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The sentinel node in breast cancer: an update

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Abstract

There has been rapid acceptance of sentinel lymph node biopsy into the management of breast cancer over the past 10 years. This article seeks to highlight the controversies and to summarise its current status.

Keywords: *Sentinel lymph node; breast cancer.*

Introduction

The prognosis of breast cancer is determined primarily by axillary lymph node status[1–3]. Axillary lymph node dissection (ALND) surgery carries a significant morbidity with complications such as lymphoedema, pain, numbness and limited shoulder movement[4–6]. The sentinel node is the first draining node on the direct drainage pathway from the primary tumour site[7]. If the sentinel node is positive there is a 40% risk that higher order nodes may also be involved with metastatic disease[8]. Sentinel lymph node biopsy (SLNB) is a minimally invasive alternative to ALND for nodal staging in breast cancer. The technique assumes orderly progression of tumour spread to the regional nodes; and biopsy of the first node in the lymphatic chain at risk for metastasis should therefore reflect involvement of the remaining nodes. Although no results from randomised trials validating SLN biopsy in breast cancer are yet available, excellent clinical outcomes using different protocols have been achieved in over 20 000 patients studied to date[8]. Comparison of the results of SLNB with ALND has shown that the sentinel node is representative of the presence or absence of metastases in the remainder of the nodal basin (with a false negative rate of less than 2% in most series)[9–13]. Other prospective studies have also validated the concept[14–18].

Technical issues

Lymphoscintigraphy

A large choice of dyes and radiopharmaceuticals (usually ^{99m}Tc sulphur colloid) are available. The colloid employed should be of a size to be taken up efficiently and retained within the sentinel node. It has been shown that the highest counts in recovered sentinel nodes were from 100–200 nm albumin colloid particles[19]. Filtered ^{99m}Tc sulphur colloid (100 nm filtered) has a faster transport rate to the regional nodes and lower radiation dosimetry. As a result it is the preferred choice if performing surgery within 2 h of injection[8]. The sentinel node is more successfully identified with radiopharmaceuticals than with dyes but a combined technique using both maximises the potential of accurate staging[15,20–22]. Preoperative lymphoscintigraphy enables faster location of radioactive nodes at surgery and the combined approach results in identification and harvesting of more nodes[23,24]. The injection technique seems to matter little as axillary nodes stained blue by intradermal, peritumoural, subdermal, periareolar and subareolar injections identify the same nodes[21,25–27]. It also appears that there is often more than one sentinel lymph node and using dual agents will assist in identifying all sentinel nodes. In a prospective multi-institutional study of 1436 patients, the false negative rate was 14.3% if a single sentinel lymph node was removed compared with 4.3% if multiple sentinel lymph nodes were removed indicating that there is often more

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than one sentinel node[28]. Despite variation in mapping techniques results have been similar worldwide with sensitivity and diagnostic accuracy rates greater than 95% and false negative rates ranging from 0 to 10%[29]. Some breast cancer programmes do not routinely utilize preoperative lymphoscintigraphy because of the added time, expense and the fact that the surgical decision making can be performed intraoperatively[8]. Others advocate the concept of the triple technique comprising preoperative lymphoscintigraphy, and injection of radiotracer with the use of a hand probe and blue dye[30]. Variables such as availability of resources, patient numbers, level of competence and local working practices mean that no standard protocol exists. Nonetheless, it is recognised that identification of the sentinel node in greater than 96% of patients and a false negative rate of less than 5% is a desirable outcome[10,31,32]. Using lymphoscintigraphy the surface location of the sentinel node can be marked with some centres marking all sentinel nodes visualised[33,34]. Although high resolution collimators should be used, a medium energy collimator will suffice[34]. The camera is placed as close to the patient as possible and images should be acquired in at least two planes. If the site of injection is close to the nodes, shielding may be necessary to visualise the sentinel node. In one centre analysing the results of 640 patients, 94% demonstrated a sentinel node in the ipsilateral axilla but 46% also had sentinel nodes outside the axilla[34]. The most important site of extra-axillary drainage was to the internal mammary nodal chain and 40% of patients demonstrated a sentinel node in this area[34]. In 5% of patients, drainage was exclusively to extra-axillary sentinel nodes. Preoperative lymphoscintigraphy enables these nodes to be identified.

Site of injection

Several theories exist concerning lymph node drainage in the human breast[35]. Although Sappey described flow to the subareolar plexus and then to the axilla, this view was not universally accepted[36]. An alternative drainage pattern proposed direct drainage to the ipsilateral axilla avoiding the subareolar plexus[35,37]. A recent study of 145 dynamic lymphoscintigrams using both intraparenchymal and subdermal injections was unable to visualise the subareolar plexus indicating that it may not act as a conduit to the ipsilateral axilla[38]. Variable drainage patterns from injections of localising agents into the subareolar plexus, subdermal breast tissue and the deep breast parenchyma have been demonstrated by several groups[39–42]. Seven sites of injection have been described (peritumoural, subdermal, periareolar, intratumoural, intradermal, subareolar and subtumoural) and one of the factors dictating choice is the intention to locate internal mammary nodes in addition to axillary nodes[43]. Peritumoural injections were the first type of injection used[44,45]. Some groups claim better success with intradermal injections than with peritumoural technique when sulphur colloid and blue dye are used[46]. Internal mammary node drainage occurs in a significant proportion after peritumoural injection but not after intradermal injection[47]. However, the intradermal technique has been shown to identify the SLN in the axilla with a frequency of 98% compared with 90% for peritumoural parenchymal technique[10,48]. Periareolar injections are made just outside the areolar border at four equally spaced sites. The injections are subdermal though a single subareolar injection lined up with the tumour can also be used[26,27,49]. This technique militates against extra-axillary node identification but is easy and efficient[50–52]. Using a combination of radioisotope and blue dye, the SLN was identified successfully in 98% of cases with no false negative results[53]. Subareolar injection of blue dye alone has been shown to demonstrate a sentinel lymph node in 98% of cases with no false negative sentinel nodes[50,54]. Likewise, it has been shown that subareolar injection of technetium is equivalent to peritumoural injection of blue dye[55,56]. One centre uses the combined intraparenchymal and subdermal injection technique because it more accurately reflects all lymphatic flow from breast tumour[38]. Intraparenchymal injections consistently visualise a more diverse pattern of lymph flow. In particular, the internal mammary chains and supraclavicular nodes are commonly seen after intraparenchymal injection but rarely after subareolar or subdermal injections. Peritumoural and subdermal injection of ^{99m}Tc sulphur colloid combined with periareolar injection of isosulphan blue dye is advocated by another group with extensive experience[32,57–59]. Overall, the identification rate, accuracy and predictive value of sentinel node biopsy seem to be unaffected by the site of injection though a difference may become apparent with long-term follow-up that examines the pattern of axillary failure correlated with the injection site[13].

When should injection be performed?

Comparable accuracies have been shown for same day and day before surgery radioisotope injections[60,61]. After injection breast massage may be performed to augment lymphatic flow[62]. However, concern exists that tumour cells might be transported from the primary tumour into the lymphatics. Pressure within the lymphatics can increase up to 22-fold following external massage and transport of tumour cells to the lymphatic spaces has been demonstrated[63–65]. However, isolated tumour cells are not true metastases and do not have malignant potential. Intraoperative injection is little used as it requires transfer of radioisotope to the operating theatre, is not as reliable and is complicated by radiation safety issues.

Pathology

The role of the pathology laboratory is pivotal to the success of the procedure. In particular the development

of multisectioning and immunohistochemistry (IHC) staining techniques has been reported to increase the rate of detection of malignant disease by up to 33%[66–68]. IHC can be particularly beneficial in patients with invasive lobular cancer[69,70]. Trials currently in progress aim to determine the significance of IHC detected micrometastases in patients treated by conventional pathological criteria[71]. It has been shown recently that patients with favourable breast cancer histology have only a small risk of axillary sentinel lymph node metastases and that biopsy is not necessary in all these patients[72].

Radiation safety

Several papers have discussed various aspects of radiation safety associated with the sentinel node in detail[73–78]. Radiation doses are low and no additional procedures are required for the protection of staff. The procedure can be performed safely during pregnancy as the foetal dose is very low.

Clinical issues

The procedure is not contraindicated in patients with clinically palpable axillary nodes[18]. Relative contraindications include prior axillary surgery and subglandular breast implants. In one centre, more than 50 patients with subpectoral implants have been associated with 100% SLN identification success rate and no clinically detected recurrences in patients with negative SLN biopsy[8]. For patients with a primary tumour greater than 4 cm, the success of SLNB shows little difference to those with smaller tumours[12]. In patients with multifocal breast cancer, sentinel node identification has been reported in 94% and is an accurate predictor of nodal status[79]. This type of cancer favours a periareolar or subareolar injection protocol. SLNB performed following excisional biopsy demonstrates satisfactory results[29,80]. Patients with ductal carcinoma-*in-situ* (DCIS) have an excellent long term prognosis (98% survival) but 10%–29% of these patients will have invasive cancer at definitive surgery[81–87]. Analysis of resected nodes from patients who had negative axillary surgery previously, demonstrated micrometastases in 13% of nodes but none in patients who had disease recurrence[88]. This would indicate that SNLB is not necessary in these patients.

False negative rate

The false negative rate is the percentage of node positive patients who are missed by mapping[8]. In one centre there has been no axillary recurrence (mean 5 years) following a negative node biopsy in 1914 patients[8]. Data from case control studies to date indicate SLN biopsy to be highly predictive of axillary node status with a false negative rate of less than 5%[89]. Reasons for false negative results are attributed to changes in surgical personnel, difficult lymph node location and absence of a thorough histological study[90]. Factors militating against sentinel node identification are increasing age and body mass index[91]. A review of ten large observational studies revealed just ten axillary recurrences in 2664 patients (0.4%) who did not undergo ALND following negative SLN biopsy[43]. A large recent study comprising 4008 patients and a median follow-up of 31 months had an overall axillary recurrence rate of 0.25%[92]. A further study in 234 patients (median follow-up 42 months) did not find an increased rate of axillary recurrence in patients with negative SLN or SLN micrometastases[93]. As the axillary recurrence rate should not exceed that seen after conventional axillary clearance surgery (1.0%–2.3%), the figures quoted above compare very favourably[94–96].

Internal mammary and intramammary lymph nodes

Intramammary nodes with metastases have been documented as independent predictors of poor outcome for patients with breast cancer[97]. In one centre analysing the results of 640 patients, 94% demonstrated a sentinel node in the ipsilateral axilla and 46% also had sentinel nodes outside the axilla[34]. In 5% of patients drainage was exclusively to non-axillary sentinel nodes. The most important non-axillary drainage was to the internal mammary nodal chain and 40% of patients demonstrated a sentinel node in this area[34]. Sentinel lymph node biopsy of internal mammary nodes is associated with a low morbidity and has been shown to improve staging and change treatment strategy[98,99]. Proponents of evaluating internal mammary nodes argue that this supports lymphatic mapping as it provides more accurate staging although its impact on outcome is less clear[100,101]. Nonetheless, it has been demonstrated that metastases in the internal mammary nodes influence survival in a manner comparable to that of metastases in axillary lymph nodes[102]. A review with 30 years of results demonstrated that patients with isolated IMN disease have a prognosis equivalent to that of patients with isolated axillary metastases[103]. A combination of metastatic disease in both axillary and internal mammary nodal chains has an especially poor prognosis with a 10-year survival of 37%[104]. Internal mammary nodes identified on preoperative lymphoscintigraphy require histopathological confirmation of disease before therapy is commenced[105]. Internal mammary nodes are best identified when peritumoural, intratumoural or subtumoural injections are made with some reports visualising these nodes in 10%–30% of patients whereas subdermal, intradermal, periareolar or subareolar injections result in much less frequent visualisation of these nodes[47,58].

Micrometastases

Micrometastases are defined as tumour deposits in nodes ranging from 0.2 to 2 mm with cells less than 0.2 mm known as isolated tumour cells[106]. Despite

the evidence of some retrospective studies there is controversy regarding the prognostic significance of micrometastases found only by immunohistochemistry staining, particularly when only isolated tumour cells are found[71]. A literature review on the clinical significance of micrometastases concluded that they were associated with a poorer prognosis than that associated with no axillary involvement[107]. In a study involving a 15-year follow-up on almost 100 patients and 1539 axillary lymph nodes with pT1 breast cancer determined that half of the patients developed distant metastases[108]. However, recent studies involving 234 patients and 84 patients (median follow-up 42 and 40 months, respectively) showed that micrometastases were not associated with an increased risk of axillary recurrence or that outcome was significantly affected by the presence of micrometastases[93,109]. Micrometastases are not reliably detected by FDG-PET imaging[110,111].

Neoadjuvant therapy

In published work to date the SLN identification rate has ranged from 84% to 97% implying that the accuracy of sentinel node biopsy is not influenced by neoadjuvant therapy[112–121]. Questions remain as to whether all nodes respond equally to therapy and a high false negative rate (up to 33%) has been reported in some of these series. Pending further clarification, it is still probably best to perform SLNB prior to commencement of neoadjuvant therapy.

Summary

Lymphatic mapping for breast cancer is rapidly becoming the standard of care but there is no single study that demonstrates conclusively which particular sentinel node protocol is best for a specific patient. The results from three multicentre trials sponsored by the National Cancer Institute (due to report in 2007) attempting to answer some of the issues discussed above are eagerly awaited.

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