Published in final edited form as:

Nat Rev Clin Oncol. 2014 May ; 11(5): 245–246. doi:10.1038/nrclinonc.2014.65.

Why is sentinel lymph node biopsy ‘standard of care’ for melanoma?

James C. Yang,

National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

Richard M. Sherry, and

National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

Steven A. Rosenberg

National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

Abstract

A large definitive trial comparing the use of sentinel lymph node biopsy and elective lymph node dissection to observation in patients with intermediate thickness melanomas fails to show improved melanoma-specific survival. These results demand reconsideration of the routine use of sentinel lymph node biopsy in the treatment of primary melanoma.

In 1992, Morton and colleagues reported that localizing and examining the first draining lymph node from a primary melanoma (the sentinel lymph node; SLN) could predict with remarkable accuracy, those patients who would not have additional nodal disease on completion lymph node dissection.¹ Since then, the prognostic value of this procedure has been validated, in that patients with disease in their SLNs (and with no other known disease) have significantly worse survival than those with SLN-negative disease. One critical question that was not answered in trials examining the prognostic significance of this procedure was whether SLN biopsy (SLNB) could be used to improve the survival of patients with primary melanoma. Several earlier randomized studies that applied elective prophylactic lymph node dissection (EPLND) to all patients with primary melanoma failed to show an overall survival benefit when compared with observation.^{2,3} However, these failures of EPLND to show a benefit was blamed on the studies being insufficiently powered rather than the null hypothesis being correct.

In 2006, the initial results of the Multicenter Selective Lymphadenectomy Trial (MSLT) trial were published in the *New England Journal of Medicine* by Morton and co-investigators.⁴ This trial was aimed at answering the question of whether selective EPLND (as directed by a positive SLNB) could improve the melanoma specific survival of patients with intermediate thickness melanoma compared to simple resection of the primary and subsequent observation (applying lymph node dissection only to those who developed clinically evident

Correspondence to: S.A.R. sar@mail.nih.gov.

Competing interests

The authors declare no competing interests.

nodal disease). The final results of this trial (MSLT-I) have now been reported⁵ and are essentially the same as the earlier report. In a well-designed and rigorously implemented study, 1,661 patients were randomly assigned in a 2:3 ratio to have resection of melanomas of at least intermediate thickness (>1.2 mm) and then either be followed up for recurrence and survival (with delayed therapeutic lymphadenectomy for those developing a lymph node recurrence), or undergo SLNB at diagnosis and have an EPLND if sampling of the nodes was positive. The primary end point of the trial was melanoma-specific survival and follow up in this report was 10 years. The clear answer from the MSLT I study is that no difference in melanoma-specific survival could be detected between the two arms. Even when patients with the thickest primary melanomas were eliminated (assuming that many of them would already have covert distant metastases), the 10-year melanoma-specific survival was 78% in the observation group and 81% in the SLNB/ EPLND group ($P=0.18$). If melanomas with a thickness of 1.0–4.0 mm (the current criterion for intermediate thickness) are considered—and a Cox model applied to correct for small differences between arms in gender, thickness, site, ulceration, etc.—the statistical significance of the difference is even less ($P=0.30$).

These results could, and perhaps should, be the end of the story. Additional analyses on overall survival with and without positive SLNs only confirm their utility as a prognostic tool. Furthermore, comparing recurrence-free survival between the randomized arms largely reflects that one group had intact lymph nodes in which recurrence was possible, and the other had already had those removed in the highest risk patients. Perhaps the most complicated analysis is the subset analysis confined to patients with nodal disease in the two arms. In the observation arm, ‘node-positive’ patients were defined by the pathologically confirmed clinical appearance of melanoma-involved lymph nodes during post-randomization follow up—a gold-standard for nodal involvement. In the SLN group, node-positive patients were defined as those with melanoma in at least one sentinel lymph node where even a single immunohistochemically identified cell is interpreted as positive. This raises the question of the specificity of such a test for identifying node-positive patients and the potential for ascertainment bias in defining the groups. In the final analysis, the percentage of node-positive patients in the two arms is 17.4% and 20.0% for observation versus SLN, respectively. This result in itself was not statistically significant, but allowing up to one in eight patients to be possibly misallocated (that is, SLN false-positive) is cause for concern when one is doing an analysis of the survival of this small subset. This is important because the melanoma-specific survival in node-positive patients is the sole basis of the main positive conclusion asserted by the authors. In the final study analysis, node-positive patients (defined by the different criteria in the two arms) had better melanoma-specific survival if they had SLNB and EPLND. The hazard ratio was 0.67 ($P=0.04$), when only melanomas of intermediate thickness are considered—there was no difference between arms for thicker melanomas. The analysis of a small subset, the possibility of subtle ascertainment bias, and the borderline statistical significance of this finding casts doubt on this conclusion.

From this study one cannot conclude that no patient with primary melanoma would benefit from a SLN-directed EPLND. One can only say that no benefit could be detected in a well-designed and meticulously executed randomized study of 1,661 patients. To determine more precisely if EPLND can affect survival, MSLT-2 will assess patients who are already defined

to have nodal involvement by a positive SLN and they will be randomly assigned to EPLND or ultrasound monitoring and observation. Yet, without the results of that study, one must ask, how has SLNB become the standard of care for intermediate thickness melanomas? Guidelines for the staging and therapy of melanoma that include SLNB have been widely accepted in the USA, Canada, Europe, Australia, and New Zealand.⁶ These guidelines go beyond the current British recommendation that this surgery is a “staging procedure... that ... has no proven therapeutic value”.⁷ Nodal staging has been advocated by some because of the availability of adjuvant interferon- α (IFN) for patients with nodal involvement, yet IFN has not been shown to clearly improve survival of patients with melanoma either.⁸ So, an expensive procedure that costs approximately US\$10,000–\$15,000⁹ and without a proven survival benefit is being used to justify the use of a toxic adjuvant that also has no clear survival benefit. Such recommendations cannot represent the best data-driven use of our healthcare dollars. The best current evidence of whether to perform SLNB when a patient and their doctor are faced with a new diagnosis of primary melanoma is provided by the definitive result of MSLT1: “No significant treatment-related difference in the 10-year melanoma-specific survival rate was seen in the overall study population...”.⁵ Certainly, there is prognostic information in a SLNB, and its use in defining patients for research studies is justifiable. Yet, without additional data showing that it can improve survival, it must be considered an expensive and optional staging tool and understood as such by patients considering this procedure.

References

1. Morton DL et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch. Surg* 127, 392–399 (1992). [PubMed: 1558490]
2. Veronesi U et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *N. Engl. J. Med* 297, 627–630 (1977). [PubMed: 895764]
3. Balch CM et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). *Ann. Surg. Oncol* 7, 87–97 (2000). [PubMed: 10761786]
4. Morton DL et al. Sentinel-node biopsy or nodal observation in melanoma. *N. Engl. J. Med* 355, 1307–1317 (2006). [PubMed: 17005948]
5. Morton DL et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N. Engl. J. Med* 370, 599–609 (2014). [PubMed: 24521106]
6. Fong ZV & Tanabe KK Comparison of melanoma guidelines in the U.S.A., Canada, Europe, Australia and New Zealand: a critical appraisal and comprehensive review. *Br. J. Dermatol* 170, 20–30 (2014). [PubMed: 24116870]
7. Marsden JR et al. Revised UK guidelines for the management of cutaneous melanoma 2010. *Br. J. Dermatol* 163, 238–256 (2010). [PubMed: 20608932]
8. Kirkwood JM et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin. Cancer Res* 10, 1670–1677 (2004). [PubMed: 15014018]
9. Agness DM Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery* 134, 542–547 (2003). [PubMed: 14605613]