



Update

Controversies in Sentinel Lymph Node Biopsy for Breast Cancer

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SUMMATION

Sentinel lymph node biopsy, validated in melanoma staging, is currently under investigation for breast cancer staging. Reports suggest that the sentinel lymph node has a high predictive value in determining the presence of axillary metastases. Identification of a sentinel lymph node that is free of metastatic tumor cells may eliminate the necessity of performing a standard axillary lymph node dissection with its attendant morbidity. Numerous techniques are utilized to identify the sentinel node with approximately the same success rate. This paper will address some of the controversial areas of sentinel lymph node biopsy and offer an option for physicians who want to develop a sentinel lymph node program in their hospital.

The dissection of axillary lymph nodes is one of the most important procedures in the staging of invasive breast cancer. Axillary nodal status is currently the most accurate prognostic indicator for the future development of systemic disease.^{1,2} The results of axillary lymph node dissection are used to determine which patients require systemic therapy and to influence the recommended type of therapy.

Removal of axillary lymph nodes for pathological examination is necessary since clinical examination is not accurate in assessing axillary lymph node metastases. Fine needle aspiration biopsy may miss metastatic disease at one pole or focus within a lymph node. Other imaging modalities, such as PET scanning, require a min-

imum tumor burden before turning positive. Approximately 10 to 25 lymph nodes may be resected in a formal axillary lymph node dissection. With extensive removal of these lymph nodes, the axillary lymph node dissection becomes the most morbid part of the surgical treatment of cancer. Problems include lymphedema, numbness, pain, and limitations to shoulder mobility.^{3,4} Published reports indicate that the incidence of lymphedema after breast cancer treatment varies according to the extent of the axillary dissection and whether breast and/or axillary radiation is used post operatively. A patient who undergoes a level I (removal of lower lymph nodes lateral to the pectoralis minor muscle edge) and level II (removal of intermediate lymph nodes posterior to the pectoralis minor muscle) axillary lymph node dissection has about a 3–7% risk of developing subsequent lymphedema without radiotherapy and 10–14% with radiotherapy. For patients who undergo a level I, II, and III (re-

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removal of highest lymph nodes medial to the medial edge of the pectoralis minor muscle) axillary dissection, there is about a 20–30% risk of developing lymphedema without radiation and a 30–40% chance of developing lymphedema with radiation.^{5–7} In order to prevent or minimize infection that can lead to delayed lymphedema, patients must be careful to avoid injury to the affected arm, and they are often instructed to avoid venipuncture or intravenous catheters in that arm.^{8,9} Another potential side effect of axillary lymph node dissection is numbness due to transection of cutaneous nerves to the skin of the axilla or upper arm (intercostobrachial nerve). Shoulder mobility may also become restricted, especially in older patients or patients with pre-existing conditions such as bursitis, tendonitis, arthritis, or rotator cuff disorders.

For many women, particularly those with smaller tumors, axillary lymph node dissection yields no evidence of metastatic disease. In patients with invasive breast cancers less than 2 cm, approximately 65–70% of axillary lymph node dissections show no tumor metastases.^{10–12} In mammographically identified tumors, axillary lymph node metastases are even less common: 3% for tumors 5mm or less (T1a), 8% for tumors 6–10mm (T1b), 30% for tumors 11–20mm (T1c), and 60% for tumors greater than 2cm (T2 and larger).¹³ In node negative patients, normal lymph nodes are removed only for the prognostic information they provide. In the future, biologic tumor markers may be discovered that may better identify those patients who require adjuvant systemic therapy rather than relying on the identification of axillary lymph node metastases.^{14,15} Until that time, however, axillary lymph node dissection will continue to be performed to acquire staging information for adjuvant treatment decisions, and is especially important for the minority of patients with small tumors that are associated with lymph node metastases.

Sentinel lymph node biopsy is an alternative to standard axillary lymph node dissection. The sentinel lymph node is the first lymph node in the afferent lymphatic drainage pathway from a tumor. Sentinel lymph node biopsy was originally described in penile carcinoma¹⁶ and later applied to melanoma.¹⁷ Its use in breast cancer was first described in 1993 by Krag¹⁸ and in 1994 by Giuliano.¹⁹ Reports suggest that the sentinel lymph node has a high predictive value in determining the presence of axillary metastases.^{20–22} Identification of a sentinel lymph node that is free of

metastatic tumor cells may eliminate the necessity of performing a standard axillary lymph node dissection with its attendant morbidity³. The sentinel lymph node can also direct the pathologist to perform a more detailed examination on the lymph node that most likely contains metastatic or micrometastatic disease.^{23,24}

SENTINEL LYMPH NODE BIOPSY TECHNIQUES

Sentinel lymph node biopsy involves injection of a lymphatic mapping agent—isosulfan blue vital dye and/or ^{99m}Tc sulfur colloid in this country and patent blue dye and/or ^{99m}Tc albumin colloid or ^{99m}Tc antimony trisulfide colloid in Europe—into the breast parenchyma around the tumor or biopsy cavity (peritumoral injection). As the lymphatic drainage of the breast may not correlate with that of the pectoralis major muscle, care should be taken to avoid inadvertent injection of the mapping agent into underlying muscle for deep-seated tumors. The mapping agent(s) is (are) carried from the breast by afferent lymphatics, and the lymph node that initially traps the dye and/or radiocolloid is identified as the sentinel lymph node. For patients with non-palpable tumors, the tumor site within the breast may be marked using breast ultrasound prior to blue dye or radiocolloid injection. Although sentinel lymph node biopsy is generally used for patients with invasive breast cancers less than 5 cm and with clinically negative axillae, it may also be applied to cases of extensive and/or high grade (comedo subtype) ductal carcinoma in situ (DCIS). In such cases, the injection is generally into the breast tissue containing the DCIS rather than around the DCIS. When radiocolloid is used as a mapping agent either alone or in conjunction with isosulfan blue dye, a lymphoscintigram may be performed preoperatively to visualize the location of the sentinel lymph node. The sentinel lymph node is most commonly located in the axilla, but may be located in the internal mammary chain or elsewhere²⁰. Our own studies of sentinel lymph nodes that visualize on preoperative lymphoscintigraphy show that about 70% are located in the axilla only, 21% are present in both the axilla and the internal mammary chain, 7% of visualized sentinel lymph nodes drain to the internal mammary chain only, and less than 2% drain elsewhere. In a study of 34 patients by Uren et al.,²⁵ preoperative lymphoscintigraphy demon-

strated unexpected drainage across the center line of the breast to axillary or internal mammary lymph nodes in 32% of patients. Many institutions do not perform preoperative lymphoscintigraphy and its role in sentinel node biopsy is under study. If the preoperative lymphoscintigram shows drainage to nodes other than those located in the axilla or does not visualize a sentinel lymph node, an axillary lymph node dissection is still performed. Internal mammary sentinel nodes are removed less commonly. However, with the resurgence of postmastectomy chest wall irradiation, including irradiation of the internal mammary chain, there is renewed interest in the status of internal mammary lymph nodes. At the present time, there is a small but increasing number of institutions that remove internal mammary sentinel lymph nodes for analysis.

At surgery, sentinel lymph nodes are identified visually by following a blue-stained lymphatic tract into a usually blue-stained lymph node and/or with the use of a handheld gamma-detection probe to detect radioactive lymph nodes. The majority of patients who do not show visualization of a sentinel lymph node on preoperative lymphoscintigraphy will still have sentinel lymph nodes identified at surgery. This is related to the increased sensitivity of the hand-held gamma probe compared to the gamma camera as well as the additional use of blue dye for sentinel lymph node identification. While radioactivity may be injected 1 to 24 hours prior to surgery, isosulfan blue dye must be injected intraoperatively since the dye may exit the sentinel lymph node after about 35 minutes. During surgery, the pulse oximeter usually shows a decrease in oxygen saturation of several points 15–30 minutes following injection that is related to the color absorbency of the dye as read by the pulse oximeter and does not reflect a true decrease in the patient's blood oxygen saturation. Intraoperative difficulty in sentinel lymph node identification using blue dye only may occur in patients with excessive axillary fat. In such cases, a "dominant node" that is increased in size and induration, in reaction to prior needle or surgical biopsy of the tumor, may be palpated and excised. The "dominant node" usually is stained blue or contains radioactivity.²⁶ Peritumoral injections of radiocolloid in the upper outer quadrant or axillary tail of the breast can be associated with "shine through" of radioactivity from the injection site into the axilla, masking the radioactivity of the sentinel lymph node and interfering with its identification

by the hand-held gamma probe. To overcome "shine through" problems, other injection sites are being investigated. Injection into the plexus of lymphatics under the nipple-areolar complex (subareolar injection)^{27,28} and intradermal injection into the skin overlying the tumor show promise in initial studies.^{29–31} The subareolar injection technique presumes that tumors from all regions of the breast drain via the subareolar plexus and that there is a primary lymphatic drainage pathway for the entire breast rather than individual pathways for different regions of the breast. Use of intradermal injection assumes that the lymphatic drainage of the skin overlying the tumor and the lymphatic drainage from the underlying breast parenchyma follow the same lymphatic pathway to the sentinel lymph node.

The choice of lymphatic mapping agent is primarily determined by the surgeon's preference at present: isosulfan blue dye alone, blue dye in conjunction with radiolabeled colloid, or radiocolloid alone. Studies suggest that the sentinel node can be identified in about 83–94% of patients using vital dye alone,^{32,33} 81–95% using both dye and radiolabeled sulfur colloid^{34,35} and 84–99% using radiocolloid alone.^{36,37} In a prospective trial comparing blue dye alone to blue dye and radiocolloid identification at a single institution, identification rates were similar (88% and 86%) and related to the surgeon's experience.³⁸ Identification of the sentinel node by the different techniques have their own advantages and disadvantages.³⁹ Use of blue dye is relatively safe and inexpensive and sentinel lymph nodes are visualized quickly. However, surgeons using only blue dye exhibit a significant learning curve. Side effects include blue stained urine or vomit for about 24 hours (due to urinary and biliary clearance of the dye) as well as potentially permanent faint blue staining of the breast skin in less than 2% of patients. Rarely, patients may exhibit allergic reactions to the dye ranging from blue hives to anaphylaxis that may require vasopressors and an overnight ICU stay (estimated at less than 1 in 500–1000 cases). There is also the possibility of not detecting internal mammary or intramammary sentinel lymph nodes. The advantages of radiocolloid use is that detection of sentinel lymph nodes is by actual radioactivity counts emitted from the node and registered by the gamma probe, and can be measured. Internal mammary nodes may be detected by radiocolloid more easily than with blue dye. Additional radioactive lymph nodes with lower counts than the

sentinel lymph node may represent second echelon lymph nodes that receive drainage from first echelon sentinel node(s) or may represent additional first echelon sentinel node drainage pathways. Use of radiocolloid requires implementation of radiation safety regulations, gamma detection instrumentation, and is complicated by the phenomenon of “shine through” that may also prevent the detection of intramammary lymph nodes. A combination of blue dye and radiocolloid accelerates the surgeon’s learning curve since both visual and radioguided investigation is possible, but has the drawbacks of each of the individual methods.

Controversy still exists in the use of filtered or unfiltered radiocolloid. Variations in ^{99m}Tc sulfur colloid preparation affect the distribution of particle size that, in turn, influence speed and migration to the regional nodes. Large particles may not easily enter the lymphatic system yet they may be more likely trapped and retained by the sentinel lymph node; small particles may migrate more rapidly to draining lymph nodes but may pass through first echelon to second echelon lymph nodes more readily. Multiple institutions

have used filtered and unfiltered radiocolloid with fairly equivalent success rates (Table 1). Goldfarb et al.,⁴⁴ compared the use of $0.22\mu\text{m}$ filtration to $5.0\mu\text{m}$ filtration of ^{99m}Tc sulfur colloid in the optimization of lymphoscintigraphy in melanoma patients. The $0.22\mu\text{m}$ filtrate substantially improved visualization of the lymphatic channel leading to increased diagnostic certainty in the identification of sentinel lymph nodes. A retrospective analysis was performed by Linehan et al.,⁴⁵ to assess sentinel node localization in two groups of breast cancer patients undergoing sentinel lymph node biopsy. All patients received radiocolloid and blue dye. They reported that unfiltered ^{99m}Tc sulfur colloid was superior to the filtered ^{99m}Tc sulfur colloid in localizing radioactive sentinel nodes (88% for unfiltered group vs 73% for filtered group) but that the addition of blue dye made the overall sentinel lymph node identification rate fairly equivalent (92% for the unfiltered group and 95% for the filtered group).

Following removal, the sentinel node (which may actually be 1–4 lymph nodes) is serially sectioned and analyzed for the presence of tumor

Table 1. Comparison of filtered and unfiltered markers used in Breast Cancer Sentinel Node Biopsy

<i>Investigator</i> \ <i>Year</i>	<i>Number</i> <i>of</i> <i>Patients</i>	<i>Marker</i> <i>Filtered/Unfiltered</i>	<i>Total</i> <i>Volume</i> <i>Injected</i> <i>(ml)</i>	<i>Area of Injection</i>	<i>SLN ID</i> <i>Rate</i> <i>(%)</i>	<i>False</i> <i>Negative</i> <i>Rate</i> <i>(%)</i>
Gulec et al., 1997 ⁴⁰	32	100 μCi unfiltered ^{99m}Tc sulfur colloid	4ml	Peritumoral	94%	0%
Rubio et al., 1998 ⁴¹	55	100 μCi unfiltered ^{99m}Tc sulfur colloid	4ml	Peritumoral	96%	11.7%
Linehan et al., 1999 ³⁰	100	300 μCi unfiltered ^{99m}Tc sulfur colloid+ Blue Dye	4ml	Intra parenchymal: around tumor	97%	6%
	100	300 μCi unfiltered ^{99m}Tc sulfur colloid+ Blue Dye	4ml	Intra dermal: directly over tumor	78%	8%
Burak et al., 1999 ⁴²	50	100 μCi filtered (0.22 μm) ^{99m}Tc sulfur colloid	4ml	Peritumoral	90%	0%
Bass et al., 1999 ³⁴	196	450 μCi filtered (0.2 μm) ^{99m}Tc sulfur colloid	6ml	Peritumoral	96%	0.83%
Barnwell et al., 1997 ⁴³	42	100 μCi filtered (0.22 μm) ^{99m}Tc sulfur colloid + Blue Dye	4ml	Peritumoral	90%	0%
Morrow et al., 1999 ³⁸	42	100 μCi filtered ^{99m}Tc sulfur colloid + Blue Dye	7ml	Peritumoral	86%	NA
Linehan et al., 1999 ⁴⁵	77	300 μCi unfiltered ^{99m}Tc sulfur colloid + Blue Dye	4ml	Peritumoral	92%	NA
	57	300 μCi filtered (0.22 μm) ^{99m}Tc sulfur colloid + Blue Dye	4ml	Peritumoral	95%	NA

NA = Data not available

metastases histologically with hematoxylin and eosin (H&E) stain. If there is no evidence of metastasis by H&E, the sentinel lymph node sections are examined using immunohistochemical (IHC) stains against cytokeratin. A sentinel lymph node is considered negative if there is no evidence of metastatic tumor cells by IHC staining.

CLINICAL TRIALS

The results of recent studies evaluating the axillary sentinel lymph node as a predictor of metastatic disease in the rest of the axilla are quite promising. Sentinel lymph node identification rates range from about 85–95% and false negative rates range from 0–15% (Table 2). However, in our opinion, large prospective trials are necessary before this technique becomes standard of care nationwide. Many of the published results are based on small numbers of patients with even smaller numbers of patients with metastatic disease in their axilla. Patients who have tumor-free axilla cannot be used to evaluate whether the axillary sentinel lymph node is truly the first site of afferent drainage. Even if there were multiple pathways for tumor drainage to axillary lymph nodes, biopsying a tumor-free node from anywhere in the body, such as the groin, would still show a high accuracy for predicting a tumor-free axilla in patients who have no axillary metastases! Most studies have 15–50 patients with metastatic disease in their axilla: too small a statistical sampling for valid analysis. Atkins and Warshaw⁵² have commented that the 95% confidence interval for Veronesi's²¹ false negative rate of 5% is actually 1–12% for his study of 163 cases, one of the larger studies; similarly the 95% confidence interval for Veronesi's false negative rate of 0% for tumors smaller than 1.5 cm was 0–15% (this study is not listed in Table 2; we included only Veronesi's updated larger study). Statisticians estimate that at least 250–300 women with axillary lymph node metastases are necessary to distinguish between false negative rates in the 5–10% range. Since about 35% of patients eligible for sentinel lymph node biopsy have axillary lymph node metastases, this would require a study of 700–850 women to achieve meaningful statistical validity. To date, the largest published series has 443 patients, of whom there were only 101 patients who had axillary lymph node metastases in whom a sentinel lymph node was identified and who underwent a

confirmatory axillary lymph node dissection. Many of the institutions that originally studied sentinel lymph node biopsies stopped performing confirmatory axillary lymph node dissections after accruing less than 100–200 cases, making it impossible to obtain the data needed for these institutions to determine the false negative rate for larger numbers of patients.

There are other problems with the published sentinel lymph node literature. There are variations in the determination of false negative rate. Since most studies do not examine internal mammary sentinel nodes, we consider the definition of false negative rate to be the number of patients with false negative sentinel lymph nodes (the number of patients with an axillary sentinel lymph node that is tumor-free but who have other non-sentinel axillary lymph nodes with metastatic disease) divided by the total number of patients with any axillary lymph node metastases in whom a sentinel lymph node was identified. Most studies use the same numerator—number of patients with false negative sentinel lymph nodes—but the denominator can range from the number in the entire study group (including node negative as well as node positive patients) to the axillary lymph node positive patients whether or not a sentinel node was identified in those patients to the axillary lymph node positive patients in whom a sentinel lymph node was identified. A third point is that many of the studies were done in academic institutions by breast surgeons who perform axillary dissections routinely. These surgeons were able to operate on enough patients to acquire skill in this procedure over a relatively short period of time. A surgeon's learning curve may influence study results and these results may not be generalizable to community surgeons. Krag's multicenter study, the largest sentinel lymph node study to date, showed a false negative rate ranging from 0–29% among 11 surgeons.

It has been suggested in a consensus statement from The American Society of Breast Surgeons (ASBS) that surgeons who perform sentinel lymph node biopsy should perform at least 30 procedures and obtain an identification rate of $\geq 85\%$ and a false negative rate of $\leq 5\%$ before proficiency is achieved.⁵³ It is important to note that the average general surgeon performs only 12 axillary lymph node dissections per year and that 50% of general surgeons perform 4 or fewer axillary lymph node dissections per year³³. This raises questions on how applicable this procedure

Table 2. Breast Cancer Sentinel Lymph Node Biopsy Studies

Institution/State/ Country	Investigator/ Year of Publication	Marker	Inj. Site	n	Patients with ALND	Patients with Node Positive		Av # SLN per case	SLN ID Rate (%)	False Negative Rate	SLN Positive only	Froze to H&E	H&E -ve to IHC
						with Axilla	with Axilla and SLN ID						
John Wayne, Santa Monica	Giuliano et al., 1994 ¹⁹	Dye	Peri	174	174	62	42	1.8	66%	9.5% (4/42)	38% (16/42)	NA (1/42)	2%
John Wayne, Santa Monica	Giuliano et al., 1997 ³³	Dye	Peri	107	107	43	42	1.8	94%	0% (0/42)	67% (28/42)	0% (9/42)	21% (9/42)
Israel	Koller et al., 1998 ⁴⁶	DyeM	SubQ	98	41	38	38	2.7	98%	7.9 (3/38)	34% (13/38)	NA	NA
Glasgow, UK	Flett et al., 1998 ⁴⁷	DyeP	Peri	68	68	21	NA	1.2	82%	14.2% (3/21)	24% (5/21)	14% (3/21)	NA
France	Bobin et al., 1999 ³²	DyeE	Peri	100	100	42	39	3.0	83%	5.1% (2/39)	NA	NA	5% (2/39)
Hartford, CT	Kern et al., 1999 ²⁷	Dye	SubA	40	40	15	15	2	98%	0% (0/15)	47% (7/15)	NA	NA
Netherlands	Borgstein et al., 1998 ²⁹	^{99m} TcA	Peri	130	112	51	45	NA	94%	2.2% (1/45)	58% (26/45)	NA	11% (5/44)
Milan, Italy	Veronesi et al., 1999 ³⁷	^{99m} TcA	Peri SubD	376	371	180	168	1.4	99%	7.1% (12/168)	43% (73/168)	15% (26/168)	NA
U Arkansas	Rubio	^{99m} Tc	Peri	55	55	17	17	1.7	96%	11.7% (2/17)	53% (9/17)	NA	NA
Little Rock, AK	et al., 1998 ⁴¹												
Washington, DC	Miner et al., 1998 ⁴⁸	^{99m} Tc	Peri	82	57	16	16	2.4	98%	6.3% (1/16)	44% (7/16)	NA	NA
U Vermont Medical Center	Krag et al., 1998 ²⁰	^{99m} Tc	Peri	443	443	114	101	2.6	93%	12.8% (13/101)	NA	NA	NA
Moffitt Center Center, Florida	Bass et al., 1999 ³⁴	^{99m} Tc+ Dye	Peri	700	186	54	53	2.03	95%	1.9% (1/53)	NA	NA	NA

Memorial Sloan-Kettering	O'Hea et al., 1998 ⁴⁹	Intra	59	59	20	2.2	93%	15% (3/20)	41% (7/17)	NA	NA
U Kansas School of Med.	Jaderborg et al., 1998 ³⁵	Peri	79	79	20	1.5	81%	5% (1/20)	22% (14/64)	NA	NA
U WA Medical Center	Eary et al., 1999 ⁵⁰	Peri	62	62	31	1.5	79%	12.9% (4/31)	NA	NA	NA
Netherlands	V an der Ent et al., 1999 ⁵¹	Peri	70	70	27	2.6	100%	3.7% (1/27)	52% (14/27)	NA	7.4% (2/27)
U Arkansas Little Rock, AK	Klimberg et al., 1999 ²⁸	SubA	69	15	15	1.5	94%	NA (8/15)	53%	NA	NA

SLN = Sentinel Lymph Node

LN = Lymph Node

NA = Data Not Available

Av # SLN per case = Mean number of sentinel nodes removed per case

False negative rates have been computed as the number of patients whose SLN showed no evidence of metastases but had other axillary lymph nodes with metastatic disease divided by the number of patients who had a SLN identified and had any LN with metastases. These numbers may differ from those reported by the original authors as the definition of false negative varies in the different studies.

Frozen -ve to H&E +ve = cases tested negative on frozen sections but were positive when tested with Hemotoxylin and Eosin stains

H&E -ve to IHC +ve = cases tested negative with H&E but were positive when tested with Immunohistochemical studies

n = number of cases

Peri = Peritumoral Dye = Isosulfan Blue Dye ^{99mTc} = ^{99mTc} sulfur colloid

SubQ = Subcutaneous DyeM = Methylene Blue Dye ^{99mTc}N = ^{99mTc} nanocolloid

SubD = Subdermal DyeP = Patent Blue Dye ^{99mTc}A = ^{99mTc} albumin colloid

SubA = Subareolar DyeE = Evans Blue Dye

Into = Into tumor

Intra = Intraparenchymal

will be for the vast majority of general surgeons in community practice. It is particularly worrisome that anecdotes abound in many communities that some surgeons use the statistics published by “experts in the field” rather than their own numbers. These surgeons may prematurely switch over to sentinel node biopsy only, without keeping track of their own false negative rates because of marketplace influences (women demanding sentinel node biopsy only without standard axillary dissection). In contrast to melanoma where a lymph node dissection may not be performed as standard of care, a false negative sentinel lymph node biopsy that supercedes standard axillary lymph node dissection in breast cancer carries the potential to leave malignant nodes in the axilla. This may influence local recurrence rates in the axilla and may potentially serve as a secondary source of malignant seeding that may ultimately affect patient survival. For this reason, we strongly recommend that patients undergo sentinel lymph node biopsies as part of approved protocols with mechanisms for long term follow-

up if a concurrent axillary dissection is not performed.

Large prospective clinical trials are now underway. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 protocol⁵⁴ randomizes clinically node-negative women with breast cancer to sentinel lymph node resection only or sentinel lymph node resection followed by conventional axillary lymph node dissection. Women randomized to the sentinel lymph node resection only group whose sentinel lymph node is pathologically positive will then undergo axillary lymph node dissection. Differences between the two groups in regional disease control rate, survival, and morbidity will be evaluated.

The American College of Surgeons Oncology Group (ACOS-OG)⁵⁵ will enroll clinically node-negative women with T1 and T2 breast cancers who are undergoing breast conservation surgery in their Z0010 and Z0011 trials. The first trial prospectively follows women who undergo sentinel lymphadenectomy only without an axillary lymph node dissection. Patients with metastatic

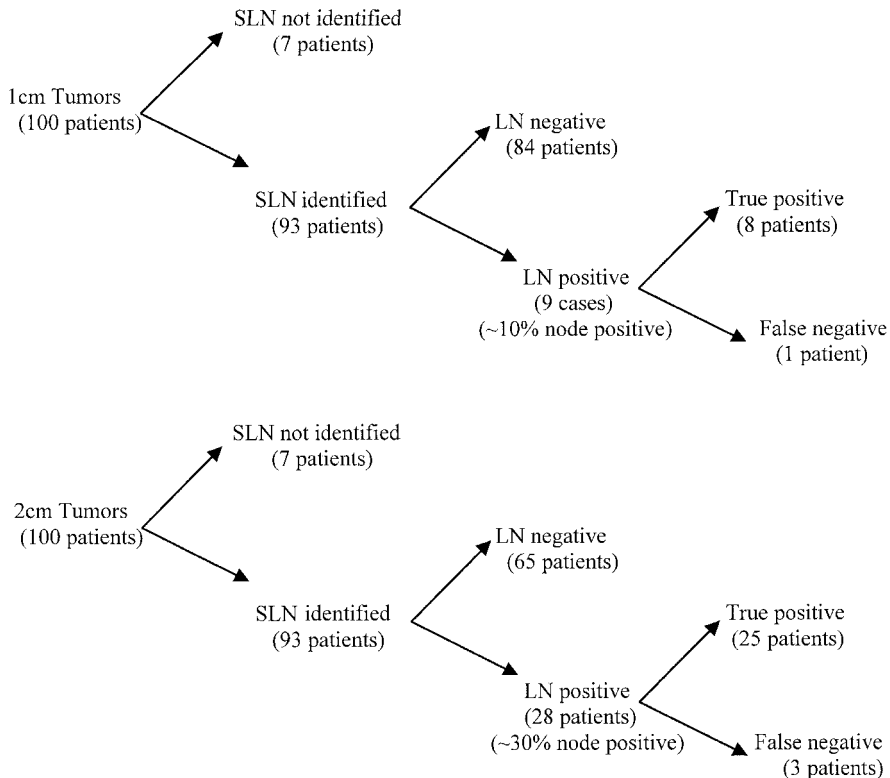


Figure 1: Hypothetical predictive values of sentinel lymph node accuracy for 100 patients with a 1 cm tumor. The calculations above are based on a 93% sentinel lymph node identification rate and a 10% false negative rate.

disease in their sentinel lymph node by routine H&E analysis are then eligible for trial Z0011 which randomizes patients with tumor-positive sentinel lymph nodes to completion axillary lymph node dissection or no axillary dissection (and no axillary radiation). Axillary recurrence rates, distant disease-free survival, and surgical morbidity will be evaluated in both studies. All sentinel lymph nodes will be examined by IHC for micrometastases, but patients and their physicians will not be informed of the results. A portion of the patients will also undergo bone marrow biopsy to determine whether the identification of tumor cells circulating in the bone marrow is more predictive of clinical outcome than lymph node metastases.

One of the most important areas that requires study is patient selection criteria: who are the patients most appropriate for this procedure and least likely to show false negative sentinel lymph nodes? Our own observations in over 440 patients with concurrent axillary lymph node dissections (Bay Area Sentinel Lymph Node Study, unpublished results) suggest that some patients show more than one primary lymphatic drainage pathway, perhaps due to normal anatomic variation or alternatively due to possible "lymphangiogenesis" (recruitment of new lymphatic channels, analogous to tumor angiogenesis). We have identified a small number of patients with two or three anatomically separate and apparently unconnected sentinel lymph nodes or lymph node clusters that drain different lymphatic channels from the breast. This may be a source of false negative sentinel lymph nodes. Another example of a false negative sentinel lymph node that we have visually observed is the shunting of lymphatic drainage around a tumor-filled lymph node to a higher non-metastatic lymph node.

Until larger studies are available, the safest selection criteria are in patients with low likelihood of axillary lymph node metastases. Figure 1 shows the hypothetical situation of 100 patients with 1cm tumors versus 100 patients with 2cm tumors. Assuming the same false negative rate of 10%, there will be three times as many patients with false negative sentinel lymph nodes in the 100 patients with 2 cm tumors than in the 100 patients with 1 cm tumors.

While awaiting the results of larger clinical trials, and understanding women's desire to avoid a potentially morbid axillary dissection when there may be a low likelihood for axillary lymph node metastases, we are offering patients sentinel

lymph node biopsies with limited axillary lymph node dissections. After identifying all sentinel lymph nodes, we carefully palpate the axilla and excise any other nodes that feel reactive to previous needle or surgical biopsy (similar to the dominant node concept mentioned earlier) and a few additional palpable nodes, usually removing about 5–6 axillary lymph nodes. We also use filtered ^{99m}Tc sulfur colloid in order to excise both first and second echelon (the next lymph nodes to drain the small particles of radiocolloid) axillary lymph nodes. The logic behind this procedure is related to British studies excising five axillary lymph nodes but with the advantage that the sentinel lymph node can be more closely examined for metastatic disease.

In summary, sentinel lymph node biopsy in breast cancer is an emerging technique that may decrease surgical morbidity while more accurately staging breast cancer patients. A number of areas of controversy need to be resolved before sentinel lymph node biopsy can replace axillary dissection as the standard of care in a community based setting. Some of these areas of controversy, as reviewed in this paper include: (1) Choice of mapping agents, (2) Patient selection criteria, (3) Management of internal mammary sentinel lymph nodes, (4) Management of the axilla in patients with micrometastases to sentinel nodes, and (5) Credentialing criteria for surgeons, nuclear medicine physicians and pathologists developing a new sentinel lymph node program. Outside of a few highly specialized breast cancer centers, it is recommended that physicians who want to offer sentinel lymph node biopsy to their patients do so in conjunction with one of the national trials described above.

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