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Predictors of non-sentinel lymph node metastasis in breast cancer patients

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Abstract

In many patients, the sentinel lymph node (SLN) is the sole site of regional nodal metastasis. This subgroup of patients would not be expected to benefit from completion axillary lymph node dissection (CALND). This study evaluated the factors that may determine the likelihood of additional positive nodes in the axilla in the presence of sentinel node metastasis. A total of 618 breast cancer patients underwent SLN biopsy based on lymphoscintigraphy, intraoperative gamma probe detection, and blue dye mapping using 99mTc-nanocolloid and Patent Blue V injected peritumourally. This was followed by standard axillary node clearance at the same operation. Of the 201 patients with a positive SLN, 105 (52%) patients had no further positive nodes in the axilla, 96 (48%) patients had additional metastasis in non-sentinel lymph nodes (NSLN) upon CALND. In patients with a positive SLN, increasing tumour size and tumour grade significantly increased the frequency of additional positive nodes on univariate analysis. The number of SLNs removed and the number of negative SLNs were significant negative predictors. Increasing tumour burden in the sentinel nodes (determined by the number of positive SLNs) was significantly associated with increasing likelihood of positive NSLNs. Multivariate analysis revealed that the rest of the axilla is more likely to be positive if there are more positive than negative SLNs removed and more likely to be negative otherwise. A group of cases from one centre (Cardiff) were subjected to further detailed analysis. Tumour burden in the positive SLN was assessed by measuring the size of metastasis, percentage replacement of the SLN by tumour and by documenting extracapsular extension (ECE) around the SLN. Of the 64 patients with a positive SLN, 34 (53%) patients had no further positive nodes in the axilla, 30 patients (47%) had additional metastasis in NSLNs upon CALND. Increasing tumour burden in the SLN was associated with additional positive nodes in the axilla. Multivariate analysis revealed that size of the SLN metastasis is the most important predictor of involvement of only the SLN. Overall, in patients with a positive SLN, the difference in the number of positive and negative SLNs removed and size of the metastasis in the SLN, all predicted the frequency of additional positive nodes.

Keywords: Breast cancer; Sentinel lymph node biopsy; Non-sentinel node metastasis; Tumour burden; Completion axillary lymph node dissection

1. Introduction

Axillary lymph node metastasis in patients with early breast cancer is the single most important prognostic factor for recurrence and survival, and forms the basis for important therapeutic decisions. Axillary dissection involves considerable use of resources, and increases the risk of acute and late morbidity that may adversely affect the patient's quality of life [1–5].

Abbreviations: SLN, sentinel lymph node; NSLN, non-sentinel lymph node; CALND, completion axillary lymph node dissection; ECE, extracapsular extension.

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Sentinel lymph node (SLN) biopsy is rapidly emerging as a new 'standard of care' in breast cancer. It has the potential to identify those patients most likely to be helped by axillary dissection, namely those with positive nodes. Conversely, node-negative patients are spared the morbidity resulting from an unnecessary extensive operation. Numerous studies have documented SLN biopsy to be highly predictive of axillary node status, with a false-negative rate of less than 5% [6,7]. Completion axillary lymph node dissection (CALND) is recommended for patients who have SLN metastasis. However, the need for routine CALND in these patients has been questioned [8,9].

In approximately 50%–65% of patients, the SLN is the sole site of regional node metastasis and these patients would not be expected to benefit from CALND [8–12]. As a result, identifying specific characteristics of the tumour and SLN that can reliably predict which patients with SLN metastasis have a low likelihood of non-sentinel lymph node (NSLN) involvement and may not benefit from CALND is an important goal.

This analysis sought to identify a subgroup of patients with a positive SLN who do not need to be exposed to the morbidity and cost associated with CALND.

2. Patients and methods

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial [13] is a multicentre randomised trial in the United Kingdom comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. The trial consists of two phases. In phase 1, a validation phase, all surgeons performed SLN biopsy in 40 patients with invasive breast cancer followed by the axillary procedure, sampling or clearance, which would be the standard treatment in that centre. The second phase of the trial is the randomised phase comparing sentinel node biopsy with conventional axillary treatment. The data presented here are from the validation phase.

From February 1998 to December 2001, 618 patients underwent SLN biopsy followed by axillary node clearance at the same operation. Patients who underwent four node sampling following SLN biopsy were excluded from this analysis. In each centre, local ethics committee approval and written consent for all patients were obtained. The study conformed to the Declaration of Helsinki. Pregnant women, patients with known multicentric tumours and those with previous surgery to the same breast or axilla were excluded. All surgeons along with their team of nuclear physicians and pathologists attended a course on SLN biopsy. The surgeons were additionally proctored in their own institution by the Principal Investigator of the trial. The SLN biopsy was performed according to a standardised protocol. The protocol involved using a combination of radiopharmaceutical, lymphoscintiscans and perri-operative blue dye. Briefly, 2 ml of 99 mTc-radiolabelled colloidal albumin (Nanocoll; Nycomed Amersham) was injected at 4 sites peritumourally. The dose was 40 MBq if injected the day before surgery or 20 MBq if injected on the day of surgery. A lymphoscintiscan was performed around 3 h after the injection. Scintigraphic images were obtained in two standard positions: anterior and oblique. The location of axillary and non-axillary SLNs was marked on the skin. After induction of general anaesthesia in the operating room, 3–5 min before the incision, 2 ml of Patent Blue V dye (Laboratoire Guerbet, Aulnay-sous-Bios, France) diluted to 5 ml was injected peritumorally. Intraoperative identification of the SLNs was based both on blue dye mapping and gamma probe detection. A SLN was defined as any blue-stained node or any node with radioactive counts more than 10 times the background count. The SLNs and NSLNs were bisected if less than 5 mm or sliced at 3 mm intervals if greater than 5 mm and assessed and assessed using single sections stained with haematoxylin and eosin (H&E). Intraoperative histological examination was not utilised.

201 patients with adequate data and one or more positive SLNs form the basis for this study. Variables analysed included patient's age, tumour size, tumour grade, tumour histology, number of SLNs removed and number of positive SLNs.

3. Analysis of detailed histopathological factors

Because of the multi-institutional nature of the present study, analysis of detailed histopathological factors (presence of tumour lymphovascular invasion, size of metastasis in the SLN, percentage replacement of the SLN by tumour, presence of extracapsular extension around the SLN) was restricted to one centre only (Cardiff). H&E stained sections of all SLNs containing tumour were retrieved from the pathology archive and viewed by a consultant histopathologist. The sizes of the lymph node and metastasis were measured in millimetres in two dimensions. A micrometastasis was defined as a tumour deposit smaller than 2 mm and macrometastasis was defined as a deposit greater than 2 mm.

To provide an objective assessment of the percentage of area replaced by tumour, the coverslip of the slides in the areas occupied by tumour were marked with a fine-point permanent black pen on each of the lymph node cross-sections to be assessed. Digital images of the marked slides were acquired and measurements were made using an image analysis application (Image Pro Plus). The programme measured the cross-sectional area of the lymph node and delineated the marked areas and

a percentage replacement was calculated. This method allowed objective calculation of the percentage occupied by the tumour.

4. Statistical analysis

The relationship between positivity of NSLNs and the predictive factors listed in Tables 1 and 2 was assessed using the χ^2 test for binary and unordered categorical variables. For predictive factors on a continuous or ordinal scale, the Mann–Whitney test was applied to the uncategorised data. Factors at or close to the nominal $\alpha = 0.05$ level in univariate analyses were entered into a stepwise logistic regression.

Table 1
Clinicopathological characteristics of 201 patients with sentinel node metastasis who proceeded to axillary clearance, and predictors of non-sentinel node metastasis[a]

Variable	Number of cases (% of series)	Positive NSLNs found (%)	Univariate analysis *P* value
Age (years)			0.54[b]
<50	66 (33)	52	
⩾ 50	134 (67)	46	
Tumour size			0.002[b]
T1	92 (47)	38	
T2	99 (50)	57	
T3	6 (3)	67	
Tumour grade			0.040[b]
I	29 (15)	41	
II	91 (46)	42	
III	76 (39)	58	
No. of SLNs removed			0.014[b]
Single	71 (35)	59	
Multiple	130 (65)	42	
No. of positive SLNs			0.019[b]
Single	149 (74)	42	
Multiple	52 (26)	65	
No. of negative SLNs			<0.001[b]
None	104 (52)	66	
Single	59 (29)	34	
Multiple	38 (19)	18	
Pathological findings			0.13[c]
Invasive ductal	156 (79)	48	
Invasive lobular	20 (10)	65	
Other	21 (11)	33	

SLNS, sentinel lymph nodes; NSLNS, non-sentinel lymph nodes.
Multiple logistic regression: logit (proportion with +ve NSLNs) = 0.614 × positive SLNs − 0.864 × negative SLNs − 0.36.
[a] Some data are missing in some of the categories.
[b] Mann–Whitney test.
[c] χ^2test.

5. Results

The overall SLN identification rate was 593/618 (96%), of which 17 (3%) were false-negatives. Analyses are based on the 201 patients who had at least one positive SLN and proceeded to axillary clearance. The median age was 54 years (range 26–80 years). Four were male. Clinicopathological characteristics are shown in Table 1. The mean number of SLNs removed per patient was 2.2 (range 1–9), of which 1.4 (range 1–6) were positive. 105 (52%) patients had no further positive nodes in the axilla, 96 (48%) had additional metastasis in NSLNs upon CALND. The mean number of NSLNs removed per patient was 15 (range 1–66).

Increasing tumour size, tumour grade and number of positive SLNs were all associated with an increased likelihood of NSLN metastasis on univariate analysis ($P = 0.002$, $P = 0.040$, $P = 0.019$, respectively; Table 1). The total number of sentinel nodes removed and number of negative sentinel nodes were significant negative predictors ($P = 0.014$, $P < 0.001$, respectively; Table 1). Only the difference in the number of positive and negative SLNs remove remained predictive of NSLN involvement on multivariate analysis ($P < 0.001$; multiple logistic regression equation–footnote of Table 1).

6. Analysis of Cardiff patients

Further analyses are based on the 64 Cardiff patients who had at least one positive SLN and proceeded to axillary clearance. All were female and their median age was 54 years (range 35–89 years). Clinicopathological characteristics are shown in Table 2. Detailed pathology data is unknown for 5 patients as their slides could not be retrieved from the pathology archive. 30 (47%) patients had positive NSLNs. The mean size of SLN metastasis was 6.2 mm (standard deviation (SD)6.0). The proportion showing extracapsular extension (ECE) around the SLN was 11/59 (19%).

On univariate analysis, increasing size of the SLN metastasis, percentage replacement of SLN by tumour and ECE around the SLN, all were significantly associated with NSLN involvement ($P < 0.001$, $P < 0.001$, $P = 0.01$, respectively; Table 2). The rate of NSLN involvement was 7% in the presence of SLN micrometastasis (<2 mm), compared with 60% when the SLN had a macrometastasis (>2 mm). All patients with metastasis of >10 mm had additional positive nodes in the axilla (Table 2).

82% of patients with ECE around the SLN had NSLN involvement, while only 40% of patients without ECE around the SLN had NSLN metastasis (Table 2).

Multivariate logistic regression analysis selected only size of metastasis for inclusion in the predictive model ($P < 0.001$; multiple logistic regression equation–

Table 2
Clinicopathological characteristics of 64 Cardiff patients with sentinel node metastasis who proceeded to axillary clearance and predictors of non-sentinel node metastasis[a]

Variable	Number of cases (% of series)	Positive NSLNs found (%)	Univariate analysis *P* value
Age (years)			0.96[b]
<50	18 (28)	50	
⩾ 50	46 (72)	46	
Tumour size			0.20[b]
T1	23 (37)	43	
T2	36 (57)	47	
T3	4 (6)	50	
Tumour grade			0.48[b]
I	6 (10)	50	
II	29 (47)	38	
III	27 (44)	52	
No. of SLNs removed			1.0[b]
Single	28 (44)	46	
Multiple	35 (56)	46	
No. of positive SLNs			0.036[b]
Single	45 (71)	38	
Multiple	18 (29)	67	
No. of negative SLNs			0.050 [b]
None	41 (65)	56	
Any	22 (35)	27	
Pathological findings			0.10[c]
Invasive ductal	53 (84)	51	
Invasive lobular	7 (11)	14	
Others	3 (5)	33	
Multifocality			0.13[c]
Present	16 (25)	63	
Absent	47 (75)	40	
Size of SLN metastasis			<0.001[b]
<2 mm	14 (24)	7	
2–10 mm	33 (56)	45	
>10 mm	12 (20)	100	
ECE around the SLN			0.01[c]
Present	11 (19)	82	
Absent	48 (81)	40	
Tumour lymphovascular invasion			0.24[b]
Present	25 (39)	56	
Absent	39 (61)	41	
% replacement of SLN by tumour			<0.001[b]
⩽ 10	16 (27)	19	
>10–50	12 (20)	42	
>50–100	31 (53)	65	

Multiple logistic regression: logit(proportion with NSLNs) = 0.257 × size of largest metastasis (mm) – 1.732.
ECE, extracapsular extension.
[a] Some data are missing in some of the categories.
[b] Mann–Whitney test.
[c] χ^2 test.

footnote of Table 2). The discriminatory ability was not improved when we combined the size of the SLN metastasis with the number of negative sentinel nodes removed.

Even though moderate discriminatory power was obtained, we were unable to identify a subgroup in whom CALND could be safely omitted.

7. Discussion

SLN biopsy is evolving as the preferred technique for axillary staging in breast cancer. What has not confidently been determined is the benefit of further axillary lymph node dissection if the SLN is positive, although this is being evaluated in ongoing studies. Although

axillary nodal status is frequently considered in making adjuvant therapy decisions, the role of axillary lymph node dissection as a therapeutic procedure remains controversial. The increased use of adjuvant systemic and radiation therapy has challenged the rationale for CALND once the axilla has been staged by SLN biopsy. 47–68% of patients have no disease in lymph nodes other than the SLN, and therefore, these patients are unlikely to benefit from further surgery [8–12]. The removal of normal lymph nodes is unlikely to be of value.

The incidence of NSLN involvement varies in reports and this is in part as a result of the sensitivity of the detection method used. Although immunohistochemical staining (IHC) would increase the incidence of NSLN metastasis, the clinical significance of tumour deposits detected by IHC is unclear [14,15]. Therefore, the SLNs and NSLNs were assessed by standard H&E staining in our study.

Most studies have found the size of the SLN metastasis and ECE around the SLN to be independent predictors of NSLN metastasis. However, there is disagreement on the impact of tumour size and lymphovascular invasion on NSLN involvement [8,9,11,12,16–18]. Our research complements these efforts.

In the present study, 48% of patients had NSLN metastasis when the SLN was positive for tumour. Univariate analyses revealed that increasing tumour size and tumour grade were significant positive predictors of residual axillary involvement. Even patients with T1 tumours had a 38% risk of residual axillary metastasis if the SLN was positive. As the tumour size increased, the incidence of NSLN metastasis increased ($P = 0.002$, Table 1). These results are consistent with those of previous studies, which demonstrated that the incidence of NSLN metastasis rises with increasing tumour size [8,9,19,20]. However, tumour size and tumour grade lost their significance on multivariate analysis.

Patients with a greater number of positive SLNs have an increased lymphatic tumour burden. These patients would therefore be more likely to have additional positive nodes in the axilla. In patients with a single positive SLN, 42% had NSLN involvement, compared with 65% of patients with multiple positive SLNs. Similar findings were reported by Chu and colleagues [21] and Wong and colleagues [22]. Our study found a statistically significant difference in the NSLN involvement between patients who had a single SLN and those who had multiple SLNs removed (59% vs. 42%). A greater number of SLNs removed might be reflected in fewer positive nodes remaining in the axillary dissection specimen. An interesting finding in our study which has not been previously reported was the association between the number of negative SLNs and NSLN involvement. The incidence of NSLN metastasis in patients with no negative SLNs was 66%, compared with 28% for patients with one or more negative SLNs ($P < 0.001$, Table 1). A greater number of negative SLNs indicates a low lymphatic tumour burden and therefore decreased probability of additional positive nodes. Multivariate analysis revealed that the rest of the axilla is more likely to be positive if there are more positive than negative SLNs removed and more likely to be negative otherwise [logit (proportion with +ve NSLNs) $= 0.614 \times$ positive SLNs $-0.864 \times$ negative SLNs -0.316; footnote of Table 1].

Other factors that have been found to be associated with NSLN metastasis include the presence of peritumoral lymphatic vascular invasion, size of SLN metastasis and ECE around the SLN. Because of the multi-institutional nature of the present study, analysis of such detailed histopathological factors was conducted for one centre only. Increasing tumour burden in the SLN (as determined by size of SLN metastasis, percentage replacement of SLN by tumour or presence of ECE) was associated with additional positive nodes in the axilla. Multivariate analysis revealed that size of SLN metastasis is the most important predictor of involvement of only the SLN [logit (proportion with NSLNs) $= 0.257 \times$ size of largest metastasis (mm) $- 1.732$; footnote of Table 2].

Several previous studies have shown size of the SLN metastasis to be associated with NSLN involvement [8,9]. In this study, SLN metastasis larger than 2.0 mm was significantly associated with NSLN involvement.

ECE around the SLN was present in 19% (11/59) of the Cardiff patients. Patients with ECE around the SLN were more likely to have NSLN involvement than patients without ECE around the SLN. Other studies including ECE around the SLN in their examination of predictors of NSLN involvement have found ECE to be significantly associated with NSLN involvement [11,16–18]. ECE around the SLN lost its significance on multivariate analysis in the present study because of the confounding effect of the size of the SLN metastasis.

In contrast to the findings of Weiser and colleagues [12], and similar to the findings of Reynolds and colleagues [9], our study did not show a relationship between lymphatic invasion and NSLN metastasis.

In the smaller series of Cardiff patients, the number of negative sentinel nodes was a significant negative predictor on univariate analysis, but lost its significance on multiple logistic regression models that included size of the SLN metastasis (Table 2). However, this may be because of the small sample size.

The clinical implications of this data are important. This information should be evaluated when considering clinical trials that include no axillary treatment as a treatment arm. It needs to be evaluated in terms of risk assessment for the patient prior to initiating such trials, and also if such trials end up showing a significant

survival advantage, these are the factors that should be scrutinised when reviewing the data.

Overall, the difference in the number of positive and negative SLNs removed and size of the SLN metastasis were identified as predictors of NSLN involvement. Unfortunately, neither of these characteristics, alone nor in combination, was a strong enough predictor of NSLN involvement to identify a subset of patients who can safely forgo CALND. Due to the high likelihood of extensive axillary tumour burden, all breast cancer patients with multiple positive SLNs and $\geqslant 10$ mm size of metastasis in the SLN should undergo a CALND. Conversely, patients with a single positive SLN and SLN micrometastasis are highly unlikely to harbour NSLN metastasis. The American College of Surgeons Oncology Group trial Z0011 is addressing the question of therapeutic value of CALND in patients with low axillary tumour burden. In this trial, patients with a tumour-involved SLN are randomised to CALND or no additional axillary therapy. Patients with >2 positive SLNs and those with gross extranodal disease in the SLN are excluded from this study. If this trial fails to demonstrate a survival advantage for patients undergoing CALND, then CALND for patients with low risk of NSLN involvement (<3 positive SLNs and no evidence of ECE around the SLN) may become obsolete, sparing many patients the short- and long-term morbidity associated with axillary lymph node dissection.

Pending further clinical experience and the results of randomised trials, we feel that CALND remains the 'standard of care' for most patients with positive SLN.

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