Enhanced Pre-operative Axillary Staging using Microbubbles and Contrast Enhanced Ultrasound in Patients with Breast Cancer

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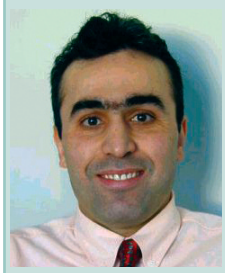

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Background

The optimal surgical treatment of the axilla in patients with breast cancer has been a matter of controversy for many decades. For 50 years we have seen a gradual progression away from the formidable radical mastectomy towards surgical conservation of the breast and axilla.

The characterisation of regional axillary lymph nodes in patients with breast cancer remains an important staging tool with prognostic significance. Modern adjuvant therapy for breast cancer also relies upon the quantification of axillary nodal involvement to guide treatment decisions for individual patients. The axillary lymph node dissection (ALND) has been used for many years to accurately provide this information.

Despite the undeniable usefulness of the ALND as a staging procedure, it is an operation that may be associated with major morbidity. The last 20 years have therefore seen the successful development of a limited axillary staging procedure for patients with early breast cancer. The sentinel node biopsy (SNB) is based on the premise that the lymphatic drainage of the breast passes initially to a small number of sentinel lymph nodes (SLN) sited within the ipsilateral axilla. The SLN can be identified intra-operatively using a combination of blue-dye and radioisotope that is injected into the affected breast before the operation [1].

Clearly, those patients who do not have SLN metastases will not require any further axillary surgery and relevant choices will be made regarding their adjuvant therapy. However, for those patients who are found to have SLN metastases the decision to advocate further axillary surgery in the form of a completion ALND is not always straightforward.

In the UK, the use of screening mammography and the widespread awareness of breast disease means that many breast cancers are detected when small. These patients are likely to have low volume metastases and if the SLN contains metastatic disease the total number of lymph nodes involved with breast cancer may be very few. Recent trial data from the USA indicates that even if SLN are positive for macrometastases, in patients with small breast cancers having adjuvant systemic therapy, further surgery in the form of completion ALND may not improve local recurrence rates or overall survival [2].

For those patients with large volume axillary metastases, historical evidence suggests that ALND may improve overall survival in the absence of modern adjuvant therapy [3]. More recent studies indicate that ALND reduces the recurrence of breast cancer in the axilla and thus provides good local control even though it may have no affect on overall survival [4].

Pre-operative Axillary Staging

Identifying those breast cancer patients with large volume axillary disease prior to excision allows a more targeted approach to surgical planning as patients with a heavy nodal burden are likely to benefit from a primary ALND. Grey–scale ultrasound of the axilla is commonly used to find morphologically abnormal lymph nodes in the axilla, which can then be biopsied to confirm the presence of metastatic cells. Notwithstanding the utility of pre-operative grey-scale axillary ultrasound, the test cannot recognise all axillary lymph node metastases. Between 21% and 63% [5] of breast cancer patients who have a SNB will require a completion ALND for metastatic SLN not visualised by grey-scale ultrasound.

An imaging test that could reliably identify and quantify all axillary lymph node metastases in patients with breast cancer prior to surgery would be an ideal addition to any breast service. Technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI) may have an important role to play in the future but at present are too expensive to be used routinely [6,7].

Grey-scale axillary ultrasound is relatively cost-effective and well tolerated by patients. Thus, methods to enhance the sensitivity of axillary ultrasound may be a practical way to detect a greater proportion of axillary lymph node metastases at the time of breast cancer diagnosis.

Identification of SLN metastases using Intradermally injected microbubbles and contrast enhanced ultrasound

Contrast enhanced ultrasound (CEUS) is well established in clinical practice and intravenous administration of contrast has provided enhanced imaging of the vasculature in many organ systems. Ultrasound contrast agents are composed of a dispersion of microbubbles, each of which is smaller than a red blood cell and act as a reflector of the ultrasound beam.

The use of ultrasound contrast agents to identify superficial lymphatics was first described in 2004. The study involved a swine melanoma model and contrast agent was injected around the tumour. Very quickly, contrast agent was seen to enter lymphatic channels and could be followed to draining SLN. In this investigation, swine SLN were accurately identified by ultrasound in 90% of cases [8].

In human subjects, injected contrast agent can also enter superficial lymphatics. In patients with breast cancer, intradermally injected contrast moves through the lymphatic channels of the breast to draining SLN. In those patients with a normal axillary grey-scale ultrasound, approximately 95% of

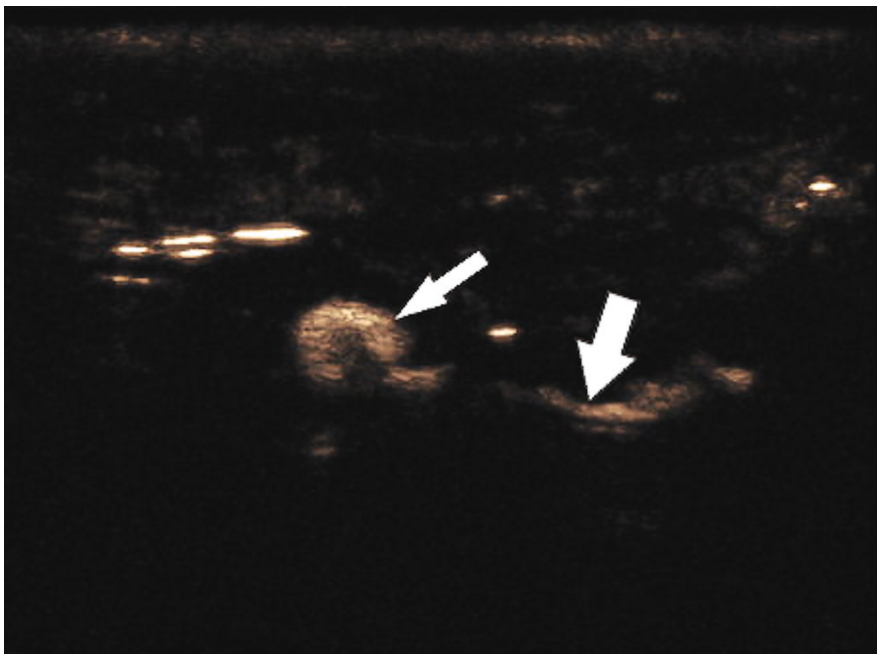

Figure 1:Contrast pulse sequencing image of an afferent lymphatic vessel (large arrow) entering a SLN (small arrow). This picture demonstrates the typical accumulation of contrast agent within the LN structure.

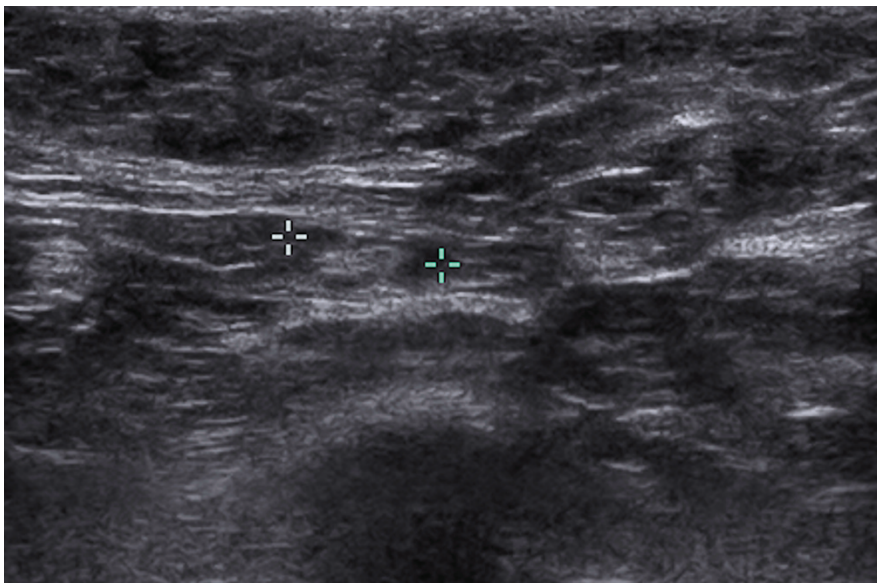

Figure 2: Conventional grey-scale ultrasound image of the SLN (bracketed) visualised in figure 1

axillary SLN can be seen using microbubbles and CEUS. Grey-scale axillary ultrasound is dependent upon the echo-pattern generated by an architecturally defined lymph node but CEUS often identifies lymph nodes as areas of contrast pooling. Once recognised, it is then technically feasible to biopsy the SLN of patients in the breast clinic. Approximately, 93% of SLN can be identified and successfully biopsied in this way [9].

Contrast enhanced ultrasound of the axilla is performed in real time Cadence Pulse Sequencing (CPS) mode with an ultrasound machine that also provides conventional grey-scale, pulse-inversion harmonic grey scale and contrast specific sonographic imaging with live dual images. A high frequency 14-MHz linear-array probe is used and in order to reduce microbubble destruction, low mechanical index values are applied (0.2-0.4). The whole procedure takes about 25 minutes to perform and does not cause patient discomfort. Occasionally, mild erythema is noted at the site of injection but to date, the incidence of genuine allergic reaction to intradermal ultrasound contrast agent is probably very low.

For the patient, the advantage of enhanced pre-operative axillary staging using CEUS is clear. If they are found to have SLN metastases on a core biopsy, they can choose to have a primary ALND. For those who are not found to have SLN metastases, they can be reassured that their likelihood of SLN metastases being subsequently found after a surgical SNB is only 8% [9].

For the breast radiologists, there is a small learning curve associated with the use of microbubbles and CEUS. The technical challenge lies mainly with achieving a successful core biopsy of the identified SLN. However, the skills required to carry out enhanced pre-operative axillary staging are only a minor modification of the competences required for routine breast ultrasound work.

Conclusions

As the debate on axillary conservation continues, there may come a time when breast cancer patients with presumed or even confirmed low volume axillary metastases are treated with limited axillary surgery and systemic therapy. Intradermal microbubbles and CEUS can identify SLN in patients newly diagnosed with breast cancer. Once identified, it is also now mechanically possible to remove SLN with a percutaneous device in the breast clinic. Thus in the near future, histologically confirmed pre-operative diagnosis and staging may be readily achievable for breast cancer patients. This information may allow patients and clinicians to make important treatment decisions much earlier in the patient pathway. ■

References

1. Veronesi U, Paganelli G, Viale G, et al. *A randomised comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.* N Engl J Med 2003;349:546-53.
2. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. *Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis.* JAMA 2011;305:569-75.
3. Atkins H, Hayward JL, Klugman DJ, Wayte AB. *Treatment of Early Breast Cancer: A Report after Ten Years of a Clinical Trial.* BMJ 1972;2:423-9.
4. Fisher B, Redmond C, Fisher ER. *Ten year results of a randomised clinical trial comparing radical mastectomy and total mastectomy with or without irradiation.* N Engl J Med 1985;312:674-81.
5. Alvarez S, Anorbe E, Alcorta P, Lopez F, Alonso I, Cortes J. *Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: A systematic review.* Am J Roent 2006;186:1342-8.
6. Robertson IJ, Hand F, Kell MR. *FDG-PET/CT in the staging of local/regional metastases in breast cancer.* Breast 2011;20:491-4.
7. Balzer PA, Dietzel M, Burmeister HP, Zoubi R, Gajda M, Camara O, Kaiser WA. *Application of MR mammography beyond local staging: is there a potential to accurately assess axillary lymph nodes? Evaluation of an extended protocol in an initial prospective study.* Am J Roentgenol 2011;196:641-7.
8. Goldberg BB, Merton DA, Liu JB et al. *Sentinel lymph nodes in a swine model with melanoma: contrast-enhanced lymphatic US.* Radiology 2004;230:324-30.
9. Sever AR, Mills P, Weeks J, Jones SE, Fish D, Jones PA, Mali W. *Pre-operative needle biopsy of sentinel lymph nodes using intradermal microbubbls and contrast-enhanced ultrasound in patients with breast cancer.* Am J Roentgenol 2012;199:465-70.