PRO/CON Clinical Controversies in the Treatment of Cancer and Blood Disorders

Sentinel Lymph Node Biopsy as the Standard of Care for Cutaneous Melanoma

PRO

Vernon K. Sondak, MD
Chief, Division of Cutaneous Oncology
H. Lee Moffitt Cancer Center & Research Institute
Professor, Departments of Interdisciplinary Oncology and Surgery
University of South Florida College of Medicine

Jonathan S. Zager, MD
Division of Cutaneous Oncology
H. Lee Moffitt Cancer Center & Research Institute
Assistant Professor, Department of Interdisciplinary Oncology
University of South Florida College of Medicine

Jane L. Messina, MD
Division of Cutaneous Oncology
H. Lee Moffitt Cancer Center & Research Institute
Associate Professor, Departments of Pathology, Interdisciplinary Oncology, and Dermatology
University of South Florida College of Medicine

Sentinel lymph node biopsy (SNB) is a widely used and accepted staging technique for cutaneous malignant melanoma and select other skin malignancies.[1-3] Why then does it need a "pro" defense? Because, as we will see, there is no proof that SNB leads to an overall survival benefit for all patients subjected to the procedure. In this discussion, we will draw from several sources—including our own extensive experience with the procedure—but most heavily from the randomized trial called the Multicenter Selective Lymphadenectomy Trial I (MSLT-I).[4,5] In doing so, we begin with the acknowledgement that there is no significant overall survival benefit from the routine application of SNB to patients with cutaneous melanoma.

Address correspondence to: Vernon K. Sondak, MD, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612; Tel: 813-745-8482; Fax: 813-745-1071; E-mail: vernon.sondak@moffitt.org

Why should an overall survival benefit be considered as a precondition for use of a staging technique? Certainly, chest x rays, blood tests, and computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans, all widely use staging techniques in melanoma patients, are unequivocally without any overall survival impact. Although these are noninvasive techniques and SNB is not, the long-term predictive accuracy of SNB, a one-time procedure, is far greater than these tests, which must be repeated frequently to have maximal value. Moreover, our patients are clearly undeterred by the lack of survival benefit—they do not require it in order to accept a low morbidity add-on to a necessary surgical procedure (wide excision of the primary). In our analysis, we will evaluate SNB purely from the standpoint of its benefits to the prospective patient; we will not argue to the cost-effectiveness of this internationally accepted procedure. So, if we start with the premise that there is no overall survival benefit for the average patient undergoing this procedure, why then would a patient choose to undergo SNB at the time of wide excision, and why do we argue for it as the standard of surgical care?

SNB Increases the Chance of Remaining Disease-free

The MSLT-I trial compared wide excision alone to wide excision and SNB in 2,001 patients with cutaneous melanoma. Results from the primary stratum (defined as those patients with melanomas 1.2–3.5 mm in thickness) have been published in detail,[4] while results for the entire cohort have been presented at national and international meetings and appear to concur in all respects with the primary stratum data.[5] Because detailed data are available for the primary stratum, we will illustrate our argument with patients whose melanomas are 1.2–3.5 mm thick, which we will refer to as intermediate-thickness melanomas, and generalize to other melanoma patients later. Based on MSLT-I results to date, an intermediate-thick-

ness melanoma patient undergoing SNB can expect a statistically significant increase in the likelihood he or she will be disease-free at 5 years (78.2% vs 73.1%; *P*=.009), based almost entirely on a lowered risk of nodal failure.[4] Nodal failure is a major issue for melanoma patients; the intermediate-thickness melanoma patients on MSLT-I who were randomized to observation experienced nodal failure at a median of only about 16 months after study entry. Thus, the gain of disease-free survival (DFS) is realized relatively quickly, and withholding SNB means many patients will experience a recurrence early after their initial diagnosis and surgical treatment. Studies of quality of life have repeatedly shown the importance cancer patients assign to DFS, even in the absence of any overall survival impact.[6] Combined with the data from MSLT-I that nodal failure is associated with a significantly greater nodal tumor burden than is encountered at the time of SNB[4] (in some cases sufficiently greater to require the addition of radiotherapy, greatly increasing the risk of lymphedema) and our personal observation that regional lymph node dissections have a higher morbidity when done for clinically palpable pathologically positive nodes versus microscopically positive sentinel nodes (SNs), the observed benefit in relapse-free survival is sufficient in and of itself to routinely recommend the performance of SNB for intermediate-thickness melanoma patients.

A potential counter to this argument is the concern that SNB trades one form of disease recurrence, nodal relapse, for a more serious and less treatable one, in-transit metastases between the primary site and the regional lymph node basin. Retrospective data from multiple institutions, as well as our own experience, show no evidence that in-transit metastases are in fact more likely to occur in patients undergoing SNB than in those treated with wide excision alone.[7,8] These retrospective observations have now been confirmed by the MSLT-I trial.[4] The incidence of local recurrence or in-transit metastasis was not significantly different for intermediate-thickness melanoma patients undergoing wide excision alone or wide excision with SNB. If anything, patients randomized to observation were slightly more likely to have a local or in-transit recurrence. Therefore, this theoretical concern has no evident basis in fact and should not be used to influence any recommendations regarding the use of SNB.

SNB Is a Superior Staging Technique and Appropriately Selects Candidates for Adjuvant Therapy

In the past, the results of elective lymph node dissection were used to stage patients with melanoma. The standard pathologic technique for examination of a regional lymph node dissection involves submitting a representative section from each lymph node identified, or sometimes one section from every 3–4 mm of nodal tissue, and staining the sections with hematoxylin and eosin (H&E). Even in smaller lymph nodes, this technique allows examination of only approximately 0.1% of the tissue.

The SNB allows the pathologist to intensively examine a smaller amount of tissue, a technique which would be impractical in large regional dissections. The use of immunohistochemistry (IHC) to highlight small metastatic deposits has further increased the sensitivity of this examination. Early studies demonstrated that the use of IHC staining with S-100 and HMB-45 could increase the detection of metastatic disease by 40%.[9] This has been validated at a number of institutions worldwide, with general agreement that IHC staining improves the yield of positive sentinel nodes by at least 10% and up to 34%.[10,11] Although there is no consensus on the exact pathologic technique(s) to utilize, most standard protocols call for, at a minimum, complete submission of all nodal tissue, sectioned at 3-mm intervals, and routine H&E staining as well as the use of at least one IHC stain such as S-100.[12]

After a negative SNB analyzed in this detailed fashion, only 3.4% of intermediate-thickness melanoma patients on the MSLT-I trial developed a regional nodal failure, indicating that the procedure is highly accurate in classifying patients for adjuvant therapy based on nodal status. The MSLT-I trial also confirms the value of SNB for predicting relapse-free and overall survival.[4] Intermediate-thickness melanoma patients with a negative sentinel node SN have a 90% chance of surviving their melanoma at 5 years compared to only a 72% chance if the SN is positive (SN+). Recurrence risk at 5 years is also significantly different (50% if the node is positive vs 20% if it is negative), making the risk of recurrence and death in a SN+ patient sufficient to justify adjuvant therapy. Many clinical trials of adjuvant therapy are available for SN+ patients, but so too is standard high-dose interferon alfa 2b. Based on multiple randomized clinical trials, high-dose interferon unequivocally prolongs relapse-free survival,[13] which we have already indicated patients value in and of itself.[6] But whereas the long-term (>10 years) survival impact of high-dose interferon is open to question,[13] a recent meta-analysis confirms a survival benefit at 2 years for interferon-treated patients that is statistically significant.[14] Opponents of SNB frequently cite the lack of adjuvant therapy as a reason not to perform the procedure. It is apparent that this is a spurious argument. A surgeon cannot possibly know ahead of time which patient will choose adjuvant therapy. Once a patient has information regarding his or her sentinel lymph node status, the patient can consult with a medical oncologist regarding adjuvant therapy options. As adjuvant therapy

improves, the potential gains the patient realizes from SNB also improve. Hence, there is no legitimate reason to deny a patient access to SNB based on perceived limitations of the available standard adjuvant therapy with interferon.

No Noninvasive Staging Alternative Is Available

According to MSLT-I, at least 18% of clinically node-negative intermediate-thickness melanoma patients will eventually develop regional nodal failure, at a median of only 1.33 years after diagnosis, if no SNB is done.[4] In those who underwent the procedure, a positive SN was found in 16% and, as previously mentioned, a further 3.4% had a nodal relapse despite negative SNs. Yet these positive SNs are not detected preoperatively by palpation, CT, PET,[15] or—in our experience—ultrasonography. For the foreseeable future, no imaging study is likely to replace SNB for identifying the small tumor foci we routinely detect at SNB. Therefore, the modest additional morbidity of this one-time surgical staging procedure provides information that is clearly superior to anything that could be obtained even with multiple noninvasive screening tests.

Patients With a Positive Sentinel Lymph Node May Have a Survival Advantage With Early Treatment

In the MSLT-I trial, patients who underwent complete node dissection after the finding of a positive sentinel node had a far better survival rate than those who underwent subsequent node dissection after nodal failure. After a median of 48 months, the rate of melanoma deaths in the SN+ group was 26% versus 49% in the observation-arm nodal failure patients. Corresponding rates of 5-year survival were 72% versus 52% (P=.007).[4] Although these dramatic numbers do not prove cause and effect, few if any patients who knew their SN was positive would willingly ignore that knowledge and defer treatment until recurrence. Moreover, it appears that few MSLT-I patients received adjuvant therapy with high-dose interferon, possibly underestimating the true survival impact for the node-positive subset if subjected to aggressive surgical and adjuvant therapy at the time of initial diagnosis. Note that while we began by saying SNB does not result in an overall survival benefit for the entire group of patients subjected to the procedure, the intriguing possibility that it may result in a survival advantage for those patients who need it most—those with a positive lymph node—is more than enough to justify the performance of this staging procedure.

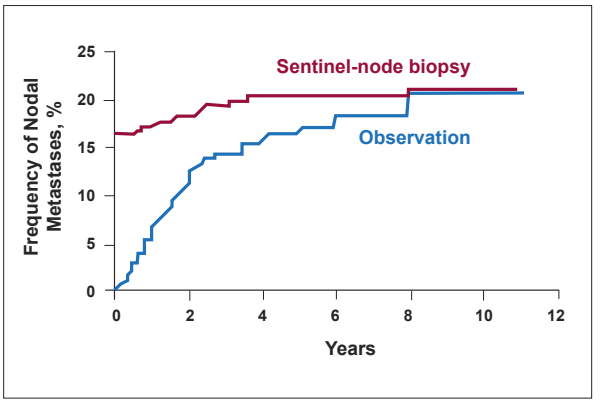

Figure 1. Cumulative frequency of nodal metastases in intermediate-thickness melanoma patients (1.2–3.5 mm thick) participating in the Multicenter Selective Lymphadenectomy Trial-1 clinical trial randomized to SNB or observation. Initially, 16% of patients on the SNB arm were found to have a positive sentinel node; over time, recurrences in the nodal basin (false-negative results) raised this frequency to about 20%. By 10 years of follow-up, a virtually identical 20% of patients on the observation arm have manifest nodal failure. Thus, there is no evidence that positive findings on SNB can be considered false-positive results, destined for dormancy or destruction.

Taken together, these four points provide compelling evidence that SNB is indeed the standard of care for patients with clinically node-negative melanoma. But there are a few questions left to address.

Does SNB Falsely Classify Some Patients as Node-positive?

A concern has been raised that SNB results in false-positive findings, incorrectly labeling some patients as node-positive when the cells observed within the lymph node were actually destined for destruction by the immune system or otherwise inconsequential.[16] Although there has never been any proof of this notion of insignificant metastasis, the initial published results of the MSLT-I trial have been misinterpreted to support the concept.[17] Specifically, in the initial results a slightly lower percentage of patients on the observation arm had nodal recurrences than the total percentage of patients on the SNB arm who had positive SNs (either histologically positive or subsequently positive after an initial negative biopsy). But of course nodal recurrence is a time-dependent phenomenon, one that can take many years or even decades to become manifest, whereas

SNB leads to an immediate accounting of the nodal status. Therefore, it is not surprising—in fact, it is exactly what should be expected—that with longer follow-up the percentages of patients with evidence of nodal involvement is now virtually identical in both study arms.[18] Figure 1 makes this case very clearly and indicates that any and all disease found in biopsied SNs must be considered to have clinical significance and the potential to grow, harm, and eventually kill the patient if left unperturbed.

Are the MSLT-I Intermediate-thickness Results Generalizable to Patients with Thick and Thin Melanoma?

Data available from presentations of the full MSLT-I trial results, including patients with melanomas less than 1.2 mm (who were required to have Clark level IV or V or ulcerated melanomas) and patients with melanomas over 3.5 mm, suggest that the results are equivalent in these other patient populations.[5] Based on our experience, SNB is a particularly valuable staging tool in patients with thicker melanomas, where the likelihood of finding a positive node is high, the disease-free interval after wide excision alone is often short, and adjuvant therapy is commonly selected by patients if their nodes are positive. The generalizability of the results to patients with thinner melanomas is less clear, particularly for melanomas less than 1 mm. Patients with thin melanomas have a relatively low likelihood of having a positive sentinel node. But our and others' research indicates that some subsets of thin melanoma patients have a significant risk of having a positive node, certainly high enough to justify the routine addition of this procedure in young, healthy patients.[19-21] Given the large number of patients now being diagnosed with thin melanomas, this is an area that needs considerable further study so that we may select the right patients for this potentially valuable procedure while sparing those with a very low risk of nodal metastasis.[22]

Summary

SNB is an effective, low morbidity, patient-friendly technique to stage the regional lymph nodes in patients with cutaneous malignant melanoma. Based on the available evidence, it offers no overall survival advantage to the large majority of SN-negative patients. But it does offer other advantages to these patients plus dramatic potential benefits to the SN+ group. SNB is here to stay and justifiably so. Efforts should focus on refining the indications for the procedure in thin melanomas[22] and in specific histologic subtypes such as desmoplastic melanoma,[23] on minimizing false-negative results (eg, by the development of new radiotracers and intraoperative gamma-detecting probes),[24] and on identifying biomarkers predictive of nodal and distant metastases to further improve selection of patients for surgery and adjuvant therapy.[25]

References

1. Morton D, Wen D, Wong J, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127:392–399.
2. Johnson TM, Sondak VK, Bichakjian CK, et al. The role of sentinel lymph node biopsy for melanoma: Evidence assessment. *J Amer Acad Dermatol*. 2006; 54:19–27.
3. Blazer DG III, Sabel MS, Sondak VK. Is there a role for sentinel lymph node biopsy in the management of sarcoma? *Surg Oncol*. 2003;12:201–206.
4. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med*. 2006;355:1307–1317.
5. Morton DL, Thompson JF, Cochran AJ, et al. Interim results of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) in clinical stage I melanoma. *J Clin Oncol*. 2005;23:710s.
6. Kilbridge KL, Weeks JC, Sober AJ, et al. Patient preferences for adjuvant interferon alfa-2b treatment. *J Clin Oncol*. 2001;19:812–823.
7. van Poll D, Thompson JF, Colman MH, et al. A sentinel node biopsy does not increase the incidence of in-transit metastasis in patients with primary cutaneous melanoma. *Ann Surg Oncol*. 2005;12:597-608.
8. Pawlik TM, Ross MI, Thompson JF, et al. The risk of in-transit melanoma metastasis depends on tumor biology and not the surgical approach to the regional lymph nodes. *J Clin Oncol*. 2005;23:4588-4590.
9. Yu LL, Flotte TJ, Tanabe KK, et al. Detection of microscopic melanoma metastases in sentinel lymph nodes. *Cancer*.1999;86:617–627.
10. Messina JL, Glass LF, Cruse CW, et al. Pathologic examination of the sentinel lymph node in malignant melanoma. *Am J Surg Pathol*. 1999;23:686–690.
11. Cochran AJ. The pathologist's role in sentinel lymph node evaluation. *Semin Nucl Med*. 2000;30:11–17.
12. Karimipour DJ, Lowe L, Su L, et al. Standard immunostains for melanoma in sentinel lymph node specimens: Which ones are most useful? *J Am Acad Dermatol*. 2004;50:759–764.
13. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of ECOG and Intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res*. 2004;10:1670–1677.
14. Verma S, Quirt I, McCready D, et al. Systematic review of systemic therapy for patients at high risk for recurrent melanoma. *Cancer*. 2006;106:1431-1442.
15. Wagner JD, Schauwecker D, Davidson D, et al. Prospective study of fluorodoxyglucose-positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel node biopsy. *J Clin Oncol*. 1999;17:1508-1515.
16. Thomas JM. Time to re-evaluate sentinel node biopsy in melanoma post-Multicenter Selective Lymphadenectomy Trial [letter]. *J Clin Oncol*. 2005;23: 9443-9444.
17. Thomas JM. Sentinel node biopsy in melanoma [letter]. *N Engl J Med*. 2007;356:418.
18. Morton DL, Cochran AJ, Thompson JF. Sentinel node biopsy in melanoma [reply]. *N Engl J Med*. 2007;356:419-420.
19. Sondak VK, Taylor JMG, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: Lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004;11:247–258.
20. Gimotty PA, Van Belle P, Elder DE, et al. Biologic and prognostic significance of dermal Ki67 expression, mitoses and tumorigenicity in thin invasive cutaneous melanoma. *J Clin Oncol*. 2005;23:8048–8056.
21. Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. Cancer 2007;109:100–108.
22. Puleo CA, Messina JL, Riker AI, et al. Sentinel node biopsy for thin melanomas: Which patients should be considered? *Cancer Control*. 2005;12:230–235.
23. Su LD, Fullen DR, Lowe L, et al. Desmoplastic and neurotropic melanoma: Analysis of 57 cases, including 33 cases with lymphatic mapping and sentinel lymph node biopsy. *Cancer*. 2004;100:598–604.
24. Wallace AM, Hoh CK, Ellner SJ, et al. Lymphoseek: A molecular imaging agent for melanoma sentinel node mapping. *Ann Surg Oncol*. 2007;14:913–921.
25. Sondak VK, Messina JL. Current status of biomarkers for melanoma metastasis. *IDrugs*. 2006;9:627–631.

CON

J. Meirion Thomas, MS, FRCP, FRCS
Consultant Surgeon
Royal Marsden Hospital
London, UK

The concept of the SN in melanoma is biologically attractive and the technique of identification was innovative. SNB offered a microanatomical method of nodal staging at the time of diagnosis of the primary tumor, thereby providing important prognostic information. Of greater significance, the procedure rekindled and renewed the hope, first expressed by Dr. Herbert Snow in 1892, that early lymphadenectomy in selected patients would improve survival.[1] For these reasons, and in the United States especially, SNB in melanoma became the standard of care, which implies that patients not offered the procedure are disadvantaged in some way. Exactly how, it is difficult to understand. However, at the time, many surgeons were routinely practicing elective lymph node dissection in melanoma, which must rank as one of the most futile and detrimental procedures in the history of surgery. SNB offered a method of selecting patients for early lymphadenectomy, thereby reducing morbidity for patients who were SN-negative (SN-), which might explain why the procedure was adopted as the standard of care. Inevitably, SN status was incorporated into the American Joint Committee on Cancer (AJCC) staging system for melanoma. It is noteworthy that Dr. Don Morton and colleagues described SNB exactly 100 years after Snow described "anticipatory lymphadenectomy." Snow regarded the lymph nodes as traps and the "incubator" hypothesis proposes that lymph nodes can delay the metastatic process for some time thereby allowing a window of opportunity for cure by early lymphadenectomy. However, no evidence of a survival advantage exists, thus giving greater credence to the "marker" hypothesis, which states that prognosis is related to the tumor burden within the regional node basin at the time of diagnosis.

The initial period of optimism for SNB in melanoma ended with the publication of the results of the MSLT-I,[2] which by conventional assessment of melanoma-specific and disease-free survival confirms that the procedure offers patients little benefit in return for the additional surgery.

Address correspondence to: J. Meirion Thomas, MS, FRCP, FRCS, Consultant Surgeon, Royal Marsden Hospital, Fulham Road, London SW3 6JJ UK, E-mail: meirion@roseway.demon.co.uk.

The conclusions of MSLT-I and other accumulated data require us to reconsider the clinical application of SNB in melanoma as currently practiced.

MSLT-I

MSLT-I entered 2,001 patients with primary melanoma who had no clinical evidence of nodal or other metastatic disease. Forty percent of patients were randomized to wide local excision (WLE) and observation with delayed lymphadenectomy when palpable lymph node metastasis appeared (the observation arm). Sixty percent were randomized to WLE plus SNB and immediate (early) lymphadenectomy was performed for patients who were SN+ (the biopsy arm). The results were published in the *New England Journal of Medicine (NEJM)* on September 28, 2006.[2] In addition to concluding that SN status has important prognostic value (which has been known since at least 1999[3]), the authors claimed a 20% survival advantage for early lymphadenectomy on the basis of an invalid postrandomization selected subgroup analysis, a calculation identical to the "matched pair" analysis.[4]

The results of MSLT-I do not conform to CONSORT guidelines.[5] The protocol-stated primary endpoint was overall survival but the article describes melanoma-specific survival (87% vs 86% at 5 years). In this first publication relating to survival, only a subgroup of 1,269 patients with intermediate-thickness tumors (1.2–3.5 mm) is presented and no information is given about the remaining 732 patients. (See Figure 1 for trial design and patient numbers.) The purpose of a randomized, controlled trial is to test how survival is affected by factors that cannot be identified and stratified before randomization, and it is for this reason that the selection of two postrandomization subgroups for comparison of survival is invalid. Within a randomized controlled trial a statistical difference in survival can only be calculated on an intention-to-treat basis from the point of randomization either for all strata or for patients identified and stratified before randomization. Therefore, it is an error to claim a 20% survival benefit for early lymphadenectomy based on the comparison of survival of 122 SN+ patients in the biopsy arm and 78 patients who underwent delayed lymphadenectomy in the observation arm (Figure 1). The authors fail to include the 26 patients who were SN false-negative and developed palpable nodal metastasis during follow up. Most, or all, of these patients were also SN+, but their true SN status was not identified by the SNB procedure. Why were these patients excluded from this seemingly important calculation? Similarly, it is mislead-

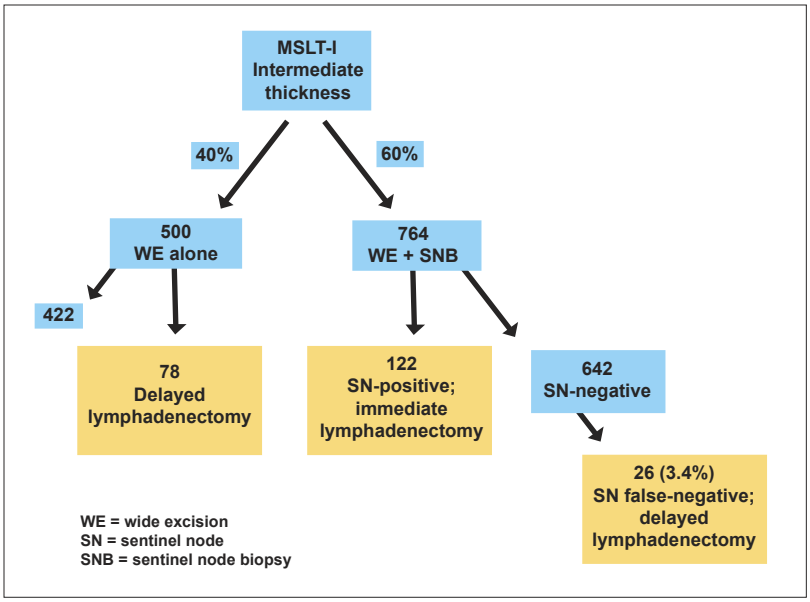

Figure 1. MSLT-I trial design.

Adapted from Morton DL, Thompson JF, Cochran AJ, et al. *N Engl J Med.* 2006;355:1307-1317.

ing to tell patients during the process of informed consent that if their SNs prove to be positive, then immediate lymphadenectomy will provide a 20% survival advantage. The results of MSLT-I do not provide Level I evidence of a survival difference as is claimed by Balch and Cascinelli in the accompanying editorial.[6]

Prognostic False-positivity

The 20% survival advantage in favor of early lymphadenectomy is explained by prognostic false-positivity within the SN, attributable to tiny clumps of melanoma cells in the peripheral sinus (often only identifiable by IHC), which possibly for immunologic reasons are not destined to progress to palpable nodal metastasis. Throughout, the fundamental error in the SNB hypothesis has been the assumption that all positive SNs would inevitably have progressed to palpable nodal disease if lymphadenectomy had not been performed, which is the basis of the 122:78 survival calculation described above. Of paramount importance, this assumption in MSLT-I ignores the 26 SN false-negative patients who developed palpable nodal metastasis during follow-up and had a delayed lymphadenectomy. These 26 patients are known to have a similar prognosis to the 78 patients in the observation arm who also had delayed lymphadenectomy. If there is no melanoma-specific survival difference from the point of randomization, and because palpable regional lymph node metastasis is a surrogate for poor survival in melanoma, the approximate incidence of prognostic false-positivity can be calculated as follows. The incidence of palpable nodal metastasis in the observation arm is 15.6% (78/500). Therefore, only 119 patients in the biopsy arm (15.6% × 764) would be expected to progress to palpable nodal recurrence. Twenty-six of these patients are already identified and, therefore, only 93 SN+ patients would be expected to progress, giving an approximate incidence of prognostic false-positivity of 24% (29/122). Therefore, the 20% survival difference claimed in MSLT-I is explained by a prognostic difference in the two groups of patients compared, and not because of a therapeutic benefit from early lymphadenectomy. It therefore follows that 24% of the SN+ patients in the intermediate-thickness group were wrongly upstaged, were given incorrect prognostic information, and underwent unnecessary lymphadenectomy and possibly unnecessary adjuvant therapy. A similar calculation for all strata[7] gives an incidence of prognostic false-positivity of 34% (77/229), partly because the rate of false-negativity almost doubles to 6.3%. Prognostic false-positivity leading to unnecessary and excessive surgery is a major clinical flaw in the SNB hypothesis. This possibility has been discussed on previous occasions[8-10] but there has not been a response from those who favor the use of SNB.

The incidence of false-positivity is likely to be much higher in MSLT-II, which requires ultrasound exclusion of patients with occult clinical disease before entry and allows SN-positivity to be confirmed by reverse transcriptase-polymerase chain reaction alone.

Breach of MSLT-I Protocol

It has always been assumed that patients in the observation arm of MSLT-I underwent delayed lymphadenectomy

when the metastatic lymph nodes became palpable.[6,7] However, recent evidence confirms that approximately half of the patients in the observation arm had lymphadenectomy performed when metastatic disease was detected by ultrasound surveillance,[11,12] thereby anteceding the clinical diagnosis of palpable nodal disease by many months. The Sydney Melanoma Unit (SMU) entered 946 of the 2,001 patients into MSLT-I and, therefore, approximately 378 of these patients were entered into the observation arm. The trial protocol stated that patients in the observation arm were to be treated by WLE of the primary tumor and clinical observation alone. At SMU, patients in the observation arm were intensively investigated by lymphoscintigraphy and the site of the SN marked by a small permanent tattoo. During follow-up, each SN was assessed by regular high-resolution ultrasound examination and lymphadenectomy was performed when nodal metastasis was detected by ultrasound and guided cytology.[11-13] The same authors previously described how nonpalpable nodal deposits of melanoma can be identified by ultrasound at a diameter of 4 mm in the groin and neck, and 4.5 mm in the axilla.[13] Anteceding the clinical diagnosis of palpable nodal disease in the observation arm has reduced the chance of proving a survival advantage (from the point of randomization) for early lymphadenectomy in SN+ patients. Why was this anomalous management not mentioned in the *NEJM* article?

Disease-free Survival

The DFS advantage for patients in the biopsy arm of MSLT-I is a mere 5% at 5 years (78% versus 73%). This means that 100 patients have to undergo SNB for 5 patients in the biopsy arm to have a DFS advantage. Because there is no trend toward a melanoma-specific survival difference, this small difference in DFS might simply mean a delay in time to recurrence rather than the prevention of recurrence. I have previously challenged the method of calculation of DFS in MSLT-I.[8,9,10,14] The design of MSLT-I directly influences the site and timing of first recurrence and inevitably there will be fewer nodal recurrences in the biopsy arm because most of the patients destined to progress to palpable nodal metastasis were SN+ and were treated by prophylactic lymphadenectomy at the outset. This is confirmed in the results relating to site of first recurrence,[2] which show a greater than 3-fold increase in nodal recurrence in the observation arm and a small increased incidence of distal recurrence in the biopsy arm (11% vs 7.8%). On this basis, and because regional nodal recurrences usually occur before distant recurrences, an apparent DFS advantage in favor of early lymphadenectomy is almost inevitable as presently calculated. Therefore, to detect a genuine therapeutic advantage, the DFS calculation should exclude the incidence of regional nodal recurrence as site of first recurrence from both arms of the study and consider only the competing incidences of in-transit and distant metastasis. This is the only way to overcome bias caused directly by trial design. Given its vital importance as the only small measure of a survival advantage, independent verification of the correct method of calculating DFS should be sought.

Sentinel Node Status and Prognosis

SN- patients have a significantly better overall survival than SN+ patients,[3] and undoubtedly many patients undergo the SNB procedure hoping that their SNs will be free of melanoma. This survival difference is at least partly explained by the inclusion of patients with occult clinical disease that could have been identified by ultrasound. In the axilla for example, and especially in obese patients, metastatic lymph nodes can reach 1.5 cm in diameter without being palpable. Ultrasound with power Doppler is now accepted as the best method to image and identify nonpalpable metastatic lymph nodes,[15] but the SNB procedure was well established before the advantages of this technique were understood. Nevertheless, ultrasound screening before SNB is still not widely practiced despite the knowledge that up to one third of patients eventually proven to be SN+ can be identified by ultrasound and guided cytology.[13,16] For this reason, the next AJCC staging system should differentiate between true micrometastases and occult clinical disease in the SN, which are currently bundled together as stage N1a but have distinctly different prognoses.[17] It remains unproven that SN status carries a prognostic significance after ultrasound exclusion of patients with occult clinical disease.

Conclusion

The results of MSLT-I as published could be misleading to physicians and patients and may result in unnecessary and excessive surgery. Prognostic false-positivity may be the fatal flaw in the SNB hypothesis in melanoma. The reality is that no group or subgroup of patients derives an overall survival benefit from the SNB procedure and any DFS advantage is minimal and the method of calculation is contested. These controversial issues should be explained to patients during the process of informed consent. An independent statistical review of the results may be warranted, especially with regard to trial violation, prognostic false-positivity, and the method of calculating DFS. It is necessary that scientific inquiry strive to find the truth even if it contradicts current practice. Currently, there is no evidence that patients with melanoma benefit from the SNB procedure.

References

1. Snow H. Abstract of a lecture on melanotic cancerous disease. *Lancet*. 1892;15:872-874.
2. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel node biopsy or nodal observation in melanoma. *N Engl J Med.* 2006;355:1307-1317.
3. Gershenwald JE, Thompson W, Mansfield PE, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999;17:976-983.
4. Morton DL, Hoon DS, Cochran AJ et al. Lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma. *Ann Surg.* 2003;238:538-549.
5. www.CONSORT-statement.org
6. Balch CM, Cascinelli N. Sentinel node biopsy in melanoma. *N Engl J Med*. 2006;355:1370-1371.
7. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma. Accuracy and morbidity in MSLT-I. *Ann Surg*. 2005;242: 302-313.
8. Thomas JM. Time for comprehensive reporting of MSLT-I. *Lancet Oncol.* 2006;7:9-11.
9. Thomas JM. Caution with sentinel node biopsy in cutaneous melanoma. *Br J Surg.* 2006;93:129-130.
10. Thomas JM. *J Clin Oncol.* 2006;24:2966-2967 [correspondence].
11. Thomas JM. Sydney Melanoma Unit patients and Multicenter Selective Lymphadectomy Trial protocol. *ANZ J Surg*. 2006;76:1038-1039.
12. Thompson JF and Shaw HM. Sydney Melanoma Unit patients and Multicenter Selective Lymphadenectomy Trial protocol [reply]. *ANZ J Surg.* 2006; 76:1039-1040.
13. Thompson JF and Shaw HM. Benefits of sentinel node biopsy for melanoma *ANZ J Surg.* 2006;76:100-103.
14. Hayes AJ, Thomas JM. Recurrence-free survival after sentinel node biopsy in melanoma? *Br J Dermatol.* 2006;155:631-632.
15. Bafounta M-L, Beaucher A, Chagnon S, et al. Ultrasound or palpation for detection of melanoma nodal invasion: a meta-analysis. *Lancet Oncol*. 2004;5: 673-680.
16. Rossi CR, Mocellin S, Scagnet B, et al. The role of preoperative ultrasound scan in detecting lymph node metastasis before sentinel node biopsy in melanoma patients. *J Surg Oncol.* 2003;83:80-84.
17. van Akkooi ACJ, de Wilt JHW, Verhoef C, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol.* 2006;17:1578-1585.