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ORIGINAL RESEARCH

Accuracy of Sentinel Lymph Node Biopsy in Breast Cancer: Pitfalls in the Application of Single Tracers

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Background: Radioisotopes and blue dyes are used as dual tracers in the current gold standard procedure of sentinel lymph node (SLN) biopsy (SLNB) performed for breast cancer. However, the blue dye or the radioisotope as a single tracer is also being applied in some institutes. We aimed to explore the risk factors for the miss-detection of SLNs with the radioisotope and the blue dye and to describe the distribution of SLNs missed by each tracer.

Patients and Methods: Patients undergoing SLNB with radioisotope and blue dye as dual mapping agents were enrolled between August 2010 and August 2018. Radioactivity count, blue dye staining status, and size and location of each SLN were prospectively documented.

Results: In total, 2382 SLNs from 1010 patients were included for statistical analyses. The sentinel node identification rate was 100% for dual tracers, 99.4% for radioisotope, and 89.1% for blue dye. SLN identification using the blue dye was more likely to fail in patients undergoing breast-conserving surgery ($p < 0.001$) and mastectomy with reconstruction ($p = 0.005$). Furthermore, miss-detection was significantly more frequent in smaller and uninvolved nodes. Among all SLNs, 8.2% were located in level II and one was in level III. Notably, single tracer of blue dye tended to fail in the detection of lymph nodes in higher levels ($p < 0.001$).

Conclusion: This study explored the association between features and the incidence of the failure to detect SLNs using radioisotope and blue dye. The locations of the miss-detected SLNs are demonstrated to provide a reference for SLNBs conducted using blue dye or radioisotope as a single tracer.

Keywords: breast cancer, sentinel lymph node, radioisotope, blue dye, single tracer

Introduction

Since axillary lymph node dissection (ALND) was replaced by sentinel lymph node (SLN) biopsy (SLNB) for axillary staging in patients with early-stage breast cancer,[1,2] several tracing methods for SLNB have evolved, including radioisotope technetium-99m sulfur colloid (^{99m}Tc),[3] blue dye,[4,5] indocyanine green fluorescence,[4,5] magnetic tracer,[6–8] and carbon nanoparticles[5] as well as clips.[9] With identification rates of 96–97% in large trials,[10,11] the radioisotope and the blue dye combination remains the most widely accepted, long-established approach and the current gold standard for SLNB.[12,13] However, given the limited accessibility to radioisotope and extra requirements for equipment, SLNBs with single tracer, especially blue dye are being adopted in a growing number of institutes, predominantly in less developed areas.[14] Additionally, blue dye use has been rejected in some institutions because of

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complications such as anaphylaxis after application of the patent blue V;[15] several studies that omitted the blue dye use do not necessarily report a poor identification rate or a high false-negative rate under certain conditions.[16]

This study aimed to assess in depth the pattern of SLN miss-detection with radioisotope and/or blue dye as tracers. Currently, in the majority of existing studies on SLNB, the subjects were individual patients. Previously, studies on single tracers were mainly carried out in two ways: 1) single-arm studies comparing the results of one tracer with existing data and 2) studies comparing two single tracers in different patients, with one group of patients undergoing SLNB with one tracer and a different group undergoing SLNB with another tracer. Distinctively, the current study prospectively documented the staining status of lymph nodes and lymphatic vessels, enrichment of nuclides, and the precise location of each lymph node retrieved during surgery, making it possible to analyze the efficacy of SLNB with radioisotope and blue dye, respectively, in a same group of patients, to perform node-targeted statistical analyses, and to describe the miss-detect pattern for the radioisotope and the blue dye. This information is of considerable importance in clinical practice.

Patients and Methods
Patients
Patients undergoing SLNB were enrolled in this prospective study between August 2010 and August 2018. Patients with pathologically diagnosed invasive breast cancer who were clinically node negative (negative on ultrasound,[17] mammography, and physical examination) and those who underwent mastectomy with pathologically diagnosed ductal carcinoma in situ were eligible. Patients with clinically positive axillary lymph nodes, those with recurrence or distant metastasis, and those with prior axillary surgeries were excluded.

Surgical Management
We applied two mapping agents for SLNB. The radioisotope (^{99m}Tc) was injected 2–18 h before surgery, and the blue dye (methylene blue) was injected 15–20 min before surgery. The radioisotope was injected intradermally at the tumor surface and/or at the periareolar site. For the blue dye, intradermal/subcutaneous injections at the tumor surface and/or at the periareolar site were adopted, based on whether the nipple-areola complex or skin at the tumor surface was conserved during surgery.

During surgery, a gamma probe of ^{99m}Tc was used to identify SLNs. Any nodes with 10% or more of the ex vivo count of the hottest node in a patient and any node with at least one blue afferent lymphatic vessel derived from the breast were removed and designated as SLNs.[18] Suspicious lymph nodes, which were firm, enlarged, and palpable, were removed and sent for pathological testing as non-SLNs. All SLNs were sent as frozen sections, and ALND was performed based on the pathological evaluation of the intraoperative frozen sections. Generally, patients with a failed SLNB and those with SLN macrometastases underwent ALND. Patients with SLNs with isolated tumor cells or metastasis-free SLNs were excluded from further axillary intervention. For SLNs with micrometastases, the decision to perform axillary dissection was made jointly by the patient and the surgery group before surgery.

We prospectively documented the radioactivity count, the status of blue dye staining of the node and lymphatic vessels, and the size and location of each SLN. To describe the distribution of SLNs, we classified the documented locations as level III, level II, and level I, with level I further classified as follows: zone A, the area around the margin of the breast tissue and the tail of Spence; zone B, the area between the lateral margin of the *pectoralis major* and the thoracodorsal vessels; and zone C, the lateral portion of the axilla. The majority of SLNs were in level I zones A and B. Additionally, we cautiously archived the demographic, clinical, and pathological data of each patient. The criteria for pathological reports were published previously.[19]

Statistical Analysis
For data analysis, negative intraoperative pathological reports of SLNs in combination with confirmed positive postoperative reports of SLNs, non-SLNs, and/or any nodes from ALND were defined as false-negative results.

Clinical and pathological features among groups were compared using one-way analysis of variance, Pearson's chi-square test, or Fisher's exact test for categorical data and independent t-tests for continuous data. The McNemar chi-square was used to compare the efficacy of the two tracers in SLNs of different locations. Furthermore, logistic regression with a backward stepwise model was used to identify risk variables for missed detection and false-negative events, with p-values reported from the Wald tests and 95% confidence interval (CI) for the odds ratio (OR). All tests were two-tailed, and the significance level

was 0.05. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Information

SLNB was successfully performed in 1011 patients. In one patient, a single radioisotope tracer was used because of a suspected anaphylaxis reaction to methylene blue; thus, this patient was excluded. Therefore, 2382 SLNs from 1010 patients who underwent SLNB with dual tracers were included in the data analysis. The clinicopathologic features of the included patients are listed in Table 1.

Incidence of Missed Detection and False-Negative Events

Among the patients, the overall rate of axillary involvement was 32.6% (329/1010). The sentinel node identification rate was 100% (1010/1010) for dual tracers, 99.4% (1004/1010) for radioisotope only, and 89.1% (900/1010) for blue dye only. The identification rate of blue dye only was significantly lower than that of radioisotope only ($p < 0.001$) and that of dual tracers ($p < 0.001$). We explored the risk indicators for the detection failure of blue dye. Breast-conserving surgery rather than mastectomy and reconstruction was risk indicators for detection failure, whereas prior excisional biopsy and number of SLNs ≥3 were protective indicators (Table 2). However, none of the indicators for detection failure for radioisotopes were identified because of the small number of failed cases.

The false-negative rate was 3.8% (38/1010) for dual tracers, 5.7% (58/1010) for radioisotope only, and 7.2% (73/1010) for blue dye only. The false-negative rate of blue dye only was significantly higher than that of dual tracers ($p = 0.001$). Logistic regression was employed to identify the risk indicators for false-negative events. The number of SLNs ≥3 was the only protective indicator for false-negative events with combined tracers (OR [95% CI] = 0.150 [0.043–0.518], $p = 0.003$). However, none of the indicators for false-negative events with a single tracer were identified.

Lymph Node-Specific Risk Factors for Missed Detection

Among the 2382 SLNs, 1243 (52.2%) were detected by both the radioisotope and the blue dye, 741 (31.1%) were detected by radioisotope only, and 398 (16.7%) were detected by blue dye only.

Table 1 Clinicopathological Characteristics of Included Patients (n=1010)

Variable	n	Percentage
Age (mean ± SD)	48.28±11.30	
Type of surgery		
Mastectomy	846	83.8%
Breast-conserving surgery	164	16.2%
Reconstruction after mastectomy		
Yes	145	14.4%
No	865	85.6%
pT classification		
Tis-T1	588	58.2%
T2–4	341	33.8%
Unknown	81	8.0%
Axillary involvement		
Yes	329	32.6%
No	681	67.4%
Excision biopsy before surgery		
Yes	207	20.5%
No	803	79.5%
Pathological diagnosis		
DCIS and Paget's disease	112	11.1%
Invasive ductal carcinoma	790	78.2%
Others[a]	108	10.7%
Tumor Location		
Upper outer quadrant	362	35.8%
Other quadrants	574	56.8%
Unknown	74	7.3%
Number of SLNs detected		
1–2	624	61.8%
3–4	334	33.1%
≥5	52	5.1%

Notes: [a]Including papillary carcinoma, mucous carcinoma, invasive lobular carcinoma, malignant phyllode tumor, secretory carcinoma, metaplastic carcinoma, squamous cell carcinoma, adenoid cystic carcinoma and mixed carcinoma.
Abbreviations: SD, standard deviation; SLNs, sentinel lymph nodes; DCIS, ductal carcinoma in situ.

We compared the lymph node-specific characteristics between SLNs that were identified and missed by each tracer. Independent of the tracing method, the miss-detected SLNs were significantly smaller in size than those successfully detected ($p < 0.001$ for both tracers). Moreover, nodes with tumor metastasis were more likely to be successfully identified than negative lymph nodes ($p = 0.014$ for radioisotope and $p < 0.001$ for blue dye). In terms of location, single tracer of blue dye tended to fail in the detection of SLNs at higher levels ($p < 0.001$). However, such a phenomenon did not occur in the setting

Table 2 Logistic Regression of Predictors for Detection Failure of Single Tracer of Blue Dye

Variable	OR	95% CI	p-value
Age			
>35	1.00		
≤35	1.202	(0.601–2.403)	0.604
Type of surgery			
Mastectomy	1.00		
Breast-conserving surgery	2.525	(1.483–4.3)	0.001*
Reconstruction			
No	1.00		
Yes	2.367	(1.289–4.347)	0.005*
pT classification			
Tis-T1	1.00		
T2–4	0.700	(0.430–1.141)	0.152
Axillary involvement			
No	1.00		
Yes	0.821	(0.505–1.336)	0.427
Excision biopsy before surgery			
No	1.00		
Yes	0.405	(0.170–0.964)	0.041*
Tumor location			
Upper outer quadrant	1.00		
Other quadrants	1.569	(0.974–2.528)	0.064
Number of SLNs retrieved			
1–2	1.00		
≥3	0.606	(0.369–0.996)	0.048*

Note: *$p < 0.05$
Abbreviations: OR, odds ratio; CI, confidence interval; SLNs, sentinel lymph nodes.

of radioisotope. Moreover, we explored whether discrepancies existed between different sites of blue dye injection, but there were no significant differences (Table 3). Notably, among the SLNs with tumor cell involvement missed by the blue dye, 14.1% (12/85) were located in level II.

Distribution of SLNs and Locations of Miss-Detected SLNs

The precise location of 2364 out of 2382 SLNs was described. The location of each SLN was summarized according to whether it was missed by the radioisotope or the blue dye (Table 4). Among the 2364 SLNs, one (0.04%) was in axillary level III and 196 (8.3%) were in level II.

McNemar test revealed that the efficacy of the radioisotope and the blue dye as single tracers was different in

SLNs of level II and level I zone B. More specifically, for SLNs in level II, 58.7% (115/196) were missed by the blue dye and only 14.3% (28/196) were missed by the radioisotope. For those in level I zone B, 32.9% (456/1388) were missed by the blue dye and 17.2% (239/1388) were missed by the radioisotope. Moreover, the only SLN identified in level III was successfully detected by the radioisotope but missed by the blue dye (Table 4).

Discussion

After the publication of the ACOSOG Z0011[20] and the diffusion of the American Society of Clinical Oncology clinical practice guidelines[21] pointing out the futility of lymphadenectomy even in the presence of metastases in the SLN, the traditional concept of axillary dissection in breast cancer is being questioned. However, while the emerging role of axillary ultrasound in the preoperative staging of the axilla[22] and in the follow-up after SLNB[23] and the possibility of avoiding SLNB are currently being evaluated in a prospective study,[24] SLNB remains the gold standard for the axillary management of early-stage breast cancers. In this study, we prospectively recorded the features of 1010 patients who successfully underwent SLNB using tracers of radioactive ^{99m}Tc and blue dye to explore the differences among tracing methods of radioisotope only, blue dye only, and dual tracers in the same individuals. In this study, the identification rates of dual tracers (100%) and single radioisotope tracer (99.4%) were high, but that for blue dye used as a single tracer (89.1%) was <90%. In addition, the false-negative rates of both tracers used as single tracers were higher than 5% (5.7% for radioisotope and 7.2% for blue dye), indicating that SLNB with single tracer of radioisotope or blue dye should be applied with extra caution in patients with breast cancer.

An analysis of the indicators for missed detection using a single tracer revealed that breast-conserving surgery, rather than mastectomy, was a risk indicator for blue dye. This might be explained by the minimal incision of the SLNB for the sake of esthetics, resulting in limited visualization and thus hampering the detection and identification of SLNs. A similar interpretation also applies to the fact that SLN identification using only the blue dye was more likely to fail in patients who underwent reconstruction after mastectomy. To preserve the appearance of the breast as much as possible, skin- and nipple-sparing mastectomies are usually performed to allow for subsequent reconstruction. When the incision was made at the upper or lateral portion of the breast

Table 3 Associations Between Node-Specific Features and Incidence of Miss-Detection by Radioisotope and Blue Dye, Respectively

Variable	Overall (n=2382)	SLNs Detected by Radioisotope (n=1984)	SLNs Missed by Radioisotope (n=398)	p-value	SLNs Detected by Blue Dye (n=1641)	SLNs Missed by Blue Dye (n=741)	p-value
Size of lymph node (mean ± SD) (mm)	10.68 ± 7.34	11.16 ± 7.47	8.28 ± 6.11	<0.001*	11.41 ± 7.72	9.02 ± 6.07	<0.001*
Involvement of lymph node				0.014*			<0.001*
Negative	2003 (84.1%)	1652 (83.3%)	351 (86.9%)		1347 (82.1%)	656 (88.5%)	
Positive	379 (15.9%)	332 (16.7%)	47 (13.1%)		294 (17.9%)	85 (11.5%)	
Location of lymph node				0.337			<0.001*
Level I	2169 (91.1%)	1803 (90.9%)	366 (92.0%)		1548 (94.3%)	621 (83.8%)	
Level II~III[a]	197 (8.3%)	169 (8.5%)	28 (7.0%)		81 (4.9%)	116 (15.7%)	
Injection site							0.241
Tumor site	1941 (81.5%)				1305 (79.5%)	636 (85.8%)	
Periareolar	55 (2.3%)				40 (2.4%)	15 (2.0%)	
Tumor site and periareolar	52 (2.2%)				40 (2.4%)	12 (1.6%)	

Notes: [a]Only one SLN of level III was detected; *p<0.05.
Abbreviations: SD, standard deviation; SLNs, sentinel lymph nodes.

Table 4 The Locations of SLNs Divided by Whether Detected by Radioisotope or Blue Dye

Location	Overall (n=2364)		SLNs Detected by Radioisotope (n=1970)		SLNs Missed by Radioisotope (n=394)		SLNs Detected by Blue Dye (n=1628)		SLNs Missed by Blue Dye (n=736)		p-value
	Number	(%)	Number	(%)	Number	(%)	Number	(%)	Number	(%)	
Level III	1	0	1	0.1	0	0	0	0	1	0.1	-
Level II	196	8.3	168	8.5	28	7.1	81	5	115	15.6	<0.001*
Level I-Zone A	680	28.8	569	28.9	111	28.2	542	33.3	138	18.8	0.099
Level I-Zone B	1388	58.7	1149	58.3	239	60.7	932	57.2	456	62	<0.001*
Level I-Zone C	99	4.2	83	4.2	16	4.1	73	4.5	26	3.5	0.164

Note: *p<0.05.
Abbreviation: SLNs, sentinel lymph nodes.

in breast-conserving surgery or nipple-sparing mastectomy, surgeons may perform SLNB using the same incision as that of the lumpectomy or nipple-sparing mastectomy rather than making an additional incision in the axilla. In such settings, extended operating distance and visualization with an improper angle might make it much more difficult to track along tiny lymphatic vessels within a limited space, leading to a lower identification rate with blue dye than with radioisotope and dual tracers.

Whether prior excisional biopsy increases the incidence of missed detection has been broadly debated. While some believed that excisional biopsy may hamper the identification of SLN, other evidence suggests that it does not significantly affect the accuracy of SLNB.[25–27] Intriguingly, our results indicated that prior excisional biopsy was associated with an increased identification rate of SLN using blue dye as a single tracer. This might be related to the fact that the blue dye was injected by surgeons in our institution, who would inject the blue dye intradermally at the site of incision in the direction of the axilla and intradermal/subcutaneously at the periareolar site in case of a prior excisional biopsy, avoiding the cut-off of the blue dye in lymphatic flow. However, the results should be validated in studies with larger sample sizes.

By recording the precise location of each SLN, we were able to map the distribution of SLNs based on whether they were successfully detected by the radioisotope and the blue dye. Several attempts have been made to describe the common locations of SLNs.[28–32] Lo and colleagues categorized the location of the hottest spot on the skin of the axilla into seven areas divided by five landmarks. They found that 98.4% of the hotspots

detected on the axilla skin before SLNB were located in the area demarcated by the four landmarks of the hairline, a line tangential to and 2 cm below the center of the hairline, the lateral border of the *pectoralis major* muscle, and the mid-axillary line.[28] Another study designed an ellipse surrounded by the lateral line of the *pectoralis major*, the axillary skin fold that divides the trunk and the upper arm, and the nipple to predict the location of SLNs.[30] These two studies correlated the location of SLNs with surface markers but lacked value in guidance for practice among genuine anatomical structures during surgery. Clough and colleagues created a new anatomical classification of the lower part of the axilla based on the intersection of two anatomical landmarks, the lateral thoracic vein and the second intercostobrachial nerve. The results suggested that in 98.2% of patients, the axillary SLN was located medially, alongside the lateral thoracic vein, either below the second intercostobrachial nerve or above it.[32] The above studies initially indicated the locations of SLNs. In the current study, we not only described the distribution of SLNs but also explored the locations potentially hiding SLNs detected by the radioisotope or the blue dye. The proportion of SLNs in levels II–III was 8.3%, which was significantly higher than the previously reported rate of 2.3% in a study with a smaller sample size.[33] More importantly, the blue dye used as a single tracer missed a notable portion of the skipped SLNs at levels II and III. We should be alert that the genuine rate of skipped SLNs might not be as low as that previously reported, and surgeons who have to apply a single tracer of the blue dye must bear in mind the SLNs in level II.

Several limitations of this study should be noted. First, the ratio of breast-conserving surgeries in this study was much lower than the international average. In the future, with more cases of lumpectomy collected, SLNBs with lumpectomy using a joint incision and that using separate incisions in the axilla and on the breast should be compared to explore the indicators for miss-detection. Second, ALND was not performed in patients with negative SLNs per the study design, and an accurate false-negative rate in our study was not calculated. Therefore, the results of this study should be validated in multicenter studies with a larger sample size.

Conclusions

The identification rate of blue dye only was lower than those of radioisotope only and dual tracers. Type of surgery, prior excisional biopsy, and number of SLNs were

indicators for detection failure, and missed detection was significantly more frequent in smaller and uninvolved nodes. In terms of the location of SLNs, the blue dye tracer missed a notable portion of the skipped SLNs in level II. Therefore, surgeons who apply the blue dye as a single tracer should exercise with extra caution.

Ethics Approval and Informed Consent

The study has been approved by the institutional review board (West China Hospital Research Ethics Committee, No. 2009 [30]). Written informed consent was obtained from all individual participants included in the study, and that this study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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