Postgraduate Course

22

Lymphatic Mapping and the Significance of Sentinel Node Biopsy

Chair:
Armando E. Giuliano, MD, FACS
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The objective of this course is to teach the indications, techniques, and theoretical concepts of lymphatic mapping and sentinel node biopsy for breast cancer and melanoma. After participating in this course, surgeons should be able to begin to perform and evaluate lymphatic mapping and sentinel node biopsy with blue dye, radioisotope, or a combination of both. The histopathologic methodology of sentinel node evaluation will be discussed. The techniques of lymphoscintigraphy for successful identification of lymph nodes will be described, and the clinical significance of micrometastases and ongoing clinical trials will be discussed.

In keeping with the practice of publishing scientific material, the authors are responsible for the accuracy and completeness of the references and bibliographies published in this syllabus.

Program

Session I
Wednesday, October 13, 8:00 am–12:00 noon
Moderator: Armando E. Giuliano, MD, FACS

Session II
Wednesday, October 13, 1:30–5:30 pm
Moderator: Armando E. Giuliano, MD, FACS

How to Do It

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Session I

Moderator:
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Wednesday, October 13, 1999
8:30 am–12:00 noon

The Sentinel Node Concept

Donald L. Morton, MD, FACS
Santa Monica, CA

Objective

Understand the concept, purpose, and potential of intraoperative lymphatic mapping to identify the sentinel lymph node on the lymphatic drainage path from solid tumors.

Performance Measures

At the completion of the course, the surgeon should be able to communicate the following:

1. The definition of a sentinel node
2. Mapping agents used to identify the sentinel node
3. Controversies of probe-directed intraoperative mapping
4. The degree of training and experience required to undertake sentinel lymphadenectomy without subsequent complete lymphadenectomy
5. Multidisciplinary components of lymphatic mapping
6. The current status of sentinel lymphadenectomy for various solid tumors

Outline

I. The sentinel node concept and development of the sentinel node technique

The concept of the sentinel node is predicated on the fact that the efferent lymphatic channel draining a primary tumor will lead directly to the first—"sentinel"—lymph node in the regional lymphatic basin. This lymphatic channel can carry malignant cells from a primary tumor to the sentinel node. The tumor cells can then lodge in the subcapsular sinus of the lymph node and proliferate into a nodal metastasis. Thus, the sentinel node is the lymph node most likely to harbor metastatic disease if a regional nodal metastasis is present.

A. Feline model

B. Early clinical studies using blue dye

II. Introduction of probe-directed mapping

The success of lymphatic mapping depends on identifying the first lymph node draining the primary tumor. However, when mapping is performed with a radiocolloidal agent, the number of hot lymph nodes will vary with the agent and with the interval between its injection and the surgical procedure. As the radiolabeled colloid flows along the lymphatic chain, the sentinel should be the first draining node and the only hot node—if the mapping procedure is performed promptly after radiocolloid injection. As additional time elapses, the radiolabeled colloid flows further up the chain of nodes, and additional nodes become hot; therefore, *not all hot nodes are sentinel nodes*. Moreover, the hottest node is not always the sentinel node. Thus, the surgeon using radiocolloid alone may not be able to determine the true sentinel node among the many hot nodes that are removed.

A. Types and kinetics of various radiopharmaceutical agents

B. Definitions of a hot sentinel node

C. Use of the hand-held gamma probe as an adjunct to visualization of the blue dye: lymphatic mapping performed using blue dye plus radiocolloid is superior to lymphatic mapping using blue dye alone

III. Summary of current studies using dye and/or radiopharmaceutical agents for patients with various solid tumors: melanoma, breast cancer, thyroid carcinoma, colon cancer, oropharyngeal carcinoma, and vulvar carcinoma

IV. The multidisciplinary approach to sentinel lymphadenectomy

Consistent results can only be obtained through the combined efforts of the nuclear medicine physician, the surgeon, and the pathologist. These individuals must have experience with the technical details of sentinel lymphadenectomy and must understand and accept the multidisciplinary nature of this technique.

V. The learning curve for sentinel lymphadenectomy

Successful lymphatic mapping is directly related to the surgeon's experience. While ascending the learning curve, the surgeon must perform complete sentinel lymphadenectomy to monitor the rate of false-negative sentinel nodes identified by dye, probe, or preferably dye plus probe. A learning phase of at least 30 consecutive cases for melanoma and at least 60 cases for breast cancer are necessary for mastery of the technique. Unless each surgeon can develop and validate his or her own accuracy, the patient may undergo an expensive procedure that does not determine the true tumor status of the sentinel node and nodal basin, which may deprive the patient of the potential therapeutic benefit of early lymphadenectomy for micrometastatic disease.

VI. Validation of the accuracy of sentinel lymphadenectomy in a multicenter setting

Initially at the 1990 meeting of the Society of Surgical Oncology,[1] and subsequently in the first report in the literature published in 1992,[2] our group at the John Wayne Cancer Institute proposed intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL) as an accurate alternative to routine elective lymph node dissection for staging the regional lymphatics in patients with cutaneous melanoma. Since that time, more than 250 peer-reviewed studies on LM/SL have been reported in the literature. The technique has been described not only for patients with melanoma and breast cancer, but also for those with thyroid carcinoma, colon cancer, oropharyngeal carcinoma, and vulvar carcinoma.[3]

The sentinel node (SN) concept is predicated on the fact that the efferent lymphatic channel draining a primary tumor will lead directly to the first, "sentinel" lymph node in the regional lymphatic basin. This channel can carry malignant cells from the primary tumor to the SN. These tumor cells can lodge in the subcapsular sinus of the SN and proliferate into a nodal metastasis. Sophisticated histopathologic techniques including multiple sectioning and immunohistochemistry support the concept that the SN is the lymph node most likely to harbor metastatic disease in patients who have regional nodal metastasis.

We first established the technical details of LM/SL with isosulfan blue dye in a feline model.[4] After intradermal injection of isosulfan blue dye, we identified the efferent lymphatic channel and followed it to the blue-stained SN in the adjacent lymphatic basin. Our initial LM/SL technique in humans involved intradermal injection of blue dye around the patient's primary melanoma.[2] A skin flap was raised in the regional lymphatic basin, and by meticulous dissection, the blue-stained lymphatic channel was followed through the fatty subcutaneous tissue of the lymph basin to the blue-stained SN. It is imperative to identify the blue-stained lymphatic channel first and follow it to the SN; otherwise more proximal blue nodes may be overlooked.

An alternative way to identify the SN is with a radiopharmaceutical and a handheld gamma probe. The technical details of LM/SL performed using a radiopharmaceutical also were first established in a feline model. The initial clinical report from Krag's group[5] involved intradermal injection of the radiopharmaceutical around the primary melanoma. A "hot spot" was identified in the regional lymphatic basin with a handheld gamma probe, and a skin incision was made. All radiolabeled—hot—SNs were excised. No attempt was made to identify the efferent lymphatic channel.

The success of LM/SL depends on identifying the first lymph node draining the primary tumor. However, when LM is performed with a radiocolloidal agent, the number of hot lymph nodes will vary with the agent and with the interval between its injection and the surgical procedure. This relation occurs because the radiocolloid starts to flow up the chain of lymph nodes as soon as it is injected. The SN, which is the first lymph node along this chain of nodes, should be among the hot nodes if all hot nodes are removed, *but not all hot nodes are SNs!* Therefore, a surgeon who performs LM with only a radiocolloid may identify 1 or more hot nodes but may not be able to determine which of these nodes is the true SN. We have demonstrated that the SN is not necessarily the hottest node in the lymphatic basin, although 92% of the time it will be among the hot nodes.[6]

Lymphatic mapping with radiocolloidal agents will not realize its full potential until it is standardized. Investigators continue to use a wide variety of radiocolloidal agents: human serum albumin, albumin colloid, sulfur colloid, trisulfide colloid, and stannous phytate. In addition, the time interval between injection and LM

ranges from zero to more than 24 hours. There are also variations in the amount of radiocolloid injected.[7] Another important variable is the distance between the lymph node basin and the primary tumor.

The result of all these variations is an alarmingly disparate set of definitions: an SN has been defined by a radioactive count of 10–25 in 10 seconds, a count of 300–3,000 in 10 seconds, an in vivo node to background count ratio ≥2 or 3, or an ex vivo SN to non-SN count ratio >10. Each of these definitions is arbitrary and subject to our limited knowledge of the intralymphatic kinetics of particular radiopharmaceutical agents.[8]

Because of these inconsistencies when radiopharmaceuticals are used, the first lymph node draining the primary tumor site and the first site of any nodal metastasis is the first *blue* node. However, although uptake of blue dye remains the gold standard for identifying the true SN, dye and radiocolloid techniques are complementary and should be used together. In our most recent series we identified the SN in 98% of lymphatic basins by using both blue dye and a radiocolloid.[9] Only 6% of SNs were identified with the radiocolloid alone, and none of these SNs contained microscopic tumor deposits; in contrast, 8% of SNs were blue but not hot, and, more important, some of these blue nodes contained microscopic tumor. Although other institutions have reported a similar success rate, the percentage of basins in which the SN is hot but not blue ranges from 20% to 40%. Our current method of LM/SL uses both a radiocolloid and a blue dye. Basically, the SN is identified by following a dye-stained lymphatic channel leading from the primary melanoma. The gamma probe is used as an adjunct in guiding the surgeon to the first blue-stained SN and identifying additional blue-stained SNs.

Numerous institutional series have reported the efficacy and accuracy of LM/SL, but as yet no prospective randomized multiinstitutional trial has demonstrated its survival benefit for patients with any tumor type. Among the several multicenter trials now under way, closest to completion is a 5-year Phase III trial of LM/SL in patients with melanoma (DL Morton, principal investigator: A Clinical Study of Wide Excision Alone Versus Wide Excision with Intraoperative Lymphatic Mapping and Selective Lymph Node Dissection in the Treatment of Patients with Cutaneous Invasive Melanoma). This trial randomizes patients with clinically localized melanoma to wide excision and nodal observation or to wide excision and LM/SL, followed by complete lymphadenectomy if the SN contains tumor. The results will indicate the prognostic significance of SN micrometastasis (< 2 mm) and the survival benefit of lymphadenectomy for melanoma patients with tumor-positive SNs. We recently examined the accuracy of LM/SL in this multicenter trial by comparing it with our experience at the John Wayne Cancer Institute.[10] The results were remarkably similar in regard to rates of successful identification of the SN and incidence of nodal metastases.

Although experienced investigators at our institution and other centers have proved that high rates of SN identification are possible, each surgeon must ascend a learning curve to acquire technical expertise in LM/SL. Our studies clearly indicate that successful mapping of regional lymphatic anatomy is directly related to the surgeon's experience; the rate of SN identification is highest in a surgeon's most recent experience and highest for the surgeon who has performed the most mapping procedures.[2,9] Regardless of the mapping agent used to identify the SN, during the learning phase the surgeon should always perform complete lymphadenectomy after LM/SL to monitor his or her false negative rate.

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Microscopic Evaluation of the Sentinel Node

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To identify individuals likely to benefit from lymphadenectomy, pathologists need to be able to identify very small numbers of tumor cells in lymph nodes. Accurate detection of small numbers of cells became possible after our group developed S-100 protein as a marker for melanocytic tumors[1,2] and after the appearance of antibodies to melanoma-associated epitopes, such as HMB-45, NKI/C3, and Melan-A.[3,4] Conventional histologic examination of specimens underestimates by 14% the number of patients with clinically localized primary melanoma who have early metastases in regional nodes[4] and underestimates by 30% tumor positivity in ostensibly tumor-free nodes of patients with node-spread melanoma.[5] In patients with occult nodal tumor, the number of nodes containing tumor was small and the number of tumor cells present was also small. The nodes that contained occult tumor were located close to the primary melanoma.[6]

The application of lymphatic mapping to melanoma patients[7] identified blue-colored afferent lymphatics and one or more sentinel lymph nodes (SLN; the first node on the direct lymphatic pathway from the primary melanoma). This technique has generated considerable enthusiasm among surgical oncologists, and there are now many reports of its successful application. Surgical pathologists are increasingly requested to examine tissues removed at SLN biopsy and render an opinion as to the tumor status of the SLN. The effectiveness of the approach and decisions about future therapy are critically dependent on the accuracy of these evaluations.

Patients and Methods

These recommendations are based on experience with 1,119 SLNs from 446 patients entered into the National Cancer Institute-sponsored multicenter trial of lymphatic mapping and sentinel lymph node dissection (John Wayne Cancer Institute, Santa Monica).

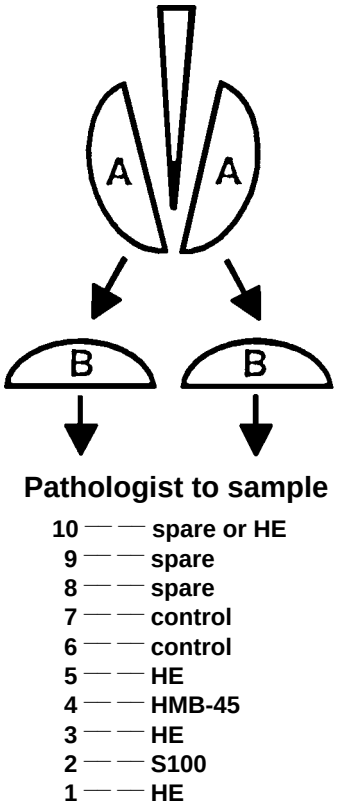
We determined the following: (1) the number of SLNs provided, (2) the number of SLNs that contained tumor on hematoxylin-eosin (H&E) evaluation, and (3) the number of SLNs that contained tumor on immunohistochemical evaluation (S-100 and HMB-45). For lymph nodes removed during completion lymph node dissections, we recorded the number of tumor-positive nonsentinel nodes (non-SLNs).

Is the Node Truly Sentinel?

Determination that a node is sentinel depends on information from the surgeon, who uses data from preoperative lymphoscintigraphy, blue coloration of afferent lymphatics and lymph nodes, and enhanced radioactivity of the lymph node detected by a handheld gamma-counter. The pathologist examines submitted lymph nodes for blue coloration of all or part of the node. Although SLNs are preferentially the site of early metastases, tumor status cannot confirm sentinel node status because not all SLNs contain tumor and some non-SNs contain tumor.

Sampling, Including the Role of Frozen Sections

We have moved away from using frozen sections, believing that the preparative steps required to obtain a full-face frozen section wastes the tissue in which occult tumor cells are most likely to be present.[6] Interpretation of frozen sections (H&E staining and rapid immunohistologic techniques) is more difficult and error prone than interpretation of well-fixed, permanent material. We strongly recommend that interpretation of SLNs be based on well-fixed, full-face sections cut close to the midline of the lymph node.



Recommended technique for lymph node sampling. The sentinel node (A) is cut into 2 exactly equal halves through its longest circumference. The 2 halves of the node (B) are placed cut face down and 10 serial "full-face" sections are cut from each (technicians are requested to minimize tissue removed during the facing-up process). Sections 1, 3, 5, and 10 are stained with H&E. Section 2 is stained with an antibody to S-100 protein, and section 4 with the antibody HMB-45 (or Melan-A). Sections 6 and 7 are used as controls, and sections 8 and 9 are spares for any required repeats of unsatisfactory sections.

Any sampling recommendation must compromise between the ideal and the possible. We recommend that the node be exactly halved through the longest circumference (Figure). The node halves are placed cut face down in cassettes and fixed for at least 24 hours. The technician is instructed to minimize "facing up" and to obtain 10 serial full-face sections. Sections 1, 3, 5, and 10 are stained with H&E, section 2 is stained for S-100 protein, and section 4 is stained for HMB-45. Sections 6 and 7 are negative controls for the immunoperoxidase studies, and sections 8 and 9 are spare. If suspicious or anomalous appearances are seen in the first 10 sections, additional groups of 10 sections can be examined if indicated.

Immunohistochemistry

All SLNs must be examined with immunohistologic techniques (antibodies to S-100 and HMB-45 or Melan-A) unless overt tumor is present on gross inspection or microscopy of H&E-stained sections. Immunohistology increases the frequency of SLNs found to contain tumor by 10%–12%.

Immunohistology with S-100 Protein

S-100 protein is a highly robust melanoma marker, staining the cells of virtually 100% of melanomas.[2] The clinician should look for epithelioid, oval, or spindle-shaped cells in the subcapsular sinus that are S-100 protein positive in both cytoplasm and the nucleus. Other nodal cells that contain S-100 protein are dendritic leukocytes of the paracortex, the cells of capsular nevi, and the Schwann cells of node-associated nerves.[3] Paracortical dendritic leukocytes are especially difficult to interpret in immune-suppressed nodes,[6] in which they may have few dendrites and adopt a round or oval morphology.

Immunohistology with HMB-45

HMB-45 is more specific for melanoma cells (cytoplasmic staining), but between 10% and 15% of melanomas (especially metastases) do not express this epitope. Antibodies to HMB-45 do not stain dendritic leukocytes and stain capsular nevocytes at relatively low intensity (or not at all). The antibody MART 1 (Melan-A) is similar to HMB-45 in target specificity, but some melanomas do not stain with this reagent.

In lymph nodes with trabecular calcification (mainly in the groin or iliac area), extracellular HMB-45 reactivity may be identified.

Handling of SLNs Identified by Radioisotopic Labeling

The isotope used is generally technetium 99, which has short penetration and a short half-life. The risk to operating room personnel and pathology staff and faculty from this radiation source is considered slight, but after bisection of the nodes it is prudent to place them in formalin and in the care of nuclear medicine for 24 hours after surgical excision.

Results

Studies of SLNs Prior to the Multicenter Trial

In preliminary studies in which SLN identification was always followed by complete lymph node dissection,[7] we evaluated 259 SLNs from 223 patients (average of 1.2 SLNs per individual). Tumor was identified in 47 (18%) of the 259 SLNs. Identification was done on H&E-stained sections in 83.2% and in the remainder (16.7%) on sections stained by immunohistologic techniques. Tumor cells occurred as single cells, small clumps of tumor cells, and larger colonies. We found tumor in a non-SLN in the absence of tumor in the SLN

in only 2 patients early in our experience. This situation has not been encountered subsequently, and it is likely that in these patients the SLN was not correctly identified.

We identified tumor-containing non-SLNs—usually 1, less often 2 or 3—in 33% of patients with positive SLNs. Tumor in non-SLNs is generally distributed as single cells or small microcolonies in the subcapsular sinus.

The Multicenter Selective Lymph Node Trial

These 446 patients represent the first patients of the trial, which will eventually enroll 1,600 patients. In this group, 860 SLNs were removed from 512 lymph node basins and 99 SLNs contained tumor (19% positive by lymph node basin). Tumor was identified in 85 nodes by H&E histology (86%) and in 14 nodes by immunohistology (14%).

Discussion

SLN technology has become widely adopted in the relatively few years since we described the technique in application to melanoma.[7] There is as yet no evidence that this approach is therapeutic. The technique certainly represents a considerable improvement in our ability to evaluate the tumor status of the regional lymph nodes for prognostication, spares many patients unnecessary surgery, and may be useful in selecting patients for adjuvant therapy. Information on the therapeutic relevance of the approach must await the outcome of the multicenter trial (in approximately 2003). Although the approach is conceptually appealing and the techniques seem simple from the surgical, pathologic, and nuclear medicine standpoints, there are clearly pitfalls.

One measure of the effectiveness of the approach will be the frequency with which metastases develop in the ipsilateral regional nodes after removal of a reportedly negative lymph node. We have encountered 6 such patients. Reexamination of the pathologic material and the clinical records of these individuals disclosed 3 patients in whom a tumor-positive SLN was incorrectly interpreted as negative by the pathologist. In 1 case scattered single tumor cells were missed. In 2 cases tumor was not visible on H&E-stained preparations. It is likely that if immunoperoxidase preparations had been used a correct interpretation would have been made in these cases. In 3 patients, despite extensive sampling of the purported SLN by H&E and immunohistochemistry techniques, no tumor was identified, making it likely that the surgeons did not correctly identify the SLNs in these patients.

Accurate determination of the tumor status of the SLN is clearly essential and depends on meticulous sampling of the node and the routine use of immunohistochemical preparations. The sampling technique that we recommend is, in our substantial experience with the approach, sufficient for the great majority of patients. In specific subsets of patients with unusually deep or thick melanoma or if the SLN is very large, additional sampling by cutting the node into serial 1-mm slices may be necessary.

The need to evaluate the role and significance of molecular biology in the analysis of SLNs is clear. Pathologists and surgeons should, however, be careful to avoid providing SLN tissue for scientific study in a manner that may compromise the diagnosis. It is inappropriate arbitrarily to provide portions of an SLN for research. We prefer to provide sections cut from the lymph node in serial fashion and interspersed with sections stained by H&E and immunohistologic techniques. This approach has the additional advantage that it facilitates interpretation of the results of the reverse transcriptase polymerase chain reaction assay by allowing close morphologic comparison.

SLN technology has much to offer melanoma patients in term of staging and may have a therapeutic role. The technology is being investigated and exploited in many different tumor systems, including breast cancer, colon cancer, and vulvar carcinoma. Pathologists have a key role to play in evaluating the effectiveness of the approach. Careful attention to sampling and interpretation of the SLNs is mandatory.

Although the lessons learned from our extensive experience with melanoma are likely broadly applicable to other tumor systems, we urge caution and care in developing the techniques for each individual cancer system.

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Nuclear Medicine Techniques in Sentinel Lymph Node Mapping

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Nuclear medicine techniques are extremely helpful in sentinel lymph node (SLN) mapping because they take advantage of the high level of sensitivity and accuracy of nuclear medicine imaging. Almost any radiolabeled agent can be used to perform lymphatic mapping; however, recently ^{99m}Tc-sulfur colloid has been used because of its particulate characteristics, which allow localization of radioactivity in a lymph node for a period of time that facilitates identification at surgery. With proper injection techniques, this agent flows rapidly to SLNs and has a long lymph node residence time. The lymph node radiation absorbed dose is relatively low, and the imaging energy of technetium 99m is optimal for visualization and high resolution with the gamma camera.

As with many other procedures, preparation and planning the injection for SLN mapping ensure a higher success in imaging SLNs. In both melanoma and breast cancer, good skin anesthesia is required, and the relationship of the injections to the primary tumor is an important consideration. Injection near infected or indurated areas, poorly healed scars, or hematomas will preclude adequate flow of the sulfur colloid. Avoiding these areas will ensure good flow and localization of the lymph node.

Nuclear medicine mapping procedures are helpful in planning surgery for both melanoma and breast cancer. In melanoma, not only the SLN but also additional in-transit nodes or SLNs in abnormal locations can be identified. Also, in mapping for truncal melanoma, bilateral drainage to 2 or more regional lymph node basins can occur, and image-guided identification of unusual sites of lymph node rests is of help in understanding the anatomy of the patient. Imaging melanoma scalp and facial lesions is particularly challenging, because the lymphatic flow is rapid and imaging often shows matted groups of nodes rather than single SLNs.

In breast cancer mapping, injection techniques depend on whether the lesion is palpable or nonpalpable, whether the patient has previously undergone excisional biopsy, and the length of time since previous surgery. These studies often require surgeons and mammographers to coordinate efforts, particularly in the case of nonpalpable lesions, which require needle localization for identification.

A variety of injection techniques can be used for lymph mapping in breast cancer. At our institution, we use approximately 1 mCi of technetium-filtered sulfur colloid in 6 mL total volume, followed by a 4-mL saline flush (in the case of needle localization). Imaging with the patient in the anterior lateral oblique position follows 3 minutes of gentle massage at the injection site to assist in dispersal of radioactivity into the SLNs. Anterior oblique images show the injection site as well as the entire axilla and lymphatic foci in the tail of the breast. The radioactivity in the node with the axilla exposed is carefully localized by means of a radioactive marker on the skin. Anterior images will also show whether there is internal mammary drainage from a breast primary lesion, which may provide information useful for planning radiation therapy fields and for predicting tumor spread to the contralateral breast. At our institution, for both melanoma and breast cancer studies, we employ a depth estimation measurement using a 45-degree angle image to mark the skin and determine the approximate depth of the lymph node, which may be of help at the time of surgical excision.

Use of the handheld radioactive probe has also facilitated identification of the SLN. In the nuclear medi

cine clinic, we use the handheld probe in both melanoma and breast cancer cases to confirm the location of the imaging-identified SLN for final marking before surgery. This use of the handheld probe also allows us to gauge the difficulties in node identification that will occur in cases in which the injection site is in close proximity to the SLN.

Radiation safety issues associated with the use of ^{99m}Tc-sulfur colloid include considerations regarding operating room (OR) and pathology laboratory personnel. No precautions are needed for shielding personnel, including pregnant women. However, OR personnel who are pregnant or intending pregnancy should consider working in another OR that day. Specimens of SLNs and other tissues that are radioactive must be labeled with the radioisotope amount and date. Often these specimens are handled by the pathologist the day after surgery when radioactive decay has occurred and the specimens no longer emit detectable levels of radiation. This time interval also allows optimal fixation of tissue samples for histopathologic examination.

Other considerations for nuclear medicine imaging in SLN mapping include adequate preparation by nuclear medicine physicians who perform the injection and imaging techniques. Surgeons who use radioactive techniques need to understand that if surgery has been delayed, lymph nodes other than the SLN may contain radioactivity. Skin marks overlying SLNs and imaging data can be very helpful in discriminating between SLNs and later-appearing downstream lymph nodes. However, if surgery is delayed, a delay of 18 hours, which is less than 4 half-lives of technetium 99m, still provides adequate levels of activity in the SLNs for surgical dissection with the use of the handheld probe. If there are any concerns regarding radiation safety issues or contamination of the work environment, the nuclear medicine physicians should be contacted immediately for advice on how best to handle the situation. Good communication between surgeons and nuclear medicine physicians is essential and results in better, more accurate detection of SLNs in a higher percentage of cases.

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Sentinel Node Dissection for Melanoma

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The controversy regarding the surgical management of regional lymph nodes in early-stage melanoma began over 100 years ago. In 1892 Herbert Snow advocated wide excision and elective node dissection (ELND) as a method of controlling metastatic permeation of the lymphatic system. His studies suggested a direct connection between the primary and the regional lymph nodes, and he indicated that the treatment of melanoma should routinely include excision of these nodes. Although multiple retrospective studies suggest a survival benefit for patients undergoing ELND in addition to excision of the primary melanoma, no randomized trial has demonstrated a survival benefit for this procedure. The interim analysis of the Intergroup Melanoma Surgical Program identified a subgroup of patients whose outcome apparently was improved by ELND,[1] but this finding has not helped resolve the confusion about the therapeutic benefit of removing clinically normal lymph nodes.

In 1977 Morton and colleagues introduced the technique of cutaneous lymphoscintigraphy as a method of identifying the drainage pattern from the site of a primary melanoma to the regional lymph node basin. By injecting a radiopharmaceutical at the primary site, nuclear medicine physicians could map the lymphatic channels and identify the regional basin at risk for metastases. This technique was instrumental for the development of sentinel lymphadenectomy.

At a scientific meeting in 1990, Morton and associates presented their initial experience with the detection of occult regional lymph node metastases by intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL). This technique, reported by them in the lit

Table 1—Success Rate of Sentinel Node Identification with Blue Dye Alone

Investigator, Year	*n*	Accuracy Rate (%)
Morton, 1992	223	82
Morton, 1993	72	90
Reintgen, 1994	42	100
Thompson, 1995	118	88
Karakousis, 1996	55	93
Lingam, 1997	35	100

erature in 1992,[2] enables the surgeon to map the direct route of lymphatic spread from a primary melanoma to the regional drainage basin and then to selectively excise the first (sentinel) draining lymph node(s) in this basin. Because the sentinel node (SN) is the most likely site of tumor cells in a regional drainage basin, focused pathologic examination of the LM/SL specimen is a useful method of ultrastaging the regional nodes. Complete lymph node dissection (CLND) is reserved for patients who are most likely to achieve a survival benefit from the procedure, that is, those with metastasis to the SN.

Operative Technique

Identification, excision, and examination of the SN is a multidisciplinary technique that requires expertise from the nuclear medicine physician, the surgeon, and the pathologist for accurate completion of preoperative lymphoscintigraphy, LM/SL, and pathologic characterization of the SN. The technique has been described in detail.[2]

Results

In their initial report of LM/SL,[2] Morton and associates at the John Wayne Cancer Institute described the feasibility of LM/SL in 223 patients. All patients underwent LM/SL performed using blue dye, followed immediately by CLND to verify the accuracy of LM/SL. SNs were identified in 194 (82%) of 237 lymph node basins. Metastases were found in at least 1 lymph node in 40 (21%) of these specimens. In only 2 (1%) of 194 lymphadenectomy specimens was the tumor status of the SN not indicative of the tumor status of the rest of the regional basin. The success rate of LM/SL was 82%, not acceptable by current standards but very impressive for a feasibility study.

In 1993 Morton's group reported their experience with 72 patients who underwent LM/SL for melanoma of the head and neck region.[3] Routine use of preoperative lymphoscintigraphy and increased experience with the technique yielded an accuracy rate of 90%. The first independent group to confirm these findings was Reintgen and associates from the Moffitt Cancer Center.[4] In their study, 42 patients underwent preoperative lymphoscintigraphy and dye-directed LM/SL. A blue-stained lymph node (SN) was found in each basin (100% accuracy). Of the 8 patients with tumor-positive SNs, 7 (88%) had no other positive nodes in the drainage basin. None of the remaining 34 patients had metastases in sentinel or nonsentinel nodes. These findings reconfirmed the importance of performing preoperative lymphoscintigraphy in all patients, regardless of the site of the primary melanoma.

Thompson and colleagues from the Sydney (Australia) Melanoma Unit reported their initial experience with preoperative lymphoscintigraphy and LM/SL.[5] The 118 patients had 120 drainage basins at risk. Blue-stained SNs were located in 105 (88%) basins, and the SN was the exclusive site of tumor in 18 (82%) of the 22 basins with metastatic disease. Their 1.9% false negative rate was similar to that reported by Morton's group.[2,3] Thompson and colleagues confirmed the learning curve associated with LM/SL: SNs were identified in 74% of cases in the first half of their experience, compared with 92% during the second half.

Other investigators have reported their experience with LM/SL using blue dye alone (Table 1). Most had no prior experience with LM/SL but achieved an accuracy rate of at least 90%. Their rapid mastery of the technique was made possible by the seminal studies of Morton and other early pioneers of LM/SL. However, dye-directed mapping remains a technically challenging procedure with a relatively shallow learning curve. To improve the accuracy of LM/SL and steepen its learning curve, a number of investigators have used radiopharmaceuticals to map lymphatic drainage to the SN. We reported our initial experience with radiolymphoscintigraphy in 1994.[6] Thirty-two patients underwent LM/SL performed using a combination of blue dye and radiopharmaceutical. The dye was visually followed; the path of the radiopharmaceutical was tracked with a handheld gamma probe. We found 90% concordance between blue-stained and radioactive SNs.

Probe-directed lymphatic mapping is technically straightforward and has great appeal; its disadvantage is lack of standardization. Most important, there is no agreement on the definition of a radioactive SN (Table 2, page 10). Our own data suggest that the in vivo count ratios for blue-stained lymph nodes can vary almost 100-fold, even when surgery is always performed within 4 hours after injection of the radiopharmaceutical.[7] A second problem is the lack of an ideal mapping agent. Larger radiopharmaceutical particles such as ^{99m}TC-sulfur colloid and albumin colloid should be trapped in the afferent lymphatics of the SN, yet some of these particles are shunted through to adjacent lymph nodes. Smaller particles such as ^{99m}TC-labeled human serum albumin pass quickly from the primary to the SN and then to adjacent non-SNs. Moreover, the transit time of

Table 2—Definitions of a Radioactive Sentinel Node

Investigator, Year	Definition
Krag, 1995	15 counts/10 s and in vivo count ratio ≥ 3
Pijpers, 1995	Lymph node with highest counts
Mudun, 1996	300–3,000 counts/10 s and in vivo count ratio ≥3
Albertini, 1996	In vivo count ratio ≥ 2 or ex vivo ratio to nonsentinel node ≥ 10:1
Bostick, 1998	In vivo count ratio ≥ 2 compared to irrelevant background

each agent varies. The ideal radiopharmaceutical for LM/SL would travel quickly from the primary site to lodge permanently in the SN without leaking to adjacent lymph nodes. Until the kinetics of the radiopharmaceuticals are better defined for LM/SL or better agents are developed, we recommend that these agents not be employed alone for LM/SL.

In fact, most investigators now use both the blue dye and radiopharmaceuticals for LM/SL. Preoperative lymphoscintigraphy is performed on the same day as surgery, using the same radiopharmaceutical that is subsequently tracked intraoperatively with the handheld gamma probe. At the time of surgery this probe directs the surgeon to the blue-stained SN. Occasionally the probe will lead the surgeon to an unexpected secondary blue-stained lymph node. Visual identification of a blue-stained lymph node remains the gold standard for this procedure.

The technique of LM/SL has been shown by a number of investigators to be a reliable indicator of the tumor status of the regional lymph nodes. Based on these studies, LM/SL has become a popular alternative to conventional ELND and has become almost standard procedure for staging the regional lymph nodes. Our group recently performed a matched-pair analysis of 534 patients that demonstrated that LM/SL is therapeutically equal to ELND and has similar strengths as a procedure for staging the regional lymph nodes.[8] The true false negative rate of LM/SL is probably less than 5%.[9]

Two major studies are examining the utility of LM/SL. In 1994 Morton and colleagues at the John Wayne Cancer Institute initiated an international multicenter randomized prospective trial comparing wide excision and LM/SL with wide excision alone in patients with AJCC stage I and II melanoma. Eligible are patients with intermediate-thickness (1- to 4-mm) melanomas who have not undergone wide excision (>1.5 cm margins), skin grafting, or other procedures that would alter the lymphatic drainage. CLND is performed only in lymphatic drainage basins containing tumor-positive SNs. The primary aim of this study is to determine the therapeutic benefit of LM/SL and the true accuracy of the technique from a multicenter basis. As of May 1999, 1,200 of the anticipated 1,600 patients had been enrolled in the study.

The Sunbelt Melanoma Trial is a prospective randomized study examining the therapeutic value of completion lymphadenectomy and interferon-α (Schering-Plough, Kenilworth, NJ) for patients whose SNs contain tumor cells identified by conventional hematoxylin-eosin staining, immunohistochemical techniques, or reverse transcriptase polymerase chain reaction. The organizers of this study anticipate that this trial should provide further insight into the therapeutic value of LM/SL.

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Preoperative Considerations and Operative Technique: How to Do It

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Introduction

The objective of melanoma lymphatic mapping is to accurately determine the histologic status of the regional lymph node basin in newly diagnosed stage I and II patients. Through this technique, the first draining lymph node(s), the sentinel nodes, can be identified, removed, and then subjected to careful pathologic examination. This minimally invasive technique promotes a selective approach to lymphadenectomy, allows the application of therapeutic node dissection early in the course of disease, and provides valuable staging information. Previous studies evaluating the accuracy of sentinel node biopsy have determined that this first node of drainage is clearly the most likely to contain disease if occult nodal metastases are present.[1–4] Therefore, it is central to the success of this approach that the sentinel node be reliably and correctly identified.

Historically, sentinel node identification was accomplished by intradermal injections of isosulfan blue dye around the primary tumor. This technique relied upon visual cues to localize the sentinel node within the nodal basin. Initial studies evaluating this technique reported sentinel node identification rates in 80% to 90% of patients evaluated.[1,2,4] Evolution of the technique to include injections of radiolabeled colloid, together with a gamma probe detection device, in addition to intraoperative injection of blue dye, has improved sentinel node identification rates to virtually 100%.[5–8] The present paper describes our own institutional approach that integrates formal preoperative lymphoscintigraphy, radiolabeled colloid injections the day of the surgery, intraoperative injections of isosulfan blue dye, and sentinel node localization.[9] While this multidisciplinary approach is consistent and reproducible, some variations may be applied, depending on anatomic location of the primary tumor and its proximity to the draining lymph node basin.

Candidates and Preoperative Assessment

One of the following primary tumor criteria is used for considering application of this technique: (1) more than 1 mm in thickness; (2) Clark's level greater than III; (3) the presence of ulceration; or (4) significant histologic regression. Eligible patients are clinical stage I or II (N0). Any suspicious lymph node enlargement in a potential draining nodal basin should be evaluated by a needle biopsy directed by palpitation or ultrasound prior to sentinel node biopsy. The accuracy of lymphatic mapping is unknown in the patients who have undergone a definitive wide local excision of the primary tumor rather than a diagnostic excisional biopsy, since the lymphatic drainage of the remaining skin may be different from that of the original lesion, possibly resulting in an incorrect sentinel node identification.

Preoperative Lymphoscintigraphy

The purpose of cutaneous lymphoscintigraphy is threefold: (1) to identify nodal basins at risk in patients who have primary melanomas in anatomic sites where ambiguous drainage is predicted (truncal and head and neck locations), or, for lesions distal to the knee and elbow, to identify drainage to the popliteal and/or epitrochlear regions, respectively; (2) to determine the number and location of sentinel nodes within the basin; and (3) to identify the presence of intransit sentinel lymph nodes located outside the formal lymph node basin.

Lymphoscintigraphy is performed with a 4-point intradermal injection using approximately 1 mCi of technetium-labeled sulfur colloid or human serum albumin. Following the injection, the material is traced, with frequent images, to potential nodal basins at risk.[10] When the injection sites are some distance from the nodal basins, the information obtained from the lymphoscintigram is generally straightforward. However, when the injection sites overlie a basin, in at least one plane, clear identification of sentinel node localization may be difficult and, at times, impossible. Multiple views must then be obtained to image the intense radioactivity in a different plane in the hope of unveiling the location of the sentinel nodes.

Occasionally, the injected colloid will not migrate from the injection site when the lymphoscintigraphy is attempted soon after an excisional biopsy. A repeat attempt should be undertaken, waiting approximately 1 week to 10 days to allow the surrounding inflammation to resolve.

We generally obtain a formal lymphoscintigram remote from the planned day of surgery to allow appropriate surgical planning. However, when the formal lymphoscintigraphy is performed on the morning of the definitive surgery, the same radioactive material injected for the lymphoscintigraphy can be used for the intraoperative gamma probe-directed localization, therefore, avoiding a second colloid injection. It is important to note that if the formal lymphoscintigraphy is performed on the day of the surgery, human serum albumin cannot be used, as this agent will migrate very quickly to the sentinel node and then pass on to other secondary echelon nodes. In this situation, the lymphoscintigraphy should always be performed with sulfur colloid.

Intraoperative Localization and Sentinel Node Biopsy

We generally use a combination of blue dye and hand-held gamma probe localizations. On the day of surgery (1 to 4 hours prior to initiation of the surgical procedure), the patient is taken to the Nuclear Medicine Department and given a 4-point intradermal injection of 0.5 to 1 mCi of unfiltered technetium-labeled sulfur colloid. A shortened interval may decrease the ability to localize the sentinel node, because not enough time will have elapsed to allow passage of the colloid particles to the nodal basin. Significantly longer waiting periods may allow time for the colloid to pass onto secondary echelon nodes, leading ultimately to the unnecessary removal of multiple lymph nodes. Studies, however, demonstrate that delays of up to 4 hours will not result in significant pass through to secondary echelon nodes.[7] Using this approach, the radioactive ratios of sentinel to non–sentinel nodes approach 100 to 1. Scanning the patient with the probe while the patient is still in the holding area can help in the decision as to when to bring the patient to the operating room.

Upon entering the operating room, the hand-held gamma probe is used to transcutaneously scan the primary injection site, the intervening soft tissues, and the nodal basin. The location of the sentinel nodes are determined and marked with an "X" on the skin. The blue dye (Lymphazurin) is then injected intradermally circumferentially around the intact primary melanoma or excisional biopsy site. Approximately 2 to 3 mL of dye is injected, using a tuberculin syringe and a 25- or 27-gauge needle. The patient is then appropriately prepared and draped, which allows adequate time for the dye to travel from the injection site to the nodal basin. Local anesthesia, along with intravenous sedation or general anesthesia, is usually employed. The type of anesthesia used depends more on what is necessary to perform the appropriate wide local excision rather than the sentinel lymph node biopsy. The nodal basin is approached first with a small biopsy incision directed by the hand-held gamma probe. We make sure that this biopsy incision can be easily incorporated into a formal lymphadenectomy incision, if that is required. Once the nodal basin is entered, the localization of the sentinel node is achieved either by following a blue channel toward the blue node or by direct visualization of the lymph node guided by increasing counts detected by the gamma probe. The visualization of the blue dye is helpful in rapidly identifying which lymph node has accumulated the radioactive colloid. This node is then elevated from the surrounding tissues. Intervening lymphatic channels, identified because of the blue dye, are tied to avoid a seroma collection. The node is removed, and ex vivo counts in the node are then recorded in the chart, on a data form, and on the pathology sheet. The lymph node is visually inspected for the presence of macroscopic metastasis or pigment. If the node is clinically normal on macroscopic examination and lacks pigment upon bisecting the lymph node, no frozen sections are performed.

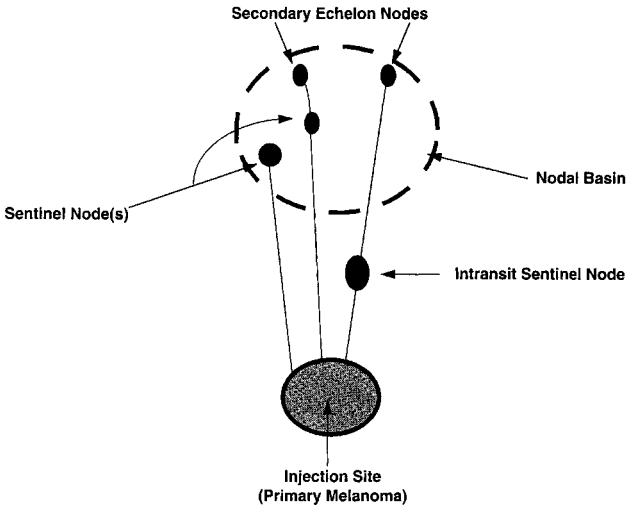
After the initial node is removed, the nodal basin is then scanned for residual radioactive counts with the hand-held gamma probe. If additional areas of increased radioactivity above background are identified, more than one sentinel node exists. If the background activity in the nodal basin is still high because of the close proximity of the injection site to the nodal basin, we will then proceed with the wide local excision of the primary site. This procedure removes any significant background and allows a more accurate evaluation of residual counts within the nodal basin and intervening tissues. Additional nodes identified by the presence of high radioactivity are then removed and labeled as sentinel nodes, with numbers assigned sequentially in the order of identification.

The sentinel node biopsy cavity is then irrigated, checked for meticulous hemostasis, and closed. In general, placement of a drain is not required, as little disruption of the lymphatic tissue is performed, particularly when the hand-held gamma probe is used.

While the technique as described can be straightforward, the following problematic issues are worthy of discussion:

1. Close Proximity of the Injection Site to the Nodal Basin

The amount of radioactive material that remains at the injection site is significantly greater than the amount that travels to the sentinel node. Therefore, when the injection site is close to the nodal basin, the amount of radioactivity at the periphery of the injection can mask or obscure the ability to localize an area of increased radioactive material within the nodal basin. For example, if the periphery of the injection site has 10,000 counts/second, and the sentinel node in the nodal basin only has 8,000 counts, it will be impossible to discrimi



Schematic presentation of the injection site in relation to the nodal basin and the sentinel nodes.

nate the sentinel node from the injection site. If we are unable to localize a sentinel node transcutaneously prior to making an incision, we will make one attempt at visually identifying the sentinel node with the blue dye. If the node cannot be identified quickly, we will then excise the primary injection site to remove the high background counts. In this way, counts accumulated within the sentinel node can be unveiled and more easily detected with the gamma probe. Thoughtful positioning of the patient in the operating room is essential to facilitate gamma probe orientation away from the injection site to minimize the background activity detection ("shine through") as well as to perform nodal basin exploration, wide excision, and scanning of the intervening tissues without changing positions.

2. Head and Neck Locations

Because of the proximity to important structures, the excision margins of primary lesions of the face have to be limited. If it is anticipated that the area of skin that will be blue-stained cannot be completely removed with the excision of the primary tumor, then colloid injections will be used alone. Residual dye left behind can tattoo the skin for long periods of time. To avoid this event, the margin of excision and exact surgical incision planned will be specifically delineated prior to dye injection. Dye injection can then be performed within the boundaries.

3. Identification of Intransit Sentinel Nodes

In specific anatomic locations, such as the trunk, 5% to 10% of the time, a lymph node(s) may be identified on a preoperative lymphoscintigraphy outside the formal lymph node basin (between the primary injection site and the nodal basin). This lymph node may be the first node of drainage for certain areas of the skin and may therefore represent the sentinel node. A similar situation occurs in the extremities, either distal to the elbow or knee, where the first draining lymph node could be in either the epitrochlear or the popliteal region, respectively. One lymphatic vessel may drain from the injection site to this first intransit node before traveling on "in series" to the formal nodal basin. However, more than one channel may be identified from an injection site: one traveling to an intransit node and then another channel traveling "in parallel" directly to the regional nodal basin. In that situation, both the intransit node and the node within the nodal basin represent sentinel nodes and must therefore be identified and removed (Figure). The best way to identify these lymph nodes is: (*a*) to know that they exist and may or may not be identified on lymphoscintigraphy; and (*b*) to remove the injection site after a lymph node is identified in the nodal basin and then to scan the intervening tissues with a handheld gamma probe. Removal of the primary injection site will help detect these intransit nodes by eliminating the background radioactivity.

It is important to remember that the sentinel node is defined as the first node(s) of drainage from a primary injection site through an afferent lymphatic channel. However, sometimes the first node that is encountered and visualized by the blue dye may not necessarily be the first node of drainage or the only sentinel node. The dye and some of the radioactive colloid can travel through the sentinel node into secondary echelon nodes. The first lymph node encountered may actually be a secondary echelon node draining "in series" from a deeper or more proximal sentinel node (Figure). The true sentinel node or another sentinel node may be difficult to identify by visual inspection alone. After removing the initial blue node that was encountered, the use of the hand-held gamma probe ensures that a sentinel node is not left behind. The surgeon will be alerted by the residual radioactivity present in the nodal basin after removal of the secondary echelon node or after removing one sentinel node if more than one sentinel node is present.

Conclusions

Successful lymphatic mapping and sentinel node biopsy is not a simple undertaking and requires the sophisticated integration of a multidisciplinary team. The information obtained from this technique is extremely valuable and, therefore, improper implementation is a disservice to the patient.

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Preoperative Considerations and Operative Technique: How to Do It

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Preoperative Considerations and Operative Technique: How to Do It

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Use of elective lymph node dissection (ELND) for melanoma assumes that the first site of melanoma metastases is the regional lymph nodes and that early removal of these nodes will halt the metastatic cascade. ELND has become increasingly controversial as a therapeutic procedure, and its cost, morbidity, and overall low yield of tumor-containing nodes make it impractical for routine use as a staging procedure. Unfortunately, there are no good nonsurgical alternatives to determine the tumor status of the regional nodes. Clinical examination and needle aspiration lead to an unacceptably high rate of false negatives. Cutaneous lymphoscintigraphy can demonstrate the drainage patterns of the primary to the regional nodes but cannot differentiate tumor-containing nodes from reactive or normal nodes. Computed tomography and magnetic resonance imaging can identify nodes larger than 1 cm in size but are not specific for malignancy. Positron emission tomography is a promising staging technique, but its cost and low yield for small tumor deposits make it impractical for detecting microscopic disease in lymph nodes.

In recent years, the detection of occult regional lymph node metastases has been improved by intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL).[1] This technique enables the surgeon to map the direct route of lymphatic spread from a primary melanoma to the regional drainage basin, and then selectively excise the first (sentinel) draining lymph node(s) in this basin. Because the sentinel node (SN) is the most likely site of tumor cells in a regional drainage basin, focused pathologic examination of the LM/SL specimen is a useful method of ultrastaging the regional nodes. Complete lymph node dissection (CLND) is reserved for patients who may benefit from the procedure, that is, those with metastasis to the SN. LM/SL can be performed with minimal morbidity and expense, and it has proved to be highly accurate and sensitive for detecting occult regional metastases in patients with early-stage melanoma.

Patient Selection

Patients eligible for LM/SL are those who would normally be considered for ELND. Patients with clinical or radiologic evidence of metastases should not undergo LM/SL. Also ineligible are patients who have undergone wide excision of the primary with margins of 1.5 cm or more and patients who have undergone any procedure that disrupts the lymphatic drainage to the regional basin.

The anatomic site and histopathologic features of the primary melanoma and the patient's sex and age are used to identify candidates for LM/SL—those who have a high risk of lymph node metastases without distant disease.[2] Histopathologic features of the primary include Clark level, thickness, ulceration, regression, and histologic subtype.

Operative Technique

LM/SL is a multidisciplinary technique that requires expertise from the nuclear medicine physician, the surgeon, and the pathologist for accurate completion of preoperative lymphoscintigraphy, intraoperative LM/SL, and pathologic examination of the SN.

Preoperative Lymphoscintigraphy

Lymphoscintigraphy is used to determine the regional lymph node basin at risk for metastases and is particularly helpful for sites on the head and neck or torso, which may have ambiguous lymph drainage patterns.[3] In the United States the most commonly employed agents are technetium-labeled albumin colloid (Cis-US, Bedford, MA), ^{99m}Tc-labeled sulfur colloid (Cis-US), and ^{99m}Tc-labeled human serum albumin (Amersham Medi-physics, Arlington Heights, IL). Approximately 18.5–30 MBq (500–800 μCi) of radiopharmaceutical is injected intradermally at the primary melanoma. A scintillation camera is used to document the drainage pattern from the primary via the dermal lymphatics to the regional nodes. The skin overlying the SN is marked. Because there is some variation in the transit time of the various radiopharmaceuticals, the nuclear medicine physician performing the procedure must be careful to differentiate the SN from non-SNs. In our experience at the John Wayne Cancer Institute, the SN can be identified within 30 minutes after injection of the radiopharmaceutical (depending on the agent and the distance from the primary to the regional nodes), and usually by 4 hours the SN can no longer be differenti

ated from adjacent non-SNs.[4] We typically perform lymphoscintigraphy on the day of surgery so that the radiopharmaceutical injected preoperatively for lymphoscintigraphy can be tracked intraoperatively by the gamma probe.

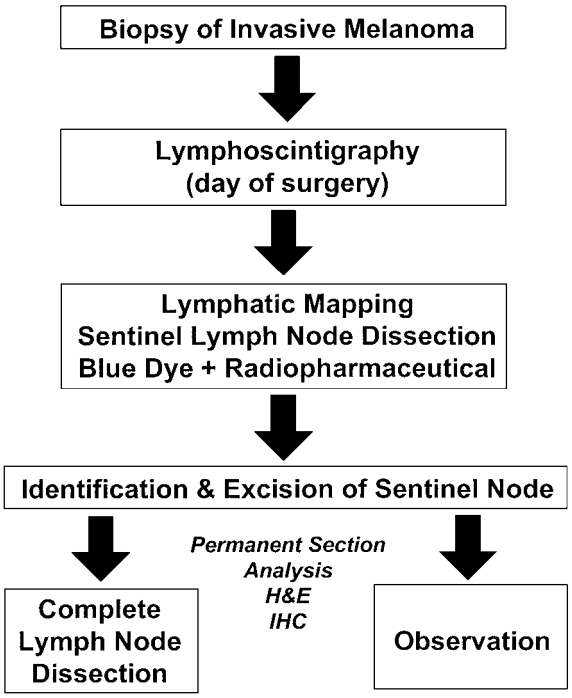
LM/SL

After induction of local or general anesthesia, 0.5–1.0 mL of isosulfan blue dye (Lymphazurin, Hirsch Industries, Richmond, VA) is injected intradermally using a 25-gauge needle at the site of the primary melanoma. If the primary lesion has already been excised, the injection is made on either side of the scar. An incision is made over the regional lymph node basin and oriented so that CLND can be performed if needed. The skin flap closest to the primary is dissected free of underlying tissue and the subdermal lymphatics are observed as they and the SN turn blue. The blue dye typically takes 5–20 minutes to reach the regional nodes; the longer the distance between the primary and the regional lymph node basin, the longer the transit time. Injections are repeated every 20 minutes during the procedure. Use of the handheld gamma probe leads in most cases to a blue-stained SN and can decrease the time needed to identify blue-stained SNs and facilitate localization of the occasional secondary SN.[5] The SN is excised and evaluated for the presence of metastases. If metastases are demonstrated, complete CLND is performed at a later date.

Pathology

Occult regional metastases are identified by both standard hematoxylin-eosin (H&E) staining and newer immunohistochemical techniques. In our original experience of 223 patients undergoing LM/SL followed by CLND, 57% of nodal metastases were found using conventional techniques; the remainder were identified by immunohistochemical staining alone.[1] The 3,338 lymph nodes excised in these patients were stained with the melanoma-specific murine monoclonal antibodies S-100 and NKI/C3 to confirm the presence of melanoma cells. Examination of serial sections of the nodes identified only a few more metastases than did examination of bivalved faces; the role of additional sectioning of the SN is unknown. Using immunohistochemical staining techniques with an antiserum to S-100 protein, Cochran and associates[6] previously demonstrated that 14% of lymph nodes harvested by ELND and that stained negative with H&E actually contained metastatic melanoma. Most laboratories now routinely use both H&E and immunohistochemical techniques for examining SNs. Newer molecular biology techniques based on melanoma-specific gene sequences may further enhance the sensitivity of detecting metastases in the SN, but their role in the routine management of melanoma is not clear at this time.

The blue-stained afferent lymphatics and nodes can be difficult to identify, especially because most surgeons have little experience in the dissection of lymphatic channels. Success requires practice. During their initial 58 cases, Morton's group[1] identified only 81% of blue-stained SNs; however, during the next 58 cases, the rate of SN identification increased to 96%, and it now approaches 100%. In their study, the early success rate was 96% for the surgeon with the most LM/SL experience, compared with 72% for the surgeon with the least experience ($P < 0.01$). We believe that a surgeon should successfully complete approximately 30 cases of LM/SL before undertaking this technique without routine CLND. Routine use of radiopharmaceuticals for LM/SL has shortened the learning time and has made LM/SL more applicable for general use. Preoperative lymphoscintigraphy is used in all cases and has played a significant role in decreasing the incidence of missed SNs (Figure). Most surgeons can master blue dye– and probe-directed LM/SL during a 30-case learning phase, but the overall success of the procedure requires a team effort by the surgeon, the nuclear medicine physician, and the pathologist.[8]



Schematic for proposed method of intraoperative lymphatic mapping and sentinel lymphadenectomy for melanoma.

Summary

LM/SL is an alternative to the traditional management of patients with early-stage melanoma. The technique has been demonstrated to be highly accurate for detecting metastases in the regional lymph nodes. The

success of LM/SL depends on the cooperative efforts of the surgeon, the pathologist, and the nuclear medicine physician. A standard approach should be adopted by each center to ensure consistently accurate results.

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Accurate Staging of Colorectal Cancer by Sentinel Lymph Node Mapping: A Prospective Study

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Colorectal cancer is the third most common cancer and the second leading cause of cancer death in the United States, with an estimated 131,600 new cases diagnosed in 1998, causing about 56,500 deaths.[1]

One of the most powerful and predictive prognostic factors for survival in CR cancer is the status of metastases in the regional lymph nodes. The presence of lymph node metastases decreases the 5-year survival rate by approximately 25%–30%. Adjuvant chemotherapy in these patients results in a reported reduction in cancer-related mortality by approximately one-third.[2] About 55% of patients with colorectal cancers initially present with American Joint Committee on Cancer (AJCC) stage I or II disease. Such patients with localized disease are usually not treated with adjuvant chemotherapy outside a protocol, owing to lack of supporting data for survival advantage in most published series. Nonetheless, about 20%–30% of patients with so-called localized disease (AJCC stages I or II) develop systemic metastases within 5 years of diagnosis. The cause of such systemic spread in patients initially presenting with localized early-stage disease may be multifactorial. It is reasonable to believe that failure of accurate pathologic evaluation to identify micrometastases in the lymph nodes may contribute to such failure. The standards of pathologic examination of lymph nodes for metastases vary greatly between individual pathologists and institutions. Unless meticulous examination of all lymph nodes is performed, micrometastases may be missed. Thus, patients with missed lymph node metastases may not receive adjuvant chemotherapy, which affects their survival. The sentinel lymph node (SLN) is the first node (or nodes) draining the primary tumor site and has the highest potential to harbor micrometastases, when present.[3] The concept of SLN identification at the time of operation was first proposed by Cabanas in 1977 in patients with carcinoma

of the penis.[4] Since then, Morton and colleagues have shown that in patients with malignant melanoma, the status of the SLNs reflects the histologic features of the remainder of the lymphatic basin with greater than 90% accuracy.[3] This observation has been confirmed by several other studies conducted at many institutions throughout the world.

Numerous publications over the past 5 years have evaluated the feasibility and potential benefits of SLN mapping in melanoma and breast cancers.[5–7] The identification of 1 or 2 such SLNs allows the pathologist to perform meticulous histologic and immunohistochemical studies on multilevel microsections of these nodes. The application of such extensive evaluation to all the lymph nodes in the resected specimens would be extremely costly. SLN mapping is already influencing therapeutic decision making in patients with malignant melanoma and breast cancers. Whether upstaging of disease by such detection of submicroscopic metastases will eventually lead to an increase in survival remains to be seen. To my knowledge, no study has been published in the English literature on the use of SLN mapping for colorectal cancers.

Personal Series

For the first time in the United States, my group has performed a prospective study for SLN mapping in 70 consecutive patients with colorectal cancer. The purpose of the study was fourfold: (1) to determine the feasibility of SLN mapping using isosulfan blue dye (Lymphazurin 1%, Ben Venue Labs, Bedford, OH), (2) to assess the accuracy of SLNs in determining the status of regional nodes, (3) to identify any aberrant or unusual mesenteric lymphatic drainage pattern, and (4) to assess the limitations of the SLN mapping technique in colorectal cancers.

Patients and Methods

From October 1996 through September 1998, 70 consecutive patients with a diagnosis or suspicion of colon or rectal cancers were prospectively entered into the study. There were 31 male and 39 female patients, with ages ranging from 36 to 95 years (mean, 71 years). Preoperative evaluation for all patients included a history and physical examination; routine laboratory studies, including liver function studies and determinations of carcinoembryonic antigen (CEA) and CA 19-9 levels; colonoscopy; and computed tomography of the abdomen and pelvis. At operation the abdomen was explored in standard fashion. In all patients, the surgeon had a prior knowledge of the approximate site of the primary tumor. The tumor-bearing area for the colon, rectosigmoid, and upper two-thirds of the rectum were mobilized, where necessary without violation of the mesenteric peritoneum. With a tuberculin syringe, 0.5–1 mL of Lymphazurin 1% was injected subserosally around the palpable lesion in 4 quadrants, without injection into the lumen. For low rectal lesions the dye was injected around the tumor visualized through a proctoscope using a spinal needle. Isosulfan blue dye is primarily concentrated in the lymphatics and thus delineates the lymphatic drainage pattern of the tumor by staining the lymph nodes blue.

The first 1–3 nodes nearest tumor that turned blue were considered the SLNs. Usually within 5 minutes after the injection, the first 1–3 blue-staining lymph nodes were identified. These nodes were marked with suture as the first, second, and third SLNs and were not immediately removed. Thereafter, a standard surgical resection of the colorectal cancer along with regional lymphadenectomy was performed according to established oncologic principles.

Surgical specimens were received in the pathology laboratory in a fresh state. Suture-tagged SLNs were dissected free from the surgical specimen and were grossly sectioned at 3-mm intervals and totally embedded for microscopic sectioning. The remainder of the specimen was fixed in formalin and dissected for pathologic evaluation by standard methods; pericolic adipose tissues were typically postfixed in Carnoy's fluid to aid in the recognition and recovery of all non-SLNs. Paraffin-embedded tissues were sectioned at a thickness of 4 μm and were stained with hematoxylin-eosin (H&E). For each SLN, 10 sections at representative levels were obtained by step-sectioning the blocks at approximately 40-μm intervals; these cuts included a section immunostained for the demonstration of low-molecular-weight cytokeratins (AE-1; Ventana Medical Systems, Tucson, AZ). In selected cases sections were also immunostained for CEA.

Results

Of the 70 patients in the study, 61 had colon cancer and 9 had rectal cancer. SLNs were successfully identified in 69 (98.6%) of the 70 patients. A total of 1,116 lymph nodes were examined (mean, 16 per patient), of which 108 lymph nodes (mean, 1.6 per patient) were designated as SLNs. One SLN was identified in 35 patients, 2 SLNs were identified in 29 patients, and 3 SLNs were identified in 5 patients. The analysis that follows is based on results in 69 patients, in all of whom at least 1 SLN was identified.

In 42 (95%) of 44 patients, the SLNs were negative for metastases. All other non-SLNs in these patients also were without metastases. In 25 patients (36%), SLNs were positive for metastases; in 14 of these 25 patients the non-SLNs also were positive. In 11 patients (16%), micrometastases were found in 1 or more sections of the first SLN, with all non-SLNs being negative. In 6

patients (9%), micrometastases were identified in only 1 of the 10 sections of a single SLN. In 4 of these 6 patients, micrometastases were detected using H&E and immunohistochemistry, but in 2 they were detected only with immunostains.

The incidence of skip metastases was 7%. The only failure of SLN identification occurred in a patient with low rectal cancer who had undergone preoperative chemotherapy and radiation therapy. Unlike in melanoma and breast cancer patients, no radionuclide dye or gamma probe was used, with a cost of only $31 per vial of dye.

The specificity of SLN mapping for colorectal cancer in our series of 70 patients was above 98%, with a high accuracy in 67 (96%) of 70 patients. In 6 patients micrometastases were identified in only 1 of the multilevel microsections of a solitary SLN; these cases thus are true cases of micrometastasis. These micrometastases most likely were discovered because of meticulous examination of the SLN by the examining pathologist, so that disease could be truly upstaged from AJCC stage I/II to stage III.

Conclusion

Many authors have confirmed the high efficacy of SLN in correctly predicting the disease status of the lymph node basins in patients with malignant melanoma and breast cancer.[5–8] The role of lymphadenectomy in the management of invasive melanoma and breast cancer in patients with negative SLNs is currently being evaluated by 2 large multiinstitutional studies, the results of which will not be available for a few years. Multiple studies have shown the high accuracy of SLN mapping in aiding the correct diagnosis of micrometastases in regional lymph nodes of patients with malignant melanoma and breast cancer.[5–8] No such prospective study has yet been published in the English literature on patients with colorectal cancers; hence, this is the first report on the feasibility of SLN mapping in patients with colorectal cancers. We confirm that as in melanoma and breast cancer, SLNs can be localized in a high (>98%) number of cases with a high degree of accuracy (96%) in colorectal cancer patients. The only failure of identification of an SLN in a patient with low rectal cancer may have been caused by submucosal fibrosis of the lymphatics resulting from neoadjuvant radiation therapy. Despite the technical difficulty associated with peritumoral injection of dye in rectal tumors, SLN mapping was successful in 8 (89%) of 9 patients with rectal cancer in this series; SLN mapping was successful in 100% of 61 patients with colon cancers. In our experience, slightly more mobilization prior to dye injection was needed for tumors located in the midrectum. Thus, the limitations of this technique in colorectal cancer may include previous radiation therapy, previous surgery, and anatomic location of the lesion in the lower two-thirds of the rectum.

In both melanoma and breast cancer, lymphoscintigraphy and the blue dye technique have been used in combination for optimal SLN mapping in most reported series. No radionuclide material was used for SLN mapping in our colorectal cancer patients, so the material cost was only $31 per vial of the dye per patient.

The success of SLN mapping in melanoma and breast cancers has correlated well with the experience of the surgeons,[3–5] with a steeper learning curve for surgeons treating patients with breast cancers. A much shorter learning time is anticipated in learning the SLN mapping technique for colorectal cancers because of the ease of identifying the blue node and most general surgeons' relative familiarity with performing routine colorectal surgery.

The ultimate aim of SLN mapping in patients with early-stage melanomas and breast cancers is to avoid routine radical lymphadenectomy. We did not establish a goal of limited lymphadenectomy in our study. At this point we cannot recommend any technical deviation from the standard oncologic resection for colorectal cancer, based on our initial data. Our study further confirmed that SLNs allow the pathologist to perform more meticulous examination of 1–3 nodes with multilevel microsections and immunohistochemistry. This ability definitely enhanced the diagnosis of nodal micrometastases in some (16%) patients that would have been missed on routine histologic evaluation. Patients whose disease is upstaged on discovery of micrometastases can be offered further adjuvant chemotherapy, with improved survival.[2]

In summary, the advantages of SLN mapping in colorectal cancer include the simplicity of the technique, high accuracy, low cost, aid to the pathologist to focus attention on 1–3 nodes for more detailed analysis, and possibly upstaging of disease in some patients. A larger multiinstitutional study is needed to evaluate the potential implications of using SLN mapping in colorectal cancer patients for appropriate therapeutic planning and to determine its impact on survival.

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Session II

Moderator:
Armando E. Giuliano, MD, FACS
Santa Monica, CA

Wednesday, October 13, 1999
1:30–5:30 pm

Sentinel Lymph Node Dissection for Breast Cancer

Monica Morrow, MD, FACS
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Learning Objectives

1. Identify advantages of sentinel node biopsy compared with those of standard management of axillary nodes with dissection.
2. Be familiar with available data on accuracy of sentinel node biopsy for axillary staging.
3. Recognize contraindications to sentinel node biopsy.
4. Be aware of areas where more data are needed before defining the final role of sentinel node biopsy.

Outline

I. Rationale
   - A. Sequelae of axillary dissection
   - B. Inability to reliably identify node-negative patients with patient/tumor factors
   - C. Potential therapeutic benefit of axillary dissection

II. Proof of principle: Studies of sentinel node dissection followed by axillary dissection
   - A. Inability to identify a sentinel node, 2%–10%
   - B. False-negative rate, 1.7%–11.0%

III. Unresolved issues
   - A. Drainage to nodal basins other than the axilla
   - B. Need for completion axillary dissection
   - C. Standardization of technique
   - D. Learning curve

Rationale

The increasing use of breast-conserving therapy has eliminated the major morbidity of the loss of the breast, focusing much greater attention on the sequelae of axillary dissection. For many women, this dissection has become the major cause of long-term morbidity after the local therapy of breast cancer.

Although major complications of axillary dissection are rare, minor complications are frequent and include seroma formation, shoulder dysfunction, loss of sensation in the distribution of the intercostobrachial nerve, and edema of the arm and breast. When carefully sought, arm problems are seen in as many as 20% to 40% of patients one year postoperatively.[1]

Efforts to reproducibly identify a group of patients with a risk of nodal metastases of less than 10% have been largely unsuccessful. Even for tumors less than 5.0 mm in size, nodal involvement is reported to occur in 3% to 12% of cases, and for those 5.0 mm to 1.0 cm in size, nodal disease is seen in 13% to 23%.[1] The only patients reproducibly noted to have a risk of axillary metastases less than 5% are those with a single focus of microinvasion, grade 1 tumors less than 5.0 mm in size if lymphatic invasion is not present, or pure tubular carcinoma less than 1.0 cm in size.

Although decisions regarding the need for adjuvant therapy can often be made on the basis of characteristics of the primary tumor, the presence of axillary node metastases remains the most important prognostic factor in breast cancer. In addition, the removal of tumor-bearing axillary nodes maintains local control in the axilla in 98% of patients, and a small therapeutic benefit for axillary dissection cannot be excluded on the basis of available data.

Results of Lymphatic Mapping and Sentinel Node Biopsy

Study	No. of patients	Technique	Sentinel node identified (%)	Node positive (%)	False-negative rate (%)
Krag et al[6]	22	R	82	39	0
Giuliano et al[4]	174	B	66	37	4.4
Albertini et al[7]	62	B+R	92	32	0
Giuliano et al[5]	107	B	94	42	0
Veronesi et al[8]	163	R	98	53	2.5
Shons et al[9]	243	B+R	92	—	0.5
Galamberti et al[10]	213	R	99	—	2.9
Guenther et al[11]	145	B	71	30	3.0
Borgstein et al[12]	130	R	94	43	1.7
Krag et al[13]	443	R	91	28	11.0

R = radioactivity; b = blue dye.

Proof of Principle

Lymphatic mapping with sentinel node biopsy offers the attractive possibility of reliably identifying patients with axillary nodal involvement, allowing axillary dissection to be limited to those who will benefit from the procedure. Results of studies of sentinel node biopsy followed by axillary dissection are summarized in the Table.[4–13] A sentinel node was identified in 71% to 99% of patients and accurately predicted the status of the remaining axillary nodes in 90% or more of the reported cases.[4–13] It is important to recognize that the patients included in these studies were a selected group. In many studies, only patients with intact primary tumors were eligible. The majority of tumors were T1 lesions, and little experience is available with tumors greater than 4.0 cm in size.

The principle that the sentinel node is an anatomically unique node, not a random node biopsy, is confirmed by the observation that in 40% to 60% of cases, it is the only axillary node that contains metastases.[4–13] It must be emphasized that sentinel node biopsy is appropriate only when there are no clinically worrisome axillary nodes, since lymphatics and nodes that are blocked with tumor cells may not take up blue dye or radioisotopes.

Unresolved Issues

Although the theory underlying sentinel node biopsy has clearly been proven to be correct, there are many questions that remain to be addressed. First, how should patients with primary lymphatic drainage to sites other than the axilla be managed? This problem occurs most commonly with drainage to internal mammary (IM) nodes. A review of 7,070 patients who had sampling of both axillary and IM nodes demonstrated that 9.9% of axillary node-negative patients had IM metastases, which occur most frequently with medial tumors larger than 2.0 cm in size.[2] Biopsy of potential IM sentinel nodes is problematic, since this drainage pathway is not readily identifiable with blue dye, and injection of radioactivity into medial tumors obscures detection of "hot" IM nodes. Cody et al[20] reported that 18% of patients had IM nodes visualized on lymphoscintigraphy, and in 8 patients (4.1%), this was the only site of nodal drainage. Although biopsy was attempted in 3 cases, nodal tissue was obtained in only 1 patient, and it apparently did not contain tumor.

Another issue is the need for completion axillary dissection once a positive sentinel node has been identified, based on data that in 40% to 60% of patients, the sentinel node is the only positive node. However, this result may be a reflection of patient selection more than tumor biology. Data from Chu et al[14] suggest that both tumor size and the size of the nodal metastases predict the likelihood of additional nodal disease and may allow selection of patients for completion dissection. The effect of completion dissection on local control and survival is being tested in a randomized trial done by the American College of Surgeons Oncology Group.

Technical issues are also not well standardized, particularly for lymphatic mapping using radiocolloids, and type of isotope, dose, and interval from injection to surgery remain to be more precisely defined. Initial studies were done with injection into the breast parenchyma, but it has subsequently been suggested that injection into the skin overlying the tumor or the periareolar skin is equally effective.

Finally, issues regarding the experience necessary to master this technique remain to be addressed.[17–20] In our experience, after the initial 10 cases, some surgeons identified a sentinel node 90% of the time, and others 60% of the time.[18] Data from Cox et al[19] indicate that approximately 30 cases are needed to master the technique.

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Patient Selection and Indications

David R. Byrd, MD
Seattle, WA

Any patient with breast cancer who has some risk of harboring metastases in regional lymph nodes should be considered for sentinel node (SN) biopsy. Although the pathologic status of the regional nodes gives prognostic information, the primary utility of SN biopsy lies in aiding decisions regarding treatment of the regional nodes and distant sites. The presentation reviews the role of SN biopsy in patients with invasive and noninvasive breast cancers.

Clinical Stage 0

Lobular Carcinoma In Situ

There is no role for SN biopsy in the management of lobular carcinoma in situ.

Ductal Carcinoma In Situ

There is an emerging indication for SN biopsy in selected patients with ductal carcinoma in situ (DCIS). Before SN biopsy became available, the incidence of lymph node metastases in patients with pure DCIS was approximately 1% when the axilla was staged by standard axillary lymph node dissection. In many patients, however, the diagnosis of DCIS is based on multiple core biopsies of nonpalpable microcalcifications seen on screening or diagnostic mammography. This limited sampling may fail to demonstrate subclinical invasive disease subsequently found on wide excision. A recent report on 208 patients with a preoperative diagnosis of DCIS who underwent SN biopsy revealed that 18 patients (8.6%) had positive nodes, especially with cytokeratin immunostaining.[1] An update of this study with the final pathologic descriptions of the primary lesions is forthcoming. It is reasonable to consider SN biopsy in selected patients with a preoperative diagnosis of DCIS based on core biopsies who are believed to be at increased risk of having occult invasive disease and regional metastases because of diffuse or extensive disease, high histologic grade with or without necrosis, or associated architectural distortion on mammography or ultrasound. Patients found to have positive SNs would be candidates for systemic treatment and possible completion lymphadenectomy, although the benefit of adjuvant therapy in these patients remains undefined. Patients with disease upstaged to a microinvasive or a macroinvasive (but < 1 cm) primary tumor after excision with a negative SN would not need further axillary staging or systemic treatment.

Clinical T1 Primary Tumor

Patients with T1 breast cancer are ideal candidates for SN biopsy because of the low (10%–30%) chance of nodal metastases; the finding of positive nodes would therefore potentially change systemic treatment recommendations.

Nonpalpable T1 Primary

The initial management of patients with a nonpalpable T1 primary is changing with the increasing use of stereotactic core biopsy to diagnose invasive disease in patients suitable for breast-conserving techniques. SN biopsy can be performed at the time of definitive lumpectomy under general or local anesthesia with sedation as an outpatient procedure. Patients with negative final pathologic margins and negative SN pathology have then completed their breast surgery. Alternatively, initial management may include a localized lumpectomy with margin evaluation by permanent pathologic sections. Although a subsequent SN biopsy may then be performed after excision, there may be a higher incidence of false negative findings in the SN.[2]

Palpable T1 Primary

Patients with a palpable T1 primary now frequently undergo core needle biopsy to diagnose invasive disease during the initial surgery clinic visit. Subsequent SN biopsy and lumpectomy can then be performed as for nonpalpable T1 disease in the outpatient setting. Many women consider an interval between the diagnosis of breast cancer and definite breast and axillary surgery important so they can thoughtfully consider their treatment options. However, a more streamlined clinical approach is easy to envision for some patients. As shown in a recent video from the H. Lee Moffitt Cancer Center at the University of South Florida in Tampa, one can easily predict the following scenario when instrumentation (large, > 2 cm, cannula core excision devices) becomes available and approved for therapy to complete a stereotactic lumpectomy with negative margins: In a single outpatient visit, a woman with a small, palpable or nonpalpable highly suspicious breast

mass will receive (1) a complete outpatient diagnosis, (2) definitive breast conservation surgery, and (3) accurate axillary staging. Under local anesthesia, with or without sedation, a stereotactic large-core excision is made to remove the lesion with radiologically negative margins (which may be pathologically confirmed by touch prep cytology). With invasive disease confirmed by frozen section, radiocolloid (and possibly isosulfan blue dye) is injected through the biopsy cavity wall into adjacent breast parenchyma. The biopsy incision is closed and the breast is massaged with the woman supine, then axillary SN biopsy is performed under local anesthesia. The hospital logistics of such a scenario are daunting, but the rapid diagnosis and treatment would be preferable to some patients.

Clinical T2 Primary Tumor

The vast majority of women with T2 disease will already have been considered for systemic therapy. The role of any lymph node removal would be to identify patients with positive nodes who might benefit from regional therapy (surgery or radiation therapy) or more intensive chemotherapy. SN biopsy identifies women with negative regional nodes who need no further axillary treatment. Patients found to have a positive SN by standard histology or immunocytochemical staining may undergo completion axillary node dissection or be eligible to participate in the American College of Surgeons Oncology Group (ACOSOG) Z0011 clinical trial to evaluate the role of completion axillary node dissection in patients undergoing breast conservation treatment.

Clinical T3 Primary Tumor

Although small subgroups of patients with tumors larger than 5 cm have undergone SN biopsy with concomitant axillary node dissection at several centers, there are insufficient data to determine the accuracy of SN biopsy in predicting the pathology of the axillary node basin in these patients.

Preoperative Chemotherapy

The increasing use of preoperative chemotherapy has led breast cancer specialists to consider preoperative chemotherapy for smaller and smaller tumors. Initial enthusiasm for the ability to downstage large primary tumors with chemotherapy and improve the chances for breast-conserving therapy to control the primary tumor led to the NSABP B-18 clinical trial, which demonstrated no change in survival and an increased use of lumpectomy over mastectomy when chemotherapy was delivered up front. Because there is a potential added benefit of testing chemosensitivity when the primary tumor is still in the breast, observing a clinical response or its absence, some investigators are considering preoperative chemotherapy for any woman who would be a candidate for postoperative chemotherapy (such as a woman with a primary tumor > 1 cm). The pathologic status of the regional nodes after preoperative chemotherapy may parallel the preoperative nodal status, but in a substantial number of women the disease will be downstaged pathologically to become node negative. We have recently reported concern over the reliability of SN biopsy after preoperative chemotherapy. An increased false negative rate of 33% was found in 3 of 10 node-positive patients receiving preoperative chemotherapy, out of a total of 66 protocol patients with invasive breast cancer who underwent successful SN biopsy and concomitant axillary node dissection.[3] The accuracy of SN biopsy prior to preoperative chemotherapy is unknown, and the clinical relevance of nodal status in this setting has not been delineated.

There is a clinical paradox in surgery on the axilla when one considers the advantages of SN biopsy versus preoperative chemotherapy. SN biopsy promises improved microstaging of regional lymph nodes with low morbidity, leading to an expanded population of patients who are candidates for lymph node surgery. Preoperative chemotherapy diminishes the importance of pretreatment lymph node staging and decreases the population of patients who are candidates for lymph node surgery. Advocates of SN biopsy argue that more accurate staging of regional metastatic disease by serial nodal sectioning and more intense scrutiny by immunohistochemistry (IHC) and perhaps even reverse transcriptase-polymerase chain reaction techniques (RT-PCR) (at the level of RNA) would better identify patients who would benefit from systemic therapy. Clearly, some patients with T2 well-differentiated primary lesions and favorable tumor markers have a low risk of metastases, and some patients with T1a or T1b poorly differentiated primary tumors and unfavorable markers have a high risk of metastases. To base systemic therapy recommendations solely on a primary lesion size in excess of 1 cm is an oversimplification of metastatic risk and ignores the importance of tumor biology. One can envision a new nodal pathologic ultrastaging system according to which a patient with a 4-cm primary tumor who was node negative by histology, IHC, and RT-PCR (T2, $N_{histo}0$, $N_{ihc}0$, $N_{pcr}0$) would receive no adjuvant treatment, whereas a patient with a 0.7-cm primary tumor who was node negative by histology but node positive by IHC and RT-PCR (T1b, $N_{histo}0$, $N_{ihc}1$, $N_{pcr}1$) would receive adjuvant treatment. This staging attempt would throw the current simple system into chaos but would eventually better select patients who would benefit from systemic therapy.

Contraindications to SN Biopsy

Clinical N1 disease, multicentric primary tumors, inflammatory breast carcinoma, previous axillary surgery

or radiation, previous breast surgery between the primary tumor and the axillary nodes, prepectoral breast implant, and a known allergy to triphenylmethane dyes (if isosulfan blue dye is used) are among the contraindications to SN biopsy.

Controversies and Precautions

Pregnancy, a previous large breast excision or lumpectomy, unresolved hematoma after an excisional biopsy, a T3 or T4 primary tumor, a primary tumor located in the axillary tail,[4] and drainage primarily to the internal mammary chain are among the conditions in which performance of SN biopsy is controversial or special precautions must be taken.

Summary

SN biopsy is expected to replace elective axillary node dissection as the standard of care in breast cancer in the near future. Noninvasive imaging techniques may eventually replace SN biopsy, but only when they can match or beat the microscope.

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Significance of Micrometastases in Breast Cancer

Nora M. Hansen, MD
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The most important prognostic factor in breast cancer patients is the status of the regional lymph nodes. Approximately 15%–20% of node-negative women assessed by routine hematoxylin-eosin (H&E) tissue staining will experience recurrence within 10 years.[1] As pathologists have become more sophisticated in the histopathologic evaluation of nodal tissues, a subgroup of patients with micrometastatic disease has emerged. Serial sectioning of axillary lymph nodes and immunohistochemical (IHC) staining has increased the detection rate of metastatic tumor up to 31%.[2–4] It is possible that this subgroup, patients with IHC-positive lymph nodes, accounts for a large proportion of the women with "node-negative" disease in whom recurrent or metastatic carcinoma develops. Currently, the natural history and clinical significance of IHC-detected micrometastases remain unknown, and conflicting studies cloud the issue (Table, page 44).

Initially, investigators used multiple sections and H&E stains to detect micrometastases not seen on histologic studies. In one of the earliest studies of occult nodal disease, Pickren[5] examined axillary dissection specimens from 199 breast cancer patients by multiple sectioning and H&E staining. In early studies occult metastases were found in 22% of cases, but the survival rate of patients with occult metastases was similar to the survival rate of patients without metastases. Friedman et al[6] serially sectioned axillary dissection specimens from 1,153 breast cancer patients and found that the relative risk of distant metastases was identical for patients with either "clandestine" nodal tumor or parenchymal nodal metastases.

The Ludwig Breast Cancer Study Group[7] looked at 921 breast cancer patients whose original histopathologic examination of axillary nodes revealed no metastases. An additional 6 levels of each axillary lymph node were

Study (year)	Increased Detection (%)		Change in Recurrence Rate (%)	Change in Overall Survival (%)
	Multiple Sections	Immunohistochemistry		
Pickren (1961)[5]	22.0			NS
Wells et al (1984)[18]		15		
Bussolati et al (1986)[19]		24		
Trojani et al (1987)[8]		12	31 vs 8 ($P = 0.0025$)	77 vs 94 ($P = 0.02$)
Friedman et al (1988)[6]	3.5		1.7 relative risk ($P < 0.05$)	
Bettelheim et al (1990)[20]	9.0		42 vs 26 ($P = 0.003$)	
Chen et al (1991)[21]		29	24 vs 9 ($P < 0.05$)	
de Mascarel et al (1992)[11]	7	6	$P = 0.01$	$P = 0.07$
Nasser et al (1993)[10]	17	14	NS	NS
Hainsworth et al (1993)[9]		12	NS	NS

cut and stained with H&E. With this extensive search, they were able to identify an additional 9% of patients with occult nodal metastases. In the group of patients with micrometastatic disease, a lower disease-free survival rate (58% versus 78%, $P = 0.003$) and a lower overall survival rate (79% versus 88%, $P = 0.002$) were noted when these patients were compared with patients without micrometastases. IHC staining was then employed to increase the detection rate of occult micrometastatic disease. Trojani et al[8] studied 150 women treated with mastectomy for breast carcinoma and used the original H&E slides of the lymph nodes for IHC examination. A cocktail of 5 monoclonal antibodies directed against epithelial antigens was used for the IHC stain. Occult micrometastases were found in 14% of cases. A higher recurrence rate ($P = 0.0025$) and a lower overall survival rate ($P = 0.02$) were seen in women with axillary micrometastases detected with IHC techniques. Multivariate analysis showed that for both recurrence and survival, the presence of micrometastases was the most significant factor ($P = 0.001$ and $P = 0.01$, respectively). Hainsworth et al[9] performed a similar study in 343 consecutive node-negative breast cancer patients but reached a different conclusion. Using a cocktail of antimucin antibodies, they detected occult metastases in 12% of patients. The survival of women with a single occult nodal metastasis did not differ from that of node-negative women. However, the presence of micrometastases in 2 or more nodes was the most significant predictor of disease recurrence and death.

Combining the techniques of multiple H&E-stained sections and IHC staining has not clarified the issue. Nasser et al[10] in 1993 reviewed the cases of 159 node-negative breast cancer patients. They sectioned each lymph node, taking samples for both routine H&E and IHC staining, which consisted of a cocktail of anticytokeratin antibodies. Routine H&E staining identified metastases in 17% of patients and IHC identified an additional 14%, for a total of 31% of patients with metastases. The investigators observed no differences in disease-free or overall survival rates in patients with occult micrometastases, defined as tumor deposit less than 2 mm in size. However, newly discovered metastases larger than 2 mm were associated with higher recurrence rates and worse disease-free survival ($P < 0.05$). A similar study by de Mascarel et al[11] found that micrometastases discovered on serial sections of H&E-stained material were associated with worse recurrence and survival rates, although on multivariate analysis micrometastases were not a statistically significant predictor. Interestingly, the patients with IHC-discovered occult disease had a worse recurrence rate but not a worse survival rate. These results led the authors to conclude that IHC adds nothing to the evaluation of nodal status.

The inherent problem with the techniques used in the previously described studies is the time and expense involved in sectioning the large number of nodes removed in a classic level I or II dissection. The emergence of sentinel lymph node dissection (SLND) has made this extensive evaluation easier. By identifying 1 or 2 sentinel nodes (SNs), the pathologist can conduct a thorough search of a smaller amount of tissue that is the most likely to harbor occult metastases. In 1995 Giuliano et al[2] reported that SLND with IHC applied to the evaluation of axillary node status in breast cancer patients improved and increased the detection rate of micrometastases less than 2 mm in size when compared with routine axillary lymph node dissection. Their protocol entailed obtaining 4 sections (8 faces) per SN, 2 of which were stained with an anticytokeratin antibody cocktail. SLND detected nodal metastases in 42% of all patients, and of these, 45% were micrometastases. IHC staining detected 47% of the micrometastases (9% of all patients). Schreiber et al[12] published a similar study in which 9.4% of the patients in the study group had their disease upstaged from stage I to stage II. Remarkably, 3 patients with disseminated carcinoma in

situ (DCIS) in this study were found to have IHC-detected metastases in the SN. This finding does not fit with the natural history of DCIS.

Alternative techniques have been proposed to identify women at increased risk of developing recurrent disease. One promising technique is the cytologic evaluation of bone marrow for micrometastases. Metastases to the skeletal system in breast cancer are very common; therefore, close examination of the bone marrow by biopsy or aspiration appears to be a rational approach. Using a variety of techniques, researchers have found bone marrow metastases in 4%–48% of women with primary breast cancer.[13–15] The question that remains to be answered is, what is the clinical significance of micrometastases in the bone marrow?

There are many techniques for examining bone marrow for occult metastases. Molino et al[16] compared 3 methods of detecting tumor cells in artificially contaminated bone marrow specimens and found that immunocytochemistry (ICC) was the superior method, not only demonstrating a greater sensitivity in the experimental model but also detecting a greater percentage of positive bone marrows in patients with metastatic disease. Diel et al[17] have published one of the largest studies to date. This group studied 727 patients who were undergoing surgery for primary breast malignancy. Overall, 55% of patients had occult bone marrow metastases, and 31% of node-negative patients had occult marrow disease. Marrow positivity was associated with large tumors with high histologic grade and lymph node involvement. Patients with tumor detected in the bone marrow were more likely to have shorter distant disease-free survival and overall survival. Remarkably, marrow status was a more powerful predictor of survival than grade, lymph node status, and stage. This group did not perform SLND. Although the preliminary data seem promising, some theoretical and data-driven questions remain about the clinical significance of bone marrow micrometastases. Are these metastatic cells detected in the bone marrow capable of invading distant sites, or are they just circulating cells that lack the ability to attach and invade? It may be that the occurrence of bone marrow metastatic cells signals a subset of patients who are indeed more likely to have life-threatening metastases and require more aggressive adjuvant therapy. A prospective trial with a large number of breast cancer patients will be needed to answer this question.

The significance of micrometastatic disease in patients with breast cancer is unknown at this time. We would like to believe that identifying occult metastases in the SN will identify a population of "node-negative" women at risk for recurrence, and that by treating them more aggressively we can improve their disease-free and overall survival rates. However, this outcome remains to be seen. The American College of Surgeons Oncology Group has launched an SN trial to address this specific question. Patients with T1 or T2 disease who are clinically node-negative will be eligible to enter the trial. Patients will undergo an SN procedure and breast-conserving therapy. If the SN is negative on standard H&E staining, a completion axillary lymph node dissection will not be performed. A section of the SN will be sent to a central laboratory for IHC staining, with the results blinded to the patient and the physician. These patients will also undergo bone marrow aspiration at the time of surgery, and the aspirate will be sent to a central laboratory for ICC evaluation, which will similarly be blinded to the patient and the physician. At the completion of the study, the investigators should better understand the significance of micrometastatic disease in the SN as well as the significance of micrometastatic disease in the bone marrow. It is an important question that many studies have tried to address. This trial will be the first prospective trial to address this question.

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Sentinel Node Evaluation for Breast Cancer

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The concept of the sentinel node (SN) did not come into existence overnight. It resulted from a series of attempts to solve specific problems, clever thinking, and a considerable amount of preexisting data. By the 1930s, detailed studies of human lymphatics were possible, which led anatomists to realize that nodal metastases probably occurred first in a focal set of nodes prior to wider dissemination. By 1950, blue dye was being used in gastric malignancies with the specific goal of targeting the primary nodes, and the conclusion was that mapping of the nodes by vital staining minimized unnecessary dissection. A big step occurred in 1976, when Ramon Cabanas clearly articulated the basic principles of the SN concept. Particularly important was the demonstration that SN biopsy could precede definitive lymphadenectomy. The pathologic status of the SN provided a rational basis for selective lymphadenectomy.

From the late 1950s through the 1970s, clinical studies were performed using colloidal radioactive tracers to define lymphatic drainage from the breast. Conclusive evidence demonstrated that although the bulk of the lymphatic flow went to the axilla, lymph drainage went also or exclusively to nonaxillary locations in a high percentage of cases. Excision and pathologic examination of the internal mammary nodes confirmed that nonaxillary locations were clinically significant, but the morbidity associated with such procedures was a limiting factor. The high accuracy of radiolabeling, coupled with intraoperative gamma-probe guidance, has allowed harvesting of internal mammary and other nonaxillary nodes with a minimum of morbidity. This ability reopens the question about the methods used to stage breast cancer.

Important issues need to be resolved regarding the optimal methods of SN resection for any given clinical situation. One of the most pressing issues is ensuring that all of the SNs are labeled, identified, and removed from each patient. There is no guarantee that any current method achieves this goal. A lymphatic duct draining a primary tumor leads directly to an SN. However, the lymphatic system is comprised of an exceedingly complex network of vessels that can carry flow in diverse directions along multiple channels that vary even with patient activity.

The concept of a single, definable, constant SN is overly simplistic. The challenges facing full development of the technique of SN surgery are (1) to develop technology that will allow identification of all possible SNs draining a primary tumor and (2) to develop surgical techniques to access these nodes in a minimally invasive manner.

The impact of developments in SN identification and surgery goes beyond surgeons. Pathologists now can focus on a limited number of nodes that justify intensive efforts to find occult metastases. The nodal component of cancer staging will likely change radically. Much data need to be acquired through well-designed clinical trials to understand the implications of this new prognostic information.

A prospective, nonrandomized study was conducted by 11 surgeons from a variety of practice settings. In 443 eligible patients with primary breast cancer, 4 mL of 37 MBq (1 mCi) ^{99m}Tc-labeled sulfur colloid was injected into the breast, around the tumor or biopsy cavity. Before surgical incision, hot spots representing underlying radiolabeled SNs were identified with a handheld gamma probe. Radiolabeled SNs subjacent to the hot spot were selectively removed. After removal of the SNs, all patients underwent completion axillary lymphadenectomy.

The overall hot spot identification rate was 93.2% (413 of 443 patients). A total of 405 patients had SNs removed. In these 405 patients, SN identification was accurate in 97% of cases, with a false negative rate of 11% (13 of 114 patients).

Of particular interest is that SNs were identified outside the axilla in 6.7% of cases. This finding was clinically relevant, because the positive SNs in 3% of all patients with positive nodes were located exclusively outside the axilla (that is, the axillary nodes contained no cancer).

In the multicenter validation study, all patients underwent completion lymphadenectomy. Long-term evaluation of patients who have undergone only SN surgery has not been performed. To ensure that resection of only the SNs (without a completion lymphadenectomy) does not lower overall and disease-free survival rates and results in good regional control, a 4,000-patient, prospective randomized clinical trial is now under way. This study is sponsored by the National Cancer Institute and is being jointly conducted by the National Surgical Adjuvant Breast and Bowel Project and the University of Vermont. This study is summarized elsewhere in this course syllabus.

Two different methods of SN identification have evolved over the past 10 years: visual detection and radioguided detection. Although there are differences, it is important to emphasize common features. The most important is that any guidance system is superior to conventional blind techniques. Surgical selection of those few nodes most likely to contain metastases is a major step forward from nonguided techniques. It is also important to realize that so-called completion lymphadenectomy is frequently not complete. Radioactive tracers injected into the skin following mastectomy and axillary lymphadenectomy frequently demonstrate residual lymph nodes.

For the purposes of this postgraduate course, this summary will emphasize and describe radioactive tracer methods of SN identification. Visual and tracer-guided techniques can be viewed as complementary.

The difference between dye- and tracer-based SN surgery is that with dye-based surgery, guidance is based on visual detection of the SNs. Light penetrates only a few millimeters, so that visual detection of the SNs only occurs once the nodes are exposed. How, then, does the surgeon choose the pathway for dissection? In the axilla, SNs are frequently in a mid-level I location. Statistics are on the surgeon's side. To the extent that the SNs are not located at mid-level I, the dissection will be greater. SNs outside the axilla are not sought, because there is no guidance to their location.

Tracer-based surgery provides a signal to the surgeon via an intraoperative handheld gamma detector. As the tip of the gamma detector approaches the SN, a sound indicates the proximity. This information tells the surgeon the precise location of the SNs before an incision is made. In the axilla, precise localization of SNs allows precise determination of the placement of the incision. During dissection, the sound accompanying an increased radioactive count guides the surgeon to the SNs, thereby minimizing the extent of surgery needed to reach the SNs. In addition, there is instant verification of whether additional SNs exist, and their location. Importantly, the probe guides the surgeon to SNs located outside the axilla. Thus, intramammary, internal mammary, and other SNs can be located and removed through a minimally invasive technique. As stated above, in 3% of patients with positive SNs the positive nodes were located only outside the axilla.

Issues being evaluated include the optimal location for tracer injection, the volume injected, the amount of radioactive technetium used, and overall indications for and contraindications to the procedure. These technical issues will take time to sort out, because current methods are already approaching 95%–100% success rates. To demonstrate success rates higher than 95% with statistical significance will take hundreds of patients.

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Lymphatic Mapping in Breast Cancer: Combination Technique

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Advances in surgical technology and the development of minimally invasive surgical techniques have heralded a new era of surgery. The current standard of care for the management of patients with invasive breast cancer is complete removal of the tumor and the documentation of negative margins by either mastectomy or lumpectomy, followed by complete axillary dissection.[1,2] Lymphatic mapping of the breast is clearly changing this long-held paradigm.[3,4] Indeed, radioguided minimally invasive surgery is positioned to become the next revolution in general surgery.

Technical Aspects

The clinical evaluation of the axilla in the management of the breast cancer patient is the responsibility of the surgeon. The identification of a positive lymph node is the primary goal of axillary surgery. Even as new mapping technologies become available, it is vital to maintain good clinical judgment. A dilated blue lymphatic channel ending abruptly in a palpably firm lymph node (which may or may not be stained blue) is clinically a positive sentinel lymph node (SLN) and should be removed. Nodes must continue to be evaluated in light of their clinical appearance and palpable abnormality.

Blue Dye Technique

The 2 agents described in the literature on mapping using the dye technique are Lymphazurin and Patent blue dye. Biochemically, these agents are essentially the same. Lymphazurin 1% (isosulfan blue), a preservative-free agent, is a contrast material used for the identification of lymphatic vessels and has no known pharmacologic action. After injection, isosulfan blue is picked up selectively by the lymphatic vessels, thus rendering the lymphatic vessels a bright blue color, which makes them easily discernible from surrounding tissues. The incidence of allergic reactions with Lymphazurin 1% (isosulfan blue) is 1.5%. There have been no reported deaths from the administration of isosulfan blue dye; however, a death has been reported

after intravenous administration of a similar compound employed to estimate the depth of a severe burn. Severe reactions may be manifested by edema of the face and glottis, respiratory distress, or shock. Such reactions may prove fatal unless promptly controlled by emergency measures such as maintenance of a clear airway and the immediate use of oxygen and resuscitative drugs.

Mixing Lymphazurin with local anesthetics in the same syringe prior to administration results in immediate precipitation of the drug complex. Similar precipitation of sulfur colloid occurs when the 2 compounds are mixed. Local anesthetics and sulfur colloid should be administered using a separate syringe and at separate times.

There are occasional reports of subdermal or intradermal injection of blue dye for lymphatic mapping in breast carcinoma. The uptake is high in lymph nodes because of the rich subdermal lymphatic plexus; however, several questions regarding the accuracy of lymphatic mapping performed using this technique remain unanswered. I recommend avoiding the subdermal or intradermal injection of Lymphazurin for the lymphatic mapping of breast carcinoma.

The preferred method of Lymphazurin injection is intraparenchymal injection of 5 mL at multiple sites around the tumor or excisional biopsy site. The dye may be injected through a 27-gauge needle and fanned through a single injection site or multiple injection sites into the upper outer (axillary) aspect of the tumor or biopsy site. The reason why radiocolloid is injected all around the tumor whereas blue dye is injected only along the axillary aspect of the tumor is to maximize the detection of the internal mammary nodes with the radiocolloid. The handheld gamma probe allows surgeons to search for SLNs in alternative sites. This approach, of course, cannot be done with blue dye, and so the blue dye is injected *only* along the axillary aspect of the tumor.

After dye injection, the breast is compressed manually and gently massaged for 5 continuous minutes to ensure migration of the blue dye into the lymphatic channels. Massage is performed just prior to skin preparation and draping of the patient for operative intervention. Immediately after this preparation, the SLN can often be found by making an incision approximately 1 cm inferior to the hairline of the axilla. Dissection may proceed quickly to the clavipectoral fascia, after which care must be taken to avoid damage to any lymphatic channels seen beyond that point. Disruption of the lymphatic channels at this level will seriously hinder the ability to find an SLN. Superficial channels may lead to the SLN; however, the deeper channels are more likely to carry the greater part of the blue dye to the SLN.

Radiocolloid Technique

Although 3 radiocolloid preparations are currently in use worldwide, sulfur colloid is used in the United States and Canada, owing both to its availability and its low cost. In Europe, microcolloidal albumin is prepared by labeling it with technetium 99m and administered by some investigators either subcutaneously or subdermally over the breast cancer lesion. Cutuli et al[5] of Strasbourg, France, Meijer et al[6] of Amsterdam, The Netherlands, and Veronesi et al[7] of Milan, Italy, all have advocated use of this technique. These groups have injected 1–5 mL of radiolabeled microcolloidal albumin (Nanocolloid) either subdermally or intradermally up to 24 hours preoperatively. The C-Track device (Care Wise Medical, MA) was used in each of the cited reports to detect the radiocolloid in the SLNs. There were high rates of successful SLN identification; however, the false negative rate ranged from 3% to 5%.

In the United States, radiocolloid lymphatic mapping is done using ^{99m}Tc-labeled sulfur colloid either in filtered or unfiltered form. This agent is injected in variable amounts, ranging from 0.450 to 1.0 mCi of specific activity. Krag and colleagues routinely use unfiltered ^{99m}Tc-labeled sulfur colloid and inject 1.0 mCi of radioactivity.[8] This amount of radioactivity is generally injected in approximately 6 mL of saline at multiple sites in the parenchyma surrounding the tumor or biopsy site. The C-Track gamma detection probe is then used intraoperatively to localize the SLN. This method appears to accurately identify the SLN. The radioactive dose, the collimation, and the sensing characteristics of the C-Track probe allow this method to work effectively. In a recently published multicenter trial, the rates of success in finding an axillary SLN ranged from 83.3% to 98.0%. However, because the trial was the initial learning experience for 11 surgeons at 11 different institutions, the overall false negative rate was 11.4%.[8]

Combination Technique

Albertini et al first reported using the combination of ^{99m}Tc-labeled sulfur colloid and Lymphazurin blue dye.[9] A dose of 450 μCi of radioactivity applied to 0.22-μm filtered sulfur colloid is used. This agent is injected in a 6-mL volume at 6 intraparenchymal locations around the tumor or the tumor bed following excisional biopsy. In the course of 700 cases of lymphatic mapping at the H. Lee Moffitt Cancer Center, this technique has been applied utilizing the Neoprobe (Neoprobe Corp, OH), C-Track, and currently the Navigator device (US Surgical Corp, Norwalk, CT). Each has allowed accurate identification of the SLN.[10,11]

Ideally, the patient is injected 2 hours before the operation with 450 μCi of filtered ^{99m}Tc-labeled sulfur col

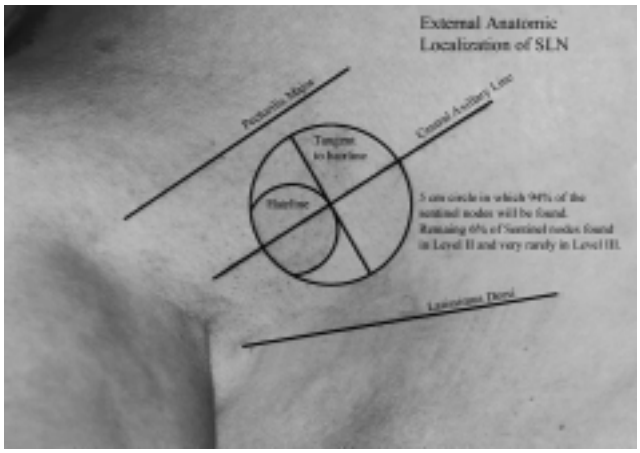

Figure 1—This figure illustrates the external anatomic location of the SLN. There is a 5-cm circle in which 94% of the sentinel nodes will be found. The remaining 6% of the sentinel nodes will be found in level II and very rarely in level III.

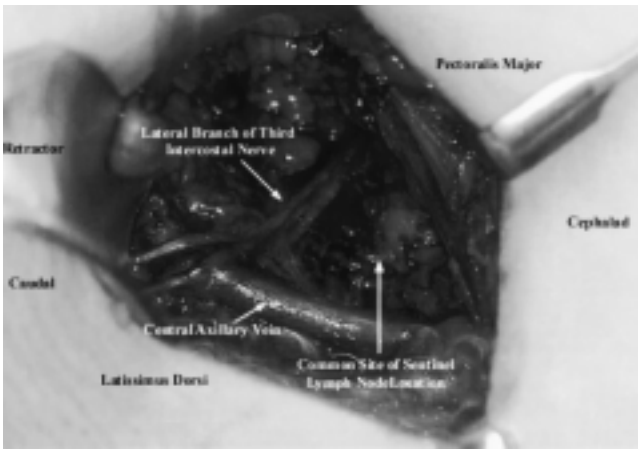

Figure 2—This figure illustrates the internal anatomic location of the SLN. The SLN is located at or around the lateral thoracic vein where it is crossed by the lateral branch of the third intercostal nerve.

loid. Five milliliters of Lymphazurin 1% (isosulfan) blue dye is injected just before the patient is prepared. The breast is compressed and massaged for 5 continuous minutes and the skin of the breast, chest wall, and axilla is prepared for operation with appropriate scrubs and disinfectant solutions (Hibiclense, Hibistat). The patient is draped to expose the breast, chest wall, and axilla. The gamma probe is sterilely sheathed and made available for axillary node mapping.

Visual observation of small lymphatic channels requires good exposure and a bloodless field. Electrocautery should be used for dissection, and positioning a Weitlander retractor in the incision assists with exposure. If local anesthetic agents are used, epinephrine should be added. Lymphatic channels should be clipped when encountered; however, it is crucial not to cut or clip a blue lymphatic channel until a node or nodes have been isolated. Cutting the blue channel will disrupt the drainage pathway of the blue dye into the SLN, rendering it recognizable only with the use of the gamma probe, and leakage of the blue dye will stain the surrounding tissues, further compromising the detection of a blue lymph node. If the blue dye channel is inadvertently cut, use of the gamma detection probe becomes critical in locating the SLN.

Mapping the axillary SLN using radiocolloid requires a properly calibrated machine with the sensitivity properly set to allow optimal detection of radioactivity. Certain anatomic considerations are useful in locating SLNs. Lines are drawn along the lateral border of the pectoralis major muscle and the lateral border of the latissimus dorsi muscle in the axilla to mark the outer borders of the axillary dissection. A tangential line is drawn at the axillary hairline in perpendicular fashion from anterior to posterior. Another line is then drawn through the axis of the axilla, through the center point of the hairline. These intersecting lines mark the center of a 5-cm circle that can be drawn on the axilla (Fig 1). A vast majority of SLNs, 94%, will be found within this 5-cm circle. The remaining 6% are most often found in a level II location. The 5-cm circle may be useful as a starting point for identifying the location of the SLN using the gamma detection probe.

Once the SLN has been localized, an arcuate incision is made overlying the area of highest activity as determined by the gamma probe. The incision generally falls at or below the hairline. Care should be taken to extend the dissection toward the chest in a fashion perpendicular to the chest wall. The tendency of most surgeons is to make the incision and then dissect cephalad. Internal landmarks useful in localizing the SLN include the lateral thoracic vein and the lateral branch of the third intercostal nerve. These anatomic structures are found beneath the clavipectoral fascia. The lateral thoracic vein can be found easily with careful dissection. The location at which the nerve crosses over the vein defines 4 quadrants, which collectively contain the vast majority of the SLNs found in breast lymphatic mapping (Fig 2).

Each of the three techniques described offers unique advantages and disadvantages. The extra advantage of the combination approach is that it significantly reduces the learning curve for achieving proficiency with this new technique (Table, page 51).

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Comparison of Lymphatic Mapping Techniques

Technique	Advantages	Disadvantages
Blue Dye	Safe Requires only surgical skill Cost-effective Intraoperative dye separation and localization Rapid localization	Surgeon-dependent localization No preoperative assessment of mapping Significant learning curve Timing Pass-through Allergic reaction Tattooing Internal mammary node not detected Intramammary node not detected
Radiocolloid	Interdisciplinary process Allows preoperative assessment of mapping Quantitative measure Attainable end point verification Scan and dissect method Internal mammary node detection	Interdisciplinary process Radiation safety regulations Radiocolloid preparation Gamma detection instrumentation Separation: shine-through Timing for maximal localization difficult Intramammary node not detected
Combination of blue dye and radiocolloid	Enhanced learning curve: visually and radioguided Safety net for technical failure: "training wheels" Preoperative localization Scan and dissect method Quantitative measure of detection Enhanced operative efficiency Internal mammary node detection Interdisciplinary process	Radiation safety regulations Radiocolloid preparation Gamma detection instrumentation Separation: shine-through Timing for maximal localization doubly difficult Intramammary node not detected Allergic reaction Tattooing Interdisciplinary process

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Blue Dye Technique

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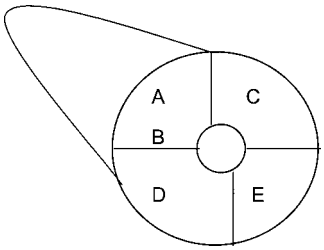
Sentinel lymph node dissection (SLND) may be performed either with isosulfan blue dye (Lymphazurin, Hirsch Industries, Inc, Richmond, VA), a radiopharmaceutical, or a combination of both. Regardless of the technique utilized, lymphoscintigraphy or intraoperative gamma counting must be performed in all patients with medial hemisphere breast tumors to ensure that the primary drainage pathway is to the ipsilateral axilla. Patients who do not have dominant or codominant drainage to the ipsilateral axilla may not be candidates for SLND.

After the induction of general anesthesia or local anesthesia with heavy intravenous sedation and preparing and draping of the patient, 4–5 mL of 1% isosulfan blue dye is injected into the breast parenchyma surrounding the primary tumor or into the wall of the cavity created by the previous biopsy. If the lesion is not palpable, mammographic or ultrasonographic localization will be required. A needle may be left in the breast parenchyma through which the blue dye can be instilled in the operating room. The breast is gently compressed to augment the action of the lymphatic pump and promote passage of blue dye to the axilla. The volume of dye injected and the timing of the axillary incision after dye injection are extremely important and depend on the location of the primary tumor. Suggestions for the volume of injectate and timing are given in the Table.

An interval of 3–10 minutes between dye injection and axillary incision allows adequate visualization of the lymphatics. Too short an interval between injection and incision may prevent identification of the afferent lymphatics and location of the SLN. Too long a delay 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, whereas those in the lower inner quadrant have longer transit times. We therefore typically allow 3–4 minutes and 7–10 minutes respectively for lesions in these locations.

After the allotted time, a 3- to 4-cm transverse incision is made just inferior to the hair-bearing region of the axilla. Blunt dissection is carefully performed with the tips of a curved hemostat to reveal a blue-stained lymphatic channel located just below the superficial axillary fascia. It is helpful to raise the arm above the woman's head (approximately 135 degrees of abduction) to facilitate identification of the blue lymphatic channel. Finding a blue lymphatic and tracing it to an SN is much easier than searching for a blue node that may be only partly blue or obscured by fat. Do not raise skin flaps. The blue lymphatic channel is followed proximally and distally until the first blue node, or SN, is identified. The SN may be sent to pathology for frozen section analysis. Depending on the histology of the sentinel node, the patient will be treated accordingly.

Blue Dye Technique: Suggested Volumes of Injection and Interval to Incision



Location of Primary Tumor	Suggested Volume of Dye to Inject (mL)	Suggested Time from Injection to Incision (min)
A. High Upper Outer Quadrant Lesions	4	3–4
B. Lower Upper Outer Quadrant Lesions	4–5	5
C. Upper Inner Quadrant Lesions	4–5	5
D. Low Outer Quadrant Lesions	5	5
E. Low Inner Quadrant Lesions	5	5

Results of a Prospective Randomized Trial Comparing Sentinel Node Identification with Blue Dye Alone Versus Blue Dye Plus Radioactivity

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Learning Objective

Compare the sentinel node identification rate, false-negative rate, and ease of learning sentinel node biopsy when lymphatic mapping is done with Lymphazurin blue dye alone or blue dye plus technetium sulfur colloid.

Outline

I. Study design

II. Eligibility criteria and methods

III. Results

   A. Sentinel node identification rate

   B. Factors associated with failure to identify a sentinel node

   C. Learning curves

An increasing body of evidence indicates that lymphatic mapping and sentinel node biopsy can reliably determine axillary node status. However, debate exists as to the best technique for lymphatic mapping, and in particular, which technique is easier to learn. Advantages of blue dye alone include simplicity and low cost, while advantages of using radioactivity include the ability to identify sentinel nodes outside of the axilla and greater ease in learning the technique. Proponents of the combined technique note that the radiolabel and the blue dye do not always identify the same node, suggesting that it might be more accurate than either technique alone.

Study Design

In order to introduce sentinel node (SN) biopsy to our practice, we performed a study randomizing patients to SN identification with isosulfan blue dye alone or blue dye plus technetium sulfur colloid. The aims were to determine (1) which technique resulted in a higher rate of SN identification and (2) if learning curves for the techniques differed.

Eligibility Criteria and Methods

Patients with unicentric T1 or T2 invasive carcinoma and clinically negative nodes were eligible. Patients were stratified on the basis of tumor size and randomized to blue dye alone (B) or blue dye plus technetium sulfur colloid (B+R). Patients requiring needle localization were assigned to B and analyzed separately. The randomization began with each surgeon's first case.

Results

A total of 139 patients entered the study, including 92 who were randomized (50 B, 42 B+R) and 47 who were assigned to B. All patients had breast conservation, and 57 had a prior excisional biopsy. Characteristics of the patients are compared in Table 1 (page 54).

An SN was identified in 110 patients (79%). The SN was found in 88% of patients randomized to B, 86% to B+R, and 64% of those requiring localization and assigned to B (Table 2, page 54). The SN contained metastases in 28 patients and was the only node with metastases in 43% of cases. The SN predicted the status of the remaining nodes in 96% of cases. No difference in the number of SN, time to SN identification, predictive value of the SN, or ability to identify an SN were noted between patients randomized to B or B+R (Table 2).

Statistically significant differences in a surgeon's ability to identify an SN and time to identify an SN were noted (Table 3, page 54). While these appeared to be related to volume, success rates for the initial 10 cases ranged from 60% to 90%. No difference in learning curves for B or B+R were noted.

Univariate and multivariate analyses of factors associated with failure to identify an SN identified tumor location, need for needle localization, sequence number of surgery, and body mass index as significant variables (Table 4, page 54).

Table 1—Patient Characteristics

	Mean ± SEM			
	Blue dye alone*	**Blue + radioactivity***	**Blue localization**	***P* value**
Age (years)	52.2 ± 1.5	52.1 ± 1.5	55.7 ± 1.4	0.14
Body mass index	26.7 ± 1.0	27.9 ± 1.0	26.9 ± 1.0	0.67
Tumor size (cm)	1.8 ± 0.2	1.9 ± 0.2	1.4 ± 0.2	0.10
Time blue dye to incision (min)	10.9 ± 0.8	15.9 ± 1.6‡	14.7 ± 1.2	0.01
% Palpable	62	55	11†	

*Randomized groups.
†Four tumors in the localization group were questionably palpable, but had a wire placed to ensure appropriate excision. The fifth patient in this group had bilateral lesions, one of which required localization, so the palpable tumor was not randomized.
‡Significantly different than blue dye alone by Tukey test.

Table 2—Sentinel Node (SN) Identification by Technique

	Blue dye alone	**Blue + radioactivity**	**Blue localization**	***P* value**
SN identified	88%	86%	64%*	< 0.01
SN predictive	95%	97%	97%	NS
Time to SN identification (min ± SEM)	8.2 ± 0.8	9.6 ± 1.2	8.9 ± 1.1	NS
Mean No. of SN identified	1.8	1.9	1.8	NS

*Significantly different than blue dye alone by Fisher exact test with Bonferroni adjustment.

Table 3—Rate of Success of Sentinel Node Identification by Surgeon

	Surgeon				
	A	**B**	**C**	**D**	
No. of cases	13	23	33	62	
SN identified	62%	70%	76%	89%	$P = 0.04$
Mean time to detection (min) ± SEM	10.9 ± 2.2	14.4 ± 1.4	10.6 ± 1.6	6.0 ± 0.5	$P < 0.0001$

Table 4—Stepwise Logistic Regression of the Probability of Sentinel Node Identification

	Univariate analysis		Multivariate analysis	
Variable	**Odds ratio (CI)***	***P* value**	**Odds ratio (CI)**	***P* value**
Location (UOQ vs other)	5.88 (2.08–16.7)	0.0009	4.35 (1.47–14.3)	0.009
Localization (no vs yes)	3.70 (1.61–9.09)	0.002	4.17 (1.49–11.2)	0.006
Sequence No. of surgery	1.03 (1.00–1.06)	0.04	1.04 (1.00–1.08)	0.03
Body mass index	0.93 (0.87–0.99)	0.02	0.93 (0.87–0.99)	0.04

*CI = 95% confidence interval.

Conclusions

Our study documents no difference in the success rate or accuracy of SN mapping with B compared with that in B+R. In a group of surgeons with no prior experience with SN biopsy for breast cancer, there was no evidence that one technique was easier to learn.

Bibliography

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American College of Surgeons Oncology Group Sentinel Node Trials

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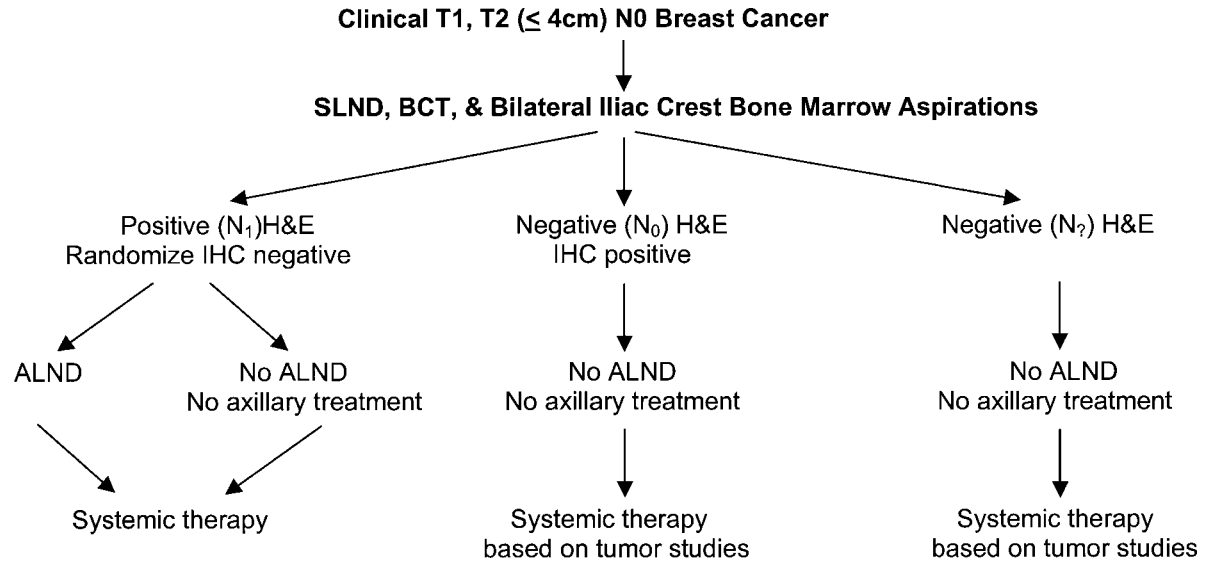
Two American College of Surgeons studies are ongoing. The first study, Z0010, "A Prognostic Study of Sentinel Node and Bone Marrow Micrometastasies in Women with Clinical Stage T1 or T2 Breast Cancer," examines the prognostic significance of microme-tastases detected by immunohistochemical staining in sentinel node (SN) and bone marrow from women with clinically node-negative breast cancer. In addition, it will examine the clinical accuracy and validity of sentinel lymph node dissection (SLND). The second trial, Z0011, "A Randomized Clinical Trial of Axillary Node Dissection in Women with Clinical Stage T1 or T2, N0, M0 Breast Cancer Who Have a Positive Sentinel Node," will compare axillary lymph node dissection (ALND) with SLND alone in node-positive women. It is hoped that this trial will determine whether axillary dissection has therapeutic and survival benefits or may be omitted. Together, these 2 studies may lead to an alteration in the management of patients with early breast cancer. Both protocols are open and accruing patients. The schema is shown in the Figure.

Z0010 Summary

Objectives

Women with clinical T1 or T2 N0 M0 breast cancer will undergo breast-conserving therapy (BCT), bilateral iliac crest bone marrow aspirations, and SLND. The objectives are:

1. To estimate the prevalence and to evaluate the prognostic significance of SN micrometastases detected by immunohistochemistry (IHC).
2. To estimate the prevalence and to evaluate the prognostic significance of bone marrow micrometastasis detected by immunocytochemistry (ICC) for the first 3,600 women.
3. To evaluate the hazard rate for regional recurrence in women whose SNs are negative by hematoxylin-eosin (H&E) staining.
4. To provide a mechanism for identifying women whose SNs contain metastases detected by H&E, so that these women can be considered candidates for Study Z0011.



Schema for participation and treatment in the ACOSOG sentinel node trials.

Study Size

Study Z0010 is projected to accrue approximately 7,600 women in 3.8 years in order to provide the required 1,900 eligible women needed for randomization in study Z0011. It is projected that 25% of the women registered in Z0010 will be eligible for and agree to be randomized in Z0011. Participation in the bone marrow aspiration part of Z0010 is optional, and this part of the study will be closed following the enrollment of 3,600 evaluable women.

Z0011 Summary

Patients must have been registered to and treated on study Z0010 in order to be eligible for this trial.

Objectives

Women with clinical stage II, T1 or T2 N0 M0 breast cancer will be registered to study Z0010 and undergo BCT as specified in the protocol for study Z0010. Women with SN metastases (identified on frozen section or permanent section analysis) will be randomized to 1 of 2 arms:

Arm 1: Completion ALND.

Arm 2: No immediate additional axillary surgery or axillary-specific irradiation.

Women in both arms will then receive whole breast irradiation and systemic adjuvant therapy.

The primary objectives (long and short term) are:

Long term: To assess whether overall survival for patients randomized to Arm 2 (no immediate ALND) is significantly worse than for patients assigned to Arm 1 (completion ALND).

Short term: To quantify and compare the surgical morbidities associated with SLND plus ALND versus SLND alone.

Study Size

This study requires the randomization of 1,900 eligible patients over a period of 3.8 years, based on a projected accrual rate of 500 eligible patients randomized per year. The randomization between the arms will be 1:1. The final analysis is projected for 8.8 years following the start of accrual.

NSABP-32: A Randomized, Phase III Clinical Trial to Compare Sentinel Node Resection with Conventional Axillary Dissection in Clinically Node-Negative Breast Cancer Patients

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With the outstanding success of sentinel node (SN) resection methods in breast cancer, the most important question is whether adopting SN resection as the standard method of managing breast cancer is in the patient's best interest. If the goal of node surgery is staging, the data support the use of SN surgery as an acceptable technique. However, abandoning current methods of breast cancer management (axillary lymphadenectomy, ALND) for less aggressive methods must be viewed with caution. Choices should be based on the results of carefully controlled, randomized studies with appropriate outcome studies. The good news is that accrual to such definitive studies can be extremely rapid if surgeons seize this opportunity on behalf of their patients. It can be expected that the skill level of participating surgeons will increase as surgeons share in the collective knowledge gained by several hundred of their colleagues.

The NSABP-32 trial (National Surgical Adjuvant Breast and Bowel Project) is designed to compare SN resection with conventional ALND in clinically node-negative patients. The key reasons for performing regional

lymphadenectomy are (1) for staging and prognosis, (2) for regional control, and (3) for the possibility of improved survival and disease-free survival (DFS) rates. Conventional ALND addresses all three intents, but at a significant physical, emotional, and economic cost to the patient. The NSABP-32 trial is designed to determine whether SN resection can result in a considerable reduction in morbidity while still providing the same prognostic information, regional control, and survival as conventional ALND in clinically node-negative breast cancer patients.

Eligible patients are women with operable invasive, primary breast cancer and clinically negative lymph nodes. Group A patients will undergo SN resection, followed immediately by conventional ALND. Group B patients will undergo SN resection and, if the nodes are found to be negative intraoperatively, will receive no further surgical treatment. Patients with positive SNs found intraoperatively and patients in whom an SN is not identified will undergo ALND. Patients who appear to be SN negative intraoperatively but on further pathologic review are determined to have positive SNs will undergo ALND.

The primary end points of the trial include measurements of overall survival, DFS, and long-term regional control. Secondary end points include morbidity measurements, including edema of the arm, range of motion, and neurologic deficits. Ancillary pathologic study of lymph nodes includes immunohistochemistry of SNs negative on hematoxylin-eosin staining.

Surgical training and standardization began in the fall of 1998, and accrual of patients began in May 1999.

Training consists of a site visit by a surgeon skilled in the technique used in the study. Training includes instruction in intraoperative probe detection of SNs and use of the blue dye technique. Careful attention will be paid to extraaxillary locations. At the site visit, surgeons will scrub in for the training session to train or standardize the technique of the site surgeon. Accrual begins after 5 cases have been satisfactorily reviewed. Each surgeon will receive case reviews over the phone of the first 15 cases entered into the trial. Surgeons so trained then are eligible to be trainers. Accrual and surgeon participation status will be presented at the meeting.