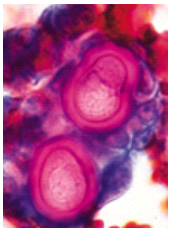

Presentation Highlights

SURGERY FOR DIAGNOSIS AND TREATMENT: SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER

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Introduction

At the John Wayne Cancer Institute, Morton et al[1] popularized the concept that the first lymph node encountered by tumor cells that had metastasized from the primary tumor, the sentinel node (SN), represented the status of the remaining nodes in the regional nodal drainage basin. His group first reported that histopathologic analysis of the SN detected by mapping the regional lymphatics with a vital blue dye accurately predicted the presence or absence of regional nodal metastases in patients with melanoma.[1]

To determine if the concept could be generalized to include breast cancer, we modified Morton's technique used in melanoma and initiated a study in 1991 to investigate the feasibility of lymphatic mapping and sentinel lymph node dissection (SLND) in breast cancer patients. With no prior experience using this technique in breast cancer, a development period was required to define the technical aspects of the procedure. As it was soon discovered, the kinetics of blue dye migration in breast lymphatics were markedly different than in cutaneous lymphatics. Several factors affected the success of this technique, including patient selection, injection technique, dissection technique, and histopathologic evaluation of the SN.

Evolution of Sentinel Lymph Node Dissection

Krag et al[2] published a pilot study in 1993 reporting the successful identification of an SN in 18 of 22 patients with breast cancer using a radioactive sulfur colloid detectable with a hand-held gamma probe. In all 18 patients, the SN was an accurate predictor of the axillary status. In 1994, we reported the results of the total sample of our initial 174 SLNDs.[3] No patients were excluded, even those prior to determining a successful SLND technique. Patients with advanced tumors and grossly involved nodes in whom we now know the technique is not appropriate were included as well. This study consisted of 172 patients, with two patients having synchronous bilateral breast cancer. All patients underwent lymphatic mapping and SLND followed by level I and II axillary lymph node dissection (ALND), as well as surgical treatment of the primary lesion. Using 1% isosulfan blue dye, an SN was identified in 114 (66%) of procedures overall. SN accurately predicted the axillary status in 109 (96%) of 114 cases. The five false-negative results occurred in the first 87 procedures, two of which were in the first 10 procedures. Three of these five patients had dye-stained axillary fat misidentified as an SN. This prompted the routine use of frozen section to confirm lymph node recovery. Another patient was subsequently found to have micrometastases in the SN after reexamination using anticytokeratin immunohistochemistry (IHC). Therefore, we have employed routine IHC to detect occult metastases since that time. Only one of these five false-negative SNs was a "true" false negative indicating the presence of metastases in non-SNs but not the SN. With all five cases considered as false negatives, the technique predicted axillary node status with 96% accuracy. If only the single "true" false negative result is considered, the technical accuracy in predicting axillary status was greater than 99%, even during its developmental stage.

Next, we examined the ALND specimens of patients with histologically involved nodes to determine if the SN could have predicted the axillary status by chance alone. Thirty-four patients had a total of 751 lymph nodes removed, of which 63 (8%) were SNs and 688 (92%) were non-SNs. Tumor was detected in 39 (62%) SNs, while only 93 (14%) of 688 non-SNs were involved with tumor ($P<0.0001$). This suggested that breast cancer metastases occur through a nonrandom pathway that can be identified by SLND. It also suggested that random axillary biopsy or sampling could not recreate these results through chance alone.

In the next report of this technique, we evaluated the first 162 patients undergoing successful SLND followed by completion ALND (SLND group) and compared them to 134 patients undergoing ALND alone (ALND group).[4] Although the groups were not randomized, they were contemporaneous and all procedures were performed at the same institutions by a single surgeon. The SN was evaluated by hematoxylin-eosin (H&E) staining and anticytokeratin IHC staining, while non-SNs were evaluated by H&E staining alone. Both groups had comparable clinical characteristics and a similar total number of axillary nodes excised. The SLND group had a 42% incidence of axillary metastases compared with 28% in the ALND group ($P<0.05$). This was primarily due to a dramatic increase in the detection of micrometastases by IHC in the SLND group. Sixteen percent of SLND patients had metastases less than 2 mm in size compared to 3% of the ALND group. Detection of micrometastases by both H&E staining (9% vs 3%) and IHC staining (7% vs 0%) increased with SLND. We concluded that SLND not only accurately predicts the status of the axillary nodes, but also improves axillary staging compared with standard ALND. This results from a focused histopathologic evaluation of the SN, which increases the detection of micrometastases using IHC staining of the SN. Unfortunately, the clinical significance of the IHC-detected nodal metastases is currently unknown, creating confusion in the clinical management of these patients who were "upstaged" by SLND.

Since the technique of SLND was evolving, we reported a more recent series of 107 patients undergoing lymphatic mapping and SLND followed by ALND, using our "mature" technique.[5] We identified the SN in 94% of patients. There were no false-negative results, indicating a sensitivity and specificity of 100%. We attribute our increased success to refinements in technical details and indications for the procedure. Based on these results, a trial to investigate lymphatic mapping and SLND alone in patients with negative SN began in October 1995. This trial is soon to be reported and included T1 and T2 (less than or equal to 4 cm) tumors. To date no axillary recurrence has been seen in more than 300 cases at our institution.

In order to determine if the SN is truly the first node to harbor metastases, we examined non-SNs using the same careful histopathologic technique with IHC that was used to examine the SN.[6] We found that when the SN was tumor-free by both routine H&E and IHC staining, the probability that a non-SN would have tumor was 1 in 1,087. This solitary metastasis was detectable with IHC but not with H&E staining. This study confirms the theoretical basis of the SN hypothesis and proves that finding a tumor-negative SN is not likely to be associated with a tumor-involved non-SN.

Investigators at several other institutions have verified the SN concept in breast cancer. Krag et al,[2] Albertini et al[7] and, more recently, Veronesi et al[8] confirmed the hypothesis that the lymphatic drainage of a breast cancer can be identified and traced to the SN intraoperatively and that the histologic status of the SN accurately predicts the status of the entire axilla. These studies differ in several aspects of patient selection, injection technique, and type of lymphatic mapping agent used. They suggest that identification of the SN may be accomplished by several techniques. However, they all confirm the validity of the SN hypothesis and its accuracy for breast cancer staging.

Krag and associates[2] used unfiltered technetium sulfur colloid alone as a mapping agent, with a range of 1 to 4 hours between colloid injection and SN excision. The SN was identified in 18 (82%) of 22 patients and predicted the histopathologic status of the axilla in each case. This report provides evidence that this technique is valid, although it contained only a few node-positive patients. Experience with breast lymphoscintigraphy has shown that the SN is labeled first, but the isotope may migrate to other nodes.

Results of SLND in Breast Cancer

Study	Number of Patients	Mapping Agent	SN Identification Rate (%)	Accuracy of SN in Determining Axillary Nodal Status (%)
Cox et al[10]	466	Dye + RC	94*	NR
Krag et al[9]	443	RC	91	97
Giuliano et al[3]	174	Dye	66	96
Veronesi et al[8]	163	RC	98	98
Guenther et al[11]	145	Dye	71	97
Borgstein et al12	130	RC	94	99 **
Giuliano et al[5]	107	Dye	94	100
Koller et al[13]	98	Dye	98	97
Albertini et al[7]	62	Dye + RC	92	100
O'Hea et al[14]	59	Dye + RC	93	95
Crossin et al[15]	50	RC	84	98
Barnwell et al[16]	42	Dye + RC	90	100
Miner et al[17]	42	RC	98	98
Offodile et al[18]	41	RC	98	100
Pijpers et al[19]	37	RC	92	100 ***
Krag et al[12]	22	RC	82	100
Dale and Williams[20]	21	Dye	66	100

SN = sentinel node
NR = not recorded
RC = radiocolloid

* phase II patients did not receive ALND if SN was negative for metastases
** 18 patients did not receive ALND
*** 2 patients refused ALND

Albertini et al[7] used a vital blue dye and filtered technetium sulfur colloid as lymphatic mapping agents. Of the 62 patients included, the SN was identified in 57 (92%) of these. Forty-five SN were identified by both blue dye and radiocolloid, and 12 were identified by radiocolloid alone. Metastases were found in 18 SNs, all of which were identified by both dye and colloid. There were no false-negative SNs, ie, patients with a negative SN and a positive non-SN. The authors concluded that the combination of dye and colloid increases identification of the SN, and this method is superior to radiocolloid or dye alone.

Veronesi and colleagues[8] reported on 163 patients who underwent SLND using technetium-labeled human serum albumin. They used an injection technique in which the radioisotope was injected subdermally superficial to the tumor, and the lymph node was identified using a gamma counter. They were able to identify the SN in 160 of 163 patients and found that the SN was predictive of the axillary status in 156 (97%) of the 160 patients with an identified SN.

These and other published series of SLND in breast cancer, which have been performed using many different mapping techniques, are summarized in the Table. Collectively, these studies confirm the diagnostic accuracy of SLND in predicting the status of the axilla. These groups who have validated SLND at their institutions by performing ALND each assembled a multidisciplinary team committed to refining the technique required to perform SLND successfully. Learning the technique as reported is also necessary to achieve accurate results. A recent multicenter trial of SLND has corroborated the validity of the SN concept.[9] This large trial, using radiocolloid as the mapping agent, reported that the SN was 97% accurate in predicting the status of the axillary nodes. An overall SN identification rate of 91%, which varied significantly among the 11 experienced breast surgeons participating in the trial, was disconcerting. The overall false-negative rate of 11.4% was also a concern, especially since the surgeons in the study who enrolled more than 40 patients had a false-negative rate of between 6.3% and 28.6%, which was not statistically significant. Each surgeon had to perform five proctored procedures before entering patients into the trial. Thus, the technique of SLND with radioisotope requires appropriate training to develop the expertise necessary to achieve dependable SLND results.

It is apparent that the SN hypothesis is correct: breast cancer drains preferentially to a single node that is the first to harbor axillary metastases if such spread has occurred. This concept is not Halstedian in the sense that no implication is made about the systemic spread of breast cancer, nor is it suggested that breast cancer does not spread directly via the blood stream. Rather, if breast cancer spreads to the lymph nodes, there is an SN that is the first to harbor the metastasis. The SN may be in level I or, as has been shown, in level II.[3] Level III SNs are not likely to be detected with any of the above technologies. The concept of "skip" metastasis is not valid since by definition the SN is the first node to exhibit metastases and cannot be skipped. However, it may be difficult to identify because of technical problems with operative or histopathologic techniques, and patients would have a falsely identified SN with no metastases.

Sentinel Lymph Node Dissection Technique

A 3- to 10-minute interval between dye injection and axillary incision is used to allow adequate visualization of the lymphatics. Too short a delay between injection and incision may prevent identification of the afferent lymphatics and location of the SN. A delay that is too long can result in dye transit to multiple non-SNs, which also inhibits identification of the SN. The time required for dye transit to the axilla is related to the location of the primary lesion within the breast. Lesions in the axillary tail closer to the lymph node basin have shorter transit times, while those in the lower inner quadrant have longer transit times. Therefore, we typically allow 3 to 4 minutes and 7 to 10 minutes, respectively, for lesions in these locations. Breast size, postbiopsy edema and ecchymosis, and the proximity of the tumor to the skin or chest wall do not appear to be related to transit time.

A 2- to 3-cm transverse incision is made in the axillary fossa in the same area used for level I and II dissection. Care is taken to extend the incision only through the skin to avoid transection of the afferent lymphatics. The lymphatic channels are located with careful blunt dissection and followed to the SN. Any blue-stained lymphatics are traced proximally and distally to locate other possible SNs and lymphatic channels. After all SNs are identified, they are excised and forwarded for pathologic evaluation. It is critical to initially search for the afferent lymphatics and not the lymph node. Lymphatic channels are then used as a "road map" to locate the node. Patience and meticulous dissection technique are essential during this part of the procedure to reliably and accurately identify the SN.

Pathologic Evaluation

All SNs are evaluated by intraoperative frozen section examination. This was initially done to confirm that nodal tissue had been removed, since misidentification of blue-

stained fat as an SN was a cause of false-negative results early in our experience. More recently, frozen section is used to identify the presence of axillary metastases in the SN, in which case the patients undergo standard level I and II axillary dissection. If axillary metastases are not identified, sentinel lymphadenectomy alone is performed. While awaiting frozen section results, the definitive procedure for the primary tumor (segmental or total mastectomy) is completed.

Frozen-section negative SNs are subsequently studied by permanent H&E staining. The nodes are bivalved, and two sections examined for the presence of metastases. If none are found, cytokeratin IHC staining is performed. Six to eight sections of the SN are examined with IHC to detect occult metastases. A portion of the lymph node is also processed for multiple marker reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. This technique identifies occult lymph node metastases not detected by IHC. We are prospectively evaluating this technique to determine the incidence and prognostic significance of metastases detected in this manner.

Conclusions

Despite differences in technique, the various studies reported confirm the SN hypothesis in breast cancer. The technical variations in themselves support the validity of the concept. The data overwhelmingly permit the simple statement that a tumor-free SN is indicative of a patient with node-negative breast cancer in nearly 100% of cases in experienced hands.

SLND can be mastered by experienced surgeons at several institutions, but it requires proper training to overcome difficulties inherent with each technique available. The procedure should not be accepted as an alternative to routine ALND until each individual surgeon has performed a sufficient number of cases with concurrent ALND to document axillary staging accuracy with SLND. This also requires support by pathologists and nuclear medicine physicians dedicated to nuances of each technique. Once the surgeon and supporting team prove their accuracy, SLND may become the axillary staging procedure of choice and may benefit many breast cancer patients by allowing accurate staging with minimal morbidity.

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