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ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy After Initial Lumpectomy (SNAIL Study)—a Prospective Validation Study

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Abstract

Tertiary oncology center clinicians are commonly faced with the problem of managing patients with a diagnosis of breast cancer made after lumpectomy in the Primary Health Care (PHC) setting. There are no studies or guidelines that address the further surgical management in this group of patients regarding sentinel lymph node biopsy (SLNB) and need for breast post-operative cavity excision. Prospective observational study was planned to evaluate the feasibility of SLNB and defining the need for definitive breast surgery in patients diagnosed with breast cancer after lumpectomy in PHC. The study was carried out from January 2015 to August 2017 in Tata Medical Center, India, approved by institutional review board (EC/TMC/36/14). Seventy patients who underwent lumpectomy with a definitive histological analysis of breast cancer were included in this study. Each patient had definitive breast surgery and SLNB using subareoral blue dye injection followed by validation axillary dissection. The identification rate (IR) for SLNB was 92% (64/70). The median number of SLNs removed was 2 (IQR 1, 3). There were 2 patients with false negative results resulting in false negative rate (FNR) of 11%. Overall, SLNB procedure has the sensitivity of 89%, NPV of 96%, and accuracy was 97%. Peri-areoral incision of initial surgery was associated with low IR (84%) and high FNR (33%). Final histopathology showed residual invasive cancer in 43% and ductal carcinoma in situ in 14% of patients. Among 21 patients where initial lumpectomy histopathology margin was free of cancer, residual malignancy was found in 57% of patients. Prior excision of lumps for breast cancer does not affect the accuracy of SLNB. Peri-areoral scar may be associated with high FNR and low IR, although further studies are needed to validate this statement. Definitive breast surgery is required for all patients, irrespective of initial lumpectomy histopathological margin status.

Keywords Breast Cancer · Sentinel lymph node biopsy

Introduction

The standard of care for patients with breast lumps mandates a good-quality core biopsy for histological diagnosis, and all guidelines are based on a clear diagnosis of breast cancer before starting any oncological treatment. However, in some parts of the world, specialized breast services are not widely available, and clinicians working in oncology centers are commonly faced with the problem of managing patients with a diagnosis of breast cancer made after lumpectomy in the primary or private health care setting [1]. These patients usually have both sub-optimal surgery and incomplete pathology reports from non-specialist laboratories. There are no studies or guidelines that address this challenge, which is more common in those countries, where specialized breast services are sparse.

When the diagnosis of breast cancer is made on post-operative histology after lumpectomy, patients are often offered completion mastectomy, although for women who desire breast conservation cavity excision might be a considered as an alternative. These patients usually have a full axillary dissection, as Sentinel Lymph Node Biopsy (SLNB) after prior lumpectomy is not a routine practice, and most SLNB studies specifically exclude patients with previous surgery [2, 3].

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The concern is that ipsilateral breast or axillary surgery could damage the lymphatic pathways, which might result in higher false negative rates and inaccurate lymph node staging. The most recent ASCO guidelines, however, do recommend SLNB in this particular subgroup, although the evidence is based on two non-randomized observational studies [4–6].

The current understanding of the lymphatic anatomy of the breast is that lymphatics from all quadrants first converge into the sub-areolar plexus, and then drain to the axilla via one or two common afferent lymphatic channels [7, 8]. This theory of a common lymphatic pathway is the basis for SLNB in multicentric tumors, where the lymphatic contrast is injected in the subareolar region [9]. Based on the same premise, SLNB may also be feasible following lumpectomy or excisional biopsy, with subareolar dye injection regardless of the initial lumpectomy site.

The aim of the present study, Sentinel Lymph Node Biopsy after Initial Lumpectomy (SNAIL), was to assess the feasibility of sentinel lymph node biopsy in women diagnosed with breast cancer who present after excision of the primary, using subareolar methylene blue dye injection. The secondary aim was to study the incidence of residual breast cancer in the re-excision specimen, and define the need for revision breast surgery along with axillary staging in this subgroup.

Materials and Methods

Sentinel Lymph Node Biopsy After Initial Lumpectomy (SNAIL) is a prospective single center study in a tertiary cancer institute, with two breast surgeons with extensive experience of SLNB. Following approval by the institutional review board (EC/TMC/36/14), informed consent was taken from a consecutive series of patients suitable for inclusion, and participants were enrolled from January 2015 to August 2017. All patients had excision of the presenting lump at other hospitals before enrollment in this study and had invasive breast cancer confirmed in our accredited hospital laboratory. Women clinically staged as T1–T3, N0 were eligible. All patients had a mammogram performed in our hospital before re-surgery. Patients with non-invasive breast cancer, clinically positive nodes, history of allergy to methylene blue dye, pregnancy, or renal failure were excluded.

All patients had SLNB performed at the same time as definitive surgical management for the breast. Depending on the extent of the previous surgery, either cavity excision or completion mastectomy was offered. The location of the primary tumor was estimated on the basis of the pre-lumpectomy clinical assessment, the surgical scar and induration, and post-op changes in mammography. Methylene blue, 2 ml of 1% solution, was injected in the subareolar region in the upper outer quadrant of the nipple areolar complex just before surgery, followed by 5 min of gentle massage of the whole breast. All nodes that were visibly blue or were contiguous with a blue lymphatic vessel were excised. For all patients, SLNB was followed by validation axillary dissection. For this study, frozen section was not performed. Sentinel nodes and the remainder of the axillary dissection specimen were submitted separately for histopathological examination (HPE).

Lymph nodes were cut into slices at 2-mm intervals in the major axis and submitted for in their entirety for hematoxylin and eosin (H&E) staining. If the initial H&E stained section was negative, four further levels were cut, three of these were stained with H&E and one randomly chosen section with anti-cytokeratin antibody cocktail (cytokeratin AE1–AE3; Dako Corporation, Denmark) with a positive control. In the axillary dissection specimen, lymph nodes more than 5 mm in maximum dimension were sliced at 2–3-mm intervals perpendicular to the long axis, and nodes less than 5 mm were submitted entirely for H&E staining. SLNs were classified as negative (no metastasis), isolated tumor cells (< 0.2 mm), micro-metastatic (0.2–2 mm), or macro-metastatic (> 2 mm). For patients having cavity excision, the outer surface of the re-excision specimen was marked by the surgeon, and the entire specimen was processed. For completion mastectomy specimens, representative sections were submitted from all gray-white or suspicious-looking areas.

Statistical Analysis

Failed SLNB was defined as the inability to identify any blue nodes during operation. Identification rate (IR), negative predictive value (NPV), sensitivity, false negative rate, (FNR) and accuracy were calculated as follows:

$$\text{IR} = \text{Subjects with successful SLN identification/total number of subjects}$$
$$\text{NPV} = \text{TN}/\text{TN} + \text{FN}$$
$$\text{Sensitivity} = \text{TP}/\text{TP} + \text{FN}$$
$$\text{False-negative rate} = \text{FN}/\text{FN} + \text{TP}$$
$$\text{Accuracy} = \text{TP} + \text{TN}/\text{TP} + \text{TN} + \text{FP} + \text{FN}$$

**TN*, true negative; *TP*, true positive; *FP*, false positive; *FN*, false negative

Chi-square test, Fisher's exact test, and Student's *t* test were used to compare predicting factors in different groups (SLN identified with failed identification, true negative with false negative). All statistical tests were two-sided, and $P < 0.05$ was considered significant. SPSS version 23.0 (SPSS Inc., Chicago, IL) was used for the analysis.

Results

During the study period from January 2015 to August 2017, 116 women presented with a post-lumpectomy diagnosis of breast cancer, and 70 met the inclusion criteria and consented to participate in this study. Patient and disease characteristics

are summarized in Table 1. Median age was 45 years (IQR 39, 55) and median BMI was 25.8 kg/m^2 (IQR 22.4, 28.6). Median interval between lumpectomy and definitive surgery was 35 days (IQR 15, 50). The median tumor size at initial lumpectomy, taken from pathology reports done outside our hospital, was 22 mm (IQR 17, 33), with pT1 in 31%, pT2 in 64%, and pT3 in 5% of patients. Margin status was not mentioned in the outside pathology report in 51% of patients, was reported as free of tumor in 30%, and as involved in 19%. The location of the primary tumor was in the lateral, medial, and central quadrants in 40%, 26%, and 34% of patients. The initial lumpectomy scar was located peripherally in 73% and peri-areolar in 27% of patients.

Results of SLNB are summarized in Tables 2 and 3. SLN localization was successful in 64 (92%) out of 70 patients. The median number of SLNs removed per patient was 2 (IQR 1, 3). Eighteen (28%) patients had positive sentinel nodes. There were 2 patients with false negative results (sentinel node negative, with positive nodes in completion axillary dissection), resulting in an accuracy of 97%. The NPV was 96%, sensitivity was 89%, and FNR was 2 out of 18, or 11%. Overall, 3% of all patients who had successful localization had a false

Table 1 Patient and disease characteristics

Age (years), median (IQR)	45 (39, 55)
BMI (kg/m^2), median (IQR)	25.8 (22.4, 28.6)
Duration in days between lumpectomy (first surgery) and second surgery, median (IQR)	35 (30, 50)
Initial lumpectomy size in cm, median (IQR)	2.2 (1.7, 3.3)
T stage—post-lumpectomy histopathology	
T1	19 (31%)
T2	39 (64%)
T3	3 (5%)
Margin status of first surgery (lumpectomy)	
Free	21 (30%)
Involved	13 (19%)
No comment	36 (51%)
Tumor location of first surgery	
Lateral	28 (40%)
Medial	18 (26%)
Central	24 (34%)
Scar location of first surgery	
Peri-areolar	19 (27%)
Peripheral	51 (73%)
Type of cancer	
Invasive mammary carcinoma (NOS)	65 (93%)
Invasive lobular carcinoma	3 (4%)
Mucinous carcinoma	1 (1.5%)
Papillary carcinoma	1 (1.5%)
Grade of tumor	
Grade 1	4 (6%)
Grade 2	31 (44%)
Grade 3	32 (46%)
Unknown (poorly processed lumpectomy slides)	3 (4%)
ER status	
Positive	45 (64%)
Negative	25 (36%)
PR status	
Positive	49 (70%)
Negative	21 (30%)
Her2 status	
Positive	6 (8.5%)
Negative	58 (83%)
Equivocal	6 (8.5%)

Table 2 Sentinel lymph node biopsy results

Total number of SLNB procedure taken ($n = 70$)	
Failed mapping procedure	6/70 (8.5%)
Sentinel node identification rate	64/70 (91.5%)
Sentinel node pathological findings	
True positive	16/64 (25%)
True negative	46/64 (72%)
False negative	2/64 (3%)
False negative rate (FNR)	2/18(11%)
Impact of false negatives on whole series	2/64 (3%)
Sensitivity	16/18 (89%)
Negative predictive value (NPV)	46/48 (96%)
Test accuracy	62/64 (97%)
Number of sentinel lymph nodes (median, IQR)	2 (1, 3)
1 SLN	20/64 (31%)
> 1 SLN	44/64 (69%)
SLN pathology	
Micrometastasis (0.2 to 2 mm)	2/16 (12.5%)
Macrometastasis (> 2 mm)	14/16 (87.5%)
True positive patients with sentinel LN as the only positive node	8/16 (50%)

negative result. The sentinel node was the only positive node in 50% of true positive patients, and more than one SLN was identified in 69% of patients.

There were no statistically significant differences in SLN identification rates or false negative rates with increasing age, tumor size, BMI, or the interval between lumpectomy and SLNB. Identification rate was not associated with the quadrant of tumor or location of scar of initial lumpectomy. FNR was not associated with the quadrant of the initial tumor. However, the position of the previous surgical was significantly associated with a false negative result, with both false negative patients had lumpectomy done through peri-areolar incisions ($P < 0.05$). Overall, a peri-areolar position of the surgical scar was significantly related to failure of the SLNB technique (non-identification + false negative result) in 26% of patients, compared to only 6% if the incision was peripherally placed.

Results of breast surgery are summarized in Table 4. Pre-lumpectomy mammography and/or USG breast was done only in 10 out of 70 (15%) patients. All patients have undergone mammography and USG of bilateral breast before second surgery (cavity excision/completion mastectomy). Mammography after initial surgery showed post-operative changes only (no residual mass or calcification) in 64 patients, of which 35 (54%) had residual cancer in their final HPE report. Breast conservation (excising the entire cavity of the previous lumpectomy) was possible in 89% of patients. Final histopathology showed residual invasive cancer in 43% of patients, ductal carcinoma in situ in 14%, and 42% with no residual disease. Among 21 patients where initial lumpectomy was reported by outside labs as having clear margins, residual malignancy, either invasive or in situ, was found in 57% of patients. Residual cancer was present in 68% of patients who had undergone lumpectomy with peri-areolar incision compared to 53% in patients with excision done by peripheral incision ($P = 0.28$).

Discussion

This study uncovered a number of important findings in this group of patients, who presented to a tertiary care cancer

Table 3 SLNB parameters (false negative defined as patients with SLN negative but metastatic axillary nodes in validation ALND)

	Identification rate (%)		NPV (%)	Sensitivity (%)	FNR (%)		Accuracy (%)
Tumor location							
Lateral	89	$P = 0.66$	100	100	0	$P = 0.16$	100
Medial	89		100	100	0		100
Central	96		89	71	29		91
Scar location							
Peri-areolar	84	$P = 0.33$	83	67	33	$P < 0.05$	88
Peripheral	94		100	100	0		100

Table 4 Breast re-excision data (cavity excision/completion mastectomy)

Type of second breast surgery	
Breast conservation	62/70 (89%)
Mastectomy	8/70 (11%)
Residual breast cancer on post-lumpectomy mammogram	
Post-operative change (no residual calcification or mass)	64/70 (91%)
Residual calcification or mass present	6/70 (9%)
Residual breast cancer in re-excision specimen	
No residual disease	30/70 (43%)
Residual invasive breast cancer	30/70 (43%)
Residual DCIS	10/70 (14%)
Residual cancer in patients with lumpectomy margin reported free of tumor ($n = 21$)	
No residual disease	9/21 (43%)
Residual invasive breast cancer	10/21 (48%)
Residual DCIS	2/21 (9%)

center with a diagnosis of breast cancer following lumpectomy done by general surgeons or gynecologists. This situation is always a challenge for clinicians working in tertiary cancer centers, as there are no guidelines available for treating these patients. The burden of this type of presentation is significant in the developing world, with almost 10% of all breast cancer patients being treated in this hospital presenting after surgery done without a pre-operative biopsy, by surgeons without oncological training. In this situation, two important decisions are required. One is related to axillary management—is SLNB possible? The second is what is to be done for the breast—should there be further surgery for the breast if the initial histology report states that margins are clear, and should that be cavity excision or completion mastectomy? This study focuses on the dilemma of decision making in these patients.

Quality indicators for SLNB [10, 11] defined a target identification rate > 90%, with > 1 SLN in more than 60% of patients, and we have previously published our own data for patients having SLNB in the upfront surgery setting [12], which met the guidelines in all measures that could be assessed. In this study too, our identification rate was 92% and more than one SLN was identified in 69% of patients, which met the quality indicator's criteria. The trials which form the basis for the American Society of Clinical Oncology clinical guidelines [4, 13–19] for SLNB in early breast cancer were reported FNRs between 4.6 and 16.7%, NPVs ranging from 90.1 to 96.1% and overall accuracy ranging from 93 to 97.6%. In this study of SLNB in patients who have undergone prior lumpectomy, FNR was 11%, NPV was 96%, and accuracy was 97%, which are similar to the results from other published trials.

We reviewed studies, which reported sentinel lymph node biopsy following excisional biopsy or lumpectomy (Table 5) [5, 6, 15, 20, 21]. The GATA study [20] was based on excision biopsies as part of a national breast cancer screening program. Similarly, other studies also reported lumpectomy in a screened population, or invasive cancers identified after surgery for a presumptive diagnosis of DCIS, and have a majority of T1 tumors. In contrast, in our series, all patients initially presented with palpable lumps, resulting in a larger median tumor size, with 70% of patients having at least T2 tumors. Despite the larger excised specimens in this study, the IR, FNR, and NPV are comparable to the data from the other series, which include patients who have already had lumpectomy, where the reported IR ranged from 83 to 97%, NPV from 89 to 100%, and FNR from 0 to 15%.

There is extensive data on the use of methylene blue dye alone as a safe alternative to radioactive dye, with high identification rate and low FNR [24, 25]. We have previously reported the cost and logistic issues related to radioactive dye, and have validated the use of methylene blue alone in our own patients [12]. The rationale for the subareolar approach is based on the embryonic origin of breast lymphatic pathways, with breast lymphatic trunks, which drain uniformly to a few SLNs [7]. A multicentric RCT has concluded that central injection is a safe technique for SLNB, with high IR and low FNR [26]. Based on this data, we used methylene blue dye as a single agent for SLNB in this trial, with subareolar injection.

We found that the use of a periareolar incision for the initial lumpectomy was associated with failure of the technique of SLNB, (low IR and high FNR). This may be explained by interruption of the peri-areolar lymphatic channels or main draining trunks, which would be more likely with a periareolar incision than with a peripheral one. Some of the published studies suggest that the interval between the first and second surgery may influence the outcome of SLNB. One study recommends early second surgery (within 2 weeks), while another has advised a 1-month interval to reduce non-identification and false negative results [20]. In our study, however, the interval between two surgeries did not show an association with either IR or FNR.

Table 5 Review of Literature - studies that evaluated SLNB after previous breast surgery (studies with validation axillary dissection and sample size > 50)

Study	Study Design (N)	Population	Method of SLNB	T (mm) median (range)	pT Staging	IR %	NPV	FNR
SNAIL (This Study) 2018	Prospective, Single center (70)	Symptomatic	Blue dye	22 (2-70)	T1 (31%) T2 (64%) T3 (5%)	92%	96%	11%
Renaudeau et al. 2016 [20]	Prospective Multicenter (138)	Screen detected	Heterogeneous	9.3 (1-35)	T1 (93%), T2 (7%)	85.5%	99%	6.25%
Coskun et al. 2012 [21]	Retrospective Single center (100)	Heterogeneous	Heterogeneous	29	NR	90%	89%	11%
Krag et al. 2007 [15]	Prospective Multicenter (177)	Subgroup of large study	Isotope & blue dye	NR	NR	97%	NR	15.3%
Celebioglu et al. 2007 [6]	Prospective Multicenter (75)	Screen detected	Isotope & blue dye	13 (2-40)	NR	96%	96%	10%
Heuts et al. 2006 [5]	Prospective Single center (88)	Screen detected	Isotope & blue dye	15 (3-70)	T1 (66%) T2 (31%) T3 (31%)	99%	100%	0%
Wong et al. 2002 [22]	Prospective multicenter (763)	Subgroup of large study	Heterogeneous	NR	T1 (71%) T2 (27%) T3 (2%)	93%	96%	8.3%
Haigh et al. 2000 [23]	Prospective Single center (181)	Mixed core & excisional biopsy	Heterogeneous	15 (1-110)	T1 (76%) T2 (20%) T3 (4%)	83%	NR	NR

• *N* sample size, *T* Tumor size, *pT* Pathological tumor, *IR* Identification Rate, *NPV* Negative Predictive Value, *FNR* False Negative Rate, *NR* Not Reported

Following our departmental protocol, all patients in this study had cavity excision or completion mastectomy. In our published series, breast conservation rate is around 45% [27]. Present study included patients who had undergone lumpectomy considering it benign in non-oncology setup, which is usual for smaller size lump and referred to our center with post-lumpectomy diagnosis of breast cancer for further management. Breast conservation (cavity excision) was possible in majority of patients (91%) due to the small size of the tumor (2.2 cm, IQR 1.7, 3.3) and oncoplastic techniques. We found that 57% of patients had residual invasive or in situ breast cancer, and even in patients where outside pathology reports showed a free margin, residual cancer was found in > 50% of patients. Although mammography was done routinely before re-surgery, it was unable to predict small foci of residual disease in this early post-operative setting. Our results support revision breast surgery for all patients who undergo lumpectomy in non-oncological centers where both surgical and pathological procedures may not be standardized. This is also supported by a study from another tertiary cancer center [28], which reported the large burden and impact in low-resource settings of the detrimental effect of inadequate or incomplete breast or axillary surgery for breast cancer when procedures were performed by non-oncological surgeons. In addition, revision breast surgery gives an opportunity to mark the tumor cavity with clips to guide subsequent radiotherapy [29]. Immune histochemical status of breast cancer patients in this cohort shows low HER 2 receptor positivity (8.5%). Overall HER 2 positivity in patients presenting to our institute is around 26% [27]. HER 2 positivity in tumor size less than 2 cm is around 10% [30, 31]. As majority of study cohort patient's tumor size was around 2 cm (median = 2.2), this may be the reason of low HER 2 positivity rate in this group.

Conclusion

Sentinel lymph node biopsy in an accurate method to stage the axilla in women with breast cancer who have prior lumpectomy for a palpable breast lump. The location of the incision of the first surgery may affect the outcome of this procedure, and our results suggest that SLNB should be used with caution following central or peri-areolar incisions although studies with a larger sample size are required to validate this. Mammography does not reliably predict the presence of residual disease in this situation and definitive breast surgery is required for all patients, irrespective of initial histopathological examination margin status.

Compliance with Ethical Standards Following approval by the institutional review board (EC/TMC/36/14), informed consent was taken from a consecutive series of patients suitable for inclusion, and participants were enrolled from January 2015 to August 2017.

Conflict of Interest The authors declare that they have no conflict of interest.

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