Proceedings of the Consensus Conference on the Role of Sentinel Lymph Node Biopsy in Carcinoma of the Breast April 19 to 22, 2001, Philadelphia, Pennsylvania

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A consensus conference on the role of sentinel node biopsy in breast cancer was held in Philadelphia in April 2001. The participants included many highly respected American and European investigators in this area. This report summarizes the deliberations of the group and promotes its current guidelines for the integration of this new technique into contemporary clinical practice. HUM PATHOL 33:579–589. Copyright 2002, Elsevier Science (USA). All rights reserved.

Surgery has witnessed few procedures that have been so rapidly adopted into clinical practice as sentinel lymph node biopsy (SLNB) in patients with breast cancer. Critics state that SLNB has been not validated by any randomized clinical trials that are the customary sine qua non for the adoption of innovations in medicine; advocates maintain that, as a diagnostic procedure, it does not require the same lengthy, randomized trials as the adoption of a new treatment mandate, and its accuracy has already been validated by studies comparing SLNB with traditional axillary dissection in the same patient(s). Which of these positions is more correct is moot, because SLNB has been adopted ubiquitously by surgical specialists around the world, and current major concerns relate to perfecting its use.

Introduced in the mid-1990s, SLNB for breast cancer has now been performed on thousands of patients with breast cancer (men as well as women); nevertheless, there remains a myriad of unanswered questions. Controversy abounds concerning patient selection criteria, surgical technique and complications, handling of the sentinel node(s) by the surgical pathologist, adjuvant therapy for axillary node "submicrometastasis" detected only by immunohistochemistry (IHC), and other details of the procedure, as well as safety for patients and personnel.

To address these various issues, an international consensus conference was convened in Philadelphia, sponsored by The Breast Health Institute and The Fashion Group International, Philadelphia, on April 19 to 22, 2001. The panel comprised individuals representing the disciplines of surgical oncology, surgical pathology, breast imaging (radiology), nuclear medicine, radiation oncology, and medical oncology, each of them highly experienced in this new technique.

The group attempted to reach consensus on the following issues:

1. The "best" definition of the "sentinel" node(s)
2. Accuracy of SLNB in finding the first node to which metastasis occurs
3. Which techniques used to identify the sentinel node(s) are better for which patients
4. Learning the procedure and maintaining this skill over time: How many axillary dissections accompanying SLNB are enough to adopt SLNB as a stand-along procedure; Definitions of "failed" SLNB and "false-negative" SLNB, and acceptable and expected rates for each
5. Safety, contraindications, and complications of the procedure
6. Handling and processing the sentinel node(s) from the time of identification and excision until the microscopic report is issued by the pathologist
7. The role of immunohistochemistry in identifying "positive" sentinel nodes and in reaching decisions on adjuvant treatment
8. Treatment of the patient with a positive hematoxylin and eosin stain after a negative intraoperative frozen section or touch preparation: reoperation, radiation therapy, or observation alone
9. Role of SLNB in patients with ductal carcinoma in situ (DCIS), if any
10. Role of SLNB in mastectomy patients.

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List of conference participants and affiliations appears at the end of the paper.

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The panelists recognized that in some situations a clear consensus cannot be reached for various reasons, including lack of convincing data or differences in judgment based on personal experience. When these occurred, the differences were noted, and majority and minority opinions were debated. In general, however, the 3 days of discussion culminated in clear areas of agreement that satisfied each panelist, and each member of the panel has approved this document as a fair representation of the consensus achieved. However, this publication must not be viewed as "evidence-based." Rather, it is an editorial about SLNB that presents the opinions of the panelists. Certainly, these views are a reflection of the extant body of "evidence-based" data, a goodly portion of which was authored by the panelists, but a bibliography has been deliberately omitted from this document.

DEFINITION

The sentinel node is the first node to which lymph drainage and metastasis from breast cancer occurs. Although usually an axillary node, and most commonly in the central group of level I, the sentinel node may be at level II (behind the pectoralis minor muscle) or at level III (infraclavicular), or may be an intramammary node, an interpectoral (Rotter's) node, or an internal mammary node. Because $<5\%$ of breast cancers with positive nodes will have clinically relevant metastasis to internal mammary nodes only, the latter is an unusual finding. Rarely, the sentinel node may even be a supraclavicular node.

ACCURACY

For surgeons and management teams with appropriate and adequate training and experience, the panel considered SLNB to be a suitable replacement for axillary dissection as a staging and diagnostic procedure in T1 and T2 (usually ≤ 3 cm) breast cancers. The accuracy of SLNB has not been verified in larger cancers. The postoperative and subsequent morbidities of SLNB are significantly less than those of axillary dissection; the major complications of the latter are pain, paresthesias, lymphedema, infection, and restriction of arm motion. Data already published, representing institutions with carefully documented series totaling thousands of cases in the United States and in Europe, document that identification of sentinel nodes in appropriately selected patients is $>95\%$. This is comparable to the failure to detect a metastatic focus in the nodes recovered from a traditional axillary dissection (usually levels I and II in the United States and most European countries) or even a complete axillary dissection. In the traditional dissection, the false-negative rate relates to a less extensive microscopic examination of the lymph nodes compared with the surgical pathology protocols for SLNB and/or to the failure to remove level III or lower or aberrant axillary nodes or nodes that lie "outside" the axilla (see Sec. 3).

Although at least 1 of the current clinical trials mandates axillary dissection after negative SLNB as a therapeutic arm, the panelists strongly felt that, because SLNB has already been validated as a diagnostic procedure when performed according to the techniques discussed herein, one need not wait for the results of these randomized trials to perform SLNB. These trials may help identify the training and experience required to achieve and maintain an acceptable rate of false-negatives as well as the correct interpretation and use of the information obtained. The observed incidence of subsequent metastasis to the remaining axillary nodes (i.e., axillary recurrence) after negative SLNB has been a rare occurrence, although the longest follow-up has been 10 years and the median follow-up is much less. Irrespective of the criticisms raised by the panelists about specific trials, the entire group strongly encouraged surgeons who perform SLNB to participate in ongoing clinical trials in the United States and Europe.

When the procedure is performed with blue dye and/or radiolabeled colloid, the sentinel node(s), the one(s) to which dye or radiocolloid has migrated, may occasionally be contiguous to a node or nodes that are clinically suspicious because of character or size. Because the purpose of the procedure is to identify the *first* node to which metastasis has spread, it is appropriate to remove this suspicious node along with those that have been identified by dye or the radiolabeled colloid. That this node does not itself pick up the dye does not vitiate the procedure, nor should this be considered a failed or false-negative biopsy. In some cases there may be no observed pickup of dye in a node, but a blue-stained lymphatic vessel can be seen leading directly to a node. This node should be considered the sentinel node and removed.

When radiocolloid is used to identify the sentinel nodes, rarely the internal mammary chain, usually a small node in the second to fourth intercostal spaces, may be the only site that picks up the isotope. More often, drainage to the internal mammary node(s) is seen along with drainage to the axillary nodes. (Thus far, drainage to the internal mammary chain has been detected only by the injection of isotope into the parenchyma of the breast [peritumoral], not by intradermal or subareolar injection.) When blue dye is used concomitantly with the radioisotope, the axillary sentinel node is usually identifiable and should be dissected, even if an internal mammary sentinel node is removed. When no axillary sentinel node can be identified by either technique (i.e., a failed sentinel node biopsy) and there is detection of only an internal mammary site, the panel was divided as to the need to dissect these nodes in addition to an axillary dissection. Most panelists felt that the internal mammary nodes should be dissected only as part of a clinical trial. Similarly, uptake of radiocolloid in internal mammary nodes only does not mandate radiation treatment to this site when these nodes are not dissected.

TECHNIQUES

The earliest reported techniques for indentifying sentinel axillary nodes in breast cancer used were the radiopharmaceutical technetium sulfur colloid and isosulfan blue dye in the United States, and technetium-labeled albumin and patent blue dye in Europe. Currently there are experienced surgeons, including several of the panelists, who have become quite expert in a single technique and use this preferred technique almost to the exclusion of the others, except under special circumstances. Nevertheless, because the use of both radiocolloid and blue dye increases recognition of the sentinel nodes by surgeons less experienced in SLNB, the panel endorsed the use of both radiocolloid and blue dye together as surgeons new to the technique learn how to perform SLNB, but individual surgeons and institutions may use either radiocolloid or blue dye alone with equal success after appropriate training and experience.

A number of established methods of injecting radiocolloid and/or blue dye to identify the axillary sentinel nodes have been published, including peritumoral, intratumoral, subcutaneous, intradermal, and subareolar. The greatest experience has been in using the peritumoral route, injecting the radiocolloid and/or blue dye outside the biopsy cavity in line with the hair-bearing area of the axilla. Substantial data now exist indicating that the intradermal technique may increase the ease of sentinel node identification because of the rich lymphatic network of the skin of the breast and less confusing than seen when the radiolabeled colloid is injected in the peritumoral area. Data are accumulating to document the efficacy of the subareolar route, which may prove equally accurate.

Individual patient circumstances often dictate technique, because surgeons may see their patients after a biopsy (incisional or excisional) has already been performed elsewhere. Although failure to identify axillary sentinel nodes was initially thought to occur more often after a previous biopsy than when the excision of the primary tumor and the SLNB are performed simultaneously, this concern is unfounded. However, extensive excisions may affect the technique's reliability. Direct injection of the radiocolloid or dye into the biopsy cavity should be avoided; migration of the material may not occur, and inaccurate lymphatic mapping may result. This may have been the reason for many of the anecdotal failures reported after a prior procedure. The depth of the injection (i.e., peritumoral rather than intradermal) may affect the likelihood of internal mammary nodes being visualized if they are the sentinel nodes; the deeper the injection, the more likely that internal mammary sentinel nodes will be visualized. Intradermal injections will not usually identify internal mammary drainage.

For the radiocolloid is used (technetium-labeled sulfur colloid in the United States and Europe, and technetium labeled albumin in Europe, because the latter is not FDA-approved in the United States), the panelists reported using varying doses of the radiolabeled colloid, from 0.1 milliCurie (mCi) (3.7 MBq) to 3 mCi (111 MBq), in varying volumes of saline, from 0.1 to 5 mL, and from a single injection to 3 or more injections, spaced about 1 cm apart at the selected site. Close cooperation between nuclear medicine (because most patients are injected by the nuclear medicine staff) and the surgeon is required to share information about minor changes in injection technique, dose of radiocolloid used, and so on. The panel felt that whenever possible, the surgeon should inject the isotope or be present to guide the injection into the appropriate location.

Most of the European panelists perform lymphoscintigraphy as part of the procedure. The optimal scheduling for imaging depends on the specific injection technique used; the more rapid clearance of colloid after intradermal injection favors performing the first image as early as 10 minutes after injection, whereas the slower drainage of colloid administered in the peritumoral areas make imaging at later time points more helpful. Dynamic imaging with multiple exposures is often used up to 2 to 4 hours after injection, with imaging repeated at a later time if these findings are negative or if local circumstances favor scheduling the procedure later. The interval between injection of radiocolloid and operation also varied, from 2 hours to the day before surgery (24 hours). The panel generally felt that the longer the wait, the more likely the sentinel node(s) would be localized on the lymphoscintigram, although it is important when using colloids with smaller particle size to scheduling imaging and surgery so that the pattern of uptake is not obscured or rendered uninterpretable by the significant onward flow, or overspill of colloid, into second-echelon lymph nodes as lymphatic drainage from the injection site progresses. A longer time interval for *unfiltered* technetium sulfur colloid apparently does not produce a difference in number of nodes identified as compared with a shorter interval. Advocates of lymphoscintigraphy felt that a lymphoscintigram may help more clearly reveal the pattern of drainage across the entire lymphatic system, identifying uptake in multiple nodes, or (infrequently) detecting a "remote" sentinel node (i.e., an intramammary, supraclavicular, or internal mammary node).

Most of the American panelists were ambivalent about the need for lymphoscintigraphy, because they felt that the probes used intraoperatively were more sensitive and could be moved easily by the surgeon to more precisely localize the "hot" node(s). Other issues raised by the "nonlymphoscintigraphers" related to the greater logistical difficulty engendered by the additional need for multiple lymphoscintigrams and the fairly significant increase in the cost of the procedure when lymphoscintigraphy is added.

When blue dye is used, the volume used depends on patient size, ranging from as little as 1 to 3 mL in very thin patients with upper outer quadrant tumors to a maximum of 5 mL in obese patients (mean, 3 to 4 mL). The time between injection and the axillary incision also varies depending on patient size and the

location of the tumor in the breast. With thin patients and upper outer lesions, the time may be as little as 3 to 4 minutes between injection and incision; for large patients with medial lesions, the wait should be longer, up to 7 to 8 minutes. Most of the panelists massage the site of blue dye injection from the completion of injection until the incision is made. At least theoretically, the massage helps "drive" the dye to the sentinel nodes. Whether massage also drives tumor cells already in the lymphatics of the breast toward the nodes was a question posed by the "nonmassagers" that could not be answered by available data. The group thought that even if this were true for a few patients, it would not have clinical significance.

There is a difference between "failed" and "false-negative" SLNBs. The latter term defines the identification of sentinel nodes that are intraoperatively (imprint or frozen section) negative, yet on further examination of the fixed material contain metastatic disease, and/or identification of sentinel nodes that are negative on frozen and permanent sections but unknowingly leave positive nonsentinel nodes behind. For those surgeons who use intraoperative frozen sections or imprint cytology, "false-negative" therefore includes both an intraoperative event, that is, the intraoperative failure to identify metastasis later documented on the hematoxylin and eosin (H&E)-stained slides, or failure of the sentinel node(s) examined to reflect the true axillary status. The true false-negative rate will be learned only if there is a concomitant full axillary dissection, or if the patient subsequently develops detectable axillary disease. The intraoperative false-negative frozen section or touch preparation may represent a failure of the pathologist's technique, whereas overlooking an axillary metastasis is an error of dye injection and/or surgical technique.

"Failed" SLNB implies inability to identify the sentinel nodes by dye, radiocolloid, or both. The failed SLNB usually leads to an immediate traditional axillary dissection. Metastasis to the axilla is unlikely to be overlooked, but the benefits of SLNB will be missed. In contrast, the false-negative SLNB, removing a putative sentinel node(s) that the pathologist calls negative for metastasis, but leaves metastasis behind, may have untoward clinical consequences. Learning and precisely practicing the SLNB technique should minimize both of these situations; failed sentinel node identification occurs in the most experienced of hands in only about 1% of attempts.

TRAINING

As pioneers in the SLNB technique, most of the panelists were self-taught, first performing sentinel node biopsy along with traditional axillary dissection to validate the accuracy of their individual techniques. Based on their own learning experiences, the panel unanimously endorsed a training period for neophytes in SLNB before substituting this technique for traditional axillary dissection. The various clinical trials examining different aspects of sentinel SLNB in the United States and Europe virtually all require that the cooperating surgeons be chaperoned in some way before embarking on sentinel node biopsy without concomitant axillary dissection. Nevertheless, and despite this caveat, most surgeons in the United States adopt and rely on SLNB after only a very brief introduction to the technique. As of this date, most hospitals have not addressed credentialing in SLNB as they have in other procedures, such as advanced laparoscopic procedures. A parallel exists for stereotactic breast biopsy, also a diagnostic procedure, but unlike for SLNB, most hospitals do mandate a given number of proctored biopsies before the physician embarks on his or her own.

If SLNB is to replace formal axillary dissection in the majority of patients with T1 and T2 clinically node-negative (N-0) breast cancers, then it must be an accurate representation of the entire axillary lymph node status. Until a surgeon documents his or her own experience with the procedure and consistently achieves a detection rate of >90% and a false-negative rate of <5%, he or she should perform a concomitant traditional axillary dissection. Maintaining this skill is also required, and periodic review of one's own data is appropriate.

How SLNB is learned was also a topic of great discussion among the panelists. It ranges from "do-it-yourself" data collection systems to official postgraduate sponsored courses taught under the direction of surgical or oncology societies or (usually) university-based teams. Both NSABP and ACOSOG require evidence of achievement in performing SLNB to participate in their clinical trials. This evidence is either performing a proctored procedure, followed by a given number of SLNBs with concomitant back-up axillary dissection, or by the documentation of accuracy of SLNB by a set number of back-up axillary dissections. The passing score is set in the 90% to 95% accuracy range (for failed and for false-negative biopsies). Several European clinical trials have set guidelines for participation in much the same way. Whichever learning technique is chosen, the surgeon's false-negative and/or failure to detect rate should be <5% before he or she embarks on SLNB alone without back-up axillary dissection. Panelists report consistent false-negative rates of <3% in their own series and even lower than that for failed sentinel lymph node identification.

SLNB should not be adopted unilaterally by a surgical team without the cooperation of the institution's nuclear medicine and surgical pathology departments, as well as the nursing staff. Each of these disciplines plays a crucial role in achieving success, and the surgeon cannot embark on a successful SLNB program without cooperation from these other disciplines.

The precise number of SLNB procedures with accompanying traditional axillary dissection required to validate a surgeon's technique engendered significant discussion. The numbers proposed by the panelists ranged from 10 to 100, reflecting in part their own self-taught experience and observations from teaching the procedure to residents as well as trained surgeons

enrolled in postgraduate courses as described before. Because data have been collected from these teaching experiences, the requisite number of negative SLNBs accompanied by full axillary dissection has fallen, so that the most of the panelists were reasonably comfortable with 20 to 30 concomitant axillary dissections to validate SLNB, with a false-negative and failure to detect rate of <5%. Parenthetically, the false-negative rate can be established only in patients with involved axillary nodes (e.g., <30% of clinical stage I cancers), so that the number of axillary dissections to establish the false-negative rate will depend on the prevalence of axillary node metastasis in any individual surgeon's patients.

Maintaining these skills was also discussed, especially because specialized breast centers and/or surgeons specializing in breast disease are not as common in the United States as in Europe. The available data suggest that maintaining the skills necessary to achieve the <5% false-negative goal requires a suitable volume of cases, but the optimal number of cases per month needed to document this impression has not yet been determined and is likely to be highly variable.

SAFETY, CONTRAINDICATIONS, AND COMPLICATIONS

In addition to the usual precautions that are part of any surgical procedure, there are specific safety issues relating to the procedure itself. Allergic reactions to both the blue dye and to the radiocolloid are very rare but have been reported; these usually take the form of urticaria, but true anaphylactic reactions have been reported. At least 1 death has been reported, presumably from an anaphylactic reaction to blue dye. The urticaria following blue dye injection may take the form of striking blue-colored wheals. Treatment should be as for any allergic reaction occurring in the perioperative situation.

Postoperative complications of SLNB are less common than those of more extensive axillary dissection. When the sentinel nodes are easily found and dissected from the contiguous axillary tissues and no further axillary dissection is required, the customary vacuum drain used after complete axillary dissection may be omitted. An occasional patient may require aspiration of a small lymph or serum collection, but this is not common, and the discomfort associated with the drain is avoided. If breast conservation surgery and radiation are chosen, then physical activity may begin much earlier than after a formal node dissection, because the patient's arm motion is virtually unrestricted after SLNB. Radiation therapy and adjuvant chemotherapy, if used, may begin sooner than after traditional axillary dissection.

The panelists have rarely encountered patients with post-SLNB lymphedema, so that the incidence of this complication after SLNB should be remote. Likewise, as long as SLNB has been performed, reported cases of axillary metastasis after negative sentinel node biopsy have been rare. Obviously, because it has been only a decade since the procedure was initiated, it may be too soon to be completely secure in this observation.

Issues of radiation safety were also discussed at length. The nuclear medicine team, the surgical staff, the pathology staff, and the environmental cleanup teams are all exposed to the radiocolloid. Each hospital has its own established guidelines for radiation safety but may require education about the data associated with SLNB.

The radiation exposure to patients, surgeons, operating room personnel, and pathology and nuclear medicine department staff from radiocolloid sentinel node techniques is extremely low, and pregnant women are not exposed to any significant risk. Each procedure results in a level of personal exposure that is a very small fraction of the maximum allowable yearly dose. Relating the radiation exposure to better-known events, the radiation exposure to the patient from SLNB using 0.5 mCi of radiolabeled colloid is about the same as from a 4-exposure exposure mammogram, 0.4 milliSievert (mSv).

A specific radiation safety issue in SLNB is that items of radioactive waste may be created in the operating room through the transfer and absorption of small volumes of the radiocolloid from exposed tissue at the injection site onto sterile gauze sponges, depending on the exact surgical procedure performed. These can also act as an extraneous focal source of radioactivity that may cause the radiation probe to generate falsely elevated counts if placed closely to an area of investigation under the probe. Care must be taken in handling them once used at the injection site. The design of the probe's sterile drape should not concentrate any radioactivity. Radiation safety badges are not considered necessary for surgeons, nurses, and pathologists. If these are worn as part of hospital practice, then caution must be taken to keep point sources of radioactivity from making direct contact with radiation badges and generating falsely elevated counts.

Local radiation safety guidelines differ, but special procedures for handling waste materials are not normally required beyond sealing and identifying this waste within the operating room, then handling it according to institutional practice for radioactive waste disposal. This may require the waste to be placed in storage for decay until the radioactive content falls below levels permitted for disposal as normal clinical waste. To achieve this conveniently, it may be possible for the waste to be transferred to the nuclear medicine department for storage within its specialized facilities.

The specimens, both breast and sentinel nodes, contain radioactivity at sufficiently low levels to cause minimally low exposure to staff involved in specimen processing and interpretation, and such specimens may be safely be processed immediately by personnel repeatedly performing or handling sentinel node biopsies. Specimens and resulting trash should be handled as described earlier. As a guide, if stored for 60 hours (10 half-lives of technetium), the radioactive content will fall 1000-fold. Some radioactivity will remain on the cutting blade of cryostats used for frozen sections of

sentinel nodes detected by radiocolloid, but no special precautions are necessary other than to clean the cryostat after its use and place tissue paper beneath the blade to contain debris from the block as it is cut. This trash should also be discarded as described earlier, according to local requirements. Transportation of specimens to a separate institution for processing may require special arrangements also dependent upon prevailing regulatory requirements.

There are specific contraindications to SLNB. These include the patient with a clinically positive axilla (N-1), because the dye or radiocolloid may be blocked from identifying the sentinel node because the efferent lymphatics may be tumor-filled and lead the dye astray. This is a clinical judgment, based on the surgeon's assessment of the axilla. In patients who otherwise would be candidates for SLNB and who have equivocal axillary findings, several members of the panel suggested preoperative axillary ultrasound and fine-needle aspiration biopsy of any suspicious nodes before the decision about surgery. If the fine-needle aspiration is negative, the SLNB is performed, and obviously, if positive, then level I and II dissection would then be the indicated procedure. Most of the panelists do not use ultrasound of the axilla; if a node is clinically suspicious when encountered at operation, then it would be removed during the sentinel node procedure to check its status, even if it is not *the* sentinel node.

SLNB has been used to a very limited degree in selected patients with locally advanced tumors and axillary metastasis who have undergone induction (neoadjuvant) chemotherapy and thus far has almost always been followed by a traditional axillary dissection. Although anecdotal data suggest a role for SLNB in this group of patients if the axillary nodes are clinically N-0 at diagnosis (or N-0 by ultrasound) or rendered N-0 by the chemotherapy, this must still be considered beyond the usual scope of SLNB, and it should not be performed outside a clinical trial.

Allergies to the blue dye or the radiocolloid should be considered contraindications to the use of that particular material. There is no cross-reactivity between them. It is a common fallacy that allergies to sulfa or sulfur predict reactions to the blue dye. According to available observations, this is not so. Allergy to cosmetics containing blue dye is a relative contraindication, however.

The risks of lymphatic mapping by blue dye or radiocolloid in pregnancy are unknown. Therefore the panel uniformly advised against SLNB in pregnant women until more data become available.

Prior axillary procedures (i.e., augmentation mammoplasty through an axillary incision, prior axillary node biopsy for another reason, and recent reduction mammoplasty) are other relative contraindications to SLNB. The performance characteristics of SLNB in patients who have undergone reduction mammoplasty are unknown. However, the crucial anatomic consideration is the presence of intact lymphatic pathways between tumor and the axilla, not the time from prior surgery. For example, if the tumor is in the intact upper outer quadrant with undisturbed lymphatic drainage, then a recent reduction procedure would not likely affect SLNB. It is probable that there is a greater false-negative or failure to identify rate in these patients that becomes less likely as the time interval from reduction procedure to SLNB lengthens.

Other than as noted above, recent breast surgery (ie., the biopsy procedure, irrespective of its character [excisional, incisional, or core] that confirmed the cancer diagnosis) is not a contraindication to SLNB and does not vitiate its success. Several panelists presented their own data (gathered because this question had arisen as the practice of SLNB evolved) to support this position.

The role of SLNB in multicentric cancer has not been established. Several members of the panel have performed SLNB in patients with 2 discontiguous tumors in the same breast, using separate injections at each site. However, experience with these patients is limited, and currently SLNB is not recommended for women with multicentric cancer outside of research protocols. Multifocal cancer (a different focus in the same quadrant) is not a contraindication to SLNB, presuming that the total diameter remains $\leq$3.0 cm for most of the panelists, $\leq$5.0 cm for some.

HANDLING THE SPECIMEN

Because SLNB removes only those nodes presumed to be the most important to the diagnosis of metastatic carcinoma, usually only 1 to 3 nodes, instead of the 15 to 20 or more nodes recovered from the traditional axillary dissection, the small specimen and its importance have led to new surgical pathology techniques. Most institutions, even those dedicated to cancer, make 1 H&E-stained slide from each node recovered from traditional axillary dissections, perhaps dividing the node in half or in thirds along its long axis, with 1 section from each tissue slice. Serial or step-sectioning of lymph nodes is not usually required except in accordance with special research protocols.

In response to SLNB, new surgical pathology protocols have emerged to ensure that the intraoperative examination of sentinel nodes is as accurate as possible, (i.e., avoiding false-negative reports) and also to ensure that the subsequent final sections do not overlook the tiniest of metastatic foci in a node. Recently added to the routine H&E staining of lymph nodes has been the additional examination of the lymph nodes by cytokeratin staining or polymerase chain reaction, techniques that may detect single malignant cells.

Pathologists have recognized that both occult and nonoccult metastases may be recognized more easily in sentinel nodes than in nonsentinel nodes, because of the intensive scrutiny that can be brought to bear on these small specimens, increasing the proportion of node-positive cases. Pathology societies have addressed the wide variation in the methods used to evaluate sentinel nodes, and the consensus panel strongly endorsed the recommendations of the College of Ameri-

can Pathologists Consensus Statement (1999), with some additional comments.[1]

Whether detected by radiocolloid or blue dye, the sentinel nodes should be prosected by an experienced surgical pathologist. Each sentinel node should be measured and cut along its longitudinal axis into 1.5 to 2.0-mm-thick sections. The pathologist should perform careful gross examination of the sections to detect focal lesions. Several panelists stated that touch preparations (imprint cytology) are preferred over frozen sections for intraoperative consultation, to avoid unnecessary sacrifice of tissue in the cryostat. However, many pathologists consider touch preparations more difficult to interpret and are reluctant to rely on them when an intraoperative consultation is requested. When frozen sections are performed, it is recommended that each of these 2-mm sections be cut at 3 levels. Intraoperative examination should find the great majority of metastatic deposits 1 mm in diameter or larger. The lymph node sections are then submitted in toto in formalin for paraffin section histology. Each paraffin block should be sectioned at 3 levels. Additional sections are indicated when questions are raised about the findings. When metastases are noted, the pathology report should note whether they are individual cells or malignant cells in clusters (colonies), as well as their location within the node(s). The size of the largest metastatic deposit should be noted.

SPECIAL TECHNIQUES TO DETECT METASTASIS

Immunohistochemical techniques such as staining with antibodies to cytokeratin and polymerase chain reaction analysis can be used to detect epithelial cells, presumed to be metastasis, or tumor DNA or RNA in sentinel lymph nodes. Epithelial cells or cellular fragments may be transported to axillary nodes after instrumentation of the breast by "core" or surgical biopsy. Whether these cells are cancer cells, and even if so, whether they have clinical significance, remain unanswered questions. Cytokeratin-positive artifacts such as degenerating cells in transit, dendritic cells, macrophages, and epidermal squamous or ductal epithelial cells may be identified in the lymph nodes as well by these techniques. They should not be misread as malignant cells.

A major focus of the panel's discussion was whether to use of IHC as an adjunct to routine (H&E) microscopic examination of sentinel nodes and whether this information should influence patient care. For more than a decade, the term "micrometastasis" has been used to describe axillary metastatic disease 0.2 cm (2 mm) or smaller. The use of IHC to detect individual malignant cells or malignant cells clusters mandates the redefinition of the term "micrometastatic" and has spawned the recognition of what should be considered a new category of metastatic disease, as yet unnamed. This panel redefined "micrometastasis" to be a cohesive cluster of malignant cells, 0.2 mm and up to and including 2.0 mm in diameter. The panel concurred that, using this definition, micrometastasis >0.2 mm diameter in a sentinel node might indicate significant axillary disease depending on the size and features of the primary cancer (perhaps in as many as 10% of patients), whereas, "submicrometastasis," 0.2 mm or less in size, was highly unlikely to be associated with significant residual metastasis, regardless of primary tumor characteristics.

That IHC may detect clusters of or individual malignant cells <0.2 mm in diameter was not disputed. Whether IHC should be used routinely by pathologists to examine H&E-negative nodes further for these "submicrometastases" is currently a contentious issue that the panel addressed at length, as was the use of this information to guide recommendations for patient care. Available data indicate that most hospital pathology laboratories in the United States have adopted 1 of the immunohistochemical techniques, usually cytokeratin analysis, as a routine step when the sentinel node(s) are H&E negative, although each of the (American) clinical trials (NSABP and ACOSOG) interdicts this study except at its own designated laboratory and does not communicate the results of the analysis to the participating surgeons or to patients. Several European trials do use immunohistochemistry routinely despite the lack of data concerning how the results should be used.

There is no current convincing evidence that clusters of malignant-appearing cells ≤ 0.2 mm in diameter (i.e., "submicrometastasis") predict an adverse outcome. Most of the panelists endorsed the position that routine IHC should not be considered standard practice, and the pathology report should state only whether metastasis are found on H&E-stained slides. IHC may be performed when the H&E-stained slides have suspicious cells that are equivocal. For example, the occasional difficulty in identifying metastasis to lymph nodes in patients with invasive lobular carcinoma has led to the use of IHC in this subgroup of patients to evaluate questionable areas seen on the H&E slides. If IHC suggests the presence of metastasis, then the same areas are reevaluated on the H&E slides and a decision made on this basis. The panel did not consider this use of IHC to violate the "not standard practice" doctrine. Whether the few malignant cells detected in this manner are of prognostic significance is also uncertain.

When IHC is performed, the panel recommended that isolated cytokeratin positive malignant cells be quantified, for example, as ≤ 10 cells, 11 to 100 cells, or >100 cells (as represented in 2 dimensions in a slide). Note should be made as to whether they are isolated cells or are identified as a single or more than 1 cluster of cells.

The panel also expressed concern that many oncologists have recommended adjuvant chemotherapy based on IHC detected metastasis only. They unanimously and strongly endorsed the position that recommendations for adjuvant therapy, either chemotherapy or hormonal treatment (or for completion axillary dis-

section or axillary radiation) should not be made solely on the basis of information obtained by IHC of sentinel lymph nodes. This is an especially important point to emphasize, because many patients undergoing SLNB have T1-a or T1-b cancers, and adjuvant systemic therapy would not be customarily recommended based on tumor size alone. For patients with T1-c or T2 cancers, current clinical practice mandates consideration of adjuvant therapy irrespective of node status. Although the IHC data would not influence this recommendation, the panel again unanimously agreed that IHC findings should not affect the choice of drugs.

MANAGEMENT OF THE (INTRAOPERATIVE) FALSE-NEGATIVE PATIENT

Fortunately, the SLNB technique has been refined so that the likelihood of a false-negative biopsy (as defined above) is currently <3%. Nevertheless, albeit infrequently, the final H&E-stained slides will document the presence of axillary node metastasis after the intraoperative imprint cytology and/or frozen sections were read as negative. This is not a failure of the sentinel node technique but a limit of frozen section or imprint cytology. These are usually very small areas of disease, although they may not always be micrometastases. What then to do?

Current practice guidelines imply axillary dissection following the intraoperative finding of metastasis in the sentinel nodes, however small. Therefore, it has been customary practice to advise that the patient return for this additional procedure (completion of level I and II dissection) if the presence of metastasis on the final H&E-stained slides is proven. Some current clinical trials have 1 arm that omits this step, remanding the patient to follow-up only, so that the omission of axillary dissection in this way has been generally considered part of a clinical trial only. The observation that the sentinel node(s) are the only nodes harboring metastasis in more than 1/2 of these patients, as well as the implied recommendation for adjuvant therapy in these situations, makes the assessment of "no further dissection" important to assess both regional control and long-term outcome. The characteristics of the primary lesion may be helpful in this decision, because tumor size and biology may predict the likelihood of additional nonsentinel metastasis in the axilla.

Radiation therapy alone, including the axilla, is an acceptable alternative for patients who choose to not undergo a second surgical procedure, that is, completion of the axillary dissection. Radiation rather than reoperation is reasonable if the number of positive nodes will not influence the choice of adjuvant treatment. Prior randomized clinical trials have shown equivalent regional control for axillary radiation therapy and for axillary dissection. The current recommendation outside clinical trials has been completion axillary dissection, although several panel members have had favorable experience with the substitution of radiation or observation alone instead of further surgery. There is an ongoing American clinical trial (ACOSOG) comparing completion axillary dissection with observation alone, and a European clinical trial that compares axillary radiation with completion dissection. A number of different techniques for axillary irradiation have been used by different investigators in the United States and Europe.

With the substitution of radiation therapy or observation alone for completion axillary dissection, whether axillary irradiation as a separate field is required in this situation is also uncertain. Current radiation techniques for breast conservation using conventional breast tangents achieve 2/3 to 3/4 coverage of the full axilla, as determined by placement of radioopaque clips during the surgical procedures. This is virtually the same area as a level I and II dissection. If the radiation oncologist uses 3 dimensional computed tomography–based planning, a small change, widening of the fields, would cover most of the axilla. Therefore, a completion axillary dissection could be avoided in the node-positive patient by substituting radiation therapy as long as the radiation oncologist makes appropriate adjustments to his field. A current European clinical trial is examining the role of axillary radiation compared to axillary dissection in sentinel node-positive patients. Observation alone may prove to be appropriate for axillary micrometastasis (both the traditional micrometastasis ≤2 mm in diameter as well as the "submicrometastasis" detected by IHC) in the sentinel node in selected patients; this is a question that hopefully will be answered by ongoing clinical trials.

SENTINEL NODE BIOPSY IN DUCTAL CARCINOMA IN SITU

The low morbidity of SLNB has led to its consideration in patients with DCIS, based on reported observations of occasional axillary node metastasis in these patients. The panel was quite insistent about separating the 2 diagnoses: DCIS alone without evidence of any invasion versus DCIS with microinvasion. Most of the panelists would not recommend SLNB in the former group but would do so in the latter, because these patients formerly were advised to undergo at least a level I axillary dissection because of the small, but real, possibility of axillary metastasis. SLNB in patients with mammographically detected DCIS (i.e., as small areas of calcifications in the breast) or the diagnosis of DCIS made as an incidental finding is not currently indicated. For those patients with DCIS detected as a palpable mass or with large areas of calcifications treated with mastectomy or very large lumpectomy, SLNB may be indicated because, although the disease is noninvasive *in the sections studied*, invasion may be overlooked because the area of disease is so large. Some of these patients require mastectomy to treat DCIS, and the addition of SLNB to the mastectomy obviates the need for subsequent axillary dissection if invasive carcinoma is found in the mastectomy specimen. Regarding the injection site for SLNB for this group of pa-

tients, when the diagnosis of DCIS is made by percutaneous needle biopsy, intradermal injection in the most involved quadrant is an appropriate choice; subareolar injection may also be considered. If prior surgical biopsy had been performed, then the injection would be as for any other SLNB for invasive cancer.

SENTINEL NODE BIOPSY DURING MASTECTOMY

Although SLNB evolved as an accompaniment to breast conservation, the panel endorsed the use of SLNB during mastectomy, using the same selection criteria as already described for patients undergoing breast conservation. Panelists reported that various techniques have been effective. Whether using blue dye, radiocolloid, or both, and whether using a single incision or separate incisions for breast and axilla, SLNB works well in patients undergoing mastectomy. The lymph node dissection during mastectomy is then influenced by these results, limiting the axillary dissection to the sentinel nodes only if they are negative, and continuing with the "standard" node dissection if metastasis is documented.

Unlike SLNB used in conjunction with breast conservation, a second axillary procedure to complete the axillary dissection after mastectomy is more technically demanding if a false negative is encountered, especially if an immediate reconstruction had been performed. If the final H&E stains detect unsuspected metastasis, the mastectomy having been completed without an additional node dissection, the panel recommended a different approach than used with breast conservation. If the metastasis is in a single node and <2 mm in diameter (i.e., a single micrometastasis), most of the panelists did not favor redissection of the axilla, if the metastasis was >2 mm in diameter or in more than 1 sentinel node, additional axillary surgery (or radiation) was indicated despite the technical challenge.

As the conference concluded, the panelists unanimously agreed that the procedure of SLNB for carcinoma of the breast is constantly being refined, and observations and recommendations made at this time may be influenced by new data reported almost contemporaneously, as well as in the future. Because this report is based on the expert opinions and individual experience of the participants listed as of the date of the conference these opinions must not be construed as dogmatic guidelines for treatment. This consensus report is not intended to establish specific standards of care or to be used as a syllabus for diagnostic or treatment management decisions by third-party payers. Management of individual patients should be based on each patient's unique clinical circumstances. Recommendations for treatment must be made by the responsible physician(s) with the participation of the patient.

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