Original Article

The ratio and size of positive sentinel lymph nodes predicts the involvement of non-sentinel lymph nodes following completion axillary lymph node dissection

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Background: The role of completion axillary lymph node dissection (CALND) following positive sentinel lymph node biopsy (SLNB) is being actively debated. The involvement of our unit in the POSNOC trial (which has a no-treatment arm), has prompted a review of our unit's CALND results, in order to examine predictors of involvement of non-sentinel lymph nodes (n-SLN).

Methods: We retrospectively analyzed our experience of SLNB between July 2008 to 2013. A total of 1,152 breast cancer patients underwent SLNB based on lymphoscintigraphy, intraoperative gamma probe detection, and blue dye mapping using 99mTc-nanocolloid and Patent Blue V injected peri-areola.

Results: Out of 1,152 SLNB performed, 224 were positive for metastatic disease; 203 patients were anesthetically capable of progressing to CALND. On univariate analysis, involved n-SLN on CALND could not be predicted by age, size of tumor, procedure performed, lymph vascular invasion, number of positive SLN, receptor status; ER, PR, HER2 or triple negative. There was a trend toward higher incidence of positive n-SLN with increasing grade, and extracapsular spread, but these did not reach statistical significance. Positive n-SLN on CALND was however predicted by macrometastases in SLN and ratio of positive nodes on SLNB.

Conclusions: In our series of more than 200 SLNB, a ratio of >0.5 positive SLN yield and presence of macrometastases in positive SLN, were associated with positive n-SLN on CALND.

Keywords: Micrometastasis; macrometastasis; sentinel lymph nodes (SLN); axillary node clearance

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Introduction

Each year, around 54,900 women in the UK are diagnosed with new breast cancer, that's around 150 every day and the majority (81%) undergo surgical treatment (1).

The results of axillary lymph node (LN) is an important prognostic factor for invasive breast cancer surgery. Sentinel lymph node biopsy (SLNB) is a recognized method for evaluating pathological status of axilla in clinically negative axilla in early breast cancer. This enables correct and reliable staging of the axilla and decreased shoulder and arm morbidity (2-5). The positive LN metastasis detected on SLNB, leads the patient to undergo completion axillary lymph node dissection (CALND). Importantly research has indicated that additional LN metastasis is not found on axillary dissection in around 40–60% of clinically detectable node-negative Axilla (6-8). Excluding CALND did not

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affect local control or prognosis for SLNB-positive patients, reported in the prospective randomized study (9,10). The Z0011 trial reported that excluding CALND did not result in poor survival or local control in SLNB-positive patients with low T stage, no more than two SLNs, and no gross extracapsular extension in the involved nodes. The trial also indicated that CALND should be avoided if SLNB metastases (SLNMs) are detected in only one or two nodes (9,10). Many authors have recommended scoring systems and nomograms to predict the involvement of non-SLNs and to avoid CALND and in order to increase the quality of life of the early breast cancer patients (11-14). Many studies have been performed to explore the question, but it is not yet concluded in which subgroup of SLNB positive patients CALND can be safely avoided.

The current UK National Institute of Clinical Excellence guidelines (15) recommend axillary node clearance or axillary radiotherapy for women with early stage breast cancer and one or two sentinel node metastases. This recommendation assumes that axillary treatment reduces the risk of axillary recurrence and might improve survival. Axillary node clearance is usually a second operation.

The purpose of our research was to identify the link between NSLNM and SLNB with the help of clinic-pathologic variables identified on primary breast cancer and positive SLNB.

Methods

This is a retrospective analysis in a single institution. Patient with SLNB were identified and data on the procedures was collected from pathology department of Pinderfield Hospital Wakefield. Once patient details were identified, the electronic notes and results were searched to obtain further data. One thousand and one hundred fifty-two patients had SLNB from July 2008 to 2013.

Statistics

For univariate analysis χ^2 and Fisher's exact test was used to determine associations between categorical data and PCR. ROC analysis was performed to determine optimum cut-offs for continuous data prior to categorizing into binary variables.

All data analysis was performed using SPSS version 20 for mac. All reported P values are two-sided.

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 99mTc-nanocolloid and Patent Blue V injected peri-areola. We used dual method blue dye and 99m Tc-Nano colloid due to higher accuracy.

Pathological evaluation

Micromets, Macromets and ITC were classified as per AJCC 6th Edition.

Macrometastatic was considered positive when metastasis of 2 mm or large were found.

Micrometastatic was considered with nodal metastasis 0.2 to 2 mm, isolated tumor cells were considered with metastasis of 0.2 mm or less.

We use immunohistochemistry for ER, PR and HER2 which are all performed and interpreted in our department. For this study ER and PR status, Quick score 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 tumor cell nuclei are positive.

For Her2, if the score on immunohistochemistry is 0 or 1+, we call this negative. If it is 3+, we call this positive. If it is 2+, this is considered borderline and we perform Her2 FISH analysis (Fluorescent In Situ Hybridization test). We do not perform or interpret FISH in our department we send sample to Leeds Teaching Hospital.

Results

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

Types of primary cancer in SLNB positive patients IDC 84%, mixed type 9%, lobular 4.74%, others 1.74%, tubular 0.43%.

Mastectomies were performed in 45% and WLE (breast conserving surgery) in 53% of patients.

CALND was not performed in 20 cases (9 macrometastases, 10 micrometastases, and 1 ITC), largely due to concerns regarding fitness for anesthesia; 1–2 SLN were removed in 65.8% patients.

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Table 1 Summary of results

Variable	Total CALND performed (n=200)		P
	Negative CALND (n=153), n [%]	Positive CALND (n=47), n [%]	
Age			
<50 (n=76)	60 [39]	16 [35]	0.311
≥50 (n=124)	92 [61]	31 [65]	
Procedure*			
Mastectomy (n=90)	68 [45]	22 [49]	0.387
WLE (n=106)	83 [55]	23 [51]	
Grade			
G0–G2 (n=135)	108 [719]	27 [57]	0.068
G3 (n=65)	45 [29]	20 [43]	
Tumour size			
<50 mm (n=190)	147 [96]	43 [91]	0.185
≥50 mm (n=10)	6 [4]	4 [9]	
LVI*			
No (n=96)	75 [52]	21 [49]	0.421
Yes (n=91)	69 [48]	22 [51]	
Size of LN Mets*			
Micromets (n=62)	53 [35]	9 [19]	0.028
Macromets (n=136)	98 [65]	38 [81]	
Number of positive nodes			
0–2 (n=194)	149 [97]	45 [96]	0.431
>2 (n=6)	4 [3]	2 [4]	
Ratio of positive nodes			
<0.5 (n=108)	91 [59]	17 [36]	0.040
≥0.5 (n=92)	62 [41]	30 [74]	
Extracapsular spread*			
No (n=146)	115 [81]	31 [69]	0.069
Yes (n=41)	27 [19]	14 [31]	
ER status*			
Neg (n=15)	11 [22]	4 [9]	0.500
Pos (n=182)	139 [78]	43 [91]	
PR status*			
Neg (n=29)	23 [16]	6 [13]	0.441
Pos (n=165)	125 [84]	40 [87]	
Her2 status*			
Neg (n=171)	129 [86]	42 [89]	0.376
Pos (n=26)	21 [14]	5 [11]	
Triple Neg*			
No (n=189)	144 [98]	45 [96]	0.608
Yes (n=8)	6 [2]	2 [4]	

*, some missing data, therefore not all variables have a total of 200 cases. CALND, completion axillary lymph node dissection; LN, lymph node.

We looked for following twelve variable and their impact on diagnosis of Non SLN on CALND. Variables are age, grade, tumor size, LVI, size of LN metastasis, number of positive nodes, ratio of Positive nodes, extra-capsular spread, ER status, PR status, HER2 status and triple negative status (*Table 1*).

From our data Size of LNs (micro & macro) metastasis and ratio of positive nodes showed statistically significant P value which are 0.028 and 0.040 respectively.

Moreover, our data, primary tumor grade and extra capsular nodal spread shows trends towards statistically significant P value which are 0.068 and 0.069 respectively but did not achieved statistically significant value.

Age, tumor size, LVI, number of positive nodes, ER status, PR status, HER 2 status and triple negative status did show any significant statistical value. See all P values in *Table 1*.

Discussion

Breast surgeons are always concerned about the risk of remnant non-SLN metastasis if they have not performed CALND. To predict the risk of non-SLN metastasis several

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nomograms example Memorial Sloan-Kettering Cancer Centre (MSKCC) nomogram, the Stanford nomogram have been proposed but none of them are perfect (16).

Literature suggests that axillary nodal status is helpful in prognosis and predicting for the staging and treating the breast cancer. It is also established that SNLB can help in staging axillary LNs in clinically axillary-negative breast cancer (17-19).

Studies suggest that about 40–70% of patients with positive SLN do not have further axillary LNs metastasis (20,21).

That is why, axillary dissection can be avoided in these patients (22,23). A recent clinical trial suggests that axillary LNs dissection is unnecessary if positive SLNM is detected in one or two nodes.

The ACOSOG Z0011 trial results showed that SLNB alone without ALND results in extremely low local and regional recurrence and excellent overall survival comparable to the patients undergoing CALND if SLNM is present in two or fewer nodes (9).

Moreover, Dutch AMAROS trial compared ALND with radiotherapy in T1–T2 patients with a positive SLNB (24). The trial showed similar results in terms of axillary control between the two treatments. However, the trial showed that patients treated with CALND had notably more morbidities than those treated with radiotherapy.

Depending on these findings many studies have highlighted factors associated with the histopathological variables of the primary tumor and the SLNB and tried to generate a nomogram to predict the risk of NSLNM (12,14,20,25-37).

These studies have indicated that different pathologic characteristics of the primary tumor and the SLNB were associated with an increased probability of additional positive NSLN.

However, there is no consensus on the predictive factors of NSLNM until now. The most commonly assessed risk factors in other studies include primary tumor size, grade of primary tumor, the maximum size of positive SLN, LVI, ECI in SLN, ER, PR, and HER2 statuses. The association of tumor size with the probability of NSLNM has been published in many studies (6,33-36).

Ozmen *et al*. also showed that tumor size over 2 cm was linked with a higher rate of SLNM and NSLNM (33). Dingemans *et al*. also reported that the primary tumor size was a predictor of NSLNM (12).

Some studies have shown that tumor size was not associated with a higher rate of NSLNM (14,20,38,39), whereas, some studies have reported contrasting results (27,30,33,36).

Research have also shown that the presence of micrometastasis in SLN was associated with lower rates of NSLNM, as compared to macrometastasis (14,26,33).

It has also been published that the size of the SLNM has no significant relationship with NSLNM after multivariate analysis (20,28,36,40).

The Memorial Sloan Kettering Cancer Center (MSKCC) model, which is the most widely used model to predict NSLNM, also did not include the size of SLNM (22).

Similarly, few studies have shown that age has notable association with positive NSLNMs in multivariate analyses (28,41). However, several studies could not find link between age and NSLNM (25,30-39).

Some investigations have demonstrated that LVI is a predictor of NSLNM (20,29,31).

However, Yildiz *et al*. and Canavese *et al*. have shown that LVI is not a significant predictor of NSLNM in logistic regression analysis (27,32).

Shigematsu *et al*. demonstrated that ECI at SLNB is an independent predictor of both NSLNM and poor prognosis for early stage breast cancer patients with SLNM (42). More over several studies have demonstrated ECI to be a predictor of NSLNM, (12,30,31,35) where as in some other studies this association was not found (23,38).

Some researchers have shown that multifocality of the primary tumor is a predictor of NSLNM (27,29). In ER/PR positive patients Axillary LN involvement has been reported to be higher (8,16). Significant relationship was shown between HER2 expression and NSLNM by Meretoja *et al*. and Sanjuán *et al*. (8,21). However, this relationship was not demonstrated in other studies (16,23,43,44).

Several nomograms have been invented to predict the presence of cancer in NSLN in the axilla. (11,16,22,23,29) The most commonly used nomogram was postulated by MSKCC (9,22). This nomogram constitutes primary tumor size, grade, number of positive and negative SLNs, SLN detection method, ER status, LVI, and tumor multifocality to predict NSLNM. Although the predictive accuracy of these nomograms has been divided as some studies approving it, (14,29,37,44) others not (38,45-47).

Conclusions

On univariate analysis, involved n-SLN on CALND could not be predicted by age, size of tumor, procedure performed, lympho-vascular invasion, number of positive

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SLN, receptor status; ER, PR, HER2 or triple negative. There was a trend toward higher incidence of positive n-SLN with increasing grade, and extracapsular spread, but these did not reach statistical significance.

Positive n-SLN on CALND was however predicted by macrometastases in SLN and ratio of positive nodes on SLNB.

In our series of more than 200 SLNB over 5 years, a ratio of >0.5 positive SLN yield and presence of macrometastases in positive SLN, were associated with positive n-SLN on CALND.

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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.2019.10.06). 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). Written in compliance with NHS data protection law where patient information was anonymized. Informed consent was waived due to the retrospective nature of the study.

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