Sentinel lymph node biopsies in cancers of the skin, colon, head and neck, and breast

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The sentinel lymph node (SLN) is the initial site of lymphatic drainage for a tumor. Biopsy of the SLN is accurate in predicting the status of the lymph node basin because cells progress from the tumor to the node in a sequential pattern. Patients whose SLN shows no signs of disease can be spared the morbidity of further node dissection. The focus is on a single lymph node, possibly two, depending on the biopsy. The procedure is safe, minimally invasive, cost effective, and can be used in melanoma, colon cancer, head and neck cancer, and breast cancer.

TECHNIQUE

The SLN is identified by using blue dye, either methylene blue or 1% isosulfan. Radiocolloids (technetium 99m sulfur colloid or technetium 99m colloidal albumin), filtered or unfiltered, can also be used; the optimal particle size is 10 to 15 nm. A 1999 study of the cumulative results from 20 SLN biopsy series demonstrated that the use of isotope combined with dye was more accurate in identifying the SLN than either method alone (*Table 1*) (1). The rate of false-negative biopsies was 4% when the combination technique was used, compared with 6% for isotope alone and 8% for dye alone. Linehan et al also compared methods of radiocolloid injection, which have been debated in the past. Their data showed a much higher success rate for intradermal injection than for intraparenchymal injection of radiocolloid (1). Therefore, the intradermal route is generally agreed to be best.

Preoperative lymphoscintigraphy to map the lymphatic system is important in some patients. The radiocolloid is injected around the tumor in the nuclear medicine suite from 30 minutes to 24 hours before surgery. At Baylor, 3 to 5 mL of blue dye is injected peritumorally 3 to 5 minutes before the biopsy begins. A handheld gamma probe is used in the operating room to locate the SLN. Lymph nodes are considered sentinel if they are "hot" (a 10:1 ex vivo radioactive count ratio), blue, or hot and blue. A completion lymphadenectomy is indicated if the SLN is positive for disease, as determined by pathologic examination. A lymph node dissection should also be done if disease is identified in the lymph nodes or if an SLN cannot be located.

Pathologic analysis of the SLN is begun in multiple 2-mm sections. Hematoxylin and eosin staining is used to evaluate the SLN. This technique identifies one tumor cell among 10,000 normal cells. Immunohistochemistry (IHC) identifies one tumor cell among 100,000 normal cells. The most sensitive test is the reverse transcriptase-polymerase chain reaction (RT-PCR),

Table 1. Comparison of tracing compounds used in SLN biopsies: cumulative results of 20 biopsy series*

Method	SLN found % (range)	False-negative SLN† % (range)	Accuracy‡ % (range)
Isotope (n = 1823)	92 (69–99)	6 (0–13)	96 (97–100)
Dye only (n = 484)	77 (66–97)	8 (0–17)	97 (95–100)
Isotope + dye (n = 196)	93 (90–100)	4 (0–15)	98 (95–100)
Total (n = 2503)	89 (69–100)	4 (0–15)	98 (95–100)

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†False-negative: denominator equals node-positive cases.

‡Accuracy: denominator equals total cases where SLN was found.

SLN indicates sentinel lymph node.

which can identify one tumor cell among one million normal cells. Two newer techniques, intraoperative touch prep cytology and intraoperative ultrarapid IHC, have varying sensitivities and false-negative rates. At present, no standard method for pathologic assessment of the SLN has been established.

MELANOMA

SLN biopsy for melanoma is minimally invasive and highly accurate in identifying occult nodal disease. Several studies have shown that SLN biopsy is the most significant prognostic factor for disease-specific and disease-free survival. According to Gershenwald et al, the hazard ratio for survival in patients whose SLN is positive for disease is 6.53, higher than for any other factor the authors studied (2). They also reported a lower survival rate and higher risk of recurrence in patients who have positive SLN biopsy results. Among patients with melanoma, the overall survival rate at 5 years was 50% for those who had disease in the SLN compared with 90% for those who did not.

Data from Baylor University Medical Center (*Figure*) correlate with the aforementioned results. At 53 months of follow-up, melanoma patients who had positive SLN biopsy findings had an overall survival rate of only 53%, compared with 92%

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Figure. Overall survival of patients with malignant melanoma according to sentinel lymph node pathology results. Data from Fincher T, Kuhn JA, Fisher TL, O'Brien JC, Preskitt JT, Lieberman ZH, Stephens JS, McCarty TM. Patterns of recurrence following sentinel lymph node biopsy for melanoma. Presented at the 55th Annual Meeting of the Southwestern Surgical Congress, April 27–30, 2003, Tucson, Arizona. Circles indicate censored data points.

for those with negative SLN biopsy findings. Likewise, the rate of disease-free survival at 53 months was much better for those with negative SLN biopsy results (87%) than those with positive SLN biopsy results (47%) (3). Thus, SLN biopsy improves the accuracy of staging and facilitates an early therapeutic lymph node dissection for patients with lymphatic disease. In addition, the procedure can identify patients who are candidates for treatment with interferon alfa-2b and help define a homogenous patient population for future clinical trials.

Preoperative lymphoscintigraphy with technetium 99m sulfur colloid is very important in melanoma because it can display lymphatic drainage patterns that are different than can be noted from anatomic guidelines. In one study, IHC identified lymphatic drainage that varied from the originally predicted pattern in 63% of patients with melanoma of head and neck and 32% of patients with melanoma through the trunk region (4). IHC is important because hematoxylin and eosin staining misses up to 21% of diseased nodes (5).

McMasters listed factors that predict SLN metastasis in patients with melanoma: tumor thickness ≥ 1 mm, the presence of ulceration, patient age < 60 years, or Clark's level $> \text{III}$ (6). Based on these criteria, approximately 15% to 25% of patients will have a positive SLN biopsy result. Therefore, 75% to 85% of patients could avoid a completion lymph node dissection. If the SLN biopsy result is positive, patients should undergo completion lymph node dissection and be offered high-dose interferon therapy.

A topic of debate is whether lymph node dissection in itself provides any survival benefit for patients. Most arguments are based on 4 randomized trials that failed to show any survival benefit, but 2 aspects of these studies should be noted. First, 80% of the patients had no evidence of nodal disease on final pathology, so only 20% would have benefited from a lymph node dissection in the first place. Second, 75% of the patients in these studies did not receive lymphoscintigraphy, which is important for lymphatic mapping. Other controversies about SLN biopsy for melanoma are related to 1) PCR testing, 2) thin melanomas

< 1 mm, 3) micrometastatic disease (< 2 mm), and 4) thick tumors (> 4 mm).

The role of PCR in patients with melanoma. Patients who have tumors 1 to 1.5 mm thick have about a 20% chance of having a PCR SLN biopsy that shows disease. What does this tell us? Is the disease solely in the SLN, or could this positive result be a predictor of distant metastases? The Sunbelt Melanoma Trial will attempt to answer these questions. Patients with disease in the SLN, as determined by PCR, will be randomized into 3 treatment arms: observation only, completion lymph node dissection, or completion lymph node dissection combined with interferon alfa treatment.

The role of SLN biopsy for melanomas < 1 mm thick. Muller et al studied 348 patients with melanomas < 0.9 mm thick, and none had SLN micrometastases (7). Jacobs et al did a similar study and found that patients with melanomas < 0.75 mm had no disease in the SLNs, but those with tumors between 0.75 mm and 1 mm had a 3% chance of having disease in the SLN (8). These intermediate data are consistent with other reports in which 3% to 7% of patients have disease in the SLN. These findings suggest that SLN biopsy is indicated in patients who have melanomas < 1 mm thick with ulceration, a Clark's level $> \text{III}$, or a palpable lymph node.

Treatment of micrometastatic disease. In patients with micrometastatic disease (< 2 mm), the standard of care is to perform a completion lymph node dissection. However, an argument can be made for not completing the dissection. The morbidity might be too high in an elderly patient. Likewise, a modified radical neck lymph node dissection may be too risky in a patient with a history of heart failure. Patients with micrometastatic disease have a low incidence of disease in nonsentinel nodes. Morton found that $< 1\%$ of patients had disease in nonsentinel nodes when micrometastatic disease was found only in the SLN (9). Long-term data from multicenter trials are needed to answer this question.

The role of SLN biopsy for thick tumors (> 4 mm). Greshenwald et al reported that the biopsy can be performed with high accuracy rates (2); however, Essner et al found no correlation between SLN status and survival in patients with thick tumors (10).

COLORECTAL CANCER

Historically, up to 30% of patients with colorectal cancer are found to have lymph nodes negative for disease and yet go on to develop metastatic disease, usually within 5 years of diagnosis. Nodal metastases are the best predictor of survival in patients, and staging is important for prognosis and treatment of colorectal cancer.

Three deficiencies exist in traditional colon lymph node analysis. The first is an insufficient number of nodes. About 6 to 15 lymph nodes are needed to adequately stage colorectal carcinoma. Perhaps the pathologist is not recovering data in sufficient lymph nodes, a situation that could be improved with fat-clearing techniques. The second deficiency is a sampling error in the lymph node analysis: generally, $< 1\%$ of the submitted tissue is actually analyzed. The third deficiency relates to limits

Table 2. Recent studies of SLN biopsies in colorectal cancer

Author (reference)	Year	N	SLN identified (%)	False negatives (%)
Feig (12)	2001	48	98	38
Paramo (13)	2001	35	71	0
Saha (14)	2001	203	98	3
Wood (15)	2001	75	96	20
Bilchik (16)	2002	100	97	5
Broderick-Villa (17)	2002	50	92	50

SLN indicates sentinel lymph node.

in microscopic evaluation of low-volume disease. This deficiency can be improved with IHC, PCR, or perhaps serial sectioning. Serial sectioning is a very expensive and labor-intensive process to use for all lymph nodes.

A safe method is needed to evaluate nodal status for patients with colorectal cancer. SLN biopsy prompts a more rigorous pathologic analysis, and it assists the pathologist in identifying critical nodes to evaluate. In colon cancer, the outcome of the SLN biopsy does not change the type of surgery that is performed; a formal lymphadenectomy is the surgery of choice, so the morbidity is unchanged. By contrast, a complete lymph node dissection can be avoided in breast cancer or melanoma if the SLN shows no signs of disease.

The technique of SLN biopsy for colorectal cancer is not standardized. Most investigators are performing 1-mL subserosal injections of the 1% isosulfan blue dye in and around the tumor circumferentially. In vivo and ex vivo injection methods are used. The ex vivo injection methods are performed mainly for patients who are undergoing laparoscopic colon resection or when the in vivo method fails. Radiocolloid has also been discussed as assisting in the SLN biopsy of colon carcinomas. Isotopes are injected preoperatively during a colonoscopy, which can be fairly inconvenient for the patient and the surgeon. Detection rate and diagnostic accuracy for patients with T1 or T2 primary colon tumors are 100% according to a study done in 2002 (11).

A review of recent data on SLN biopsy for colorectal cancer reveals that the SLN was identified in 71% to 99% of patients; however, the false-negative rates varied widely, from 0% to 50% (Table 2). One explanation for the wide range is that two studies with especially high false-negative rates included patients with larger tumors; the majority of the patients in those series had T3 or T4 tumors. Thus, the SLN may have been replaced by tumor, decreasing the accuracy and increasing the rate of false negatives.

SLN biopsy has benefits in colorectal cancer. Patients can be up-staged from stage I or II to stage III, and these patients may benefit from chemotherapy: among colorectal carcinoma patients whose SLN biopsy results were positive, the mortality rate was decreased with chemotherapy. Second, SLN biopsy can identify aberrant lymphatic drainage, which is noted in 2% to 14% of patients. This important information can help the surgeon more accurately determine the extent of surgery needed. Third, micrometastatic disease may be missed by conventional methods. Finally, SLN biopsy has no apparent side effects in patients with colon cancer. Future study is needed to determine whether the

substantial number of patients whose disease is up-staged by SLN biopsy corresponds to those patients who are initially thought to have disease-free nodes but later develop metastatic disease.

HEAD AND NECK CANCER

SLN biopsy is used in melanoma, thyroid, and squamous cell carcinoma of the head and neck. Ultrasound, physical examination, computed tomography, positron emission tomography, and magnetic resonance imaging are not reliable in assessing the nodal status of patients with these cancers. About 30% of such patients will have some type of metastatic disease that is not evident clinically. That means that 70% to 80% of those with head and neck carcinomas but without nodal disease could possibly be spared the morbidity of complete neck lymph node dissection. In early cervical disease, preliminary results indicate that SLN biopsy combined with radiotherapy may offer regional control similar to that provided by modified radical neck lymph node dissection.

In 2002, Ross et al evaluated the accuracy of SLN biopsy data from 22 centers; they studied 316 patients with squamous cell carcinoma of the head and neck (N0 disease). The SLN was identified in 95% of these patients, with an overall sensitivity of 90% (18).

Oral tumors are injected with the radiotracer in the nuclear medical suite while the patient is awake. Patients who have a laryngeal or hypopharyngeal tumor undergo general anesthesia, and the injection occurs in the operating room. The SLN is usually identified after skin flaps are created. SLN biopsy and intraoperative imprint cytology can predict nodal status in many patients with oral cancer.

Difficulties exist in performing SLN biopsy in patients with head and neck cancer. In patients with thyroid cancer, the parathyroid glands preferentially take up the blue dye that normally identifies the SLN. In oral cancers, the SLN may be close to the primary tumor in the oral cavity and difficult to identify in a level I dissection; the radiocolloid produces a "shine-through" effect, with an increasing background signal from the primary tumor. This effect is common in the submental and submandibular regions. Finally, the number of false-negative results in SLN biopsy of head and neck cancer is unknown, since follow-up neck dissections have not been done in all cases. Proposed solutions for some of these problems include using interoral lead shielding, removing the primary tumor first, requiring a level I dissection, and using blue dye.

BREAST CANCER

In breast cancer, regional node status is the most important predictor of prognosis, while tumor size is the most accurate indicator of the risk of metastatic disease. As tumor size increases, so does the number of SLNs positive for disease (19).

SLN biopsy is accurate for evaluating axillary nodes, with rates of identification ranging from 82% to 99%. At Baylor, the accuracy rate is 90% to 100%, and the false-negative rate is quite low. The SLN biopsy is widely used, but guidelines establishing it as the standard of care have not been written. In evaluating nodal status, the published success rates of SLN biopsy are comparable to those of axillary node dissection, and the rates of recurrence are low.

Table 3. Studies involving the use of neoadjuvant therapy prior to SLN biopsy in breast cancer

Author (reference)	Year	N*	SLN identified (%)	False negatives (%)
Breslin (22)	2000	51	84	12
Nason (23)	2000	15	NR	33
Julian (24)	2001	31	93	0
Stearns (25)	2001	34	89	6
Tafra (26)	2001	29	93	0
Brady (27)	2002	14	93	0
Balch (28)	2003	32	97	5

*Refers only to patients who received neoadjuvant therapy; total number of patients studied may have been larger.

SLN indicates sentinel lymph node; NR, not reported.

Focused IHC can detect metastatic breast cancer in a single SLN. The addition of IHC to SLN biopsy can improve staging for patients in about 10% to 15% of cases. Location, multifocal disease, neoadjuvant therapy, and prior breast surgery do not appear to affect the SLN biopsy results.

Nonsentinel nodes rarely have tumor cells if the SLN does not. Conversely, the chance of nonsentinel nodes having metastatic disease increases when the SLN biopsy result in breast cancer is positive. Micrometastatic disease can be detected by IHC alone, but there is some question about whether these test results can predict patient outcomes. In 2001, Turner found that 26% of patients with micrometastases in the SLN had metastasis in the lymph nodes with completion axillary lymph node dissection (20). In a larger study of 683 patients, Hansen found that patients with positive SLN biopsy results identified only by IHC had the same overall survival as patients with negative SLN biopsy results (21). Thus, although we can identify micrometastatic disease in SLNs, the survival rates for such patients may be no different than for those with no disease in the SLN.

The role of neoadjuvant therapy prior to SLN biopsy in breast cancer patients has been studied extensively (Table 3). Success in identifying the SLN after such therapy ranges from 84% to 97%, and the rate of false negatives ranges from 0% to 33%. The advantages of neoadjuvant therapy prior to SLN biopsy include a decrease in the tumor burden of these patients and an increase in the rate of breast conservation. Patients are sometimes spared the morbidity of an axillary lymph node dissection, and local failure is absent.

Disadvantages to neoadjuvant therapy prior to SLN biopsy have also been identified. Some believe that preoperative treatment may impair the flow of the radiocolloid or the blue dye. In addition, it is argued that the flow through the lymphatic system could be disrupted by tumor, fibrosis, or inflammation. The regression of metastatic disease may be selective, meaning that the cytotoxic effect is not uniform—it affects some lymph nodes and not others. Some believe that the results of neoadjuvant therapy are unlikely to change their treatment of these patients.

In summary, the success rate for SLN biopsy after neoadjuvant therapy for breast cancer is about 90%. The technique could be used in young patients who have relatively large tumors (T3 or

T4), but long-term follow-up is needed to determine the accuracy of the procedure under these circumstances.

Questions have been posed about many other aspects of SLN biopsy in breast cancer. Some have been resolved; others are still debated:

- *What is the appropriate treatment of micrometastatic disease identified by IHC?* The standard of care continues to be axillary lymph node dissection, but clinicians can also offer participation in a clinical trial. In the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, patients who have had lumpectomy and a positive SLN biopsy result are randomized to axillary lymph node dissection or to observation.
- *What is the optimal location for the injection of radiocolloid?* At Baylor we mainly do peritumoral injections.
- *Can SLN biopsy be done in patients who have had prior axillary dissections?* The answer may depend on the amount of axillary dissection previously done.
- *What is the role of the SLN in ductal carcinoma in situ?* Although the survival rate for ductal carcinoma in situ is very good, an estimated 10% to 30% of these patients will have invasive cancer, so lymph node staging is important.
- *What is the role of SLN biopsy in prophylactic mastectomy?* This question is important for patients who have the BRCA1 or BRCA2 gene. Patients who undergo surgery have about a 5% chance of having an incidental carcinoma. If they have invasive cancer, their lymph nodes need to be staged. An SLN biopsy may rule out the need for completion lymph node dissection.

FUTURE DIRECTIONS

Many questions about the role of SLN biopsy in the diagnosis and treatment of cancer remain unanswered. To help resolve them, several studies involving SLN biopsy are planned or in progress. Studies not previously mentioned include the following:

- ACOSOG Z0010: studies the prognostic value of SLN biopsy and bone marrow micrometastases in women with clinical stage T1 or T2 breast cancer
- ACOSOG Z0360: examines the role of SLN biopsy in oral cavity squamous cell cancer
- National Surgical Adjuvant Breast and Bowel Project B-32: randomizes patients with breast cancer and a negative SLN biopsy result to either axillary lymph node dissection or observation alone
- The Florida Melanoma II Trial: includes patients who have disease in the SLN and receive interferon, with or without completion lymph node dissection

CONCLUSION

SLN biopsy has gained great acceptance in the areas of melanoma and breast cancer, and it has the potential to be used in all solid tumors. The procedure is minimally invasive, provides accurate results, and can offer a more rigorous pathologic evaluation of lymph nodes. Although SLN biopsy has been successful and continues to be refined, many controversies about the procedure remain. SLN biopsy is being investigated for use in esophageal and gastric cancers, gynecological carcinomas, non-small cell lung cancer, Merkel cell cancer, and ophthalmic tumors.

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