Use of Reoperative Sentinel Lymph Node Biopsy in Breast Cancer Patients

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BACKGROUND: Ipsilateral breast recurrence or second primary breast cancer can develop in patients who have undergone breast conservation and sentinel lymph node biopsy (SLNB). This brings into question the necessity of complete axillary lymph node dissection (CALND) versus a second SLNB (remapping). Our objective is to determine the feasibility of a reoperative SLNB.

STUDY DESIGN: A review of patients receiving a reoperative SLNB between April 1994 and December 2006 was conducted with IRB approval. Fifty-six patients underwent a second SLNB on the ipsilateral side an average of 42.5 months after their first SLNB.

RESULTS: Sentinel lymph nodes were successfully remapped in 45 of 56 (80.4%) patients. Of 45 patients successfully remapped, 36 (80%) were node negative and were spared CALND. There was only 1 patient (2.2%) in whom a sentinel lymph node was identified outside of the ipsilateral axilla. At 26 months mean followup for the second SLNB, there have been no axillary recurrences and 1 death.

CONCLUSIONS: Our findings demonstrate that remapping sentinel nodes in patients with ipsilateral recurrence or new primary breast cancer after SLNB achieved success in 80.4% of patients. Overall, 80.0% (36 of 45) of the successfully remapped patients were spared a CALND. (J Am Coll Surg 2008; 207:57–61. © 2008 by the American College of Surgeons)

Sentinel lymph node biopsy (SLNB) has become the primary means of assessing the axillary lymph node basin in patients with primary breast cancer. Many studies have proved that the findings in the sentinel lymph node (SLN) accurately predict the status of the remaining axillary nodes.[1-3]

The majority of patients with primary breast cancer receives breast-conserving therapy in the form of a lumpectomy and can present with a recurrence to the ipsilateral breast. It has been stated that up to 10% to 15% of these patients will locally recur within 10 years of their followup.[4,5] In addition, a new breast cancer can develop later in life in patients who receive axillary staging with SLNB for breast cancer, requiring a second axillary assessment.[6] In such cases, patients have been recommended a complete axillary lymph node dissection (CALND). Reconstitution of lymphatic drainage can result in new nodes receiving primary drainage from the breast area affected by the new or recurrent cancer. For these patients, feasibility of the SLNB in the reoperative setting needs to be accurately assessed.

Current SLN mapping guidelines state that SLNB should be continued until all blue, hot, or suspicious nodes are removed, and there is no absolute upper threshold for the number of SLNs that can be removed.[7] SLNB only requires one intact lymphatic pathway from the tumor to the SLN. Initial studies have shown that the axillary basin has a variable network of resilient lymphatic pathways with the potential to be mapped multiple times.[8-12] The objective for this study is to validate this hypothesis.

METHODS

After meeting current compliance standards and IRB approval (IRB No. 102552), we conducted a retrospective review of our comprehensive breast cancer database, which is updated daily, for patients who received an SLNB between April 1994 and December 2006. We then reviewed all patients from this group who received reoperative SLNB on the ipsilateral side at a later date. Patients' demographic, clinical, and treatment variables were recorded. Clinico-

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Abbreviations and Acronyms

CALND = complete axillary lymph node dissection
SLN = sentinel lymph node
SLNB = sentinel lymph node biopsy

pathologic factors were analyzed about indications, operative details, and disease-free survival.

The SLNB was conducted according to methods described previously.[13,14] The combination technique of injection of technetium sulfur colloid and isosulfan blue dye[15] was used in all but one patient (radiocolloid was not injected in the prophylactic mastectomy). Injection sites for technetium sulfur colloid consisted of periareolar (n = 17) and peritumoral (n = 38). Injection sites for isosulfan blue (5 mL) consisted of periareolar (n = 18) and peritumoral (n = 38). Preoperative lymphoscintigraphy was used in 13 of 56 patients (23%). Site of radiocolloid and blue dye injection, along with the decision for preoperative lymphoscintigraphy, was at the discretion of the primary surgeon. SLNs were evaluated intraoperatively with imprint cytology and permanent pathology, which consisted of serial node sectioning and staining with both hematoxylin and eosin and cytokeratin. CALND was performed if no SLNs were identified in a patient with recurrent invasive disease or if the SLN was positive.

RESULTS

Fifty-six of the 6,225 (0.9%) patients received a reoperative SLNB between April 1994 and December 2006. Reasons for remapping are depicted in Figure 1. Fifty-two (93%) of 56 patients were remapped as the result of a breast cancer recurrence. Other reasons for remapping include a new ipsilateral, primary breast cancer (1 of 56), prophylactic mastectomy at a later date (1 of 56), and as a result of a referral from an outside institution where the initial SLNB was performed (2 of 56). These last two reasons for remapping are nontraditional and require some brief explanation. Often, when a cancer develops in one breast, a patient can undergo mapping on that side and later a new cancer develops on the contralateral side. One of the treatment options available for these patients is a bilateral mastectomy with a bilateral SLNB. Patients receiving such treatment receive two SLNBs on the same side and are technically remapped. With respect to the latter reason, patients are frequently referred to Moffitt from outside institutions and consequently have undergone earlier treatment. Two of the patients in this study received an SLNB from an outside institution and underwent reoperative SLNB at Moffitt to eliminate any chance of false-negative SLN.

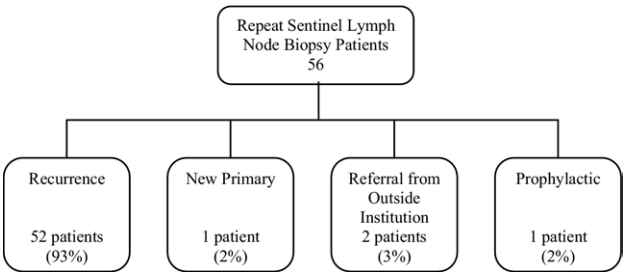

Figure 1. Four different reasons for which our patient population received a reoperative sentinel lymph node biopsy.

All 56 patients received SLNB for their first and second axillary assessment. Mean patient age was 55 years, with a mean followup of 26 months after the second remapping. Mean time between first and second SLNB was 42 months (range 46 days to 117.7 months). For the first axillary assessment, 30 patients had invasive cancer with a mean tumor size of 1.31 cm (range 0.1 to 3.5 cm). All other SLNBs were performed because of noninvasive cancer. For the second axillary assessment, 35 patients had invasive tumors with a mean tumor size of 1.75 cm (range 0.1 to 6.0 cm). All other SLNBs were performed because of either noninvasive cancer or at the time of prophylactic mastectomy.

SLNs were successfully remapped in 45 of 56 (80.4%) patients. Table 1 describes how the SLNs were identified at the second operation. More than half of the patients, 60.7% (34 of 56), had SLNs that were both "hot" by radiocolloid and "blue." Three patients had blue-only SLNs, six patients had hot-only SLNs, and two patients had SLN identified by palpation. There were 11 mapping failures. For the initial SLNB, a median of 2 SLNs were removed (range 0 to 7), with a median number of 0 non-SLNs (range 0 to 4). The second SLNB yielded a median SLN of 2 (range 0 to 5), with a median of 0 non-SLN (range 0 to 10). None of the non-SLNs proved to be positive for metastases. There was only 1 patient (2.2%) in whom an SLN was identified outside of the ipsilateral axilla (internal mammary). Preoperative lymphoscintigraphy imaging was performed in only 23% of patients. Although lymphoscintigraphy would be preferred in all of these patients, it is not routinely done at our institution because of financial reimbursement issues.

Figure 1 shows the breakdown of our patient population, and Figure 2 demonstrates a flow chart of the patients in our study. Of the 45 patients successfully remapped, 9 (20%) had positive nodes. Of these 9 patients, 3 (33.3%) had 1 or 2 additional positive non-SLNs. Eleven patients were mapping failures, meaning the SLN was unable to be located. CALND was performed in only two of these patients, because the pathology of the recurrent tumor was

Table 1. How Remapping Sentinel Lymph Node Was Identified after Injection of Technetium Sulfur Colloid and Isosulfan Blue Dye

How SLN was identified	n (n = 56)
Both radiocolloid and blue dye	34
Blue dye only	3
Radiocolloid only	6
Failed SLN biopsy	11
Palpable	2

SLN, sentinel lymph node.

invasive cancer; 13 nodes were removed in both patients, with positive nodes in 1 patient. CALND was not performed in the other patients, because their mastectomy was for noninvasive cancer or prophylactic reasons. At 26 months mean followup for the second SLNB, there were no axillary recurrences and 1 death, the cause of which is unknown.

Of 56 patients in the study, 41 (73.2%) underwent whole breast radiation after their first SLNB. Success rate for repeat SLNB was 78.0% (32 of 41) for this population. This compares with a success rate of 86.7% (13 of 15) for repeat SLNB in patients without a history of radiation. This difference between the radiation group and the no-radiation group was not statistically significant ($p = 0.7$ by Fisher's exact test). There were no differences noted in the success of a second SLNB based on a history of chemotherapy.

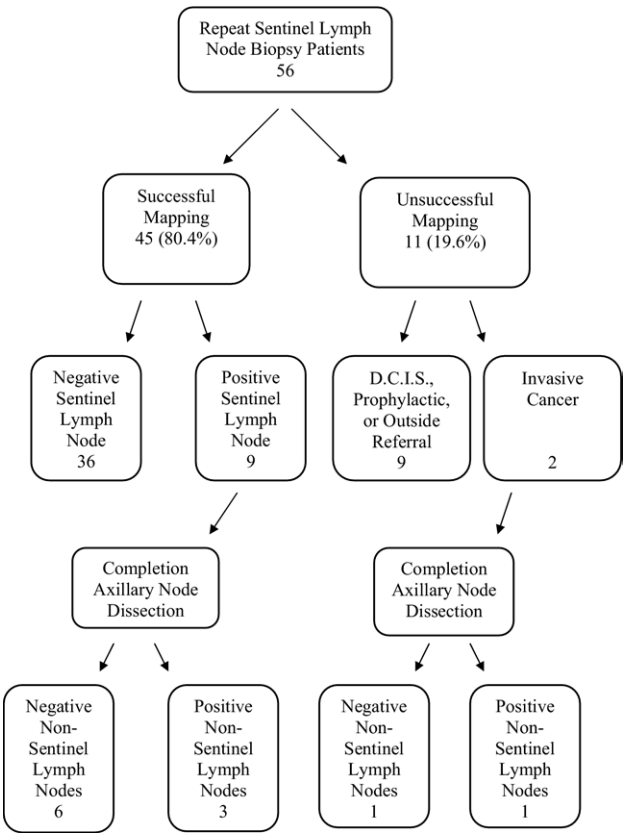

Figure 2. Flow diagram for patients undergoing reoperative sentinel lymph node biopsy.

DISCUSSION

Remapping SLNs in patients with recurrent breast cancer or new primary cancer after previous SLNB was successful for 80.4% of our patient population, which is comparable with success rates of the early SLNB era.[16] Reoperative SLNB failed in 11 of 56 patients (19.6%). One patient was morbidly obese and 9 of the 11 failed patients had received radiation therapy after lumpectomy with primary lymphatic mapping. This would substantiate our belief that there is inherent scarring associated with primary radiation therapy to the lymphatic system, which in some patients would preclude the ability to remap. Although not statistically significant, it is generally our comment to patients who have been mapped previously and radiated that there can be a risk of not being able to be remapped and that this would require CALND. Perhaps a larger study would be powered to demonstrate statistical significance of radiation on the success of lymphatic mapping.

The ability of reoperative SLNB to predict the presence or absence of axillary nodes positive for metastasis has proved to be reliable. Positive SLNs were found in 9 of 45 (20%) successful reoperative procedures and are within the range of published values for patients undergoing SLNB for the first time.[7,13,16-18] There have been no local, axillary recurrences in any patients after a mean of 26 months followup. Although the number of patients is low, it appears that a second SLNB is accurate and feasible. In addition to determining the feasibility of reoperative SLNB, we also wanted to determine the ability of reoperative SLNB to prevent a CALND. In our series, 80% (36 of 45) of the successfully remapped patients were spared a CALND. These results are similar to data published previously.[8-12] Table 2 lists the articles extant in the literature in which at least 5 patients with a history of SLNB underwent repeat SLNB. The most recent published data were from Memorial Sloan-Kettering and the European Institute of Oncology[11,12] for the table rather than their initial reports.[8,9] Successful identification of the repeat operation ranged from 74% to 97% without any axillary recurrences in 152 patients after 2.0 to 3.8 years of followup. The high identification rate from the European Institute of Oncology (97%) could be partly attributed to their selection criteria. Of 202 patients with ipsilateral recurrences, repeat SLNB was only offered to 65 (32%) patients. Interestingly, there

Table 2. Comparison of Published Institutional Remapping Series in Patients with a Prior Sentinel Lymph Node Biopsy That Included More Than Five Patients

Institution	Patients with previous SLNB who underwent second SLNB (n)	Successful mapping (n)	Success rate (%)	Cases where drainage identified outside ipsilateral axilla		Second SLN positive for metastatic disease		Axillary recurrences and followup
				n	%	n	%	
Moffitt Cancer Center	56	45	80.4	1/45	2.2	9/45	20	0 cases at 2.2 y
John Wayne Cancer Institute[10]	6	5	88	2/5	40	0/5	0	0 cases at 3.1 y
Memorial Sloan-Kettering[11]	54	40	74	3/40	7.5	5/40	12.5	0 cases at 2.2 y
European Institute of Oncology[12]	65	63	97	7/63	7.9	7/63	11.1	0 cases at 3.8 y
Total	181	152	84	11/152	7.2	20/152	13.2	0 cases at 2.9 y

SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

has been noted a high percentage of extraaxillary sentinel nodes for repeat axillary operations with an extraanatomic localization of nodes in 7.2% (11 of 152) of the patients in the published series to date. Although we only identified 1 patient (2.2%) with extraaxillary drainage on lymphoscintigraphy, the increased probability of finding such nodes in patients with previous axillary operation clearly supports the need of undergoing a second lymphatic mapping injection and lymphoscintigraphy before SLNB, because the drainage is not as predictable as patients with a virgin axilla.

In conclusion, it is apparent that reoperative SLNB is both feasible and is highly useful in treatment of recurrent breast cancer or newly diagnosed breast second primary cancer in patients with earlier SLNB. Although factors of surgical scarring and lymphatic disruption associated with earlier operation and radiation therapy can increase mapping failure in the remapping population, remapping still remains viable in 80.4% of patients. The only downside to remapping is that patients might require CALND in the event of mapping failure, which is what they would have received had remapping not been attempted. In our series, 80% (36 of 45) of the successfully remapped patients were spared CALND.

Surgeons must certainly be aware of previous operations or axillary assessments and use good clinical judgment in determining if the integrity of the lymphatics has been jeopardized before conducting reoperative SLN mapping. To improve the likelihood of success, a combination technique of isosulfan blue and radiocolloid is recommended, even in the reoperative setting. This technique has been successful in our hands,[19] and others have shown that it increases mapping success by 8% to 14%.[20] Use of preoperative lymphoscintigraphy can also be warranted to assess the increased likelihood of extraanatomic lymphatic drainage in this remapping group. Our findings are consistent with earlier studies that indicate remapping is feasible and can offer an advantageous alternative to CALND in patients with a breast cancer recurrence or a new primary breast cancer with a history of previous SLNB or earlier axillary operation.

Author Contributions

Study conception and design: Cox, Furman, Kiluk
Acquisition of data: Furman, Kiluk, Jara, Koeppel, Meade, White, Allred, Meyers
Analysis and interpretation of data: Cox, Furman, Kiluk
Drafting of manuscript: Cox, Furman, Kiluk
Critical revision: Cox, Furman, Kiluk, Dupont

REFERENCES

1. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994;220:391–398; discussion 398−401.
2. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998; 339:941–946.
3. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet 1997;349:1864–1867.
4. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989;320:822–828.
5. van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J Natl Cancer Inst Monogr 1992;15–18.
6. Weinberg E, Cox C, Dupont E, et al. Local recurrence in lumpectomy patients after imprint cytology margin evaluation. Am J Surg 2004;188:349–354.
7. McCarter M, Yeung H, Fey J, et al. The breast cancer patient with multiple sentinel nodes: when to stop? J Am Coll Surg 2000;192:692–697.
8. Port ER, Fey J, Gemignani ML, et al. Reoperative sentinel lymph node biopsy: a new option for patients with primary or

locally recurrent breast carcinoma. J Am Coll Surg 2002;195: 167–172.
9. Intra M, Trifiro G, Viale G, et al. Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 2005;12:895–899.
10. Taback B, Nguyen P, Hansen N, et al. Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. Ann Surg Oncol 2006;13:1099–1104.
11. Port ER, Garcia-Etienne CA, Park J, et al. Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. Ann Surg Oncol 2007;14: 2209–2214.
12. Intra M, Trifiro G, Galimberti V, et al. Second axillary sentinel lymph node biopsy for ipsilateral breast tumour recurrence. Br J Surg 2007;94:1216–1219.
13. Cox CE, Bass SS, Reintgen DS. Techniques for lymphatic mapping in breast carcinoma. Surg Oncol Clin N Am 1999;8:447–468, viii.
14. Cody HS 3rd, Borgen PI. State-of-the-art approaches to sentinel node biopsy for breast cancer: study design, patient selection, technique, and quality control at Memorial Sloan-Kettering Cancer Center. Surg Oncol 1999;8:85–91.
15. Cox CE. Lymphatic mapping in breast cancer: combination technique. Ann Surg Oncol 2001;8[Suppl]:67S−70S.
16. Cox CE, Bass SS, McCann C, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer. Ann Rev Med 2000;51:525–542.
17. Hoar F, Stonelake P. A prospective study of the value of axillary node sampling in addition to sentinel lymph node biopsy in patients with breast cancer. Eur J Surg Oncol 2003;29:526–531.
18. Jakub JW, Pendas S, Reintgen DS. Current status of sentinel lymph node mapping and biopsy: facts and controversies. Oncologist 2003;8:59–68.
19. Cox CE, Pendas S, Cox JM, et al. Guidelines for sentinel node biopsy and lymphatic mapping of patients with breast cancer. Ann Surg 1998;227:645–651.
20. Cody HS 3rd, Fey J, Akhurst T, et al. Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. Ann Surg Oncol 2001;8:13–19.