



Wassily Kandinsky (1866-1944). *Improvisation V (Park)*, 1911.

The application and the effects of the lymphatic mapping technique in patients with several different epithelial cancers are reviewed.

Lymphatic Mapping in Solid Neoplasms: State of the Art

Emmanuel E. Zervos, MD, and William E. Burak, Jr, MD

Background: *Lymphatic mapping and sentinel lymph node biopsy is an established technique for the staging and treatment of melanoma. The success of lymphatic mapping in this realm has broadened its application to other solid neoplasms. This update reviews the status of sentinel lymph node biopsy in its most widely cited applications.*

Methods: *Seminal manuscripts on lymphatic mapping in melanoma, breast, colon, vulvar, cervical, lung, gastric, and head and neck cancers are reviewed.*

Results: *Studies suggest that the application of lymphatic mapping as a staging tool in breast cancer and melanoma is justified when applied by trained surgeons. Additional validation is necessary before sentinel node biopsy is advocated in gynecologic, colon, lung, and head and neck cancer.*

Conclusions: *As in breast cancer and melanoma, validation of the sentinel node concept in other solid tumors must occur in institutions other than those in which the technique is being developed before it is generally applied to other neoplasms.*

From the Department of Clinical Investigations, at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, Florida (EEZ), and the Division of Surgical Oncology at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at the Ohio State University, Columbus, Ohio (WBE).

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Address reprint requests to Emmanuel E. Zervos, MD, at the University of South Florida, Moffitt Cancer Center, Department of Clinical Investigations, MRC-3037, 12901 Magnolia Drive, Tampa, FL 33612 E-mail: zervosee@moffitt.usf.edu

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Historical Perspective: Lymphatic Mapping and Sentinel Node Biopsy

The origins of lymphatic mapping date back to more than 100 years ago, when Sappey injected mercury into the skin of cadavers to delineate cutaneous lymphatic pathways.¹ Lymphoscintigraphy was described by Sherman and Ter-Pogossian² in 1953, and they confirmed Sappey's hypothesis that lymphatic drainage occurs in an orderly and predictable fashion. Cabanas³ introduced the concept of the "sentinel node" in 1977 when he identified it as the first lymph node to drain a penile tumor. He reasoned that if nodal metas-

tases were to occur, they would most likely occur in this node. This was proven using contrast lymphangiography to correlate sentinel node histopathology with outcome. In 40 patients with penile cancer with noninvolved sentinel nodes, he documented a 5-year survival rate of 90% (which was significantly better than those patients with involved nodes). The work by Cabanas predates modern sentinel node identification techniques such as intraoperative lymphatic mapping with blue dye or radio sulfur colloid, but the strong correlation noted between sentinel node pathology and prognosis created enough interest in the concept to motivate physicians to investigate its applicability in other solid tumors.

Morton and colleagues⁴ were the first to apply the sentinel node concept to another tumor type. In 1992, they reported results of sentinel node biopsy in malignant melanoma. Using blue dye as a mapping agent, they identified sentinel nodes in 194 of 237 lymphatic basins. They noted metastases in 21% of these nodes and found nonsentinel node metastases in only 2 of over 3,000 nodes harvested. In 1993, Alex and Krag⁵ described lymphatic mapping in melanoma using a hand-held gamma detection probe to localize technetium-99 sulfur colloid in the sentinel node. They noted the inherent advantages of the radiolabeled tracer: it expedited the procedure, facilitated its application by surgeons with minimal mapping experience, and provided even less invasive localization than obtained with blue dye alone. Ultimately, the blue dye and radiolabeled colloid techniques were combined and refined such that sentinel node nonlocalization and false-negative rates diminished to a level that supported its application outside of the centers that developed and perfected the technique.

The next major step in lymphatic mapping occurred when investigators from John Wayne Cancer Center⁶ applied the principles established in melanoma to breast cancer. Their success in doing so ignited a revolution in the management of all solid neoplasms that brought into question traditional concepts of the prognostic and therapeutic implications of traditional lymphadenectomy in all solid tumors. In 1998, their group reported results of universal application the sentinel node concept in patients with thyroid, gastrointestinal, gynecologic, Merkel cell, and squamous cell cancer of the head and neck. Sentinel nodes could be identified in 96% of these patients.⁷ These data encouraged other centers to apply the concept in settings other than melanoma. While the technical details regarding localization differ somewhat for each individual tumor, the underlying rationale is preserved in all disease processes. Through comparatively less invasive means, the sentinel node provides an optimal

amount of highly predictive tissue for pathologic analysis that, in turn, provides new and meaningful staging and prognostic information (Table 1). Using melanoma and breast cancer as platforms for proof of principle, we review the state of the art of lymphatic mapping in solid neoplasms.

Breast Cancer

Rationale

The role of axillary node dissection for invasive breast cancer has been challenged over the last decade for a number of reasons. Because adjuvant therapy has been shown to increase overall survival in both axillary node-positive and node-negative patients, its indication has expanded to include all patients with tumors larger than 1 cm in size, regardless of axillary nodal status.⁸ Current chemotherapy regimens do not differ in intensity or duration because of nodal status. Routine axillary node dissection in all patients with invasive breast cancer will yield positive findings in only one third of patients as the majority of patients are node-negative, particularly with the increased use of screening mammography. Furthermore, there does not appear to be a survival advantage to axillary node dissection, although there are some limitations with the studies that have tried to examine this issue.

Axillary node dissection is accompanied by significant morbidity, including a risk for lymphedema, chronic arm numbness, and delayed wound healing.⁹⁻¹¹ This procedure also adds significant cost to the surgical

Table 1. — Summary of Localization, False-Negative, and Upstaging Rates of the Sentinel Node in Various Solid Tumors

Tumor Type	Localization Rate (%)	False-Negative Rate (%)	Upstaging Rate (%) ^a
Breast ¹²⁻³⁰	90-95	0-5	5-15
Melanoma ³²⁻⁵⁰	95-100	0-5	12
Colon ⁵⁶⁻⁶³	70-99	4-60	10-18
Vulvar ⁶⁵⁻⁶⁸	78-86	0	NA
Cervical ⁶⁹⁻⁷²	60-93	0	NA
Head and Neck ⁷⁴⁻⁸¹	78-100	0-1.5	NA
Gastric ⁸²⁻⁸⁷	99	1.3	NA
Lung ^{88, 89}	47-82	0-5	22-29 ^b

NA = not available

^a Percent of patients in whom special handling of the sentinel node resulted in primary tumor upstaging that would not have occurred with traditional staging methods.

^b These patients had histologically involved mediastinal lymph nodes that were discovered only through lymphatic mapping.

treatment of breast cancer as a result of the prolonged anesthesia, operating room time, and postoperative care. Regardless of these facts, nodal status remains the most important prognostic indicator of survival, and treatment decisions are made based on the number of involved nodes. Unfortunately, a noninvasive, accurate method of determining nodal status has not been identified, although this is an area of intense investigation.

By applying the sentinel node concept to breast cancer, most patients can be spared the morbidity of a complete axillary node dissection. This concept has been validated in both the community and the academic setting as shown by the overwhelming number of publications on this subject over the past 5 years. These publications report the results of single-institution validation studies and multicenter trials conducted both in the United States and Europe.¹²

Methodology

Lymphatic mapping refers to the technique used to identify the sentinel lymph node(s) during surgery. For the technique to be accurate, a combination of proper patient selection, effective mapping pharmaceuticals, and surgical expertise is necessary. Also essential is a multidisciplinary approach, which requires the expertise and cooperation of radiologists and pathologists.

Patient Selection

While most breast cancer patients would be considered acceptable candidates for lymphatic mapping, there are well-recognized contraindications. These can be divided into two categories: tumor characteristics and patient characteristics.

Because patients with large tumors (greater than 5 cm in maximum dimension) or locally advanced disease are generally believed to have a high chance of harboring nodal metastases, the mapping procedure will not spare many patients a complete node dissection. Also, with this increased chance of nodal metastases, the tumor cells may obstruct the lymphatics or completely replace the sentinel node, which will result in an inaccurate mapping. Patients with palpable axillary lymph nodes have a greater than 90% chance of axillary node metastases and are not candidates. Patients with pure ductal carcinoma in situ (DCIS) and no invasive carcinoma should not be mapped routinely. There are circumstances when mapping may be appropriate in this clinical scenario; these exceptions occur when there is a strong possibility of invasive cancer that may not have been diagnosed preoperatively. This “upstaging” of DCIS to invasive carcinoma most commonly occurs with high-grade DCIS, particu-

larly in situations where a core needle biopsy is used to diagnose the malignancy. In these cases, the surgeon may feel the risk of invasive tumor is high enough to warrant lymphatic mapping at the time of surgical resection of the primary tumor in anticipation that invasive cancer is present. This is a subjective indication requiring the experience and judgment of the radiologist, surgeon, and pathologist. The role of sentinel lymph node biopsy in pure DCIS is debatable and is the focus of ongoing studies.¹³

Patient characteristics that prohibit successful mapping are generally a result of anything that may have altered the native lymphatic drainage pathway of the tumor. These include prior surgical procedures such as breast implants, reduction mammoplasty, or axillary surgery. In addition, preoperative chemotherapy or radiation therapy may also adversely affect the original lymphatic channels and result in false findings. Patients with multiple tumors within their breast, particularly if in different quadrants, are also poor candidates as their tumors may each have unique drainage pathways that may not be appreciated during surgery.

Technique

The technical aspects of lymphatic mapping and sentinel node biopsy for breast cancer have been refined over the last 10 years. The most common approach utilizes two pharmaceuticals — radiolabeled colloid and blue dye — used in combination but each serving a unique purpose. Several different radiolabeled colloids have been used as mapping agents with excellent results. In the United States, technetium-labeled sulfur colloid has been used extensively. The radiopharmaceutical can be either filtered with a 0.2-micron filter or unfiltered for use. Generally, 400 to 500 μ Ci of filtered technetium sulfur colloid is diluted in a volume of 4 mL of buffered saline for injection. Unfiltered material requires approximately 1 mCi of activity diluted in 4 to 5 mL of buffered saline. Both radiopharmaceutical preparations are effective for mapping. Although much of the earlier literature suggested that peritumoral injections (in the breast parenchyma but surrounding the tumor or biopsy cavity) were successful, recent work indicates that injection into the dermis overlying the tumor may be equally effective.¹⁴

Lymphoscintigraphy, utilizing a large-field gamma camera, is sometimes used to determine the draining basin. Although this has not been shown to improve the ability of the surgeon to locate the sentinel node or to increase the accuracy of sentinel node biopsy,^{15,16} it may have a role in identifying patients with non-axillary sentinel nodes, such as to the internal mammary basin.¹⁷

Approximately 2 to 24 hours after injection of the radiopharmaceutical, patients will proceed to surgery for lymphatic mapping. Excision of the primary tumor (lumpectomy or mastectomy) is commonly performed at the same setting. Five to 10 minutes prior to surgical incision, 4 to 5 mL of the second mapping agent, a blue dye, is injected into the affected breast. Although most literature suggests that injection of the dye into the peritumoral region is effective, recent reports advocate injection into the subareolar plexus, which may be less technically demanding without compromising results.¹⁸

Five to 10 minutes following blue dye detection, the gamma detector probe is used to survey the skin over the draining lymphatic basin in search of an area of increased radioactivity, representing the sentinel lymph node. A small incision is made over this area of increased activity, and on entering the subcutaneous tissue, a blue lymphatic can be seen, which represents the afferent lymphatic leading to the sentinel node. Using a combination of visualization and the gamma detector probe (sound), the lymphatic basin is explored until the sentinel node is identified. It is then removed and sent to the pathologist for evaluation. If it shows no tumor cells, the remaining lymph nodes are left intact. A thorough evaluation of the remaining lymphatic basin is undertaken, since more than one sentinel node can be found. This requires a combination of palpation, visualization, and gamma probe survey for evidence of enlarged, blue, or radioactive nodes. The combination of these techniques results in an accuracy rate of more than 95% in predicting a negative lymphatic basin when the sentinel node is negative for malignancy.^{15,19,22}

Others have reported excellent results using blue dye alone.²³ This technique involves a low axillary incision and identification of a blue afferent lymphatic and subsequent blue node. It is essential to see the lymphatic channel exit the breast tissue so a more proximal node will not be missed. Although localization rates and false-negative rates have been excellent, this technique may be associated with a longer learning curve and preoperative lymphoscintigraphy may be required for medial quadrant tumors, which are more likely to drain to internal mammary nodes.

Several authors^{24,25} have reported using a subareolar injection of blue dye, regardless of where the tumor lies within the breast. Results are limited but encouraging. This technique has the potential for eliminating the necessity of image-guided injection techniques and will allow the lumpectomy to be performed without the blue-stained breast tissue interfering with the dissection.

Pathology

The main advantages of sentinel node biopsy for breast cancer lie both in its predictive value of a negative lymphatic basin and in its ability to identify the single node that is most likely to contain cancer. Data presented in abstract form in melanoma suggest that node-negative patients staged with sentinel lymph node biopsy may even enjoy improved survival over their nonsentinel node counterparts because the pathologist can focus attention on this single node in search of malignancy. If routine tests such as hematoxylin-eosin (H&E) staining do not show metastases, more sensitive studies can be performed. These include serial sectioning and immunohistochemistry (for epithelial cell markers) that can identify an additional 5% to 15% of patients with positive nodes. While micrometastases seen on H&E serial sectioning portend a worse prognosis when compared to node-negative patients, the clinical significance of immunohistochemistry-positive axillary lymph nodes is unclear and is currently under study in a large, prospective clinical trial sponsored by the American College of Surgeons Oncology Group (ACOSOG-Z0010).

Results

After completing a validation learning curve of approximately 20 cases, lymphatic mapping can be performed successfully. The use of a combination of blue dye and a radiopharmaceutical will result in a sentinel node identification rate of 90% to 95%. The ability to find the "correct" node (true positive rate) has also been found to be in the 95% range following the initial learning curve.^{26,27}

Long-term results with regard to survival and regional recurrence rates are currently undergoing intense clinical evaluation. Single institutions have reported a 0% incidence of axillary recurrences in sentinel node-negative patients, although follow-up is short.¹⁹ Lessened morbidity of sentinel node biopsy (compared to axillary node dissection) has been reported, particularly with respect to arm circumference (a surrogate marker for lymphedema) and subjective arm complaints.²⁸

The use of lymphatic mapping following neoadjuvant chemotherapy is controversial, with conflicting reports in the literature.^{29,30} One of the concerns with performing the procedure after chemotherapy is that tumor-filled lymphatics may respond to the chemotherapy, resulting in fibrosis and obliteration of the native channels, with resultant aberrant drainage and a false-negative result. Larger trials will be required to fully elucidate this issue.

Another controversial area is whether internal mammary nodes (IMNs) should be mapped. Although the reported frequency of isolated metastases to this chain (without axillary involvement) ranges from 2% to 11%, this is based on older literature in the era of extended radical mastectomy and may not hold true today since patients are presenting with smaller tumors.³¹ These studies failed to show a survival advantage with dissection or treatment of these nodes so they have been largely ignored until the era of lymphatic mapping. Since there are no published reports on the incidence of internal mammary sentinel node positivity, much of our approach must be garnered from our understanding of lymphatic drainage as documented by lymphoscintigraphy. This is generally thought to be in the 5% to 15% range.³¹ Fortunately, most patients with involved internal mammary nodes also have involved axillary nodes, so only a small percentage of patients (those who are axillary node-negative but IMN-positive) would have a subsequent change in treatment. This raises the question of whether the improved staging with sentinel node biopsy (both by identification of extra-axillary nodes and more intense pathologic analysis) will result in improved survival through better selection of patients for adjuvant therapies. Currently, however, the benefit of IMN sentinel node biopsy is debatable, and there is no clear consensus.

Ongoing Trials

Currently, two large prospective trials should resolve several important issues. The National Surgical Adjuvant Breast and Bowel Project is conducting a multicenter trial (NSABP-B-32) in which sentinel node-negative patients are randomized to either subsequent axillary node dissection or no further axillary treatment. This trial will evaluate the impact of the false-negative rate on regional recurrence and survival. The American College of Surgeons Oncology Group sentinel node trials will examine the clinical significance of micrometastases in the sentinel node and bone marrow of node-negative patients (ACOSOG-Z0010) and determine the therapeutic value of axillary node dissection in sentinel lymph node-positive patients by randomizing them to axillary node dissection vs no further axillary treatment (ACOSOG-Z0011).

Summary

Lymphatic mapping with sentinel lymph node biopsy is being used with increased frequency as an alternative to axillary node dissection in selected patients with breast cancer. The gamma detector device is an intraoperative tool that allows the surgeon to readily identify the sentinel node through transcutaneous and open surgical probing. Using a combination of a radiopharma-

ceutical and blue dye, a sentinel node can be identified more than 90% to 95% of the time. As an alternative to axillary node dissection, sentinel node biopsy has the potential to result in less patient morbidity, more accurate nodal staging, and lower health care costs.

Melanoma

Rationale

Lymphatic mapping in melanoma is predicated on the hypothesis that melanoma metastasizes in an orderly and predictable manner to regional lymphatics. The sentinel node concept is based on the hypothesis that a single lymph node exists in the draining basin of a particular anatomic region that is the *first* node exposed to metastatic tumor cells and that this exact node may be identified through manipulation of lymphatic channels surrounding the primary tumor. The *biologic* definition of the sentinel node is that it will always be the first node to manifest with metastatic disease and that tumor cells will never bypass this node to metastasize elsewhere. Acceptance of this definition has not only changed the way that melanoma is treated, but also caused the oncologic community to reevaluate aspects of the care and management of patients with melanoma.

In 1992, Morton et al³² rationalized the sentinel node concept by hoping to spare node negative patients (approximately 80%) the potential morbidity of elective lymphadenectomy. Validation of the sentinel node hypothesis in these patients was confirmed by performing completion lymph node dissections in all patients undergoing sentinel lymph node biopsy and comparing the pathology of the sentinel node to the remaining nodes harvested. Early results were excellent, with virtually no skip metastases identified and with low false-negative rates. Soon thereafter, the technique was independently verified by Ross and colleagues,³³ and interest in developing the best and most efficient means of identifying the sentinel node gained priority in cancer centers across the country.

Mapping Strategies

Prior to the introduction of sentinel node biopsy, lymphoscintigraphy was routinely used to identify drainage patterns in melanoma patients, especially in those patients whose primary lesions were located in areas of ambiguous drainage such as the head and neck or trunk.³⁴⁻³⁶ Morton et al³² described the injection of lymphazurin (vital blue) dye around the primary tumor preoperatively to provide visual clues to the sentinel node and its afferent lymphatic channel. Although this

strategy worked in the majority of patients, there were several inherent flaws. First, mapping with vital blue dye still required a large incision to expose the entire basin at risk. Second, it offered no real-time feedback to guide the surgeon in identifying the sentinel node and provided no information regarding the completeness of sentinel lymphadenectomy. Identification of these shortcomings ultimately led Alex and Krag³⁷ to draw the critical link between the meaningful information provided by preoperative lymphoscintigraphy and gamma detection probes that were being used at that time for other intraoperative applications. They cited the unique advantages of intraoperative use of the gamma detection probe as allowing surgeons to (1) precisely locate on the surface of the skin the position of an underlying lymph node, (2) intraoperatively guide them to the lymph node during dissection, (3) verify that the correct node has been biopsied, (4) determine the possibility of residual lymph nodes, (5) allow lymph nodes to be harvested through a small incision as opposed to raising a skin flap, and (6) rapidly and easily perform the procedure.

The introduction of intraoperative detection of the sentinel node using the hand-held gamma counter immediately improved localization rates over those described with blue dye alone. The combination of the techniques, as described by Albertini and colleagues,³⁸ further improved localization such that a sentinel node could be identified in nearly all patients with melanoma, including those located in anatomic regions with traditionally ambiguous drainage patterns. This combined strategy shortened the learning curve and put the technique into the hands of all surgeons interested in learning it. As such, focus quickly shifted to the prognostic and therapeutic implications of the various spectra of sentinel node pathology.

Impact of Sentinel Node Biopsy on the Treatment of Melanoma

In the sentinel node era, clinicians have been forced to critically reevaluate two previously unresolved issues in the care of patients with melanoma: (1) the role of elective lymph node dissection and (2) the role of adjuvant therapy.

Although the role of therapeutic lymph node dissection is well established, no study to date has shown that elective lymph node dissection impacts overall survival when compared to observation alone. The Intergroup Melanoma Trial³⁹ first attempted to address this issue by following outcomes in 740 node-negative patients randomized to elective lymph node dissection vs observation. This study was first published in 1996 and reported that patients less than 60 years of age with intermediate-thickness melanomas may benefit

from elective lymph node dissection. Unfortunately, the conclusions were considered statistically unfounded by many because this subgroup was not identified prior to commencement of the study. Nonetheless, 10-year follow-up data are now available, and the earlier conclusions drawn for these and other patients (ie, ulceration and tumor thickness are dominant predictive factors) were further validated.⁴⁰ These subgroups include patients with non-ulcerated melanomas, those with tumor thickness between 1 and 2 mm, and those with extremity melanoma. Despite the post hoc identification of these groups, the melanoma staging committee deemed the findings sufficiently important to propose a major staging revision to the American Joint Committee on Cancer (AJCC) that takes into account these new data.⁴¹

Sentinel node biopsy raises two important questions in the decision-making process regarding elective lymph node dissection in melanoma. First, do the unique staging advantages offered by sentinel node biopsy provide a valid criterion by which patients can be selected for elective lymph node dissection? Second, what are the therapeutic implications of sentinel node biopsy in the absence of clinically positive nodes?

In addition to the minimally invasive advantages of sentinel node biopsy, proponents of lymphatic mapping soon recognized that there are discrete advantages for the pathologist as well. Pathologic examination of 1 or 2 lymph nodes, rather than 20 or 30, allows for a more thorough and focused pathologic evaluation of the submitted tissue. Immunohistochemical staining using HMB45 and S100 antibodies upstages as many as 12% of patients with melanoma and supports early elective lymph node dissection in these patients.⁴² Such analysis in all lymph nodes from patients undergoing traditional elective node dissection is both cost prohibitive and labor intensive. As such, the sentinel lymph node provides previously unavailable pathologic information that guides the management of patients with melanoma.

The therapeutic implications of sentinel lymph node biopsy are based on observations noted in the World Health Organization Melanoma Program. In this powerful, prospective database, 78% of melanoma patients with nodal disease manifested with that disease *only* in the sentinel lymph node.⁴³ Based on these and similar findings in other studies, the Multicenter Selected Lymphadenectomy Trial has been initiated that randomizes patients with clinically node-negative melanoma to receive wide local excision (WLE) alone vs WLE plus sentinel node biopsy. This trial should shed light on the question of whether sentinel node biopsy alone affects survival in patients with known nodal metastases.

The second arena in melanoma in which the sentinel node concept has had significant implications is in deciding which patients should receive adjuvant therapy. Currently, the therapy approved by the US Food and Drug Administration for adjuvant use in patients with melanoma is high-dose interferon alfa-2b. This approval was based on findings of prolonged disease-free interval and improved overall survival in the Eastern Cooperative Oncology Group Trial (EST 1684).⁴⁴ Because of the high toxicity associated with this treatment, however, a second trial was initiated by the same group evaluating high- vs low-dose interferon alfa-2b.⁴⁵ This trial confirmed the role of high-dose therapy but failed to show any benefit for low-dose therapy. Interestingly, in contrast to the original study, the trial has failed to confirm an overall survival benefit with either regimen at 52 months. Now, with conflicting data in the backdrop of a highly toxic regimen, the question as to who would most benefit from such therapy has been posed based on the results of sentinel node biopsy.

Current Indications and Recommendations for Lymphatic Mapping in Melanoma

Current recommendations are that patients with pathologically involved sentinel nodes should undergo completion lymphadenectomy and possibly receive high-dose interferon or be enrolled in a clinical trial evaluating other treatment strategies.⁴⁶ To ensure that sentinel node biopsy continues to provide reliable and meaningful prognostic information, an expert consensus panel recently met in Augsburg, Germany, to formulate guidelines for the proper application of the technique.⁴⁷ They recommended that sentinel node biopsy be performed in the context of a multidisciplinary team approach including surgeons, nuclear medicine physicians, and pathologists. Patients who have undergone previous WLE are ineligible, as drainage patterns may have been altered. Mapping should be undertaken in melanomas >1 mm in depth, although vertical growth phase by Clark's criterion should also be taken into account in thinner lesions (those lesions extending through the papillary dermis have a higher likelihood of nodal metastases and should be mapped). Dynamic lymphoscintigraphy should be applied in all patients and should incorporate the antecubital and popliteal fossae in patients with extremity lesions to detect intermediate draining nodes. The gamma detection probe should be used intraoperatively to help the surgeon localize nodes detected on lymphoscintigram.

Whether sentinel node biopsy should be undertaken in patients with clinically negative thick (≥ 4 mm) melanoma remains controversial. These patients have a high likelihood of metastatic disease and many recommend that they should receive adjuvant treatment

regardless of nodal status. In one study⁴⁸ enrolling 131 patients with thick melanomas, 39% had histologic involvement of the sentinel node, and those patients demonstrated a 23% decrease in 3-year survival compared to those with histologically negative sentinel nodes. These findings suggest that the results of sentinel node biopsy can offer meaningful prognostic information in patients with thick lesions. Sentinel node positivity in these patients poses a strong argument for earlier lymph node dissection and adjuvant therapy and may further be used to stratify patients to treatment arms in new studies evaluating potential therapies.

Results from the recently completed Sunbelt Melanoma Trial are now being disseminated. As a consequence of the meticulous data accrual mandated by the trial, a broader understanding of the true definition of the sentinel node is being formulated. A recent update⁴⁹ reports that predictive nodes in this trial were always the hottest nodes (ie, most radioactive), blue nodes, the first or second node identified, or nodes containing >10% of the radioactive counts of the hottest node. This operational definition of the sentinel node may be used in the future to limit the extent of sentinel node biopsy and provide even less (highly predictive) tissue for focused pathologic examination.

Future Directions

Management of patients with melanoma is constantly evolving both in terms of diagnosis and treatment. Melanoma is thought to occur as the end result of a breakdown in normal immune surveillance and, as such, is uniquely suited for present and future immunotherapy trials. These trials represent the next major advance in the therapy of this and other immunoreactive diseases. On the diagnostic side, the role of positron emission tomography (PET) scanning is currently being investigated in melanoma, and early trials suggest that PET findings will change the planned clinical management of patients 15% of the time.⁵⁰ Interestingly, PET may someday further refine sentinel node biopsy altogether by allowing for excision of only those sentinel nodes with presumed metastatic disease as shown by PET and detected intraoperatively with new generation probes sensitive to the isotope commonly employed in PET,^{18F}

Colon Cancer

Because extensive lymphadenectomy has never been shown to impact survival or recurrence in colon cancer,⁵¹⁻⁵³ the most important reason for performing nodal dissection is to determine the need for additional therapy.⁵⁴ Systemic therapy in colorectal cancer has

been shown to positively affect survival in patients with nodal metastases.⁵⁵ However, its role in patients with nonmetastatic disease is controversial, although in one third of these patients, disease will recur or systemic disease will develop. Some theories proposed to explain the high failure rate in node-negative patients is that occult or micrometastatic disease was missed during the original pathologic examination or that cancer-bearing lymph nodes were left behind at surgery.

The sentinel node concept was first applied in colon cancer as a potential means to reconcile each of these issues by providing optimal amounts of predictive tissue to facilitate pathologic ultrastaging using serial sectioning techniques and immunohistochemical stains. Although lymphadenectomy in colon cancer adds little morbidity, increasing enthusiasm for laparoscopic colectomy (even in the setting of malignancy) may accentuate the putative benefits of sentinel lymphadenectomy by further minimizing this less invasive alternative to traditional resection.

The first published report of lymphatic mapping in colon cancer was made in the British literature in 1999.⁵⁶ Blue dye was intraoperatively injected around the tumors in 50 patients with colorectal cancer. After resection, the specimen was examined for blue-stained nodes that were identified in 35 patients (70%). Sixty percent of those "sentinel nodes" failed to show metastatic disease that was evident in other, nonsentinel nodes creating a prohibitively low sensitivity. The authors concluded that although lymphatic mapping is feasible in colon cancer, blue-stained nodes do not predict the presence of nodal disease. They further cautioned that care must be exercised when extrapolating the success of this technique in melanoma and breast cancer to other types of cancer such as colon cancer. Nonetheless, the technique was pursued vigorously in North America at both the John Wayne Cancer Center and at a satellite of Michigan State University in Flint, Michigan. The first American report came from Flint and included 86 patients in whom sentinel nodes were successfully identified in 85 patients using subserosal injection of 1% lymphazurin around the tumor. Of these 85 patients, 29 had positive sentinel nodes while 56 were negative. Three of the 56 patients with negative nodes had positive nonsentinel nodes yielding a false-negative rate of 5%. Also important was the finding that "special" handling of the identified sentinel nodes with immunostaining techniques upstaged 18% of patients.⁵⁷

In 2000, investigators at the John Wayne Cancer Center reported the results from their initial 50 patients in which nodes were identified in 47 patients. In these 47, the sentinel node identified an aberrant drainage pathway that altered the extent of surgical resection in

7 patients (14%). The sentinel node accurately predicted nodal status in 94% of cases, and there were only 3 false-negative nodes.⁵⁸ A follow-up report from the same institution including 75 patients also showed successful mapping in 72 patients with accurate staging in 68 of these patients. This study included 9 patients undergoing laparoscopic resection in which all were successfully mapped, and the sentinel node accurately predicted nodal status.⁵⁹ Other centers are now beginning to report their experience; a recent publication from Mount Sinai Hospital in Miami showed a 71% localization rate and 0% false-negative rate in 35 patients using the subserosal injection technique.⁶⁰

Molecular Markers in the Sentinel Node in Colon Cancer

Unlike breast cancer, where adjuvant therapy is often used in patients with nonmetastatic disease, the use of chemotherapy in node-negative colon cancer remains controversial. As such, a multicenter phase II trial⁶¹ was undertaken to evaluate the usefulness of molecular staging techniques on the sentinel node in colon cancer. This study utilized reverse transcriptase polymerase chain reaction (RT-PCR) to look for a series of markers including beta-chain human chorionic gonadotropin (β -hCG), hepatocyte growth factor, and the universal melanoma-associated antigen. In 40 patients undergoing the procedure, sentinel nodes were identified in all, and there were no "skip" metastases. Ten patients had H&E evidence of metastases, and 4 patients had immunohistochemical evidence of metastases. Twelve of the remaining 26 patients had positive RT-PCR results, with a 79% concordance rate with the marker profile in the primary tumor and an 86% concordance rate with histopathologically positive sentinel nodes. More recent data⁶² from 203 patients accrued at both institutions show a 98% success rate, skip metastases in 4%, and occult micrometastases in 14%. Long-term follow-up in these patients will be required to determine the prognostic significance of these molecular markers in colon cancer.

Technique

The principal concerns regarding lymphatic mapping in colon cancer currently revolve around the technique of injection and identification of sentinel nodes. Those centers with the greatest experience^{57,58} continue to advocate subserosal (rather than peritumoral or intratumoral) injection of blue dye with in vivo identification of blue-stained nodes. They theorize that subserosal injections provide a more rapid and accurate means of identifying the sentinel lymph node while minimizing intraluminal contamination with dye (causing misidentification) or non-identification of a sentinel

node due to malignant lymphatic obstruction within the tumor. Ex vivo identification of sentinel nodes using blue dye only is common in Japan and has been recently reported in the American literature by the University of Hawaii.⁶³ In this small study, sentinel nodes were identified in 24 of 26 patients, 12 of which harbored metastatic disease by H&E staining. In 11 of these 12 patients, at least one blue node harbored H&E-positive or immunohistochemical evidence of metastatic disease, yielding a false-negative rate of 8.3%. Four patients (17%) were upstaged by immunohistochemical staining. Less encouraging results have recently been reported by a group from New Zealand.⁶⁴ This group was able to identify the sentinel node in 23 of 26 patients using a combined ^{99m}Tc colloidal antimony and patent blue dye subserosal injection technique, but only 55% of these nodes accurately predicted metastatic disease.

Lymphatic mapping has proven feasible in colon cancer, with rates of identification and false negativity approaching those observed in melanoma and breast cancer in the larger series at two centers in North America. Data from England and the Pacific Rim are less encouraging in colon cancer. Most importantly, these data do not refute the ability to localize the sentinel node but rather the biologic significance of those nodes labeled as such (a discrepancy that will be much more difficult to resolve). Major issues that need to be addressed in the future include the optimal means of detecting the sentinel node and the role of lymphoscintigraphy and intraoperative mapping with the gamma detection probe. The significance of micrometastases as detected by immunohistochemistry is being addressed in a multicenter trial initiated by the American College of Surgeons Oncology Group, the results of which will significantly influence the routine application of lymphatic mapping in colon cancer.

Gynecologic Cancer

Vulvar Cancer

The standard of care in the treatment of vulvar cancer includes radical vulvectomy with inguinal femoral node dissection. Sentinel node biopsy in these patients could spare them the potential morbidity of such procedures while offering important staging information. Vulvar cancer represents the embryologic counterpart to Cabanas' observations in penile cancer, and the putative benefits of truncated lymphadenectomy in these patients are similarly attractive to both patient and surgeon.

Early reports from the M.D. Anderson Cancer Center in the mid 1990s showed that intradermal injection of

isosulfan blue dye at the junction of vulvar tumors and normal skin in 9 patients identified sentinel nodes in 7 of 12 basins (6 patients had unilateral lesions).⁶⁵ The false-negative rate in this small series was 0%. A subsequent report describing this group's expanded experience in 21 patients showed localization in 86% of patients and 66% of the basins at risk. Again, there were no false negatives.⁶⁶ These studies utilized blue dye only. Combined use of lymphoscintigraphy with the gamma detection probe and isosulfan blue dye at the University of Hawaii found sentinel nodes in 6 of 10 basins at risk, with all nodes having radioactive counts at least 3 times background, and 6 of 7 sentinel nodes taking up blue dye.⁶⁷

Cervical Cancer

More recently, application of lymphatic mapping in gynecologic malignancy has occurred in cervical cancer. In 1971, Plentl and Friedman⁶⁸ described a predictable pattern of lymphatic drainage in cervical cancer. Thirty years later, these data are being used to guide application of lymphatic mapping and sentinel node biopsy in patients with cervical cancer. Traditionally, patients with cervical cancer undergo radical hysterectomy and pelvic lymphadenectomy. Of the 16,000 new cases of cervical cancer diagnosed each year, less than 20% will have nodal metastases. Pelvic lymphadenectomy is a potentially morbid procedure with complications such as neural or vascular injury, lymphocele formation, and adhesion formation described in as many as 30% of patients undergoing the procedure.^{69,70} Similar to melanoma, application of sentinel node technology to these patients has been proposed as a means to avoid the unnecessary risk of such complications in the 80% of patients without nodal extension of their cervical cancer.

The first report of sentinel node biopsy in cervical cancer was made in March 2000 and describes 3 patients.⁷¹ Isosulfan blue dye was injected in the lateral fornices of the cervix transvaginally prior to hysterectomy. The sentinel node was identified as blue stained during open hysterectomy. In all 3 patients, the sentinel lymph node was positive for metastatic disease, while the remaining nodes dissected were not involved. A subsequent study involving 21 patients at the University of Texas Southwestern Medical Center was carried out to further define the technique of lymphatic mapping in cervical cancer.⁷² In this study, 1 patient was excluded due to grossly involved pelvic nodes, and sentinel nodes were identified in 12 (60%) of the 20 remaining patients. Using an intracervical injection technique of isosulfan blue dye, 5 patients mapped to 2 nodal basins and a total of 23 sentinel nodes were harvested. Of a total of 4 patients with positive nodal metastases, 3 had sentinel nodes identified,

all of which were positive. The authors conclude that, when identified, the sentinel node accurately predicts the pathologic status of the draining basin but that the failure to identify sentinel nodes in 40% of patients undergoing the procedure remained a major obstacle in widespread implementation of the technique. Similar to its evolution in breast cancer and melanoma, application of adjunctive mapping strategies to vulvar and cervical cancer may help to improve localization rates. To date, there have been no published reports of lymphoscintigraphy with intraoperative mapping using a gamma detection device in cervical cancer, although this technique has been described in vulvar cancer.^{66,73} The true predictive value of the sentinel node in cervical cancer will be known only when sentinel nodes can be identified in a high enough proportion of patients to make meaningful comparisons to nonsentinel nodes.

Head and Neck Cancer

Presently, the most accurate method for staging the clinically node-negative neck is a neck dissection with pathologic examination of the excised cervical lymph nodes. The sentinel node concept may provide an alternative to routine lymph node dissection (or neck irradiation) when the probability of occult node metastasis is high. Lymphatic mapping with sentinel node biopsy for squamous cell carcinoma of the head and neck has unique challenges because of the inaccessibility of most of the primary sites to local injection of radiolabeled colloid. Also, proximity of most head and neck tumors to their respective draining nodal basin makes differentiation of the sentinel node from the injection site difficult to due excessive “glow” or background. Koch et al⁷⁴ and Alex et al⁷⁵ described the mapping procedure in a small group of patients with oral cavity tumors with excellent results. Further studies⁷⁶⁻⁷⁸ indicate that a radiolabeled colloid may be more effective in identifying sentinel nodes than blue dye, which does not appear to migrate to draining nodes as readily. In a larger French study,⁷⁹ sentinel node biopsy was found to be an accurate procedure, with only a 1.5% incidence of skip nodal metastases in 464 patients who had this staging procedure.

More recent studies^{80,81} have evaluated the use of lymphoscintigraphy and fine-needle aspiration of sentinel nodes (as a preoperative staging procedure) with encouraging results. Clearly, sentinel node evaluation has multiple potential applications in squamous cell carcinoma of the head and neck. Radiolabeled colloid and preoperative lymphoscintigraphy are essential for high localization rates and accurate results. Multicenter studies will be required to confirm the results of these smaller studies.

Gastric Cancer

The clinical significance of gastric cancer regional nodal metastasis has been studied extensively. Gastrectomy with regional lymphadenectomy is a critical component in the surgical treatment of this malignancy, although the extent of nodal dissection remains a controversial topic. Asian (particularly Japanese) surgeons report that extensive dissection leads to improved survival, and routinely perform extensive lymphadenectomy.^{82,83} These results have not been reproduced in Western studies. Nevertheless, lymph node status is an important prognostic indicator, and proper staging requires complete pathologic assessment of regional nodal stations.

Lymphatic mapping and sentinel node biopsy has been studied in patients with gastric cancer, and the results have been reported in several small studies. A study of 74 patients by Hiratsuka et al⁸⁴ published in 2000 showed that lymphatic mapping was successful in 73 of 74 patients, and a false negative occurred in only 1 of 74 patients, indicating the validity of the sentinel node concept in gastric cancer. Although some would argue that the lymphatic drainage of the stomach is more extensive and ambiguous than many other solid tumors,⁸⁵ the potential application of sentinel node biopsy lies in its ability to spare node-negative patients an unnecessary extensive regional lymphadenectomy, while reserving this procedure for node-positive patients.⁸⁶ In addition, more extensive pathologic evaluation of sentinel nodes may result in improved staging and allow for more appropriate adjuvant therapy strategies.⁸⁷ Further studies will be required to validate or disprove these hypotheses. In addition, the methodology is unclear, particularly in regard to the lymphatic mapping agent of choice. Technical limitations may prohibit the preoperative administration of a radiolabeled colloid, so most available data have been obtained with the use of intraoperatively administered dyes. Ongoing clinical trials will further elucidate these issues.

Lung Cancer

Non-small cell lung cancer is a major health problem in Western countries. Surgery offers the only chance for cure, although most patients will eventually succumb to their disease. Since lymph node status is the single most important prognostic factor with respect to survival, there has been a recent interest in applying lymphatic mapping and sentinel node biopsy to this group of patients.^{88,89} Little et al⁸⁸ reported results of blue dye mapping in 36 patients with non-small cell lung cancer. A sentinel node was identified in

17 (47%) of these patients, while 19 did not localize to an identifiable node. In all 9 patients with negative sentinel node(s), no positive nodes were found in the regional lymphadenectomy specimen (no false-negative cases). In addition, 5 (29%) of the 17 patients were found to have histologically positive mediastinal sentinel nodes that presumably would not have been identified otherwise. Liptay et al⁸⁹ reported their results using a technique of intraoperative administration of radiolabeled colloid and gamma detector probe-directed sentinel node identification in a similar group of patients. The procedure involves the intratumoral injection of the mapping agent and resulted in a superior localization rate of 82% (37 of 55 patients). In 35 of 37 cases, the sentinel nodes reflected the status of the resected regional nodes, while in 2 cases (5%), the sentinel node was negative and 1 or more nonsentinel nodes were positive for metastatic disease. Eight patients (22%) had mediastinal sentinel nodes identified with the mapping technique.

These results support the feasibility of sentinel lymph node biopsy in this group of patients. In addition, the technique may identify nodal metastases outside of the traditional field of dissection and provide the pathologist with the lymph node most likely to harbor metastases, allowing a focused examination.

Current Clinical Trials

The prognostic value of sentinel lymphadenectomy has been well established in breast cancer and melanoma. In these diseases, focus is now beginning to shift towards the therapeutic benefit of the procedure and the prognostic implications of histologically involved sentinel nodes, immunoreactive sentinel nodes, and sentinel nodes that are positive for molecular markers. Current clinical trials examining the therapeutic efficacy of sentinel node biopsy alone (with no further therapy) include the ACOSOG-Z0011 Trial in

Table 2. — Current Selective Lymphadenectomy Trials

Trial	Disease	Design ^a	Trial Start Date	Expected Accrual	No. of Sites
National Surgical Adjuvant Breast and Bowel Project (NSABP-B-32)	Breast	SN(-) patients randomized to completion ALND vs no additional axillary treatment	1999	4,500	59
American College of Surgeons Oncology Group (ACOSOG-Z0011)	Breast	SN(+) (by H&E) patients randomized to completion ALND vs observation	1999	1,900	50
American College of Surgeons Oncology Group (ACOSOG-Z0010)	Breast	Immunoreactive (H&E negative) SN patients observed to determine prognostic significance; bone marrow also assayed for immunoreactivity to determine incidence and significance	1999	5,300	89
Multicenter Selective Lymphadenectomy Trial	Melanoma	Wide excision ± SNB with completion lymphadenectomy in SN(+) patients; Subgroup: 1.2–3.5-mm melanomas	1994	2,200 ^b 1,285	30 (Australia and US)
Sunbelt Melanoma Trial	Melanoma	SN(+)-> completion lymphadenectomy → patients with only 1(+) node randomized to observation vs adjuvant interferon alfa for 1 month; 2nd arm: PCR(+) only randomized to observation vs completion node dissection	1997	3,200	60
Florida Melanoma Trial	Melanoma	H&E, S100, or PCR(+) SN randomized to adjuvant interferon alfa ± completion lymphadenectomy	2001	3,200	20

^a All prospective, randomized trials.
^b As of January 1, 2002, 1,921 patients have been enrolled in this study.
 SN = sentinel node
 H&E = hematoxylin-eosin stain
 PCR = polymerase chain reaction
 ALND = axillary lymph node dissection

breast cancer and the Florida Melanoma Trial in melanoma. The Multicenter Selective Lymphadenectomy Trial is designed to determine the role of prophylactic lymph node dissection in melanoma. The prognostic implications of immunoreactive or PCR-positive sentinel nodes are being studied in the ACOSOG-Z0010 Trial in breast cancer (immunoreactive) and the Sunbelt Melanoma Trial (PCR). Also, the incidence and significance of bone marrow immunoreactivity are being evaluated in ACOSOG-Z0010. The therapeutic benefit of completion axillary lymphadenectomy in sentinel node-negative patients is being evaluated in the NSABP-B32 Trial. In melanoma, the Florida Melanoma Trial is designed to determine the therapeutic benefit of completion lymphadenectomy in patients with positive sentinel nodes by H&E stains, PCR, or immunostains. The Sunbelt Melanoma Trial is also designed to determine the role of adjuvant interferon alfa in patients with minimal nodal disease (1 positive sentinel node). These multicenter, prospective, randomized trials are summarized in Table 2.

Conclusions

Questions regarding the feasibility of sentinel node biopsy in breast cancer and melanoma have abated with refinements in the technique and with improvements in the equipment necessary to carry out the procedure. Now, broader issues regarding its application in other solid tumors and the therapeutic efficacy of sentinel lymph node biopsy and the implications of disease identified in sentinel lymph nodes that would not have been identified by traditional methods have moved to the forefront. The aspect of lymphatic mapping and sentinel node biopsy that is common to all solid tumors is its ability to identify and harvest a pathologically manageable amount of highly predictive tissue. Although the therapeutic aspects of sentinel lymphadenectomy are beginning to be studied in nationally organized multicenter trials, the unique staging opportunities posed by the procedure have been well established. The concept of the sentinel lymph node is most applicable in patients in whom nodal status is a critical determinant in the decision to provide adjuvant therapy but in whom the therapeutic efficacy of elective lymph node dissection is either undetermined or known to be nontherapeutic. Each of the solid tumors presented herein fulfills these criteria to some extent. Answers to these questions will become more reliable as the technique is used to a wider degree in each tumor type.

In many nonmelanoma or breast cancer studies, blue dye alone was used as the mapping agent. Just as in breast cancer and melanoma, it is probable that the

techniques of blue dye and radiolabeled colloid will be combined to further improve identification rates. The prognostic significance of the sentinel node in these initial study patients will most certainly determine the vigor with which the technique is pursued by others in the future. Just as in breast cancer and melanoma, validation of the sentinel node concept in other solid tumors needs to occur in institutions other than those in which the technique is being developed before it can be widely applied in these tumors.

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