Original Study

Repeat Sentinel Lymph Node Surgery in Recurrent Breast Cancer: Peritumoral vs. Periareolar Injections

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Abstract

There are limited data on the optimal injection technique for repeat sentinel lymph node (rSLN) surgery. We conducted an institutional review of rSLN. A total of 141 patients were included; 103 (73%) underwent successful rSLN biopsy procedure with aberrant drainage in 32 (26%). Preoperative lymphoscintigraphy is beneficial in patients with recurrent breast cancer. Periareolar and peritumoral injections had similar incidence of sentinel lymph node identification and aberrant drainage.

Background: In the setting of recurrent cancer, there is no standard methodology regarding the technical aspects of repeat sentinel lymph node (rSLN) surgery. We analyzed our institutional experience with attempted rSLN surgery to determine the optimal injection technique. **Materials and Methods:** Single site, retrospective review of patients with prior lumpectomy for breast cancer who presented with recurrent or new ipsilateral breast cancer and underwent attempt at rSLN surgery from 2008 to 2017. Patients with prior mastectomy or no prior ipsilateral axillary operation were excluded. **Results:** A total of 141 patients were included; 103 (73%) underwent successful rSLN biopsy procedure. Lymphoscintigraphy showed aberrant drainage in 32 (26%). Periareolar (PA) injection resulted in failed mapping in 23/99 (23%) and aberrant drainage in 25/85 (29%). By comparison, peritumoral (PT) injection had a 14/38 (37%) incidence of failed mapping and 7/37 (19%) aberrant drainage ($P = .11$ and .23, respectively). Of the patients with successful sentinel lymph node (SLN) biopsy procedure via PA injection, 11/76 (14%) were positive for metastatic disease as compared with 2/24 (8%) in PT injection. Sixteen patients had lymph node metastases; 13 (81%) were SLNs, including 3 positive aberrant SLNs. Five-year regional recurrence rates were 11.4% (95% confidence interval, 0%-21.5%) and 0% for PA and PT injection techniques, respectively. **Conclusion:** PA and PT injections had a similar incidence of SLN identification and aberrant drainage. Preoperative lymphoscintigraphy is beneficial in patients with recurrent breast cancer given the higher incidence of aberrant drainage in this population. Patients who underwent PA injections had a higher incidence of regional recurrences but this difference was not statistically significant.

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Introduction

Sentinel lymph node (SLN) surgery is standard for patients with clinically node-negative disease undergoing definitive surgery. Unfortunately, 5% to 10% of patients undergoing breast-conserving therapy develop a local recurrence within 10 years.[1] Recent studies have demonstrated repeat SLN biopsy (rSLNB) procedure for recurrent breast cancer can influence treatment recommendations[2]; however, no standard methodology has been established regarding the technical aspects of repeat SLN (rSLN) surgery.

In the setting of a primary breast cancer, periareolar (PA) injections have gained popularity because of their reliability, simplicity, and shorter learning curve.[3] The rich subareolar lymphatic network augments uptake of the injected material and eliminates the need for image guidance in nonpalpable tumors.[4] As compared with other intraparenchymal injections, PA injections were found to have higher SLN identification rates and lower false-negative rates.[5] PA injections reliably stage the axilla but identification of aberrant lymphatic drainage to nonaxillary basins, such as the inter-

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nal mammary, supraclavicular, or contralateral axillary lymph nodes, is relatively infrequent.[6]

Lymphatic mapping and sentinel lymph node biopsy (SLNB) procedure are associated with a much higher rate of failed mapping and extra-axillary SLN identification in the setting of recurrent breast cancer or a new ipsilateral primary breast cancer in a previously treated breast/axilla.[7] In the rSLNB setting, some studies have demonstrated that PA injection of radiotracer results in lower SLN identification rates compared with other injection sites.[8] This is secondary to damaged lymphatic networks from previous interventions such as breast and lymph node surgery, as well as radiation.

Our breast surgical group has standardized our approach to lymphatic mapping and SLN tracer injection for primary breast cancer. We have come to a consensus that the major goal is to reliably stage the axilla and thus PA injections, without lymphoscintigraphy, are performed. Our group has not standardized our injection techniques for recurrent breast cancer; as a result, there is a heterogenous approach. Some surgeons utilize a similar PA technique, with or without lymphoscintigraphy, whereas others have adopted a PT injection technique in this setting, secondary to a desire to map the lymphatic drainage pathway more reliably from the tumor, as opposed to mapping the native breast mound in the setting of prior breast/axillary surgery. It is believed by some that identifying aberrant, nonaxillary drainage may provide valuable staging information with important prognostic implications in this situation.[9]

As a result of our large breast surgical volume and disparate approaches, we are uniquely poised to address the question of what is the optimal injection technique for SLNB in the scenario of a recurrent breast cancer/new ipsilateral primary. One of our goals was to standardize our clinical approach to a best evidence–based practice.

Materials and Methods

Following institutional review board approval, the Breast Continuous Quality Assessment Tool, which is a prospectively maintained database of breast operations performed at Mayo Clinic Rochester, was queried. A retrospective review was conducted to identify female patients aged > 18 years who underwent rSLN surgery for a recurrent tumor or a new ipsilateral breast cancer between October 1, 2008 and September 1, 2017, at Mayo Clinic, Rochester. Patients with a prior history of ipsilateral breast cancer who underwent lumpectomy and ipsilateral axillary surgery (SLNB or axillary lymph node dissection [ALND]) with resection of ≥ 1 axillary lymph node were included. Patients who underwent mastectomy for their primary tumor, ipsilateral breast surgery for benign breast disease alone, or had no prior axillary interventions were excluded.

Patient demographics were captured. The TNM (tumor, node, metastases) breast cancer staging was verified per the American Joint Committee on Cancer (AJCC) seventh edition. Clinical and pathologic variables collected regarding the breast primary and the recurrent tumor included quadrants involved, focality, histopathology, receptor status, involvement of the skin and/or underlying chest wall, and lymphovascular invasion. Throughout this manuscript, the term ipsilateral breast tumor recurrence is utilized for simplicity to encompass both a true recurrence and a new ipsilateral primary, as this distinction is imperfect. Details regarding the location of injection of each mapping agent, such as PA, PT, intradermal, and intraparenchymal, were noted as was the agent used: blue dye and/or Tc-99. The primary analysis was a comparison between PA and PT injection of radiocolloid. We also analyzed the PT injection technique, comparing the outcomes for an intradermal injection over the tumor versus an intraparenchymal injection around the tumor, the latter was most commonly image guided. The characteristics of each SLN including radioactivity, bluish discoloration, suspicion of involvement based on palpation, and pathologic determination of tumor metastasis were captured. Successful SLN mapping was defined as retrieval of a radioactive or blue regional lymph node. Failed mapping referred to injection of mapping agent that did not result in resection of an SLN regardless of lymphoscintigraphy findings. The handheld gamma probe is more accurate than the lymphoscintigraphy and thus even in the setting of failed lymphoscintigraphy surgeons frequently probe the ipsilateral axilla intraoperatively and will be able to identify a focal hot spot and trace it to an SLN. Aberrant drainage was defined as SLNs identified outside the ipsilateral axillary region by virtue of imaging on lymphoscintigraphy and thus only patients undergoing lymphoscintigraphy were included to address this question. This definition was chosen as it could not be reliably ascertained if patients without lymphoscintigraphy had an intraoperative assessment of all regional nodal basins with the gamma probe to rule out aberrant drainage. Regional nodal recurrence included the ipsilateral axilla, internal mammary, supraclavicular, and contralateral axilla.

Statistical Analysis

Quantitative variables were summarized using median and range; categorical variables were summarized using frequencies and percentages.[10] Factors associated with failed SLN mapping and aberrant drainage were assessed using univariate logistic regression and reported with odds ratios (OR) and 95% confidence intervals (CI). The ability to perform multivariable analysis was limited by sample size and the number of patients with failed mapping or aberrant drainage; however, limited multivariable analysis was performed using the best subset selection method based on the score criterion.[11] Time-to-event methods were used to analyze subsequent axillary recurrence; the Kaplan-Meier method was used to estimate 5-year regional recurrence probability, which was compared between groups using a log-rank test. *P* values <.05 were considered statistically significant. Analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Primary and Recurrent Tumor Characteristics

One hundred and forty-one patients with a recurrence or new ipsilateral tumor following prior lumpectomy and axillary surgical staging procedure were included. Table 1 shows the patient demographics, tumor features, and management of the primary breast cancer for the entire study population and comparison of the PA and PT cohorts. The median time from primary tumor treatment to recurrence was 9.8 years (range: 2 months to 24.3 years). The median age of patients at the time of recurrence was 64 years (range: 20-88 years). Thirteen (9.2%) patients underwent neoadjuvant chemotherapy, and 7 (5.0%) underwent neoadjuvant hormone

Table 1 Patient, Tumor, and Treatment Characteristics of the Index Primary Tumor

	Total[a] (N = 141)	PA Radiotracer Injection (N = 99)	PT Radiotracer Injection (N = 38)	*P* Value
Age at primary cancer diagnosis, years				.02
Median (range)	53 (29-84)	55 (29-84)	50 (30-71)	
UOQ location				.17
Yes	79 (56.8%)	58 (59.2%)	17 (45.9%)	
No	60 (43.2%)	40 (40.8%)	20 (54.1%)	
Missing	2	1	1	
Multifocal or multicentric				.005
No	125 (92.6%)	91 (96.8%)	30 (81.1%)	
Yes	10 (7.4%)	3 (3.2%)	7 (18.9%)	
Missing	6	5	1	
Histology				.40
DCIS	15 (10.8%)	11 (11.3%)	4 (10.5%)	
IDC	99 (71.2%)	65 (67.0%)	31 (81.6%)	
ILC	10 (7.2%)	7 (7.2%)	2 (5.3%)	
IMC	8 (5.8%)	7 (7.2%)	1 (2.6%)	
Other invasive	7 (5.0%)	7 (7.2%)	0 (0.0%)	
Missing	2	2	0	
Grade				.41
1	24 (18.0%)	18 (19.6%)	5 (13.5%)	
2	52 (39.1%)	37 (40.2%)	15 (40.5%)	
3	57 (42.9%)	37 (40.2%)	17 (45.9%)	
Missing	8	7	1	
Estrogen receptor status				.30
Positive	104 (80.6%)	69 (78.4%)	32 (86.5%)	
Negative	25 (19.4%)	19 (21.6%)	5 (13.5%)	
Missing	12	11	1	
Primary surgical management				1.0
Breast conserving surgery	140 (99.3%)	98 (99.0%)	38 (100.0%)	
No breast surgery	1 (0.7%)	1 (1.0%)	0 (0.0%)	
ALND				.11
No	94 (66.7%)	69 (69.7%)	21 (55.3%)	
Yes	47 (33.3%)	30 (30.3%)	17 (44.7%)	
Path T stage				.09
Tis	15 (11.2%)	12 (12.9%)	3 (8.1%)	
T1	88 (65.7%)	65 (69.9%)	22 (59.5%)	
T2	26 (19.4%)	14 (15.1%)	10 (27.0%)	
T3	4 (3.0%)	1 (1.1%)	2 (5.4%)	
T4	1 (0.7%)	1 (1.1%)	0 (0.0%)	
Missing	7	6	1	
Path N stage				.40
N0	119 (86.2%)	86 (88.7%)	29 (78.4%)	
N1	17 (12.3%)	9 (9.3%)	8 (21.6%)	
N2	1 (0.7%)	1 (1.0%)	0 (0.0%)	
N3	1 (0.7%)	1 (1.0%)	0 (0.0%)	
Missing	3	2	1	
Lymph node status				.13
Negative	119 (86.2%)	86 (88.7%)	29 (78.4%)	
Positive	19 (13.8%)	11 (11.3%)	8 (21.6%)	
Missing	3	2	1	

(*continued on next page*)

Table 1 (*continued*)

	Total[a] (N = 141)	PA Radiotracer Injection (N = 99)	PT Radiotracer Injection (N = 38)	*P* Value
Total nodes removed at primary				.10
Median (range) (N = 6 missing)	3 (1-34)	3 (1-34)	4 (1-25)	
> 5 nodes removed at primary				.13
1-5 nodes removed	88 (65.2%)	64 (68.1%)	20 (54.1%)	
> 5 nodes removed	47 (34.8%)	30 (31.9%)	17 (45.9%)	
Missing	6	5	1	
Adjuvant hormone therapy				.10
No	76 (53.9%)	57 (57.6%)	16 (42.1%)	
Yes	65 (46.1%)	42 (42.4%)	22 (57.9%)	
Adjuvant chemotherapy				< .001
No	98 (69.5%)	78 (78.8%)	18 (47.4%)	
Yes	43 (30.5%)	21 (21.2%)	20 (52.6%)	
Adjuvant radiotherapy				.54
No	31 (22.0%)	23 (23.2%)	7 (18.4%)	
Yes	110 (78.0%)	76 (76.8%)	31 (81.6%)	

Abbreviations: ALND = axillary lymph node dissection; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IMC = invasive mammary carcinoma; PA = periareolar; PT = peritumoral; UOQ = upper outer quadrant
[a] The total column includes 4 additional patients not summarized in the PA only or PT only columns because they had radiotracer injection in both the PA and PT locations.

therapy for their recurrent tumor (Table 2), including comparison of the PA and PT cohorts.

Mapping Agent and Location of Injection

Tc-99 radioactive colloid was used alone in 22.0% (31/141), and per surgeon preference, dual agent mapping with both Tc-99 and blue dye in 78.0% (110/141). Ninety-nine (70%) patients were injected with radiotracer in the PA location, 38 (27%) PT, and 4 (3%) in both locations. Surgeon preference was the primary factor driving the choice, and the use of PA versus PT injection varied per surgeon with PA injection used in 36.4% to 100% of cases, depending on surgeon (P <.001). Patients' who received a PT injection more often had upper outer quadrant recurrences, more often received adjuvant chemotherapy for their primary tumor, were on average younger, and more frequently had multifocal/multicentric disease in the setting of both their primary and recurrent tumor.

Successful SLN Mapping and Aberrant Drainage

Of the 141 patients injected with radiotracer, preoperative lymphoscintigraphy was performed in 88.7% (125/141) and 30 of 125 (24.0%) who underwent lymphoscintigraphy had no nodes visualized. Overall, rSLNB procedure was successful in surgical retrieval of an SLN in 103/141 (73%) patients; 77% (76/99) in the PA radiotracer injection group, 63% (24/38) in the PT radiotracer group, and 75% (3/4) in patients who were injected in both locations. The percent with successful SLN mapping did not differ significantly between the 2 tracer injection locations (P = .11). Of the patients with successful rSLNB, 72.8% (75/103) had undergone a prior SLNB alone and 27.2% (28/103) had undergone prior ALND. Those with prior ALND had successful rSLNB in 59.6% (28/47) compared with 79.8% (75/94) of those without prior ALND (P = .01).

Ipsilateral axillary lymph node visualization, aberrant drainage, and failed mapping comparisons are shown in Table 3. The 2 injection locations did not differ significantly with respect to aberrant drainage on lymphoscintigraphy or lack of nodal visualization. In addition to the 25 patients with aberrant drainage by lymphoscintigraphy, one patient with PA radiotracer injection, but without lymphoscintigraphy, had a supraclavicular node detected by the intraoperative gamma probe. Of patients with aberrant drainage, 53.1% had prior SLNB and 46.9% had undergone prior ALND.

Intraoperative Blue Dye Injections

Among the 110 patients in whom intraoperative blue dye was also used, the blue dye was injected in the PA location in 92 (83.6%), PT in 13 (11.8%), both locations in 3 (2.7%), and other location in 2 (1.8%). Among these 110 patients with both radiotracer and blue dye, 179 SLNs were removed, of which only 3/179 (1.7%) were identified by blue dye alone; ie, blue but not radioactive. All 3 of these nodes were negative for metastatic disease. The SLN status based on radioactive, blue, and palpable suspicious is summarized in Figure 1.

Positive SLN and Management

Positive SLN(s) were identified in 13 of 103 (12.6%) patients with successful rSLNB procedure. Among the 103 patients who

Table 2 Patient, Tumor, and Treatment Characteristics of the Recurrent Tumor

	Total[a] (N = 141)	PA Radiotracer Injection (N = 99)	PT Radiotracer Injection (N = 38)	*P* Value
Ag of th patient at th tim of recurrence, years				.01
Median (range)	64 (20-88)	66 (20-88)	60 (38-82)	
BMI				.47
< 25	41 (29.1%)	29 (29.3%)	11 (28.9%)	
25-30	45 (31.9%)	34 (34.3%)	9 (23.7%)	
≥ 30	55 (39.0%)	36 (36.4%)	18 (47.4%)	
Months elapse between surgery for th primary and recurrent cancer				.86
Median (range)	118 (2-292)	118 (7-292)	121 (2-227)	
Neoadjuvant therapy				.73
Chemotherapy (± hormone therapy)	13 (9.2%)	10 (10.1%)	2 (5.3%)	
Hormone therapy only	5 (3.5%)	4 (4.0%)	1 (2.6%)	
None	123 (87.2%)	85 (85.9%)	35 (92.1%)	
Recurrent tumor UOQ				< .001
Yes	52 (36.9%)	45 (45.5%)	4 (10.5%)	
No	89 (63.1%)	54 (54.5%)	34 (89.5%)	
Multifocal or multicentric recurrent tumor				.04
No	109 (77.3%)	72 (72.7%)	34 (89.5%)	
Yes	32 (22.7%)	27 (27.3%)	4 (10.5%)	
Histology of recurrent tumor				.18
DCIS	10 (7.1%)	9 (9.1%)	1 (2.6%)	
IDC	102 (72.3%)	66 (66.7%)	33 (86.8%)	
ILC	11 (7.8%)	10 (10.1%)	1 (2.6%)	
IMC	15 (10.6%)	12 (12.1%)	2 (5.3%)	
Other invasive	3 (2.1%)	2 (2.0%)	1 (2.6%)	
Grade recurrent tumor				.65
1	26 (18.7%)	19 (19.6%)	6 (15.8%)	
2	66 (47.5%)	47 (48.5%)	19 (50.0%)	
3	47 (33.8%)	31 (32.0%)	13 (34.2%)	
Unknown	2			
Estrogen receptor status recurrent tumor				.33
Positive	109 (77.9%)	75 (76.5%)	32 (84.2%)	
Negative	31 (22.1%)	23 (23.5%)	6 (15.8%)	
Missing	1	1	0	
Biologic subtype recurrent tumor (among those with invasive cancer, n = 131)				.80
HR^+/HER^-	96 (75.0%)	66 (74.2%)	27 (77.1%)	
$HER2^+$	16 (12.5%)	11 (12.4%)	5 (14.3%)	
TNBC	16 (12.5%)	12 (13.5%)	3 (8.6%)	
Missing	3	1	2	

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Table 2 (*continued*)

	Total[a] (N = 141)	PA Radiotracer Injection (N = 99)	PT Radiotracer Injection (N = 38)	*P* Value
Surgery for recurrent tumor				.75
Lumpectomy	14 (9.9%)	9 (9.1%)	4 (10.5%)	
Mastectomy	127 (90.1%)	90 (90.9%)	34 (89.5%)	
Successful SLN mapping				.11
Yes	103 (73.0%)	76 (76.8%)	24 (63.2%)	
No	38 (27.0%)	23 (23.2%)	14 (36.8%)	
Axillary dissection performed				1.0
No	131 (92.9%)	92 (92.9%)	36 (94.7%)	
Yes	10 (7.1%)	7 (7.1%)	2 (5.3%)	
Tumor size (cm) recurrent tumor				.78
Median (range)	1.4 (0.1-14)	1.4 (0.1-14)	1.4 (0.1-9)	
Pathologic N category recurrent tumor				.20
pN0	92 (65.2%)	66 (66.7%)	22 (57.9%)	
pN1	16 (11.3%)	13 (13.1%)	3 (7.9%)	
pNX – nodes could not be assessed	33 (23.4%)	20 (20.2%)	13 (34.2%)	
Total number of sentinel nodes retrieved (among those with successful mapping n = 103)				.67
Median (range)	2 (1-7)	2 (1-7)	2 (1-6)	
SLN positive (among those with successful mapping n = 103)				.73
No	90 (87.4%)	65 (85.5%)	22 (91.7%)	
Yes	13 (12.6%)	11 (14.5%)	2 (8.3%)	
Adjuvant hormone therapy				.84
No	76 (53.9%)	54 (54.5%)	20 (52.6%)	
Yes	65 (46.1%)	45 (45.5%)	18 (47.4%)	
Adjuvant chemotherapy				.23
No	112 (79.4%)	82 (82.8%)	28 (73.7%)	
Yes	29 (20.6%)	17 (17.2%)	10 (26.3%)	
Adjuvant radiotherapy				.74
No	127 (90.1%)	91 (91.9%)	34 (89.5%)	
Yes	14 (9.9%)	8 (8.1%)	4 (10.5%)	

Abbreviations: BMI = body mass index; DCIS = ductal carcinoma in situ; HR = hormone receptor; HER = human epidermal growth factor receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IMC = invasive mammary carcinoma; PA = periareolar; PT = peritumoral; SLN = sentinel lymph node; TNBC = triple-negative breast cancer; UOQ = upper outer quadrant
[a] The total column includes 4 additional patients not summarized in the PA only or PT only columns because they had radiotracer injection in both the PA and PT locations.

underwent successful rSLNB, the rate of a positive SLN was 15% (11/76) in the PA radiotracer group, 8% (2/24) in the PT group, and 0% in the 3 patients injected in both locations.

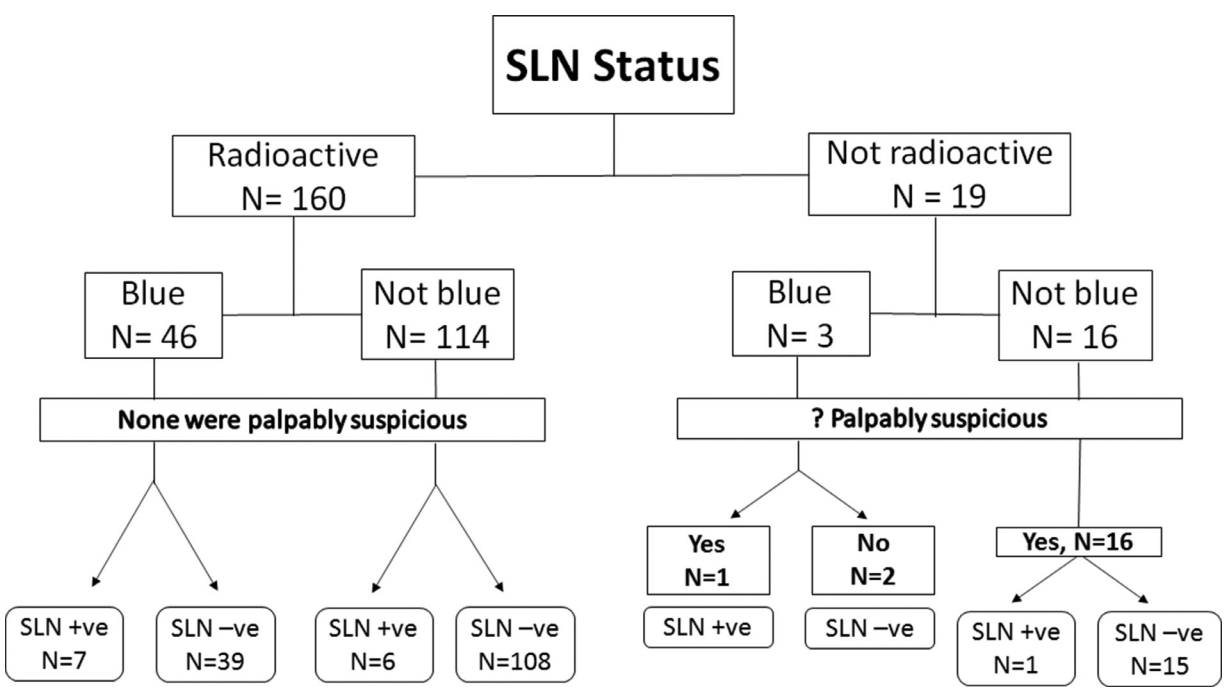
Overall, 14 SLNs (in 13 patients) were positive; 11 were ipsilateral axillary nodes of which 10 were identified by PA injection of Tc-99 ± blue dye, and 1 was palpable suspicious but neither radioactive nor blue. There were 3 positive aberrant SLNs, including 1 in the contralateral axilla detected by PA radiocolloid but not by PA blue dye, and 2 detected by the radiotracer injected in the PT location but not by the PA blue dye injection (1 contralateral axilla, 1 internal mammary node). Of the 14 positive SLNs, 3 (21.4%) were in an aberrant location, representing 3 of the 103 (2.9%) successful SLNB.

Table 3 Lymph Node Visualization Among Patients with Lymphoscintigraphy, Summarized by Radiotracer Injection Location

	PA Radiotracer Injection	PT Radiotracer Injection	Both Locations Radiotracer Injection	*P* Value Comparing PA to PT
	N = 85	N = 37	N = 3	
Ipsilateral axillary LN visualization, n (%)				.16
Yes	53 (62.4%)	18 (48.6%)	2 (66.7%)	
No	32 (37.6%)	19 (51.4%)	1 (33.3%)	
Aberrant drainage, n (%)				.23
Yes	25 (29.4%)	7 (18.9%)	0 (0%)	
No	60 (70.6%)	30 (81.1%)	3 (100%)	
No nodes visualized, n (%)				.14
Yes	17 (20%)	12 (32.4%)	1 (33.3%)	
No	68 (80%)	25 (67.6%)	2 (66.7%)	

Abbreviations: LN = lymph node; PA = periareolar; PT = peritumoral.

Figure 1 Summary of method of detection and status for n = 179 sentinel lymph nodes (SLNs) removed among n = 110 patients with both radiotracer and intraoperative blue dye injection.



Of those with positive SLN, 4/13 underwent an axillary dissection and 1/4 had additional positive axillary nodes. Of those with negative SLN, 1/90 went on to an ALND with none of the additional 23 nodes examined positive. Among the 38 patients with failed SLN mapping, 5/38 (13.2%) underwent ALND and 2 had positive nodes. In total, 16 patients had lymph node metastases at attempted rSLNB; 13 (81%) were identified via SLNB; 2 were identified via ALND after failed SLNB, and 1 was not blue or radioactive but palpable suspicious.

Failed Mapping and Aberrant Drainage

Factors associated with failed mapping and aberrant drainage in univariate analysis are shown in Table 4. History of prior radiation to the breast or axilla, prior ALND, resection of > 5 nodes at prior axillary surgery, prior tumor in upper outer quadrant, and BMI ≥ 30 were associated with failed mapping at the time of rSLN surgery. Factors associated with aberrant lymphatic drainage on lymphoscintigraphy include a history of prior ALND, > 5 nodes removed at prior axillary surgery, and a time interval of > 5 years between the primary tumor treatment and diagnosis of recurrence.

Table 4 Univariate Associations of Patient and Clinical Factors with the Outcomes of Failed Sentinel Lymph Node Mapping and Aberrant Drainage on Lymphoscintigraphy in Patients with Redo Sentinel Lymph Node Biopsy Procedure for Recurrent Ipsilateral Breast Cancer

	SLN Failed Mapping (N = 141)		Aberrant Drainage on Lymphoscintigraphy (N = 125)	
	Odds Ratio(95% CI)	*P* Value[a]	Odds Ratio(95% CI)	*P* Value[a]
Age at recurrence, years		0.44		.28
< 50	1.68 (0.42, 6.18)		0.72 (0.16, 2.72)	
50-70	1.25 (0.56, 2.91)		0.53 (0.23, 1.26)	
> 70	1.0 (reference)		1.0 (reference)	
BMI		0.004		.39
< 25	1.0 (reference)		1.0 (reference)	
25-30	1.62 (0.56, 5.00)		1.17 (0.45, 3.06)	
≥ 30	3.67 (1.42, 10.60)		0.65 (0.24, 1.73)	
Prior radiation		0.045		.40
Yes vs. No	2.76 (1.02, 9.17)		1.57 (0.59, 4.82)	
Prior ALND		0.01		.02
Yes vs. No	2.65 (1.24, 5.72)		2.73 (1.21, 6.24)	
# LNs removed in prior LN surgery		0.03		.04
> 5 vs. ≤ 5 nodes	2.39 (1.10, 5.22)		2.37 (1.04, 5.51)	
Quadrant of prior cancer		0.02		.29
UOQ vs. other	2.66 (1.22, 6.19)		1.57 (0.69, 3.68)	
Time between primary surgery and recurrence		0.09		.01
> 5 vs. ≤ 5 years	2.11 (0.93, 5.23)		4.02 (1.49, 13.41)	
Neoadjuvant therapy		0.86		.40
Yes vs. No	1.10 (0.35, 3.07)		0.53 (0.10, 1.93)	

Abbreviations: ALND = axillary lymph node dissection; BMI = body mass index; CI = confidence interval; LN = lymph node; SLN = sentinel lymph node; UOQ = upper outer quadrant
[a] *P* values are for linear trend across levels for variables analyzed as ordered categories.

As described earlier, radiotracer injection location was not significantly associated with either failed mapping or aberrant drainage in univariate analysis.

On multivariable analysis, the most important variables predicting failed mapping were BMI ≥ 30 versus < 25 (adjusted OR 4.8; $P = .002$), prior ALND (adjusted OR 2.6; $P = .02$), and prior tumor in the upper outer quadrant (adjusted OR 3.2; $P = .006$). No model with multiple significant variables was identified for the outcome of aberrant drainage, but time interval of > 5 years between the primary tumor treatment and diagnosis of recurrence was the best single-variable model by the score criterion. Tracer injection location did not reach the level of statistical significance in multivariable modeling.

Intradermal vs. Intraparenchymal Injections

In terms of PT injections, we compared intradermal and intraparenchymal. Of 38 patients with PT radiotracer injection, 24 (63.2%) were injected intradermal, 13 (34.2%) intraparenchymal, and 1 (2.6%) had both. Patients with intradermal injection had higher SLN success at 75.0% (18/24) compared with patients with intraparenchymal injection at 38.5% (5/13; $P = .03$). The percent with aberrant drainage was not significantly different (20.8% vs. 15.4%; $P = .68$).

Regional Recurrences

Six regional recurrences were observed in patients with PA injections and none in patients with a PT injection. The 5-year regional recurrence probabilities were 11.4% (95% CI, 0%-21.5%) and 0% for PA and PT injection techniques, respectively ($P = .10$). Of the 6 regional recurrences in the PA group, 66.6% (4/6) were in the ipsilateral axilla, and 2 were in aberrant regional basins; 16% (1/6) in the internal mammary node, and 16% (1/6) in the contralateral axilla (Table 5).

Discussion

This study demonstrates a high risk of failed mapping and a high rate of aberrant drainage in the setting of rSLNB (27% and 23%, respectively). We did not find a statistically significant difference in the success of SLN mapping, aberrant drainage, or rate of detection of positive SLN between PT or PA injection techniques. The estimated regional recurrence rate of 0% in the PT subgroup as compared with 11.4% in the PA subgroup at 5 years was also not statistically different ($P = .10$). Our group has come to consensus and we have implemented a process of PA and intradermal PT injection of Tc-99 overlying the tumor with lymphoscintigraphy as our new standard for rSLNB. Intraoperative utilization of blue dye to complement radiotracer injection remains at the surgeon's discretion.

Table 5 Listing of Patients who Experienced Axillary Recurrence after Redo Sentinel Lymph Node Biopsy Procedure

Patient	Primary Tumor	Recurrent Cancer	Redo SLNB Approach and Result	Recurrent Cancer Treatment	Subsequent Regional recurrence
1	Unifocal UIQ grade 2, ER^+/PR^+, 0.5-cm DCIS and pleomorphic LCIS, 2 SLNs examined, 0/2 positive, treated with adjuvant WBRT	Unifocal LOQ grade 3, $ER^+/PR^-/HER2^-$ 1.4-cm ILC diagnosed 7.2 years later	Periareolar and intradermal radiotracer injection with mapping to ipsilateral axilla, periareolar blue dye injection, 2 SLNs removed, both hot, neither blue, 0/2 positive	Mastectomy and adjuvant hormone therapy	Ipsilateral axilla recurrence 18 months later
2	Unifocal UOQ grade 2, $ER^+/PR^+/HER2^-$, 1.6-cm IMC, 5 SLNs examined, 0/5 positive, no adjuvant treatments given	Recurrent unifocal grade 3, $ER^+/PR^+/HER2^-$ 0.4-cm IMC in the tumor bed diagnosed 5.6 years later	Periareolar and intradermal radiotracer injection with mapping to ipsilateral axilla and infraclavicular nodes, periareolar blue dye injection, 1 hot but not blue SLN removed, 0/1 positive	Lumpectomy without additional systemic or radiation therapy	Ipsilateral axilla recurrence 4.4 years later
3	Multifocal UOQ grade 3, $ER^-/PR^-/HER2^-$, 3.4-cm IDC, 4 SLNs examined, 0/4 positive, treated with adjuvant chemotherapy	Recurrent multifocal UOQ, grade 3, $ER^-/PR^-/HER2^-$ 2.8-cm IDC in the tumor bed diagnosed 7 months later with chest wall invasion	Periareolar and intradermal radiotracer injection with mapping to ipsilateral axilla and intramammary nodes, periareolar blue dye injection, 3 SLNs removed (3 hot, 2 blue), 0/3 positive	Lumpectomy and adjuvant radiation therapy	Internal mammary chain, supraclavicular, and infraclavicular node recurrence 10 months later
4	Unifocal UOQ grade 2, $ER^+/PR^-/HER2^-$, 1.6-cm IDC with cutaneous involvement, 1 SLN examined, 0/1 positive, treated with adjuvant hormone therapy and WBRT	Recurrent unifocal UOQ grade 2, $ER^+/PR^-/HER2^-$ 0.9-cm IDC in the tumor bed diagnosed 5.5 years later	Periareolar and intradermal radiotracer injection with no ipsilateral axillary nodes mapped, aberrant drainage only to the intramammary nodes; peritumoral, periareolar, and intradermal blue dye injected; 3 ipsilateral axillary SLNs removed (1 hot, 2 palpably suspicious, none blue), 0/3 positive; 2 NSLNs removed (1 ipsilateral axilla NSLN, 1 intramammary NSLN); positive intramammary node	Mastectomy, adjuvant chemotherapy, and adjuvant hormone therapy	Contralateral axilla recurrence 4.1 years later
5	Unifocal, central location, grade 3 $ER^+/PR^+/HER2$ unknown 1.3-cm IDC, axillary dissection with 14 nodes examined, 0/14 positive, treated with adjuvant WBRT	Recurrent unifocal, central location, grade 2 $ER^+/PR^+/HER2^-$ 4-cm IMC in the tumor bed diagnosed 12.8 years later with cutaneous involvement	Periareolar and intradermal radiotracer injection with mapping to ipsilateral axilla, no blue dye injected, 1 ipsilateral axilla SLN removed, 1/1 positive with 1 mm metastasis size and no extranodal extension	Mastectomy, adjuvant chemotherapy, and adjuvant hormone therapy	Ipsilateral axilla recurrence 5.8 years later
6	Unifocal UOQ grade 3, unknown ER/PR/HER2 status, 0.9-cm IDC, 1 SLN examined, 0/1 positive, no adjuvant treatments given	Recurrent UOQ multifocal grade 3 $ER^-/PR^-/HER2^-$ 1.1-cm IDC in the tumor bed diagnosed 2.3 years later	Periareolar and intradermal radiotracer injection with mapping to ipsilateral axilla, periareolar blue dye injection, 2 SLNs removed (1 hot and blue, 1 palpably suspicious), 0/2 positive	Mastectomy without additional systemic or radiation therapy	Ipsilateral axilla recurrence 15 months later

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IMC = invasive mammary carcinoma; LCIS = lobular carcinoma in situ; LOQ = lower outer quadrant; NSLN = nonsentinel lymph node; PR = progesterone receptor; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; UIQ = upper inner quadrant; UOQ = upper outer quadrant; WBRT = whole brain radiation therapy

Our findings are consistent with those of the Sentinel Node and Recurrent Breast Cancer (SNARB) group, which demonstrated a low risk of regional recurrence in the setting of a negative rSLNB[12] and a low risk of regional recurrence if lymphatic mapping fails.[13] Similar to their conclusions, we do not recommend an ALND in the setting of failed lymphatic mapping secondary to the low risk of regional recurrence and the high risk of a regional recurrence being in an aberrant basin; 2/6 (33%) in our study and 7/7 in the Poodt et al.[12] series.

We were able to demonstrate a 73% success rate at identifying and retrieving an SLN in rSLNB, with a positive rSLN detection rate of 13%, which is similar to other studies.[7,14,15] Factors associated with both failed mapping and aberrant drainage included extent of prior axillary surgery (prior ALND and resection of > 5 nodes). Failed mapping was also associated with prior radiation, prior upper outer quadrant tumor, and BMI > 30, whereas aberrant drainage was also associated with a time interval of > 5 years between the primary tumor treatment and recurrence. This is consistent with previous studies that looked into outcomes of SLNB in the reoperative setting,[7,16] and a meta-analysis of aberrant drainage in recurrent breast cancer.[2] Several studies have demonstrated that patients with contralateral axillary metastases have a relatively poor prognosis,[17,18] which makes it clinically relevant to identify aberrant drainage.

In the setting of primary breast cancer, it is well established that PA and PT injections are both reliable and identify the same lymphatic basins regardless of the location of primary tumor.[19] However, in the setting of prior breast and axillary surgery, with or without radiation, the lymphatic channels can be significantly disrupted and scarred. In this setting, a PA injection may map the central breast mound; however, this may not reflect lymphatic drainage from the tumor secondary to prior incisions, scarring, breast mobilization, axillary disruption, and potentially radiation fibrosis. Alternative routes of breast drainage from different quadrants may have been established and this is supported by our results demonstrating the longer time interval from primary surgery to rSLNB, the higher the likelihood of aberrant drainage. As a result, we theorized PT injections might be more reflective of the newly established lymphatic pathways draining the tumor. To our knowledge, this is the first study of a single institutional review attempting to compare both techniques in recurrent breast cancer.

Our comparison of the 2 techniques did not demonstrate superiority of either approach in terms of SLN identification rate, aberrant drainage, rate of detection of positive SLNs, or regional recurrence. As in many situations there is lack of high-level data to drive an evidence-based best practice. Despite this our group elected to come to a consensus approach of PT and PA injection with lymphoscintigraphy. Our approach to PT injection is intradermal as opposed to intraparenchymal secondary to higher SLN mapping success, no significant difference in aberrant drainage in the techniques and the markedly more efficient workflow of an intradermal injection compared with PT for nonpalpable tumors.

Limitations of our study include its retrospective design. Although identifying a positive or negative SLNs in rSLNB setting can influence multidisciplinary decisions on whether to deliver adjuvant radiation, the fields to be treated, as well as systemic therapy considerations, our study lacks a control group who did not undergo attempt at rSLNB and thus we do not know how the findings and downstream clinical interventions ultimately influence recurrence rates. This is a similar limitation to other studies evaluating the benefits of rSLNB.[20] Another limitation was sample size for assessment of factors associated with failed SLN mapping and aberrant drainage. With < 40 events for each outcome, our study may not have been able to identify all clinically important factors, particularly in multivariable analysis.

Conclusion

Preoperative lymphoscintigraphy is beneficial in patients with recurrent breast cancer given the higher incidence of failed mapping and aberrant drainage in this population. Patients who underwent PA injections had a higher incidence of regional recurrences, but this difference was not statistically significant.

Clinical Practice Points

Lymphatic mapping and SLNB procedures are associated with a much higher rate of failed mapping and extra-axillary SLN identification in the setting of recurrent breast cancer, or a new ipsilateral primary breast cancer in a previously treated breast/axilla.[7]

The optimal technique for performing rSLNB procedures has not been well studied.

Our study revealed similar failed mapping (approximately 25%) and aberrant drainage (approximately 25%) with a PA and PT injection technique. Our findings (5-year regional recurrence probabilities 11% PT and 0% PA; $P = 0.10$) are consistent with those of the Sentinel Node and Recurrent Breast Cancer (SNARB) group, which demonstrated a low risk of regional recurrence in the setting of a negative rSLNB,[12] and a low risk of regional recurrence if lymphatic mapping fails.[13]

Similar to their conclusions, we do not recommend an ALND in the setting of failed lymphatic mapping secondary to the low risk of regional recurrence and the high risk of a regional recurrence being in an aberrant basin; 2/6 (33%) in our study and 7/7 in the Poodt et al.[12] series.

Unlike in the setting of SLNB for primary breast cancer, based on the earlier described findings, we suggest lymphoscintigraphy when performing rSLNB.

Disclosure

The authors have stated that they have no conflicts of interest.

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