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THE SENTINEL NODE IN BREAST CANCER

A Multicenter Validation Study

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ABSTRACT

Background Pilot studies indicate that probe-guided resection of radioactive sentinel nodes (the first nodes that receive drainage from tumors) can identify regional metastases in patients with breast cancer. To confirm this finding, we conducted a multicenter study of the method as used by 11 surgeons in a variety of practice settings.

Methods We enrolled 443 patients with breast cancer. The technique involved the injection of 4 ml of technetium-99m sulfur colloid (1 mCi [37 MBq]) into the breast around the tumor or biopsy cavity. "Hot spots" representing underlying sentinel nodes were identified with a gamma probe. Sentinel nodes subjacent to hot spots were removed. All patients underwent a complete axillary lymphadenectomy.

Results The overall rate of identification of hot spots was 93 percent (in 413 of 443 patients). The pathological status of the sentinel nodes was compared with that of the remaining axillary nodes. The accuracy of the sentinel nodes with respect to the positive or negative status of the axillary nodes was 97 percent (392 of 405); the specificity of the method was 100 percent, the positive predictive value was 100 percent, the negative predictive value was 96 percent (291 of 304), and the sensitivity was 89 percent (101 of 114). The sentinel nodes were outside the axilla in 8 percent of cases and outside of level 1 nodes in 11 percent of cases. Three percent of positive sentinel nodes were in nonaxillary locations.

Conclusions Biopsy of sentinel nodes can predict the presence or absence of axillary-node metastases in patients with breast cancer. However, the procedure can be technically challenging, and the success rate varies according to the surgeon and the characteristics of the patient. (N Engl J Med 1998; 339:941-6.)

THE histologic status of axillary lymph nodes, one of the most important prognostic indicators in patients with breast cancer, directly affects clinical management.[1] However, over 80 percent of women who undergo axillary dissection have at least one postoperative complication in the arm, and psychological distress is common.[2-5] A potential alternative to axillary lymphadenectomy is sentinel-node resection.

The first stop along the route of lymphatic drainage from a primary tumor is a limited set of regional lymph nodes.[6] Dyes, radiographic contrast agents, and radioactive tracers have been used to identify such lymph nodes.[7-13] More than 20 years ago, Cabanas proposed that the lymph nodes that first receive drainage from a tumor, termed sentinel nodes, could be removed by limited surgery and examined to determine whether more extensive lymphadenectomy should be performed.[14] In 1992 Morton et al. used a blue dye to identify the lymphatic duct that drained into the sentinel nodes in patients with melanoma.[15] Alex and Krag described direct localization of sentinel nodes with radioactive tracers and a handheld gamma probe, demonstrating in an animal model that the radioactive-tracer and blue-dye methods were equally effective in locating lymph nodes.[16] Be-

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cause the preliminary results with radioactive tracers were encouraging in patients with melanoma[17,18] and patients with breast cancer,[19,20] we conducted a study in 11 centers to evaluate this method of identifying sentinel nodes in patients with breast cancer.

METHODS

Patients

Patients were enrolled between May 1995 and September 1997 and gave informed consent. The protocol was approved by an institutional review committee at the University of Vermont and at each participating institution. Participating surgeons were trained in the procedure in their own institutions by one of us. Each surgeon performed five training procedures, the results of which are not part of the analysis. The target for each surgeon was 50 cases.

The inclusion criteria were the presence of invasive breast cancer, clinically negative results from examination of the ipsilateral axilla, and a treatment plan that included axillary lymphadenectomy. The exclusion criteria were the presence of clinically suspicious or overtly abnormal axillary nodes, pregnancy, previous axillary lymphadenectomy, or multiple primary breast tumors.

Radioactive Tracer

Thirty minutes to eight hours before surgery, 1 mCi (37 MBq) of technetium-99m sulfur colloid (CIS-US, Bedford, Mass.) in a volume of 4 ml was injected in divided aliquots at the 3-, 6-, 9-, and 12-o'clock positions into the breast tissue surrounding the primary tumor or biopsy cavity. Technetium-99m sulfur colloid was prepared according to instructions on the package insert. A hand-held gamma counter (C-Trak, Care Wise Medical Products, Morgan Hill, Calif.) was then used to locate radioactive sentinel nodes. The surgeon first defined the perimeter of the radioactive-tracer diffusion zone around the injection site, then examined the breast and surrounding tissue for discrete regions of radioactivity. A "hot spot" was defined as an area of localized radioactivity separate from the injection site with counts of at least 25 per 10 seconds; the measurement was performed before the incision was made. Inability to identify a hot spot was considered a technical failure, even if underlying radioactive sentinel nodes were subsequently identified.

After all hot spots had been found, an appropriate incision was made for an axillary lymphadenectomy. Separate incisions were made for sentinel nodes outside the axilla. Sentinel nodes were identified by placing the gamma probe in the wound directly under the previously identified hot spot. The surgeon followed the "line of sight" established by aiming the gamma probe toward the site of maximal radioactivity emitted from the sentinel nodes and dissecting directly toward the sentinel nodes. The radioactivity of each excised node was measured with a gamma counter. The radioactive nodes were removed until the background radiation in the bed of the sentinel-node resection site was less than 10 percent of that of the most radioactive resected sentinel node.

A conventional lymphadenectomy including level I and II nodes was then performed: level III nodes were removed if the surgeon considered them suspicious. Once removed, the lymphadenectomy specimen was examined for radioactive nodes. Such nodes were not considered sentinel nodes. For pathological examination, each sentinel node was processed separately, and the slides were stained with hematoxylin and eosin. Deep sections and immunohistochemical stains were not routinely employed.

Statistical Analysis

The rates of technical success for each surgeon and for all patients are reported with exact 95 percent binomial confidence intervals. Fisher's exact test for nominal variables and the Wilcoxon rank-sum test for ordinal variables were used to compare the rates of success according to the surgeon, the patient's age and race, tumor size, location of the primary tumor, type of tumor, method used to guide the injection, time from injection to surgery, and type of previous biopsy. A forward variable-selection method was used to examine these same variables in combination with 10 indicator variables representing the 11 surgeons to develop multivariate logistic-regression models to predict technical failure. Potential predictors of technical failure were added to the model if the likelihood-ratio chi-square statistic indicated a significant improvement ($P<0.10$) in predicting the observed data. The Hosmer–Lemeshow goodness-of-fit criterion was used to determine the adequacy of the final model.

For the comparison of the rates of false negative sentinel nodes and true positive sentinel nodes, we used Fisher's exact test and the Wilcoxon rank-sum test, as well as two-sample t-tests for tumor size and total number of involved nodes. A Spearman rank-correlation coefficient was used to examine the relation between the numbers of pathologically positive sentinel and nonsentinel nodes. Fisher's exact test was used to assess the distribution of hot-spot locations, given the total number of hot spots observed for each patient. We used SAS statistical software[21] for data management and statistical analysis, StatXact 3[22] to obtain 95 percent confidence intervals for technical success rates, and BMDP software[23] to develop multivariate logistic-regression models. All reported P values are two-tailed.

RESULTS

Between May 1995 and September 1997, we enrolled 443 women in the study. The mean (±SD) age of these patients was 56±12 years, and 78 percent of them were white. The mean tumor size was 1.9±1.3 cm. The tumors were classified in terms of subtype as ductal (83.7 percent), lobular (8.6 percent), mixed (2.3 percent), or other (5.4 percent). The surgery performed was mastectomy (in 31.4 percent of the women) or partial mastectomy (in 68.6 percent).

The mean interval between the injection of the radioactive tracer and surgery was 2.9±1.9 hours. On average, 18.9±6.9 lymph nodes were removed from each patient, and the mean number of sentinel nodes was 2.6±2.2. The overall rate of identification of hot spots was 93.2 percent, but this value varied significantly according to the surgeon ($P=0.001$) (Table 1). There was no significant univariate relation between the successful identification of a hot spot and the patient's age or race; the size, location, or histologic type of the tumor; the method of injecting the tracer; the interval between injection and surgery; or whether the patient had had a prior biopsy.

On the basis of statistical modeling, which reflected a good fit to the data (Hosmer–Lemeshow chi-square=7.5, 8 df; $P=0.48$), it appears that a prior excisional biopsy, an age of 50 years or more, and a primary tumor in a medial location were associated with the failure to identify a hot spot (Table 2). These three factors were independent of variables related to the techniques used by individual surgeons (Table 2).

Among the 413 patients in whom one or more hot spots were identified, the hot spots were limited to one location in 92.7 percent, were in two locations in 6.8 percent, and were in three locations in 0.5 percent of cases (Table 3). The distribution of

TABLE 1. RATE OF TECHNICAL SUCCESS IN IDENTIFYING A HOT SPOT, ACCORDING TO SURGEON, BEFORE INCISION.

SURGEON NO.	NO. OF PATIENTS	SUCCESS RATE (%)*	EXACT 95% BINOMIAL CONFIDENCE INTERVAL
1	51	98.0	89.6–100.0
2	51	98.0	89.6–100.0
3	51	98.0	89.6–100.0
4	50	98.0	89.4–100.0
5	49	95.9	86.0–99.5
6	47	95.7	85.5–99.5
7	43	79.1	64.0–90.0
8	33	93.9	79.8–99.3
9	30	83.3	65.3–94.4
10	22	81.8	59.7–94.8
11	16	87.5	61.7–98.5
Total	443	93.2†	90.5–95.4

*P=0.001 by Fisher's exact test for the comparison of technical-success rates among surgeons.

†Hot spots were identified in 413 of the 443 patients.

TABLE 2. RESULTS OF THE LOGISTIC-REGRESSION MODEL PREDICTING FAILURE TO IDENTIFY A HOT SPOT.*

VARIABLE†	ODDS RATIO (95% CI)
Age	
<50 yr	1.00
≥50 yr	3.41 (1.14–10.2)
Previous biopsy	
Fine-needle aspiration, core biopsy, or none	1.00
Excisional	7.10 (2.17–23.3)
Primary location	
Medial	1.00
Central	0.37 (0.10–1.35)
Lateral	0.34 (0.13–0.88)

*Hosmer–Lemeshow goodness of fit for the model, chi-square=7.54, 8 df (P=0.48).

†Indicator variables for the 11 surgeons were included in the model but are not shown.

TABLE 3. LOCATION AND NUMBER OF HOT SPOTS.*

LOCATION	HOT SPOTS: NO. PRESENT IN PATIENT 1	2	3	TOTAL
	no. (%) of hot spots			
Level I (low axillary)	365 (95.3)	28 (50.0)	3 (50.0)	396 (89.0)
Level II (midaxillary)	13 (3.4)	5 (8.9)	0	18 (4.0)
Level III (apical axillary)	0	2 (3.6)	1 (16.7)	3 (0.7)
Internal mammary	1 (0.3)	16 (28.6)	2 (33.3)	19 (4.3)
Interpectoral	2 (0.5)	1 (1.8)	0	3 (0.7)
Lower chest wall	1 (0.3)	1 (1.8)	0	2 (0.4)
Tail of Spence	1 (0.3)	0	0	1 (0.2)
Supraclavicular	0	1 (1.8)	0	1 (0.2)
Lateral breast	0	1 (1.8)	0	1 (0.2)
Thyroid	0	1 (1.8)	0	1 (0.2)
Total hot spots	383 (100)	56 (100)	6 (100)	445 (100)
Total patients with hot spots	383 (92.7)	28 (6.8)	2 (0.5)	413 (100)

*Because of rounding, percentages do not always total 100.

TABLE 4. PATHOLOGICAL STATUS OF SENTINEL NODES AND NODES OBTAINED BY AXILLARY LYMPHADENECTOMY.

SENTINEL NODES	AXILLARY NODES: POSITIVE	NEGATIVE	TOTAL
	no. of patients		
Positive	101	0	101
Negative	13	291	304
Total	114	291	405

hot spots differed, depending on the number of hot spots identified (P=0.001). Overall, the 445 hot spots were found in level I (low axillary) nodes (in 89.0 percent of cases), internal mammary lymph nodes (4.3 percent), level II (midaxillary) nodes (4.0 percent), or other locations. Patients with two or more hot spots tended to have more internal mammary hot spots and fewer level I hot spots than patients with only one hot spot. A sentinel node was not identified underneath the hot spot in 1.9 percent of patients (8 of 413).

Table 4 shows the pathological results for the 405 patients in whom a sentinel node was resected. The observed sensitivity of the finding of a histologically positive sentinel node was 88.6 percent (101 of 114); by definition, the specificity was 100 percent. The observed accuracy of sentinel nodes for the detection of metastatic disease was 96.8 percent (392 of 405); the positive predictive value was 100 percent (101 of 101), and the negative predictive value (i.e., the correlation of negative sentinel nodes with negative axillary nodes) was 95.7 percent (291 of 304).

The false negative rate did not vary significantly among the surgeons (Table 5). There were too few false negative results (13) for extensive comparison with true positive results (101) in terms of variables that may have affected the likelihood of a false negative result. Univariate analysis indicated that all 13

TABLE 5. SENTINEL-NODE FALSE NEGATIVE RATE ACCORDING TO SURGEON.

SURGEON NO.	NO. OF CASES PATHOLOGICALLY POSITIVE	FALSE NEGATIVE RATE (%)*
1	10	10.0
2	15	13.3
3	14	28.6
4	10	10.0
5	16	6.3
6	13	15.4
7	14	7.1
8	7	0.0
9	6	16.7
10	5	0.0
11	4	0.0
Total	114	11.4

*P=0.84 by Fisher's exact test for the comparison of false negative rates among surgeons.

false negative results occurred when the primary tumor was in the lateral half of the breast (P=0.004). None of the other variables tested were statistically associated with a false negative result.

There was a significant correlation between the number of pathologically positive sentinel nodes and the number of positive nonsentinel nodes obtained at axillary lymphadenectomy (Spearman's rank-correlation coefficient, 0.49; P<0.001) (Table 6). Among 304 patients with no positive sentinel nodes, 4.3 percent had nonsentinel nodes that were pathologically positive. Among 95 patients with one to three positive sentinel nodes, 37.9 percent had positive nonsentinel nodes. Among six patients with four or more positive sentinel nodes, 83.3 percent had positive nonsentinel nodes.

DISCUSSION

In this study of a method of identifying sentinel lymph nodes in women with breast cancer by means of a locally injected radioactive colloid, we found localized radioactivity (hot spots), presumably representing sentinel nodes, in 93.2 percent of cases. There was, however, considerable variation in the rate of success in detecting such nodes among the participating surgeons, even after each had performed five training procedures. Before this method can be broadly applied in clinical practice, technical improvements in identifying sentinel nodes will be necessary.

Injections of the radioactive colloid were more widely spaced around a prior biopsy cavity than around a primary tumor. The deposition of insufficient amounts of colloid between injection sites may explain why a previous excisional biopsy reduces the probability of finding a hot spot. Perhaps excisional biopsy should be avoided if a search for sentinel nodes is planned.

The patient's age and the location of the primary tumor affected the success rate of the method we used. In older patients the capacity of lymph nodes to retain the radioactive colloid may be decreased, because lymph nodes are replaced by fat in elderly persons. Increasing the volume of the diluent and the amount of tracer can increase its uptake by sentinel nodes by a factor of 10 and may offset this problem (unpublished data). The relatively high rate of failure to identify sentinel nodes in medial tumors is probably related to overshadowing (masking) of internal mammary nodes by the injection site.

Among the 405 patients with sentinel nodes, the accuracy of the sentinel nodes (the number of cases in which the pathological status of the sentinel nodes corresponded to the pathological status of the axillary nodes, divided by the number of cases) was 97 percent. Whereas the positive predictive value was

TABLE 6. RELATION BETWEEN PATHOLOGICALLY POSITIVE SENTINEL NODES AND PATHOLOGICALLY POSITIVE NONSENTINEL NODES.*

PATHOLOGICALLY POSITIVE SENTINEL NODES	PATHOLOGICALLY POSITIVE NONSENTINEL NODES					
	0	1	2	3	≥4	TOTAL
	no. (%) of patients					
0	291 (82.9)	8 (44.4)	3 (25.0)	0	2 (13.3)	304 (75.1)
1	47 (13.4)	5 (27.8)	7 (58.3)	5 (55.6)	6 (40.0)	70 (17.3)
2	10 (2.8)	4 (22.2)	1 (8.3)	3 (33.3)	2 (13.3)	20 (4.9)
3	2 (0.6)	1 (5.6)	0	1 (11.1)	1 (6.7)	5 (1.2)
≥4	1 (0.3)	0	1 (8.3)	0	4 (26.7)	6 (1.5)
Total	351 (100)	18 (100)	12 (100)	9 (100)	15 (100)	405 (100)

*Spearman's rank-correlation coefficient, 0.49 (P<0.001), for the overall correlation between the numbers of pathologically positive sentinel and nonsentinel nodes. Because of rounding, percentages do not always total 100.

100 percent by definition, the negative predictive value was also very good, at 96 percent. These results appear to support, at least in part, the hypothesis that the status of the sentinel node can accurately predict whether nodal metastases are present. However, the sensitivity was 89 percent, and the false negative rate for this study was 11 percent.

After injection, the tracer diffuses, resulting in a variable area of radioactivity with a diameter of several centimeters. Probe counts over this diffusion zone are generally much higher than those over sentinel nodes. Sentinel nodes located away from the injection site were readily located, because background counts around the sentinel nodes were low. By contrast, sentinel nodes located near or within the zone of diffusion were not readily identified, because background counts could exceed the counts for the sentinel nodes. These two situations highlight the strengths and pitfalls of probe-guided resection of sentinel nodes: the farther the sentinel nodes are from the tumor, the more readily they are identified, whereas the closer the sentinel nodes are to the tumor, the more difficult they are to identify.

All false negative results occurred when the primary tumor was in the lateral half of the breast. The control resection was an axillary lymphadenectomy. To fully test the false negative rate would require a control resection of all possible drainage basins (internal mammary, infraclavicular, and supraclavicular), which is not feasible. With tumors closer to the potential lymph-node basin, technical problems occurred. In the case of a lesion in the lateral half of the breast that drained only to lower axillary nodes, with at least one cancer-containing sentinel node that was missed by the probe, a false negative result would be recorded. For this reason, an improved sentinel-node procedure may not be successful in all patients with breast cancer, even with technical modifications. Increasing the volume of tracer injected can increase the rate of successful identification of sentinel nodes to 100 percent, according to a report from one institution.[20] Increased volume, which increases the count rate of sentinel nodes (unpublished data), makes the nodes more readily apparent and should lower the false negative rate when the lesion is in the lateral half of the breast. Vital dyes that provide a visual aid[24-26] may be complementary to probe-guided surgery and lower the false negative rate.

This study may underestimate the number of cases in which primary lymphatic drainage occurs outside the axilla. By using locally injected radioactive colloids, Hultborn et al. found a high rate of nonaxillary drainage in patients with breast cancer.[27] In a study of 250 women without pathologic changes in the breast, there was primary lymphatic drainage to the internal mammary nodes in 20 percent to 86 percent of cases, depending on the quadrant injected.[28] Nonaxillary drainage is clinically relevant, because metastases that are exclusive to internal mammary nodes occur in 5 percent to 10 percent of women with breast cancer. The prognosis is the same for these women as for those with axillary metastases.[29] An autopsy study reported that 90 percent of women who died of breast cancer had metastases in the internal mammary nodes.[30] Moreover, a first pleural effusion from breast cancer occurs more frequently on the same side as the breast cancer, suggesting regional thoracic involvement through the internal mammary nodes.[31,32] Probe guidance virtually eliminates the morbidity associated with resection of internal mammary nodes and hence may improve the accuracy of node staging by extending the procedure to patients with nonaxillary sentinel nodes.

With probe-guided surgery and the use of colloidal albumin (Nanocoll, Sorin Biomedica, Saluggia, Italy) injected into the parenchyma[33] or subdermis[26] of the breast, the rates of sentinel-node identification were 94 percent and 98 percent, and the false negative rates were 2.3 percent and 4.7 percent, respectively. With blue dye alone injected into the parenchyma of the breast, rates of sentinel-node identification ranged from 65 percent to 93 percent, and false negative rates from 0 to 12 percent.[25,34]

Our reasons for requiring that sentinel nodes be located before the incision was made were to document the success rates of individual surgeons, allow optimal placement of the incision, and allow accurate targeting in the axillary and nonaxillary nodes. In 3 percent of cases with positive nodes, only nonaxillary sentinel nodes were positive. Removal of nonaxillary nodes has not been reported by other investigators. When only blue dye is used, the incision begins over level I nodes and continues until a blue-stained lymphatic duct is identified. With blue dye, the location of the incision is always the same; however, the location of axillary sentinel lymph nodes varies. To the extent that the location of the nodes varies, so will the amount of dissection. Sentinel nodes that are not in the axilla are not identified with blue dye.

The completeness of resection of the sentinel nodes was rapidly confirmed by placing the gamma detector back into the wound after removal of the initial sentinel node. When only blue dye was used, the method of establishing whether multiple sentinel nodes were present was additional random dissection, of which the end point is not clear.

On the basis of the results of this study, we conclude that it is feasible to perform the sentinel-node procedure successfully in a variety of surgical settings. The procedure can be technically challenging, as indicated by the fact that the success rate varied among surgeons and according to the patients' characteristics. Since the study began in 1995, modifications of the technique, such as increasing the volume of tracer injected, have improved the uptake of tracer by the sentinel nodes. Other investigators, using a variety of techniques, have also had good results, and combining complementary methods may further improve the technical ability to identify all draining sentinel nodes.

Pathological examination of the sentinel nodes revealed that their status accurately predicts the status of the axillary nodes. In particular, examination of the sentinel nodes has good negative predictive value. However, false negative results were observed in the case of lesions located in the lateral half of the breast, probably because of the closeness of the injection site to the underlying sentinel nodes.

By using radioactive tracers, we could identify clinically relevant sentinel nodes outside the axilla; these would have been missed by a conventional axillary lymphadenectomy, since 3 percent of all patients with positive nodes in this series had positive nodes only outside the axilla. On the basis of these results, it is overly simplistic to name a single location as the repository of all lymphatic metastases from a primary breast cancer.

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