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Diagnosing and Managing the Malignant Axilla in Breast Cancer

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Abstract

Purpose of Review The management of the malignant axilla remains a controversial topic. Although many issues have been resolved with the results of randomised controlled trials, there are still areas where evidence is lacking. This review will focus on the current diagnostic methods used to detect lymph node (LN) metastases as well as the impact of volume of LN disease on the choice of axillary management. The roles of surgical excision, radiotherapy and systemic therapy as treatment modalities for LN metastases will also be explored with particular emphasis on the use of neo-adjuvant chemotherapy (NACT). Lastly, new innovations in contrast-enhanced ultrasound (CEUS) will be discussed as a potential test for precise and personalised axillary staging.

Recent Findings The results of the ACOSOG Z011 trial are widely accepted and axillary conservation is now part of mainstream practice in many parts of the World for patients with sentinel lymph node (SLN) metastases and clinical T1/ T2 N0 M0 tumours who had breast-conserving surgery alongside adjuvant whole breast radiotherapy and systemic therapy. Determining the volume of metastatic disease in the axilla is important for treatment decisions and de-escalation of axillary surgery after NACT in patients with biopsy proven pretreatment LN metastases may become part of routine practice for selected patients once long-term outcomes are known. Novel methods to identify LN metastases have been developed over the last 10 years including the use of injected microbubbles and CEUS to locate and biopsy sentinel lymph nodes (SLN). Technological advances including ultrafast and super-resolution ultrasound have the potential to increase the diagnostic accuracy of axillary CEUS.

Summary The main drawback to current axillary management is the lack of a reliable objective test to quantify LN metastases. The de-escalation of axillary surgery is timely but without an objective non-invasive imaging test to replace the axillary lymph node dissection (ALND), clinicians are reliant on predictive medicine rather than precision diagnostics to plan individual treatment. New innovations in CEUS have the potential to provide a reproducible non-invasive test, which can be used in the future to investigate LN metastases in patients with breast cancer.

Keywords Breast cancer · Axillary staging · Lymph node metastases · Sentinel lymph node · Contrast-enhanced ultrasound (CEUS) · Microbubbles · Neo-adjuvant chemotherapy · Ultrafast ultrasound · Super-resolution ultrasound

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Introduction

Over the last two decades, there has been a radical shift in the way that the axilla is treated. The centuries old paradigm of breast cancer as a disease that spreads in a step-wise fashion from breast to axilla to body [1] has been conclusively replaced by the concept of breast cancer as a multi-clonal systemic disease albeit with a local origin [2]. In tandem, as medical treatments for breast cancers have improved, there has been a drive towards de-escalation of surgical treatment in the axilla. The long-term results of the ACOSOG Z011 study [3•] together with the low axillary events seen in SLN trials [4] despite an acknowledged false negative rate indicate that the treatment of LN metastases is not solely dependent on surgical excision.

Approximately 30% of patients presenting with early breast cancer will have LN metastases [5]. However, axillary metastases can range in size from a few isolated tumour cells (ITC) in a single LN to multiple metastatic LN, each containing large clusters of cancer cells and evaluating the volume of disease in metastatic axillary LN is important for planning local therapy [6].

One of the major problems with current axillary management is the lack of a robust non-invasive test to identify and quantify LN metastases. Clinicians are therefore reliant on physically counting metastases in excised LNs rather than using precision imaging to guide treatment. There are several imaging modalities theoretically capable of visualizing human LN but innovations in ultrasound may hold the greatest promise.

In this review, the current diagnostic tests for detecting LN metastases will be appraised as will the impact of volume of LN disease on the choice of axillary management. The roles of surgical excision, radiotherapy, and systemic therapy as treatment modalities for LN metastases will also be explored with particular emphasis on the use of neo-adjuvant chemotherapy. Lastly, new innovations in contrast-enhanced ultrasound (CEUS) will be discussed as a potential test for precise and personalised axillary staging.

Diagnosis of Axillary LN Metastases

In patients with cancer, LN metastases are considered relevant because of their potential to grow and disseminate, thus leading to a failure of locoregional control and systemic metastases respectively. Malignant processes are often associated with the formation of new lymphatic vessels in and around the tumour (lymphangiogenesis) as well as in regional draining LN, which can occur even before metastatic infiltration [7]. Malignant infiltration may also change the pattern of blood flow in LN with metastatic LN more likely to show peripheral rather than hilar flow [8] In addition, LN could act as a permissive lymphovascular niche to support the survival and proliferation of metastatic cells and promote their movement to distant sites [9]. The goals of axillary treatment are therefore to halt this process and theoretically improve patient survival and locoregional control. In addition, LN metastases act as a surrogate marker for systemic spread and are used to help guide treatment decisions [10] making the identification of LN metastases early on in the diagnostic pathway an important step.

Patients with normal feeling LN are unlikely to have sentinel lymph node (SLN) metastases, regardless of body mass index [11] but clinical examination is not very reliable. Only a third of patients with LN metastases will have palpably enlarged LN and a small proportion of patients with lymphadenopathy will not have axillary metastases at all [12]. In the UK and much of Europe, all patients newly diagnosed with breast cancer will have a grey-scale axillary ultrasound with a biopsy of morphologically abnormal LN [13]. Conventional grey-scale ultrasound combined with fine needle aspiration cytology (FNAC) or core biopsy has limited diagnostic accuracy for LN metastases with an overall sensitivity of around 50% [14] although the negative predictive value may be as high as 84% in patients with screen-detected cancers [15].

Grey-scale axillary ultrasound can be enhanced with the use of intradermally injected contrast agent. The contrast is made up of microbubbles containing an inert gas and once injected, microbubbles can be visualised trafficking through the breast lymphatics to the draining axillary sentinel lymph nodes (SLN), which are then targeted for biopsy [16]. Adapted from a swine melanoma model [17], it was initially described in 2009 by Sever at al at Maidstone, Kent [18] and Omoto et al. in Japan [19]. Axillary LN can often be occult on conventional grey-scale ultrasound and may be only visible as areas of contrast pooling [18].

Sentinel lymph nodes identified with contrast-enhanced ultrasound (CEUS) correlate well with those identified using standard intra-operative tracers [15]. Other units in England [20•], Europe [21, 22], China [23], India [24], and the USA [25] have adopted the procedure confirming that it is a reproducible technique [26]. The whole procedural time is 15–30 min [27] and is safe and well tolerated by patients [28]. The sensitivity of the test is approximately 50% with a negative predictive value of 87% and when used in conjunction with grey-scale ultrasound, the combined procedures become an effective 'filter' to separate patients with high volume axillary metastases from those with no metastases or low volume (< 2 macrometastases) axillary disease [20•]. In a large prospective dataset, 11.6% of patients with invasive breast cancer having primary surgical treatment who tested negative with a microbubble/CEUS SLN biopsy were subsequently found to have SLN metastases at the time of surgery and when the volume of missed metastases was taken into account, only 1.6% who tested negative had 2 or more LN macrometastases identified at the end of primary surgical treatment [20•].

Malignant infiltration of LN can alter their stiffness or elasticity and this can be measured using ultrasound elastography. This technique may aid the diagnosis of metastatic LN when used together with grey-scale ultrasound but further studies are needed to validate this. Many of the limitations of grey-scale ultrasound also apply to elastography such as the inability to actually visualise LN as defined structures within the fatty tissue of the axilla [29].

Other imaging modalities in common use include CT, MRI, and PET scanning. Gadolinium-enhanced MRI has a reasonable sensitivity and specificity (88% and 73% respectively) for detecting malignant axillary LN and ultra-small super-paramagnetic iron oxide (USPIO)-enhanced MRI has a reported sensitivity and specificity of 98% and 96%, respectively [30] but lacks the facility to biopsy abnormal LN if required.

Staging the axilla with CT and ultrasound is not superior to ultrasound alone and the addition of PET to CT results in a mean sensitivity of 56% and specificity of 96% [29].

The current gold standard for diagnosing axillary metastases is surgical excision and the axillary lymph node dissection (ALND) was routinely used for decades because it provided clinicians with information regarding the number of LN metastases as well as delivering locoregional control [31•]. Unfortunately, the major problem with using ALND as a staging test for all breast cancer patients was the significant morbidity associated with the procedure [32] especially as approximately 70% of patients presenting with early breast cancer do not have LN metastases [5]. The ALND has therefore largely been superceded by the limited sentinel lymph node excision (SLNE) as the standard of care for modern axillary staging [13].

Although the associated morbidities of SLNE are less severe than the ALND, there are acknowledged complications and it remains a surgical procedure performed under general anaesthetic. The operation is associated with short-term problems such as infection (11%) and long-term problems with sensory loss (11%) and arm lymphoedema (5%) at 12 months [32]. Sentinel lymph nodes are found intra-operatively with the use of lymphatic tracers that are injected into the breast. There is an acknowledged false negative rate (FNR) with SLNE and many centres use a combination of injected radioisotope before surgery and blue dye to ensure that no more than 6% of test negatives have LN metastases [33]. However, blue dye carries a risk of allergic reaction/anaphylaxis [34] and the procurement of medical grade isotopes can be logistically challenging for many hospitals.

Other variables that may affect the FNR include the number of retrieved SLN. Many studies have shown that this value will incrementally decrease with increasing numbers of retrieved SLN and the FNR can be greater than 10% with only a single excised SLN [35, 36]. Whether or not the high FNR associated with single SLN excision impacts on recurrence and survival is debatable. Retrospective analyses are conflicting with Kim et al. reporting a decreased recurrence-free survival in this group [37] and Wilkerson et al. showing no difference in recurrence-free survival and overall survival between patients with a single excised negative SLN and those with 2 or more negative SLN [38]. The patients in the Wilkerson et al. study all had normal preoperative grey-scale axillary ultrasound so it may be reasonable to speculate that the patients in this study were less likely to have extensive axillary metastases.

Volume of Axillary LN Metastases: Does Size Matters?

The clinical relevance of very low volume axillary metastases such as isolated tumour cells (ITC) and micrometastases has been a contentious issue. The presence of LN micrometastases is used as a parameter in algorithms such as Predict Version 2.1, which is used to guide decisions regarding adjuvant systemic therapy. Isolated tumour cells in LN are generally regarded as node negative when considering adjuvant treatment [13] but a recently published cohort study indicated that patients with ITC might have a worse prognosis [39]. Other analyses show that whilst ITC are not clinically relevant, the presence of LN micrometastases is an adverse prognostic marker and these patients may require systemic treatment [40]. The MIRROR study demonstrated that both ITC and micrometastases were associated with a reduced 5-year disease-free survival, which improved with adjuvant treatment [41].

With regards to axillary management, the investigators involved in the IBCSG 23-01 multicentre, randomised controlled trial recently reported their long-term outcomes. This non-inferiority trial was designed to compare ALND versus no ALND in breast cancer patients with SLN micrometastases with disease-free survival as the primary end-point. At a median follow-up of 9.7 years, there were no disease-free survival or overall survival differences between the groups but the no ALND group had a small but higher rate of axillary failure (2% versus < 1% in the ALND group) [42•].

For patients having breast-conserving surgery (BCS) with planned adjuvant radiotherapy, finding low volume SLN macrometastases (1–2 LN) no longer mandates a completion ALND [13] as a second operation. The 10-year results of the ACOSOG Z011 trial have shown that a completion ALND does not improve overall survival or regional recurrence rates [3•]. The limitations of the Z0011 study are now being addressed by 2 European randomised controlled trials that have widened the scope of recruitment of patients with SLN metastases to include those requiring mastectomy and those with larger (T3) and multifocal cancers. The SENOMAC trial is aiming to recruit 3500 patients including those who have had neo-adjuvant chemotherapy (NACT), those with T3 tumours, and patients scheduled for mastectomy with or without reconstruction [43]. The POSNOC trial is enrolling patients with tumours up to T3, those with multifocal tumours, and again those scheduled for mastectomy [44]. The POSNOC trial has also recently started recruiting T1/2 patients with 1–2 SLN macrometastases found at SLNE with planned NACT.

At the opposite end of the spectrum are patients with high volume axillary disease containing multiple LN macrometastases. Identifying these patients early on in the diagnostic pathway is important because they may benefit from NACT and will require systemic staging investigations [45]. The reconstructive choices for patients scheduled for mastectomy may also change if they are found to have LN metastases before surgical treatment [46]. Detecting malignant LN by grey-scale ultrasound rather than SLNE appears to predict for a higher LN burden [47, 48] and 50% of patients with a normal grey-scale ultrasound but a malignant SLN core

biopsy using microbubbles/CEUS will have 2 or more axillary LN metastases found at the end of primary surgical treatment [49]. High volume axillary LN metastases also have an implication for radiotherapy planning as regional nodal irradiation reduces the rate of axillary failure in patients with 4 or more malignant LN [50]. In addition, regional nodal irradiation may be applicable to patients with 1–3 malignant LN [51].

Treatment of Axillary Metastases and Neo-adjuvant Systemic Therapy

As has been previously described, ALND surgery together with appropriate systemic therapy and adjuvant radiotherapy can be very effective in treating axillary metastases [31•]. As a sole treatment, axillary radiotherapy without surgery is associated with slightly reduced overall survival when compared to ALND and a small improvement in local recurrence [31•]. For patients with metastases detected in excised SLN with T1–2 primary breast cancer, the AMAROS trial showed that axillary radiotherapy was not inferior to completion ALND in terms of locoregional control. Likewise, there were no significant differences between the 2 groups in terms of overall survival and disease-free survival [52].

In the context of malignant SLN, one of the major criticisms of axillary radiotherapy rather than ALND is the loss of prognostic information regarding the residual LN burden of disease. However, limited surgical axillary staging may be augmented by new genomic and molecular assays as well as updated algorithms to predict response to adjuvant treatment. In the USA, the existing weaknesses of anatomical staging as a prognostic marker have been acknowledged by the American Joint Committee on Cancer (AJCC) Expert Panels and have led to the addition of oestrogen receptor (ER) status, Her2 status, grade, and molecular characteristics into the 8th Edition Revision published in 2016 [53]. This change was mainly brought about by the development of new staging systems such as Bioscore that incorporate treatment amenable biologic factors [54].

Increasingly, NACT is being used to downstage breast cancer before surgical treatment and SLNE can be safely offered to those patients who were LN negative at the outset [55]. Patients who are found to have incidental metastases discovered in retrieved SLN may be regarded as having chemo-resistant disease [56] and should be offered completion ALND as their risk of non-SLN metastases is high enough to warrant further surgery [57]. However, controversy still exists regarding the ideal axillary treatment for patients with documented pretreatment LN metastases.

There is plenty of evidence to indicate that LN metastases can respond to systemic therapy [58] especially in patients with oestrogen receptor negative and Her-2 positive breast cancer [59]. However, there are concerns that lymphatic drainage from the breast can be altered by the presence of malignant disease in LN, thus making SLNE unreliable [60]. Two studies have addressed this issue and both the SENTINA and American College of Surgeons Oncology Group Z1071 trials showed that the overall false negative rate of SLNE after systemic therapy was higher than 10% [61, 62].

In a sub-group analysis, the use of dual tracer mapping and the removal of more than 3 SLN were found to reduce the false negative rate below 10% [63]. This information has facilitated a drive towards limited axillary surgery in selected patients with pretreatment LN metastases and no palpable LN at the end of NACT [59]. Another approach is to localise the malignant LN pretreatment and perform a targeted ALND at the end of treatment by excising the previously clipped LN together with SLN.

In a recent study from MD Anderson Cancer Center, this protocol reduced the false negative rate to 1.4% and interestingly in 23% of the cases, the clipped LN was not retrieved as a SLN [64]. In the Netherlands, the MARI (marking the axillary lymph with radioactive iodine seeds) technique uses radioactive iodine seeds to mark malignant axillary nodes before NACT. The marked LN is then removed after treatment. In a validation study of 100 patients, the MARI procedure correctly identified 65 of 70 with residual nodal disease [65].

The drawback for all of these limited surgical approaches in patients with pretreatment LN metastases is the absence of long-term outcomes especially as any false negative cases may be considered to be chemo non-respondant and may even harbour chemo-resistant disease. The evidence base for firm surgical treatment recommendations is therefore lacking. Trials such as SENOMAC and POSNOC [43, 44] may be able to give some insights regarding the risks of leaving disease in the axilla as undoubtedly a small proportion of patients with 1–2 pretreatment SLN metastases randomised to no ALND at the end of NACT will have residual un-resected LN disease present as they commence neo-adjuvant therapy. However, the number of events may be too small to generate any meaningful data.

Other ongoing trials such as the NSABP B-51/Radiation Therapy Oncology Group 1304 study may provide more answers [66]. The trial is designed to explore whether the addition of postmastectomy chest wall and regional LN irradiation/post-lumpectomy regional node irradiation is of benefit in those patients who have a pathological complete response in retrieved SLN (with or without ALND) or ALND post NACT with a primary end-point of invasive breast cancer recurrence-free interval. In the UK, the issue of altered lymphatic drainage after NACT is being addressed by the MicroNACT study with intradermally injected microbubbles and CEUS being used to dynamically map lymphatics and biopsy SLN before and after NACT in patients with pretreatment LN metastases.

Innovations in Contrast-Enhanced Ultrasound and Personalised Axillary Staging

One of the major drawbacks for axillary management is the lack of a reliable non-invasive imaging test to identify and quantify LN metastases. Clinicians are therefore dependent upon using information from axillary surgery and tumour characteristics together with predictive algorithms to devise treatment plans for individual patients. The existing method of using contrast-enhanced ultrasound to identify SLN with intradermally injected microbubbles has a variable success rate [20•]. This may be due to the significant noise and imaging artefacts which results in low image signal to noise ratios. Existing CEUS does not have enough spatial resolution and image contrast to consistently characterise metastases within SLN. In addition, human axillary LN are sited deeply within surrounding fatty tissue and they can be technically difficult to biopsy [20•].

Two key recent advances in medical ultrasound are the development of ultrafast imaging techniques and systems [67, 68] and super-resolution imaging [69, 70]. In ultrafast ultrasound, data is acquired from all transducer elements and beam forming is performed in parallel instead of the traditional line-by-line method. This offers up to tens of thousands of imaging frames per second, which not only allows improved tracking of fast moving targets such as the heart and arterial flow [67], but can significantly improve imaging contrast and reduce artefacts by leveraging the large amount of data acquired in a short period of time. In super-resolution imaging, spatially isolated bubbles are identified and their positions localised and accumulated over time to generate a super-resolution map. Spatial resolution at 20 μm or less at centimetre depths using a clinical ultrasound system has recently been demonstrated in vivo [69]. Ultrafast CEUS has also been used in 3D super-resolution imaging of a rat's brain using a customised preclinical probe [70].

The advantage that ultrasound-based technologies have over other imaging modalities such as MRI is that ultrasound is generally well tolerated by patients and is already embedded in routine clinical practice. Ultrasound also offers the opportunity to readily biopsy abnormal or indeterminate LN for a histological diagnosis if required [29]. The potential application of ultrafast and super-resolution ultrasound techniques to the human lymphatic system presents an exciting opportunity to meet the challenges of axillary staging in invasive breast cancer patients: (a) the high imaging contrast may allow better visualisation of lymphatic vessels and hence a reduced failure rate in detection of SLN; (b) the high contrast and super-resolution may allow detection and sizing of metastases within SLN and other axillary LN; (c) the procedure is potentially reproducible and may be used to monitor treatment and offer surveillance in high-risk patients after axillary conservation.

Conclusions

Determining the optimal management strategies for malignant axillary LN in different clinical scenarios remains challenging for all oncologists. The consequences of over-treatment can profoundly affect patient quality of life but equally under-treatment can increase the risk of axillary failure and may impact survival. In the context of the malignant axilla, the de-escalation of axillary surgery is timely but without an objective non-invasive imaging test to replace ALND, clinicians are reliant on predictive medicine rather than precision diagnostics to plan individual treatment. New innovations in CEUS with ultrafast and super-resolution ultrasound have the potential to revolutionise axillary treatment in patients with breast cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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