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Original article

Non-visualization of axillary pathological lymph nodes in breast cancer patients on SPECT/CT and during operation

Shenghua Zhu[a], Ramin Akbarian Aghdam[b], Sophia Liu[c], Rebecca E. Thornhill[a], Wanzhen Zeng[b,*]

[a] Department of Radiology, Radiation Oncology and Medical Physics, University of Ottawa, Ottawa, Ontario, Canada
[b] Division of Nuclear Medicine and Molecular Imaging, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[c] Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

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ABSTRACT

Background: Recent studies have shown that an increased number of axillary lymph node metastases is associated with non-visualized lymph nodes. The purpose of the study was to retrospectively analyze the incidence and characteristics of non-visualized sentinel lymph nodes (SLNs) in nodal metastases in breast cancer patients.

Methods: Consecutive women with breast cancer referred for lymphoscintigraphy from January 2021 to November 2022 were reviewed retrospectively. Findings from resected SLNs and non-SLNs and relevant histopathology were collected and analyzed.

Results: 500 patients diagnosed with breast cancer were reviewed, excluding 93 patients due to neoadjuvant therapy, DCIS, recurrence, or incomplete clinical documentation. Of the 407 remaining patients, 108 patients were positive for axillary lymph node metastases (24 %) and were the focus of the study. Of this patient cohort, 38 patients (35 %) had non-detected SLNs by intraoperative gamma probe and 43 (40 %) had non-visualized SLNs by lymphoscintigraphy. There was statistically significant difference in primary tumor size (39.8 mm versus 28.9 mm), number of resected (6.9 ± 4.4 versus 4.6 ± 2.4) and positive (3.4 ± 2.2 versus 1.6 ± 1.3) lymph nodes, size (13.8 ± 6.1 mm versus 8.1 ± 4.5 mm), tumor grade and tumor stage between the SLN non-visualized and visualized groups. The multivariate logistic regression analysis showed that only lymph node size and number of lymph nodes resected were independent factors associated with SLN non-visualization.

Conclusions: We reported a high non-visualization rate of SLN in breast cancer patients with pathology-proven positive axillary nodes. The causes of the SLN non-visualization are not well understood and warrants further exploration.

1. Introduction

Breast cancer is the leading cause of cancer death despite early diagnosis via screening and surgery remains the major treatment [1]. Lymphogenic dissemination is the primary route for breast tumor metastasis [2]. The involvement of regional axillary lymph nodes is a crucial prognostic factor and has significant impact on tumor staging and treatment options [3]. Sentinel lymph nodes (SLNs) are defined as the first nodes reached by tumor cells through the lymphatic channels. Thus, SLN mapping and biopsy have become the routine procedure used to assess the tumor status of the regional lymph nodes in breast cancer patients, particularly contributing to the development of less invasive surgical procedures [4].

While SLN dissection has proved to be effective and highly accurate with a low false negative rate [5,6], studies have shown that evidence of an increased number of axillary lymph node metastases is associated with non-visualized lymph nodes using preoperative sentinel node lymphoscintigraphy [7–9]. Several hypotheses have been proposed to address the potential underlying pathophysiology of this observation [7,10]. Aside from technical and patient related factors, it has been speculated that massive lymphatic tumor invasion alters the homeostasis of the sentinel lymph nodes, which in turn impedes

Abbreviations: ALND, Axillary lymph node dissection; DCIS, Ductal carcinoma in situ; FDG, (^{18}F)-fluorodeoxyglucose; H&E, Hematoxylin-eosin; IHC, Immunohistochemical (IHC); OR, Operating room; ORs, Odds ratios; SLN, Sentinel lymph node; LNs, Lymph nodes; SPECT/CT, Single photon emission tomography/computed tomography

* Corresponding author at: Division of Nuclear Medicine and Molecular Imaging, Department of Medicine, University of Ottawa, 1053 Carling Ave, Ottawa, Ontario, Canada, K1Y 4E9.
E-mail address: Wzeng@toh.ca (W. Zeng).

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or obstructs normal lymph flow, ultimately preventing tracer migration [8]. To date, it remains controversial whether or not the non-visualization of SLN is associated with a higher disease burden [11,12].

The purpose of the present study was to retrospectively analyze the incidence and characteristics of non-visualized sentinel lymph nodes for breast cancer and discuss the causes and potential clinical implications.

2. Materials and methods

2.1. Patient population

This single center, retrospective study was approved by the local Research Ethics Board. Five hundred women with breast cancer from January 1st 2021 to November 30th 2022 were reviewed in this study and preoperative lymphoscintigraphy data were collected. At our institute, breast cancer patients are routinely administered with radiopharmaceuticals preoperatively followed by lymphoscintigraphy mapping. During the same day, sentinel nodes are identified by an intraoperative gamma probe for resection. The number of resected lymph nodes and corresponding histopathology and radioactivity as assessed by intraoperative gamma probe were identified. Patients with disease recurrence, ductal carcinoma in situ (DCIS), neoadjuvant treatment before surgery and/or incomplete or missing operative notes after surgery were excluded. DCIS is a non-invasive or pre-invasive breast cancer and is considered stage 0. It usually does not metastasize beyond the breast and therefore it was excluded. In addition, there is insufficient evidence for lymphoscintigraphy in patients with DCIS [13].

Patients with pathological axillary lymph nodes were divided into nodal "***visualization***" and "***non-visualization***" groups, based on lymphoscintigraphy. The group definition also applied to the setting of lymph node resection in the operation room based on the detected nodal radioactivity by intraoperative gamma probe. This patient cohort with positive axillary lymph nodes is the focus of the current study. Note that the terms "hot" or "cold" node have been used interchangeably with the presence or absence of radioactivity, either detected by the probe or on imaging.

2.2. Lymphoscintigraphy

Lymphoscintigraphy was coordinated with the surgical department prior to the scheduled (same day) surgery. Patients received an average dose of 37 MBq (1 mCi) technetium-99 m (^{99}mTc) radiolabeled sulfur colloid filtered by a 0.22 μm filter diluted in 1 ml solution and mixed with 1 ml lidocaine in a total volume of 2 ml via a periareolar subcutaneous injection by experienced nuclear medicine technologists. Single-photon emission computed tomography (SPECT)/CT (low energy high resolution collimator, 360° coverage, step-and-shoot, contour orbit, 64 steps, 30 s per projection, 140 keV ± 7.5 %, 128 × 128; 130 keV, automatic mA) was obtained at 30 mins postinjection using a two-headed SPECT/CT system (Symbia-T SPECT-CT, Siemens Medical Solutions, USA). SPECT images were then reconstructed using a commercial software package (HybridRecon 2.1, Hermes Medical Solutions, Stockholm, Sweden) with attenuation, scatter, and resolution recovery corrections incorporating ordered subset expectation maximization with 4 iterations, 16 subsets and 0.89 mm full width at half maximum Gaussian post-filtering. Focal accumulations in at least one axillary lymph node were defined as SLN.

2.3. SLN dissection

The axillary SLN identification was performed using handheld gamma-ray detection probe and/or blue dye methods. Depending on the surgeons' preference, blue dye injection was performed in some patients approximately 10 min before surgery to help visualize sentinel nodes. Lymph nodes exhibiting radioactivity uptake, blue dye uptake, or both were identified as SLN and excised. Clinically suspicious lymph nodes without radioactivity or blue dye were also excised. SLN that could not be detected using a gamma probe were classified as non-visualized SLN, in which case, lymph node dissection was performed. All excised lymph nodes were labeled with the information of radioactivity count and sent individually for histologic evaluation. The duration between radiotracer administration and the operation ranged from 2 to 6 h (median 273 min).

2.4. Histology

The dissected sentinel lymph nodes were fixed in formalin, embedded in paraffin, and cut in serial sections. Sections were stained with hematoxylin-eosin (H&E) for macrometastasis and immunohistochemical staining (IHC) for cytokeratin to detect micrometastasis (< 2 mm and > 0.1 mm in diameter). A SLN was considered positive if tumor cells were identified by H&E or IHC staining. For the current study, only SLNs with macrometastasis (> 2 mm) were considered positive.

2.5. Statistical analysis

Patient, tumor, and radiotracer characteristics were evaluated using descriptive statistics (mean±SD, and median(range)). Differences in parameters between non-visualized SLN and visualized SLN groups were assessed using Mann–Whitney U tests, as the distribution of the parameters were not normal (based on Shapiro-Wilk normality tests). Fisher's exact tests were used to assess differences in proportion between groups for tumor grade and stage. Logistic-regression was used to examine the relationships between the different characteristics and SLN non-visualization. All statistical tests were two-tailed and a p value below 5 % was considered statistically significant.

3. Results

3.1. Tumor and intraoperative SLN characteristics

A total of 500 consecutive patients were reviewed and 93 patients were excluded from the study if they received neoadjuvant chemotherapy or had recurrent disease (49), were diagnosed with DCIS (31) or had incomplete or missing operative notes after surgery (13). Of the 407 remaining patients, 108 patients had positive axillary lymph node metastases (24 %). The patient group with biopsy proven axillary lymph node metastases (n = 108) was the focus of the current study and the data were further analyzed for tumor/lymph node characteristics and image/probe findings. The breakdown of participants is shown in Fig. 1.

The patient characteristics as well as tumor and nodal parameters are presented in Table 1. Of the 108 patients with axillary lymph node metastases, 38 patients (35.5 %) had non-visualized pathological lymph nodes by intraoperative gamma probe, as determined from reviewing the operation and pathology reports. Statistically significant difference was identified in the primary tumor size (39.8 mm versus 28.9 mm, p = 0.027), number of resected lymph nodes (6.9 ± 4.4 versus 4.6 ± 2.4, p < 0.017), number of positive lymph nodes (3.4 ± 2.2 versus 1.6 ± 1.3, p < 0.001), and size of the largest resected axillary lymph node (13.8 ± 6.1 mm versus 8.1 ± 4.5 mm, p < 0.001) between the non-visualized and visualized groups (Table 1). Based on the Fisher's Exact test, there was statistically significant difference between the non-visualized and visualized groups in tumor grade (p = 0.0432) and tumor stage (p = 0.0025). The subsequent multivariate logistic regression analysis including patient age,

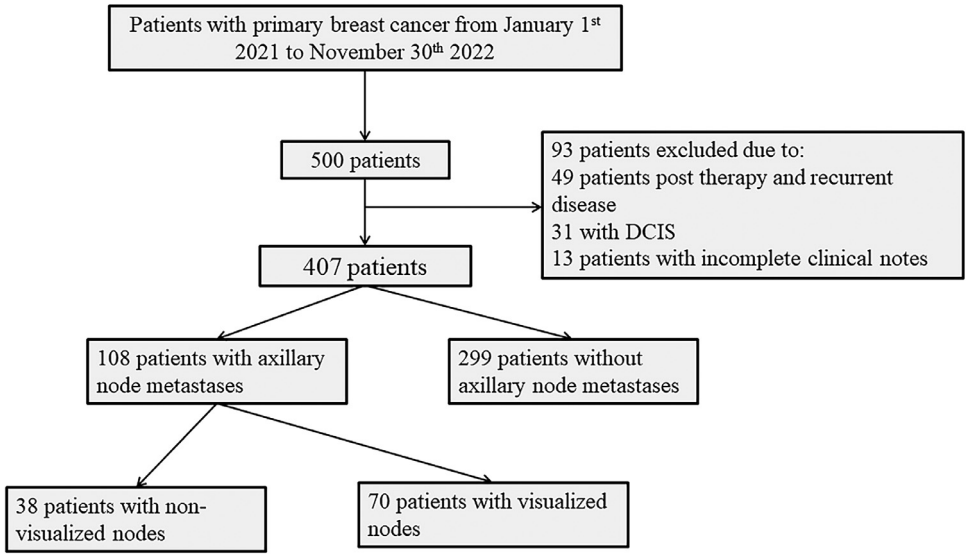

Fig. 1. Flow chart of selecting patients with breast cancer.

number of nodes resected, node size, primary tumor size, tumor grade and clinical tumor stage showed that only lymph node size (odds ratio (standard error) 0.85 (0.06), p = 0.003) and number of lymph nodes resected (0.83 (0.09), p = 0.038) were independent factors associated with SLN non-visualization (Table 2).

3.2. Non-visualization patient group

Of the non-visualization patient group (n = 38), there were no pathological hot nodes in 19 patients (50 %), both hot and cold lymph nodes in 12 patients (32 %), and hot nodes negative and cold nodes positive in 7 patients (18 %). In 7 (18 %) of those patients, there was detected lymph node activity by intraoperative probe and on imaging, yet no corresponding pathological findings, while the pathological lymph nodes were not visualized by imaging and probe. This may suggestive of an alternative lymphatic channel diverting flow to a neo-SLN instead of the original true SLN. An example of this discordant situation from a 53-year-old female with pT2N1a left breast cancer is provided in Fig. 2. Eleven out of the 38 patients (29 %) demonstrated a complete absence of lymphatic drainage to the axillary nodes. There was evidence of gross disease with marked edema and palpable lymph nodes observed in 7 out of these 11 patients during SLN dissection.

3.3. SLN detection with SPECT/CT, intra-operative gamma probe and blue dyes

Of the 407 consecutive patients reviewed, SLNs were identified in 266 patients on imaging (65 %) and in 347 patients in the OR (85 %) overall. SLNs were identified in 201 patients (67 %) on imaging and in 277 patients (93 %) in the OR in patients with negative axillary metastases, compared to 65 (61 %) on imaging and 70 (65 %) in the OR in patients with positive axillary lymph nodes.

Table 1
Patient characteristics. p-value in bold is indicative of statistically significant.

	Non-visualization group		Visualization group		
Number of patients	38 Mean ± SD number (%)**	Median (range)	70 Mean ± SD	Median (range)	p values
Age	61.1 ± 11.5	64 (38,77)	60.5 ± 12.1	62 (32,91)	0.4196
Stage					**0.0025**
2A	4 (11 %)		19 (27 %)		
2B	15 (39 %)		37 (53 %)		
3A	13 (34 %)		13 (19 %)		
3B/C	6 (16 %)		1 (1.4 %)		
Tumor grade					**0.0432**
1	2 (5 %)		15 (21 %)		
2	18 (47 %)		34 (49 %)		
3	18 (47 %)		21 (30 %)		
Tumor size (mm)	39.8 ± 28.3	30 (13,146)	28.9 ± 15.6	25 (9.80)	**0.0270**
$T \leq 20$	6 (16 %)		20 (29 %)		0.186
$20 < T \leq 50$	25 (66 %)		42 (60 %)		0.156
$50 < T$	7 (18 %)		8 (11 %)		**0.045**
No. of resected nodes	6.9 ± 0.44	5 (1,16)	4.6 ± 2.4	4 (1,12)	**0.0170**
No. of positive nodes	3.4 ± 2.2	3 (1,9)	1.6 ± 1.3	1 (1,8)	**<0.0001**
Lymph node size (mm)	13.8 ± 6.1	12.5 (3.0, 27.0)	8.1 ± 4.5	8.0 (2.2, 24.0)	**<0.0001**

* A total number of 500 patients were reviewed and only 108 patients with biopsy proven positive axillary lymph nodes were analysed and presented.

** Tumor stage, grade and primary tumor size were divided into categories, and expressed as the number and percentage for each category.

Table 2
Logistic regression analysis.

Characteristic	Odd ratio (OR)	Standard error	*p* values
Age	0.963	0.028	0.172
Stage	0.505	0.421	0.105
Tumor grade	0.784	0.428	0.570
Tumor size	0.990	0.017	0.560
Resected nodes	0.826	0.092	* **0.038**
Lymph node size	0.847	0.055	* **0.003**

Blue dye injection immediately prior to the operation was performed in some patients, depending on the surgeon's preference. In our cohort group with pathological lymph nodes, 68 patients (63 %) had both radiotracer and blue dye injections. A total of 142 hot and 88 blue nodes were identified (excluded 3 patients with the OR statement of several hot and blue nodes without quantification). More hot nodes were identified in 32 patients (49 %) while only 6 patients (9 %) had more blue nodes. There were 27 patients (42 %) with identical hot and blue nodes.

4. Discussion

A high SLN non-visualization rate of 35 % was identified in our study in patients with pathological axillary lymph nodes. We also demonstrated statistically significant difference in axillary nodal tumor burden (number and the size), primary tumor size, tumor grade and clinical stage between the non-visualized and visualized patient groups. In logistic regression analyses, we found that lymph node size and number of lymph nodes resected were independent factors associated with SLN non-visualization. This is consistent with other reported studies which have shown that the success rate of visualizing SLN decreases as the number of involved lymph nodes in axilla increases [7,9,14]. The other variables evaluated, such as patient's age, tumor grade, tumor size and clinical stage showed no significant relation to unsuccessful detection of SLN in the operating room.

Tumor metastasis is a complex process requiring sequential biological steps including cancer cells dissociation and dissemination through the blood and lymphatic circulation [2]. The SLN biopsy is based on the concept that the lymphatic drainage pathway is the first to be involved in tumor metastasis in breast cancer. In patients with tumor invasion of the lymph nodes, the concept of tumor blockage and rerouting of lymphatic drainage has been proposed [17]**.** A study by Goyal et al. showed that in an individual SLN, the percentage replacement by tumor is associated with reduced radiotracer uptake [18]. Our present study supports the concept that cancer cell invasion of the SLN prevents normal uptake of injected radiopharmaceuticals, thus masking SLN visualization both by nuclear medicine physicians in pre-operative lymphoscintigraphy, and by surgeons with intraoperative probe.

We reported 12 out of the 108 cases with axillary node metastases in which no axillary lymph nodes could be detected, suggesting that completely invaded nodes may lead to unsuccessful axillary node detection due to a lack of tracer uptake in the leading node and a higher nodal burden affects the sentinel lymph nodes detection. Although the finding is in agreement with a study by Goyal et al. [18], some studies found no significant association between the nodal disease burden and SLN identification rate [11,12]. These discrepant observations could possibly be related to mixed patient population including patients who received neoadjuvant treatment prior to SLN biopsy [12]. In our study we have excluded patients post neoadjuvant therapy as it is uncertain if the treatment could alter lymphatic drainage pathway and sentinel node detection [19]. Despite the higher non-visualization rate among axillary nodal positive breast cancer patients, the absolute recurrence risk is low given the advances in systemic and radiation therapy have significantly reduced the risk of the regional recurrence [14,20]. In 7 patients, we observed that visualized SLNs were not pathological while non-visualized lymph nodes were pathological. We speculate that the original lymphatic channel to the truly involved SLN blocked by the tumor cell becomes congested and then diverts the lymph flow to a neo-SLN that may not yet be involved, in which case a false negative result could be expected if this was the only SLN sampled by the surgeon. Without sequential images, it is unclear if the observation is related to rapidly growing SLNs or more aggressive disease. Future studies are need to better understand the observed phenomenon.

There are many factors associated with non-visualization of the SLN during lymphoscintigraphy including patient demographics, injection and imaging techniques, and tumor

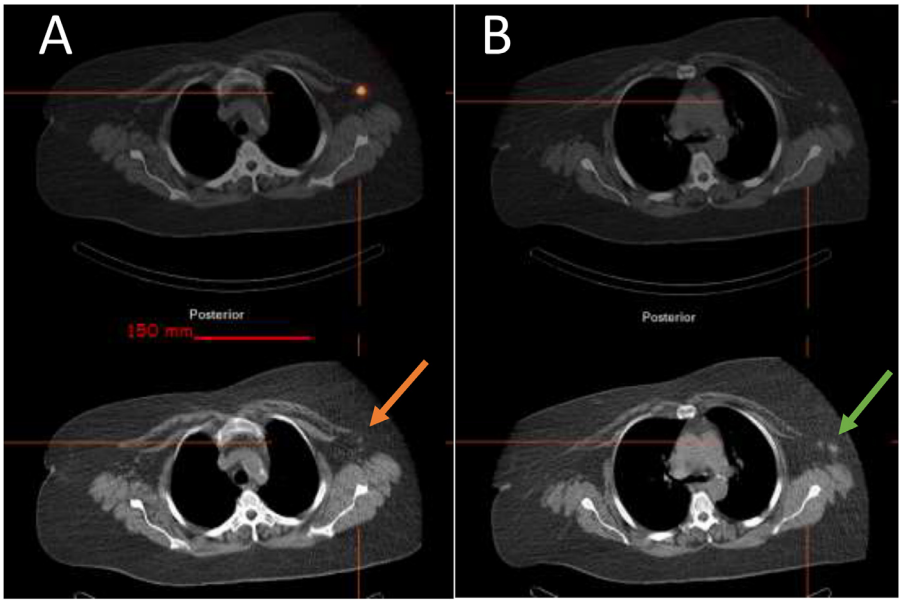

Fig. 2. 53-year-old female with pT2N1a left breast cancer. SPECT/CT and low dose CT showed a sentinel node (golden arrow) on lymphoscintigraphy (A) which is negative for nodal metastasis following excision. A larger "cold" lymph node without activity on imaging and during the OR (Green arrow) was excised and biopsy proven to be a nodal metastasis (B).

characteristics [14,21–23]. Older age and higher body mass index have been reported to be associated with a higher rate of unsuccessful visualization of SLN [11,14,22]. It has been hypothesized that lymph nodes in older or more obese patients consist of more fat which decreases the capacity for colloid uptake in the nodes [11]. Indeed, a recent study showed that breast density, not the age or BMI, was associated with SLN detectability [24]. A receptor based radiotracer more suitable for imaging dense breast has been proposed [25]. In this study we didn't assess the breast density and BMI association as we mainly focused on other parameters. Our study did not identify potential impact of patents' age on the rate of non-visualization rate of SLN. Interestingly, we did observe that the primary breast tumor size was significantly larger in the non-visualized patient group than in the visualized patient group, although the primary tumor size was not an impact factor for non-visualization of SLN. Presumably, large primary tumors may have increased lymphatic drainage pathways and increased lymph node metastasis. Therefore, some authors have reported an inverse correlation between the visualization rate of SLN and the tumor size [17]. Similarly, there are also inconsistent findings supporting an association between tumor location and non-visualized SLN [26,27].

In this study, we report a SLN visualization rate of 65 % from preoperative lymphoscintigraphy, which is lower than the rates previously reported in the literature [21,28]. This observed discrepancy could partially be related to the subcutaneous injection technique utilized at our institute, which was suggested by surgeons to reduce pain associated with radiotracer administration. It has been well recognized that intradermal and peri-tumoral/intratumoral injection techniques are associated with higher success rates in identifying SLN in breast cancer patients than subcutaneous injection, which is mainly because the dermal and parenchymal lymphatics drain to the same axillary nodes [14,28]. In addition, the 30 min imaging protocol may carry an inherent user bias of underestimating the visualization of the lymph nodes. Consequently, the intraoperative SLN visualization rate was used in this study as there is longer migration time of the radiopharmaceuticals. With the gamma probe device, the SLN visualization rate was 85 % overall and 93 % in patients with negative axillary node pathology. The finding from the study may help inform revision of the injection method. As more nuclear medicine centres are shifting from planar imaging to SPECT/CT, the finding of the significance of non-visualized SLNs may encourage imaging professionals to report suspicious SLNs based on low-dose CT despite negative findings on SPECT.

Considering that patients with non-visualized SLN are associated with a higher tumor burden and therefore a higher nodal stage, the finding may impact the patient management. It has been shown that patients with non-visualized SLN experience worse survival compared to patients with a successful SLN procedure, with a 5-year survival rate of 91.3 % for the visualized versus 86.1 % for the non-visualized SLN groups [14]. The patients in the non-visualized SLN group may need axillary lymph node dissection based on the nodal status [4]. This remains controversial, however, there are currently no guidance documents or recommendations for nodal dissection in patients with non-visualized SLNs [13,15]. Prospective randomized clinical trials are required to provide guidelines for this patient group. The management of the patients with neoadjuvant therapy is evolving and the finding of increased tumor burden in the SLN non-visualized group may change the indication for neoadjuvant therapy [16].

The standard diagnostic approach for breast cancer patients includes radiological imaging (mammogram, ultrasound, MRI, CT), lymphoscintigraphy for sentinel nodes and more recently FDG PET/CT. In our centre, FDG PET is only indicated for locally advanced breast cancer (clinical stage IIB and III). Although the presence of non-visualized positive SLNs is not included the indication criteria for FDG PET, if the finding is associated with more aggressive breast cancer including rapid growth of SLNs, FDG PET would be a suitable imaging modality for the patient group, but this requires validation. Despite the lack of specific recommendations for additional imaging or medical management at present for non-visualized SLNs, it is crucial to emphasize that careful consideration and ongoing monitoring may be necessary to address any potential impact on treatment planning and patient outcomes.

Our study was limited by a relatively small number of patients (108) with axillary nodal metastases. Consequently, the number of variables included in our regression model may underestimate the power of the association that we found. Secondly, the injection technique using a relatively large volume (2 ml versus 0.4 ml) with peri-areolar injection may be different from other centers although this was partially compensated by intraoperative assessment in the study.

5. Conclusions

In conclusion, we reported a high SLN non-visualization rate among breast cancer patients with positive axillary nodes based on intraoperative radioactivity uptake. The causes of the observed SLN non-visualization are not well understood and may be due to obstructed lymphatic channels by tumor cells and rerouting of the lymphatic pathway. The finding of increased tumor burden in the axilla in this patient group may potentially impact patient management.

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Author role statement

WZ was responsible for overall study design and supervision

SZ performed literature search, data analysis and drafted manuscript.

RA and SL collected data and participated in the discussion of study design.

RT performed regression analysis and provided critical comments

All authors commented and contributed to the revision of the manuscript.

Ethics approval and consent

This is a retrospective review of imaging and histopathological data. The study has received approval from the regional Research Ethic Board. We have followed The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the institutional ethics board (CRRF ID 3571). Patient's consent was waived.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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