



In patients with micrometastases in sentinel lymph node biopsies, involvement of the non-sentinel lymph nodes cannot be predicted by clinicopathological variables

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Background: The sentinel lymph node biopsy (SLNB) procedure is long considered as an accurate method of staging the axilla for axillary involvement in early stage breast cancer. The question remains as to whether patients with micrometastases should undergo axillary clearance. We aimed to assess the indicators for positive non-sentinel lymph nodes (SLN) following completion axillary lymph node dissection (CALND).

Methods: We retrospectively analysed our experience of SLNB between July 2008 and July 2013. A total of 1,152 breast cancer patients underwent SLNB based on lymphoscintigraphy, intra-operative gamma probe detection, and blue dye mapping using 99m Tc-nanocolloid and Patent Blue V injected peri-areola. Statistical analysis was performed using Fisher's exact and χ^2 for categorical data.

Results: Out of 1,152 SLNBs performed, 224 (19.4%) were positive for metastatic disease; macrometastases in 150 (67.0%), micrometastases in 72 (32.1%) and isolated tumour cells (ITC) in 2 (0.9%). CALND was not performed in 20 cases (9 macrometastases, 10 micrometastases, and 1 ITC), largely due to concerns regarding fitness for anaesthesia. On univariate analysis, positive non-SLN in CALND for patients with micrometastases on SLNB was not predicted by grade (G0–G2, 6/43; G3; 3/19; $P=0.565$), size of primary breast tumour (<40 mm, 8/58; ≥ 40 mm, 1/4; $P=0.475$), lymph vascular invasion (5/30 vs. 4/31; $P=0.503$), age (<50 years, 3/24 vs. ≥ 50 years, 6/38; $P=0.496$), or number of positive SLNB.

Conclusions: In our series, 14.5% (9/62) of patients with micrometastases had positive non-SLN on CALND, which was not predicted by any clinicopathological characteristics. However, it is important to inform our patients that 14.5% of patients with micrometastases on SLNB may have positive non-SLN.

Keywords: Breast cancer; sentinel lymph node biopsy (SLNB); micrometastases; macrometastases; completion axillary lymph node dissection (CALND)

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Introduction

Each year, about 54,900 women in the UK are diagnosed with breast cancer, that's around 150 every day and the most of them (81%) undergo surgery (1). There is strong evidence that in the early stages of breast cancer, sentinel lymph node biopsy (SLNB) can accurately stage the axillary disease leading to low axillary recurrence rates, comparable survival and reduced morbidity when compared with axillary dissection (2,3).

SLNB has showed its effectiveness in reducing the risk of lymphoedema, shoulder pain, sensory deficits, and surgical site infection than axillary node clearance (ANC). Quality of life is also found to be superior in patients who undergo SLNB only (4). These results have led this technique to become a treatment of choice and has become a standard technique around the world and the Department of Health in the UK (5).

It is now an accepted rule that patients who have positive sentinel lymph node (SLN) require further treatment either Axillary node clearance or Radiotherapy. But patients whose SLNB is negative do not require any further axillary specific treatment.

The current UK National Institute for Health and Care Excellence (NICE) guidelines (6) recommend that ANC or axillary radiotherapy (ART) for women with early stage breast cancer with one or two positive sentinel nodes. This recommendation assumes that axillary treatment with surgery and or radiotherapy reduces the risk of axillary recurrence and can increase the chances of survival. Axillary node clearance is usually done as a second stage procedure.

Due to recent advances in Breast cancer investigations and patient awareness, 60–70% of patients are early breast cancer which are node negative at the time of diagnosis (7). Axillary surgery affects the lymphatic drainage from the arm and exposes patients to risk of both short- and long-term morbidities (8). Completion axillary lymph node dissection (CALND) is associated with an overall complication rates of 20–30% according to literature which includes seroma formation, local swelling, numbness of the arm and shoulder, impaired shoulder movement, neuropathy, surgical site infection, and chronic lymphoedema (9).

These complications of axillary surgery are very distressing which impairs the quality of life and daily activities. They have financial implications to the NHS in terms of rehabilitative treatments as they are often irreversible and symptom relief is not achievable in most of the cases.

The incidence of non-SLN involvement changes considerably with the extent of disease in the SLNB. The results of studies have shown that 53% of patients with a positive SLNB were found to have disease in non-SLNs (10). For patients whose SLNB was involved by macro metastatic disease (tumour metastases greater than 2 mm), the incidence of non-SLN involvement is reported to be 40% to 58% (11). When the SLN is involved by micrometastatic disease (nodal metastasis 0.2 to 2 mm), the incidence of non-SLN involvement is 20% (12) and in the case of the SLN with isolated tumour cells (ITC) (=0.2 mm), the incidence decreases to 12% (13).

Factors that influence the degree of non-SLN involvement are histology and grade of tumour, tumour size, multifocality, lympho-vascular invasion, estrogen receptor (ER) status, and the ratio of positive SLNs to the total number of sentinel nodes removed (14–16). These findings have played significant role in developing trends for doing CALND in certain patients, particularly those thought to be at risk of having additional disease in the non-SLNs.

The American Society of Breast Surgeons issued a consensus statement in 2005 acknowledging this trend (17): “Outside of clinical trials, usual treatment for SLN-positive patients is a level I-II ALND. However, since axillary node metastases are limited to the SLN in more than half of SLN-positive individuals, there may be low-risk subsets for whom a completion ALND is not required. The decision to omit completion axillary dissection in such a case requires a balanced discussion between the surgeon and the patient regarding the risks of further surgery and any potential for improved outcome with more complete information and/or axillary clearance.”

The SLN has been demonstrated to be the only positive lymph node in many cases. Data from high-volume breast cancer centres indicate that the SLN is the only site of metastases in 40% to 60% of axillary dissections (18).

From the above discussion we can conclude that future of SLNB and CALND is dependent on the assessment of risk factors which can lead to prediction of non-SLN positivity or negativity, which will lead to avoidance of CALND and its related morbidities. Many Normograms have already been developed to predict this. But we think the future of breast cancer management of the axilla lies in a prediction tool for non-SLN biopsy.

Considering the above discussion and unanswered questions about CALND, we decided to conduct this study to identify clinicopathological variables which can predict the involvement of non-SLN.

Table 1 Brief overview

Total SLNB	Total + Ve (%)	Macrometastases (%)	Micrometastases (%)	ITC (%)
1,152	224 (19.4)	150 (67.0)	72 (32.1)	2 (0.9)

SLNB, sentinel lymph node biopsy; Ve, positive; ITC, isolated tumour cells.

Methods

We retrospectively analysed our experience of SNLB between July 2008 and July 2013. A total of 1,152 breast cancer patients underwent SLNB.

This is a retrospective analysis in a single institution. Data on procedures performed was prospectively collected by the theatre admin team, and once patient details were identified, the electronic notes and results were searched to obtain further data retrospectively for this study.

We looked for the clinicopathological variables to predict non-SLN status in SLNB with micrometastasis & macrometastasis. The variables were tumour grade, size of primary breast tumour, lymphovascular invasion, age and number of positive SLNB (nearly all patients had <2 positive nodes on SLNB).

Surgery and procedure

A total of 1,152 breast cancer patients underwent SLNB based on lymphoscintigraphy, intra-operative gamma probe detection, and blue dye mapping using 99m Tc-nanocolloid and Patent Blue V injected peri-areola. We used dual method blue dye and 99m Tc-nanocolloid due to higher accuracy.

Statistical analysis was performed using Fisher's exact and χ^2 for categorical data. All data analysis was performed using SPSS version 20 for mac. All reported P values are two-sided.

Pathological evaluation

Micrometastases, macrometastases and ITC were classified as per AJCC 6th Edition.

Tumour deposits measuring 2 mm or more were classified as macrometastases. Tumour deposits measuring 0.2 to 2 mm were classified as micrometastases. Tumour deposits measuring less than 0.2 mm were classified as ITC.

Immunohistochemistry for ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2) are all performed and interpreted in our department. For this study, ER and PR Quickscore of 4 or more was considered positive. However, current guidelines for ER

and PR state that they should be considered positive if 1% or more of tumour cell nuclei are positive.

For Her2, an immunohistochemistry score of 0 or 1+ is negative and a score of 3+ is positive. A score of 2+ is considered borderline and is therefore referred to Leeds Teaching Hospitals NHS Trust for fluorescent in situ hybridization (FISH) analysis.

Results

Out of 1,152 SLNB biopsies performed, 224 (19.4%) were positive for metastatic disease which includes macrometastases in 150 (67.0%), micrometastases in 72 (32.1%) and ITC in 2 (0.9%) (Table 1).

Types of primary breast cancer in all SLNB positive patients invasive ductal carcinoma (IDC) =84%, Mixed type 9%, Lobular 4.74%, Others 1.74%, Tubular 0.43%.

Types of cancer in micrometastasis group only Ductal 85.5%, Lobular 4.8%, Tubular 3.2%, Mixed 4.8%, Others 1.6%. CALND was not performed in 20 cases (9 macrometastases, 10 micrometastases, and 1 ITC), largely due to concerns regarding fitness for anaesthesia.

Mastectomies =53%, breast conserving surgeries (wide local excision) =47%. About 65.8% 1–2 SLN were removed (Figure 1).

Primary cancer was IDC in 85.5% (53/62) of cases in group and 9/62 with micrometastases had n-SNB positive on CALND. In micrometastases all positive nodes at ANC belong IDC group i.e., 17.0% (9/53) (Figure 2).

On univariate analysis, positive non-SLN in CALND for patients with micrometastases on SLNB was not predicted by grade (G0–G2, 6/43; G3, 3/19; P=0.565), size of primary breast tumour (<40 mm, 8/58; ≥40 mm, 1/4; P=0.475), lympho-vascular invasion (5/30 vs. 4/31, P=0.503), age (<50 years, 3/24 vs. ≥50 years, 6/38; P=0.496), or number of positive SLNB (all patients had <2 positive nodes on SLNB) (Figure 3).

Macrometastases on SNLB were more likely to predict positive non-SLN on ANC [macrometastases; 39/141(27.7%) vs. micrometastases; 9/62 (14.5%), P=0.029] (Table 2).

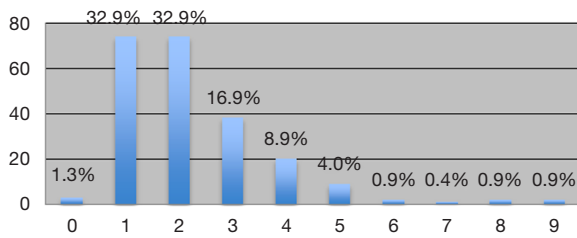


Figure 1 Number of SLN removed. SLN, sentinel lymph node.

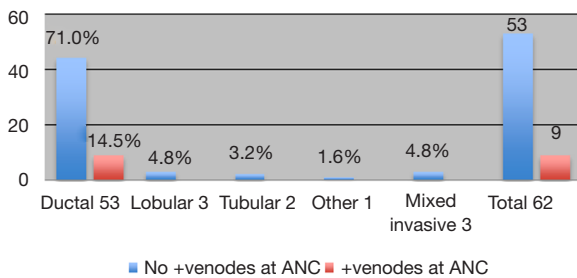


Figure 2 History type and number of positive axillary nodes. Ve, positive; ANC, axillary node clearance.

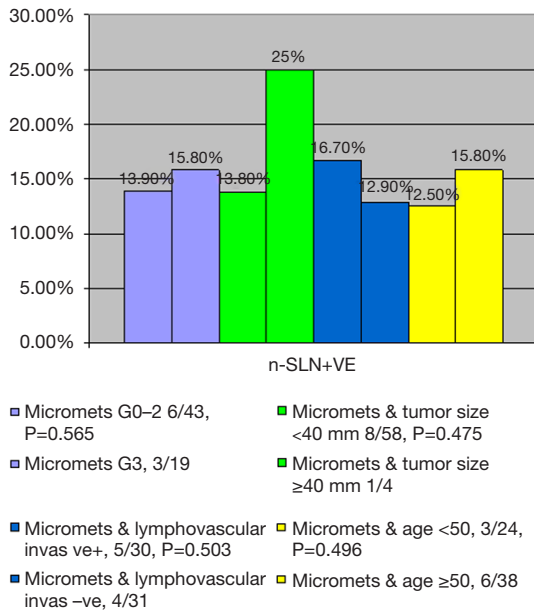


Figure 3 Univariate analysis of non-SLN. SLN, sentinel lymph node; Ve, positive.

Discussion

The American Joint Committee on Cancer (AJCC) defined

Table 2 Univariate analysis of non-SLN with micrometastasis in SLN

Characteristics	Lymph node +Ve	Lymph node -Ve	P value
Age			
<50	3/24	21/24	0.496
≥50	6/38	32/38	
Grade			
0-2	6/43	37/43	0.565
3	3/19	16/19	
Tumour size			
<40 mm	8/58	50/58	0.475
≥40 mm	1/4	3/4	
LV invasion			
+Ve	5/30	25/30	0.503
-Ve	4/31	27/31	
Micrometastases +Ve (%)	9/62 (14.5)		
Macrometastases +Ve (%)	39/141 (27.7)		0.029

SLN, sentinel lymph node; Ve, positive; LV, lymphovascular invasion.

a lymph node metastatic tumour with maximum diameter of >2 mm as macrometastases (pN1) while the diameter of deposit is 0.2–2 mm as micrometastases (pNm1). The lesion of single tumour cells or small cell clusters with diameter <0.2 mm is defined as ITCs [pN0(i+)] (19).

The management of patients with minimal SLN involvement is challenging and has been an increasingly important question since the start of SLNB.

Since the recognition of terminologies of macrometastases, micrometastases, and ITC it has prompted research on the management of these conditions as well. As far as literature is concerned there are studies which support and oppose further treatment with micro and macrometastases.

In our study, clinicopathological variables (age, size of tumour, Grade & lymphovascular involvement) of micrometastases have not predicted the involvement of non-SLN. However, we found that 14.5% of patients with micrometastases on SLNB may have positive non-SLN which is important because if CALND is not being undertaken in these patients, patients must be informed about the chance of having further positive nodes in

remaining Axilla.

AMAROS explores the benefit of a CALND *vs.* ART in patients with SLN-positive breast cancer (20). A sub study investigated the identification rate and the nodal involvement of the first 2,000 patients, data was collected for 4 years from 26 European institutions (20). The sentinel node identification rate was 97%. Total of 34% SLN were positive of whom 63% had macrometastases, 25% had micrometastases, and 12% had ITCs. In patients with complete axillary node dissection non-SLN involvement was found to be 41% with macrometastases and 18% had either micrometastases or ITCs.

Many researchers have probed the incidence of non-SLN involvement in patients with SLN micrometastases to characterise which group of patients should get further axillary treatment. Wada and Imoto accumulated 22 studies from 1999 to 2006 related to the frequency of SLN micrometastases in patients with breast cancer and the rate of non-SLN involvement in those patients after ALND (21). The count of SLN micrometastases was 38% with non-SLN micrometastases ranged from 0 to 57%. Moreover, a wide range of non-SLN macrometastases was found (0–18%). As the count of non-SLN micrometastases was low, the prognostic impact was uncertain. Most of the studies had small numbers and short follow up and concluded that there is no benefit from CALND. The largest study; however, found a significantly worse disease-free survival for women with micrometastases who did not undergo CALND (22).

In the largest published multicenter retrospective study of 187 SLN-ITCs patients undergoing CALND, Houvenaeghel *et al.* found an incidence of 16% non-SLN involvement (23,24). The difference in the risk of non-SLN involvement between sentinel nodes with ITCs (16%) and those with micrometastases (14%) was not statistically significant. However, it was not clear that whether the presence of non-SLN metastases should affect the treatment decision in these patients. In contradiction to the above conclusions comes the MIRROR trial results (25). MIRROR was a large Dutch cohort retrospective study which evaluated the effect of SLN-ITCs and micrometastases on 5-year disease free survival in patients with favourable primary tumour characteristics.

Patients with SNB micrometastases and those who have ITCs who did not undergo CALND had a higher 5-year axillary recurrence rate, 6% in comparison to 1% of SNB negative patients who did not undergo CALND. Moreover, patients with SLN micrometastases and ITCs

had a higher 5-year disease-free survival improved by 10% with adjuvant systemic therapy. Pertinent to mention that micrometastases and ITCs had comparable prognostic impact (26). MIRROR results recommended an aggressive approach for treatment in patients with either SLN micrometastases or ITCs.

Lastly it will be interesting to know the outcome of POSNOC trial in connection with management of the Axilla in early breast cancer. POSNOC study design has two arms, one arm with adjuvant therapy but no treatment to axilla after surgery, while in the other arm adjuvant therapy plus treatment to axilla after surgery. Study is expected to be completed in 2024.

Conclusions

CALND in patients with micrometastases is still under debate in surgical communities. Although macrometastases have a higher predictive value to detect non-SLN involvement compared to presence of micrometastases, risk is still there that patients who have micrometastases may have positive non-SLNB. Our study suggests that patients with micrometastases should not be routinely offered axillary clearance but should be informed of the small risk of having non-SLN involvement which is not predicted by any clinicopathological characteristics.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/abs.2019.08.05>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was not required as anonymous data is used in compliance with NHS Data Act 2006. Individual informed consent was waived.

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