VOLUME 23 · NUMBER 8 · MARCH 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Lymphatic Mapping and Sentinel Lymph Node Biopsy for Breast Cancer: Developments and Resolving Controversies

Henry M. Kuerer and Lisa A. Newman

J Clin Oncol 23:1698-1705. © 2005 by American Society of Clinical Oncology

From the Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; and the Breast Care Center, University of Michigan, Ann Arbor, MI.

Submitted September 10, 2004; accepted December 7, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Henry M. Kuerer, MD, PhD, FACS, Department of Surgical Oncology, Unit 444, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: hkuerer@mdanderson.org.

0732-183X/05/2308-1698/$20.00

DOI: 10.1200/JCO.2005.09.047

INTRODUCTION

It has now been over 10 years since lymphatic mapping and sentinel lymph node (SLN) biopsy was first used in patients with breast cancer.[1,2] Since the procedure was introduced, over 1,500 studies on SLN biopsy in breast cancer have been published in the cited world medical literature. Over 11,000 women have been enrolled in National Cancer Institute–sponsored SLN biopsy trials for breast cancer, the final results of which will not be available until several years from now. In the meantime, both the National Comprehensive Cancer Network treatment guidelines in the United States[3] and the Saint Gallen International Consensus Conference[4] on the treatment of breast cancer have now indicated that SLN biopsy is an acceptable alternative to axillary lymph node dissection in patients with clinically node-negative breast cancer, provided that the SLN team has documented experience with this technique. Simply stated, although long-term follow-up data are not yet available from randomized trials comparing SLN biopsy with axillary lymph node dissection, SLN biopsy has become an acceptable alternative to routine level I and II axillary lymph node dissection for women with clinically node-negative early-stage breast cancer in the United States and in several other developed countries. However, despite a clear picture of increasing integration of SLN biopsy into standard diagnostic and therapeutic strategies for breast cancer, there are several clinical scenarios in which the utility of this technique has been questioned. This article will focus on current and resolving controversies associated with breast cancer lymphatic mapping and SLN biopsy.

SNL BIOPSY IN PATIENTS WITH A CLINICALLY POSITIVE AXILLA

A clinically positive axilla (palpable axillary adenopathy) is generally considered an absolute contraindication to SLN biopsy. At present, when axillary lymph node metastases are documented by fine-needle aspiration (FNA) biopsy of a clinically suspicious node, with or without the use of ultrasound guidance before surgery, the current consensus is that a complete level I and II axillary dissection should be performed. However, some surgeons would feel comfortable performing lymphatic mapping and SLN biopsy, along with excision of palpable lymph nodes, in a patient without FNA-documented metastases but with palpable adenopathy. The reasons is that in the absence of FNA-documented metastases, clinical assessment of the presence of axillary metastases is notoriously inaccurate,[5] and the presence of palpable lymphadenopathy is often due to a normal physiologic reaction to biopsy of the breast rather than to metastases from cancer. In this clinical scenario, if the SLN (also often the palpable reactive lymph node) and the

palpable axillary lymph nodes were found to be negative for metastases, no further axillary surgery would be indicated. The use of SLN biopsy in patients with palpable lymphadenopathy is controversial, and there are currently no published data to support this procedure. However, the procedure theoretically appears to be entirely safe.

MULTICENTRIC BREAST CANCER

There is mounting evidence indicating that the breast has a predictable lymphatic drainage and that the actual site of injection of mapping agents within the breast may not be critical for accurate detection of the SLN. Embryologically, the breast and mammary lymphatics develop as radial extensions from the centrally located nipple breast bud. Most of the lymphatic drainage of the breast passes through the subareolar plexus and then to the axillary nodal basin. This pattern prompted speculation that dermal and/or subareolar injections might be reasonable approaches for lymphatic mapping. It is possible that each breast has a single cluster of primary SLNs rather than different areas of the breast having distinct and individual drainage patterns. This concept is supported by findings of Jin Kim et al[6] in a study of lymphatic mapping for patients with multicentric tumors. In each patient, one lesion was mapped using peritumorally injected blue dye, and another was mapped using peritumorally injected isotope. In all cases, at least one SLN demonstrated uptake of both blue dye and isotope.

Klimberg et al[7] evaluated the subareolar mapping approach in a study from the University of Arkansas (Little Rock, AK) involving 68 breast cancer patients, all of whom received 1.0 mCi of technetium Tc99-sulfur colloid diluted in 4 mL of normal saline injected into the subareolar tissue and 2 to 5 mL of blue dye injected peritumorally. Overall, mapping was successful in 64 patients (94%). The isotope SLN identification rate was 94%, compared to 90% for the blue dye. Furthermore, all of the blue nodes were radioactive. These findings indicate not only that subareolar isotope improves the SLN identification rate, but also that missed axillary SLNs are unlikely with this technique. The patients in this series did not have preoperative scans performed, and therefore no comment can be made regarding extra-axillary lymphatic drainage.

Beitsch et al[8] compared subareolar radioisotope injected into the mirror-image quadrant of the nipple-areolar tissue and blue dye injected intraparenchymally. The SLN identification rate was 94% for the dye and 99% for the radioisotope; 99% of the blue SLNs were also radioactive. Bauer et al[9] also evaluated subareolar mapping. This group of investigators used intraparenchymal isotope injections in 332 patients in conjunction with subareolar blue dye in 249 patients and intraparenchymal blue dye in the other 83. The concordance rates were 87% in the pure intraparenchymal mapping group and 90% in the combined intraparenchymal isotope-subareolar blue dye group.

Kern[10] provides a detailed, illustrated discussion of lymphatic mapping utilizing subareolar injections of blue dye and radioisotope (1.0 mCi in 3 mL of normal saline) at the upper, outer aspect of the nipple-areolar complex. The radioisotope injection is given after induction of local anesthesia with 3 mL of 1% lidocaine. In Kern's series, preoperative lymphoscintigraphy was performed in 105 patients, and no internal mammary drainage was identified. Resolution of blue dye staining in the breast occurred in 5 to 6 months.

The demonstration that different breast injection sites yield the same clusters of SLNs representing the primary drainage for the entire gland have set the stage for employing lymphatic mapping in patients with multicentric breast cancer. As shown in Table 1, several investigators have evaluated the accuracy of lymphatic mapping in this setting.[6,11-16] Various injection sites and techniques have been employed, including subareolar, peritumoral or intraparenchymal, and dermal. In general, the studies reported thus far support the validity and safety of utilizing SLN biopsy to document the nodal status of patients with multiple breast tumors. The SLN identification rates are 90% to 100%, the average false-negative rate is less than 10%, and in a substantial proportion of patients, axillary metastases are limited to the SLNs. As was learned in patients with unifocal disease, results from the procedure are improved with combined use of both an isotope and a blue dye as mapping agents.

NEOADJUVANT SYSTEMIC THERAPY

As most women who receive neoadjuvant chemotherapy have large primary tumors or locally advanced breast cancer, it is important to consider whether lymphatic mapping and SLN biopsy is accurate in such patients. Two recent studies demonstrated that this technique is extremely accurate in patients with large primary breast cancer.[17,18] The false-negative rates in these studies were 1% to 2%.

Only about 25% of patients with large primary breast cancer do not have axillary metastases. However, most would agree that sparing these patients the morbidity associated with axillary dissection would be quite worthwhile. With this in mind, some clinicians have suggested that SLN biopsy be performed before neoadjuvant chemotherapy, and that patients in whom axillary metastases are detected be treated with axillary dissection after neoadjuvant chemotherapy.[19] In this way, not all patients would need a formal axillary dissection for local control of disease. In fact, many clinicians also state that they would prefer to have information about axillary metastases for prognostic purposes before neoadjuvant chemotherapy is begun. A possible way of addressing this concern is by

Table 1. Results of Breast Cancer Lymphatic Mapping in Multicentric Breast Cancer

Study	No. of Patients	Method of Lymphatic Mapping	Axillary Metastases		SLN Identified		False-Negative Rate		Blue Dye/Isotope Concordance Rate	
			No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Mertz, 1999[11]	16	• Subareolar isotope injection; 7.2 MBq Tc-sulfur colloid (one day) before surgery • Completion ALND in all cases	NR		NR		0	0	NA	
Schrenk, 2001[12]*	19	• Subareolar blue dye only (11 cases) • Subareolar blue dye and 40 MBq Tc-nanocolloid (eight cases) • Completion ALND in all cases	10/19	53	19/19	100	0/10	0	6/8	75
Jin Kim, 2002[6]†	5	• Intradermal isotope injection; 0.1 mCi Tc-sulfur colloid over one tumor • Peritumoral blue dye around a second tumor • Completion ALND in two cases	0	0	5/5	100	NA		5/5	100
Fernandez, 2002[13]	53	• Isotope and blue dye; technique varied among multicenter surgeon participants	18/52	35	52/53	98	0/18	0	NR	
Kumar, 2003[14]‡	59	• Intradermal injections over each tumor; 10 MBq Tc- sulfur colloid (day of surgery) in all cases • Peritumoral blue dye in 46 cases • Completion ALND in 48 cases	19/55	35	55/59	93	0/19	0	42/46	91
Tousimis, 2003[15]§	73	• Intradermal isotope injection over largest tumor (63 cases) or peritumoral (five cases) • Peritumoral blue dye at superolateral aspect of largest tumor (67 cases) or two tumors (two cases) • Completion ALND in all cases	38/70	54	70/73	96	3/38	8	NR	
Kumar, 2004[16]	10	• Peritumoral or subareolar isotope; 1.0 mCi filtered Tc-sulfur colloid (day of surgery) • Subareolar blue dye, 3 mL • Completion ALND in eight cases	7/10	70	10/10	100	0/7	0	NR	
Total	235	Various	92/206	45	211/219	96	3/92	3	53/59	90

NOTE. 3.7 MBq = 0.1 mCi.
Abbreviations: SLN, sentinel lymph node; ALND, axillay lymph node dissection; NR, not reported; NA, not applicable.
*Sixteen cases with tumors in at least two different quadrants; three cases with tumors in three different quadrants; metastatic disease limited to the SLN in two of 10 cases (20%).
†Five cases with tumors located in separate quadrants of the breast.
‡Thirty-two cases with tumors located in different quadrants; 27 cases with multifocal tumors; metastatic disease limited to a single SLN in 12 (63%) of 19 cases.
§Forty-four cases with tumors located in different quadrants; 26 cases with multifocal tumors; metastatic disease limited to SLN in 14 (37%) of 38 cases.

using a potential alternative to SLN biopsy before neoadjuvant chemotherapy. Before enrolling patients in neoadjuvant chemotherapy protocols, investigators from M. D. Anderson Cancer Center (Houston, TX) routinely use ultrasound-guided FNA biopsy to detect and document axillary nodal disease.[20] For patients with biopsy-proven axillary metastases, SLN biopsy performed after neoadjuvant therapy can provide a measure of the response of axillary metastases to chemotherapy, and some patients can be spared an axillary lymph node dissection.[21] Furthermore, residual disease in the axillary nodes after neoadjuvant chemotherapy has powerful independent prognostic value.[20] The main questions to be answered are whether and how the patient's systemic therapy would change if information about metastatic nodal disease were available before, rather than after, neoadjuvant chemotherapy. Currently, in almost all circumstances, decisions about systemic therapy would be based on the primary tumor characteristics and therefore would not be altered.

Studies of patients who have not previously been treated with chemotherapy have demonstrated that the disease status of the SLN accurately reflects the disease status of the entire axilla. However, SLN biopsy in patients treated with neoadjuvant chemotherapy will be accurate only if the metastatic deposits within each axillary lymph node respond identically to the effects of chemotherapy. Some reasons why lymphatic mapping may not be successful after neoadjuvant chemotherapy include (1) excessive fibrosis of the primary tumor and lymphatics, (2) blockage of lymphatic channels with viable or dead cellular material, and (3) the fact that patients given neoadjuvant therapy are more likely to have axillary lymph node involvement than are those not given neoadjuvant chemotherapy before lymphatic mapping.

Several investigators have recently examined the role of SLN biopsy in patients treated with neoadjuvant therapy. Twelve studies, with a total of more than 600 patients, have systematically evaluated SLN after neoadjuvant chemotherapy for breast cancer (Table 2). In one recent report, Aihara et al[34] also included results of SLN biopsy following neoadjuvant hormonal therapy in 16 patients. In the majority of studies, patients with various stages of breast

Table 2. Results of SLN Biopsy after Neoadjuvant Systemic Therapy

Study	Method of Lymphatic Mapping	SLN Identified		Metastases in SLN Only		False-Negative Rate
		No. of Patients	%	No. of Patients	%	
Breslin et al, 2000[21]	Dye alone Dye + probe	43/51	84	10/22	46	12*
Nason et al, 2000[24]	Dye + probe	13/15	87	3/9	33	25
Fernandez et al, 2001[25]	Probe alone	34/40	85	4/16	25	25
Mamounas et al, 2001[26]	Dye alone Probe alone Dye + probe	271/428†	85	55/125	44	11
Haid et al, 2001[27]	Dye + probe	29/33	88	11/29	38	0
Julian et al, 2001[28]	Dye alone Probe alone Dye + probe	29/31	94	5/11	46	0
Tafra et al, 2001[29]	Dye + probe	27/29‡	93	Not stated		0
Balch et al, 2003[30]	Dye + probe	25/26	96	8/13	62	7
Montgomery et al, 2002[31]	Dye + probe	29/33	88	5/18	28	5
Reitsamer et al, 2003[32]	Dye + probe	26/30	87	8/14	57	7
Schwartz and Meltzer, 2003[33]	Dye alone	21/21	100	7/11	64	9
Aihara et al, 2004[34]	Dye alone	33/36§	92	2/11	18	8

NOTE. False-negative rates in patients who had successful lymphatic mapping were calculated or recalculated using the following formula: false-negative rate = No. of false negatives/(No. of false negatives + No. of true positives).
Abbreviations: SLN, sentinel lymph node.
*If the two patients with persistent axillary disease after neoadjuvant chemotherapy were excluded, the false-negative rate would be 4.3%.
†Completion axillary dissection was performed in 262 patients.
‡Completion axillary dissection was performed in 26 patients.
§Sixteen patients had neoadjuvant hormonal therapy, and 20 patients had neoadjuvant chemotherapy.

cancer underwent neoadjuvant chemotherapy followed by SLN biopsy by one of several methods followed by completion axillary lymph node dissection to determine the false-negative rates (Table 2). The single-institution study populations ranged from seven[23] to 51 patients.[21,22]

The largest study included 428 patients treated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 randomized, multicenter, clinical trial.[26] However, it should be noted that lymphatic mapping and SLN biopsy in the NSABP study was not performed according to a set protocol. Regardless of the many different treatment and treating institution variables, the rates for successfully identifying an SLN in the neoadjuvant chemotherapy studies compare favorably with the rates reported in the initial studies of SLN biopsy in earlier-stage primary breast cancer, ranging from 83% to 100% (Table 2).

To permit appropriate comparisons between these studies, the false-negative rates were calculated for the patients with successful lymphatic mapping procedures according to the following formula: (No. of false negatives)/(No. of false-negatives + No. of true positives). The false-negative rates reported for these initial studies ranged from 0% in three studies to 25% in two studies (Table 2). The reason for the broad range of false-negative rates is not clear, but it may simply be a matter of the investigators' experience with the technique. One additional reason for the variability in false-negative rates may be the small number of patients in each single-institution study. In one study, the overall SLN identification rate (84%) was lower than that reported in current series of SLN biopsy before systemic therapy for early breast cancer; however, that rate reflected the investigators learning curve with the procedure. In the same institution, the identification rate has improved over time, with a corresponding decrease in the false-negative rate.

From these initial studies, it seems that lymphatic mapping and SLN biopsy may be a safe way to guide axillary treatment for patients who are clinically node-negative after neoadjuvant chemotherapy. In this way, the use of neoadjuvant chemotherapy for women with known axillary metastases may result in the need for less radical surgery, not only in the breast but also in the axilla. But what about patients who have completed chemotherapy and are found to have metastases in the SLN? Patients in this situation are at significant risk for local failure if they do not undergo further axillary therapy. One potentially effective way to address residual axillary disease in such patients is to use radiation therapy instead of axillary dissection. This hypothesis is currently being tested at M. D. Anderson Cancer Center in ongoing and planned neoadjuvant chemotherapy protocols for operable disease.

SNL BIOPSY DURING PREGNANCY

Breast cancer is the most common malignancy occurring in pregnant women, with an incidence of about 1 in 3,000 pregnancies. Although the incidence is low, it may be increasing because of the increasing number of women who are becoming pregnant at later ages.[35] The current

standard of care for evaluation of the axilla in pregnant women with a diagnosis of invasive breast cancer is axillary lymph node dissection. Because of safety concerns, pregnant women with breast cancer were not allowed to participate on the American College of Surgeons Oncology Group trial but were permitted to participate in the NSABP-32 trial. Isosulfan blue dye has never been studied in animals or humans and therefore is classified as a pregnancy category C drug. With regard to the radiopharmaceutical, a genuine fear of fetal malformations and childhood cancers as a result of fetal radiation exposure exists. However, technetium Tc-99m has been studied in humans and has favorable radiation properties with respect to safety. Analyses of operating rooms and of pathologists and surgeon hands have shown that radiation exposure from technetium Tc-99m used for lymphatic mapping is low.[36] It has also been established that a number of radiopharmaceuticals may be used in pregnant females without sequellae to the patient or fetus.

Currently there are no published studies addressing the use of technetium Tc-99m sulfur colloid for SLN biopsy in pregnant breast cancer patients. A study to determine the potential absorbed dose to the embryo/fetus from administration of filtered technetium Tc-99m sulfur colloid to the mother during breast lymphatic mapping procedures was recently completed at M. D. Anderson Cancer Center. The maximum absorbed dose to the embryo/fetus in pregnant women undergoing breast lymphoscintigraphy with 92.5 MBq (2.5 mCi) of technetium Tc-99m sulfur colloid was found to be 0.0043 Gy under the most adverse conditions in the theoretical model (all the injected radiopharmaceutical travels immediately to the bladder and is eliminated through the process of physical decay). The threshold absorbed dose for adverse fetal effects is thought to fall between 0.05 Gy[37] and 0.11 Gy.[38] Thus, the potentially largest absorbed dose with lymphoscintigraphy remains approximately 12 to 23 times less than the threshold associated with reported risk of fetal adverse effects associated with radiation exposure. On the basis of these results, the use of technetium Tc-99m sulfur colloid for pregnant patients with a clinically negative axilla is theoretically safe for the developing embryo/fetus. The accuracy of this technique with respect to the physiologic breast changes associated with pregnancy remains to be determined.

SNL BIOPSY IN PATIENTS WITH DUCTAL CARCINOMA-IN-SITU

By definition, ductal carcinoma-in-situ (DCIS) of the breast is a noninvasive lesion that does not have the ability to metastasize. For the most part, this disease is treated to prevent the occurrence of invasive breast cancer. Given this background, axillary dissection or SLN biopsy should be considered inappropriate in patients with DCIS. However, patients with DCIS sometimes also have microinvasive or, frankly, invasive carcinoma that can be missed. In fact, patients treated for DCIS sometimes, although very rarely, die of metastatic breast cancer, most likely as a result of an otherwise missed invasive component of disease.[39]

It would be difficult to justify SLN biopsy in the majority of patients treated for DCIS with segmental resection, as this tissue can be thoroughly evaluated for the presence of invasive disease and SLN biopsy can be performed as a subsequent surgical procedure. However, for patients undergoing a mastectomy for the treatment of DCIS, the ability to perform SLN biopsy is lost if the breast is removed and invasive carcinoma is identified. In this situation, axillary lymph node dissection is indicated to assess critical staging information. In a large series from the M. D. Anderson Cancer Center, 399 patients with an initial diagnosis of DCIS were identified to determine which factors were associated with finding invasive carcinoma on final pathologic evaluation.[40] On multivariate analysis, significant independent predictors of finding invasive carcinoma were: age younger than or equal to 55 years; diagnosis made with a core biopsy; mammographic primary tumor size greater than 4 cm; and high-grade tumor status. Overall, 20% of the patients with an initial diagnosis of DCIS were found to have invasive carcinoma, and 35% of these patients underwent a SLN biopsy. Patients in this series were more often offered SLN biopsy if they had a mastectomy. Ten percent of the patients were found to have a positive SLN and the only independent predictor of finding axillary metastases in patients initially believed to have only DCIS was the presence of a palpable tumor at diagnosis. On the basis of this analysis, the investigators from that study do not routinely perform SLN biopsy on all patients with an initial diagnosis of DCIS. Instead, the risks and benefits of SLN biopsy are discussed with patients scheduled to undergo mastectomy, younger patients, and patients with large or high-grade DCIS.

Investigators at the Moffitt Cancer Center (Tampa, FL) were the first to report the results of SLN biopsy in patients with DCIS, finding positive SLNs in 6% to 9% of consecutive unselected patients.[41-44] The use of SLN biopsy for DCIS has been more selective at Memorial Sloan-Kettering Cancer Center (New York, NY).[45] In their initial publication, they performed SLN biopsy in 21% of all patients with DCIS whom they considered at high risk for the presence of invasion. In this highly selected group of patients, 12% of patients had a positive SLN. At the European Institute of Oncology (Milan, Italy), approximately 3% of unselected patients with pure DCIS were found to have a positive SLN.[46] Taken together, the results of these studies indicate that lymphatic mapping and SLN biopsy for DCIS should not be routinely done in all patients.

Patients with a diagnosis of DCIS who are scheduled to undergo mastectomy, and other patients considered at high risk for having invasive disease, can be offered SLN biopsy as part of their initial surgical management.

SNL BIOPSY AS A BRIDGE TO COMPLETE ELIMINATION OF AXILLARY LYMPH NODE DISSECTION

The immediate risk of leaving residual disease in the axilla when one SLN is positive ranges from about 10% to 40%, depending on the size of the primary tumor and that of SNL metastases.[47,48] Therefore, the current standard of care is to recommend completion axillary lymph node dissection in patients with positive SLNs. However, most surgeons would not recommend completion axillary lymph node dissection in patients with only immunohistochemically detected cells where no cluster is greater than 0.2 mm in size, as the risk of finding additional nodes with carcinoma in this situation is exceedingly rare. The prognostic significance of isolated immunohistochemically detected tumor cells in SLNs will be determined by large prospective clinical trials by both the American College of Surgeons Oncology Group study Z0010 and NSABP study B-32. Both of these trials have now closed and together have enrolled more than 11,000 women with stage I and II breast cancer.

Clinicopathologic models have now also been developed to predict which patients are at most risk of having residual axillary nodal disease and to assist clinicians and patients in making informed surgical decisions.[47,48] Investigators at the M. D. Anderson Cancer Center have determined that the likelihood of positive non-SLNs correlates with primary tumor size, size of the largest SLN metastasis, and presence of lymphovascular invasion. They have developed a mathematical scoring system algorithm that incorporated these factors to help determine which patients would benefit from additional axillary surgery.[47] Similarly, a nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy was developed at Memorial Sloan-Kettering Cancer Center and is also available online to assist clinicians and patients in better understanding their actual risk for additional disease.[48] It is important to note, however, that the immediate risk of leaving residual disease in the axilla does not equate to always leaving this disease as untreated. It is important to realize that the use of systemic adjuvant therapy as well as the use of radiation tangents with breast conservation therapy following SLN biopsy may result in significant treatment of residual microscopic axillary nodal disease.[20,49] Therefore, removal of further axillary nodes may not benefit the patient. This hypothesis is currently being tested by the American College of Surgeons Oncology Group randomized trial of axillary dissection versus observation in patients with a positive SLN who are receiving breast conservation therapy. It is clear that the number of lymph nodes with axillary metastases is a critical determinant of prognosis in patients with breast cancer. However, if adjuvant systemic therapy decisions are not affected by this additional information, the additional morbidity associated with axillary lymph node dissection may not be justified.

Given that there is a risk of additional axillary lymph node metastases in patients with a positive SLN, one potential use for SLN biopsy in early-stage breast cancer may be the selection of patients for additional axillary treatment in the form of axillary irradiation. Some investigators have suggested that no axillary surgery is necessary in patients with early-stage breast cancer and that all such patients could receive axillary irradiation as part of their standard whole-breast radiation therapy with breast conservation surgery.[50] However, this would result in potential overtreatment in many patients, and the concept of partial breast irradiation may necessitate revision of this hypothesis.[51]

Randomized trials of axillary dissection versus axillary irradiation have not shown a survival impact related to the type of axillary treatment.[50] Unselected patients with early-stage breast cancer treated with axillary irradiation without axillary dissection have been found to have an absolute increase in the rate of axillary recurrence of about 2% compared with patients treated with standard level I and II axillary dissection.[50] Several investigators have evaluated the use of axillary irradiation as the sole treatment modality for breast cancer patients with a clinically negative axilla. In such patients, and with a median follow-up of 5 years (range, 54 to 126 months), an axillary failure rate of about 1% to 2% has been demonstrated.[52] This rate is comparable to the axillary failure rates seen for axillary lymph node dissection in similar patients. Given that clinically occult axillary metastases would be expected in 30% to 40% of patients with a clinically negative axilla, primary axillary irradiation seems to be an excellent method for controlling occult axillary metastases. Further, the Early Breast Cancer Trialists' Collaborative Group meta-analysis found no apparent differences in mortality between axillary lymph node dissection and axillary irradiation in the treatment of early breast cancer.[52,53] In terms of morbidity, axillary irradiation compares favorably with axillary dissection.[52] In fact, the risk of lymphedema after primary axillary radiotherapy has been reported to be about half the risk of lymphedema seen after standard axillary lymph node dissection, and the rates of brachial plexopathy and shoulder immobility are also reduced with radiotherapy.[52,54,55]

Given this background, lymphatic mapping and SLN biopsy might be an appropriate way to select patients for primary axillary radiotherapy (ie, those in whom the

SLN is found to contain metastases). Additionally, for patients undergoing breast conservation therapy, tangential radiation fields would be expected to effectively treat about one third to two thirds of the axilla.[56] In this situation, breast irradiation might also be sufficient to treat any remaining axillary metastases in patients with a positive SLN. Naturally, these new concepts would have to be validated in randomized clinical trials before widely adopted in clinical practice.[57]

SUMMARY

Over the past decade, lymphatic mapping and SLN biopsy has been increasingly integrated into the diagnosis and treatment of early-stage breast cancer. Although some of the long-term results from pivotal, large prospective trials of SLN biopsy for breast cancer are not yet available, more than 1,500 articles have now been published on this subject. On the basis of these data, lymphatic mapping and SLN biopsy has become a standard surgical procedure both in the United States and other developed countries. Despite a clear picture of increasing integration of SLN biopsy into standard diagnostic and therapeutic strategies for breast cancer, several areas of controversy remain. One of the promising future directions with SLN biopsy could be its use as a bridge to the complete elimination of axillary dissection, despite the presence of nodal metastases.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant: Henry M. Kuerer, Pfizer. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

REFERENCES

1. Krag DN, Weaver DL, Alex JC, et al: Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 2:335-340, 1993

2. Giuliano AE, Kigram DM, Guenther JM, et al: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 220:391-401, 1994

3. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology. http://www.nccn.org/physician_gls/f_guidelines.html

4. Senn HJ, Thurlimann B, Goldhirsch A, et al: Comments on the St. Gallen Consensus 2003 on the Primary Therapy of Early Breast Cancer. Breast 12:569-582, 2003

5. Fisher B, Wolmark N, Bauer M, et al: The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 152:765-772, 1981

6. Jin Kim H, Heerdt AS, Cody HS, et al: Sentinel lymph node drainage in multicentric breast cancers. Breast J 8:356-361, 2002

7. Klimberg VS, Rubio IT, Henry R, et al: Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg 229: 860-865, 1999

8. Beitsch PD, Clifford E, Whitworth P, et al: Improved lymphatic mapping technique for breast cancer. Breast J 7:219-223, 2001

9. Bauer TW, Spitz FR, Callans LS, et al: Subareolar and peritumoral injection identify similar sentinel nodes for breast cancer. Ann Surg Oncol 9:169-176, 2002

10. Kern KA: Breast lymphatic mapping using subareolar injections of blue dye and radiocolloid: Illustrated technique. J Am Coll Surg 192:545-550, 2001

11. Mertz L, Mathelin C, Marin C: Subareolar injection of Tc99m-sulphur colloid for sentinel node identification in multifocal invasive breast cancer. Bull Cancer 86:939-945, 1999

12. Schrenk P, Wayand W: Sentinel-node biopsy in axillary lymph-node staging for patients with multicentric breast cancer. Lancet 357: 122, 2001

13. Fernandez K, Swanson M, Verbanac K, et al: Is sentinel lymphadenectomy accurate in multifocal and multicentric breast cancer? Proceedings of the 55th Annual Cancer Symposium of the Society of Surgical Oncology S9:S16, 2002 (abstr 29)

14. Kumar R, Jana S, Heiba SI, et al: Retrospective analysis of sentinel node localization in multifocal, multicentric, palpable, or nonpalpable breast cancer. J Nucl Med 44:7-10, 2003

15. Tousimis E, Van Zee KJ, Fey JV, et al: The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. J Am Coll Surg 197:529-535, 2003

16. Kumar R, Potenta S, Alavi A: Sentinel lymph node biopsy in multifocal and multicentric breast cancer. J Am Coll Surg 198:674-676, 2004

17. Bedrosian I, Reynolds C, Mick R, et al: Accuracy of sentinel lymph node biopsy in patients with large primary breast tumors. Cancer 88:2540-2545, 2000

18. Chung MH, Ye W, Giuliano AE: Role for sentinel lymph node dissection in the management of large (> or = 5 cm) invasive breast cancer. Ann Surg Oncol 8:688-692, 2001

19. Sabel MS, Schott AF, Kleer CG, et al: Sentinel node biopsy prior to neoadjuvant chemotherapy. Am J Surg 186:102-105, 2003

20. Kuerer HM, Sahin A, Hunt KK, et al: Incidence and impact of documented eradication of breast cancer axillary lymph node metastases prior to surgery in patients treated with neoadjuvant chemotherapy. Ann Surg 230:72-78, 1999

21. Breslin TM, Cohen L, Sahin A, et al: Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 18:3480-3486, 2000

22. Breslin T, Fox L, Fleming J, et al: Lymphatic mapping and sentinel node biopsy is accurate following preoperative chemotherapy for breast cancer. Proceedings of the 52nd Annual Meeting of Society of Surgical Oncology: 1999 (abstr P29)

23. Dookeran KA, Zaren HA: Sentinel lymph node biopsy in breast cancer patients treated with neoadjuvant chemotherapy. Proc Am Soc Clin Oncol 18:72A, 1999 (abstr 269)

24. Nason KS, Anderson BO, Byrd DR, et al: Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. Cancer 89:2187-2194, 2000

25. Fernandez A, Cortes M, Benito E, et al: Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme. Nucl Med Commun 22:361-366, 2001

26. Mamounas EP: Sentinel lymph node biopsy after neoadjuvant systemic therapy. Surg Clin North Am 83:931-942, 2003

27. Haid A, Tausch C, Lang A, et al: Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast carcinoma? Cancer 92:1080-1084, 2001

28. Julian TB, Patel N, Dusi D, et al: Sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 182:407-410, 2001

29. Tafra L, Verbanac KM, Lannin DR: Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. Am J Surg 182:312-315, 2001

30. Balch GC, Mithani SK, Richards K, et al: Lymphatic mapping and sentinel lymphadenectomy after preoperative therapy for stage II and III breast cancer. Ann Surg Oncol 10:616-621, 2003

31. Montgomery LL, Van Zee KJ, Fey JV, et al: Sentinel lymph node accuracy following neoadjuvant chemotherapy in breast cancer. Proceedings of the 55th Annual Meeting of the Society of Surgical Oncology 9:S49, 2002 (abstr P33)

32. Reitsamer R, Peintinger F, Rettenbacher L, et al: Sentinel lymph node biopsy in breast cancer patients after neoadjuvant chemotherapy. J Surg Oncol 84:63-67, 2003

33. Schwartz GF, Meltzer AJ: Accuracy of axillary sentinel lymph node biopsy following neoadjuvant (induction) chemotherapy for carcinoma of the breast. Breast J 9:374-379, 2003

34. Aihara T, Munakata S, Morino H, et al: Feasibility of sentinel node biopsy for breast cancer after neoadjuvant endocrine therapy: A pilot study. J Surg Oncol 85:77-81, 2004

35. Keleher AJ, Theriault RL, Gwyn KM, et al: Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg 194: 54-64, 2002

36. Veronesi U, Paganelli G, Viale G, et al: Sentinel lymph node biopsy and axillary dissection in breast cancer: Results in a large series. J Natl Cancer Inst 91:368-373, 1999

37. Stabin MG: Fetal Dose Calculation Workbook. Oak Ridge, TN, Oak Ridge Institute for Science and Education, 1997

38. Hall EJ: Radiobiology for radiologists (ed 4). Philadelphia, PA, JB Lippincott, 1994, p 376

39. Cody HS 3rd, Klauber-Demore N, Borgen PI, et al: Is it really duct carcinoma in situ? Ann Surg Oncol 8:617-619, 2001

40. Yen T, Mirza N, Hunt K, et al: Predictors of invasive breast cancer in patients with an initial diagnosis of ductal carcinoma in situ: A guide to the selective carcinoma in Situ. Ann Surg Oncol 11:93, 2004 (abstr P31)

41. Pendas S, Dauway E, Giuliano AE, et al: Sentinel node biopsy in duct carcinoma in situ patients. Ann Surg Oncol 7:15-20, 2000

42. Bass SS, Lyman GH, McCann CR, et al: Lymphatic mapping and sentinel lymph node biopsy. Breast J 5:288-295, 1999

43. Cox CE, Haddad F, Bass S, et al: Lymphatic mapping in the treatment of breast cancer. Oncology (Huntingt) 12:1283-1292, 1998

44. Bass SS, Dauway E, Mahatme A, et al: Lymphatic mapping with sentinel lymph node biopsy in patients with breast cancers <1 centimeter (T1A-T1B). Am Surg 65:857-861, 1999

45. Klauber-DeMore N, Tan LK, Liberman L, et al: Sentinel lymph node biopsy: Is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 7:636-642, 2000

46. Intra M, Veronesi P, Mazzarol G, et al: Axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. Arch Surg 138:309-313, 2003

47. Hwang RF, Krishnamurthy S, Hunt KK, et al: Clinicopathologic factors predicting involvement of nonsentinel axillary nodes in women with breast cancer. Ann Surg Oncol 10:248-254, 2003

48. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al: A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 10:1140-1151, 2003

49. Buchholz TA, Strom EA, McNeese MD, et al: Radiation therapy as an adjuvant treatment after sentinel lymph node surgery for breast cancer. Surg Clin North Am 83:911-930, 2003

50. Louis-Sylvestre C, Clough K, Asselain B, et al: Axillary treatment in conservative management of operable breast cancer: Dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol 22:97-101, 2004

51. Kuerer HM, Julian TB, Strom EA, et al: Accelerated partial breast irradiation after conservative surgery for breast cancer. Ann Surg 239:338-351, 2004

52. Singletary SE: New approaches to surgery for breast cancer. Endocr Relat Cancer 8:265-286, 2001

53. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 333:1444-1455, 1995

54. Pierce SM, Recht A, Lingos TI, et al: Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. Int J Radiat Oncol Biol Phys 23:915-923, 1992

55. Hoebers FJ, Borger JH, Hart AA, et al: Primary axillary radiotherapy as axillary treatment in breast-conserving therapy for patients with breast carcinoma and clinically negative axillary lymph nodes. Cancer 88:1633-1642, 2000

56. Schlembach PJ, Buchholz TA, Ross MI, et al: Relationship of sentinel and axillary level I-II lymph nodes to tangential fields used in breast irradiation. Int J Radiat Oncol Biol Phys 51:671-678, 2001

57. Rutgers EJ, Meijnen P, Bonnefoi H, et al: Clinical trials update of the European Organization for Research and Treatment of Cancer Breast Cancer Group. Breast Cancer Res 6: 165-169, 2004