Predicting the Status of the Nonsentinel Axillary Nodes

A Multicenter Study

Sandra L. Wong, MD; Michael J. Edwards, MD; Celia Chao, MD; Todd M. Tuttle, MD; R. Dirk Noyes, MD; Claudine Woo, MPH; Patricia B. Cerrito, PhD; Kelly M. McMasters, MD, PhD; for the University of Louisville Breast Cancer Sentinel Lymph Node Study Group

Background: Sentinel lymph node (SLN) biopsy is a minimally invasive procedure that provides accurate nodal staging information. The need for completion axillary dissection after finding a positive SLN for breast cancer has been questioned.

Hypothesis: The presence of nonsentinel node (NSN) metastases in the axillary dissection specimen correlates with tumor size, the number of SLNs removed, and the number of positive SLNs.

Design: Prospective, multi-institutional study.

Participants and Methods: The University of Louisville Breast Cancer Sentinel Lymph Node Study is a nationwide study involving 148 surgeons. All patients underwent SLN biopsy, followed by level I/II axillary dissection. All SLNs were evaluated histologically at a minimum of 2-mm intervals. Immunohistochemical analysis using antibodies for cytokeratin was performed at the discretion of each participating institution. All NSNs were evaluated by routine histologic examination.

Results: An SLN was identified in 1268 (90%) of 1415 patients. Increasing tumor size was significantly correlated with increasing likelihood of positive NSNs: T1a, 14%; T1b, 22%; T1c, 30%; T2, 45%; and T3, 57% (P=.002, \( \chi^2 \) test). The presence of positive NSNs was not significantly associated with the number of SLNs removed. Patients with more than 1 positive SLN were more likely to have positive NSNs than those with only 1 positive SLN (50% vs 32%; \( P<.001, \chi^2 \) test). Increasing tumor size and the presence of multiple positive SLNs were also associated with the presence 4 or more positive axillary nodes. Multivariate analysis confirmed that tumor size and the number of positive SLNs were independent factors predicting the presence of positive NSNs.

Conclusions: The likelihood of positive NSNs correlates with increasing tumor size and the presence of multiple positive SLNs. However, even patients with small primary tumors have a substantial risk of residual axillary nodal disease after SLN biopsy. These data will be helpful in counseling patients regarding the need for completion axillary dissection after a positive SLN is identified.
PARTICIPANTS AND METHODS

The University of Louisville Breast Cancer Sentinel Lymph Node Study is a prospective multi-institutional study involving 148 surgeons. Investigators represent a variety of practice environments from across the United States, most from private general surgery practices. The study was approved by the institutional review board of each participating institution, and informed consent was obtained from all patients after discussion of risks and benefits with the surgeon. Patients with biopsy-proven clinical stage T1-2 N0 breast cancer were eligible for participation. Some patients with T2 tumors clinically were found to have T3 tumors pathologically after resection of the primary tumor; these patients were included in this study.

All patients underwent SLN biopsy using blue dye alone, radioactive colloid alone, or both at the discretion of the surgeon. All patients had a completion level I/II axillary dissection after the SLN procedure. An SLN was defined as any blue-stained node or any node with radioactive counts 10% or more of the ex vivo count of the most radioactive SLN. Sentinel nodes were evaluated histologically with hematoxylin-eosin (HE) staining at a minimum of 2-mm intervals. Immunohistochemical (IHC) staining for cytokeratins was performed at the discretion of the participating institution; 49% of patients in this study had IHC staining of the SLNs. Nonsentinel nodes were evaluated by routine histologic examination.

Multivariate analysis was performed to determine any possible effects of the following variables on the finding of NSNs: tumor size, number of positive SLNs, and histologic subtype, patient age, type of surgery performed, and tumor location. Statistical analysis was performed using \( \chi^2 \) analysis and analysis of variance, where appropriate. Logistic regression analysis was performed using Stata (Version 6.0, Stata Corp, College Station, Tex). Significance was determined at \( P < .05 \).

poses and that there is no survival benefit associated with axillary lymph node dissection.19 There is substantial evidence10-23 however, that axillary dissection provides excellent locoregional control and, therefore, potential for improved overall survival. Furthermore, a recent meta-analysis24 of randomized trials involving axillary lymph node dissection concluded that there is a 5.4% survival benefit associated with prophylactic axillary dissection for clinically node-negative patients. Despite years of controversy, the therapeutic value of axillary dissection is still unresolved.

This analysis was performed to assess factors predictive of positive NSNs in the axilla in a large multi-institutional study.

RESULTS

A total of 1415 patients were enrolled in the study between August 1, 1997, and January 1, 2000. The clinicopathologic characteristics of the patients enrolled in the study are shown in Table 1. An SLN was identified in 1268 patients (90%), with an overall false-negative rate of 7.6%. The mean number of SLNs removed per patient was 2.18.

Overall, 389 (31%) of 1268 patients had at least 1 positive SLN. Axillary nodal metastases were confined to the SLNs in 245 (63%) of these 389 patients. Of patients with SLN metastases, the mean number of positive SLNs was 1.43 per patient (range, 1-3). The mean number of NSNs removed per patient was 13.0.

The frequency of positive SLNs and NSNs according to tumor size is shown in Table 2. Overall, 37% of patients with positive SLNs had residual disease in the...
The status of the axillary lymph nodes in patients with breast cancer is a powerful predictor of recurrence and survival. Furthermore, the number of lymph nodes with metastases also has prognostic importance. Although axillary nodal status is frequently considered in making adjuvant therapy decisions, the role of axillary lymph node dissection as a therapeutic procedure remains controversial.

In the present study, 37% of patients had NSN metastases when the SLN was positive for tumor. Even patients with T1 tumors had a 28% risk of residual axillary metastases if the SLN was positive. These results are consistent with those of previous studies, which demonstrated that the incidence of NSN metastases rises with increasing tumor size. In addition, we found a higher incidence of patients with 4 or more total positive axillary nodes as tumor size increased.

Chu et al reported that the number of SLNs with metastases was a significant predictor of residual axillary involvement on univariate analysis, but it was not a significant independent factor on multivariate analysis because of the confounding covariate of primary tumor size. However, in another analysis by the same investigators, the number of positive SLNs was an independent predictor of IHC-detected NSN metastases. Our study also found a statistically significant difference in NSN metastases between patients who had a single positive SLN and those who had multiple positive SLNs. In addition, we showed on multivariate analysis that increasing tumor size and multiple positive SLNs were independent predictors of positive NSNs. We also found that the presence of multiple positive SLNs was associated with an increased risk of finding 4 or more total positive axillary lymph nodes. Taken together, these results suggest that metastases in patients with 4 or more positive axillary nodes (SLN + NSN) as tumor size increased (Table 2). The presence of positive NSNs was not significantly associated with the number of SLNs removed (Table 3). Patients with more than 1 positive SLN were more likely to have positive NSNs than were those with only 1 positive SLN (Table 4). Patients with multiple positive SLNs also were more likely to have 4 or more total positive axillary nodes compared with patients with a single positive SLN.

Logistic regression models were used to assess the association between the finding of positive NSNs and tumor stage, multiple SLNs removed, multiple positive SLNs, age, tumor location, histologic subtype, and type of surgery. Only tumor stage and number of positive SLNs were significant on univariate analysis. Both factors remained significant independent predictors of positive NSNs on logistic regression analysis (Table 5). The likelihood (odds ratio) of finding residual disease in the axilla was nearly 2 times greater for patients with multiple positive SLNs ($P < .001$; 95% confidence interval, $1.20$-$3.10$) and 2.5 times more likely with T2 or T3 tumors compared with T1 tumors ($P < .001$; 95% confidence interval, $1.60$-$3.94$).

Twenty-eight (7%) of 389 patients had metastases within the SLN on IHC examination that were not otherwise found on serial sections with H&E stains. The detection of IHC-only micrometastases resulted in the “upstaging” of these patients. In 3 (11%) of these 28 patients there were metastases in the NSNs found by routine HE examination.

**Comment**

The status of the axillary lymph nodes in patients with breast cancer is a powerful predictor of recurrence and survival. Furthermore, the number of lymph nodes with metastases also has prognostic importance. Although axillary nodal status is frequently considered in making adjuvant therapy decisions, the role of axillary lymph node dissection as a therapeutic procedure remains controversial.

In the present study, 37% of patients had NSN metastases when the SLN was positive for tumor. Even patients with T1 tumors had a 28% risk of residual axillary metastases if the SLN was positive. These results are consistent with those of previous studies, which demonstrated that the incidence of NSN metastases rises with increasing tumor size. In addition, we found a higher incidence of patients with 4 or more total positive axillary nodes as tumor size increased.

Chu et al reported that the number of SLNs with metastases was a significant predictor of residual axillary involvement on univariate analysis, but it was not a significant independent factor on multivariate analysis because of the confounding covariate of primary tumor size. However, in another analysis by the same investigators, the number of positive SLNs was an independent predictor of IHC-detected NSN metastases. Our study also found a statistically significant difference in NSN metastases between patients who had a single positive SLN and those who had multiple positive SLNs. In addition, we showed on multivariate analysis that increasing tumor size and multiple positive SLNs were independent predictors of positive NSNs. We also found that the presence of multiple positive SLNs was associated with an increased risk of finding 4 or more total positive axillary lymph nodes. Taken together, these results suggest that...
the number of positive SLNs affects the presence and frequency of NSN metastases.

Other factors that have been found to be associated with NSN metastases include the presence of peritumoral lymphatic vascular invasion and extranodal hilar tissue invasion. Because of the multi-institutional nature of the present study, analysis of such detailed histopathologic factors on the presence of NSNs was not possible.

Other studies have sought to further define a patient population with positive SLNs for which axillary lymph node dissection might be unnecessary. In a study of 60 patients with positive SLNs, Reynolds et al found that those with T1 tumors and SLN micrometastases (≤2-mm foci of tumor) never had evidence of NSN metastases, even when the NSNs were evaluated with serial sections and IHC staining for cytokeratins. Similarly, in a larger study, Chu et al found that the rate of NSN metastases was less than 5% for the same patient population. Our study did not specifically address the size of the metastatic foci in the SLN because these data were not routinely reported and were not included in our database. By using tumor size in conjunction with the size of micrometastases in the SLN, it may be possible to better define subgroups of patients with minimal risk of NSN metastases.

The NSN metastases found in the present study represent metastatic foci that were obvious on routine HE staining through the center of the lymph node, representing 37% of patients. Chu et al found that IHC evaluation of the NSN resulted in detection of occult metastases in 14.7% of patients who had negative NSNs by routine HE staining, which increased the overall rate of positive NSNs to 44.6%. Therefore, routine HE staining of NSNs might underestimate the risk of axillary nodal recurrence (or persistent disease) if completion axillary dissection is not performed. With modern adjuvant therapy, the exact risk is difficult to estimate.

Routine use of IHC examination to detect micro-metastatic disease remains controversial. Approximately half of our patients had IHC examination of their SLNs, and 7.2% were upstaged as a result. Furthermore, 11% of these patients with SLN micrometastases had NSNs that harbored disease seen on routine HE staining. These results are consistent with those of previous studies. Although the prognostic significance of IHC-only positive lymph nodes is not clear, IHC examination identifies a small population of patients who have obvious NSN metastases on routine histologic examination that would have been missed if IHC examination had not been performed on the SLNs.

In conclusion, the likelihood of positive NSNs correlates with increasing tumor size and the presence of multiple positive SLNs. Even patients with small tumors, however, have a substantial risk of residual axillary nodal disease after positive SLN biopsy. There is also a greater likelihood of axillary metastases involving 4 or more lymph nodes as tumor size increases and if more than 1 positive SLN is found. Clearly, lymph node metastasis is an important predictor of recurrence and mortality for patients with breast cancer. Completion axillary lymph node dissection in patients with SLN metastases for improving regional disease control and overall survival remains controversial. This important question is presently being addressed in the ongoing American College of Surgeons Oncology Group Z11 trial. Outside of a clinical trial, however, the potential benefit of removing residual nodal metastases must be considered, and completion axillary dissection is recommended for patients with positive SLNs.

This study was supported by the Center for Advanced Surgical Technologies of Norton Hospital and the Links for Life Foundation, Louisville, Ky.

Presented at the 108th Scientific Session of the Western Surgical Association, Dana Point, Calif, November 14, 2000.

The following were major contributors to the University of Louisville Breast Cancer Sentinel Lymph Node Study: David J. Carlson, MD (St Mary’s Medical Center and Deaconess Hospital, Evansville, Ind); C. Matthew Brown, MD (Norton Hospital); Rebecca L. Glaser, MD (Kettering Memorial Hospital, Kettering, Ohio); Peter S. Turk, MD (Presbyterian Hospital, Charlotte, NC); Alison L. Laidley, MD (Medical City Dallas, Dallas, Tex); Armando Sardi, MD (St Agnes Healthcare, Baltimore Md); and Diana Simpson, RN (Center for Advanced Surgical Technologies of Norton Hospital).

We thank Sherri Matthews for expert assistance with manuscript preparation and data management and the members of the University of Louisville Breast Cancer Sentinel Lymph Node Study Group, most of whom are not listed among the authors.

Corresponding author and reprints: Kelly M. McMasters, MD, PhD, J. Graham Brown Cancer Center, University of Louisville, 529 S Jackson St, Louisville, KY 40202 (e-mail: kelly.mcmasters@nortonhealthcare.org).

REFERENCES

DISCUSSION

Armando E. Giuliano, MD, Santa Monica, Calif: The increased use of adjuvant systemic therapy, the increased use of radiation therapy, and the increased acceptance of sentinel node dissection have greatly challenged the rationale for routine axillary lymph node dissection in breast cancer. Axillary management of the clinically node-negative patient could justifiably include routine level I and II axillary dissection, no surgery, only sentinel node dissection for sentinel node–negative patients, and even only sentinel node dissection for sentinel node–positive patients. Dr McMasters and his colleagues attempt to identify nonsentinel node–positive patients who may be those who might possibly benefit from completion axillary lymph node dissection after sentinel node metastases have been identified. Remember, about two thirds of patients have no disease in lymph nodes other than the sentinel node, and, therefore, these two thirds of patients with breast cancer are unlikely to benefit from further surgery. The removal of normal lymph nodes is unlikely to be of value.

In this work, the authors have achieved several extremely important accomplishments. Most importantly they have shown that sentinel lymph node biopsy can be performed by surgeons in community hospitals with no or limited prior experience. Their false-negative rate of 7.6% is only slightly higher than that reported by single institutions. I think we should expect such results when a new procedure becomes widely performed. I am pleased that the false-negative rate was not higher, and I appreciate their work in promoting this operation.

Permit me to ask Dr McMasters to comment on what is an acceptable false-negative rate, and how difficult is it for the practicing surgeon to achieve? The authors state that routine immunohistochemical staining to detect cytokeratins was used in nearly half of their cases. Yet, in only 3 of the cases with only positive immunohistochemistry were nonsentinel nodes found to have metastases. Is the routine use of such stains justifiable? Is completion reoperative axillary lymph node dissection for these patients justifiable? Was IHC done on nonsentinel nodes? Do you think this would increase the detection of nonsentinel node metastases?

In the presentation and in the abstract the authors relate the likelihood of nonsentinel node metastases to the number of positive sentinel nodes. Isn’t it more important to look at the number of nonsentinel nodes positive in relation to the total number of patients undergoing operation? I point out that among patients with T1a tumors, 7% had positive sentinel nodes but only 1 of 89 patients had a positive nonsentinel node. Is reoperation necessary in these patients? What about those patients with T1b tumors where only 9 of 268 patients had positive nonsentinel nodes? Where should surgeons draw the line, ie, when should we do as a reoperation a procedure whose value itself as a primary operation is questionable?

In our group we have wrestled with these questions and have no answers. However, we are not likely to reoperate on sentinel node–positive patients with small tumors or those with IHC-only detectable metastases. Has your own data affected your own practice?

Finally, you advocate completion of an axillary lymph node dissection for patients with sentinel node metastases. The most important question I have for you is, does that mean you advocate not completing an axillary node dissection in general practice for patients whose sentinel node is tumor free? These are difficult issues.

J. Craig Collins, MD, Los Angeles, Calif: I hesitate to use the term "fuzzy math," but you reported a false-negative rate of 7.6% and yet the denominator for the positive nonsentinel node–positive patients only 1 of 89 patients had a positive nonsentinel node. Is completion reoperative axillary lymph node dissection for these patients justifiable? Was IHC done on nonsentinel nodes? Do you think this would increase the detection of nonsentinel node metastases?

Gerard V. Aranha, MD, Maywood, Ill: I would like to ask if your patients had both methods of sentinel lymph node de-
recognition, radiolabeled colloid and blue dye, especially those who had both the sentinel node and nonsentinel positive nodes?

Dr Mcmasters: An acceptable false-negative rate for this procedure has been defined at about 5%, and we certainly accept a false-negative rate with routine axillary dissection by not taking out level III lymph nodes that is about 2% to 3%. How difficult is this for surgeons to achieve? I think that certainly surgeon experience is important in reducing the false-negative rate, and it is incumbent upon each surgeon and institution to make sure they are doing this well. We hope to be presenting data later this year that will shed some light on how many cases surgeons should perform prior to abandoning axillary dissection in order to achieve an acceptably low false-negative rate.

The use of immunohistochemistry: Should we use it routinely? I was swayed by Dr Giuliano’s eloquent argument at the American College of Surgeons this year and the consensus panel statement regarding the use of immunohistochemical stains. This has really become a hotbed of controversy and has become more controversial rather than less controversial as time has gone on; David Page, a prominent breast pathologist, is now saying that he believes that we see breast cells and breast cancer cells translocated to normal lymph nodes as a result of breast biopsy that are not really metastases.

Perhaps the most compelling piece of evidence against immunohistochemistry is the 8% to 12% rate of positive sentinel nodes when immunohistochemical staining is used for routine, “garden-variety” ductal carcinoma in situ, a disease that is 98% curable by mastectomy or partial mastectomy. Certainly, we run the risk with routine use of immunohistochemical stains of finding isolated cells in sentinel nodes that may not have clinical significance, and we might be overtreating a number of patients with DCIS (ductal carcinoma in situ) by axillary dissection and in some cases chemotherapy. Therefore, I think it is time to back off of the position for routine use of the immunohistochemical stains. However, we and others have found that if you use immunohistochemistry, about 10% or 11% of the time you find a nonsentinel lymph node that is positive for tumor on just routine H&E staining—an obvious false-negative rate. But the second conclusion that I come to is that sentinel node biopsy absolutely can replace axillary dissection as the means by which we stage the axilla. It can be done accurately. But the second conclusion that I come to is that sentinel node biopsy can be performed badly, with unacceptably high false-negative rates. It is important for each surgeon and institution to prove to themselves and to their patients that they are doing this well, with a low false-negative rate, before routinely abandoning axillary dissection.

Dr Collins commented on some fuzzy math. The same fuzziness precluded me from completely understanding his question, which had to do with the definition of a false-negative rate as we have defined. The false-negative rate is the proportion of patients who have positive axillary lymph nodes who are found to have a negative sentinel lymph node and therefore are incorrectly staged. In other words, the sentinel node was negative, yet another lymph node in the axillary dissection specimen was positive. The frequency of nonsentinel node metastases was calculated using the patients who had true-positive sentinel nodes, since these are the patients for whom the decision must be made to perform completion axillary dissection. That’s how we have consistently calculated the false-negative rate throughout our studies and most of the other literature.

Most patients in this study (79%) had concomitant blue dye and radioactive colloid injection. There were about 5% who had radioactive colloid alone and about 16% who had blue dye alone in this study.