Lymph Node Imaging: A Clinical Perspective

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The assessment of locoregional lymph node spread is a key prognostic factor in breast cancer, colorectal cancer and other solid tumours. Breast cancer is a common cancer with over 1,000,000 news cases per annum worldwide. Surgical staging of the axilla is a key factor in defining prognosis and determining the need for adjuvant chemotherapy. Although there have been significant advances in imaging the breast, there is no readily available, and reliable method of imaging the axillary basin that can avoid the need for sentinel node biopsy.

Sentinel lymph node biopsy

Sentinel node biopsy (SLNB) relies on the observation that the sentinel node(s) are the first and most likely place for lymph node metastasis and reliably reflect the likely presence of further metastases in the remaining lymphatic basin. The sentinel lymph node (SLN) was first described by Cabanas (1) when penile lymphangiography for cancer consistently identified one node, which first received lymphatic flow. This was histologically confirmed to be the first, and in some cases the only site, of metastatic spread of penile cancer. The technique of SLNB, was popularized by Morton et al. (2) who demonstrated that SLNB could be performed using patent blue dye to stage cutaneous malignant melanoma. Giuliano et al. (3), later used peritumoural injection of isosulphan blue dye to perform SLNB in breast cancer. Veronesi et al. (4) demonstrated that SLNB can be undertaken using radioisotope (technetium-99m labelled albumin) with the additional advantage of a hand-held gamma probe to guide the surgeon intra-operatively. Histological examination of the SLN identifies those patients with an involved SLN who require an axillary lymph node dissection (ALND), whilst sparing those with a normal SLN the further morbidity of more extensive surgery. Sentinel nodes that have macrometastases (>2mm) or micrometastases (≤ 2mm) are regarded as involved and an ALND recommended. Anatomically, the axillary basin is divided into 3 levels by the pectoralis minor muscle. Most SLNs are found below and lateral to the pectoralis minor, within level 1. Axillary node clearance commonly involves excision of axillary levels 1-2 (including level 2 nodes deep to pectoralis minor) or levels 1 – 3 (including level 3 nodes which lie above and medial to pectoralis minor).

Sentinel node identification rates are very high and the combination of blue dye with radioisotope improves detection rates for SLNB to greater than 90% with a false negative rate of less than 10% (5). Although SLNB causes significantly less morbidity than ALND (lower risk of lymphoedema, nerve injury, injury to axillary vein and shoulder stiffness) and requires a shorter hospital stay, it is an invasive procedure with complications (including about a 5%

risk of lymphoedema) and over 50% of patients are subsequently found to have negative sentinel node (6,7,8,9). It is also well recognised that a lymph node completely replaced by tumour, can divert the transition of tracer or blue dye to uninvolved nodes which may also result in a false-negative result. There is thus a clinical need to develop reliable pre-operative imaging technique for axillary staging of breast cancer.

Pre-operative axillary imaging

Axillary ultrasound (US) is now used routinely in patients with newly diagnosed breast cancer. It is cheap, non-invasive and readily available in the clinic. Axillary nodes can be characterized as normal, indeterminate, suspicious, or metastatic. Recognised sonographic criteria for metastatic nodes include a thickened cortex, cortical lobulation and loss of hilar fat when compared with other ipsilateral or contralateral lymph nodes (10). Pre-operative ultrasound-guided fine needle aspiration cytology (FNAC) or core-biopsy can identify patients with a histologically involved axilla who require ALND rather than SLNB. Over 35% of patients with an involved axilla (11) can be diagnosed pre-operatively but identification rates vary in the literature reflecting operator variability. Axillary ultrasound is more sensitive in patients with symptomatic cancers than with screen-detected cancer(12) and is also more likely to detect macrometastases rather than micrometastases. Microbubble contrast agents have been demonstrated to help identify the SLN when injected subcutaneously(13) but are of limited value in terms of improving characterization of nodes. After axillary ultrasound and biopsy, those remaining patients who undergo SLNB are even more likely to have a negative sentinel node biopsy.

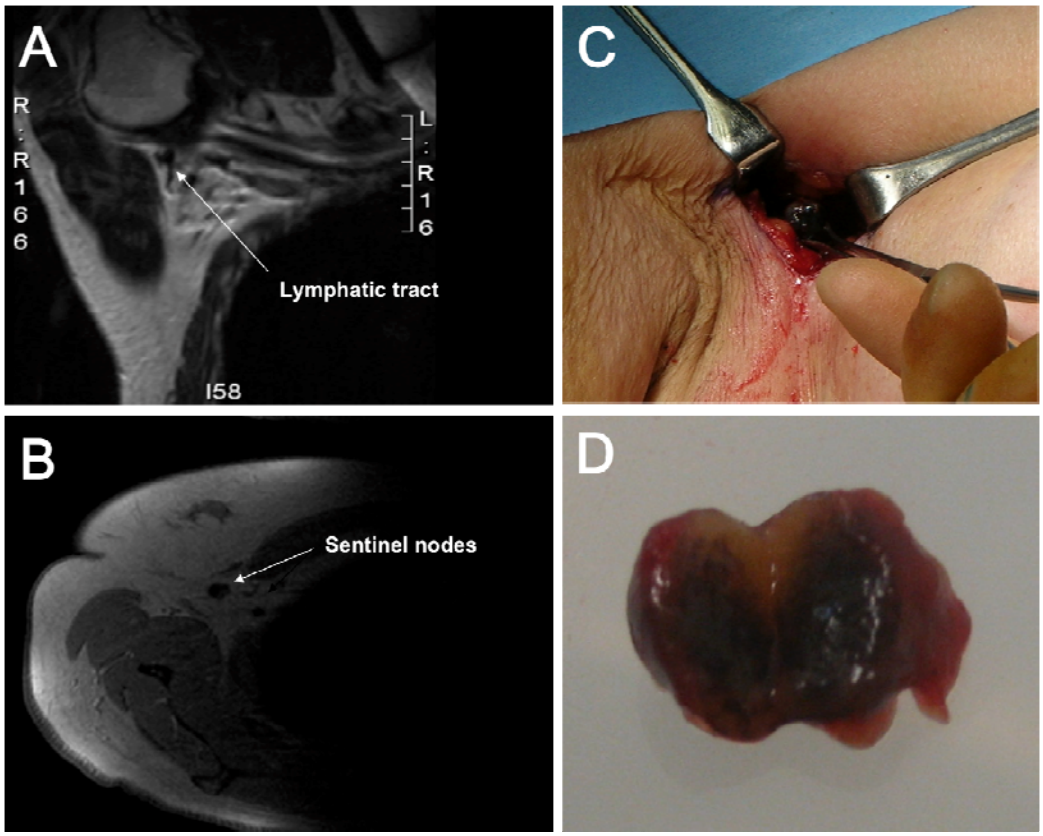
Pre-operative lymphoscintigraphy using technetium-99m labeled nanocolloid can confirm the presence of a sentinel node but anatomical spatial resolution is very low. In view of the high lymph node detection rates of SLNB, many centres no longer perform routine lymphoscintigraphy.

Positron emission tomography (PET) integrated with computed tomography (CT) scanning (PET/CT) can detect over 20% of patients with an involved axilla pre-operatively with a 77.1% sensitivity and 100% specificity (14). PET/CT is however not widely available, is expensive and exposes patients and clinicians to ionising radiation.

Modern magnetic resonance imaging (MRI) can now be undertaken rapidly with a high spatial resolution. Interestingly, the need to achieve complete coverage of the breast can lead to incomplete coverage of the axillary basis, omitting axillary level 3 nodes. Furthermore, although the spatial resolution of MRI is within reach of the clinical requirement to detect macro and micrometastases ($\leq$ 2mm), dynamic protocols are sometimes set to slice thicknesses of over 3mm to reduce acquisition time and achieve complete coverage. Developments in nanomedicine are generating MRI contrast agents including superparamagnetic iron oxide (SPIO) and ultrasmall SPIO (USPIO), which have been the

focus of much attention for imaging lymph nodes. Following intravenous administration SPIOs and USPIOs are taken up by lymph nodes where they have a negative (darkening) effect on MRI with T2 and T2*-weighted protocols. Involved axillary lymph nodes can be identified 24 hours post-injection, with a sensitivity of 82% and specificity of 100% (15). It is also feasible to perform dual USPIO contrast enhanced MRI and PET scanning of the axilla, but studies to date are too small to draw any conclusions (16). Using an SPIO (Endorem, Guerbet, Paris) injected directly into the breast of women with breast cancer before surgery, we were able to visualize the sentinel node on MRI (figure) and later find the sentinel node intra-operatively using a hand-held magnetometer (SentiMag, Endomagnetics, UK). This is very promising entirely novel method that enables the surgeon to identify and excise a node based on small changes in magnetic fields (17). Once found, the SLN is also identified by its black colour caused by SPIO deposition within the node.

Figure: Contrast enhanced MRI following subcutaneous injection of SPIO (Endorem, Guerbet, Paris) into the breast, demonstrating a lymphatic tract (A) and a sentinel node (B). At operation (C) the node is seen to be black with macroscopic deposition of SPIO, seen on cross-section (D).



Nanotechnology and nanomedicine are generating several novel contrast agents (18,19,20). Further novel MRI contrast agents that are also more tissue-specific may even offer the hope of synchronous diagnosis and treatment, in the future. Most of the research in this area is still

at the bench side as clinical translation is restricted by factors including toxicity, difficult regulatory approval processes and need for significant resources.

Conclusion

Assessment of locoregional lymph node spread, is a key prognostic indicator in many cancers including breast cancer. SLNB is now the gold standard for staging the axilla in patients with early breast cancer and a clinically and radiologically negative axilla. Pre-operative ultrasound and ultrasound-guided biopsy can identify patients with an involved axilla who are not suitable for sentinel node biopsy. However, sentinel node biopsy is an invasive procedure with associated morbidity and a significant number of patients with a negative axilla, are still undergoing sentinel node biopsy. There is thus a clinical need for new axillary imaging modalities with a high enough spatial resolution to detect macro and micrometastases. This is within reach of MRI and studies using SPIO and USPIO are very promising but too small to reach any clinically relevant conclusion.

Nanotechnology and nanomedicine are generating several novel contrast agents. Further research is needed to select the most promising clinical application and expedite translation from the bench to the bedside. In the future we may even be able to perform SLNB as a diagnostic procedure or avoid unnecessary SLNB altogether, in patents with a negative axilla.

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