PAPER

Are 3 Sentinel Nodes Sufficient?

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Hypothesis: It has recently been proposed that only 3 sentinel lymph nodes (SLNs) are required for an adequate SLN biopsy. Others have advocated removing all nodes that are blue, hot, at the end of a blue lymphatic channel, or palpably suspicious or that have radioactive counts of 10% or greater of the most radioactive SLN. Our objective was to determine the false-negative rate (FNR) associated with limiting SLN biopsy to 3 nodes.

Design: Multicenter prospective study.

Setting: Both academic and private practice.

Patients: A total of 4131 patients underwent SLN biopsy followed by completion axillary node dissection.

Main Outcome Measure: The FNR associated with 3-node SLN biopsy.

Results: Of the 4131 patients in this study, an SLN was identified in 3882 (94.0%). The median number of SLNs identified was 2; more than 3 SLNs were removed in 738 patients (17.9%). Of the patients in whom a SLN was identified, 1358 (35.0%) were node positive. The overall FNR in this study was 7.7%. In 89.7% of node-positive patients, a positive SLN was found in the first 3 SLNs removed. If SLN biopsy had been limited to the first 3 nodes, the FNR would be 10.3% ($P=.005$ compared with removing >3 SLNs). The FNR increased with the strategy of limiting SLN biopsy to fewer SLNs ($P<.001$).

Conclusion: Removing only 3 SLNs cannot be recommended, because it is associated with a substantially increased FNR.

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SENTINEL LYMPH NODE (SLN) BIOPSY is a well-accepted, minimally invasive technique that has been shown to accurately stage the axilla in patients with breast cancer. In this technique, a radioactive colloid and/or a blue dye is used to identify the first draining lymph node(s) in the axilla, which are subsequently removed. It has been recommended that all "hot" (or radioactive) nodes, all blue nodes, all nodes at the end of a blue lymphatic channel, all nodes with radioactive counts greater than 10% of the hottest node, and all palpably suspicious nodes be removed as sentinel nodes, the status of which dictates the need for further axillary dissection.[1,2]

On average, 2 to 3 SLNs are removed. However, on occasion, multiple SLNs can be identified. Although it is known that the false-negative rate (FNR) of SLN biopsy is greater in patients in whom only 1 SLN is removed,[3] controversy exists regarding how many SLNs are sufficient for accurate staging of the axilla.[4-7] Recently, it has been proposed that the SLN biopsy procedure should be terminated after 3 SLNs are identified.[8] Adoption of such a policy, it is argued, will reduce the cost of the procedure by lessening operative time and decreasing the costs of pathologic analysis.[8] If no benefit is to be gained by removing more than 3 SLNs, this policy certainly would be advantageous. The objective of this study, therefore, was to determine the FNR associated with limiting SLN biopsy to 3 SLNs. We hypothesized that removal of only 3 SLNs would be associated with a higher FNR than removal of all SLNs identified.

METHODS

The University of Louisville Breast Sentinel Lymph Node Study is a multi-institutional prospective study in which patients with clinical stage I or II breast cancer underwent SLN biopsy followed by completion axillary lymph node dissection. Three hundred thirty-six surgeons from Canada and the United States participated in this study. The study was approved by the institutional review board at each site, and the patients signed informed consent forms before their participation. The technique of SLN biopsy used was left to the discretion of each surgeon.

Table 1. Clinicopathologic Features of the Node-Positive Cohort

Feature	Patients, No. (%) (N = 1358)
Tumor size, cm*	
<2	740 (54.5)
2-5	536 (39.5)
>5	56 (4.1)
Tumor palpable	919 (67.7)
Histologic subtype	
Infiltrating ductal	1131 (83.3)
Infiltrating lobular	133 (9.8)
Other	94 (6.9)
Tumor location†	
Upper outer quadrant	707 (52.1)
Upper inner quadrant	136 (10.0)
Lower outer quadrant	172 (12.7)
Lower inner quadrant	97 (7.1)
Central	217 (16.0)

*Tumor size not specified in 26 cases (1.9%).
†Tumor location not specified in 29 cases (2.1%).

Table 2. Number of SLNs Removed

No. of SLNs Removed	Patients, No. (%) (N = 1358)
1	414 (30.5)
2	376 (27.7)
3	268 (19.7)
4	135 (9.9)
5	67 (4.9)
>5	98 (7.3)

Abbreviation: SLNs, sentinel lymph nodes.

Sentinel node biopsy was not limited to a certain number of nodes in this study. To evaluate the FNR that would be expected if the procedure was terminated after finding 3 SLNs, the order in which SLNs were identified and the pathologic findings of each SLN were recorded. The FNR was defined as the percentage of node-positive patients in whom the results of the SLN biopsy were negative. Comparisons of the FNR between limiting SLN biopsy to 3 nodes or not were performed using the Fisher exact test, and the overall influence of the number of SLNs on the FNR was evaluated using the Mann-Whitney *U* test. All statistical analyses were performed using SPSS statistical software, version 13.0 (SPSS Inc, Chicago, Ill), with significance set at $P = .05$.

RESULTS

From May 7, 1998, to August 2, 2004, 4131 patients were enrolled in this study. The median patient age was 60 years (range, 27-100 years), and the median tumor size was 1.5 cm (range, 0.1-11.0 cm). A sentinel node was identified in 3882 patients (94.0%). A median of 2 SLNs were removed (range, 1-18), with more than 3 nodes removed in 738 patients (17.9%). Of the patients in whom more than 3 SLNs were removed, the median number of SLNs removed was 5.

Of the patients in whom a SLN was identified, 1358 (35.0%) were node positive on final pathologic analysis.

Table 3. First Positive Node and Cumulative True-Positive Rate

No. of SLNs	First Positive Node Frequency, No. (%) (N=1358)	Cumulative True-Positive Rate, %
1	1011 (74.4)	74.4
2	151 (11.1)	85.5
3	56 (4.1)	89.7
4	13 (1.0)	90.6
5	8 (0.6)	91.2
6	7 (0.5)	91.7
7	2 (0.1)	91.8
8	1 (0.1)	91.9
9	2 (0.1)	92.0
≥10	2 (0.1)	92.2

Abbreviation: SLNs, sentinel lymph nodes.

Table 4. False-Negative Rate Associated With Limiting Number of SLNs Removed

No. of SLNs	False-Negative Rate, %
1	25.4
2	14.5
3	10.3
4	9.4
5	8.8
>5	7.7

Abbreviation: SLNs, sentinel lymph nodes.

These node-positive patients formed the cohort of interest for this study. The clinicopathologic features of this cohort are given in **Table 1**. The distribution of node-positive cases according to the number of SLNs removed is given in **Table 2**. A median of 13 nodes were removed after completion axillary dissection (range, 3-45), with a median of 2 positive nodes on final pathologic analysis (range, 1-28).

Overall, 105 node-positive patients had a negative SLN biopsy result, yielding a FNR of 7.7%. The frequency of having the first sign of metastasis in the n^{th} sentinel node and the cumulative true-positive rate for a given number of SLNs removed are given in **Table 3**. All of the SLN metastases were identified when 11 SLNs were removed. In this study, surgeons did not terminate the SLN biopsy procedure after any given number of SLNs were removed. However, the FNR that would have been realized if the number of SLNs removed was limited is given in **Table 4**. Overall, the FNR decreased with the increasing number of SLNs removed ($P < .001$).

In 89.7% of node-positive patients, a positive SLN biopsy result was found in the first 3 SLNs removed. If SLN biopsy had been limited to the first 3 nodes, a positive SLN biopsy result would have been missed in 140 patients, yielding a FNR of 10.3% ($P = .005$ compared with removing >3 SLNs). In these patients, more than 1 positive node was found in 49 patients (35.0%). In addition, the SLN metastasis was found using hematoxylin-eosin staining in 50 (35.7%) of these cases.

COMMENT

Sentinel node biopsy has become a cornerstone of breast cancer management and has been shown to accurately stage the axilla in patients with breast cancer. Although the median number of SLNs identified is 2, more than 3 SLNs are found in 17.9% of cases. The significance of these latter SLNs has been questioned in recent studies.[4-8]

Sabel et al[8] recently argued that SLN biopsy procedures should be terminated after finding 3 SLNs. In their study of 729 patients who underwent an SLN biopsy for breast cancer, the median number of SLNs removed was 2.5 (range, 1-9).[8] More than 3 SLNs were removed in 40.7% of patients. Of the 133 node-positive patients in their study, metastatic disease was identified within the first 3 SLNs removed.[8] Similarly, Schrenk et al[6] found in a study of 263 patients with a mean of 1.8 SLNs removed (range, 1-5) that SLN metastases were found within the first 3 SLNs removed in all of the 105 node-positive patients. In addition, Low and Littlejohn,[4] in a study of 113 patients with a mean of 1.9 SLNs removed (range, 0-6), found that all of the 33 node-positive patients were identified with the first 3 SLNs.

In our larger study of 4131 patients, we found that 10.3% of the 1358 node-positive patients would have lymph node metastases that would have been missed if the procedure was terminated at 3 SLNs vs the overall FNR of 7.7% when no limit is placed on the number of SLNs removed. Therefore, 2.6% of the SLN-positive patients had their first sign of metastasis in their fourth or higher SLN.

These data are similar to the Memorial Sloan-Kettering experience, which found in a study of 1561 patients that 2% of the 449 sentinel node–positive patients had their first sign of metastasis at their fourth or greater SLN.[5] They found that 100% of the SLN metastases could only be found when 13 SLNs were removed.[5] In addition, in a study of 720 patients, Woznick et al[7] found 3% of the 172 SLN-positive patients had their first sign of metastasis in their fourth or higher SLN. In their study, however, only 6 nodes were required to identify all of the SLN metastases.[7]

Although the 2% to 3% rate of finding SLN metastases in higher-order SLNs may seem trivial, it must be understood that this is an *incremental* rate. In other words, limiting SLN biopsy to a particular threshold would increase the intrinsic FNR of SLN biopsy by 2% to 3%. In this study, in which many surgeons had little prior experience with SLN biopsy, the FNR was 7.7%. Other studies[9-20] have found FNRs ranging from 0% to 29%, with an average of 8.4%. Given the current American Society of Clinical Oncology's recommendation that the FNR of SLN biopsy should be less than 5%,[20] it seems impractical to limit SLN biopsy to a given number of SLNs, thereby increasing the FNR. However, as previously reported, the FNR declines to below 5% with surgeon experience of greater than 20 SLN cases.[21]

The rationale for suggestions to limit the number of SLNs has been to contain costs.[8] However, because most patients will have 3 or fewer nodes identified, cost savings will be limited to few patients. Some, however, have suggested that costs can be contained by performing "focused" pathologic analyses only on the first 2 to 3 nodes and submitting the remaining SLNs for routine examination.[22,23] In a study of 662 SLN biopsy procedures, Dabbs and Johnson[22] found that in all of the patients in whom the first sign of metastasis was in the fourth or higher SLN, the micrometastasis was found by immunohistochemical analysis alone. Zervos et al,[23] in their study of 509 SLN biopsy procedures, similarly found that metastatic disease detected by histologic criteria was always found within the first 2 SLNs. Interestingly, in our study, we found that more than 35% of patients whose first sign of metastasis was found in their fourth or higher SLN had disease detected by hematoxylin-eosin staining, suggesting that in at least a third of these patients the nodal metastases have clear prognostic significance.

There may be concern that as many as 11 SLNs were removed in this study, which is nearly equivalent to the number of nodes removed at axillary dissection. However, the median number of SLNs removed was 2 in this study, and only 7.3% of patients had more than 5 SLNs removed. Clearly, removal of 11 SLNs is an outlier and an infrequent event possibly related to surgeon inexperience with the technique. Review of the data in Table 3 suggests that the incremental benefit of removing more than 5 SLNs is small.

In conclusion, most patients will have 3 or fewer SLNs identified. However, if more than 3 SLNs are identified, these SLNs should be removed because there is a significantly higher FNR associated with limiting SLN biopsy procedures to 3 SLNs. It is not clear that the cost savings associated with restricting SLN biopsy procedures to 3 SLNs is worth the incremental FNR associated with this approach.

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DISCUSSION

Baiba J. Grube, MD, New Haven, Conn: In 1991, Dr Morton's group at the John Wayne Cancer Institute presented the scientific studies that confirmed the concept of sentinel node in an animal model. The feasibility of lymphatic mapping for breast disease was then first tested by Giuliano and colleagues in 1991 at the John Wayne Cancer Institute. The proof of principle was demonstrated by complete histopathologic analysis of all axillary nodes by Giuliano and colleagues in 1997. These results have been substantiated by others and have lead to the acceptance of intraoperative lymphatic mapping as an accurate and less invasive option for staging of the axilla in women with early breast cancer.

The sentinel node hypothesis states that the sentinel node is the first draining lymph node from the primary tumor and that the sentinel node is the most likely node to harbor metastases if present. It is a functional, biological definition, not an operational, technical definition. The optimal number of nodes removed is really not the issue. The issue is the identification and removal of the true sentinel node. The presence of second-echelon nodes may occur because of injection technique, timing to dissection, location of tumor, surgeon experience, and patient characteristics. Identification of a second-echelon node may occur upon entry into the axillary space at the level of a secondary blue or hot node distal to the true sentinel node. Therefore, it is not unreasonable to discover that a more proximal node or deeper node is the true sentinel node. The criteria for removal of all blue nodes, nodes with blue lymphatic channels, and all radioactive nodes with a count of 10% of the hottest node as well as suspicious palpable nodes have resulted in axillary recurrence rates after sentinel node biopsy alone in the range of 0.4%.

Many different techniques have been described to identify a node stained with vital dye, containing radioactivity or a combination of indicators. In the cumulative data from large series, recently reported by the ASCO [American Society of Clinical Oncology] group in 2005, with defined methodology, patient characterization, and experienced breast surgeons performing lymphatic mapping, the sentinel node identification rate is 96%, the false-negative rate is 7%, and the mean number of sentinel nodes removed is 1.92. The removal of multiple nodes, up to 11, as described in this study represents the equivalent of an axillary dissection and really defeats one of the goals of sentinel lymphadenectomy (ie, less morbidity with a minimally invasive technique), but this must be contrasted against a false-negative staging that could impair the adjuvant treatment decisions for a given patient.

I am going to discuss 3 aspects of the study and ask 3 questions.

1. The American Society of Breast Surgeons has proposed guidelines for surgeons learning the technique of sentinel node biopsy. These include the performance of 20 cases with a backup axillary lymph node dissection or the performance of sentinel node biopsy in the mentored situation in 20 cases. The identification rate should be at least 85% with a false-negative rate of 5%. The 300 surgeons who participated in the Louisville Sentinel Node Registry performed 4131 sentinel node procedures with an identification rate of 94%. Most surgeons had minimal experience prior to entry into the study. In previous studies from the Louisville Sentinel Node Registry, the predominant cluster of false-negative cases occurred within the first 10 cases in a surgeon's experience. My first question is: Did the number of sentinel nodes removed change as a function of the number of sentinel node procedures performed by each surgeon who initially required more than 4 nodes removed to accurately stage the axilla?

2. The first major multi-institutional trial evaluating lymphatic mapping in breast disease presented by Krag and colleagues in 1998 demonstrated a wide variability in surgeons' abilities, even in the hands of experienced breast surgeons, to accurately identify a true sentinel node and found that some individuals may never be able to learn the technique. Can the

authors determine if the outliers in their study (ie, those who needed to remove more than 4 sentinel nodes to stage the axilla accurately) were the surgeons with lower rates of identifying any sentinel node?

3. The goal of axillary staging with either axillary dissection or lymphatic mapping is to accurately stage the axilla for local control and adjuvant systemic treatment decisions and to minimize morbidity. In this cohort of surgeons, the false-negative rate even with multiple sentinel nodes removed was 7.7%, well below that recommended by the American Society of Breast Surgeons. The recent data from the NSABP B-32 [National Surgical Adjuvant Breast and Bowel Project B-32] sentinel node trial is also a reflection of community and academic surgeons using the sentinel node technique. The false-negative rate in this trial was 9.7%, but the number of nodes removed was not reported. Cox and colleagues have demonstrated that identification is higher by surgeons who perform more than 6 sentinel lymphadenectomies per month. My third question: What is the surgical volume for breast cases for each of the surgeons who removed more than 4 nodes to finally remove the true sentinel node and was there a difference in success rates for those who performed fewer cases than those who performed more cases?

I would like to congratulate the authors on presenting the cumulative experience of a large number of surgeons representing academic practices, breast-only practices, and those with typical general surgery practices with limited volume of breast disease, using a variety of sentinel lymph node mapping techniques.

Dr Chagpar: To begin with, it is clear that the false-negative rate associated with sentinel lymph node biopsy does improve with surgical experience. We and others have previously reported that having at least 20 cases does improve the false-negative rate. However, this is independent of the number of sentinel lymph nodes removed.

Relative to the second question regarding surgeons who needed to remove more than 4 sentinel nodes having a lower rate of identifying any sentinel node, I need to be clear that this study was restricted to the patients in whom a sentinel node was identified. So those surgeons who could not identify any sentinel node clearly would not be in this cohort.

Finally, as to the question of surgical volume and its impact on sentinel lymph node biopsy false-negative rates, this has also previously been reported. We did not look at surgical volume per se in determining whether surgical volume impacted whether surgeons removed more than 4 nodes or not.

Anton J. Bilchik, MD, Santa Monica, Calif: It appears that the 18% of patients who had up to 5 sentinel lymph nodes removed had a mini-axillary lymph node dissection. Would you suggest to the surgeons here that perhaps if more than 1 to 2 sentinel nodes are found that the surgeon proceed with an axillary lymph node dissection?

Dr Chagpar: I think that we need to be clear as to whether you mean 1 to 2 sentinel lymph nodes can't be found or whether those 1 to 2 sentinel lymph nodes are negative. Clearly, if no sentinel lymph node can be identified, then standard management would indicate that you would go ahead and do an axillary dissection.

However, the question here was, if you find 1 to 2 sentinel lymph nodes and yet there is still another blue lymph node there, do you go ahead and remove it? Or do you say, "I have removed my 2 sentinel lymph nodes, I am done," as would be suggested by Dr Sabel and his colleagues who presented at the Society of Surgical Oncology?

I think that our data suggest that it behooves you to go ahead and remove all of the sentinel lymph nodes that you can identify, that is to say, any hot node, any blue node, any node at the end of a blue lymphatic channel, any node with counts greater than 10% of the hottest node, or any palpably suspicious node, as you will increase your false-negative rate by failure to remove those sentinel nodes.

Theodore X. O'Connell, MD, Los Angeles, Calif: Begging the question of surgeon experience etcetera as brought up in the first discussion, the other question is whether the true-positive rate of approximately 90% with 3 lymph nodes recovered and a 92% true-positive rate with greater then 5 recovered, a difference of only 2%, is clinically significant.

More important, what is the clinical impact of missing that 2%? I don't think this study or other studies have shown that there is a significant impact on survival, on local recurrence, or on the use of adjuvant therapy, especially now when the vast majority of patients get adjuvant therapy even with negative nodes. So what is the benefit to the patient of taking out more nodes vis-à-vis the negative impact as far as operating time and morbidity is concerned?

Dr Chagpar: An excellent question. I think that to begin with we have to realize that this study did not address survival or local recurrence. However, I think that what our study did do is it demonstrated that in those patients in whom the fourth sentinel lymph node would be positive or the fifth sentinel lymph node would be positive when the first 3 were negative, remember that there was at least 1 positive node and more than 1 positive node in 35% of those cases.

So one has to ask the question that if there is going to be more than 1 positive node left in the axilla, it then behooves us to remove that. It may in fact impact adjutant therapy, although I agree with you that we tend to give chemotherapy to nearly everyone these days. But remember that postmastectomy radiation, for example, is dictated by the number of positive nodes, so patients who have 4 or more positive nodes will have postmastectomy radiation therapy, and the absolute number of nodes that are positive now affects staging per the new AJCC [American Joint Committee on Cancer] staging system.

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