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Lessons Learned From 500 Cases of Lymphatic Mapping for Breast Cancer

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Objective

To evaluate the factors affecting the identification and accuracy of the sentinel node in breast cancer in a single institutional experience.

Summary Background Data

Few of the many published feasibility studies of lymphatic mapping for breast cancer have adequate numbers to assess in detail the factors affecting failed and falsely negative mapping procedures.

Methods

Five hundred consecutive sentinel lymph node biopsies were performed using isosulfan blue dye and technetium-labeled sulfur colloid. A planned conventional axillary dissection was performed in 104 cases.

Results

Sentinel nodes were identified in 458 of 492 (92%) evaluable cases. The mean number of sentinel nodes removed was 2.1. The sentinel node was successfully identified by blue dye in 80% (393/492), by isotope in 85% (419/492), and by the combination of blue dye and isotope in 93% (458/492) of patients. Success in locating the sentinel node was unrelated to tumor size, type, location, or multicentricity; the presence of lymphovascular invasion; histologic or nuclear grade; or a previous surgical biopsy. The false-negative rate of 10.6% (5/47) was calculated using only those 104 cases where a conventional axillary dissection was planned before surgery.

Conclusions

Sentinel node biopsy in patients with early breast cancer is a safe and effective alternative to routine axillary dissection for patients with negative nodes. Because of a small but definite rate of false-negative results, this procedure is most valuable in patients with a low risk of axillary nodal metastases. Both blue dye and radioisotope should be used to maximize the yield and accuracy of successful localizations.

The histologic status of the axillary nodes remains the single best predictor of survival in patients with breast cancer.[1] The sentinel node is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumor. Several investigators have confirmed the hypothesis that lymphatic drainage of a breast cancer can be identified and traced to the sentinel node during surgery, and that the histologic status of the sentinel node accurately predicts the pathologic status of the entire axilla.[2–8] The aim of this study was to evaluate in detail a single institutional experience in establishing and developing lymphatic mapping for breast cancer. Particular focus was on unsuccessful mapping procedures, the relative value of blue dye and radioisotope in localizing the sentinel node, false-negative results, and patients with positive nodal disease.

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PATIENTS AND METHODS

Patients

In a prospective study from October 1996 to May 1998, 500 patients with clinical T1–3N0 breast cancer had a sentinel lymph node biopsy at Memorial Sloan-Kettering Cancer Center. This series includes the first case performed in the institution and the ensuing 499 consecutive cases.

Informed consent, approved by the institutional review board (protocol 96-049), was obtained before the procedure. All patients had biopsy-proven invasive cancer; seven patients were subsequently excluded when final pathologic review showed only ductal carcinoma *in situ*. Both mastectomy and breast conservation patients were equally eligible. Patients who were pregnant or clinically node-positive (N1 or N2) were excluded. The first 60 cases are the subject of a previous report in which the sentinel node hypothesis—that the sentinel node accurately predicts the axillary node status—was verified.[9]

Lymphatic Mapping

On the morning of surgery, 0.3 mCi of Tc-99m unfiltered sulfur colloid (CisUS, Bedford, MA) was administered. The isotope was injected into the breast parenchyma around the tumor in the majority of cases. A pilot study in the early part of the series (involving cases 82 to 145) addressed the benefit of using a 0.22-micron filter to facilitate localizing the sentinel node. More recently, a second study using intradermal injection of unfiltered Tc-99m sulfur colloid (involving cases 225 to 499) was performed, confirming that in this setting the lymphatic drainage of intradermal and parenchymal isotope injections is identical (unpublished data). Lymphoscintigraphy was performed with a standard interval of 50 to 60 minutes between injection and imaging. The time between injection and surgery varied from 2 to 4 hours.

At surgery, 4 cc of isosulfan blue dye (Lymphazurin; Zenith Parenterals, Rosemont, IL) was injected around the tumor, and within 5 to 10 minutes an axillary incision was made and a sentinel node biopsy performed, guided by both the gamma probe (C-Trak, Care-Wise Medical, Morgan, CA) and the appearance of blue dye in the node or nodes. Counts were taken of the node or nodes *in situ* and *ex vivo*, and then of the axillary background, seeking at least four-fold reduction in axillary counts. A standard axillary lymph node dissection was then performed in the first 60 patients. After the first 60 cases, surgeons who were inexperienced with the technique continued to perform conventional axillary dissections after sentinel node biopsies. The remaining patients being treated by surgeons experienced in the technique underwent an axillary dissection only if the tumor was T2 in size or if the sentinel node was positive.

Using blue dye, a successful sentinel node biopsy was defined as a lymph node with visible blue staining (if a blue-stained lymphatic vessel was found, it must have been traced to a specific blue node). Successful radioisotope localization required the postexcision axillary bed counts to be 25% or less of sentinel node counts *ex vivo*. In all patients in whom the sentinel lymph node was not successfully identified, a conventional axillary dissection was performed.

Pathology

In our first 60 cases, while we were validating the sentinel node hypothesis, pathologic specimens were examined by routine hematoxylin and eosin methods, correlating the findings in the sentinel lymph node with those in the remainder of the axilla. No frozen sections were taken of the sentinel node in the first 52 cases.

After this, sentinel nodes were routinely evaluated by intraoperative frozen section. If the frozen section revealed axillary metastases, the patient underwent a conventional axillary dissection. All remaining frozen tissue was submitted for analysis. The nonfrozen portion of the sentinel node remaining after frozen section was processed in three sections for routine hematoxylin and eosin staining and immunohistochemistry. Immunohistochemistry for cytokeratin was performed using CAM5.2 and AE1:AE3 (Becton Dickinson Immunocytometry Systems, San Jose, CA). Immunohistochemistry was performed retrospectively on the 3 false-negative cases that occurred in the first 60 cases. Estrogen and progesterone receptor status was assessed by immunohistochemistry on paraffin sections.

Statistics

Statistical analysis of unsuccessful mapping procedures was calculated using Fisher's exact test. The number of failures in a particular category of patients was compared to the number of failures in the remaining patients in a 2×2 contingency table. The statistical package Instat 2.0 (Graphpad software) was used for the analyses.

RESULTS

Patient demographics are outlined in Table 1. The mean patient age was 56 years (range 21 to 87). Three hundred nineteen (65%) patients had a previous surgical biopsy; this reflects the institutional referral practice, as does the breast conservation rate of 87%. Table 2 outlines the results of lymphatic mapping. Three surgeons performed the majority of the cases (84%). The remaining five surgeons performed an average of 16 cases. Eight patients were excluded from the analysis because their final pathology review revealed only ductal carcinoma *in situ*. In 34 (7%) cases, the sentinel lymph node was not identified. The sentinel node was successfully identified by blue dye in 80% (393/492), by isotope in 85% (419/492), and by the combination of blue dye and isotope in 93% (458/492) of all 492 evaluable patients (see Table 2). Success in finding the sentinel node was unrelated to the route of administration of the isotope or tumor size (see Table 2). The mean number of sentinel lymph nodes removed was 2.1 (range 1 to 8). The sentinel node was located at level 1 in 97% of cases. There were four cases where the sentinel node was in Rotter's space, and two

Table 1. PATIENT CHARACTERISTICS

	No. of Patients	%
Sex		
Female	490	99
Male	2	1
Laterality		
Right	239	49
Left	241	49
Bilateral	6	1
Initial presentation		
Palpable mass	282	57
Nonpalpable abnormality	200	41
Unknown	10	2
Diagnosis by		
Fine-needle aspiration	51	10
Core biopsy	88	18
Prior excisional biopsy	319	65
Concurrent excisional biopsy	34	7
Tumor location		
Upper outer quadrant	256	52
Lower outer quadrant	57	12
Upper inner quadrant	66	13
Lower inner quadrant	41	8
Central	72	15
Treated by		
Mastectomy	65	13
Breast conservation	427	87

cases of intramammary sentinel nodes. Internal mammary nodes were identified on lymphoscintigraphy on 35 occasions (see Table 2). Biopsy of these was attempted on three occasions when the lesion was medially placed but was successful on only one occasion at obtaining nodal tissue.

Pathology

Frozen section analysis of the sentinel lymph node was positive in 17% (68/405) of cases. However, on 10 occasions the frozen section report was incorrectly negative, yielding a 13% (10/78) false-negative rate among the 405 patients having frozen section. Among the 458 successful sentinel node localizations, there were 31 cases where the positive sentinel node was detected only by immunohistochemistry. The outcome of these 31 cases was as follows. Five (17%) refused further axillary surgery. In seven (23%) cases, further axillary surgery was not recommended because the patient was elderly. Nineteen (61%) patients returned to the operating room for an axillary dissection; only 3 of these cases (16%) had further nodal disease.

Relative Value of Blue Dye and Radioisotope in Localizing the Sentinel Node

The sentinel lymph node was identified by blue dye only in 9%, by isotope only in 14%, and by the combination in

Table 2. RESULTS OF SENTINEL LYMPHATIC MAPPING

	No.	%
Total number of cases performed	500	100
Cases with DCIS only	8	2
Total number of evaluable cases	492	98
Failed mapping procedures	34	7
Successful evaluable cases	458	92
Success rate related to:		
Mapping technique		
Blue dye	393/492	80
Radioisotope	419/492	85
Dye + isotope	458/492	93
Route of administration of the isotope		
Parenchymal filtered	53/56	95
Parenchymal unfiltered	310/340	91
Intradermal	92/93	99
No isotope given	3/3	100
Tumor size		
T1 (n = 437)	407/437	93
T1a (n = 76)	74/76	97
T1b (n = 137)	132/137	96
T1c (n = 224)	201/224	90
T2-3 (n = 55)	51/55	93
Anatomic location of sentinel nodes		
Level 1	442/458	97
Level 2	2/458	0.4
Level 1 and 2	11/458	2
Rotter's space	4/458	0.8
Internal mammary	1/458	0.2
Intramammary	2/458	0.4
Lymphoscintigraphy		
Positive	195	40
Negative	287	58
Not done	10	2
Positive lymphoscintigram sites		
Axilla only	160/195	82
Axilla + internal mammary	22/195	11
Axilla + int. mammary + supraclavicular	5/195	2
Internal mammary only	8/195	4
Pathology		
Frozen section analysis		
Negative	338/406	83
Positive	68/406	17
Not done	52/458	11
Hematoxylin & eosin analysis		
Negative	363/458	79
Positive	95/458	21
Immunohistochemistry analysis		
Negative	275/336	82
Positive	61/336	18
Not done	122/458	27
Estrogen receptor status		
Negative	54/268	20
Positive	214/268	80
Not done	190/458	41
Progesterone receptor status		
Negative	79/268	29
Positive	189/268	71
Not done	190/458	41

DCIS, ductal carcinoma *in situ*.

Table 3. RELATIVE CONTRIBUTION OF BLUE DYE AND ISOTOPE IN IDENTIFYING THE SENTINEL NODE AT EACH SITE

Sentinel Node Sites	Blue Only (no. of pts)	Hot Only (no. of pts)	Blue and Hot (no. of pts)	Total no. of pts
Single site				
Total	16 (8%)	34 (18%)	143 (74%)	193
Two sites				
Site 1	15	20	137	
Site 2	16	20	61	
Isotope counts unknown	—	5	5	
Total	16 (8%)	25 (12%)	161 (80%)	202
Three or more sites				
Site 1	6	6	43	
Site 2	7	6	38	
Site 3 or more	7	6	43	
Isotope counts unknown	—	—	3	
Total	7 (11%)	6 (10%)	50 (79%)	63
TOTAL	39 (9%)	65 (14%)	354 (77%)	458

77% of cases (Table 3). These proportions were similar whether one, two, or three or more sentinel nodes were removed.

Unsuccessful Mapping Procedures

Success in locating the sentinel node was unrelated to tumor size, type, location, or multicentricity; the presence of lymphovascular invasion; histologic or nuclear grade; or a previous surgical biopsy (Table 4). A positive result on lymphoscintigraphy was significantly associated with the successful location of a sentinel node ($p = 0.0001$).

False-Negative Cases

The false-negative rate of 10.6% (5/47) was calculated using only the 104 cases where a conventional axillary dissection was planned before surgery. The number of patients in this group with positive nodal disease ($n = 47$) was used as the denominator. Detailed analyses of these five cases are shown in Table 5. All five patients had axillary metastases at level 1, and none had skip metastases.

- *Case 3:* A 49-year-old woman with a previous biopsy of a 1.6-cm lesion in the upper outer quadrant with a positive Rotter's node and a negative blue and hot node at level 1. During surgery the Rotter's node was thought to be suspicious.
- *Case 11*: A 68-year-old with a 4-cm lesion in the upper outer quadrant with a negative hot and blue node at level 1. During surgery the level 1 nodes were suspicious. Six of 15 nonsentinel nodes were positive.
- *Case 272*: A 71-year-old who 7 days previously had a large excision in the upper outer quadrant ($7 \times 6 \times 3$ cm), including the tail of the breast, for a 1.2-cm invasive lobular cancer had a hot sentinel node with no blue dye. Subsequent dissection revealed eight positive nodes.
- *Case 349*: A 48-year-old with a 0.8-cm invasive ductal carcinoma who had one blue and hot node and a second nonblue hot node removed from level 1. Of note, the residual axillary bed counts were higher than the *ex vivo* counts of the second sentinel node, which would suggest that a further sentinel node was present; however, this was ignored. Subsequent axillary dissection revealed two positive lymph nodes.
- *Case 418*: A 40-year-old with a 1.9-cm invasive ductal carcinoma in the axillary tail of the breast. Sentinel node biopsy revealed three hot nodes, one of which was slightly blue. The frozen section of these was reported as a few atypical cells, but the permanent section and immunohistochemistry revealed no evidence of malignancy. During surgery a clinically malignant node was palpated. Completion dissection revealed two positive nodes.

Patients With Positive Nodal Disease

The relative value of blue dye and radioisotope in localizing the positive sentinel node was similar to that for benign nodes (Table 6). Positive sentinel nodes were detected by blue dye only in 11%, by isotope only in 15%, and by the combination in 77% of cases. In patients with positive nodal disease, an immediate dissection was performed in 58% (68/125) because the frozen section was positive. Axillary dissection was performed as a

Table 4. UNSUCCESSFUL MAPPING PROCEDURES

Category of Patients	Number of Failures/Total in That Category	%	Significant p values
All patients	34/492	7	
Lymphoscintigram			
Positive	3/195	2	0.001
Negative	31/286	10	
Diagnosis by			
Previous excisional biopsy	18/319	6	
Concurrent surgical biopsy	2/34	6	
FNA only	5/51	10	
Core biopsy only	9/88	10	
Tumor location			
Upper outer quadrant	17/256	7	
Lower outer quadrant	4/56	7	
Upper inner quadrant	6/66	9	
Lower inner quadrant	2/41	5	
Central	5/72	7	
Tumor size			
T1a	2/76	3	
T1b	5/137	4	
T1c	23/224	10	
T2-3	4/55	7	
Tumor type			
Ductal	25/409	6	
Lobular	7/53	13	
Other	2/30	7	
Lymphovascular invasion			
Present	8/86	9	
Absent	24/396	6	
Unknown	2/10	20	
Multicentric tumor			
Present	5/60	8	
Absent	29/425	7	
Unknown	0/7	0	
Histologic grade			
I	1/42	2	
II	11/135	8	
III	16/208	8	
Unknown	6/107	6	
Nuclear grade			
I	1/33	3	
II	13/187	7	
III	11/140	8	
Unknown	9/132	7	

FNA, fine-needle aspiration biopsy.

second operative procedure in 36% (45/125) of the patients with positive nodal disease. Sixty-one percent (69/114) of patients who had an axillary dissection had positive nodal disease in their sentinel node only. Thirty-nine percent (45/114) of patients with a positive sentinel node had tumor in the nodal basin outside of their sentinel node.

The node positivity rate for the sentinel nodes after three sections and immunohistochemistry on each node was 24% for T1 lesions and 57% for T2 lesions (Table 7). The majority of positive sentinel nodes (98%) were at level 1, but 2% were in Rotter's space. In 18 patients with positive sentinel nodes, the first sentinel node was benign. In 6 of these 18 cases, the first sentinel node stained blue but was not malignant, and the subsequent positive sentinel node was detected by isotope alone. Thus, 5% (6/126) of cases required the use of isotope to detect the positive sentinel node.

Table 5. DATA ON FALSE-NEGATIVE CASES

Calculating the False-Negative Rate	No.	%
Preoperatively planned axillary dissection (protocol 1)	104	21
Protocol 1 cases with positive nodal disease	47	45
Protocol 1 cases with falsely negative sentinel node	5	
False-negative rate for protocol 1 cases	5/47	10.6
False-negative rate for T1 (<2 cm) protocol 1 cases	4/27	15
False-negative rate for T2 (2–5 cm) protocol 1 cases	1/20	5

Category	Number of False-Negatives in Category/Total	%
Lymphoscintigram		
Positive	1/5	20
Negative	3/5	60
Not done	1/5	20
Tumor diagnosis by		
Previous excisional biopsy	3/5	60
FNA only	2/5	40
Tumor location		
Upper outer quadrant	5/5	100
Tumor Size		
T1	4/5	80
T2	1/5	20
Tumor type		
Ductal	4/5	80
Lobular	1/5	20
Lymphovascular invasion		
Present	2/5	40
Absent	3/5	60
Multicentric tumor		
Present	1/5	20
Absent	4/5	80
Histologic grade		
II	1/5	20
III	2/5	40
Unknown	2/5	40
Nuclear grade		
I	1/5	20
II	1/5	20
III	1/5	20
Unknown	2/5	40

FNA, fine-needle aspiration biopsy.

Table 6. RELATIVE CONTRIBUTION OF BLUE DYE AND ISOTOPE IN IDENTIFYING 126 POSITIVE SENTINEL NODE CASES AT EACH SITE

Sentinel Node Sites	Blue Only (no. of pts)	Hot Only (no. of pts)	Blue and Hot (no. of pts)	Total no. of pts
Single site				
Total	6 (12%)	6 (12%)	40 (78%)	52
Two sites				
Site 1	7	4	34	
Site 2	6	3	9	
Isotope counts unknown	—	3	3	
Total	7 (13%)	7 (13%)	40 (74%)	54
Three or more sites				
Site 1	1	2	15	
Site 2	1	2	15	
Site 3 or more	1	2	15	
Isotope counts unknown	—	—	2	
Total	1 (5%)	2 (10%)	17 (85%)	20
TOTAL	14 (11%)	15 (12%)	97 (77%)	126

DISCUSSION

The sentinel lymph node hypothesis for breast cancer is that the sentinel node accurately predicts the axillary node status. Histologic support for this hypothesis is provided by Turner et al,[10] who used cytokeratin immunohistochemical staining to examine the sentinel and nonsentinel lymph nodes in 103 patients. In 60 patients whose sentinel nodes were metastasis-free by hematoxylin and eosin staining and immunohistochemistry, only one additional tumor-positive lymph node was identified in 1087 nonsentinel nodes. They concluded that the sentinel lymph node was indeed the most likely axillary node to harbor metastatic breast cancer.

Success at identifying the sentinel node was not affected by pathologic features of the tumor such as size, type, or grade. The location of the tumor within the breast did not affect the success of lymphatic mapping. In this study, we have found that blue dye and radioisotope are complementary techniques, achieving a 93% success rate in identifying the sentinel node in 500 patients. Our success rate using blue dye alone was 80%. The overall success of the procedure was maximized when the two techniques—blue dye and radioisotope—were used together. In this study we found that 9% of nodes were found only by blue dye and 14% only by isotope. However, of greater importance is the fact that 5% of positive sentinel nodes would not have been detected without the use of isotope if blue dye alone had been used to detect the sentinel lymph node. We believe that the value of using both techniques in maximizing the success rate and in providing a safety mechanism for identifying all positive sentinel nodes far outweighs the small added cost of using isotope.

A positive result on a lymphoscintigram was more likely to be associated with successful localization of a sentinel node. However, lymphoscintigram results were positive in only 40% of patients; this may be explained by the practice of obtaining the lymphoscintigram image approximately 1 hour after injection of isotope. More positive results on lymphoscintigrams may have been obtained if delayed films had been taken. In melanoma, the lymphoscintigram can guide the surgeon to the correct nodal basin; lymphoscintigraphy for breast cancer provides directional guidance only in cases where the identification (by biopsy) of a positive internal mammary node would prompt the use of systemic adjuvant therapy, or of an internal mammary radiotherapy port.

The sentinel lymph node hypothesis for early breast cancer has been well validated in many institutions,[3,4,6–8,11–13] including our own.[9] In our first 60 cases, we observed an 8% false-negative rate for T1 lesions and a 25% false-negative rate for T2 lesions.[9] After this, patients with a T1 lesion and clinically negative axillary nodes were offered sentinel lymph node biopsy alone if the sentinel node was negative. Patients with positive sentinel nodes by either immediate frozen section or the subsequent hematoxylin and eosin and immunohistochemistry examination underwent a standard axillary dissection. Our larger series of 500 cases suggests that our initial concern about the high false-negative rate in T2 lesions was probably the result of small numbers. The overall false-negative rate (among the 104 patients having a planned axillary dissection) for lesions of all sizes was 10%. The majority of these false-negative cases were early in each individual surgeon's experience. No surgeon had more than one false-negative case, suggest-

Table 7. DETAILS OF 126 PATIENTS WITH POSITIVE SENTINEL NODES

	Number	%
Anatomic location of positive sentinel nodes		
Level 1	123/126	98
Level 2 (Rotter's space)	3/126	2
Node positivity rate related to tumor size		
T1 (n = 407)	97/407	24
T1a (n = 74)	7/74	9
T1b (n = 132)	25/132	19
T1c (n = 201)	65/201	32
T2-3 (n = 51)	29/51	57
Order in which positive sentinel nodes were retrieved		
Site 1		
Positive sentinel nodes	108/126	86
Negative sentinel nodes	18/126	14
Site 2		
Positive sentinel nodes	41/66	62
Negative sentinel nodes	24/66	36
Site 3		
Positive sentinel nodes	15/32	47
Negative sentinel nodes	17/32	53
Site 4		
Positive sentinel nodes	2/8	25
Negative sentinel nodes	6/8	75
18 positive cases in which the first sentinel node is negative		
Number with the first sentinel node benign and blue	16/18	89
Number in which a further sentinel node is blue and positive	10/16	63
Cases that required isotope to find the positive node	6/126	5

ing that there may be a learning curve involved in breast lymphatic mapping.

Frozen section analysis of the sentinel lymph nodes was used routinely after the first 60 cases. A 13% false-negative rate for the frozen section result was observed in this series. Although this may appear high, 87% of patients were spared a second operative procedure. Patients who have positive sentinel nodes on immunohistochemistry may need to return to the operating room. In this series, 19 patients had an axillary dissection after a sentinel node was positive on immunohistochemistry only. Only three had further nodal disease. The value of a completion axillary dissection in those with positive nodes detected only on immunohistochemistry requires evaluation in a randomized trial.

The false-negative rate of 10% may appear higher than expected, but that is because many series in the literature report their false-negative rate using the total number of cases as their denominator.[2,14] No individual surgeon had more than one false-negative case, and most of these occurred early in their experience. Our data include every case of lymphatic mapping ever performed at our institution. Our five false-negative cases have certain characteristics in common. All were upper outer quadrant tumors (two of these were high in the axillary tail), and most had a previous large biopsy cavity. Such patients should have a backup axillary dissection. Clinically suspicious nonsentinel nodes were present in three false-negative cases; if found, a liberal biopsy should be taken. Surgeons should be aware that the sentinel node can be found in Rotter's space. Strict adherence to the guidelines for sentinel node biopsy will reduce false-negative cases, such as the one in our series that allowed the postexcision axillary bed count to be higher than the sentinel node count *ex vivo*.

In patients with positive nodal disease, 39% of patients had tumor in the nodal basin outside of their sentinel node. This is an important point if one is considering performing only sentinel node biopsy for sentinel node-positive patients, as is being proposed in a trial by the American College of Surgeons Oncology Group.[15]

In conclusion, sentinel node biopsy in patients with early breast cancer is a safe and effective alternative to routine axillary dissection for node-negative patients. Because of a small but definite rate of false-negative results, this procedure is most valuable in patients with a low risk of axillary nodal metastases. Both blue dye and radioisotope should be used to maximize the yield and accuracy of successful localizations.

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