Time to reconsider the role of sentinel lymph node biopsy in melanoma

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The Multicenter Selective Lymphadenectomy Trials indicate that there are no overall or melanoma-specific survival advantages to performing sentinel lymph node biopsy (SLNB) followed by immediate completion lymph node dissection compared with wide excision and observation for patients with positive sentinel nodes. These results make SLNB solely a staging procedure. The role of SLNB in the management of patients with melanoma deserves reappraisal. The potential marginal benefit of SLNB beyond the clinical and pathologic features of the melanoma has not been well studied. The use of sentinel lymph node status alone to accept and stratify patients into trials or to receive adjuvant treatment is not rational. (J Am Acad Dermatol 2019;80:1168-71.)

Key words: Breslow thickness; hazard ration; immediate completion lymph node dissection; melanoma; multicenter selective lymphadenectomy trial; prognosis; sentinel lymph node biopsy; survival.

The Multicenter Selective Lymphadenectomy Trials (MSLTs) were practice-changing randomized controlled trials.[1,2] MSLT-I demonstrated that in patients with cutaneous melanoma wide excision and sentinel lymph node biopsy (SLNB) followed by immediate completion lymph node dissection (ICLND) for patients with positive sentinel nodes did not provide overall or melanoma-specific survival advantage over wide excision and observation.[1,3] MSLT-II demonstrated that ICLND did not increase overall or melanoma-specific survival compared with close clinical observation and delayed CLND, even among patients with melanoma and positive SLNs.[2] These results indicate that SLN biopsy (SLNB) followed by ICLND has no survival value, and SLNB should now be regarded solely as a staging procedure. Its role as a staging procedure in the management of patients with melanoma deserves reappraisal.

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
ICLND:	immediate completion lymph node dissection
MSLT:	Multicenter Selective Lymphadenectomy Trial
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy

THE MSLTs WERE PRACTICE-CHANGING RANDOMIZED CONTROLLED TRIALS

The results of MSLT-I and MSLT-II have provoked a wide discussion of the utility of SLNB and of ICLND for patients with melanoma. In MSLT-I, 1661 patients were randomly assigned to the SLNB-lymphadenectomy group (SLNB group, wide excision plus SLNB with ICLND if sentinel nodes were positive) or the observation group (wide excision plus nodal observation, with lymphadenectomy if nodal metastases developed during observation).[1,3] Patients in both groups were followed actively with examination, blood testing, and chest x-rays every 3 months during the first 2 years, every 4 months during year 3, every 6 months up to year 5 and then annually until year 10. In some centers, nodal ultrasound, positron-emission tomography scans, computed tomography scans, or testing for

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melanoma markers (S-100 and lactate dehydrogenase) were performed if they were part of the centers routine follow-up procedures.[1]

The final 10-year follow-up report failed to demonstrate a significant treatment-related difference in the overall survival rate in the overall study population: absolute risk reduction 0.005 (95% confidence interval [CI] −0.039 to 0.051) and number needed to treat 189 (95% CI 20 to −25).[3] Ten-year melanoma-specific survival rates in the intent-to-treat analysis were not significantly higher in the SLNB group than the observation group among patients with intermediate-thickness melanomas (81% for SNLB group vs 78% for observation group, hazard ratio [HR] 0.84, 95% CI 0.65-1.08, P = .18).[1] SLNB and ICLND did not prolong disease-free survival. The apparent prolongation of disease-free survival was due to lead-time bias and was an inevitable consequence of the trial design.[3]

The data and safety monitoring board recommended that the primary end-point data from MSLT-II be released earlier than expected because data showed that ICLND did not increase overall or melanoma-specific survival among patients with melanoma and positive sentinel nodes when compared with treatment by nodal observation and delayed lymphadenectomy in patients who developed clinical or ultrasound-detected lymphadenopathy.[2] ICLND was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to treat analysis or in the 1755 patients in the per-protocol analysis after 3 years of observation (survival 86% in both groups).[2]

The results of MSLT-II unequivocally indicate that ICLND did not increase overall or melanoma-specific survival in patients with positive sentinel nodes. Given the lack of survival benefit and the significant harm of SLNB and ICLND (24% incidence of lymphedema in the SLNB and ICLND group and 6% in the SLNB and observation group),[2] ICLND should be abandoned as a therapeutic intervention, and patients with high-risk melanomas should have close clinical and ultrasound monitoring of their lymph nodes for melanoma involvement. In MSLT-II, patients in both groups were examined every 4 months in the first 2 years, every 6 months in years 3-5, and then annually. Nodal ultrasound of the sentinel nodal basin was performed at each visit for the first 5 years in the observation group.[2]

In several melanoma centers, the frequency of ICLND after a positive SLNB had already decreased before MSLT-I or MSLT-II results were published. For example, ICLND was performed in less than half of the patients with positive SLNB since 2011 and is now performed in a minority of patients with positive SLNBs at Memorial Sloan Kettering Cancer Center.[4]

Claims that ICLND might benefit some patients by requiring less extensive and mutilating surgery and leading to better regional control do not justify continuing to perform ICLND.[1-6] If patients who undergo wide excision and observation are actively followed as they were in MSLT-I and MSLT-II, they can be treated successfully with delayed lymphadenectomy without requiring more extensive and mutilating surgery.[6] It is not surprising that ICLND decreased the rate of regional nodal disease because patients who have had CLND no longer have regional nodes in which to develop disease. Regional nodal recurrence is not the same as loss of regional control.[6]

SLNB IS NOW SOLELY A STAGING PROCEDURE

Can SLNB be justified solely as a staging procedure? The claim that lymph node status is the strongest predictor of disease-specific survival for patients with intermediate-thickness melanoma has been repeated so often that physicians, patients, and patient advocacy groups are convinced of its veracity, and they insist on the procedure to their surgeons and on melanoma guidelines committees.

The assertion that lymph node status is the strongest predictor of survival stems primarily from case series in which patients with positive sentinel nodes had ICLND.[7-9] Most of these studies examine disease-free survival and disease-specific survival but often not overall survival. Many of the studies report survival of <5 years. When surgeons and oncologists make the claim that SLNB status is the strongest predictor of prognosis, they are usually comparing the HRs in these reports.

However, the evidence does not support this assertion. One cannot compare the relative predictive power of SLN status, ulceration, and Breslow thickness simply by comparing their HRs because the covariates are measured on different scales.[10] SLNB status and ulceration are dichotomous results, positive or negative, and present or absent, respectively. Breslow thickness, however, is almost always expressed as per millimeter.[10]

In MSLT-I, the authors note that patients with positive SLNs have an HR of 2.4, meaning that a patient with a positive SLN is 2.4 times more likely to die of melanoma than a patient with a negative SLN.[1] The authors next list an HR of 1.59 for Breslow thickness for each 1-mm increment. Those numbers do not at all suggest that SLNB is more powerful than Breslow thickness for prognosis. Instead, they mean that a patient with a 2-mm–thick melanoma is 1.59

times more likely to die from melanoma than a patient with a 1-mm–thick melanoma. However, a patient with a 3-mm–thick melanoma is 2.53 times more likely to die than a patient with a 1-mm–thick melanoma. A patient with a 4-mm melanoma is 4.02 times more likely to die than a patient with a 1-mm–thick melanoma. Therefore, when using the logic that the power of a prognostic factor is based on its HR, the data suggests that Breslow thickness is a better indicator than lymph node status in predicting overall death from melanoma because of its HR and dose-response effect.

Sentinel node status is highly correlated to Breslow thickness.[7-9] Because ICLND should no longer be recommended, the important question is what additional prognostic information is provided by SLNB above and beyond the clinical and pathologic features of the tumor, and do they outweigh the cost (around €10,000 in Spain during 2007-2010 and $14,000-$18,000 in the United States in 2018) and morbidity of the procedure (6% incidence of lymphedema).[2,11,12]

The potential marginal benefit of SLNB beyond the clinical and pathologic features of the tumor has not been well studied.[9,13] A model combining clinical and pathologic features readily available at the time of the excision of the primary tumor (thickness, mitotic count, ulceration, vessel invasion, site, age, and sex) better predict relapse and overall survival in melanoma than SLN status alone. The area under the receiver operating characteristic curve for overall survival was 55% for SLN status alone and was 70% for the model.[12] The addition of SLN status to the model increased the predictive power of the model by only 4% (from 70% to 74%).[13]

Little work has gone into developing predictive models of survival on the basis of clinical and pathologic features of the excised tumor, in spite of the fact that the data exist and should be readily available. One reason for the lack of attention is the reliance on SLNB, which should now be reconsidered. However, one such model is available on the internet.[14]

UTILITY OF SLNB AS AN ENTRY CRITERION FOR CLINICAL TRIALS

The second main justification for SLNB as a staging procedure is that it is required for patients to be stratified and entered into adjuvant trials and trials of new drugs for the prevention of melanoma progression. For example, the entry criteria for a trial of high-dose ipilimumab required SLN ≥1 mm and having an ICLND.[15]

Can requirements such as these continue to be justified? Given the high rate of significant morbidity and 1% mortality of some regimens, it is imperative to choose patients with a high risk of recurrence and death for adjuvant trials. Whereas SLNB is currently serving that role, some patients who have high-risk melanomas on the basis of pathologic and clinical criteria (Breslow thickness, mitotic count, ulceration, vessel invasion, site, age, and sex) should be eligible for clinical trials because their prognosis is poor regardless of their SLN status.[13,16]

The test performance characteristics of SLNB are poor. The sensitivity, specificity, positive predictive value, and negative predictive value of SLN status on overall 10-year mortality according to MSLT-1 intention-to-treat data were 33%, 87%, 26%, and 90%, respectively.[1,17]

The predictive value of SLN status is limited. For example, 15% and 35% of patients with intermediate and thick melanomas, respectively, who have a negative sentinel node will die of melanoma within 10 years.[5] In total, 62% and 48% of patients with intermediate and thick melanomas, respectively, who have positive results will be alive at 10 years.[5] Some patients with positive results (~14%)[14] would not have gone on to develop clinically relevant nodal disease because the test was either false positive (melanoma was not in the node) or biologically false positive (melanoma was in the node but did not produce clinically meaningful progression).[16-19]

It is for these reasons that entry criteria into melanoma trials should not rely only on SLNB status but on the usual measures of Breslow thickness and ulceration. These data are readily available from the pathology report and do not require a separate surgical procedure.

Data on the prognostic value of SLNB, Breslow thickness, ulceration, and location exists in many databases and in some published papers. A systematic comparison of them has not been performed. The test characteristics of SLN status and pathologic and clinical features of the tumor should be systematically studied. A prospective study would be ideal. In the meantime, physicians caring for patients with melanoma should not be afraid of future lawsuits for advising them to not have a SLNB.

OPPORTUNITY COSTS

Continuing to perform SLNB without a reappraisal of its value has obvious opportunity costs. Research to improve ultrasound monitoring of lymph nodes is underinvestigated and is underutilized in many countries. In experienced hands, high-resolution ultrasound can now detect small melanoma deposits in lymph nodes, and melanoma-specific survival is not compromised in patients who do not undergo SLNB.[20]

Table I. Barriers to incorporating evidence into practice

Overemphasis on vivid, personal anecdotal occurrences and underemphasis on significant, statistically strong evidence.
Bias in recognizing, remembering, and recalling evidence that supports pre-existing knowledge structures and parallel failure to recognize, remember, and recall evi dence that is more valid.
Inability to detect and distinguish statistical association and causality.
Persistence of long held, cherished beliefs in spite of overwhelming contrary evidence.

Table II. Potential reasons that physicians continue to recommend SLNB or ICLND

Concerns about loss of income by physicians performing SLNB and ICLND.
Sense of being less relevant.
Inherent practice conservatism.
Skepticism regarding clinical trial results.
Reluctance to admit error.
Habit.

ICLND, Immediate completion lymph node dissection; *SLNB*, sentinel lymph node biopsy.

Developing better predictive models will not occur until the role of SLNB is not blindly accepted as an undeserving standard of care. The use of biologic or molecular markers (eg, gene expression profiles) to provide prognostic information to patients with melanoma without the surgical risks of SLNB is hampered by the current place of SLNB in the decision-making process. The performance of biomarkers is dependent on the test sets to which they have been applied. Biomarkers should be compared with SLNB and to pathologic and clinical models in prospective trials.

BARRIERS TO CHANGE

The evidence that SLNB followed by ICLND does not have overall or melanoma-specific survival value is well supported by the results of MSLT-I and MSLT-II. However, there are many barriers to incorporating this evidence into practice. One major obstacle is physicians' personal experience with SLNB and ICLND. Nisbett and Ross have extensively reviewed people's ability to draw inferences from personal experience and describe several of the pitfalls (Table I).[21] There are many potential reasons that surgeons are continuing to perform SLNB and ICLND and for physicians to continue to insist on SLNB in spite of the evidence from MSLT-I and MSLT-II (Table II).

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