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Prediction of negative axillary node clearance by sentinel node-positive to total node ratio: a retrospective cohort study

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Introduction: Increasing evidence suggests that de-escalation of axillary surgery is safe, without significantly impacting patient outcome. Obtaining positive lymph nodes at a sentinel lymph node biopsy (SNB) can guide decisions toward the requirement of axillary nodal clearance (ANC). However, methods to predict how many further nodes will be positive are not available. This study investigates the feasibility of predicting the likelihood of a negative ANC based on the ratio between positive nodes and the total number of lymph nodes excised at SNB.

Methods: Retrospective data from January 2017 to March 2022 was collected from electronic medical records. Patients with oestrogen receptor (ER) positive and HER2 negative receptor disease were included in the study. ER-negative and HER2-positive disease was excluded, alongside patients who had chemotherapy before ANC.

Results: Of 102 patients, 58.8% ($n = 60$) had no macrometastasis at ANC. On average, 2.76 lymph nodes were removed at SNB. A higher SNB ratio of positive to total nodes [OR 11.09 (CI 95% 2.33–52.72), $P = 0.002$] had a significant association with positive nodes during ANC. SNB ratio less than or equal to 0.33 (1/3) had a specificity of 79.2% in identifying cases that later had a negative completion ANC, with a 95.8% specificity of no further upgrade of nodal staging.

Conclusion: A low SNB ratio of less than 0.33 (1/3) has a high specificity in excluding the upgradation of nodal staging on completion of ANC, with a false-negative rate of less than 5%. This may be used to identify patients with a low risk of axillary metastasis, who can avoid ANC.

Keywords: axillary node clearance, axillary surgery, breast cancer, breast surgery, sentinel node biopsy

Introduction

Breast cancer is the most common cancer worldwide, with more than 2.26 million women being diagnosed in 2020 and ~48 000 within in the UK in 2019[1]. Effective screening programmes are in place with an estimated 2 million women having breast cancer screening in the UK each year[2]. However, patients are still presenting with metastatic spread, even in the early stages of the disease. Most commonly, the earliest detectable clinical presentation of distant metastasis is within the axillary lymph nodes[3].

Sentinel lymph node biopsy (SNB) is a diagnostic procedure undertaken in those with no palpable axillary adenopathy. Prior to the operation, the sentinel lymph node (SLN) is located with dual identification technique: blue dye injection and radioactive labelling with the radioisotope technetium-99. During the operation, the SLN can be detected visually from the blue dye, alongside the use of a geiger counter to measure the ionising radiation emitted. The SLN can then be excised for analysis[4]. Studies have shown that success rates of identification of the SLN have approached 96–100%[4,5]. The pathological status of the sentinel node (positive or negative) is crucial to guide a physician's treatment decision. For those with a positive SNB, axillary lymph node clearance (ANC) has been regarded as the gold standard for several years as it is an effective method of maintaining regional control and providing accurate staging[3,6]. However, it is associated with a higher risk of morbidity due to side effects such as lymphoedema (2–38%), shoulder dysfunction (1%) and neuropathies (<1%)[3]. In addition, studies have demonstrated that in 40–70% of cases with metastasis to axillary lymph nodes, the SLN was the only positive node[7]. As a result, there is more emphasis on providing less invasive treatment options.

Recent findings from the ASCOSOG Z0011 trial showed that the 10-year regional recurrence rate in patients with SLN metastases did not differ significantly between those who received SNB alone versus ANC[6]. The AMAROS trial found further evidence to show that the axillary recurrence-free rate of patients with a positive SNB treated with radiotherapy is noninferior to those treated with ANC[8].

There have been various attempts to predict the likelihood of identifying metastasis in ANC in patients with a positive SNB,

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with the MSKCC nomogram being the most validated model in the current literature[9,10]. Subsequent studies have developed additional nomograms in various populations to improve predictability for the relevant patient demographic[3,7]. As of now, there is no guidance on the number of nodes to remove while carrying out a SNB. In most of the centres in the UK, there is a variation in the management of axillary metastatic disease once macrometastasis is identified in SNB. Some centres would perform ANC on most cases who are found to have macrometastasis in SNB, while other centres may treat these patients with either radiotherapy to the axilla or performing ANC. In our breast unit, most patients with macrometastasis on SNB undergo ANC unless they are elderly and unfit for further procedures[6]. This is commonly practised in other breast units across the country. An alternative to ANC is axillary radiotherapy, but fewer patients receive this treatment[6]. The advantage of performing ANC is that it can identify more nodes and accurately provide nodal staging for the patient.

Currently, most studies have focused on the likelihood of finding macrometastasis in ANC in SNB-positive patients. They have devised prediction models that involve patient characteristics and disease pathological features. This study aims to determine whether it is possible to predict the likelihood of a negative ANC based on a simple SNB ratio of the positive nodes to the total number of nodes. The secondary aim of the study is to identify pathological factors associated with macrometastasis and upgrading of nodal staging. The focus of the study is to identify those patients with a positive SNB who will not have further macrometastasis. This way, an additional completion of ANC operation can be avoided.

Methods

Retrospective data was collected from the electronic medical record system. The data was collected from 1st January 2017 to 1st March 2022 in the Department of Breast Surgery. Both screen-detected and symptomatic patients were included in the study. Multidisciplinary team meeting records were studied to select patients initially diagnosed with oestrogen receptor (ER) positive and human epidermal growth factor 2 receptor (HER2) negative breast cancer with normal ultrasound imaging of the ipsilateral axilla. These patients would have undergone either a mastectomy or wide local excision after diagnosis. During the operation, all these patients underwent SNB excision using a dual detection technique with blue dye and radioactive isotope labelling. Patients found to have macrometastasis in the SNB in the final histology results then underwent follow-up completion level II ANC before having adjuvant chemotherapy. These patients were included in the study. Patients who were diagnosed with ER-negative and HER2-positive breast cancer were excluded as the majority of these patients would have undergone neoadjuvant chemotherapy prior to SNB, and this would have made the interpretation of the final nodal count with macrometastasis difficult as some of the nodes would have responded to chemotherapy and would be free of macrometastasis. Similarly, patients who were ER-positive/HER2-negative and who had neoadjuvant chemotherapy or endocrine therapy prior to the operation were also excluded from the study.

Details of patient characteristics retrieved from electronic medical records were sex, age at presentation, history of previous breast surgery, history of previous benign breast disease, history of previous breast cancer, current or previous use of hormone replacement therapy, smoking status, BMI and family history of breast cancer. It was used to collect the histology results, including tumour size and type, immunohistochemistry receptors, tumour type, grading, associated DCIS, operation, positive and total sentinel nodes, positive and total nodes on ANC, any chemotherapy prior to ANC, any mention of recurrence postoperatively and any mention of lymphoedema postoperatively.

The work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) Criteria[11]. This study has been retrospectively registered with the Research Registry[12], with the unique identifying number (UIN) 'researchregistry8785'.

Statistical analysis

The data was collected in a Microsoft Excel sheet (Microsoft MSO version 2108). It was used to analyse the descriptive statistics of the study population. Specificity was calculated for different ranges of SNB ratios (number of positive nodes to total number of nodes) to assess their accuracy in identifying those patients with no macrometastasis and no further upgradation of nodal staging in completion ANC. A logistic regression analysis was conducted to assess the pathological factors associated with macrometastasis in further ANC.

Results

The power calculation for sample size was conducted with a beta-error of 20%. The incidence of false-negative rate of ultrasound scans to assess nodal staging is 20–30%[3,7]. The acceptable false-negative rate of a procedure for oncological safety is less than 10%[3,7]. Based on this estimated difference in incidence, we found the sample size to be 98. The baseline characteristics are summarised in Table 1.

The average number of nodes retrieved in SNB was 2.76 (SD 1.50). 24.5% of patients ($n = 25/102$) had three or more nodes removed during SNB, with the remainder of patients having two or fewer nodes removed. In all patients with two or fewer nodes removed, the nodes were all detected with the dual technique of blue dye and radioisotope activity. 92% ($n = 23/25$) of patients with three or more excised nodes had extra palpable nodes removed in addition to the primary sentinel nodes identified by staining/radiation. 65.2% of these patients ($n = 15/23$) with removed palpable nodes had macrometastasis in them. Conversely, four patients (17.4%) had macrometastasis in the palpable nodes without having any macrometastasis in the radioactive blue sentinel nodes.

19.6% of patients ($n = 20/102$) were also noted to have extracapsular spread (ECS) on the pathology of SNB. 30% of these patients ($n = 6/20$) with ECS had palpable nodes detected and excised during sentinel node biopsy. The average number of positive lymph nodes in SNB was 1.5 (SD 0.90). The average number of positive nodes in ANC was 1.45 (SD 2.89), but 60 patients (58.8%) were not found to have any positive nodes in the clearance. Four patients (3.9%) had significant lymphoedema following ANC that required intervention by the lymphoedema clinic team.

The SNB ratio (number of positive nodes to total number of nodes retrieved) was used to assess the specificity of having all

Table 1

Baseline characteristics.

Characteristics	Total, $n=102$ (%)
Female	102 (100)
Age, mean ± SD	60.86 ± 13.40
Previous breast disease	
Breast cancer with surgical management	3 (2.9)
Benign breast disease	6 (5.8)
None	93 (91.2)
HRT	12 (11.6)
Smoking	
Current smoker	4 (3.9)
Ex-smoker	13 (12.6)
Nonsmoker	20 (19.6)
BMI > 25 kg/m^2	6 (5.8)
Family history of breast cancer	10 (9.7)
Tumour type	
Ductal	76 (74.5)
Lobular/Mixed	20 (19.6)
Associated DCIS	34 (33.3)
Tumour size[a]	
T1	30 (29.1)
T2	48 (46.6)
T3	24 (23.3)
T4	1 (1.0)
ER score[b]	
> 5	99 (97.1)
3–5	3 (2.9)
HER2-positive	2 (1.9)

Values are *n* (%) or mean ± SD.

[a]Tumour size graded according to TNM staging – T1 (< 20 mm), T2 (20–50 mm), T3 (> 50 mm), and T4 (skin/muscle involvement).

[b]Estrogen receptor scoring based on the Allred scoring system, determined during immunohistochemistry analysis.

DCIS, ductal carcinoma in-situ; ER, oestrogen receptor; HRT, hormone replacement therapy.

negative nodes in the ANC. Different cut-off ratios were used to assess the specificity of negative nodes, the reliability of the low SNB ratio to determine unnecessary completion of the ANC, and the chance of missing a positive node in the ANC (false-negative rate). As Table 2 suggests, the specificity of a SNB ratio of less than 0.33 (1/3) to identify cases with negative ANC and no further upgrade of nodal staging was 79.2 and 95.8%, respectively. The specificity of SNB ratio of less 0.25 (1/4) to identify cases with negative ANC and no further upgrade of nodal staging was 87.5 and 100%, respectively. There were 27 patients (26.5%) that were premenopausal. Eleven patients were found to have a positive node in the ANC and three patients had an upgrade of nodal staging as a result of the completion of the ANC.

There were 17 patients (16.7%) who had nodal staging upgrades on the TNM staging system after the follow-up axillary node clearance. The chance of upgrade of nodal staging by the number of positives nodes identified in the SNB is as follows: one positive node on SNB: $n=5/59$ (8.5%), two positive nodes on SNB: $n=6/27$ (22.2%), and three positive nodes on SNB: $n=6/8$ (75%).

The number of positive nodes in the SNB [OR 2.40 (CI 95% 1.27–4.53), $P=0.006$] and the SNB ratio of positive to total nodes [OR 11.09 (CI 95% 2.33–52.72), $P=0.002$] had a significant association with the identification of positive nodes in the ANC (Table 3). There were three disease characteristics that had a significant association with the upgrading of nodal staging as a result of the completion of ANC (Table 4). These factors were the

Table 2

Specificity of different cut-off SNB ratio (positive to total nodes) for identifying negative ANC and no further upgrade of nodal staging in completion ANC.

Ratio of SNB (positive node/ total number of nodes)	Total number of patients	Positive node in ANC	Specificity	Number of patients with upgrade of ANC	Specificity
< 1.0	102	42	58.8%	19	81.40%
< 0.75	67	22	67.2%	9	86.60%
< 0.5	57	14	75.0%	2	96.50%
< 0.33	24	5	79.2%	1	95.80%
< 0.25	8	1	87.5%	0	100%

ANC, axillary nodal clearance; SNB, sentinel lymph node biopsy.

number of positive nodes in SNB [OR 3.07 (CI 95% 1.50–6.28), $P=0.002$], SNB ratio [OR 17.71 (CI 95% 2.33–134.58), $P=0.006$] and ECS [OR 3.44 (CI 95% 1.11–10.67), $P=0.03$].

Discussion

The positive to total number of lymph nodes ratio in SNB is a key determinant of finding more nodes with macrometastasis in completion ANC. Similarly, a low SNB-positive to total number of nodes with macrometastasis ratio of less than 0.25 indicates that there is minimal chance of finding another node with macrometastasis and upgrade of nodal staging. Similarly, the chance of finding another positive node in the ANC and upgrade in nodal staging as a result of it is less than 5%. The palpable lymph nodes found intraoperatively should be excised as a large proportion of them were found to have macrometastasis in them, particularly, those patients with extracapsular spread.

The benefit of SNB in patients who are SLN negative is the avoidance of ANC, which is associated with greater postoperative morbidity and the risk of lymphoedema[3,13,14]. Those who are SLN-positive have conventionally undergone ANC to identify possible nonsentinel lymph node (NSLN) involvement to provide accurate nodal staging and guide treatment[3,6]. However, studies have shown that the SLN is the only positive node in 40–70% of cases with axillary metastasis, rendering ANC unnecessary in these patients[13]. This is supported by observational studies which highlight the low incidence of regional recurrence in patients with 1–2 positive SLNs who did not undergo ANC[15]. The subsequent need to re-evaluate the role of ANC in SLN-positive patients has led to a number of rando-

Table 3

Disease characteristics associated with positive node in the ANC.

Disease characteristics	Odds ratio	95% CI	*P*
Premenopausal status	1.37	(0.5413–3.5125)	0.50
T stage	1.70	(0.9786–3.0760)	0.06
Grade	0.90	(0.4436–1.8295)	0.77
Low HER2 score (+1/+2)	0.91	(0.4096–2.0088)	0.81
Number of positives nodes in SNB	2.40	(1.2743–4.5301)	0.006
Total nodes in SNB	1.10	(0.7779–1.3241)	0.90
SNB ratio positive to total nodes	11.09	(2.3330–52.7272)	0.002
ECS (extracapsular spread)	2.49	(0.8956–6.9530)	0.08

HER2, human epidermal growth factor 2 receptor; SNB, sentinel lymph node biopsy.

Table 4

Disease characteristics associated with the upgrading of nodal staging in ANC.

Disease characteristics	Odds ratio	95% CI	P
Premenopausal status	0.81	(0.2398–2.7647)	0.74
T stage	1.70	(0.8498–3.4216)	0.13
Grade	1.17	(0.4827–2.8476)	0.72
Low HER2 score (+1/+2)	1.39	(0.5668–3.4231)	0.47
Number of positives nodes in SNB	3.07	(1.5052–6.2895)	0.002
Total nodes in SNB	1.18	(0.8651–1.6002)	0.30
SNB ratio positive to total nodes	17.71	(2.3313–134.5879)	0.006
ECS (extracapsular spread)	3.44	(1.1133–10.6722)	0.03

HER2, human epidermal growth factor 2 receptor; SNB, sentinel lymph node biopsy.

mised control trials to address the issue. These studies show ANC can be safely avoided in early breast cancer with axillary metastasis, where breast conserving surgery with adjuvant therapy is sufficient for disease control[6,8,16]. The IBCSG-23-01 study showed disease-free survival in patients with micrometastasis on SNB without ANC was noninferior to the arm undergoing the procedure[16]. The ACOSOG Z0011 trial showed that even in macrometastasis on SNB, a subset of patients did not benefit from ANC in terms of recurrence rate or survival[6]. Adding to this evidence, the AMAROS trial also showed the axillary recurrence rate of patients treated with radiotherapy was noninferior to those treated with ANC[8]. Breast cancer treatment, even in the presence of SLN involvement, is subsequently shifting towards minimising axillary surgery[17].

However, the generalisability of these trials should be carefully considered. Eligibility for the Z0011 trial included patients with one or two positive SLN and this was the case for the majority (82%) of patients included in the IBCSG-23-01 study, of which 70% also had low volume micrometastasis less than 1 mm[6,16]. For those with positive SLN not eligible for these studies, the role of ANC is still debated.

The incidence of NSLN metastasis ranges from 24 to 65.7% and SNB has a false-negative rate as high as 16.7%[17–20]. In our study, a large proportion of palpable nodes other than those identified by the dual technique of SNB identification were found to contain macrometastasis. It is therefore important to predict patients likely to have NSLN metastasis who may benefit from ANC, and, conversely, those in which ANC is unlikely to be beneficial[21].

A growing number of studies have attempted to identify factors predictive of NSLN metastasis[3,7,9,20,21]. The clinicopathologic characteristics most strongly associated with NSLN metastasis include tumour size, number of positive nodes, size of metastasis and extracapsular spread[20,21]. In our study, the number of positive nodes was significantly associated with the identification of a positive node in ANC. In addition to this, extracapsular spread was also associated with the upgrading of nodal disease, which is consistent with the findings in other studies[20,22]. However, in isolation, these commonly explored factors have not been able to identify a subset of patients in whom ANC is unnecessary. Several nomograms containing various combinations of predictive factors have been developed and have performed well in their institutions, though external validation results have been variable[3,7,9,10,20,22,23]. The Memorial Sloan Kettering Cancer Centre model (MSKCC) is the most widely validated, based on nine factors, including age, tumour size, type, location, lymphovascular invasion, multifocality, histologic grade and receptor status[9]. In validation studies, variations in the AUC ranged from 0.58 to 0.86, attributed in part to differences in SNB and pathology evaluation[3,10,22,24,25]. Furthermore, the complexity of these models has subsequently made implementation in clinical practice challenging.

Our aim was to use a simple SNB ratio to predict the likelihood of a negative ANC, a less well-explored determinant of NSLN metastasis[20]. The proportion of positive lymph nodes greater than 50% of total lymph nodes has been recognised as a risk factor for NSLN metastasis and is included in the Cambridge model and Tenon score to predict the risk of NSLN positivity[20]. In our study, a high SNB ratio was the most strongly associated with both positive nodes in ANC and upgrading of staging compared to other characteristics. Moreover, a low SNB ratio of less than 0.33 (1/3) had a high specificity to identify cases with negative ANC, and crucially, exclude upgrading of nodal staging at ANC with a false-negative rate of less than 5%.

This is comparable to the performance of a number of nomograms published in the literature[7,10,23,26].

Our study has some limitations. As in the ACOSOG Z0011 and IBCSG-23-01 study, the patients in our study were ER-positive and therefore may not be applicable to other biological subtypes. We did not include patients with neoadjuvant chemotherapy to attribute results such as negative clearance to clinicopathological characteristics rather than a response to chemotherapy. As a single-centre cohort study, it would be beneficial to apply this prospectively to cases in different centres to add to the data available.

Based on the results of our study, we do not recommend completion of axillary node clearance if the SNB-positive to the total number of nodes ratio is low because the likelihood of finding another positive node with macrometastasis in ANC is low and there is a less than 5% chance of upgrading of nodal staging. These patients may have more benefits of having axillary radiotherapy, which have similar therapeutic benefit to ANC without a higher risk of lymphoedema [6]. This study identifies a routinely available, single-parameter indicator of low risk for NSLN metastasis, which can be used to inform patients and identify patients with positive SNB who are unlikely to have further axillary metastasis and would not benefit from ANC.

Ethical approval

Ethical approval from the local surgical audits department.

Consent

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Author contribution

J.R.: data collection and writing the paper; L.R.M.: writing the paper; A.P.: data collection; T.G.: study concept and design; A.R.:

study concept and design, data analysis and interpretation, and writing the paper.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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