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The Effect of Prior Breast Biopsy Method and Concurrent Definitive Breast Procedure on Success and Accuracy of Sentinel Lymph Node Biopsy

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Background: It has been suggested that sentinel lymph node (SLN) biopsy for breast cancer may be less accurate after excisional biopsy of the primary tumor compared with core needle biopsy. Furthermore, some have suggested an improved ability to identify the SLN when total mastectomy is performed compared with lumpectomy. This analysis was performed to determine the impact of the type of breast biopsy (needle vs. excisional) or definitive surgical procedure (lumpectomy vs. mastectomy) on the accuracy of SLN biopsy.

Methods: The University of Louisville Breast Cancer Sentinel Lymph Node Study is a prospective multi-institutional study. Patients with clinical stage T1-2, N0 breast cancer were eligible. All patients underwent SLN biopsy and completion level I/II axillary dissection. Statistical comparison was performed by χ^2 analysis.

Results: A total of 2206 patients were enrolled in the study. There were no statistically significant differences in SLN identification rate or false-negative rate between patients undergoing excisional versus needle biopsy. The SLN identification and false-negative rates also were not statistically different between patients who had total mastectomy compared with those who had a lumpectomy.

Conclusions: Excisional biopsy does not significantly affect the accuracy of SLN biopsy, nor does the type of definitive surgical procedure.

Key Words: Sentinel lymph node—Breast cancer—Excisional biopsy—Axillary node dissection

Sentinel lymph node (SLN) biopsy has become increasingly accepted as a minimally invasive alternative to level I/II axillary dissection for nodal staging. Multiple studies have validated the procedure and demonstrate that SLN biopsy can accurately determine the nodal status of patients with invasive breast carcinoma.[1–16] SLN biopsy continues to evolve as investigators work to optimize the technical aspects of the procedure.

Some studies have suggested that SLN biopsy for breast cancer may be less accurate after excisional biopsy of the primary tumor compared with core needle biopsy or fine-needle aspiration biopsy.[2,6,8,17–19] There is concern that large-volume excisional biopsy results in subsequent disruption of breast lymphatics. Some authors have suggested that altered lymphatic drainage

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decreases the likelihood of successful lymphatic mapping, and indeed, that any nodes removed after an excisional biopsy may not actually be an accurate reflection of lymphatic drainage from the site of the primary tumor.

Furthermore, there has been anecdotal suggestion that SLN identification may be easier when total mastectomy is performed as the definitive procedure for the primary tumor because of improved exposure and visualization of the axilla compared with breast conservation therapy. However, if patients require mastectomy because the primary breast cancer is too large to accommodate a lumpectomy, some surgeons have been hesitant to trust a negative SLN result.[20]

This analysis was performed to determine the effect of the type of breast biopsy and definitive surgical procedure on the accuracy of SLN biopsy.

METHODS

The University of Louisville Breast Cancer Sentinel Lymph Node Study is a prospective multi-institutional study involving 229 surgeons, mostly from community general surgery practices. The study was approved by the institutional review board of each participating center. Patients were enrolled from August 1997 to October 2000. Informed consent was obtained from all patients. Patients with clinical stage T1 to T2, N0 breast cancer were eligible. Some patients who had T3 tumors on final pathology were included in this analysis.

All patients had biopsy-proven invasive breast cancer before enrollment in this study. Patients who had open surgical incisional or excisional biopsies were compared with those who underwent either fine-needle aspiration or core needle biopsy for diagnosis. SLN biopsy was performed at the same setting as the definitive procedure for the primary tumor. Definitive surgical management of the primary tumor was classified as either lumpectomy (partial mastectomy) or mastectomy.

Blue dye alone, radioactive colloid alone, or both agents in combination were used at the discretion of the operating surgeon for the localization of SLNs, in accordance with study protocol guidelines, as described previously.[4,21–24] Briefly, preoperative radioactive colloid injections were performed with .5 mCi ^{99m}Tc-labeled sulfur colloid in the peritumoral, dermal, subdermal, or peri- or subareolar locations. For peritumoral injection, the volume of radioactive colloid was 6 mL; for dermal, subdermal, or other injection techniques, the volume was .5 mL or less. Although the majority of centers used filtered (.2-μm) ^{99m}Tc-labeled sulfur colloid, unfiltered colloid was allowed. Preoperative lymphoscintigraphy (nuclear medicine scan) was optional. At the time of surgery, 5 mL of isosulfan blue was injected peritumorally in the majority of cases.

Patients with nonpalpable tumors who had a needle biopsy for diagnosis underwent needle or wire localization of their lesions before the SLN procedure. In some cases, ultrasound localization was used. We specifically recommended not injecting all of the blue dye or radioactive colloid down the localization needle, because this does not disperse the tracer agents well and may concentrate the dye or radioactive colloid deep within the breast tissue. If the patient had a prior excisional biopsy, peritumoral injection of blue dye was performed around the previous biopsy cavity but not into the cavity itself.

All patients underwent attempted SLN biopsy followed by completion level I/II axillary dissection. The removal of nonaxillary nodes, such as internal mammary nodes, was not required as part of this study. SLNs were examined in serial sections by hematoxylin and eosin (H&E) at no more than 2-mm intervals. Evaluation of the SLNs by cytokeratin immunohistochemistry (IHC) was not required as part of the standard protocol but was performed at each institution's discretion. Nonsentinel axillary nodes were subjected to routine H&E examination.

The false-negative rate was calculated as follows: number of false negatives/(number of true positives + number of false negatives).[25] Statistical comparison of the false-negative rate and SLN identification rate was performed by χ^2 analysis. Significance was determined at $P < .05$.

RESULTS

A total of 2206 patients were entered onto the study. SLN biopsy was performed with blue dye alone, radioactive colloid alone, or both agents in 239, 115, and 1852 patients, respectively. When radioactive colloid was injected, peritumoral, subdermal, dermal, and subareolar/periareolar injection methods were used in 54.6%, 15.1%, 26.0%, and 4.3% of the cases, respectively. Clinicopathologic characteristics of the patient population are listed in Table 1.

Among patients with an SLN identified, the rate of nodal metastasis was 33.9%. Overall, the SLN identification rate was 92.5% (2041 of 2206), and the overall false-negative rate was 8.0%. Forty-nine percent of patients underwent IHC evaluation of the SLN. Only 6.7% of tumor-positive SLNs were detected by IHC alone and not confirmed by H&E.

There were no statistically significant differences in SLN identification rate or false-negative rate (Table 2) between patients undergoing excisional versus needle biopsy. The SLN identification and false-negative rates

TABLE 1. *Clinicopathologic characteristics of patients undergoing sentinel lymph node biopsy*

Characteristic	Value
Age (y)	
Median	60
Range	26–96
Tumor size (%)	
T1	71.0
T2	26.7
T3	2.3
Palpable tumor (%)	53.7
Tumor location (%)	
Central	14.9
Upper outer quadrant	51.4
Upper inner quadrant	14.8
Lower outer quadrant	12.3
Lower inner quadrant	6.7
Pathology (%)	
Invasive ductal carcinoma	81.3
Invasive lobular carcinoma	10.1
Other	8.5
Axillary node metastasis (%)	33.9
SLNs removed	
n	2.32
range	1–16
Axillary LNs removed	
n	14.76
range	1–42

SLN, sentinel lymph node; LN, lymph node.

also were not statistically different between patients who had total mastectomy compared with those who had partial mastectomy (Table 3).

The SLN was identified more frequently in patients with palpable tumors compared with nonpalpable lesions (Table 4), and this difference was significant (94.1% vs. 90.7%, respectively; $P = .0024$). Patients who required needle or wire localization of a nonpalpable tumor after needle biopsy had much lower SLN identification rates than those patients with palpable tumors (Table 4). There was no statistically significant difference in false-negative rates between palpable and nonpalpable tumors.

As shown in Table 5, the identification rate is significantly improved with use of the dermal versus peritumoral injection techniques for radioactive colloid after

TABLE 2. *The effect of biopsy type on sentinel lymph node identification rate and false-negative rate*

Biopsy type	n	SLN ID rate[a], n (%)	FN[b], n	TP, n	FN rate[c], %	Mean No. of SLNs removed
Excisional	763	708 (92.8)	18	199	8.3	2.38
Needle	1443	1333 (92.4)	38	442	7.9	2.27

[a] $P = .73$, χ^2.
[b] FN rate was calculated as follows: FN/[FN + TP].
[c] $P = .87$, χ^2.
SLN, sentinel lymph node; ID, identification; FN, false negative; TP, true positive.

TABLE 3. *The effect of type of surgery on sentinel lymph node identification rate and false-negative rate*

Surgery type	n	SLN ID rate,[a] n (%)	FN, n	TP, n	FN rate,[b] %	Mean No. of SLNs removed
Mastectomy	687	643 (93.6)	18	252	6.7	2.38
Lumpectomy	1519	1398 (92.0)	38	389	8.9	2.28

SLN, sentinel lymph node; ID, identification; FN, false negative; TP, true positive.
[a] $P = .20$, [b] $P = .29$, χ^2.

either excisional or needle biopsy. After excisional biopsy, there was a trend toward an improved false-negative rate with use of dermal injection compared with peritumoral injection of radioactive colloid, but this result was not statistically significant (5.4% vs. 10.4%; $P = .28$).

When patients were analyzed by T1, T2, and T3 tumor size, more patients underwent total mastectomy as their definitive procedure as tumor size increased (26%, 42%, and 66%, respectively). There were no statistically significant differences in SLN identification rates (92.2%, 93.3%, and 98.0%, respectively) or false-negative rates (9.1%, 7.0%, and 5.1%, respectively) with increasing tumor size.

DISCUSSION

It has been suggested that SLN biopsy for breast cancer may be less accurate after excisional biopsy of the primary tumor compared with core needle biopsy.[2,6,8,17–19] Indeed, some studies have even excluded patients with previous excisional biopsy from SLN procedures.[2,6] Investigators have cited lymphatic disruption stemming from prior excisional biopsy and inflammatory

TABLE 4. *Sentinel lymph node results in patients with palpable tumors compared with nonpalpable tumors*

Variable	SLN identification rate, n (%)	SLN false-negative rate, n (%)
Nonpalpable tumor	926/1021 (90.7)	18/207 (8.7)
Palpable tumor	1115/1185 (94.1)[a]	38/490 (7.8)[b]
Excisional biopsy		
Nonpalpable tumor	315/340 (92.6)	5/68 (7.4)[c]
Palpable tumor	393/423 (92.9)	13/149 (8.7)[c]
Needle biopsy		
Nonpalpable tumor	611/681 (89.7)	13/139 (9.4)[c]
Palpable tumor	722/762 (94.8)[d]	25/341 (7.3)[c]

SLN, sentinel lymph node.
[a] Compared with nonpalpable tumors; $P = .0024$; χ^2.
[b] Compared with nonpalpable tumors; $P = .70$; χ^2.
[c] $P = .87$, χ^2.
[d] Compared with needle biopsy performed in a nonpalpable tumor; $P = .0003$; χ^2.

TABLE 5. *Effect of radioactive colloid injection type on SLN identification andfalse-negative rates*

Variable	Peritumoral radioactive colloid,*[a] n (%)	Dermal radioactive colloid,[b] n (%)	*P* value
SLN identification rate			
Needle biopsy	635/708 (89.7)	338/345 (98.0)	<.0001
Excisional biopsy	330/366 (90.2)	163/166 (98.2)	.0009
SLN false-negative rate			
Needle biopsy	18/243 (7.4)	8/112 (7.1)	.39
Excisional biopsy	10/96 (10.4)	3/56 (5.4)	.28

SLN, sentinel lymph node.
[a] A total of 92.6% had concomitant peritumoral blue dye injection.
[b] A total of 93.3% had concomitant peritumoral blue dye injection.

changes as possible causes for failure of lymphatic mapping.

A greater than 7-fold increase in failed SLN identification after excisional biopsy was described by Krag et al.[8] Borgstein et al.[17] also showed a significantly higher lymphatic mapping failure rate after excisional biopsy. Feldman et al.[18] reported that false-negative results were seen only in patients who had prior excisional biopsies. However, they also reported increased accuracy of their SLN biopsies once their protocols were altered to increase the number and volume of injections. In all three studies, only radioactive colloid was used for lymphatic mapping via peritumoral (into the breast parenchyma around the tumor or biopsy sites) injection.

The results of this study, which represent a large multi-institutional experience, do not support such concerns regarding SLN biopsy after excisional biopsy of the primary tumor. We did not find any significant differences in either the SLN identification rate or false-negative rate for patients in whom excisional biopsies were performed compared with needle biopsies.

In agreement with our data, Haigh et al.[26] recently reported that SLN biopsy was highly successful in breast cancer patients regardless of biopsy method (stereotactic core biopsy, fine-needle aspiration, or excisional biopsy), excision volume, and the interval between the biopsy and the SLN procedure. In addition, Miner et al.[27] also demonstrated successful SLN biopsy regardless of the extent of prior biopsy. Our study did not capture any values for primary tumor excision volume. It is reasonable to expect, however, that the excision volumes increased with increasing tumor size. However, our data indicate that the SLN identification rates and false-negative rates for larger tumors are comparable to, if not better than, those for larger tumors.[23] We did not capture data regarding the time interval between the primary tumor biopsy and the SLN biopsy. Other smaller studies[28–30] have also found that successful SLN biopsy is not impeded by prior excisional biopsy.

In this study, palpable tumors were significantly associated with an increased SLN identification rate compared with nonpalpable tumors, with no difference in the false-negative rates. It is interesting to note that patients with nonpalpable tumors who had needle biopsies had a significantly lower SLN identification rate compared with patients with palpable tumors who had needle biopsies. Differences in the accuracy of blue dye or radioactive colloid injection are likely explanations for these findings. The fact that such a difference exists even with an intact tumor (after needle biopsy) lends further strength to this explanation. That is, it may be more difficult to accurately inject either blue dye or radioactive colloid into the peritumoral region when the tumor is not palpable. Of course, once an excisional biopsy has been performed, the incision site and resultant biopsy cavity can help guide the location of the injection. Accordingly, a difference in identification rate is not seen when comparing palpable and nonpalpable tumors after excisional biopsy. An alternative explanation, perhaps, is that palpable tumors are associated with collateral or more abundant and reliable lymphatic drainage to the axillary nodes. This may be related to the fact that, size for size, palpable tumors may be closer to the skin and the rich dermal and subdermal lymphatic plexus. The use of the dermal injection technique for radioactive colloid obviates problems associated with peritumoral isotope injection, although we still recommend concomitant peritumoral blue dye injection.[22,24]

It has been reported previously that optimal SLN biopsy results can be seen with dual agent injection: blue dye injected peritumorally and radioactive colloid injected dermally.[4,22,24,31–34] Certainly, the careful use of multiple injection sites around (but not into) the biopsy cavity can increase the amount of tracer agent traveling to the axilla. Because of the richness of the cutaneous lymphatics from the breast to the axilla, however, dermal injection of radioactive colloid (into the skin overlying the tumor or biopsy site) results in enhanced ability to identify the SLN. In our experience with dermal injection of radioactive colloid, we found a 98% SLN identification rate, which is superior to that of peritumoral injection (90%). Dermal injection of radioactive colloid was associated with a false-negative rate of 6.5% vs. 9.5% for peritumoral injection.[22] Dermal injection allows reliable and accurate identification of SLNs, even after excisional biopsy, as demonstrated in this study. In addition, the dermal technique prevents accidental injection directly

into the previous biopsy cavity itself, where the tracer agent tends to concentrate rather than disperse into the lymphatics.

Previously reported differences in SLN biopsy success rates may have to do more with differences in injection techniques than with disruption of lymphatics or inflammatory changes. Particular care must be taken when performing peritumoral injections for nonpalpable tumors. Therefore, it is important to localize the tumor site accurately to guide the injection of blue dye and radioactive colloid. This can be accomplished by standard needle localization of the tumor to guide the injections or by ultrasound guidance.[35] These data show that after either excisional or needle biopsy, there is a statistically significant increase in the identification rate with use of dermal injection.

Some have suggested that it is easier to identify the SLN when a total mastectomy is performed because the exposure and visualization of the axilla are better. We found no significant differences in SLN identification rates or false-negative rates between patients undergoing total mastectomy compared with partial mastectomy. In our personal experience, we have found that it is helpful to perform the SLN biopsy first by opening a small part of the axillary portion of the mastectomy incision before raising the flaps. In fact, raising the entire superior flap may result in blue dye spillage into the axilla, and this can actually make it more difficult to identify the SLN.

This study encompasses a wide range of surgical practices and hospital environments and is reflective of community-based general surgery. Most surgeons in our study had little prior experience with SLN biopsy, and the results reported here reflect their relative inexperience. As surgeons gain more experience, the SLN identification rate improves and the false-negative rate decreases further; this substantiates a significant learning curve for SLN biopsy.[9,12,13,24]

In conclusion, neither biopsy type nor type of definitive surgical procedure significantly affects the accuracy of SLN biopsy for breast cancer. SLN biopsy can be performed accurately after excisional breast biopsy and is equally effective for patients undergoing partial mastectomy or total mastectomy.

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