The Role of redo-Sentinel Lymph Node Biopsy in Patients With Prior Ipsilateral Breast Cancer Surgery

Margo-Rose F. Macnab,[1] Gabrielle Slater,[2] Mairi Fuller,[2,3] Beatrix Elsberger,[2,3] Lesley Lovell,[1] Roger T. Staff,[1] Yazan A. Masannat[2,3]

Abstract

This a retrospective study comparing redo-Sentinel Lymph Node Biopsy (reSLNB) and Axillary node sample looking at patients with recurrence with history of breast-conserving surgery. Our data shows that 35(72.9%) of reSLNB were successful with node positivity that is comparable to Axillary node sampling. reSLNB success rate was lower amongst patients with previous axillary surgery and previous positive nodes.

Background: Sentinel Lymph Node Biopsy (SLNB) is used to stage the axilla, but there is limited data in patients with prior ipsilateral breast cancer. This study compares redo-SLNB (reSLNB) and Axillary node sample (ANS) in this sub-cohort of patients. **Materials and Methods:** This is a retrospective study looking at patients with a new ipsilateral primary or recurrence with history of breast-conserving surgery. Planned and performed surgery, patient demographics and previous treatments were recorded. Node positivity and success rate of reSLNB was analyzed. **Results:** A total of 86 patients were identified that had mastectomy for ipsilateral recurrent disease with radiologically negative axilla. Out of the 48 that had reSLNB, 35(72.9%) were successful. Nineteen percent of the reSLNB had positive axillae and 20% of the ANS patients. reSLNB success rate was significantly lower amongst patients with previous axillary surgery ($P = .014$) and previous positive nodes($P = .001$). **Conclusion:** reSLNB should be considered to restage the axilla in patients with previous history of ipsilateral cancer especially that there is growing evidence showing good identification rate.

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Keywords: Axillary node sample, Breast cancer recurrence, Sentinel node biopsy, Axillary Surgery, Breast surgery

Introduction

Breast cancer is one of the leading causes of cancer deaths in women.[1] Around 55,000 new cases are diagnosed in the UK every year, with a 5-year survival of 85% or more.[2] However, up to 41% of breast cancer survivors with T2N2 disease will experience recurrence; this drops to 26% for T2N0 and 13% for T1N0.[3] The optimum management of these patients is unclear, particularly the surgical management of the axilla.

There is a trend for de-escalation of surgery in the axilla that have evolved over the years. For the past 2 decades, Sentinel Lymph Node Biopsy (SLNB) has been used to stage clinically node-negative axillae supported by many randomized controlled trials (RCTs) showing no difference in survival or recurrence, with significantly less morbidity.[4,5] Unfortunately, there is limited published data with no prospective randomized control trials comparing SLNB with other treatment options in those with recurrent ipsilateral breast cancer. The reports that exist are retrospective with various recruitment strategies, conducted in a range of settings with the technique's success ranging from 55% to 77%.[6-9] A recent meta-analysis has highlighted the weaknesses in the literature as there is heterogeneity in the surgical technique, mapping method and radiation history.[10] This analysis reported an aggregated success rate of 71.9% with a false negative rate of the successful reSLNB of less than 10%. A meta-analysis stratified by Maaskant-Braat et al reported a significantly higher identification rate among patients who had undergone the previous SLNB than previous ALND (81.0% vs. 52.2%).[11] These results suggest that surgical history influences the likelihood of success, although it is not clear which other factors play a role.

This study compares redo-SLNB (reSLNB) and Axillary node sample (ANS) in surgically staging the axilla with either ipsilateral new breast primary or breast cancer recurrence, with previous breast conservation with or without previous axillary surgery. Here we document the local shift in surgical practice, which effectively created a dual-arm study simultaneously acquired. The shift in practice came about mainly by new surgeons who trained elsewhere

Abbreviations: SLNB, Sentinel Lymph Node Biopsy; reSLNB, redo-Sentinel Lymph Node Biopsy; ANC, Axillary Node Clearance; ANS, Axillary Node Sample; DCIS, Ductal Carcinoma in Situ; RCT, Randomized Controlled Trial; ITC, Isolated tumor cells.

[1]Nuclear Medicine Department, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK
[2]The School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, Scotland, UK
[3]The Breast Unit, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

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Address for correspondence: Yazan Masannat, MBBS, MRCSI, MRCSEd, DBRM, FEBS, FRCSEd, MD, The Breast Unit, Aberdeen Royal Infirmary, Aberdeen, Scotland AB25 2ZN, UK.
E-mail contact: yazanmas@hotmail.com, yazan.masannat2@nhs.scot

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and existing staff embracing the new technique once exposed to the new approach. Axillary node sampling has been used to stage the axilla in Scotland before introducing SLNB. It is considered a conservative approach to stage the axilla with equivalent outcomes compared to an axillary clearance[12] and comparable results to SLNB.[13] We aim to examine the success rate using reSLNB in comparison to ANS to restage the axilla and identify the patient characteristics associated with the surgical node identification and node positivity in our local cohort.

Methods

This is a retrospective study, looking at our local data extracted from the clinical archive of all breast cancer surgery patients operated on between January 1, 2014 until December 31, 2019 at Aberdeen Royal Infirmary (NHS Grampian). This setting is the tertiary referral centre for the North East of Scotland. We identified the electronic record for all patients with a new ipsilateral primary or recurrent cancer with history of breast-conserving surgery (with or without previous axillary surgery) that had clinically and radiologically negative axilla on presentation. Planned and performed surgery, patient demographics and previous treatments were recorded. We compared node histology between the reSLNB and ANS groups, excluding patients that were found on final histology to have pure in situ disease. We considered both micro-metastasis (metastatic deposit 0.2 mm-2 mm) and macro-metastasis (deposit of $>$ 2 mm) as a node-positive disease while isolated tumor cells (ITC) as node-negative (deposit of $<$ 0.2 mm).

The database identified 3 regimes from the previous radiotherapy treatments: (1) Patients who received 1 course to the breast of 40Gy (15 fractions); (2) patients who received 42.6Gy (20 fractions) and 15Gy (5 fractions) to the breast; (3) patients who received radiotherapy to the breast and supraclavicular/axilla region.

The local clinical governance department and Caldicott guardian approved this retrospective study's data collection and analysis. IBM SPSS 25 (Armonk, New York, USA) was used to perform the statistical analysis.

Results

In the 6-year study period, we identified 1026 patients that had mastectomies in our hospital. Eighty-six of those patients were for either a new ipsilateral primary or recurrent disease and all these patients' axillae were assessed and found to be clinically and radiologically negative preoperatively. These 86 patients were planned to have either ANS (38) or reSLNB (48) according to the operating surgeon's preference, and these patients were operated on by eleven different surgeons. None of the surgeons over this period used exclusively 1 technique but there was a noticeable shift of practice from ANS to reSLNB at the end of the observed period, showing the dominance of the reSLNB approach at our local practice (Figure 1A).

Figure 1B shows the completed procedures and treatment pathways for each cohort. Out of the 48 that had reSLNB as their planned operation, 35 (72.9%) were successfully done. In 11 cases, there were no identifiable sentinel nodes and, therefore, an axillary node sample was performed. In 2 patients, there were no identifiable nodes at all 1 of which had likely a full axillary node clearance but that wasn't confirmed as their initial surgery was elsewhere (Figure 1). In the ANS arm, no axillary lymph nodes were found intraoperatively in 1 patient only out of 38 (ANS identification rate of 97.4%).

Table 1 shows the similarities and differences between the groups analyzed according to the performed surgery as per protocol. The groups were not significantly different in terms of age, Lymphovascular invasion, HER2 status and Tumor size (Mann-Whitney test, $P > .05$). As expected, there were more nodes sampled from the ANS group as we aim surgically for a 4-node sample. There were no differences between the groups regarding DCIS, invasive disease, IDC, IDC or grade and the number of patients with positive nodes. For the node positivity, the analysis included 35 patients in the reSLNB group and 48 ANS group. The ANS group consisted of 37 planned ANS, and 11 failed reSLNB that defaulted to an ANS. We excluded twelve patients with Ductal Carcinoma in Situ (DCIS) from the final pathology comparison, 8 from the reSLNB group and 4 ANS group when looking at node positivity. Of the remaining 27 reSLNB patients, 5 (19%) had positive axillae, including 3 macro- and 2 micro-metastases. From the 44 ANS patients, 9 (20%) exhibited positive nodes in the axillae, which showed no significant difference compared to reSLNB positive rates ($P = .842$). Three further ANS patients exhibited ITC, 1 in the axilla and 2 in internal mammary nodes.

We examined previous local treatments to assess their effect on the reSLNB identification rate (Table 2). Success rates were significantly lower amongst patients who had previous axillary surgery ($P = .014$) and in the patient who had previous positive nodes ($P = .001$). Success was not associated with the previous SLNB or ANS ($P = .770$) or the time between the original breast cancer and the recurrence. Patients who had previous radiotherapy to the breast and axilla (regime 3) had significantly lower success rates of reSLNB when compared to patients who had received 1 course to the breast only (regime 1) (Table 2). Those patients who had previously received regime 2 to the breast showed no significant difference in success rates compared to regimes 1 or 3. Comparing regimes 1&2 with those who received breast and axilla radiotherapy (regime 3) showed that axilla radiotherapy reduced success.

Discussion

This study reports a success rate of 73% of reSLNB for recurrence breast cancer patients, keeping with previous studies.[6-9] The majority of cases in our study that had a failed reSLNB underwent an ANS instead. Another important finding is that there is no significant difference in detecting axillary spread when comparing successful reSLNB against ANS. The majority of cases in our study that had a failed reSLNBx underwent an ANS instead. Another important finding is that there is no significant difference in detecting axillary spread when comparing successful reSLNB against ANS. However, treatment history has a substantial effect on the success of rates of reSLNB procedures. Significantly lower success rates are present in patients who had previously undergone axillary surgery, particularly those with previously positive axilla. Patients with previous external beam radiotherapy to the axilla or supraclavicular region also demonstrated significantly lower success rates of reSLNB when compared to the breast only radiotherapy.

Table 1 Demographic, Pathological and Surgical Comparison Between the Successful reSLNB and ANS Samples

Surgery Completed	reSLNB	ANS
Number of patients	35	48
Median age (y) (range)	67.2 (39-84)	70.2 (51-89)
LVSI	7 (20%)	7 (15%)
HER2 positive	4 (11%)	5 (10%)
Largest tumor size median (mm) (range)	22 (4-154)	20 (6-54)
Median nodes removed (range)	2 (1-8)	5 (2-12)[a]
DCIS only (no invasive disease)	8 (23%)	4 (8%)
Patients with invasive disease	27 (77%)	44 (92%)
IDC	23 (85%)	30 (68%)
ILC	4 (15%)	9 (20%)
Invasive		
Grade 1	2 (7%)	1 (2%)
Grade 2	14 (52%)	24 (55%)
Grade 3	11 (41%)	19 (43%)
Node positive (Axilla) in patients with invasive disease *(Macro and Micro Mets)*	5/27 (19%)	9/44 (20%)
Previous Axillary surgery		
SLNB	5	15
None	11	6
ANS or C	12	20
Missing	7	7

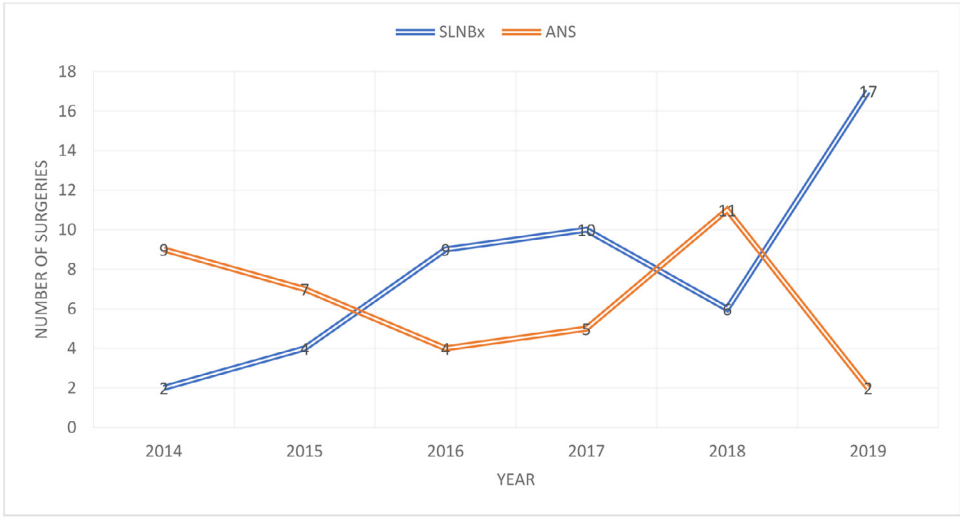
[a] Indicated a significant difference between the 2 groups $P < .05$ (Mann-Whitney test).

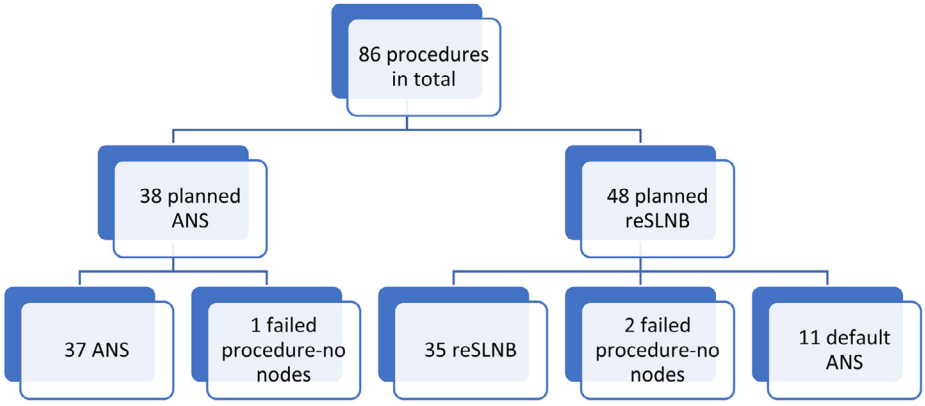
Table 2 A History Comparison Between the Successful reSLNB Patients and the Failed reSLNB

	Successful reSLNB					Failed reSLNB				
Previous axillary surgery	19/35					12/13				
P value	.014[a]									
Surgery type	SLNB	ANS	ANC	Unknown		SLNB	ANS	ANC	Unknown	
	7	11	0	1		5	6	1	1	
P value (between SLNB and ANS)	.770									
Previous node positivity	Positive	Negative	Unknown			Positive	Negative	Unknown		
	0	15	4			6	4	3		
P value	.001[b]									
Previous radiotherapy	33/35					13/13				
P value	.260									
Radiotherapy regime	1 breast only	2 breast x2	3 breast +axilla	Oth	Un	1 breast only	2 breast x2	3 breast +axilla	Oth	Un
	12	4	0	3	14	2	3	3	0	5
P value between regimes[a]: 1 v 3	.014[a]									
1&2 v 3	0.009[b]									
Years between recurrence and initial cancer (mean)	12.6					11.4				
P value	.218									

P values have been found using Fisher's exact test or independent sample *t* test as appropriate. Radiotherapy regimes are as follows: regime 1: 40Gy to the breast over 15 fractions, regime 2; 42.6Gy in 20 fractions plus 15Gy in 5 fractions, regime 3: any dose with fields to both the breast and supraclavicular region/axilla. Oth denotes other, Un denotes unknown.
[a] A significant difference between groups is indicated at 0.05.
[b] A significant difference between groups is indicated at 0.01.

Figure 1 (A) The use of each time technique over the observed period. (B) The planned initial surgical strategy at reoccurrence and final technique for the retrospectively identified patients. ANS = axillary node sampling; reSLNB = repeat sentinel lymph node biopsy.





The strength of this study is in this analysis of previous treatments with reSLNB success rates and that the 2 arms of the study show no differences. A range of prior therapies was included for analysis and directly compared with reSLNB success rates, including data from consecutive recurrence mastectomy patients over 6 years. However, the main weaknesses are the small number of patients in each arm and the single-site nature.

The success rate of 73% found in this study is comparable to previous studies and includes higher or similar patient numbers.[7,9,14-17] The results show no difference in the positive rates between the reSLNB and ANS techniques, suggesting that reSLNBx has a low false-negative rates. The results also add to the growing body of evidence supporting the feasibility and use of reSLNB following previous breast conserving surgery.[10]

These results demonstrate the appropriateness of reSLNB in a setting with varied surgical and radiotherapy treatment histories. Here we partly address the lack of data on particular patient groups highlighted in a recent meta-analysis.[10] Patients who have previously only undergone axillary node samples are underrepresented in the literature and included here.

The significant overall success rate of reSLNB suggests that the lymphatic structure in the axilla posttreatment for the original disease restructures or recruits new sentinel pathways. The success rates observed here indicate that lymphatic pathways remain in more than two-thirds of patients. This restructuring, however, is probably affected by specific surgical and radiotherapy treatments. The time between initial breast cancer and recurrence does not significantly differ between successful and unsuccessful reSLNB procedures. When this restructuring occurs is unclear, but given

the absence of any association with time, it would suggest that it appears early in the posttreatment period. If time was a factor, then we would expect success to increase with time. Although this was an observational study examining the impact on local practice, the use of advanced imaging techniques such as SPECT/CT and PET/CT and potentially virtual reality may reduce the number of surgical fails and inform surgical planning. [Taumberger 2020 https://doi.org/10.1159/000496504].

In the past 2 decades, there has been a gradual de-escalation of axillary surgery supported by a large body of evidence moving from axillary node clearance to SLNB.[4,5] This is followed by further de-escalation and not clearing the positive axillae on SLNB in a selected sub-cohort of patients.[18] However, there is always a limit on de-escalation strategies where there is a lack of evidence. While some will aim for re-exploration and clearing every axilla in patients with new ipsilateral primary or recurrence, others may withhold axillary staging in the clinically and radiologically node-negative axillae. Our approach with reSLNB is a middle ground that we feel should be the primary option for this specific patient group. The combination of surgical and radiotherapy history, possibly combined with imaging, may guide optimum patient outcomes, and reduce surgical failure. Groups such as Sloan Kettering have investigated redoing SLNB and indicated that it is feasible but may not be worth it,[7] arguing that biology is the best guide for therapeutic decisions. However, restaging may be of value and de-escalation is preferred. These findings indicate that SLNB is a viable tool in that restaging process. However, restaging may be of value if de-escalation is preferred. Our findings indicate that SLNB is a viable tool in the restaging process. Future studies to strengthen the knowledge base would include replicating our results in a larger sample or, ideally, a prospective, multicentered, randomized trial. At a more basic level, studies focused on understanding how radiotherapy and surgery change the axially lymphatic structure leading to a successful reSLNB in the future, would be of interest and may modify the initial surgical strategies.

Clinical Practice Points

Sentinel Lymph Node Biopsy (SLNB) is used to stage the axilla, but there is limited data in patients with prior ipsilateral breast cancer.

This study compares redo-SLNB (reSLNB) and Axillary node sample (ANS) in this sub-cohort of patients.

In our cohort, 72.9% of patients that had reSLNB it was successful.

Node positivity is 19% of the reSLNB and 20% of the ANS patients which is showing that both have node positivity and comparable in staging the axilla. reSLNB success rate was significantly lower amongst patients with previous axillary surgery($P = .014$) and previous positive nodes ($P = .001$). reSLNB should be considered to restage the axilla in patients with previous history of ipsilateral cancer especially that there is growing evidence showing good identification rate.

Statement of Ethics

This study was a retrospective review of our usual practice, so it did not need to have ethics committee approval. Because there is patient information included in the data collected for analysis, we applied for a Caldicott Guardian Approval through the local clinical governance department at NHS Grampian and that was approved.

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Disclosure

The authors have no conflicts of interest to declare.

Authors' Contributions

Yazan Masannat (YM) and Roger Staff (RS) designed the study. Gabriella Slater (GS), Margo-Rose Macnab (MM), Lesley Lovell (LL), Mairi Fuller (MF), Beatrix Elsberger (BE), YM and RS all helped collecting the data. Data was analyzed initially by YM, RS, MM, and then revised by all authors. The manuscript was read and approved by all authors.

Data Availability Statement

The data collected was anonymized and analyzed and the data analyzed is included in the tables. We don't have the permission to publicly share the data from the Caldicott Guardian application through the local governance department, but the data will be kept for few years after publication with the corresponding Author (YM) and any further enquiries can be directed to him.

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