Sentinel Node Biopsy for Melanoma:
An Update After Two Decades of Experience

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When detected and treated early, melanoma has an excellent prognosis. Unfortunately, as the tumor invades deeper into tissue the risk of metastatic spread to regional lymph nodes and beyond increases and the prognosis worsens significantly. Therefore, accurately detecting any regional lymphatic metastasis would significantly aid in determining a patient's prognosis and help guide his or her treatment plan. In 1991, Don Morton and colleagues presented new paradigm in diagnosing regional lymphatic involvement of tumors termed sentinel lymph node biopsy (SLNB). By mapping the regional lymph system around a tumor and tracing the lymphatic flow, a determination of the most likely lymph node or nodes the cancer will spread to first is made. Then, a limited biopsy of the most likely nodes is performed rather than a more-invasive removal of the entire local lymphatic chain. In 20 years that have followed, a great deal of information has been gained as to its accuracy, prognostic value, appropriate candidates, and its impact on regional disease control and survival. The SLNB has been shown to accurately stage regional lymph node basins in stage I and II melanoma patients with minimal morbidity. More sensitive histologic techniques are now being applied that may allow even greater accuracy in the staging of melanoma patients. Although specific percent risk thresholds are still in question, recommendation for SLNB when melanomas are 1 mm or thicker has gained wide acceptance. SLNB may also be appropriate for patients with melanomas that are between 0.76 and 1 mm thick and have ulceration, high mitotic rates, or reach a Clark level IV. Therefore, melanomas with IB or greater staging should be considered for SLNB.
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Most of the primary melanomas in the United States are diagnosed by the dermatology community. Because of screening programs and public and physician education programs, awareness about the early signs of melanoma has been heightened, making early diagnosis commonplace; now more than 85% of newly diagnosed patients have disease clinically localized to the primary cutaneous site (American Joint Committee on Cancer [AJCC] stage I and II). Although most of these patients have an excellent prognosis and can be cured with wide excisions alone, a significant percentage have already developed metastatic spread to the regional lymph nodes and/or to distant sites at the microscopic (clinically and radiographically occult) level and therefore have a more guarded prognosis.[1] The technique of lymphatic mapping and sentinel node biopsy (sentinel lymph node biopsy; SLNB) was introduced as a minimally invasive method of identifying the greater-risk patients and to facilitate the selec-

tive use of more aggressive surgical and systemic therapies with the hope of improving the expected outcomes with little additional morbidity.

The initial experience with SLNB was first presented in 1991 and published in 1992 by Morton et al[2] as a new paradigm in the initial management of the newly diagnosed stage I and I melanoma patients. Global interest in such a rational management strategy developed quickly. Several confirmation studies and the design and completion of prospective randomized trials has generated a wealth of information regarding a variety of issues related to the use of SLNB, including its accuracy, prognostic value, appropriate candidates, the use of sensitive histologic techniques, novel lymphatic drainage imaging studies, impact on regional disease control and survival, and morbidity. Although this technique has been widely regarded as one of the most important advances in melanoma treatment, some questions and controversies about its use have also emerged. After 2 decades of SLNB experience, it seems worthwhile to update its current role in the management of stage I and II melanoma and discuss some of the major controversies.

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The Evolution of SLNB as a Rational Management Strategy

Surgical strategies for the stage I and II patients have included 2 main components: wide excision of the primary tumor or biopsy site and regional lymph node evaluation.[3] Although recommendations for the extent of excision margins are well established and widely accepted, the approach to the clinically uninvolved regional lymph nodes has been the center of ongoing controversy.[3] How to best manage the following clinical scenario is often called into question: A 36-year-old patient presents after a punch biopsy of a changing pigmented lesion over the left scapula diagnosed as a 1.8-mm melanoma. Physical examination reveals the absence of enlarged lymph nodes in any potential regional lymph node group. The chest X-ray is normal, and the patient is otherwise healthy. Traditionally, this patient would have been offered 1 of 2 options in addition to excision of the primary tumor: (1) observation of the regional lymph nodes and formal node dissection only if the patient subsequently develops clinically evident (palpable) nodal disease, an approach termed therapeutic lymph node dissection (TLND), or (2) a formal lymph node dissection as a component of the initial surgical treatment, referred to as elective lymph node dissection (ELND). Unfortunately, both approaches have theoretic as well as very real disadvantages.[3]

A significant percentage of patients, predicted by increasing primary tumor thickness, ulceration, or other unfavorable histologic features of the primary tumor,[4] mitotic rate in particular,[1] harbor clinically undetectable regional lymph node metastases, which in most patients will lead to palpable (macroscopic) nodal disease if left untreated. Once clinical nodal involvement develops, the ability to achieve long-term survival and durable regional disease control with a TLND may be compromised compared with surgical approaches targeted at treating microscopic nodal burden.[3] The harsh reality is that after TLND the rate of distant metastatic disease and relapse in the treated nodal basin is at least 50%[4,5] and 15%-50%,[6-11] respectively. The practice of ELND was popularized for the sole intent of reducing these high rates of disease recurrence. Proponents of ELND suggested that removal of microscopically involved lymph nodes would prevent the development of clinically apparent lymph node disease, which in turn could in a significant percentage of patients eliminate a potential source of distant failure. Furthermore, a dissection performed when the lymph node involvement is microscopic would more completely eradicate regional micrometastases and prevent recurrence in the treated basin and the potential sequelae of pain, skin ulceration, blood vessel and nerve involvement, and advanced lymphedema that can be associated with this pattern of failure. In most patients, however, microscopic nodal disease is absent at diagnosis and therefore cannot benefit from an ELND and are subjected to the cost and morbidity of an unnecessary operation. Because the incidence of occult nodal metastases is approximately 15%-20% it was not surprising that an overall survival advantage with ELND was not ob-

served in prospective randomized trials that compared the outcome of stage I and II patients receiving either ELND or nodal observation,[12-15] and as a result, the routine practice of ELND was appropriately challenged. A rational compromise emerged when the technique of lymphatic mapping and SLN biopsy was introduced as a minimally invasive method for determining whether occult nodal metastases are present.[2] Patients with proven occult nodal disease in the SLN could then undergo an early TLND, and those without disease could be safely observed, an approach popularized as selective lymphadenectomy.[16] This approach has been extensively studied worldwide.

Scientific Support for the Sentinel Node Concept

Lymphatic mapping relies on the hypothesis that the dermal lymphatic drainage from cutaneous sites to the regional lymph node basin is an orderly and definable process and that these lymphatic drainage patterns should mimic the metastatic spread of melanoma cells in the lymphatics (Fig. 1). In this way, the first lymph node(s) receiving lymphatic drainage (the sentinel nodes) are the most likely to contain metastatic disease. The successful identification, surgical removal, and careful histologic examination of these nodes should provide accurate nodal staging.

To test this hypothesis, clinical studies were performed by the use of intradermal injections of blue lymphatic dyes (isosulfan blue or patent blue V) at the primary tumor site followed by the visual identification of the SLNs in the nodal basin. These studies established the following: (1) SLN identification rates, and (2) the accuracy of the SLN in determining the presence or absence of regional nodal metastases.

In the first report published, Morton et al[2] in 1992 evaluated 237 patients and demonstrated an 82% SLN identifica-
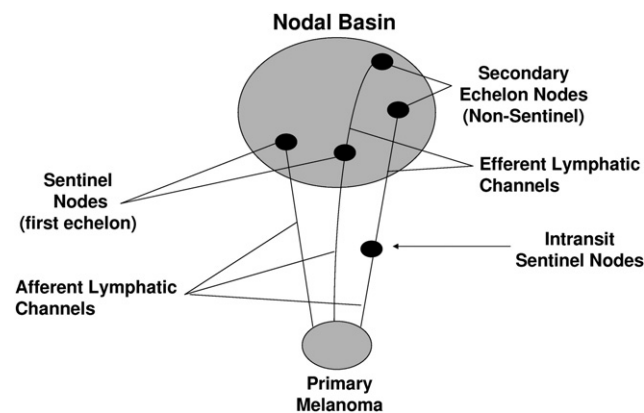
Figure 1 Lymphatic mapping concept. Schematic of potential afferent lymphatic channels draining from a primary cutaneous site to sentinel (first echelon) nodes in the nodal basin. Secondary echelon nodes may be identified by pass through of the intradermally injected blue dye or radiolabeled colloid. Occasionally a sentinel node is located between the injection site and the formal nodal basin defined here as "intransit" sentinel node, but also referred to as "interval" or "ectopic" sentinel node.

tion rate. The authors of subsequent studies from the M. D. Anderson and Moffitt Cancer Centers[16,17] and the Sydney Melanoma Unit reported similar findings.[18] Accuracy assessment was accomplished through the use of synchronous ELND performed at the time of the SLN biopsy. A false-negative event was defined as the detection of microscopic disease in a non-SLN when the SLN from the same basin was histologically negative. Accordingly, the false-negative rate was then calculated as the number of false-negative events divided by the total number of patients with microscopic nodal disease. Collectively, these initial studies evaluated 402 patients with successful SLN localization, 86 of which were found to have regional node metastases (81 patients with a positive SLN and 5 additional patients with disease only in a non-SLN).[2,16-18] This low false-negative rate of 5% supported the SLN concept.

Additional evidence that regional node metastasis is an orderly and nonrandom event is provided from the M. D. Anderson Cancer Center, whose researchers reported on the examination of 105 completion lymphadenectomy specimens in patients with at least 1 positive SLN.[19] Investigators found that the SLN was the only node involved in 83 (79%) of the basins, with disease in additional nodes identified in 21% of the lymphadenectomy specimens. Presented in another way, 68% of all the SLNs removed and only 1.8% of all non-SLNs were involved with metastatic disease.[19]

In further support of the accuracy of SLNB was a report of nearly 250 SLN-negative patients followed for more than 3 years; in this study, the authors found that only 10 patients (4%) developed nodal failure within the previously mapped regional basin.[20] Such failures represent a false-negative rate similar to the 5% determined by concomitant ELND. The development of clinical nodal disease in a nodal basin previously determined to be without microscopic involvement defines a false negative event and occurs in approximately 3%-5% of these patients. Theoretically, 3 explanations exist for these events: (1) the main SLN was not properly identified during the SLN procedure, leaving behind a microscopically involved lymph node, (2) the original SLN procedure was accurate, but microscopic in-transit disease was present at the onset that had not yet traveled to the nodal basin, (3) the correct SLN was removed and microscopic disease was present but undetected by the histologic examination either a result of a very small burden of disease or within a portion of the node that was not sampled.

More careful histologic scrutiny of the negative SLNs from these same 10 patients revealed the presence of disease in 8.[20] In reality, only the results of 2 of these patients were false-negative events because of the technique not identifying the correct lymph with micrometastases. These data not only further supported the validity of the SLN concept but also suggested that routine histologic examinations of SLNs may fail to detect clinically relevant disease.

Histologic Examination of SLNs

The fundamental goal of SLN biopsy is to accurately stage the regional basin. This is accomplished first by the accurate identification and complete surgical removal of all the SLNs from the appropriate nodal basins at risk and then by the careful histologic examination of these nodes. Although the definition of careful histologic examination continues to evolve, it is clear that as pathologic scrutiny becomes more extensive, it is more feasible to apply novel and sensitive techniques to 1 or 2 nodes (SLNs) rather than 20-30 nodes submitted after an ELND. By the careful evaluation of the most likely nodes to contain metastatic disease, more accurate nodal staging is possible and is accomplished with little morbidity to the patient.

Historically, the standard approach for evaluating lymph nodes, and therefore initially applied to SLNs as well, was to bivalve a clinically negative node and stain a section from each half with hematoxylin and eosin (H&E) staining. As a result, only a small percent of the lymph node(s) are sampled and likely explains why conventional histologic techniques underestimates the incidence of regional nodal disease in stage I and II patients. For example, the incidence of nodal failure after surgical excision alone for primary melanomas 2-4 mm is approximately 35%-50%, whereas the incidence of microscopic nodal disease as determined by ELND or SLN biopsy specimens, when applying the routine pathologic technique of bivalving the nodes, is approximately 25%-40%.

Although subsequent nodal failure may in part result from clinically occult intransit disease, several lines of evidence support the concept that nodal disease is more often present at diagnosis than is demonstrated by conventional histology: (1) step sectioning (ie, better sampling) improves the ability to detect microscopic disease, (2) 80% of patients who develop nodal basin failure after a negative SLN biopsy initially assessed by routine pathology are determined to be node positive after more careful analysis of the paraffin blocks,[20,21] and (3) evaluation of SLNs by the use of the reverse transcriptase-polymerase chain reaction to detect the presence of messenger-RNA encoding for melanoma-specific proteins (ie, tyrosinase) as potential surrogate markers of nodal disease results in greater SLN-positive rates.[22-24] Reports indicate that all H&E-positive SLNs and anywhere from 25% to 50% of H&E-negative SLNs are positive via polymerase chain reaction (PCR). Although preliminary clinical correlation studies demonstrate that the PCR positive-H&E-negative group exhibit recurrence rates intermediate between the PCR-negative and H&E-positive patients,[23-26] long-term follow-up failed to demonstrate an overall decreased survival in the PCR-positive patients compared with the PCR-negative patients in 2 recently published series.[25,26] As histologic techniques become more sensitive, specificity may be compromised, but the more careful and complete the evaluation of SLNs, the more likely we are to define a true and homogeneous SLN-negative subset.

Current recommendations include multiple H&E sections and immunohistology with the use of HMB-45 and MART-1, but established standards are still evolving.[21,27,28] Frozen section at the time of SLN biopsy probably reduces the sensitivity and is therefore not recommended,[29,30] but imprint touch cytology performed on multiple sections of the SLN at the time of the procedure can accurately detect microscopic dis-

ease in a significant percentage with occult metastases and facilitate same day completion dissections without compromising the formal permanent histologic examination.[31] PCR evaluation at the present should only be used in the setting of a clinical trial.

Technical Aspects of SLN Identification

Initial SLN identification rates of 80% to 85% with the use of blue dye injections provided a promising beginning. The use of high-resolution cutaneous lymphoscintography[32-34] and an intraoperative hand-held gamma detection device to locate radiolabeled colloids that have accumulated in SLNs after being injected at the primary site have yielded greater SLN identification rates.[19,35-38] The use of a gamma probe was first described by Krag et al,[38] who reported a 95% SLN identification rate.[39] In studies that compared combined modality techniques (radiocolloid plus blue dye) versus blue dye alone the authors demonstrated a significant increase in SLN identification to 99% with the combined approach.[19,37] Figure 2 summarizes the components necessary for successful identification and removal of a sentinel node.

These techniques can also aid in the localization of SLNs that may exist outside and/or proximal to the formal nodal basin; referred to as interval, in-transit, or ectopic SLNs (Fig. 3).[38-43] According to published studies, the frequency of such SLN locations is in the range of 5% to 10% of patients, and the frequency of involvement with microscopic disease is the same as that of SLNs harvested from formal basins.[41] The failure to identify these nodes risks the understaging of some patients and leaving behind potential sources of clinical recurrences.[44] More recently, the use of SPECT/CT (ie, single-photon emission computed tomography/computed tomography; a fusion imaging technique of nuclear and CT images) provides enhanced and 3-dimensional spatial resolution of areas of increased focal radiotracer uptake activity that correspond to SLNs and is particularly helpful in identifying the anatomic location of SLNs in the head and neck region.[45]

Biological and Prognostic Significance of the Sentinel Node

Studies have demonstrated that the incidence of SLN metastases correlates directly with increasing tumor thickness (Table 1).[19,46-49] SLN involvement is also associated with a vari-
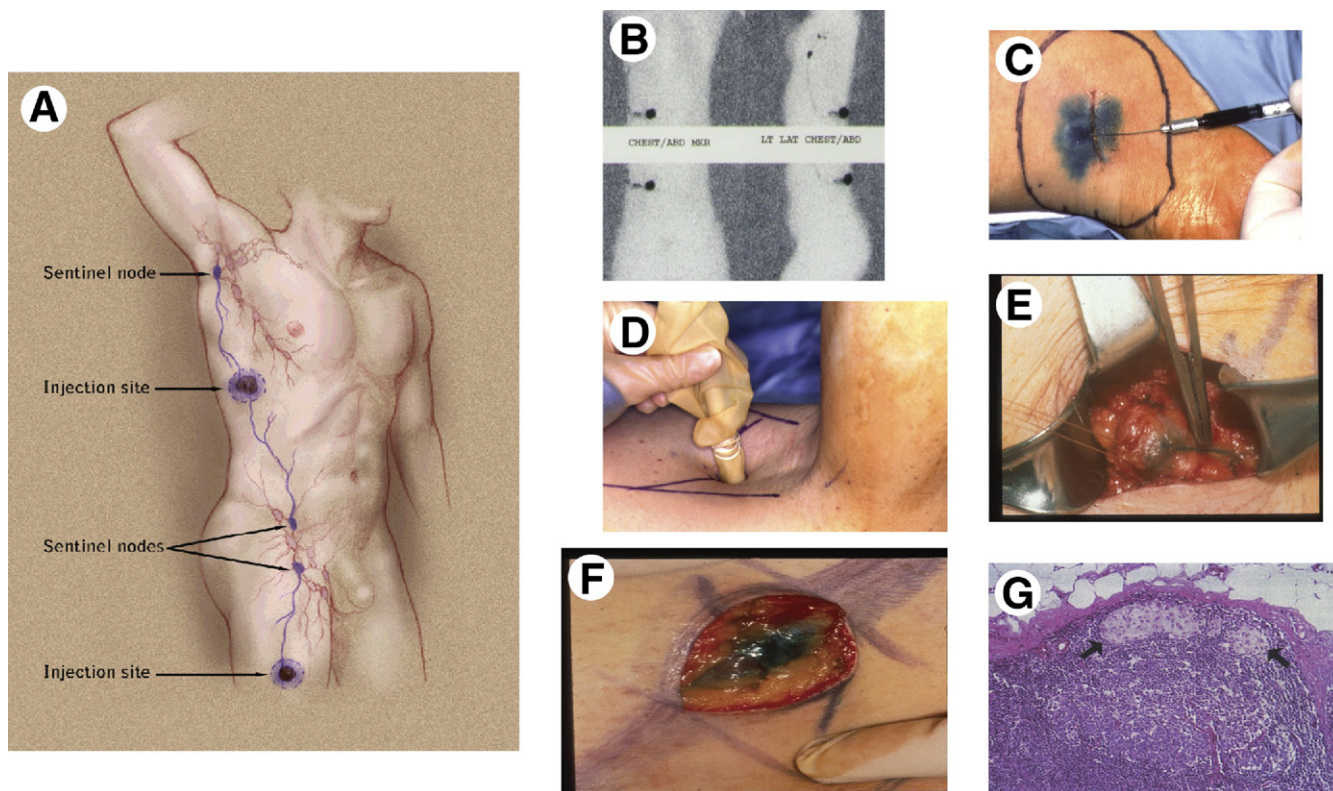
Figure 2 Lymphatic mapping and SLN concept and technique. The SLN concept is illustrated demonstrating potential afferent drainage patterns from primary tumor sites to the first draining nodes (sentinel node) in the regional basins in (A). Lymphoscintigraphy (B) is an important component of the procedure which identifies nodal basin(s) at risk for primary melanomas arising in ambiguous lymphatic drainage sites and the number sentinel nodes in the basin. In panel B, lymphatic drainage from the low back is to the axilla rather thn the closer inguinal basin. Injection of isosulfan blue intradermally around biopsy site in (C), Transcutaneous localization of SLN using gamma detection probe in (D), exploration of nodal basin and visualization of SLN in (E) and (F) and histologic detection of occult metastases in subcapsular sinus in (G).
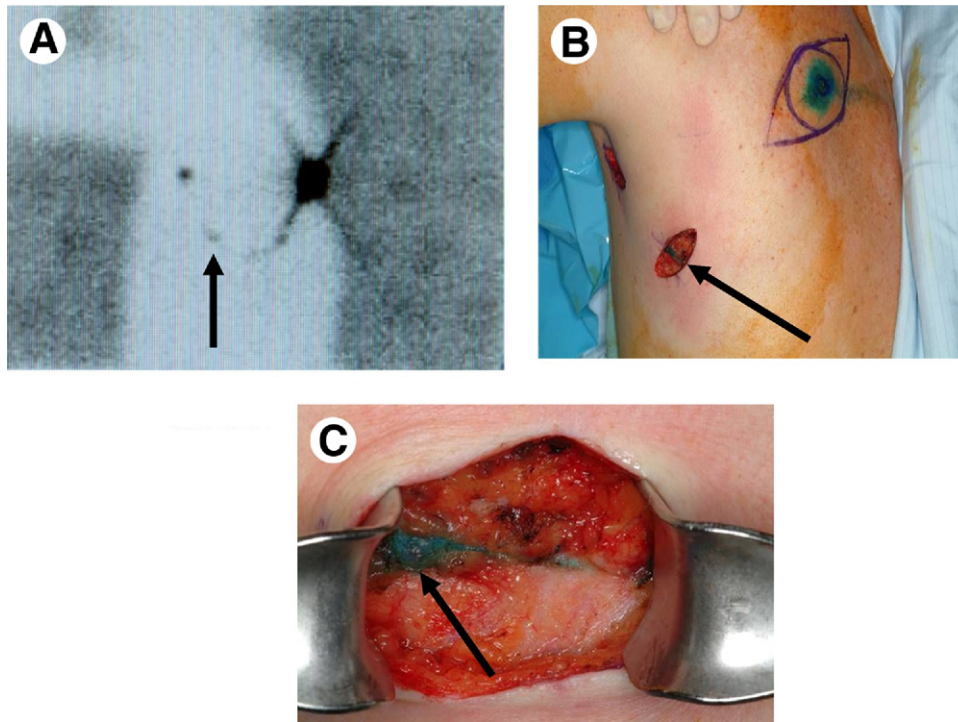
Figure 3 Intransit sentinel node. Lymphoscinitgraphy (A) shows lymphatic drainage pattern from injection site over left upper back to the ipsilateral axilla and an intransit sentinel node (arrow) over the scapular spine. Intraoperative (B) showing the primary site over the upper back and sentinel node biopsy sites in the axilla and intransit region (arrow). Close-up view of exposed intransit node (arrow) with blue afferent channel (C).

ety of other known primary tumor factors predictive of overall survival (OS), including ulceration, lymphatic invasion, mitotic rate, Clark level, anatomic site, and host factors, such as age.[46-54] In a multivariate analysis, the 2 variables that independently predicted SLN involvement were tumor thickness and the presence of ulceration.[48] Interestingly, the 2 most recent analysis from the AJCC melanoma staging committee demonstrated that the same 2 factors were also the strongest predictors of survival in stage I and II patients.[1,4] This analysis uncovered a unique interaction between tumor thickness and ulceration in that the presence of ulceration within a specific tumor thickness stage worsened the prognosis of patients equivalent to those in the next greater thickness group without ulceration.[1,4] A similar relationship between thickness and ulceration in predicting the incidence of

SLN metastases exists as shown in Table 1.[48] These observations support the hypothesis that the prognostic value of tumor thickness and ulceration is largely dependent on the fact that these 2 same factors predict SLN metastases and in this way offer convincing evidence that SLN involvement is a biologically important event.

Further supporting this conclusion are findings from survival analyses of large numbers of stage I and II patients managed in prospective selective lymphadenectomy programs. Consistently, these reports revealed that the SLN-positive patients experienced a significantly lower survival compared with SLN-negative patients (Fig. 4) and that the histologic status of the SLN was the most powerful indepen-

Table 1 Incidence of SLN Metastases According to Primary Tumor Factors

Tumor Thickness, mm	Total No. Patients	Positive SLN		
		All, %	Non-Ulcerated, %	Ulcerated, %
≤1.00	326	4.2	3.9	12.5
1.01–2.00	490	11.4	10.8	21.2
2.01–4.00	310	28.5	23.1	37.0
4.01+	190	45.5	31.2	55.4
Total	1316	17.4	11.9	37.0

SLN, sentinel lymph node.
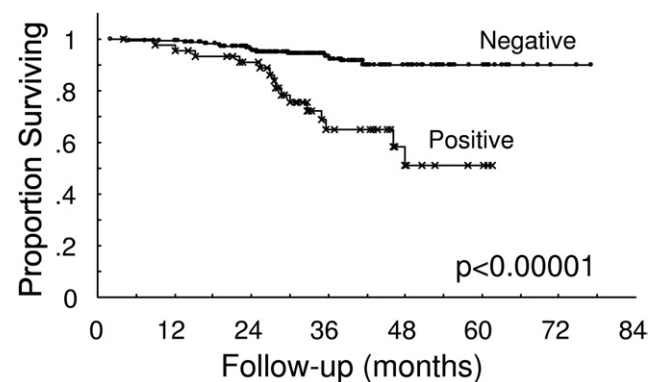
Figure 4 Melanoma-specific survival of stage I and II patients according to SLN status.

Table 2 AJCC Collaborative Melanoma Database Stage I/II 5-Year Survival Rate by T-Classification

T-Category	6th Edition	7th Edition SLN Subset*
T1a	95 ± 0.4	97 ± 1.1
T1b	91 ± 1.0	95 ± 1.5
T2a	89 ± 0.7	95 ± 0.6
T2b	77 ± 1.7	86 ± 2.0
T3a	79 ± 1.2	85 ± 1.5
T3b	63 ± 1.5	76 ± 2.5
T4a	67 ± 2.4	76 ± 3.6
T4b	45 ± 1.9	67 ± 3.6

AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node.
*Stage-appropriate use of SLN biopsy.

dent predictor of OS in the clinically node-negative melanoma patients when analyses were carried out, including previously described primary tumor prognostic factors (Table 2).[55] Several similar analyses have since been published from large single-institution as well as multicentered experiences corroborating these findings.[56-58]

Although the patients with a negative SLN as a whole enjoy an excellent survival, a negative SLN is not a perfect prognostic factor. Five-year melanoma specific survival rates are generally 90% for the SLN-negative patients, with recurrence and death occurring secondary to the following reasons: a false-negative SLN or pure hematogenous pattern of metastases. Predictors of relapse and death in the SLN negative group include increasing tumor thickness and primary tumor ulceration. The impact of SLN evaluation on staging and prognosis is nicely demonstrated in the most recent AJCC analysis that compared the 5- and 10-year survival of the substages of patients whose node negative status was determined by SLNB to patients whose nodal status was determined in most patients by clinical examination only. In the subset of patients who underwent pathologic assessment of the regional lymph node basins survival rates were greater and did not drop below 75% until the stage IIc category (Table 3).[1]

Questions and Controversies

The original motivation to study SLN biopsy was to establish an effective method of preventing the development of clinically palpable regional disease in the stage I and II melanoma patients without performing unnecessary formal lymph node dissections. The collective experience with SLN biopsy demonstrates that this has been accomplished. Furthermore, its role as a staging tool has been well established and offers another motivation for its use. However, many have questioned its therapeutic value and several other questions and controversies have emerged that are worthy of discussion.

Does Early Node Dissection Impart a Survival Benefit?

The potential for improved survival with early node dissection was the goal for the routine application of ELND as part of the initial management of newly diagnosed stage I and II patients. The question of survival impact with the use of ELND relative to nodal observation and therapeutic dissection for those patients who develop clinically detectable nodal disease has been evaluated in 4 prospective randomized trials. The first 2 trials (1 from the World Health Organization and 1 from the Mayo Clinic),[14,15] which were performed in the 1970s and before knowledge concerning primary tumor prognostic factors, demonstrated no survival advantage. Accordingly, ELND was strongly contested and largely abandoned. These trials were subsequently criticized because the study populations were at low risk for occult nodal disease and therefore unlikely to benefit from the surgical treatment being tested.

Two additional ELND trials were performed targeting the greater-risk clinically node-negative patients.[12,13] Trends for improved survival after ELND were observed in both trials; however, these differences were not statistically significant. Although many researchers concluded that early treatment of nodal metastases had little impact on disease progression, others suggested that these trials were underpowered because only the 20% of patients harboring nodal disease could potentially benefit from the procedure.[12,13] Long-term results published in 1998 from the World Health Organization ELND Trial, which included patients with trunk primaries >1.5 mm, demonstrated that patients with microscopic nodal disease in the ELND treatment arm experienced improved OS compared with patients who developed clinical adenopathy after randomization to excision alone.[13] Results published in 2000 from the Intergroup ELND Trial in which patients with melanomas 1-4 mm in thickness were studied demonstrated that prospectively stratified subgroups (1-2 mm and all nonulcerated primaries) derived a survival benefit with ELND.[12] Although OS rates for the entire study cohorts in both trials were not statistically different, confirming that not all patients can benefit from ELND, these studies do suggest that specific subsets of patients (most notably those with microscopic nodal disease and possibly additional patients with nodal disease undetected by routine histologic techniques) can benefit from earlier dissections. These data offer evidence-based credence to the theoretic concerns of delaying the lymphadenectomy until palpable nodal disease

Table 3 Prognostic Factors Influencing Disease-Specific Survival in Stage I and II Patients Undergoing SLN Biopsy

Prognostic Factor	Univariate	Multiple Covariate Hazard Ratio	P-value
Age	NS	–	NS
Sex	NS	–	NS
Axial location	0.03	–	NS
Tumor thickness	<0.0001	1.1	0.04
Clark level > III	0.001	2.3	0.01
Ulceration	<0.0001	3.3	<0.0001
SLN status	<0.0001	6.5	<0.0001

SLN, sentinel lymph node.
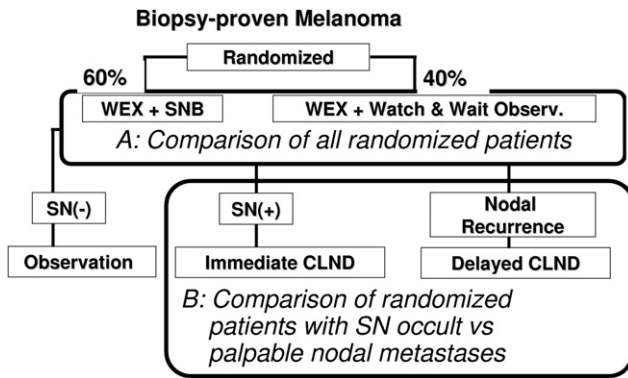
Figure 5 Treatment algorithm for MSLT-1.

develops and supports the selective lymphadenectomy approach.

The survival impact of the selective lymphadenectomy strategy with the use of SLN biopsy as an alternative to ELND was formally studied in a prospective randomized multicentered international trial comparing the outcomes of nodal observation after wide excision to SLN biopsy and completion dissection for patients with microscopic nodal involvement.[57] The design and primary and secondary endpoints of the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) are schematized in Fig. 5. The results of the third interim analysis of the MSLT-1 were published in the *New England Journal of Medicine*.[57] Data were available for 1269 patients. In the biopsy group, the presence of metastases in the SLN was the most important prognostic factor. The 5-year melanoma-specific survival rate was $72.3 \pm 4.6\%$ among patients with tumor-positive SLNs and $90.2 \pm 1.3\%$ among those with tumor-negative SLNs ($P < 0.001$), confirming the previously reported observations from several other groups.

Melanoma-specific death rate at 5 years was similar in the 2 groups (13.8% in the observation group and 12.5% in the biopsy group), as was melanoma-specific survival rate at 3 years ($90.1 \pm 1.4\%$ and $93.2 \pm 0.9\%$, respectively) and 5 years ($86.6 \pm 1.6\%$ and $87.1 \pm 1.3\%$, respectively). Although no overall survival advantage was observed when the entire cohort of patients randomized to SLN biopsy was compared with those patients who received a wide excision only and nodal observation, a small but statistically different disease-free survival advantage was observed ($78.3 \pm 1.6\%$ vs $73.1 \pm 2.1\%$, hazard ratio 0.74, 95% confidence interval 0.59-0.93; $P = 0.009$). The incidence of SLN micrometastases was 16%, whereas the rate of relapse in regional nodes in the observation group was 15.6%. The mean number of tumor-involved nodes at lymphadenectomy was 1.4 in the SLNB group and 3.3 in the observation group ($P < 0.001$). A pronounced overall survival advantage was observed when the analysis was performed, including only the node-positive patients. Compared with the patients who underwent a therapeutic (delayed dissection) for clinical nodal failure after being randomized to nodal observation, the SLN-positive patients enjoyed an improved 5-year survival of 20% ($72.3 \pm$

4.6% vs $52.4 \pm 5.9\%$; hazard ratio for death 0.51, 95% confidence 0.32-0.81; $P = 0.004$) as shown in Figure 6.

The interim results of the MSLT-I trial provide important insights into the value of selective lymphadenectomy compared with delayed lymphadenectomy. The lack of an OS difference between the 2 treatment arms is not surprising. This trial suffers from the same limitations as the ELND trials: it is underpowered because of the low percentage of patients (16% in this trial) who could benefit from complete lymphadenectomy. Assuming that early lymphadenectomy for SLN-positive patients is associated with a 20% survival benefit, one would predict an OS advantage of no more than 3.2% compared with delayed lymphadenectomy. Nonetheless, survival differences can emerge with longer follow-up, particularly because disease-free survival differences have already been reported. If future events follow the patterns observed in the 2 ELND trials, more recurrences in the nodal observation arm may develop over time than in the SNB arm.[58]

The results of the secondary survival analysis comparing SLN-positive patients with those who developed clinically palpable nodes after nodal observation are particularly noteworthy. The improved survival of the SLN-positive group not only corroborates the results of the World Health Organization trial but also supports the concept that—if left intact—microscopic nodal disease progresses and is associated with a worse prognosis. In some patients, therefore, increasing nodal burden can be a source of systemic dissemination; early treatment of nodal disease can favorably alter the natural history of their disease.[59]

Is Regional Disease Control Improved by Treating Nodal Disease When It Is Microscopic?

The most common first recurrence in primary melanoma patients initially treated with excision alone is palpable lymph node metastases. These patients are then generally treated with a TLND for attempts at cure and regional control
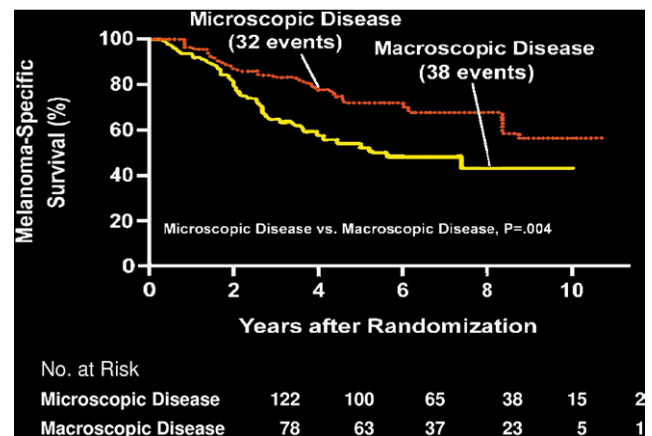
Figure 6 Melanoma-specific survival curves of node-positive patients in the MSLT-1. SLN-positive patients enjoyed better survival than patients randomized to receive nodal observation and underwent node dissection after developing clinically involved nodes.

of disease. Reported in-basin, postdissection failure rates range from 9% to 50% depending on a variety of factors, including basin site, number and size of involved nodes, and presence of extracapsular extension.[6,7,9] In-basin recurrences are very difficult to treat surgically and may be the source of significant morbidity in the form of pain, severe lymphedema, venous obstruction, skin ulceration, nerve involvement, and bleeding. In-basin failures in patients treated with ELND and found to harbor microscopic disease, occur in <10% of patients,[10] and reported to be even lower after completion dissection in SLN-positive patients.[11] The potential for improved regional disease control when dissections are performed for microscopic disease further supports the use of SLN biopsy.

Is Completion Dissection in Patients with a Positive SLN Necessary?

This is the next important question that needs to be asked and answered in respect to SLN biopsy. Only 12%-25% of patients with a positive SLN will be found to have additional microscopic nodal disease within non-sentinel nodes removed by a subsequent therapeutic dissection.[60-62] These data must be viewed with some concern of underestimating disease because the pathologic techniques used to evaluate additional non-SLN(s) removed through a therapeutic lymphadenectomy procedure have been limited to bisecting lymph nodes rather than multiple-step section or special histochemical stains. Several predictors of nonsentinel node involvement have been identified, including features of the primary tumor, increasing tumor thickness in particular, and more importantly increasing microscopic tumor burden within the SLN[62] an international randomized trial (MSLT-2) is currently accruing patents by the use of the basic framework design of a randomization to therapeutic node dissection versus nodal basin observation after a positive SLN biopsy. This trial will attempt to answer the following questions: (1) the incidence of nodal failure after removal of a positive SLN in the absence of a completion dissection, (2) the incidence and predictors of additional positive nodes in the same basin, and (3) the survival impact if any, for completion dissection. Some surgeons are already inconsistently omitting the completion dissection in SLN-positive patients and others are selectively not recommending completion dissection based on published predictors of non-SLN involvement, including patients with primary tumors <2 mm and SLN tumor burden of <2 mm in diameter. Such practices outside of a clinical trial should be discouraged until evidence is available supporting its safety, and therefore completion dissection should be considered the current standard of care.

Complications and Morbidity after Lymphatic Mapping and SLNB

Complications after lymphatic mapping and SLNB are relatively uncommon. Investigators from the Sunbelt Melanoma Trial reported the complication rates after SLN biopsy alone in more than 1202 trial patients and in 277 patients who required a complete lymph node dissection as part of the trial. The incidence of seroma, lymphedema, and wound problems was 3% vs 7.9%, 0.7% vs 9.8%, and 1.7% vs 11.9%, respectively. Each significant difference favored the SLN dissection-alone arm.[63] The observation of low complication rates after SLN biopsy has also been reported by others,[39,64] as well as in the Multicenter Selective lymphadenectomy Trial,[58] in which an overall complication rate of 10% after lymphatic mapping and sentinel node biopsy (wound infection, 46%; wound separation, 1.2%; seroma/hematoma, 4.6%) increased to 32.7% after completion lymph node dissection.[56] Although allergic reactions to the blue dye, including anaphylaxis has been reported, the incidence is very low.[65]

Is There an Increased Risk of Intransit Metastasis (a biologic "complication) after SLN biopsies?

Although the SLN biopsy technique has gained widespread acceptance for several reasons—accurate nodal staging, enhanced regional control, possible survival benefit, limited surgical morbidity compared with formal lymphadenectomy—some authors have suggested that SLN biopsy should not be used outside the confines of a formal clinical investigation.[66,67] Among their concerns is that SLN biopsy may increase the risk of in-transit metastasis (ITM), thereby reducing, eliminating, or reversing any potential survival advantage associated with the SLN biopsy technique. The hypothesis that the SLN biopsy technique and subsequent completion lymph node dissection in SLN-positive patients may disturb lymph flow by mechanical disruption of the proximal nodal basin and lead to increased rates of ITM—if accurate—is of particular concern because SLN biopsy has been widely adopted as the standard of care for many patients with clinically localized melanoma. In considering whether ITM is promoted by regional lymph node basin intervention, a full appreciation of the biology and incidence of ITM in melanoma patients before the advent of SLN biopsy is helpful. The collective experience at several large academic centers does not support the hypothesis that SLN biopsy increases the risk of ITM.[68-71] Among 1395 patients who underwent SLN biopsy at the University of Texas M. D. Anderson Cancer Center, the overall incidence of ITM as a first site of recurrence was 6.2%.[70] Compared with SLN-negative patients, SLN-positive patients had thicker tumors (median, 3.0 mm vs 1.3 mm), a greater incidence of ulceration (45% vs 12%), and a greater rate of ITM (12% vs 3.5%).[70] Among patients with primary melanomas at least 1.0 mm thick treated between 1993 and 2003 at the Sydney Melanoma Unit, rates of ITM among 1035 patients treated with wide local extension alone and 754 patients with similar primary tumor characteristics treated with wide local extension plus SLN biopsy were not significantly different (6.5% and 3.7%, respectively).[68] These data have also been corroborated by the experiences of researchers at the John Wayne Cancer Institute[71] and by the results of the MSLT-1 trial,[57] both of which also demonstrated no increased risk of ITM

after SLNB. Taken together, these results strongly support the proposition that the risk of ITM metastasis depends on tumor biology and not the surgical approach to regional lymph nodes.[69]

Patient Selection for SLNB

Probably the most important information that physicians should be familiar with is who are the appropriate patients to consider for referral for SLNB. Candidates for SLNB include newly diagnosed primary, clinically node-negative patients predicted to be at intermediate or high-risk of harboring occult nodal disease, on the basis of primary tumor characteristics.[47,48,72] Specific percent risk thresholds are still in question, but tumor thickness thresholds of 0.76-1 mm have gained wide consensus. The routine use of SLNB in patients with thin (<1 mm) is not cost-effective because of the overall low risk of nodal involvement in this group.[73] However, a selective approach in patients with thin melanomas[74] on the basis of the presence of specific features of the primary tumor, such as Clark level IV, or ulceration is rational as both of these predict an SLN-positive rate similar to that of patients with tumor thickness of 1 mm. An emerging important primary tumor risk factor for SLN involvement is the presence and number of mitotic figures in the vertical growth phase as a surrogate for aggressive biology.[75,76] In a study from the University of Pennsylvania, those patients with thin melanomas of at least 0.76 mm and exhibiting 1 or more mitotic figures per mm² the incidence SLN metastases was 12.5%[75] increasingly, the presence of mitotic figures is being used to identify the higher risk subset of patients as candidates for SLNB.

It should be emphasized that SLNB is also appropriate for patients with thick melanomas (>4 mm) even though this group is also at high risk for distant disease, as recently published experiences from more than 1 center demonstrates that SLN status is the single most important independent predictor of survival.[77-81] Simply stated, stage IB and greater may be offered SLNB.

Other clinical scenarios arise in which SLNB may be useful: (1) in patients who develop a true local recurrence after a relatively narrow excision as previous treatment of a primary melanoma; (2) for patients in whom the exact tumor thickness cannot be ascertained because of improper placement in the paraffin block, resulting in tangential sectioning when tumor is present at the base secondary to a superficial shave biopsy; when a manipulation, such as cryotherapy or cauterization has been performed on the same lesion before the diagnosis of melanoma; (3) when the pathologic diagnosis of an atypical melanocytic lesion is ambiguous but may possibly include a primary melanomas >1 mm in the differential diagnosis[82]; or (4) for patients who have already received a formal wide excision with or without a skin graft and then wish to have accurate assessment of their draining lymph node basins. In this latter situation, the accuracy of the technique is in question because the lymphatic drainage of the remaining skin may be different from the skin that existed immediately adjacent to the original primary melanoma. A few small published series compared the incidence of positive SLNs in groups of patients who had already undergone a 1 cm or wider excision to patients who had intact lesions or an excion for diagnosis. The patient groups were matched in primary tumor factors and the incidence of positive SLNs was similar, suggesting that SLN biopsy may still be accurate in these patients.[83]

Is SLNB the Standard of Care?

This question is difficult to answer because of the ambiguity associated with defining the "standard of care." On the basis a publication that described the outcome of a consensus panel held at the most recent congress of the International Sentinel Node Society, SLNB for the appropriate patients would be considered a standard procedure for the following reasons: SLNB is incorporated in staging guidelines by the AJCC, incorporated in treatment guidelines by the National Comprehensive Cancer Network, and is practiced by most surgical specialists who treat melanoma in the United States, Western Europe, and Australia.[84] Although the consensus panel was composed of only surgeons and therefore likely to be biased, the panels that comprised the National Comprehensive Cancer Network guideline committee and the AJCC staging committee are broad based and include dermatologists, medical oncologists, and surgical oncologists.

Concluding Comments

SLNB is proven to accurately stage the regional lymph node basins in stage I and II melanoma patients with little morbidity and promotes the selective application of formal node dissections. The SLN-positive patients are then treated when the nodal tumor burden is microscopic, optimizing the chance for long-term survival and durable regional control. With the introduction of more sensitive histologic techniques, SLNB offers the physician the opportunity to more accurately stage patients and defines a more pure and homogeneous node-negative population when the SLN is negative. The node-positive patients can receive standard adjuvant therapy or participate in prospective clinical trials assessing the value of novel adjuvant therapy regimens. The low-risk patients can be safely spared the morbidity of additional surgery and adjuvant therapy. Until molecular studies are readily available and have the ability to accurately determine the metastatic phenotype in primary melanomas, SLNB currently offers an opportunity to accomplish the aforementioned goals in managing stage I and II patients: optimizing the chance for cure, providing durable regional control, accurate staging, and minimizing treatment morbidity. It is therefore appropriate for dermatologists to at least discuss the potential role of SLNB in the management of newly diagnosed melanoma patients. Information concerning the likelihood for SLN involvement, how the results of the SLNB may impact prognosis and therapy, and the potential risks and benefits of the procedure may be provided by the dermatologist who made the diagnosis.

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