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Defining the Optimal Surgeon Experience for Breast Cancer Sentinel Lymph Node Biopsy: A Model for Implementation of New Surgical Techniques

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Objective

To determine the optimal experience required to minimize the false-negative rate of sentinel lymph node (SLN) biopsy for breast cancer.

Summary Background Data

Before abandoning routine axillary dissection in favor of SLN biopsy for breast cancer, each surgeon and institution must document acceptable SLN identification and false-negative rates. Although some studies have examined the impact of individual surgeon experience on the SLN identification rate, minimal data exist to determine the optimal experience required to minimize the more crucial false-negative rate.

Methods

Analysis was performed of a large prospective multiinstitutional study involving 226 surgeons. SLN biopsy was performed using blue dye, radioactive colloid, or both. SLN biopsy was performed with completion axillary LN dissection in all patients. The impact of surgeon experience on the SLN identification and false-negative rates was examined. Logistic regression analysis was performed to evaluate independent factors in addition to surgeon experience associated with these outcomes.

Results

A total of 2,148 patients were enrolled in the study. Improvement in the SLN identification and false-negative rates was found after 20 cases had been performed. Multivariate analysis revealed that patient age, nonpalpable tumors, and injection of blue dye alone for SLN biopsy were independently associated with decreased SLN identification rates, whereas upper outer quadrant tumor location was the only factor associated with an increased false-negative rate.

Conclusions

Surgeons should perform at least 20 SLN cases with acceptable results before abandoning routine axillary dissection. This study provides a model for surgeon training and experience that may be applicable to the implementation of other new surgical technologies.

Sentinel lymph node (SLN) biopsy has become increasingly accepted as a minimally invasive alternative to level I/II axillary dissection for the staging of breast cancer. Because approximately 70% of patients with clinical stage T1 to 2, N0 breast cancer have pathologically negative axillary nodes, SLN biopsy has the potential to eliminate the complications of axillary dissection in most patients. Patients with axillary metastasis are then selected for completion axillary dissection.

There are two key parameters of successful SLN biopsy: the SLN identification rate and the false-negative rate. The

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SLN identification rate is defined as the proportion of patients in whom an SLN is identified and removed. The false-negative rate is defined as the proportion of patients with axillary nodal metastases who have a negative SLN biopsy. For SLN biopsy to be clinically useful, it is essential to be able to identify the SLN in most patients (>90%). More important, however, is the false-negative rate, which should be as low as possible, preferably 5% or less. A false-negative result can be detrimental to the patient because it results in understaging and could adversely affect adjuvant therapy decisions. The false-negative rate can be determined only with prospective studies in which SLN biopsy is performed and followed by planned completion axillary dissection to compare the SLN result with the remainder of the axillary nodes.

More than 5,000 patients around the world have been enrolled in clinical trials of SLN biopsy for breast cancer in which backup axillary LN dissection was performed to assess the false-negative rate. Several conclusions can be reached when all of this literature is taken into account. First, SLN biopsy can be performed accurately, with acceptable SLN identification rates and false-negative rates, and is a suitable alternative to axillary dissection in qualified hands. Second, SLN biopsy can be performed poorly, with unacceptably low SLN identification rates and high false-negative rates. Third, the success and accuracy of SLN biopsy improves with increasing surgeon experience. Finally, there is marked variability in the injection methods and other technical aspects of SLN biopsy that may affect the ability of surgeons to identify SLNs reproducibly and accurately.

Before abandoning routine axillary dissection in favor of SLN biopsy for breast cancer, each surgeon and institution must document acceptable SLN identification and false-negative rates. Although several reports have investigated the impact of surgeon experience on the SLN identification rate, few data exist to determine the optimal experience required to minimize the more crucial false-negative rate. Therefore, the purpose of this analysis is to examine, in a large prospective multiinstitutional study, the impact of surgeon experience on the accuracy of SLN biopsy.

METHODS

The University of Louisville Breast Cancer Sentinel Lymph Node Study is a prospective multiinstitutional study involving 226 surgeons across the United States. The study was approved by the institutional review boards of all participating institutions. Informed consent was obtained from all patients. Peritumoral blue dye injection as a single agent was used in 228 patients. When radioactive colloid was used, the injection was performed using the peritumoral, subdermal, or dermal technique in 1053, 290, and 494 patients, respectively. A total of 83 patients underwent either subareolar or periareolar injection of radioactive colloid. Most patients (94%) who underwent radioactive colloid injection also received peritumoral blue dye injection. All patients underwent SLN biopsy, followed by completion level 1/2 axillary dissection.

Patients with clinical stage T1 to 2, N0 biopsy-proven invasive breast cancer were eligible for enrollment. Some patients found to have T3 tumors on final pathologic examination were included in the study. No patients received neoadjuvant chemotherapy. Lymphoscintigraphy was not required as part of the procedure. A sentinel node was defined as any blue node or any node with a radioactive count greater than 10% of the ex vivo count from the hottest node removed. SLNs underwent histopathologic analysis with hematoxylin and eosin staining in serial sections at intervals no greater than 2 mm. Immunohistochemical staining of the SLN for cytokeratins was performed in approximately 50% of cases. Nonsentinel nodes were subjected to routine examination with hematoxylin and eosin.

The impact of surgeon experience on the SLN identification and false-negative rates was examined. Surgeons participating in the study provided information about their surgical practice as well as any training courses attended and past experience with SLN biopsy before the accrual of patients to this study.

Univariate analyses were performed to determine whether there was any relationship between several independent variables and the dependent variables of SLN identification rate and false-negative rate. The following variables were analyzed by logistic regression: age, tumor size, tumor palpability, tumor location, type of biopsy performed, type of surgery performed for definitive treatment of the primary tumor, histologic subtype, and injection technique. A multivariate model was then used to analyze those variables found to be significant on univariate analysis. Comparisons of SLN identification and false-negative rates based on surgeon experience were made using chi-square analysis. Analyses were performed using Stata software version 6.0 (Stata Corp., College Station, TX). Significance was determined at $P < .05$.

RESULTS

A total of 2,148 patients were enrolled in the study between August 1997 and October 2000. Clinicopathologic characteristics of the patients are shown in Table 1. Demographic and practice characteristics of the 226 surgeons are shown in Table 2. Most of the participants were general surgeons in private practice, with little or no prior experience in SLN biopsy. Most surgeons had enrolled in an SLN training course. A few surgeons had prior experience with SLN biopsy, either for melanoma or for breast cancer. As shown in Table 3, prior experience with breast SLN biopsy was the only factor found to improve the SLN identification rate; no other demographic or practice-related factors resulted in different SLN identification or false-negative rates.

The effect of surgeon experience on SLN identification and false-negative rates was examined for the group of surgeons as a whole. Results were summarized by surgeons'

Table 1. PATIENT CHARACTERISTICS

Age (mean)	60 years
Tumor stage	
T1a	7.4%
T1b	22.0%
T1c	42.4%
T2	26.1%
T3	2.1%
Tumor location	
Upper outer quadrant	51.0%
Upper inner quadrant	15.1%
Lower outer quadrant	12.6%
Lower inner quadrant	6.5%
Central	14.8%
Pathology	
Ductal	81.3%
Lobular	8.4%
Other	10.3%
Type of surgery	
Total mastectomy	30.7%
Partial mastectomy	69.3%
Type of biopsy	
Excisional	33.3%
Needle	66.7%
Axillary nodal metastases	30.6%
Mean # sentinel lymph nodes removed	2.31
Mean # axillary nodes removed	14.7

Table 2. SURGEON CHARACTERISTICS

Practice type	
Breast only	11 (4.9%)
General surgery	182 (80.5%)
Surgical oncology	27 (11.9%)
Other	6 (2.7%)
Community size (population)	
<50,000	50 (22.1%)
50,000–100,000	39 (17.3%)
100,000–500,000	85 (37.6%)
>500,000	50 (22.1%)
Not stated	2 (0.9%)
University affiliation	
None	137 (60.7%)
Adjuvant clinical faculty	69 (30.5%)
Full-time academic faculty	15 (6.6%)
Not stated	5 (2.2%)
Breast cases as % of practice	
0–10%	58 (25.7%)
11–25%	105 (46.5%)
26–50%	42 (18.6%)
>50%	17 (7.5%)
Not stated	4 (1.8%)
Prior experience with breast SLN biopsy	
None	102 (45.1%)
1–10 cases	87 (38.5%)
11–20 cases	17 (7.5%)
21–30 cases	13 (5.8%)
>30 cases	7 (3.1%)
Prior experience with melanoma SLN biopsy	
None	130 (57.5%)
1–10 cases	67 (29.6%)
11–20 cases	10 (4.4%)
21–30 cases	7 (3.1%)
> 30 cases	12 (5.3%)
Completion of SLN biopsy training course	
Yes	156 (69.0%)
No	70 (31.0%)*

SLN; sentinel lymph node.
* 18 surgeons (25.7%) who did not enroll in a training course had significant experience in SLN biopsy (either breast cancer or melanoma).

sequential experience in increments of five cases. Improvement in the SLN identification and false-negative rates was noted after 20 cases had been performed (Fig. 1). A significant difference in both SLN identification and false-negative rates could be seen when results were compared between 1 to 20 cases and greater than 20 cases performed (Table 4).

The effects of the various injection techniques on the learning curves for the SLN identification and false-negative rates are shown in Figure 2. There was a trend toward improved SLN identification and false-negative rates after the completion of fewer cases in the subdermal or dermal radioactive colloid injection groups compared with either peritumoral injection of radioactive colloid or the use of blue dye alone.

Univariate analysis revealed that age older than 50 years, nonpalpable tumors, and injection of the blue dye alone for lymphatic mapping were factors associated with decreased SLN identification rates (Table 5). Multivariate logistic regression analysis showed that these factors were independent predictors of lower SLN identification rates. After accounting for patient age and tumor palpability, the use of dermal injection was associated with a significantly better SLN identification rate than either subdermal or peritumoral injection (Table 6).

Tumors in the upper outer quadrant of the breast were associated with an increased false-negative rate (Table 7). Because only a single factor was found to predict a higher false-negative rate, multivariate analysis was not performed.

DISCUSSION

Sentinel node biopsy has been adopted at many major centers as an alternative to routine level I/II axillary dissection for patients with clinically node-negative breast cancer. As this technology has been more widely disseminated, issues regarding training and quality assurance have been raised.[1–4] Whereas most agree that it is inappropriate to offer SLN biopsy without backup axillary dissection in the absence of some training and experience, the exact level of surgeon experience required to master the technique remains controversial.

It is critical to define a successful SLN biopsy accurately. Although some studies have examined the impact of individual surgeon experience on the SLN identification rate, it is clear that SLN identification is not an appropriate endpoint: many studies have documented excellent SLN identification rates with unacceptably high false-negative rates. The more important issue is the experience required to achieve an acceptably low false-negative rate.[5]

Our results, representing 2,148 patients and 226 surgeons in a prospective, multiinstitutional study, show that SLN

Table 3. IMPACT OF SURGEON DEMOGRAPHICS ON SLN IDENTIFICATION AND FALSE-NEGATIVE RATES

Surgeon Demographic Variable	SLN ID Rate	FN Rate
Practice type*		
General surgery	90.7%	8.3%
Other	91.8%	7.6%
Community size*		
<100,000	91.6%	8.6%
>100,000	92.9%	7.8%
University affiliation*		
None	93.0%	7.6%
Adjuvant clinical or full-time academic faculty	91.8%	8.5%
Breast cases as % of practice*		
0–10%	90.7%	7.4%
>10%	92.5%	8.1%
Prior breast SLN experience**		
No	90.8%	9.2%
Yes	93.4%	7.5%
Prior melanoma SLN experience*		
No	91.8%	8.4%
Yes	93.3%	7.7%
Completion of SLN biopsy training course*		
No	92.2%	6.3%
Yes	92.5%	8.7%

SLN, sentinel lymph node; ID, identification; FN, false-negative.
* No statistically significant difference in SLN ID rate or FN rate.
** $P = .026$ (chi-square) for SLN ID rate; P = NS for SLN FN rate.

Table 4. IMPACT OF SURGEON EXPERIENCE ON SLN IDENTIFICATION AND FALSE-NEGATIVE RATES

# Cases Performed	# Patients	# Surgeons	SLN ID Rate	FN Rate
1–20	1,817	226	91.7%	9.0%
>20	331	28	96.7%*	1.9%**

SLN, sentinel lymph node; ID, identification; FN, false-negative.
* $P = .0015$; ** $P = .014$ vs. 1–20 cases, chi square.

identification and false-negative rates are significantly improved after the completion of 20 cases. This benchmark is lower than the previously advocated experience level of 30 cases with completion axillary dissection advocated by the American Society of Breast Surgeons[4] and required by the American College of Surgeons Oncology Group for participation in breast cancer SLN studies.

Other studies have examined the impact of surgeon experience and training on SLN biopsy results. A multiinstitutional experience with 48 surgeons and 435 SLN cases, reported by Tafra et al,[6] found that the SLN identification rate improved significantly after 10 cases (82.1% vs. 91.8%), whereas the false-negative rate did not improve substantially until 30 cases were performed (15.5% to 4.3%). Of note, all the participating surgeons in this study had attended an SLN course before enrolling patients. Peritumoral injection of both blue dye and radioactive colloid was used in all patients.

In a report of a multiinstitutional study by Krag et al[7] in which SLN identification was performed by peritumoral radioactive colloid injection alone, all participating surgeons performed five "training procedures" before accruing

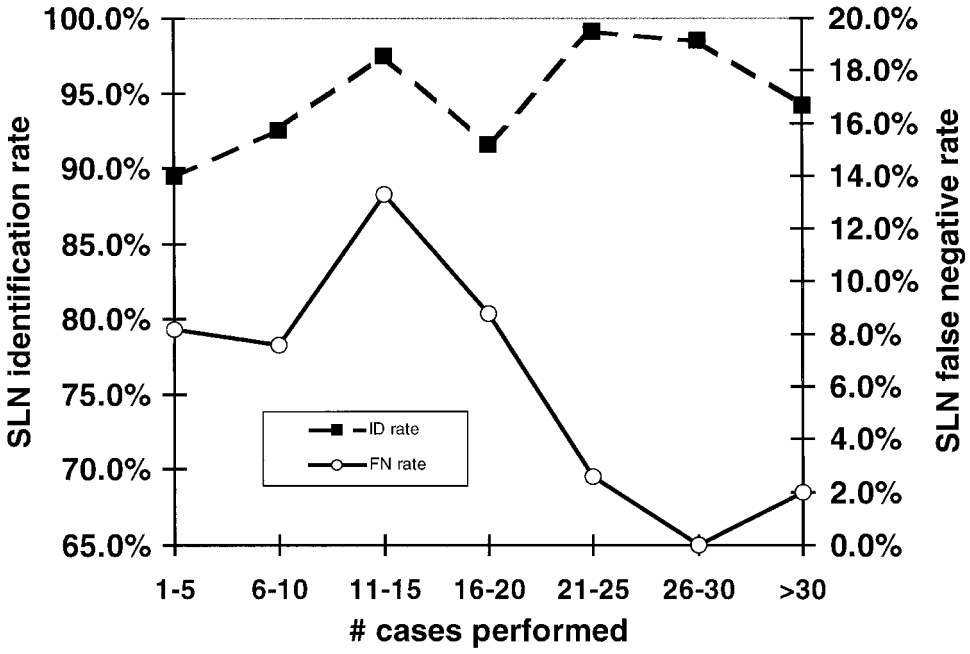

Figure 1. The learning curve: effect of increasing surgeon experience on the sentinel lymph node identification rate and false-negative rate.

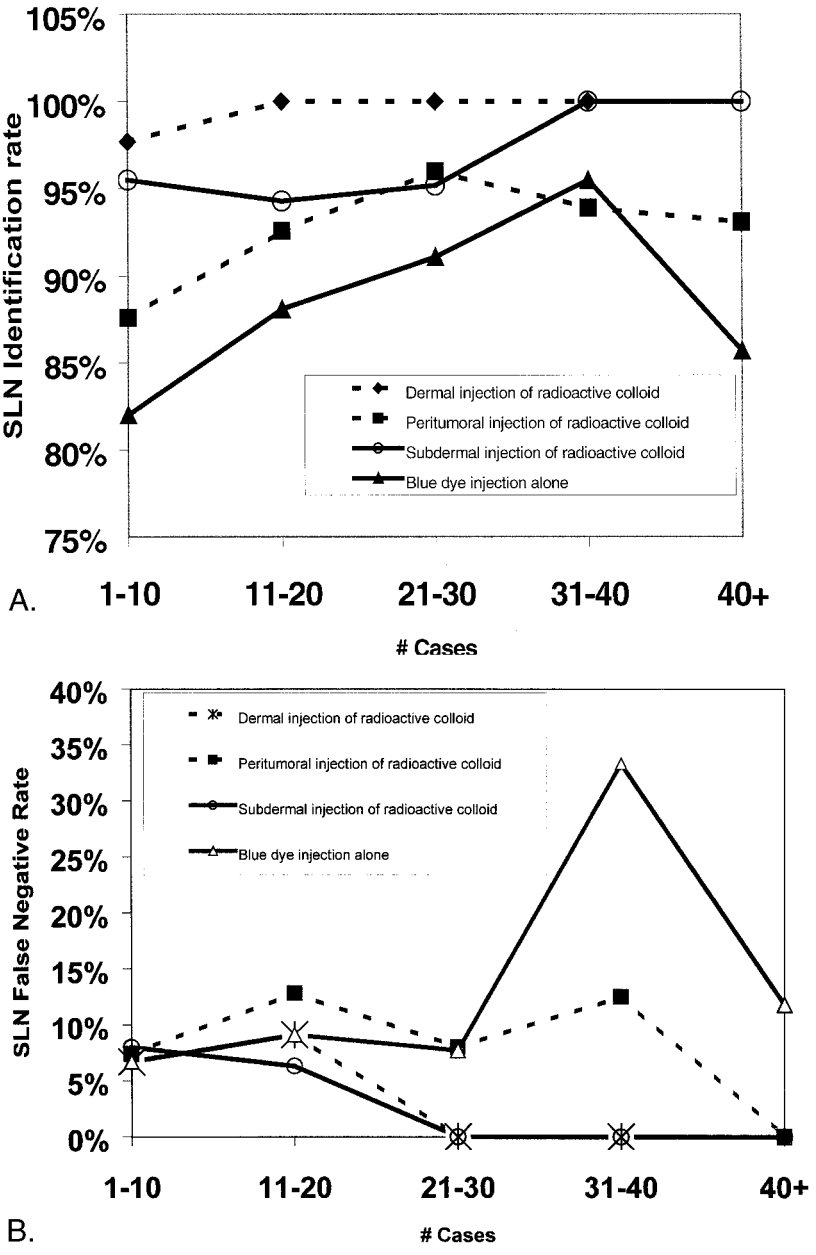

Figure 2. Learning curves associated with various injection techniques used for sentinel lymph node mapping. (A) Sentinel lymph node identification rate. (B) False-negative rate. RC, radioactive colloid.

patients to the trial. The overall SLN identification and false-negative rates, which excluded results from the five training cases, were 93.2% and 11.4%, respectively. There was substantial variability in results among surgeons.

Many single-institution studies have reported learning curves from the experiences of the surgeons at their particular institution. Bass et al[8] reported the results from five surgeons at a single institution and found varying levels of success between individuals. The mean institutional experience showed that 23 procedures were necessary to achieve a 90% identification rate and that 53 cases were needed for a 95% identification rate. The results from a study by Morrow et al[9] corroborate the finding that results vary significantly by surgeon. When all patients were considered collectively in their study, however, the SLN identification rate increased from 73% with a surgeon's first 10 cases to 91% after 30 cases. However, the learning curves for the false-negative rate were not presented in either study.

The current study represents the collective results of a large group of surgeons, most of whom are in community general surgery practices. We found no difference in SLN biopsy results between surgeons practicing in small communities versus larger communities, surgeons with university affiliation versus those without, and surgeons who perform a large volume of breast cases versus those who do not. Surgeons who had experience with breast SLN biopsy before entering patients in the study did have a higher SLN identification rate, confirming the notion that increasing experience leads to improved results. There was no statistically significant difference in either the SLN identification

Table 5. FACTORS AFFECTING SENTINEL LYMPH NODE IDENTIFICATION RATE

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Univariate Analysis			
Age			
<50 vs. ≥50 years	0.43	0.27–0.68	<.001
Injection type			
Blue dye alone vs. radioactive colloid alone	2.20	0.97–4.99	.052
Blue dye alone vs. blue dye + radioactive colloid	2.15	1.40–3.27	<.001
Tumor palpability			
Nonpalpable vs. palpable	1.57	1.14–2.17	.006
Tumor size			
T1 vs. T2	1.18	0.80–1.72	.41
T1 vs. T3	3.68	0.50–27.03	.17
Tumor location			
Upper outer quadrant vs. other	0.82	0.59–1.13	.22
Biopsy type			
Excisional vs. needle	0.90	0.64–1.26	.52
Surgery type			
Partial mastectomy vs. total mastectomy	1.29	0.89–1.85	.18
Histologic subtype			
Ductal vs. lobular	0.96	0.54–1.71	.89
Ductal vs. other	0.98	0.58–1.65	.93
Multivariate Analysis			
Age			
<50 vs. ≥50 years	0.45	0.28–0.73	.001
Injection type			
Blue dye alone vs. radioactive colloid alone vs. blue dye + radioactive colloid	1.45	1.18–1.80	.001
Tumor palpability			
Nonpalpable vs. palpable	1.42	1.02–1.98	.036

rate or the false-negative rate among surgeons who took a formal training course versus those who did not. In some instances, those who did not complete a training course had prior experience with the technique for breast cancer or melanoma; in others we suspect that they may have learned the procedure from experienced colleagues who had attended such a course. Therefore, we continue to encourage formal SLN training courses whenever possible. Importantly, however, these results suggest that general surgeons in community practice can perform SLN biopsy with results

Table 6. EFFECT OF LOCATION OF RADIOACTIVE COLLOID INJECTION ON SENTINEL LYMPH NODE IDENTIFICATION RATE

Injection Location*	Odds Ratio	95% Confidence Interval	*P* Value
Dermal injection	1.00		
Subdermal injection	0.37	0.16–0.88	.021
Peritumoral injection	0.15	0.07–0.30	<.0001

* Adjusted for patient age and tumor palpability.

Table 7. UNIVARIATE LOGISTIC REGRESSION ANALYSIS OF FACTORS AFFECTING THE FALSE-NEGATIVE RATE

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Tumor location			
Upper outer quadrant vs. other	0.34	0.18–0.64	.001
Age			
<50 vs. ≥50 years	0.85	0.46–1.56	.59
Tumor size			
T1 vs. T2	0.71	0.39–1.30	.27
T1 vs. T3	0.31	0.04–2.34	.23
Tumor palpability			
Nonpalpable vs. palpable	0.87	0.48–1.57	.64
Biopsy type			
Excisional vs. needle	0.92	0.51–1.67	.79
Surgery type			
Partial mastectomy vs. total mastectomy	0.692	0.38–1.27	.24
Histologic subtype			
Ductal vs. lobular	1.22	0.50–3.01	.66
Ductal vs. other	1.16	0.44–3.07	.76
Injection type			
Blue dye alone vs. radioactive colloid alone	0.22	0.03–1.97	.14
blue dye alone vs. blue dye + radioactive colloid	0.69	0.29–1.59	.38

equivalent to those with more specialized practices and those in academic institutions.

Although we have evaluated the impact of individual surgeon experience on the results of SLN biopsy, it must be recognized that this is a multidisciplinary procedure. As such, surgeons must ensure that colleagues in nuclear medicine, radiology, and pathology are actively involved with the successful implementation of this new technology. The learning curve of the individual surgeon, therefore, undoubtedly reflects the experience of the other disciplines as well. The implications of the SLN procedure must be effectively communicated to the radiation oncologists and medical oncologists. The coordination of effort among the various disciplines is an essential component of the learning process.

Surgery has long held the attitude: "see one, do one, teach one." However, such a philosophy no longer holds true, and nothing has made the point more clear than the advent of minimally invasive procedures. The learning curve applicable to laparoscopic cases is different for many reasons, but mainly because any failure of such a procedure usually is immediately obvious and lends itself to correction by conversion to an open procedure. Complications of such procedures often are evident early on. Unlike other procedures, SLN biopsy is essentially a diagnostic test, designed to stage the axillary nodes. Therefore, the results of this test can be verified immediately by performing backup axillary dissection. The most important complication associated with this technique, a false-negative result, may not become apparent for years but could adversely affect adjuvant therapy decisions in the short term.

The technique of SLN biopsy has evolved since its inception. Technical refinements in the procedure have made it easier for those learning SLN biopsy to master the technique. For example, Giuliano et al[10] initially reported results with SLN biopsy for breast cancer in 1994 with a 66% identification rate and a 12% false-negative rate while the technique was being developed. With increasing experience and improved technique, the same group has reported a 94% SLN identification rate and a 0% false-negative rate.[11] Admittedly, however, the use of blue dye injection alone for SLN biopsy is a difficult technique to master, and our results corroborate the belief that the learning curve for this technique is substantial.

We recently reported that in a multiinstitutional setting, the use of dermal injection of radioactive colloid in conjunction with peritumoral blue dye injection led to optimal SLN biopsy results, with an SLN identification rate of 98% and a false-negative rate of 6.5% overall.[12] Because the technique of dermal injection is simple and reliable to use, we believe that its use may obviate the shallow learning curve for SLN biopsy. The 98% overall SLN identification rate with dermal radioactive colloid injection indicates that this technical modification has virtually eliminated the learning curve for SLN identification. In the current analysis, the impact of dermal radioactive colloid injection is evident in the learning curves (see Fig. 2). We believe that this technical modification simplifies the learning process, but further study is necessary to determine whether the number of cases required to achieve low false-negative rates with this technique is truly less than 20.

Other factors besides surgeon experience and technical variations in the procedure affect the success of SLN biopsy. Multivariate analysis revealed that patient age older than 50 years, nonpalpable tumors, and use of blue dye alone were independent factors associated with decreased SLN identification rates. Further, an upper outer quadrant tumor location was associated with an increased risk of a false-negative result. These factors should be taken into account when counseling patients about SLN biopsy and when selecting patients for the procedure.

A recent report from Zervos et al[13] found that more than 60% of surgeons participating in an SLN training course initiated an SLN program at their home institution. However, 28% of new programs were implemented without institutional review board approval, and only 35% of these surgeons completed any sort of validation phase during which completion axillary dissections were performed after the SLN biopsy. Although such a report might be interpreted as an example of successful dissemination of new surgical technology, it also points out a disturbing failure by some surgeons to apply this technique thoughtfully.

We believe that the present study may serve as a model for implementation of new surgical technologies. The study was (and remains) open to all who wish to participate. It is a formal study with institutional review board approval, which provides appropriate protection of the confidentiality and rights of research subjects, as well as some degree of medicolegal protection for surgeons who enroll patients. The case report forms for entering data were made deliberately simple so that surgeons could manage the study without the need to employ a research coordinator. The endpoints chosen were the SLN identification and false-negative rates, which do not require long-term patient follow-up. The degree of surgeon participation is remarkable given the fact that the study was voluntary—no reimbursement was provided for study participation. This suggests that, overall, surgeons are reluctant to adopt new techniques without proper training and experience and are willing to participate in such studies to document and validate new procedures. Few of the participating institutions could accrue enough patients on their own to provide a meaningful analysis of factors related to the accuracy of SLN biopsy. However, the collective effort has resulted in a large database, providing a wealth of information that should help surgeons to perform this procedure in a more reproducible, accurate, and safe manner.

We believe that it is appropriate, after the appropriate learning phase, for surgeons to offer SLN biopsy to patients without planned axillary dissection. However, the surgeon and the patient must understand the implications of this procedure. The risks and benefits must be clearly understood. The plan of action in the event of failure to find an SLN (axillary dissection in most cases) should be clearly stated. False-negative results can and will occur even after appropriate surgeon training. Patients must understand the trade-off between a less invasive procedure and the small risk of a false-negative result. Surgeons are encouraged to continue to participate in national studies of SLN biopsy, particularly the American College of Surgeons Oncology Group Trials Z0010 and Z0011.

Our results indicate, in the largest analysis reported to date, that the SLN identification and false-negative rates improve significantly after 20 cases have been performed. Although we recognize that the ability of individual surgeons to master the technique may vary, the 20-case requirement seems reasonable given the existing data. This 20-case guideline should necessarily carry the provision that the SLN identification and false-negative rates are within the acceptable range during this validation phase. Whether surgeons should receive credit for cases proctored by a surgeon experienced in SLN biopsy, or those performed in a residency or fellowship training program, in which backup axillary dissection was not routinely performed is not addressed in this study. However, we believe it is reasonable to include these cases when considering the experience of any individual surgeon.

CONCLUSIONS

Surgeons should perform at least 20 SLN cases with acceptable results before abandoning routine axillary dissection. This study provides a model for surgeon training and experience that may be applicable to the implementation of other new surgical technologies.

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DISCUSSION

DR. EDWARD M. COPELAND, III (Gainesville, Florida): Dr. McMasters and colleagues are to be congratulated for studying the more important false negative rate rather than the identification rate of the sentinel nodes. The pathologically accurate sentinel node is important to appropriately stage the patient, prevent axillary recurrence, and potentially improve survival.

In this country, surgeons are adequately trained to do axillary dissections. The average number of axillary dissections done by graduating surgical residents in 1997 was 29. At the time of ten-year recertification, the average number done per year by practicing surgeons was 13. But 50% of these surgeons did only four or fewer dissections per year.

In Dr. McMasters' study, 20 dissections were required to obtain an acceptable false negative rate when the procedure was done by surgeons trained to do axillary dissections. As sentinel node biopsy gains popularity many fewer axillary dissections will be done.

Dr. McMasters, does the ability to find the pathologically accurate sentinel node correlate with the surgeon's technical ability to perform an axillary dissection and also possibly the number of dissections done per year? If so, we have a looming dilemma, since surgical residents soon will be inadequately trained to do the procedure.

Lastly, further define the false negative rate. If a positive node was found at the time of biopsy but was not hot or blue, was it recorded as a false negative?

PRESENTER DR. KELLY M. MCMASTERS (Louisville, Kentucky): Thank you, Dr. Copeland. You asked a question of whether surgeons who were more proficient at finding the sentinel lymph nodes were also those that were better at doing axillary lymph node dissections, and we really don't have data that can substantiate that. It seems that the average number of lymph nodes removed in the entire study was 15, indicating that most surgeons did a good job of removing an adequate number of lymph nodes. We assume that our study is also somewhat biased with surgeons, although in a very broadly based experience, who are more interested in breast cancer than some of their colleagues. You raise an important point about surgeon training and proficiency at axillary dissection. It certainly will be increasingly difficult to train residents to an axillary dissection properly. We must find ways to assure that our trainees learn to perform this operation adequately.

The false negative rate is defined as the proportion of patients who have positive axillary lymph nodes who are incorrectly staged as having a negative sentinel lymph node. We did not use the criteria that if the surgeon sent a lymph node that was not hot or blue but was palpable at the time of sentinel node biopsy, that that would be called a sentinel node. It had to fulfill the criteria of having blue staining, having a blue lymphatic channel entering the lymph node, or being radioactive. Those are the criteria that we used for identifying sentinel nodes.

DR. MARSHALL M. URIST (Birmingham, Alabama): Dr. McMasters and his associates have done a masterful job in introducing a method in which a practicing surgeon can monitor his or her progress with the development of a new technique. Their study generates a number of important questions.

The first is that you do not require scintigraphy in this study. Are there any circumstances in which it is important and should be included?

Second, you have evaluated two variables which are changing at the same time, that is surgeon experience and the identification technique. It appears that as experience increases, one can use any of these techniques with great accuracy. Is it true that if you keep going, you eventually get there and with more cases? You have identified 20 cases as a minimum. Yet the skill level continues to improve. Is that number 20 really a break point? Should greater than 20 be the number, therefore 30 or 40 cases?

You have identified in your manuscript that a primary tumor in the upper outer quadrant is associated with a higher failure rate to identify a positive node. Should there be a minimum number of cases in this particular sub-site if that is a particular problem area?

And lastly, as Dr. Copeland mentioned, how does the resident in training fit into this as far as the required number of cases? Does it require more than 20? Or if you learned at the hands of someone who mastered the technique, can you do it in less than 20 cases?

DR. KELLY M. MCMASTERS: Thank you, Dr. Urist. You asked specifically about lymphoscintigraphy. We performed a previous analysis in which we found that the lymphoscintigram, which is a preoperative nuclear medicine scan that tells us where the sentinel node is located, really didn't help us reduce the false negative rate or find the axillary sentinel lymph nodes more frequently.

Now, some institutions are looking also for internal mammary nodes. We have decided in our study that it is probably not worthwhile in most cases to do that and only are staging the axillary nodes — the same nodes we have always staged. So it is clear that you don't need to do lymphoscintigraphy to accurately identify nodes in the axilla because we can do that intraoperatively quite easily. But it is not wrong to do so and it may be helpful for some people to perform lymphoscintigraphy, especially early on in their experience.

You did note that with increasing surgeon experience, it seemed that surgeons do better. And it may be that they do better even after 20 or 30 or 40 cases. We believe that surgeons do get better as time goes on. Please realize that in this study we are analyzing surgeons who are just getting started in general community practice and performing sentinel node biopsies. So this is a study of how sentinel lymph node biopsy is being performed across

the United States in an average practice. That doesn't mean that, using any given technique, excellent results cannot be obtained among institutions and surgeons who have great experience with that technique.

Using blue dye alone can certainly be used with good success in the hands of people who are very experienced. But our data suggests and other data suggests that the learning curve is very shallow and prolonged. False negative results and failure to find the sentinel nodes continues even after 20-30 cases.

We also will identify factors that make it easier for surgeons to learn how to perform this procedure and we believe that the dermal radioactive colloid injection technique is optimal. With dermal injection you see very early that sentinel node identification hits the 100% mark, and also that the false negative rate drops off precipitously very early on. Thus, dermal or even subdermal injection of radioactive colloid will make it easier for surgeons to learn and shorten that learning curve.

I didn't present the data on the upper outer quadrant tumor location, as you mentioned, because of time. That is the one factor associated with increased false negative results. We do believe that with dermal injection and with adequate experience this can be overcome. As you see, the 1.9% false negative rate after 20 cases includes a lot of cases that had upper outer quadrant tumors, half of them, so we think that experience and technical considerations probably will obviate that tumor location problem.

And we do not address what to do with resident training in this paper and how to count cases that are proctored by attending surgeons in residency, although we think that those probably should count in some way towards the resident's experience when he or she gets into practice.

DR. CHARLES M. BALCH (Baltimore, Maryland): Over the past few years, there has been a worldwide validation of the staging accuracy and reproducibility of lymphatic mapping and sentinel node lymphadenectomy, first pioneered by Dr. Donald Morton, who also described the accuracy of this technique in a prospective series of melanoma patients presented at this meeting two years ago.

This technology represents a major advance in the staging of a variety of cancers, first in melanoma and now with this important study by Dr. McMasters and colleagues in breast cancer. In the next few years, this technology will also be a major focus in GI cancers.

In fact, I believe we will have to reexamine the standards of care derived from many previous cancer clinical trials involving node negative patients because we now know that many of these patients were, in fact, understaged and had stage III disease with nodal metastases and a significantly lower survival rate compared to those patients accurately staged with sentinel node staging who were truly node negative. I have two questions for Dr. McMasters.

First, do you have any evidence that there was an increased yield of finding metastatic nodes using this technique in breast cancer compared to standard processing of the pathological specimen after a complete lymph node dissection?

And second, besides the value of this procedure which reduces the need for complete lymphadenectomy for staging, is there any evidence that this technique will in fact improve survival rates in breast cancer patients?

I want to congratulate you on this important surgical trial which is part of a renewed interest in examining the role of the lymphatics in cancer metastases.

DR. KELLY M. MCMASTERS: Thank you, Dr. Balch. It is true that with sentinel lymph node biopsy we find smaller deposits of metastatic disease within the lymph node because we focus the pathologist's attention on the lymph nodes or nodes most likely to contain metastases. Whether or not that improves survival remains undetermined. There are a couple of prospective randomized trials underway that may help with that from the American College of Surgeons and the NSABP. We did not specifically address whether or not in this patient population we are finding a greater proportion of positive lymph nodes than if we had done just axillary lymph node dissection. There is the potential that, by identifying more accurately the node positive patient population, and adjusting adjuvant therapy decisions accordingly, that survival could be affected.

DR. QUAN-YANG DUH (San Francisco, California): I enjoyed your paper. Not being a breast surgeon myself, I would just comment and ask a question about the method itself. My comments will be limited to how the data is analyzed.

A learning curve implies improvement in the same person, and so the comparison should be done with the same surgeon for his or her first 20 cases and the subsequent cases. So my question is, why did you analyze your data comparing the 28 surgeons with the 226 surgeons? Have you just compared the 28 surgeons with themselves, their first 20 cases versus their subsequent 20 cases? Because I think that would be the true learning curve.

DR. KELLY M. MCMASTERS: We did do those learning curves for individual surgeons and see a similar trend, that is the false negative rates and sentinel lymph node identification rates improved after 20 cases. And that validated the 20-case rate point that we presented to you — although I did not present individual surgeon learning curves here for you.

DR. MONICA MORROW (Chicago, Illinois): Let me also congratulate you on amassing this large amount of data. I have two questions.

In addition to analyzing simply the total number of cases done, did you look at whether or not the time over which those cases were accrued made a difference? In other words, if it takes you two and a half years to get 20 cases, do you ever reach the same false negative rate as people who accrue those cases within a one-year time period?

And secondly, as I understand your database from your previous publications, this is in essence a registry. Do you have any idea how complete your capture is of the cases that the surgeons who are reporting to you are doing? Have you checked claims data or anything else to make sure that they are in fact reporting their complete experience to you?

DR. KELLY M. McMASTERS: Thank you, Dr. Morrow. That is a good point. We have not examined whether or not surgeons who accrue cases over a long period of time have a more difficult time climbing the learning curve than surgeons who accrue more rapidly.

Our study is designed as a prospective IRB approved study in which patients have to sign a consent form. And like any other prospective study, it is IRB approved. And the data must be captured on every patient who signs the consent form. Such data is subject to auditing at each institution by the IRB. So in that sense it is not really a registry because it requires the patient to sign consent and that all patients who sign that consent will have data reported.

Now, with any study there is a concern that you could have selective reporting of data. And I can't tell you for certain that that has never occurred, except to tell you that in order to explain some of the findings in our study, such as the fact that the false negative rate is higher among surgeons who use blue dye, we would have to postulate that surgeons who use blue dye are more likely to accurately report their results than surgeons who use other techniques. So we think that based upon the analysis of these data, which match very nicely other multi-institutional or single institutional studies, we are capturing all the important information.

DR. ABRAHAM SHAKED (Philadelphia, Pennsylvania): Dr. Miller, I enjoyed very much your presentation. We must recognize that the advancement in surgical techniques and understanding the processes of liver regeneration brought the field of liver transplantation to a stage where without a doubt segmental transplantation is possible. You have shown us the outstanding results where surgery, at least with the right lobe, is comparable with cadaveric transplantation.

I have two questions for you. The first is related to indication for transplantation. Now that we have an "unlimited" number of livers available for donors, does it mean that the indication for transplantation is changing? Let me give you an example.

We never did patients with large hepatocellular carcinoma. We did not do patients with large cholangiocarcinoma. Now these patients are coming to us with their own donors and telling us that they are willing to undergo these procedures even though the success rate is low. Should we accept those? Should we modify our criteria for recipient selection? Do we have to have any criteria for recipient selection at all if they bring their own donors? It is not a precious commodity anymore.

The second question is related to data that I saw in your manuscript and you did not touch it. The fact is that you have a very interesting dichotomy between the adults and the children in terms of rejection rate. In the adults, the rejection rate in the living studies was about 18% whereas in the children it was 32%. Now, 32% is more similar to cadaveric. We also noticed decreased rates of rejection in the adults with living donors. The only variable that is different between the two (both are living donations), is the fact that in the children the liver does not have to regenerate while in adult it does have to regenerate. Does regeneration decrease the rate of rejection?