Review

Sentinel node biopsy in breast cancer revisited

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Abstract

The axilla has long been a focus of clinicians’ attention in the management of breast cancer. The approach to the axilla has undergone dramatic changes over the last century, from radical and extended radical excisions, through the introduction of sentinel node biopsy for node negative patients to the current situation where selective management of those with nodal involvement is being introduced.

The introduction of lymphatic mapping and sentinel node biopsy in the 1990’s has been key to the major changes that have occurred. In less than 20 years it has moved from a hypothesis to a situation where it is the default approach to almost all clinically node negative patients and is being considered in other situations where axillary clearance was previously considered standard. This article reviews the development and introduction of sentinel node biopsy, its current uncertainties and limitations, and possible future developments.

Introduction

Axillary nodal surgery has been an important part of treatment for invasive breast cancer since Halsted and others demonstrated that a complete axillary dissection as part of the radical mastectomy resulted in very low rates of loco-regional recurrence. Axillary lymph node status remains an important prognostic factor and determinant of adjuvant therapy. The presence and number of involved lymph nodes is the best indicator of the risk of distant recurrence and death from breast cancer. The status of axilla has also been historically used to direct the need for and choice of adjuvant chemo/radiotherapy treatment. Excision of involved axillary lymph nodes has traditionally been considered essential in maximizing loco-regional control.

In the National Surgical Adjuvant Breast Program NSABP B04 study, patients treated with radical mastectomy, total mastectomy with axillary radiation and total mastectomy alone were compared and followed for 25 years, with similar overall survival in all groups. Axillary surgery or irradiation was found to lead to significant improvement in loco-regional control with 5% axillary recurrence, compared to 20% in population who did not undergo any axillary treatment.
Notably, the rate of axillary recurrence in the group without axillary treatment was substantially less than the incidence of axillary nodal metastasis in the group undergoing radical mastectomy – indicating that not all pathologically involved nodes are destined to become clinically evident. Despite evidence from the NSABP-B04 of the lack of impact of axillary dissection on overall survival, it remained a routine part of surgical management of invasive breast cancer until the 1990s.

**Sentinel node biopsy (SNB)**

There is significant morbidity associated with ALND (Axillary lymph node dissection), including seroma formation, impaired shoulder function, neuropathy and in particular arm lymphoedema. Some level of lymphoedema was reported by 16%–28% of patients post-operatively.4–6 As the size of breast cancers diagnosed through screening programs reduced, the proportion of elective and non-therapeutic axillary lymph node dissections increased. For every 100 ALNDs in patients with T1 and T2 tumours, 70 will not contain cancer7 and the scene was set for a less invasive method of staging the clinically node negative axilla.

The concept of a sentinel node was first introduced by Cabanas following his work on carcinoma of the penis8 and then Morton2 developed and demonstrated the accuracy of lymphatic mapping and sentinel node biopsy in malignant melanoma. In the early 1990s it was introduced in breast cancer, with series from Giuliano, Krag and Veronesi10–12 showing that sentinel node biopsy using blue dye and/or radioisotope was feasible and accurate in patients with clinically node negative breast cancer. Several randomized controlled trials have compared the difference in morbidity, recurrence and survival rates between ALND and SNB with completion ALND when the SLN was found to be involved. Veronesi et al.13 prospectively randomized 516 patients with a similar incidence of positive SNB was noted in both groups (32.3% and 35.5%). Overall accuracy of SNB was 96.9%, with sensitivity of 91.2% and the specificity of 100%. Patients who underwent SNB had less pain and better arm mobility compared to those having ALND. In the patients who did not have ALND, there was only one axillary recurrence and short term survival was the same as the patients who had ALND. The NSABP B-32 trial of over 5600 patients having SNB followed by ALND or SNB alone found that the accuracy of SNB was found to be 97.1%, with a false negative rate of 9.8%, which was dependent on tumour location, type of biopsy and number of sentinel lymph nodes removed. There was an overall survival of 91.8% in SLNB then ALND group and 90.3% in the SLNB only group. No statistically significant differences were observed in local recurrence, overall survival, disease free survival or regional control between the two groups.14

The multicentre randomized ALMANAC trial of 1031 clinically node negative patients found better quality of life (QOL) and significantly better arm functioning was found with SNB ($p < 0.003$) than standard ALND.15 The Royal Australasian College of Surgeons (RACS) SNB vs Axillary Clearance (SNAC) trial16 of around 1000 patients had a strong focus on QOL. There was a statistically significant increase in arm volume in ALND group compared to SNB. QOL was also found to be better in SNB group with lower rating of arm swelling, symptoms and dysfunction but not disabilities, with no differences in oncological outcomes.16

When carried out by an experienced multi-disciplinary team, a negative sentinel node is strongly suggestive of a disease free axilla, with a false negative rate of between 5 and 10% and a very high accuracy rate, which depends on the underlying rate of nodal positivity.17 Consensus guidelines from ASCO, NCCN and NICE amongst others recommend SNB for patients with clinically negative lymph nodes.18

**SLNB in special circumstances**

**SLNB in multifocal/multicentric breast cancer**

The randomised trials supporting SNB were conducted on unifocal small size tumours while large and multicentric cancers were excluded. Following the success of SLNB the procedure has been applied to patients with larger, multifocal and multicentric cancers. In these circumstances SLNB identification rate was found to be in the region of 91–94.7% and false negative rate 8.8%.19,20 As the rate of nodal metastasis is higher in these cancers, the sensitivity, negative predictive value, and overall accuracy are somewhat lower than for unifocal smaller cancers.21 Despite this, a low rate of regional recurrence has been reported when relying on SLNB, suggesting it is reasonable for these patients.22 The Royal Australasian College of Surgeons’ SNAC2 trial is specifically assessing the question of SLNB in large and multifocal cancers.

**SLNB in DCIS**

Prior to the introduction of SLNB, axillary assessment was considered unnecessary in patients with DCIS, as the morbidity of axillary dissection outweighed any benefits. The lower morbidity of SLNB has changed the risk/benefit analysis, and the main question relates to which patients with DCIS on core biopsy should have SLNB as part of their initial surgery. In a study of 854 patients SLN metastases were detected in 12 (1.4%) DCIS patients. In 7 cases only micrometastases (<2 mm) were diagnosed and in 5 cases macro-metastases.23 Kurniawan et al. analysed a large group of patients with DCIS on core biopsy, and found that those with palpable DCIS, and those with microinvasion on core were very likely to have invasive cancer on definitive excision.24 Of the others, patients with mammographic abnormalities >20 mm, those with mammographic findings other than pure microcalcification, and those with a long screening interval were significantly more likely to have invasive cancer in the excised specimen, and there was a trend for those with high grade DCIS to be more likely to have invasion. The authors suggested that SLNB should be used when DCIS is being treated with mastectomy, when the DCIS is palpable or when there is microcalcification, and when 2 or more of the other factors were present.25 Metastasis to the SNL is rare in pure DCIS, it is more often seen when associated invasive carcinoma is found on full examination of the resected lesion.26
SLNB following neoadjuvant chemotherapy

The initial trials of SLNB excluded patients with locally advanced tumours and those who received neoadjuvant chemotherapy. As more neoadjuvant chemotherapy is used, the role of SLNB in these patients has been controversial. Studies of the accuracy and feasibility of SLNB after neoadjuvant chemotherapy suggest that the rate of false negative may be higher.26,27 In a study of 3746 patients with clinically negative T1–T3 breast cancer underwent SLNB, Hunt et al. showed that SLN identification rates were 97.4% in the neoadjuvant group and 98.7% in the surgery first group (p = 0.02). In this study the false negative rates were similar between groups – 5.9% in neoadjuvant vs 4.1% in the surgery first group (p = 0.39), with the conclusion that SLN surgery after chemotherapy is as accurate for axillary staging as SLN surgery prior to chemotherapy.26

A systematic review of 27 studies including 2148 patients found inadequate evidence to recommend SLNB as a routine procedure following neoadjuvant chemotherapy (sensitivity of 90% and false negative rate of 10.5%).29 If neoadjuvant chemotherapy is used to downstage tumours in patients with positive axillary lymph nodes, many surgeons continue to recommend axillary dissection following chemotherapy even if there is a clinical response in the nodal disease, however SLNB may be appropriate for those with negative axillary assessment at presentation. In a meta-analysis of 21 studies Xing et al. found that SLNB is a reliable tool for planning treatment after neoadjuvant chemotherapy.30 The results of the multicentre ACOSOG Z1071 trial were presented in the 2012 San Antonio Breast Cancer Symposium by Judy Boughey, and showed that in certain breast cancer patients who had positive axillary lymph nodes prior to neoadjuvant chemotherapy, SLNB had a false negative rate of 13%. Forty percent of the patients in whom an SLN could be identified had negative nodes after chemotherapy. Depending on how this is interpreted, it may provide a less invasive option for those patients.

Preoperative assessment of axilla

The introduction of SNB meant that a number of patients require two operations to complete axillary staging and surgical management. This led to the investigation of a variety of techniques for pre- or intraoperative assessment of the sentinel node.

Physical examination alone is not reliable, with high false positive (25–40%) and false negative (27–32%) rates.31–35 Preoperative imaging with US, magnetic resonance imaging (MRI)36 and FDG-PET37 have been investigated, with US being the most widely used.

US can detect changes in the size, shape and contours of lymph node, also changes in the cortical morphology and texture that is suggestive of metastases.38–42 The two most important criteria to determine the positivity of nodes is the cortical thickness (>3 mm) and the morphology (a rounded shape, hypoechogenicity, obliteration of the hilum and lobulation).35 Some studies found using the combination of size and morphological criteria to give better results.44

The combination of US and fine needle aspiration cytology in patients with breast cancer was first introduced by Bonnema.43 Specificity of 100% and sensitivity from 80 to 91% have been reported,44 depending on definitions. In general, preoperative assessment is much better at detecting macro-metastatic rather than micrometastatic disease. When the findings are positive, the patient undergoes ALND without having SLNB, which may reduce the number of surgeries.45,47,48

Further studies have indicated higher sensitivity of US FNA with higher grade or size of the primary cancer and extensive nodal involvement. Krishnamurthy et al.39 found 100% detection rate for US FNA with >2 positive lymph nodes, 93% of all those with metastatic size >0.5 cm and just 44% with metastatic <0.5 cm. Bauruah et al.40 found that the sensitivity was 15% in patients with grade 1 cancer compared to 43% with grade 3 cancer. Diepstraten et al. in a recent meta-analysis of preoperative US found that approximately 50% of women with axillary involvement can be identified preoperatively. Some 25% of US FNA negative axillae had a positive SNB.51

Intraoperative assessment of SLNB

Intraoperative frozen section analysis of the SLN is used during surgery in many centres.52,53 The sensitivity of intraoperative frozen section analysis for identifying SLN metastases has been reported to vary from 44% to 95%,4–17 with most series reporting in the range of 60%–75%. Invasive lobular carcinoma may be more difficult to interpret, yet Horvath et al. showed no differences in sensitivity and specificity between invasive lobular and invasive ductal carcinoma.34 Touch imprint cytology of axillary sentinel nodes has also been used with similar sensitivities to frozen section. Depending on local expertise some centres found it to be feasible and a reliable method for evaluating axillary nodes.35 More recently intraoperative molecular analysis using RT-PCR has been reported, and many centres in the UK are using it. The one step nucleic acid amplification (OSNA) whereby the detection of CK19 mRNA using the transcription-reverse transcription concerted reaction (TRC) test as found in many studies and in a multicentre trial to be an accurate and rapid method for detection of SLN metastasis and can be applied as an intraoperative molecular diagnosis in breast cancer patients.56,57 Layfield reviewed the topic of intraoperative assessment of sentinel nodes and concluded that molecular techniques have significant potential.58

Subsequently, a NICE committee report suggested that intraoperative analysis of sentinel lymph nodes using the RD-100i OSNA system had considerable advantages over traditional histopathology testing and had the potential to reduce both clinical complications, and patient anxiety and distress and therefore recommended its use (NICE 7th August 2013).

Micrometastases and isolated tumour cells

The introduction of SNB has allowed pathologists to focus attention on fewer nodes. The use of step sectioning and immunohistochemical (IHC) analysis with antibodies to cytokeratin has resulted in upstaging in approximately
10–20% of patients who might otherwise have had a negative SLN with the detection of micrometastasis (0.2–2.0 mm) and isolated tumour cells and cluster of tumour cells (<0.2 mm). The prognostic significance of isolated tumour cell or micrometastases is questionable. The NSABP B32 study showed that IHC-detected metastases in SLNB were an independent prognostic variable, however the magnitude of the difference in outcome at 5 years was small (1.2%). These data do not indicate a clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes in patients with breast cancer. Importantly the MIRROR study from the Netherlands showed a definite advantage of adjuvant treatment for patients with early breast cancer whose SLN showed isolated tumour cells or micrometastasis.

Predicting non-SNB metastasis after positive SNB

A recommendation to perform a completion nodal dissection when the sentinel node is involved is based on the knowledge that other lymph nodes might be involved. Various studies have identified pathological features associated with the incidence of non-sentinel lymph node involvement after a positive SNB. These include age, primary tumour-related factors (type, size, grade, lymphovascular invasion (LVI) and hormone receptor status) and node related factors (method of detection, size of metastasis, extracapsular extension, number of positive sentinel lymph nodes and number of negative sentinel lymph nodes).

A number of nomograms have been developed to accurately predict the likelihood of non-SLN metastasis. Van Zee et al. from Memorial Sloan-Kettering Cancer Center (MSKCC) proposed the first nomogram in 2003. Parameters were identified after a multivariate logistic regression analysis of a retrospective group of patients. Several studies from variety of centres across have attempted to validate the MSKCC nomogram, with an ROC ranging in between 0.71–0.86, with two studies reporting a poorer performance. Other nomograms have also been developed, which include Tenon model, Cambridge model and Stanford model.

Reports of the outcomes of patients with involved sentinel nodes managed with selective axillary dissection indicate that such nomograms can be valuable clinically.

Future role of completion ALND in sentinel lymph node (SLN) positive patients

Validation that axillary metastasis are limited to the SN in 60–70% of patients overall, and in 90% for low volume involvement (micrometastasis/ITC), raised the possibility of selective completion dissection. The infrequency of axillary recurrence in patients having SNB alone, compared to the number of patients with presumed undissected disease (based on the known false negative rate) indicated that a substantial proportion did not progress to clinically relevant disease. Series of cases emerged where patients with involved SN either chose, or were recommended, to omit the completion ALND, with no apparent detriment to their oncological outcomes. Despite this, there was no high-level evidence on the safety of omitting completion ALND, a retrospective review of SEER data suggested that removal of regional lymph nodes, even if they were interpreted as negative, have a survival advantage and the main randomized study addressing the question of the need for a completion ALND closed early having failed to meet its accrual targets. The presentation and publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 study has provoked controversy around the world regarding the extent to which this is a practice-changing study.

ACOSOG Z0011 was designed as a non-inferiority study comparing completion ALND to no further axillary treatment in patients with limited sentinel node involvement who were to undergo whole breast RT after breast conservative surgery. Patients with T1 or T2 tumours and 1 or 2 involved sentinel nodes without gross extranodal extension were eligible. Its planned accrual was 1900, but it closed early on the advice of the DSMC with 891 patients enrolled due to slow accrual and a low event rate. There was no significant difference in either regional recurrence or disease free survival between the two arms. Five year overall survival was 91.8% in the ALND arm and 92.5% in the SNB alone arm with axillary recurrence rates of 0.5% and 0.9% respectively.

The investigators concluded from these results: “Among patients with limited SN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SNB alone compared with ALND did not result in inferior survival.”

Translation of the results of ACOSOG Z0011 into practice has varied around the world. A number of major US cancer centres have altered their practice, but many surgeons and MDTs have been more cautious. There have been a number of concerns raised, some relating to the fact that the study did not meet its accrual targets, others to the nature of patients actually taking part in the study (as opposed to those who were potentially eligible for the study), and others to the extent of other therapies the patients in the study received.

Statistical analysis suggests that with the results found in the study of 891 patients, it is next to impossible that even if the trial had accrued its planned 1900 patients that SNB alone would have been found to be inferior. It is therefore appropriate to conclude that, in the group studied, the authors’ conclusions are correct. It is critical to note that the patients participating in the study were not a true reflection of the group who were potentially eligible. Around 70% of the cancers were T1, 82% ER positive, 40% had micrometastatic disease in the SN and 96% received some form of adjuvant systemic therapy. 27% of completion ALND specimens contained additional nodal disease. Thus it was effectively a study of heavily treated low risk patients. The requirement for all patients to receive adjuvant radiotherapy suggests that the therapeutic effect of RT was considered potentially important. Details on the extent of radiotherapy actually received by patients in the study are seen by some as important to assessing the generalizability of the ACOSOG Z0011 study results.

Confirmation that not all patients with involved SNs require completion axillary dissection came from the IBCSG B23 study, that randomized over 900 patients with
micrometastases to completion ALND or not. This study included about 10% of patients with mastectomy, and showed no clinically significant differences in oncological outcomes.

It is important to note that in the MIRROR study, the regional recurrence rate was 5.6% at 5 years for those with micrometastases not receiving further axillary treatment, 1% in those receiving ALND, and 0 in those receiving axillary RT. A doubling in tumour size, high grade and negative hormone receptor status were strongly and significantly associated with increased regional recurrence rate, although there large confidence intervals around these factors. This study raises a precautionary note about doing to further axillary treatment if no systemic therapy is being considered.61

The AMAROS trial randomized SLN positive patients with cT1-2N0 breast cancer having breast conservation or mastectomy to axillary clearance or axillary radiotherapy. There were no significant differences at 5 years in disease free (86.9% vs 82.7%; \( P = 0.1788 \)) or overall survival (93.3% vs 92.5%; \( P = 0.3386 \)) with more lymphoedema in the surgery group (28% vs 14%).65 Analysis of adjuvant systemic therapy in the two arms of the AMAROS trial was analysed, suggesting that absence of knowledge regarding the extent of nodal involvement appears to have no major impact on the administration of adjuvant systemic therapy.66

However, the results of AMAROS, and those of the NCIC MA20 study that suggest patients with node positive breast cancer treated with additional regional nodal irradiation have improved disease free survival,65 indicate that further analysis and clinical trials will be needed to precisely define the role and nature of regional therapy in patients with positive sentinel nodes.

**Summary**

Axillary management has rapidly evolved in the last 20 years. For some 90 years after Halsted’s seminal publication, complete axillary dissection was standard for most patients with invasive breast cancer. Since the early 1990’s, sentinel node biopsy has been developed, proven and widely introduced for the management of most clinically node negative patients. A variety of techniques can be used for pre- or intraoperative assessment of the sentinel node, and mathematical models can predict the likelihood of non-sentinel nodal involvement.

The current key question is identification of patients with involved sentinel nodes who either do or do not require further axillary treatment. While the findings of Z0011 trial question the role of ALND after positive SNB, further evidence is required before the optimal management of various groups of patients with involved sentinel nodes can be considered resolved.

**References**


