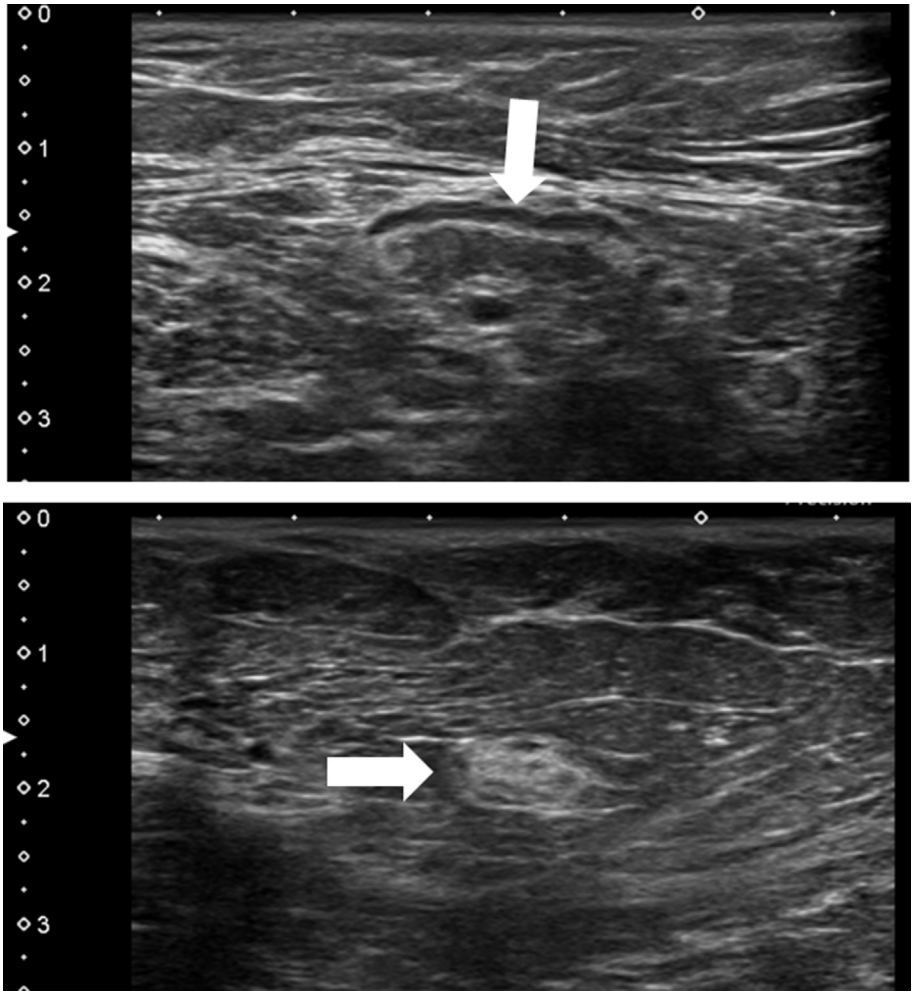

Figure 2 Sonographically normal axillary lymph nodes. Top: Typical normal-appearing node with a uniformly thin hypoechoic cortex (white arrow) and fatty hilum. The hilum is usually isoechoic to the surrounding axillary fat. Bottom: Hyper-reflective node (white arrow) with almost no visible cortex.

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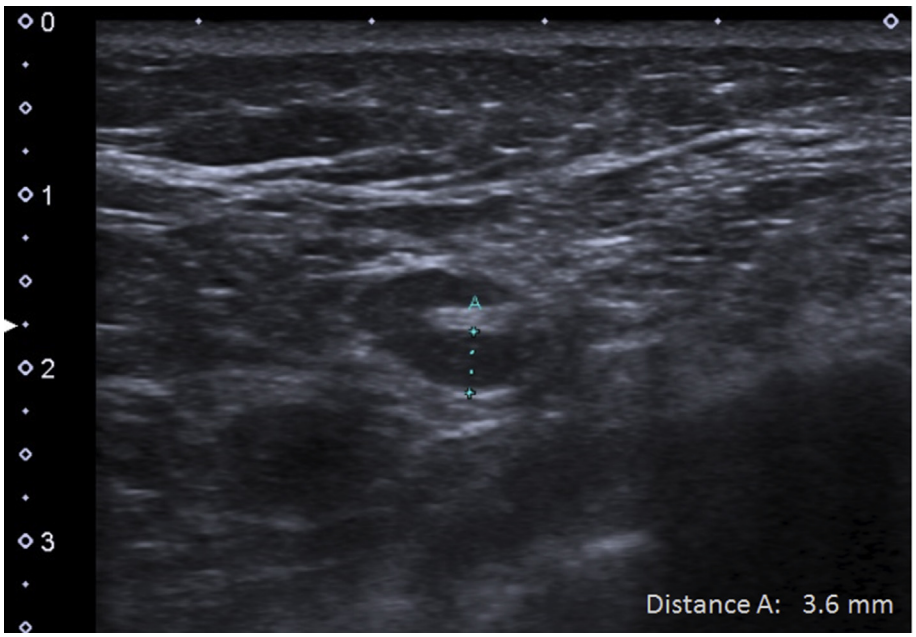

Figure 3 Indeterminate lymph node demonstrating a diffusely thickened cortex.

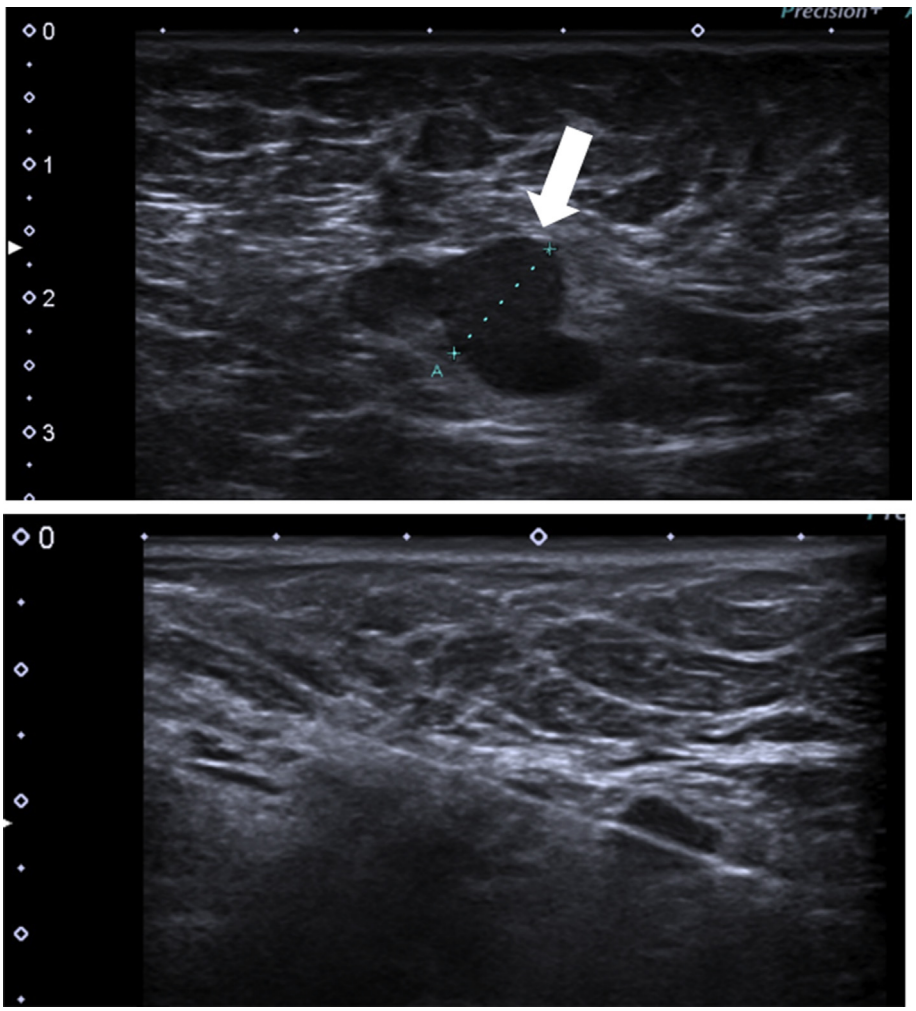

Figure 4 Areas of focal cortical thickening/bulging are highly suspicious for metastatic involvement (top image, white arrow). Ideally, needle biopsy should be targeted to these foci (bottom image).

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specimens, Bedi *et al.* suggest that focal cortical lobulation should be regarded as highly suspicious for metastases and biopsied accordingly; however, they did report a number of false positives due to the possibility of normal-variant lobulation or inflammatory reactive changes in a node (positive predictive value [PPV] 29%).[14] When such nodes are seen on ultrasound, it is recommended that the needle biopsy is targeted specifically to the area of focal cortical lobulation (Fig 4).[14] In other types of cancer, measuring the overall size of the node, typically by using its short axis diameter, is often used to assess whether nodes are likely to be metastatic; however, for breast cancers, despite comparable sensitivity, this is a less specific criterion than using the other described morphological features.[17,18]

As metastatic involvement of lymph nodes progresses and the normal nodal tissue becomes replaced, they begin to lose their fatty hilum until they are totally hypoechoic[14] (Fig 5). This is a less sensitive feature on ultrasound than cortical thickening, but is more specific.[14,19] Furthermore, in their *ex vivo* study, Bedi *et al.* reported a PPV of 58%, as reactive nodes may also give this appearance (as can lymphoma).[14]

Changes in blood flow patterns can also indicate malignancy. On colour Doppler imaging, metastatic nodes are more likely to show peripheral blood flow than the hilar pattern of flow seen in benign nodes,[20] which represents "parasitic neovascularisation". With the advent of improved Doppler technology where the smaller vasculature can be better appreciated, this may become a more helpful feature in discriminating a benign from malignant nodes, but needs further evaluation.[21,22]

Despite the existence of multiple morphological indicators of malignancy, conventional ultrasound still has limitations. Many studies have shown that these features have variable sensitivities and are subjective.[18] A systematic review has shown significant variation between institutions, with overall sensitivity values ranging between 26–76% based on lymph node morphology, and specificity values between 88 and 98%[17]; ultrasound-guided biopsy of suspicious-appearing nodes showed sensitivities between 31% and 63% and a specificity of 100%.[17] A more recent meta-analysis involving 21 studies found ultrasound assessment of abnormal nodes gave a median sensitivity of 64%, with a specificity of 82%; for those who underwent ultrasound-guided needle biopsy the sensitivity and specificity values were 79% and 100%, respectively.[23]

Not only does grey-scale ultrasound have variable sensitivity in detecting disease, it also has a questionable NPV, as nodes can remain morphologically normal despite containing metastases.[18] As might be predicted, ultrasound is better at detecting abnormal nodes in patients with a higher nodal disease burden or with larger primary tumours.[18]

When grey-scale ultrasound is able to positively identify metastatic nodes it can provide important preoperative diagnostic information to guide best management of the patient, particularly when supported with needle biopsy, but there is scope to improve both sensitivity and NPV. One way this might be achieved is by using adjuncts to conventional grey-scale ultrasound, such as elastography.

Elastography

As well as changing the shape of nodes, malignant infiltration also alters their "stiffness" or elasticity. Elasticity is an inherent mechanical property that represents the force required to deform a tissue. Malignant tissue has been shown to have higher stiffness than benign tissue, and this

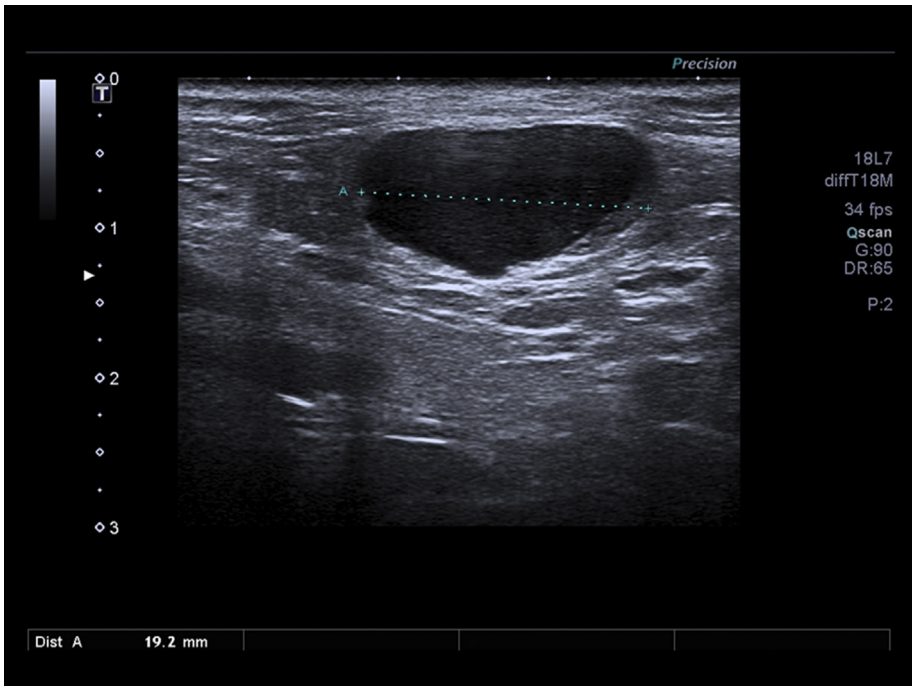

Figure 5 A metastatic axillary lymph node that is entirely hypoechoic, demonstrating complete replacement of the fatty hilum.

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property can be measured non-invasively using ultrasound elastography, a function available on many modern ultrasound machines.

There are two main types of elastography: conventional strain elastography and shear wave elastography (SWE). Strain elastography was the first form of ultrasound elastography to be developed and is carried out by eliciting manual axial displacement of the tissues by freehand compression using the ultrasound probe. The resulting strain data are displayed as a two-dimensional map of the relative tissue strain, called an elastogram.[24] These are usually displayed as a colour-code superimposed onto the conventional grey-scale images. Using this strain method, two types of elasticity measurements can be obtained. First there is qualitative assessment using visual scoring of the colours within and around the area of interest using a four- or five-point elastographic scale. The second method involves calculating a strain ratio between two regions of interest (ROIs), one drawn over the target region, the other over and an adjacent reference region consisting of normal tissue such as subcutaneous fat. Lesions with a strain ratio >1 have a higher stiffness than the surrounding tissue. As the strain ratio increases, so does the likelihood of malignancy. This has been demonstrated both in breast lesions and in axillary nodes. In cases with biopsy-proven histology, Fischer *et al.*[25] found that using strain ratio has a higher sensitivity and specificity in differentiating between benign and malignant lesions than either grey-scale ultrasound or subjective evaluation using elastography; sensitivity and specificity values were 95% and 74% for strain ratios, 85% and 60% for grey-scale ultrasound, and 85% and 68% for subjective elastography. As well as strain ratio, it is also possible to calculate the length ratio, which is the ratio of the maximal horizontal length of the lesion measured before and during compression. A systematic review by Sadigh *et al.*[26] found that both the strain ratio and length ratio provide good diagnostic accuracy for detecting malignant breast lesions; based on nine studies involving 1,875 patients and 2,087 breast masses, overall sensitivity and specificity values for strain ratio were 88% and 83%, respectively. For length ratios, three studies involving 395 patients and 450 breast masses showed overall sensitivity and specificity values of 98% and 72%, respectively.

Choi *et al.*[27] carried out a retrospective study using strain elastography on 64 axillary nodes from 62 breast cancer patients and found the technique showed good discrimination between malignant and reactive nodes, with malignant nodes showing a higher elasticity score than benign nodes. Elastography showed a sensitivity of 81% and a specificity of 67%. Grey-scale ultrasound showed a sensitivity of 74% and a specificity of 79%, with a combined grey-scale and elastography sensitivity of 87%, higher than either technique alone. Potential problems with direct node-to-node correlation between the ultrasound findings and the actual nodes biopsied or surgically excised were noted. Wojcinski *et al.*[28] looked at 165 lymph nodes in healthy volunteers and 15 metastatic lymph nodes in breast cancer patients and found the cortex in metastatic nodes to be significantly stiffer than that of normal nodes. Metastatic nodes also showed features on grey-scale ultrasound indicative of malignant involvement. Sensitivity and specificity for grey-scale ultrasound in detecting malignant nodes (defined by a cortical thickness >3 mm) were 40% and 97% respectively; sensitivity and specificity for strain elastography were 60% and 80% respectively. When grey-scale ultrasound and elastography were combined, the sensitivity and specificity rose to 73% and 99%, respectively.

A key limitation of strain elastography is that it is highly dependent on the compression technique, making it susceptible to both intra- and inter-operator variability.[24] SWE, on the other hand, does not reply upon manual freehand compression, and consequently, is more reproducible. In SWE, focused high-intensity, short-duration acoustic pulses are generated by the ultrasound transducer and produce "shear waves" by absorbing acoustic energy.[24] In this technique the probe is applied with the minimum amount of pressure required to make sufficient contact against the tissue of interest. The resultant shear wave speeds (m/s) are related to the tissue stiffness, and from these values, together with the tissue density, the elastic modulus value (E) of the lesion of interest can be calculated (kPa). Depending on the exact system used, it is possible to display real-time, colour-coded elastograms of the shear wave velocity (m/s) or the elastic modulus (kPa) of the tissue of interest, and it is possible to obtain quantitative measurements for ROIs using static elastograms.[24]

Although there is strong evidence that SWE is effective at distinguishing between benign and malignant breast lesions,[29,30] there is currently very little information on the effectiveness of SWE on the assessment of axillary nodes. Using SWE data obtained from primary breast tumours, Evans *et al.*[31] retrospectively found that the mean stiffness of the primary breast tumour measured by SWE is an independent predictor of lymph node metastasis. Although this may provide additional prognostic information to that obtained from conventional preoperative tumour assessment and staging,[31] it does not provide information about individual nodes. In an *ex vivo* study using freshly excised lymph nodes, Kilic *et al.* found that the mean cortical stiffness (10.7 versus 25.5 kPa) and hilar stiffness (7.5 versus 11.3 kPa) were statistically higher in metastatic lymph nodes.[32]

Thus elastography shows potential in improving identification of malignant axillary nodes when used alongside grey-scale ultrasound, but further studies are needed to validate this. By identifying focal areas of abnormality with a node it may help to guide biopsies more accurately and improve sensitivity. Furthermore by assessing all visible nodes in the axilla it may allow a better assessment of overall axillary disease burden, particularly when the grey-scale appearances are normal. Nevertheless, the data and assessment parameters are not yet established sufficiently for this to be used routinely in axillary staging. It is also dependent on many of the same limitations of grey-scale ultrasound. For example, some axillary nodes can be very difficult to detect on grey-scale assessment, meaning that assessment of morphology and elastography are simply not possible.

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The ultimate goal would be for radiologists to be able to identify and sample the SLN using image guidance. If we could achieve this using ultrasound, irrespective of its grey-scale appearance, this could prove a significant step towards altering the way axillary staging of breast cancer is carried out, and one possible way we might achieve this is using contrast-enhanced ultrasound (CEUS) with "microbubbles".

Microbubbles

A fundamental problem with conventional grey-scale ultrasound is that the SLN has to be identified in order for it to be examined. The SLN is often deep and isoreflective, and is therefore frequently missed on grey-scale ultrasound.[33] The SLN is also one of many lymph nodes within the axilla with a variable position, and, as such, usually cannot be differentiated from non-SLNs. Subsequent ultrasound-guided lymph node needle sampling cannot therefore be confident of which node within the node chain has been biopsied. Contrast ultrasound to identify the SLN has been used to address this problem.

CEUS techniques are perhaps best known for their utility in characterising liver lesions, but are now used widely for many other applications in radiology departments. The contrast agent used comprises a suspension of microbubbles, which are phospholipid-stabilised microspheres smaller than the size of a red blood cell, that act as contrast agents by reflecting the ultrasound beam.[34,35]

In the context of the axilla they are used to highlight the SLN with ultrasound and allow direct percutaneous needle sampling, providing more specific/targeted SLN information preoperatively for multidisciplinary discussion and treatment planning. Unlike in other applications, where the contrast medium is injected intravenously, a tiny volume of the microbubble suspension is injected intradermally into the periareolar region. The microbubbles rapidly enter the lymphatics of the breast tissue, and, using dedicated software on the ultrasound machine, can be traced within seconds to the SLN (Fig 6). This is a useful technique on several levels. If nodes initially appear occult on grey-scale ultrasound, the microbubbles can reveal the SLN and aid successful grey-scale identification, which in turn allows targeted SLN needle biopsy, something that would previously only have been possible with surgical dissection. Another potential advantage is that tumour deposits within nodes have been reported to appear as defects with no uptake, which could give information about disease burden within the node as well as providing a target for needle biopsy.[36] This technique was first described in a swine melanoma model by Goldberg *et al.*,[36] and it was first applied to axillary nodes in patients with breast cancer by Sever and colleagues in Maidstone[33] and Omoto *et al.* in Japan.[37] In the initial Maidstone study, 48/54 patients with breast cancer had SLN successfully identified with intradermal microbubbles and CEUS before a targeted percutaneous SLN biopsy and localisation with a guidewire. The patients then underwent conventional surgical SLNB using radioactive tracer and blue dye injection, excising all SLNs together with the guidewire-localised lymph node. When compared with the standard surgical SLN localisation technique, the retrieved guidewire localised lymph nodes were either radioactive and blue (41 cases) or radioactive only (seven cases) which indicates that preoperative injection of intradermal microbubbles and CEUS can accurately identify tumour draining SLN in breast cancer. Interestingly, in 18 of the 48 patients with successful identification of SLN using CEUS, the SLN was only visible upon microbubble enhancement. These findings have been supported by further work using the same approach.[38,39]

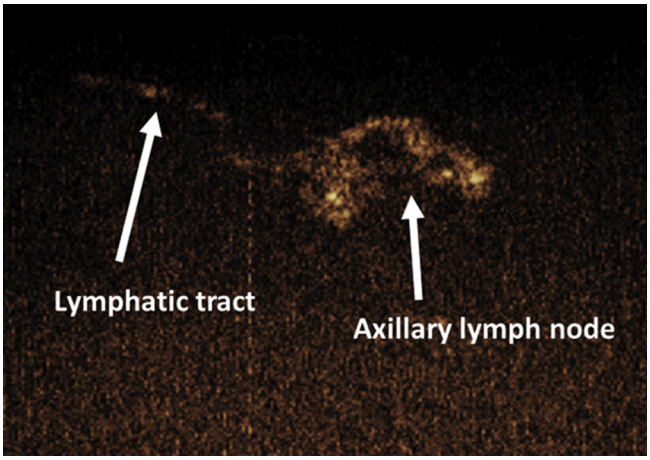

Figure 6 Microbubbles technique. Once injected into the periareolar region, the ultrasound machine is switched to the dedicated contrast setting, and the microbubbles can be tracked along the lymphatic drainage pathway to the SLN. The machine can then be switched back to conventional grey-scale imaging to visualise the node and facilitate needle biopsy.

The most substantial microbubbles dataset to date was published in 2016,[40] with data analysis available for 654 women with a diagnosis of invasive breast cancer with a normal grey-scale axillary ultrasound, had SLNs identified and biopsied using the microbubble technique, and went on to have primary surgical excision of their breast cancer together with axillary surgery. Of these, SLNs were clearly visualised in 605 patients (93%) and successfully core biopsied in 555 (85%), giving a failure of the technique in 99 patients (15%). The prevalence of axillary lymph node metastases in the 555 patients was 23% (16.8% macrometastases, 4.5% micrometastases, and 1.8% isolated tumour cells [ITCs]). Of these, microbubbles identified 53% of SLN metastases, with a NPV of 88%.

Of the 60 patients who were deemed false negative following detection of metastases at surgical SLNB, 47 proceeded to ALND. Of these, 14 (30%) had lymph node micrometastases, 23 (49%) had low-volume macrometastatic disease (one lymph node macrometastasis ± an additional micrometastasis or lymph node ITC), and 10 (21%) had high-volume axillary metastases (two or more lymph node macrometastases). Of the 37 patients with either lymph node micrometastases or low-volume lymph node macrometastases, 31 had metastases only in the SLN, with no further positive nodes in the ALND specimens.

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These data suggest that those with a false-negative core biopsy following microbubbles assessment are unlikely to have extensive axillary disease. Conversely, those with an initial malignant core biopsy result are more likely to have larger volume disease, with 52% of patients in this group found to have two or more lymph node macrometastases.[40] A recently increasing apprehension about possible over-treatment/unnecessarily aggressive axillary surgery (ALND) in patients with micrometastases has prompted the Maidstone group to introduce measurement of the metastasis within the axillary lymph node core biopsy specimens. This provides further information to the multidisciplinary team when counselling patients about the relative benefits and harms of SLNB versus ALND as a first axillary surgical procedure.

It has been proposed that the false-negative rate of the microbubbles with 14 G core biopsy procedure is due to geographical miss of the metastasis by the needle within the SLN. Work has also been carried out using microbubbles to perform large-bore vacuum-assisted core needle diagnostic excision of the whole SLN under local anaesthetic,[41] with a sensitivity of 59% for detecting metastases; however, although the procedure was generally well tolerated, the large-volume vacuum-assisted approach was found to interfere adversely with subsequent surgical SLNB, with surgeons reporting moderate or severe interference in 48% of patients and an additional 8% with complete failure of SLNB.

The role of microbubbles in surgical lymph node localisation has also been investigated. A recent study has looked into placing radioactive iodine (I-125) seeds into the SLN using microbubbles, as a potential alternative for localisation with nanocolloid.[42] Success was, however, limited, and the trial was terminated after 15 cases, nine of which were deemed successful. In three patients no microbubble-enhancing lymph node could be detected. Intraoperatively, nine seeds were found within 0.5 cm of the nanocolloid-confirmed SLN, one seed was found next to a non-SLN and two seeds were not near any lymph node.[42]

Experience of using microbubbles to identify axillary SLNs has grown in recent years in the UK. In addition to Maidstone and its associated site in Tunbridge Wells, there are several breast units in the UK that are now trialling this technique with a view to possibly eventually negating, or at least minimising, the need for axillary surgery.

One of the challenges of breast microbubbles is that the microbubbles are not currently licensed in the UK for percutaneous use. We are unaware of any published or anecdotal reports of complications of using microbubbles intradermally. Published data for the safety of CEUS overall (which mainly comprises intravenous use) quotes a reported serious adverse events rate of 0.0086%.[35,43]

The technology involved in CEUS is rapidly advancing with novel innovations such as super-resolution imaging,[44] ultrafast ultrasound,[45] and improved microbubble transit.[46] These advances have the promise to achieve both qualitative and quantitative imaging information on size and total number of axillary metastases. In swine LN, metastases can be seen as areas devoid of contrast medium,[36] and Xie *et al.* have already managed to perform a detailed clinical study to classify enhancement patterns in LN to increase the sensitivity of the test to 81.8%.[47] Comprehensive assessment of regional LN early on in the patient pathway would revolutionise treatment decision making, direct additional staging investigations and allow targeted axillary surgery. As CEUS is a reproducible technique, for patients undergoing NACT it may be feasible in the future to repeat to repeat the test during and after treatment to measure response.

Computed tomography, magnetic resonance imaging, and positron-emission tomography

At present, computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) are not routinely used to assess specifically for axillary disease burden, but additional information on the axilla can be obtained when it is carried out for related indications, such as staging CT or breast MRI.

MRI shows reasonable sensitivity and specificity for metastatic nodes. A systematic review found that of three studies using contrast-enhanced MRI, the mean sensitivity and specificity values were 88% and 73%.[48] Similar findings were reported in a subsequent study using axial non-enhanced T1-weighted MRI in patients with newly diagnosed breast cancer, with sensitivity and specificity values of 88% and 82%.[49] An observer-performance study, however, found that MRI was not significantly different to ultrasound in terms of sensitivity, specificity, PPV, or NPV at detecting metastatic nodes, although when both techniques are combined, there are statistically significant improvements in specificity and PPV compared with either technique on its own.[50] In clinical practice, the majority of patients undergoing breast MRI with a known breast cancer will already have had an initial ultrasound of the axilla, and if further suspicious findings are demonstrated on MRI then a “second look” ultrasound may be indicated to characterise, and if appropriate, biopsy the abnormality, if this will influence further management.

CT is generally carried out as a whole-body study to stage women with known axillary or distal disease, so it has a limited role in assessing the axilla. Indeed, a recent study has shown that staging the axilla using both CT and ultrasound is no more accurate than ultrasound alone.[51] CT combined with PET is also used for staging many types of cancer, but it is not yet recommended for local staging of breast cancer, and thus, does not currently have an established role in assessing the axilla. A systematic review found that, of seven studies evaluating PET-CT, the mean sensitivity and specificity values were 56% and 96%, respectively.[48] Of 19 studies investigating PET only, the mean sensitivity and specificity values were 66% and 93%, respectively.[48] Although PET was able to detect metastatic nodes as small as 3 mm, it failed to detect some nodes measuring up to 15 mm. For micrometastases (deposits measuring $\leq$2 mm), mean sensitivity was 11%; for macrometastases (deposits $>$2 mm), sensitivity was 57%.

Thus at the present time, CT, MRI, and PET are not on their own superior to ultrasound, and have the limitation

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that, even if abnormal nodes are detected, a second-look ultrasound will still be required to characterise the nodes further and to allow biopsy.

Preoperative axillary node sampling using needle biopsy: core biopsy versus fine-needle aspiration

As described above, ultrasound-guided needle biopsy of suspicious nodes is a useful adjunct to imaging in staging the axilla and is helpful in deciding whether patients can proceed directly to ALND or whether SLNB is the most appropriate first step.[23] One question that is not fully answered, however, is whether the best approach to needle biopsy is wide-bore needle (core) biopsy or fine-needle aspiration (FNA). Core biopsy (typically 14 G) has the advantage of obtaining whole pieces of nodal tissue, and as such one may expect an increased sensitivity compared to FNA, particularly in those nodes where micrometastases or isolated tumour cells are present. Interestingly, however, although core biopsy appears to show a trend of increased sensitivity values compared to FNA, the data shows no statistically significant difference.[23,52] Nevertheless, in the UK, anecdotal evidence suggests that core biopsy is now widely used and is replacing FNA as the technique of choice.

Perspectives on the surgical management of the axilla in breast cancer

Surgical management of breast cancer has changed over many decades from radical mastectomy and complete ALND to breast-conserving surgery with SLNB, only progressing to ALND if the SLNB demonstrates positive nodes. Avoiding unnecessary ALND has a significant impact on patients; those with a negative SLNB who do not undergo subsequent ALND, have an improved quality of life with no negative impact on eventual disease outcome compared with those who undergo ALND.[53]

As well as accepting that women with a negative SLNB do not need ALND, questions have also been raised about whether ALND is necessary even in women with positive axillary nodes. One key study was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 clinical trial, which commenced in 1971 and for which 25-year follow-up data were published in 2002.[54] This investigated 1,665 women with primary operable breast cancer randomly assigned to different treatments according to the clinical assessment of their axillary nodes at the time of diagnosis (summarised in Fig 7). Although no significant difference among the three treatment groups was seen for disease-free survival, relapse-free survival, distant disease-free survival, or overall survival, there were significant differences in local/regional recurrence, which was lowest in the group who underwent total mastectomy with irradiation (but without ALND) and highest in those who underwent mastectomy alone. In the group of women with clinically positive axillary nodes at diagnosis, there were no significant differences in disease-free survival, relapse-free survival, distant disease-free survival, or overall survival, and no significant difference in cumulative local/regional recurrence.

More recently, significant attention has been given to the Z0011 trial, which was initiated in 1999 by the American College of Surgeons Oncology Group (ACOSOG) as a prospective, randomised, multicentre trial comparing survival and locoregional recurrence rates in women with positive SLNB who underwent complete ALND against those who underwent SLNB without complete ALND (summarised in Fig 8).[12,55] This study included patients with T1 or T2 N0 M0 breast cancer treated with breast-conserving surgery and SLNB with at least one but no greater than two histologically tumour-positive nodes. Patients were randomised to completion or no ALND with no further axillary-specific treatment, specifically no third field nodal radiotherapy. All patients did, however, receive postoperative opposing tangential-field whole-breast irradiation. At pathological analysis, 27% of those who underwent ALND were found to have tumour-positive nodes beyond the SLNs, implying that in the “no ALND” arm, about the same proportion can be assumed to have had tumour-positive nodes beyond the SLNs; however, there was no significant difference in locoregional disease control between the two groups with no difference in survival, and these findings have persisted after 10 years of follow-up.[56] This suggests that not all non-SLN metastases develop into clinical disease and that ALND confers no advantage to women with a positive SLNB meeting the trial eligibility criteria. Furthermore, minimising surgery to only SLNB confers significantly lower long-term morbidity than ALND, as already described.[2]

It should be noted, however, that over 95% of women in both arms of the Z011 trial underwent systemic adjuvant therapy, which may have contributed to the effective locoregional disease control, as in these early-stage breast cancer patients with a low burden of axillary disease, where nodal metastases comprising micrometastases or ITCs may have been more responsive to the systemic therapy. In addition, it is highly likely that, although the patients received no axillary-specific radiotherapy, they did receive opposing tangential field whole-breast irradiation, which also likely irradiated the axilla.

The data apply to a select group of patients with early-stage breast cancer and clinically negative nodes undergoing specific surgical and adjuvant treatment, and the results will therefore not necessarily be applicable to those women found to have extensive metastases on SLNB, those with palpable nodal disease, T3 or T4 disease, or those undergoing mastectomy.[12,55] To address the limitations of the ACOSOG Z0011 trial, two European trials, namely SENOMAC and POSNOC are also investigating the axillary management of patients with SLN metastases, but have widened the scope of recruitment to include patients with larger/multifocal tumours as well as those having mastectomies.[57,58]

Nevertheless, the results from the ACOSOG Z0011 trial have been central to a proposed change of practice in the United States for patients with similar clinico-pathological features as those enrolled in the study. The American Society of Clinical Oncology Clinical Practice has recently

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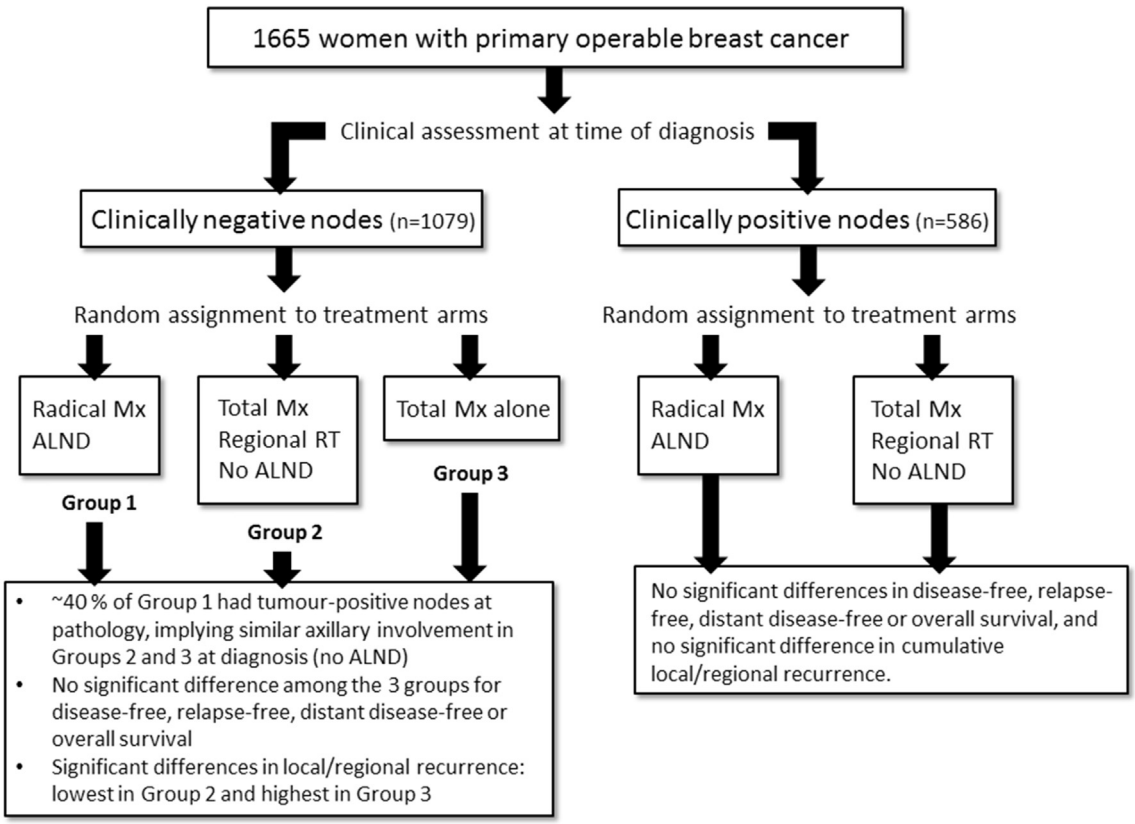

Figure 7 Selective overview of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 clinical trial treatment arms and results.[54] Mx, mastectomy; ALND, axillary lymph node dissection; RT, radiotherapy.

published key recommendations on SLNB and ALND. Women without SLN metastases should not receive ALND. Women with one to two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND.[59] The guidelines do not apply to women with large or locally advanced invasive breast cancers (T3 and T4), inflammatory breast cancer, during pregnancy, in the setting of prior non-oncological breast surgery or axillary surgery, or in the presence of suspicious palpable axillary lymph nodes.

Since the Z011 trial, Dengel *et al.*[60] showed that in a consecutive series of women undergoing breast-conserving therapy meeting the Z0011 criteria, ALND was avoided in 84% of women. Not only will this help avoid significant long-term morbidity in a large proportion of women, it also suggests that most patients meeting the ACOSOG Z0011 eligibility criteria have a low axillary tumour burden.[60]

The evidence gained in these trials has affected the management of the axilla in early-stage breast cancer, where a more conservative approach is being adopted. In the UK, the Association of Breast Surgeons published a guidance statement in 2015.[11] It suggests that if the SLN(s) shows ITCs (metastases measuring <0.2 mm) and/or micrometastases (0.2–2 mm) no further axillary treatment is required in addition to breast-conserving surgery or mastectomy. If there are one to two SLNs with macrometastases (metastases measuring >2 mm), further axillary treatment is no longer mandatory in low-risk patients who are receiving breast conservation with whole-breast radiotherapy (and who are post-menopausal with T1, grade 1 or 2, oestrogen receptor [ER] positive and human epidermal growth factor receptor 2 [HER2] negative tumours). Further axillary treatment should usually be recommended for patients undergoing mastectomy, or with tumours with one or more of the following features: T3, grade 3, ER negative, or HER2 positive. No consensus has yet been reached on the management of patients with one or more of the following features: premenopausal, T2 tumours, lymphovascular invasion, or extranodal spread. Women with three or more SLNs with macrometastases should usually be recommended to have further axillary treatment.[11]

In the case of neoadjuvant chemotherapy, SLNB can be offered after treatment for those who were lymph node negative at the outset,[61] but there is controversy regarding the ideal axillary staging technique to use in patients with biopsy proven pre-treatment LN metastases. Despite long-standing evidence that a complete pathological response is possible in nodal tissue,[62] especially for oestrogen receptor negative and HER2-positive tumours with dual anti-HER2 therapy,[63] the majority of patients will undergo ALND mainly because of concerns that the SLNB is not predictive in this clinical setting.[64] The SENTINA and American College of Surgeons Oncology Group Z1071 trials both showed that the false-negative rate of SLNB after chemotherapy were

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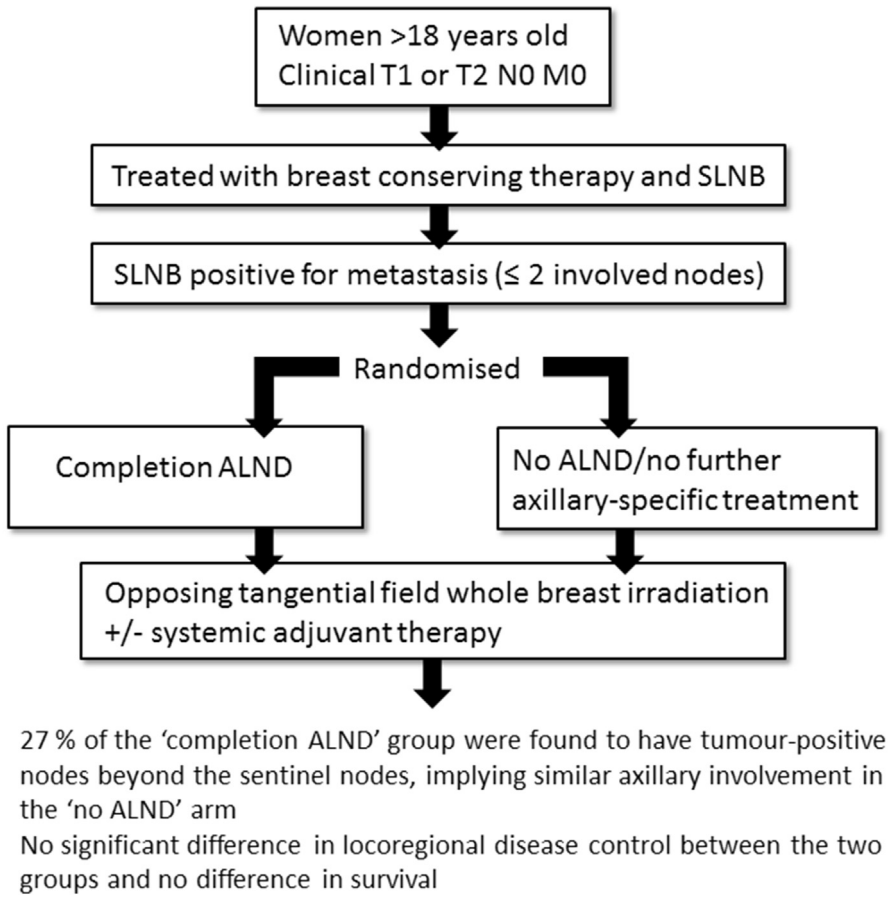

Figure 8 Selective overview of the Z0011 trial treatment arms and results.[12] SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

above the acceptable cut-off rate of 10%,[65,66] but separate analysis showed that the SLN localisation rate can be improved with the use of dual-agent mapping and the retrieval of more than three SLNs.[67]

Attempts have been made to optimise the SLNB after neoadjuvant chemotherapy in patients presenting with axillary lymph node metastases. One group have described a protocol where ALND is omitted in those patients with no palpable lymph nodes at the end of treatment who had three or more SLN that did not contain metastases.[63] Alternatively, a full ALND may be avoided by performing targeted axillary dissection where the pre-treatment malignant lymph nodes are localised and then removed after neoadjuvant chemotherapy together with SLN. In a recent study, this approach reduced the false-negative rate to 1.4%, and in 23% of cases the clipped lymph node was not retrieved as a SLN.[68] The drawback to both of these approaches is the lack of long-term outcomes and clinical trials are needed before implementation into routine practice.

Impact on radiological assessment of the axilla

The results of the Z011 trial suggest that patients with early-stage breast cancer and clinically negative axillary nodes should be staged by SLNB and their subsequent management based on its outcome, and questions have been raised about the need for any preoperative axillary imaging in these patients.[69] Further to this, it has been suggested that preoperative diagnosis of axillary lymph node metastasis condemns the patient (who may have very low bulk disease: for example, a single micrometastasis) to over-treatment (ALND), where a SLNB may have been sufficient. There are several responses for this. First, it is difficult to know at the time of radiological assessment of the primary breast cancer which women will fall into the Z0011 pathway. T1/2 status will be ascertained at the time of ultrasound so some presumptions can be made, but until multidisciplinary team discussions regarding management have taken place, including discussion with the patient, it is controversial to assume that axillary imaging is unnecessary. Indeed, finding morphologically abnormal axillary nodes at ultrasound coupled with ultrasound-guided needle biopsy, may avoid initial SLNB and may streamline the pathway directly to ALND in appropriate cases, even in those with T1/2 tumours who may have otherwise met the Z0011 criteria.[70] A single, patient-appropriate surgical axillary procedure is currently considered optimal patient management, with added morbidity if a completion ALND is required at a later date following SLNB.

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Preoperative assessment of the axilla with ultrasound and guided biopsy does provide added information to empower the patient, surgeon, and rest of the multidisciplinary team in its decision-making process. This information does not force the hand of the surgeon to commit unnecessarily extensive surgery (ALND) and should be used to guide the team towards best possible management of each individual patient. Where axillary ultrasound does not suggest high-volume metastatic disease, but a microbubble-guided lymph node core biopsy contains <2 mm metastasis, for example, the multidisciplinary team may still recommend SLNB (perhaps with a guidewire to the biopsied node) to the informed patient.

Furthermore, we must not overlook the fact that our imaging capabilities continue to evolve. We may not yet have reached the limits of what we as radiologists can offer. The microbubble technique offers exciting potential to be able to target the SLN preoperatively, and with further refinements and experience, we may be able to avoid surgical SLNB and subsequent ALND in certain patient groups. The SLNB may, for example, be replaced by US-guided biopsy of a microbubble-identified SLN, further evaluated by SWE. There will still be a risk that we miss a low volume of axillary metastases, such as micrometastases or small macrometastases, but as our knowledge of tumour biology improves, this may not be as crucial as we once believed; we already know from the surgical trials described that leaving a low volume of tumour burden in the axilla does not adversely affect outcome.[2,12,54,55] This disease either remains subclinical as part of the natural course of the disease or, more likely, is treated incidentally with regional irradiation or by systemic therapy, or a combination of the two.

One clinical trial that could help to emphasise the importance of axillary ultrasound in staging breast cancer is the SOUND trial (SLN versus Observation after axillary UltraSouND).[71] Based on the described observations that there is no significant difference in outcomes between ALND and no further axillary surgery in patients with in early-stage breast cancers and a positive SLNB, doubts have been cast on the role of SLNB itself. The SOUND trial, which is still ongoing, compares the outcomes of women with breast cancer and a normal preoperative axillary ultrasound who undergo SLNB against those who undergo observation only.

As new data from surgical trials emerges, we need to re-evaluate how the information we provide fits in with the changing approaches to disease management. We will find further ways to refine the treatment pathway and improve the outcomes and experiences of the patient. Thus, even in light of changing surgical practice, we must continue our endeavours to provide the best possible axillary staging information, continually exploring new ways to improve and refine the increasingly less invasive approaches to breast cancer diagnosis and management. Breast radiologists are an integral part of the multidisciplinary breast cancer team and are ideally placed to help lead the way on these minimally invasive approaches.

Conclusions

Placing a greater emphasis on conservative management of axillary disease through staging by surgical SLNB for certain patient groups represents a significant move towards avoiding unnecessarily radical axillary surgery. This changing practice does not diminish the role of the radiologist in axillary staging. We must continue to refine our techniques to provide more accurate preoperative staging, aiding progress toward minimal intervention with preserved or enhanced patient outcome. More accurate preoperative axillary staging, perhaps developing radiological SLNB or non-invasive SLN assessment, using microbubbles for example, may obviate the need for surgical SLNB in select patient populations in the future.

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