



Catherine Hickson. *Figs in Alizarin Crimson*. Oil on Belgian linen, 60 cm × 90 cm.

Sentinel lymph node biopsy is recommended for most patients with melanomas ≥ 0.76 mm and for all good surgical candidates with melanomas ≥ 1.0 mm.

Sentinel Lymph Node Biopsy for Melanoma: Indications and Rationale

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Background: *The disease status of regional lymph nodes is the most important prognostic indicator for patients with melanoma. Sentinel lymph node biopsy (SLNB) was developed as a technique to surgically assess the regional lymph nodes and spare node-negative patients unnecessary and potentially morbid complete lymphadenectomies.*

Methods: *We reviewed the literature on SLNB for cutaneous melanoma to provide insight into the rationale for the current widespread use of SLNB.*

Results: *Multiple studies show that the status of the SLN is an important prognostic indicator. Those with positive SLNs have significantly decreased disease-free and melanoma-specific survival compared with those who have negative SLNs. In the Multicenter Selective Lymphadenectomy Trial I (MSLFI), in which patients with intermediate-thickness melanoma were randomized to SLNB (and immediate completion lymphadenectomy if the SLN was positive) vs observation (and a lymphadenectomy only after presenting with clinically evident recurrence), the 5-year survival rate was 72.3% for patients with positive sentinel nodes and 90.2% for those with negative sentinel nodes ($P < .001$). Although overall survival was not increased in patients who underwent SLNB compared with those who were randomized to observation, patients who underwent SLNB had a significantly increased 5-year disease-free survival rate compared with those who underwent observation alone (78.3% in the biopsy group and 73.1% in the observation group; $P = .009$). For those with nodal metastases, patients who underwent SLNB and immediate lymphadenectomy had an increased overall 5-year survival rate compared with those who had lymphadenectomy only after presenting with clinically evident disease (72.3% vs 52.4%; $P = .004$). Moreover, other studies show that for patients with thin melanomas ≤ 1.0 mm, the overall survival rate is significantly worse for those with positive SLNs compared to those with negative SLNs. For thin melanomas, Breslow depth ≥ 0.76 mm and increased mitotic rate have been shown to be associated with an increased incidence of SLN metastases.*

Conclusions: *SLNB provides important prognostic and staging data with minimal morbidity and can be used to identify regional node-negative patients who would not benefit from a complete nodal dissection. In our opinion, SLNB should be performed on most patients (with acceptable surgical and anesthesia risk) who have melanomas with a Breslow depth ≥ 0.76 mm.*

Introduction

In 2008 in the United States, approximately 62,400 patients were diagnosed with invasive melanoma and more than 8,400 patients died of the disease.¹ Because the disease status of regional lymph nodes is the most important prognostic indicator for melanoma,^{2,3} elective regional lymphadenectomy was previously routinely performed for all patients with melanoma. However, most patients with thin (≤ 1.0 mm Breslow depth) or intermediate thickness (> 1.0 mm but ≤ 4.0 mm) melanomas will not harbor nodal metastases; 1% of patients with lesions ≤ 0.75 mm, 15% of those with lesions between 1.0 and 2.0 mm, and 30% of those with lesions > 2.0 mm but ≤ 4.0 mm have nodal metastases.^{4,5} As a result, elective lymphadenectomy has exposed many patients to unnecessary risks of wound infection, seromas, deep venous thrombosis, and potential life-long lymphedema, and several prospective randomized trials have shown that it has not improved survival.^{6,8}

Sentinel lymph node biopsy (SLNB) was introduced as a less invasive alternative to allow evaluation of the “sentinel” lymph node (SLN), ie, the first node or nodes draining the primary melanoma along its lymphatic pathway.⁹ SLNB has minimal complication risks compared to a standard lymphadenectomy.^{10,11} Morton et al^{9,12} demonstrated a learning phase of 30 cases for proficiency of the procedure. When SLNB is performed properly and this SLN is not involved with tumor, the chance that a routine lymphadenectomy would yield metastatic disease (ie, the false-negative rate) is $< 5\%$.^{9,12,13} in most studies at high-volume centers. This technique has been verified and is now widely accepted as a staging tool not only for melanoma but also for breast cancer and other selected malignancies.

The Sentinel Lymph Node

The initial route of metastasis for the vast majority of patients with melanoma is via the lymphatics.⁹ In general, nodal metastases in most melanomas occur in an “orderly” manner, with involvement of the “sentinel”

lymph node first, then the more distal (second and third echelon) lymph nodes later. In multiple studies in which the SLNs were removed first and then followed by an elective complete nodal dissection during the same operation, the incidence of “skip” metastases (in which the SLN is negative for metastasis but the non-sentinel nodes in the remaining complete node dissection contain metastases) was $< 5\%$.^{9,12,13} Thus SLNB is an excellent staging technique and can be used to identify patients who would not benefit from a complete lymphadenectomy. For patients who do not have clinically evident nodal metastases, only those who have positive SLNs should be considered for a complete nodal dissection.

Before the advent of SLNB, elective lymph node dissection was routinely used to stage patients with melanoma since the status of regional lymph nodes (and continues to be) the most important prognostic factor for survival. The standard histological technique for evaluating a nodal dissection specimen involves evaluating representative sections from each identified lymph node using hematoxylin and eosin (H&E). In actuality, given the large size of the nodal dissection specimen, $< 1\%$ of the whole specimen is routinely evaluated.¹⁴ With a smaller sample from an SLNB, the SLN can be evaluated more intensively using a combination of H&E and immunohistochemistry (IHC) to stain for melanoma-associated antigens such as S-100, HMB-45, and MART-1/Melan-A. Most SLN protocols evaluate the SLN at 2- to 3-mm intervals using H&E and at least one IHC stain. IHC has been shown to increase the yield of positive SLNs by up to 34%,^{15,16} but it is impractical to obtain innumerable thin slices and perform IHC routinely for the large specimen from a complete lymphadenectomy. Thus, despite the less invasive nature of an SLNB, the staging data obtained from an SLNB can actually be more accurate than an elective lymph node dissection.

SLNB using lymphoscintigraphy allows the identification of affected lymph nodes that would not be routinely evaluated during an elective nodal dissection such as in-transit lymph nodes (eg, near the tip of the 12th rib for a truncal melanoma or along the trapezius), and lymph nodes in minor nodal basins (eg, popliteal and epitrochlear). Lymphoscintigraphy is essential especially for SLNB for head and neck melanomas that are technically more challenging due to the complex and less predictable lymphatic drainage pattern in this region, resulting in lower SLN identification rates and higher false-negative rates.^{12,17,18}

Although the SLNB evaluation technique can identify very early micrometastases, including isolated tumor cells, the significance of these isolated tumor cells is controversial with respect to prognosis. Some have advocated the “prognostic false-positivity” theory on SLNs.¹⁹ This theory suggests that there are micrometastases that are clinically irrelevant and are not destined to

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Abbreviations used in this paper: SLNB = sentinel lymph node biopsy, MSLT = Multicenter Selective Lymphadenectomy Trial.

develop into clinically relevant disease, and thus some positive SLNs are “false” in their prognostic relevance. Some smaller studies suggest that those with isolated metastases ≤ 0.1 mm²⁰ or < 0.2 mm²¹ have prognosis similar to patients with negative SLNs.

In contrast, the largest study specifically evaluating isolated tumor cells reports 12% of patients with micrometastases ≤ 0.2 mm have further metastases upon completion nodal dissection.²² The 5-year melanoma-specific survival rate was significantly less for these patients with micrometastases (89%) compared to those with negative SLNs (94%; $P = .02$). As these studies are retrospective in nature, a definitive conclusion is not possible until a randomized, controlled trial is done. At this time, since the majority of studies suggest that micrometastases do affect prognosis, for the appropriately-selected patient with good surgical and anesthesia risk, most surgical oncologists specializing in melanoma would recommend completion lymphadenectomy for those with positive SLNs, even those with isolated micrometastases.²³ Ariyan et al²⁴ recently showed the prognostic significance of metastases in nonsentinel lymph nodes found in the completion lymphadenectomy specimen. The median survival for patients with no metastases in the completion lymphadenectomy specimen was 104 months, while median survival for those with metastases to these nonsentinel lymph nodes was 36 months ($P < .001$).

Multicenter Selective Lymphadenectomy Trial I

The definitive trial published thus far evaluating the role of SLNB for melanoma is the Multicenter Selective Lymphadenectomy Trial I (MSLT-I).²⁵ This study randomized 2,001 patients with cutaneous melanoma to one of two arms: (1) wide local excision alone with observation only and subsequent lymphadenectomy if nodal relapse occurred, or (2) wide local excision and SLNB with lymphadenectomy if metastases were found in the SLN. Results from 1,269 patients with intermediate-thickness primary melanoma (defined as 1.2 mm to 3.5 mm in this study) are published thus far²⁵ and show that 16% percent of SLNs had micrometastases, while 3.4% of those with “negative” SLNs developed nodal metastases, which is consistent with the accepted false-negative rates of the procedure. In the observation group, 15.6% of patients developed nodal relapse. Interestingly, updated data show that at 10 years, the projected incidence of nodal metastases in the observation group (20.5%) reaches the total incidence of nodal metastases detected by SLNB plus the false-negative SLNB cases (20.8%),²⁶ suggesting that micrometastatic disease not removed will eventually become clinically detectable disease. Furthermore, the mean number of nodes with metastases in the SLNB group (with immediate lymphadenectomy) was 1.4

nodes, while the mean number in the observation group (with delayed lymphadenectomy) was 3.3 nodes, suggesting disease progression in higher echelon nodes during the observation period ($P < .001$).

Although there was no difference in overall survival, the 5-year disease-free survival rate was significantly higher in the SLNB group (78.3%) compared with the observation group (73.1%), regardless of nodal status ($P = .009$). The status of the SLN significantly correlated with melanoma-specific survival. The 5-year survival rate of patients with negative SLNs (90.2%) was significantly higher than those with positive SLNs (72.3%; $P < .001$), further confirming the prognostic significance of the SLN. Most importantly, among those with nodal metastases, the 5-year overall survival rate of those who underwent SLNB with immediate lymphadenectomy (72.3%) was significantly higher than those in the observation group who had lymphadenectomy only when clinically evident (52.4%; $P = .004$). This suggests, although does not prove, that occult micrometastases in the SLN can progress to clinically evident, higher-volume regional disease that adversely affects overall survival.

SLNB for Thin Melanomas

Prior studies on SLNB have not focused on patients with thin melanomas, as the majority of patients with melanomas ≤ 1.0 mm Breslow-depth do well after wide local excision. Long-term follow-up shows that a small but definite percentage of patients relapse with recurrent disease. In a retrospective study by Karakousis et al²⁷ with a median follow-up of 16.4 years involving 882 patients with thin melanomas, 4.3% of patients developed regional nodal recurrence and 3.9% of patients developed distant metastases. Multivariate analyses show the factors associated with regional nodal metastases include male gender (odds ratio [OR] = 2.5; $P = .01$), mitotic rate > 0 (OR = 3.3; $P = .003$), ulceration (OR = 7.6; $P = .002$), and vertical growth phase (OR = 7.9; $P = .009$). In another study by Kalady et al²⁸ involving 1,158 patients with thin melanomas with a median follow-up of 11 years, 3.7% of patients developed nodal recurrence and 3.9% developed distant metastases. Male gender (OR = 1.4; $P = .01$) and Breslow depth ≥ 0.75 mm (OR = 1.4; $P = .009$) were associated with recurrence. These data have led some to advocate performing SLNB in patients with thin melanomas.

Retrospective studies evaluating melanoma lesions of all thicknesses show that age, mitotic rate, Breslow depth, ulceration, angiolymphatic invasion, and microsatellitosis are factors associated with having a positive SLN.²⁹⁻³¹ When focused in thin melanomas, mitotic rate and Breslow depth are significant predictors of having metastases to SLN.^{27,28,32,33} Kesmodel et al³² show that among 181 patients with thin lesions, the incidence of SLN positivity is 5%; however, those with

mitotic rate of > 0 and tumor thickness ≥ 0.76 mm have a 12.3% incidence of SLN positivity. Ranieri et al³³ analyzed 184 patients with thin melanomas and found 6.5% had metastases to SLNs. Separated by Breslow depth, 2.3% of those with lesions < 0.75 mm had positive SLNs while 10.2% of those with lesions ≥ 0.75 mm had positive SLNs. For their patients, increased mitotic rate was also associated with SLN metastases.³³ We reviewed our own experience with 409 patients with thin melanomas who underwent SLNB and found that 4.9% of those with a thickness of ≥ 0.76 mm have SLN metastases.³⁴

Wright et al³⁵ recently evaluated 631 patients with thin melanomas who underwent SLNB. Metastases in the SLN were present in 5% of these patients. In this study, the factors associated with SLN positivity included female gender ($P = .02$) and age ≤ 50 years ($P = .04$). With a median follow-up of 57 months, those with positive SLNs had an 84% 10-year melanoma-specific survival rate compared to 98% for those with negative SLNs ($P < .001$).

Although some conflicting data exist, these larger studies show that having Breslow depth > 0.75 mm and increased mitotic rate are associated with having metastases to SLNs. Furthermore, a positive SLN is consistently associated with worse survival, again further proof against the “prognostic false-positivity” theory of SLNs. Metastases to the SLN do matter, even in thin melanomas, and SLNB provides important prognostic information.

Arguments Against SLNB

As mentioned above, some critics claim that SLNB provides “prognostic false-positivity,” implying that a positive SLN can give false-positive prognostic information.¹⁹ These critics cite some studies showing that when a nodal micrometastasis can be detected only by IHC³⁶ or when it is below a certain size²⁰ (eg, < 0.1 mm), patient outcomes are similar to those having negative SLNs. However, it is not possible to know prior to performing an SLNB which patient will have nodal micrometastases below a certain size (and thus allegedly an SLNB can be avoided according to these critics) and which patient will have a larger amount of tumor involvement. One fact that persists through all studies is that patients with positive SLNs have a worse overall survival than those with negative SLNs, thus confirming the prognostic significance of a positive SLN.

While multiple studies have confirmed the prognostic significance of a positive SLN in both overall and recurrence-free survival, those who challenge the utility or value of SLNB make a valid point when they contend that there are limited adjuvant treatment options for melanoma. In fact, interferon alpha-2b is currently the only drug approved by the US Food and Drug Administration for resected stage III disease, and it improves only disease-free survival but not stage III disease.³⁷

However, patients value increased disease-free survival despite knowing that there is no improvement in overall survival.³⁸ Thus the information gained from an SLNB allows the patient to make an educated, informed decision regarding the use of adjuvant therapy. The information also allows the physician to tailor follow-up schedules knowing that a patient with a positive SLN has a higher likelihood of a recurrence. Furthermore, patients may choose to enroll in clinical trials evaluating other adjuvant therapies,³⁹⁻⁴⁵ some of which have shown promising preliminary data.

Besides the lack of “home runs” in adjuvant therapy for melanoma, a valid criticism of SLNB is that there is no significant overall survival difference between those who undergo SLNB followed by immediate completion lymphadenectomy if the SLN is positive compared with those who undergo observation first and lymphadenectomy only after presenting with clinically detectable disease.²⁵ However, disease-free survival is improved in those who undergo SLNB. Given that SLNB provides the most important prognostic data in melanoma with limited morbidity, it is reasonable to recommend the procedure to patients with suitable surgical and anesthesia risk once it is explained to them that while their overall survival is not changed whether or not they undergo an SLN, valuable prognostic information is gained from the procedure.

Future Directions

Current work is in progress to improve SLNB techniques to decrease false-positive rates and permit more specific identification of SLNs. Technetium^{99m} sulfur colloid, the standard radiopharmaceutical for sentinel node imaging, has a prolonged injection site clearance half-life that can impede identification of the SLNs, especially if the SLNs are spatially close to the primary lesion. Lymphoseek (Neoprobe Corp, Dublin, Ohio), which clears from the injection site much more quickly yet stays in the first few SLNs,^{46,47} is currently being investigated in a phase III trial for use in melanoma and breast cancer patients.

It has been observed that no further nodal metastases have been found in the majority of patients who have micrometastases in their SLN when they undergo completion lymphadenectomy.²³ A large, multicenter randomized trial is currently underway to evaluate whether a completion lymphadenectomy should be performed in those who have a positive SLN (Multicenter Selective Lymphadenectomy Trial II; MSLT-II). Patients with positive SLNs are randomized to (1) completion lymphadenectomy or (2) close observation with physical examinations and nodal ultrasounds and completion lymphadenectomy only after demonstration of nodal recurrence. This trial may help reduce the number of completion lymphadenectomies performed after a positive SLN.

Given that the current standard adjuvant therapy (interferon alpha-2b) for those with positive lymph nodes is limited, multiple investigators are working on developing new adjuvant therapy.³⁹⁻⁴⁵ More efficacious adjuvant therapy will allow the important prognostic data conferred by SLNB to reach fruition.

Conclusions

SLNB is an accurate, minimally invasive staging procedure that provides important prognostic data for both the patient and the physician. At this time, overall survival appears to be equivalent for those who undergo SLNB followed by immediate completion lymphadenectomy if the SLN is positive compared with those who undergo observation followed by lymphadenectomy only after presenting with clinically palpable recurrence.²⁵ However, the 5-year disease-free survival rate is significantly increased in the patients who undergo SLNB and immediate completion lymphadenectomy (78.3% vs 73.1%; $P = .009$). Updated MSLT-I data suggest that nodal micrometastases detected by SLNB will develop into clinically relevant disease if left in place.²⁶

Nodal recurrence is an important issue for melanoma patients. Beyond the negative psychological impact of being diagnosed with a recurrence, the greater tumor burden often associated with a recurrence sometimes requires more extensive surgery and postoperative radiation, thus increasing the complication rates.¹⁴ Furthermore, among those with nodal metastases, overall survival is significantly higher in patients who undergo SLNB and immediate lymphadenectomy compared with those who have lymphadenectomy only after having clinically detectable disease (72.3% vs 52.4%; $P = .004$).²⁵ Even for patients with thin melanoma, patients with positive SLNs have poorer prognosis. Our group recommends SLNB for all patients with acceptable surgical and anesthesia risk who have melanomas with a Breslow depth of ≥ 0.76 mm. Further research is needed to define more precisely which patients with thin lesions will benefit from SLNB.

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