Sentinel Lymph Node Biopsy for Melanoma: A Plea to Let the Data be Heard

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In his companion editorial, Dr. Coit lauds the final analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), reported recently in the *New England Journal of Medicine*, saying that it “has provided clinicians with invaluable very high quality information to interpret and use in the management of their melanoma patients”.¹ However, he expresses concern about “how the authors have presented this information to the readers”. The planning and conduct of MSLT-I was a mammoth project, and the fact that the final report was not publishable until 20 years after the first of the 2001 trial patients was randomized highlights not only the scale of the undertaking but also the dedication and commitment of clinicians, trial personnel, and patients around the world to its successful completion, when 10 years of follow-up had been achieved for all trial participants. The mass of data collected in MSLT-I over the 20-year period was large, making it impossible to report and discuss all the results in a single journal publication. However, we can reassure Dr. Coit and others that hitherto unreported trial data will be presented in subsequent publications.

The broad statement by Dr. Coit that “this is a negative trial” refers only to the primary endpoint—improvement in melanoma-specific survival. This sweeping claim ignores the multiple statistically significant benefits that were demonstrated for critically important, predetermined secondary endpoints, notably a significant improvement in disease-free survival in the sentinel lymph node biopsy

(SLNB) group and significantly improved melanoma-specific survival in sentinel lymph node (SLN)-positive patients treated by immediate completion lymph node dissection (CLND).

In relation to melanoma-specific survival, the results of MSLT-I are consistent with those of previous randomized trials of elective lymph node dissection (ELND), and Dr. Coit concedes this. Although these previous trials were insufficiently powered (as was MSLT-I) to demonstrate an overall survival benefit for patients undergoing ELND (or SLNB/CLND), they consistently demonstrated a likely survival benefit for the cohort of patients with intermediate-thickness melanomas. In addition, although neither MSLT-I nor the earlier ELND trials showed a statistically significant improvement in overall melanoma-specific survival following early nodal surgery, they demonstrated a consistent advantage that falls short of statistical significance. Lack of statistical significance in an underpowered trial should not be interpreted as a demonstration of equality.

For patients with thick melanomas, Dr. Coit accepts that MSLT-I data (Fig. 3b) support the concept that finding melanoma cells in an SLN predicts the eventual development of clinically detectable nodal disease (if the SLN is not removed). However, he is unwilling to accept that the same is true for patients with intermediate thickness melanomas because the incidence of ‘positive’ nodes after 10 years is 2.4 % higher after SLN biopsy and follow-up than after observation alone. He suggests that the curves in Fig. 3a are “remarkably parallel” beyond 5–6 years follow-up. This is not true. As we have previously indicated, over 25 % of the numerical difference between the curves reporting cumulative incidence of nodal metastasis vanishes between 8 and 10 years of follow-up.² Formal follow-up of MSLT-I patients did not extend beyond 10 years, but

several investigators have reported nodal recurrences after 10 years. At the Melanoma Institute Australia (MIA), where 946 of the 2,001 patients in MSLT-1 were treated, one patient in the observation arm developed an isolated node field recurrence after 15.2 years of follow-up. Whereas the curves converge after approximately 6 years in patients with thick melanomas (Fig. 3b), it is likely (and predictable) that the curves will converge later for patients with more slowly evolving intermediate-thickness melanomas (Fig. 3a). The odd speculations on ‘prognostic false positivity’, for which there never was a firm data base, cannot be supported by the MSLT-I results without stretching interpretation beyond reason. This said, we agree with Dr. Coit that SLN staging is unlikely to be 100 % accurate—few staging tests in medicine approach complete accuracy. Nevertheless, every effort was made in MSLT-I to minimize the possibility of false positive results by rigorous central review by an experienced pathology team of all nodes reported by the site pathologists as SLN-positive. Members of this team, who developed the pathology approaches widely used to evaluate SLNs, are unlikely to have mis-identified nodal nevi and histiocytes as melanoma cells, a matter that concerns Dr. Coit, especially as the protocol required that nodes be stained for S-100, Mart-1 and HMB-45.

It is important to keep in mind that SLN biopsy is primarily intended to be a minimally invasive staging procedure and Dr. Coit concedes that the MSLT-I final report “reaffirms that SLNB is an effective staging procedure, one that currently provides more important prognostic information than can be derived from characteristics of the primary tumor”. When MSLT-I started, the SLN procedure was new, which likely accounts for initial complication rates and false negative rates that are considerably higher than those currently reported from high-volume melanoma treatment centers worldwide. At MIA in Sydney, for example, careful quality assurance monitoring indicates a current complication rate of only 1.8 % (wound infection or seroma) following SLN biopsy, and clinically detectable lymphedema following the procedure is rare (and when it does occur, it is often apparent that it is primarily due to wide local excision of a distal limb primary melanoma).

Our main and strong disagreement with Dr. Coit relates to his rather nonchalant dismissal of the survival benefits of management determined by SLN staging, i.e. immediate CLND in SLN-positive patients. He bases his arguments on calculations for the entire cohort of patients with intermediate-thickness melanomas and states, correctly, that only 3–4 % of this cohort will have been spared death at 10 years if they had an SLNB. However, it appears to us that he is using the wrong starting point. The MSLT-I data confirm that it is simple and safe to obtain accurate nodal

staging from a minimally invasive SLNB procedure. Today, most patients with intermediate-thickness melanomas are staged in this way, as recommended in evidence-based guidelines issued by the world’s leading medical oncology and surgical oncology societies, the American Society of Clinical Oncology and the Society of Surgical Oncology.³ The melanoma guidelines issued by the Melanoma Panel of the National Comprehensive Cancer Network (of which Dr. Coit is Chair) also recommend that SLNB staging be offered to patients with melanomas >1.0 mm in thickness.⁴

The staging information provided by SLNB defines two distinct subgroups of patients with intermediate-thickness melanomas. One subgroup is SLN-negative, and the MSLT-I results demonstrate that such patients have a good prognosis without further regional node surgery. The other subgroup is SLN-positive, with metastatic disease in regional lymph node(s) but no detectable metastatic disease at other sites. In this group, a decision about further treatment (or not) must be made. This subgroup, comprising approximately 20 % of patients with intermediate-thickness melanomas, is the group for which the MSLT-I results are of greatest importance. In this group, the MSLT-I results indicate a 44 % improvement in 10-year survival (hazard ratio 0.56) if immediate CLND is performed, relative to patients who do not have SLN staging and later develop clinically detectable disease, and for which they have a (delayed) therapeutic CLND.

The situation is similar to that in breast cancer, where a subgroup of patients who are HER2-positive is defined. In each case, the result of the staging process (SLNB $\pm$ or Her2neu $\pm$) allows rational management decisions to be made. Such decisions are not relevant to the entire population of melanoma or breast cancer patients. In the 20 % of patients with intermediate-thickness melanomas who are SLN-positive, the MSLT-I results indicate that the improvement in 10-year survival following immediate CLND is substantial (62.1 vs. 41.5 %), a survival enhancement that most patients and their treating clinicians would consider justified the morbidity of CLND.

The most important discussion with our patients should therefore be *after* they have been staged by SLNB. If this is done, Dr. Coit will have no need to emphasize that “at best SLNB could impact the outcome of a very small minority of patients with intermediate thickness melanomas”. For those who are SLN-positive, CLND can be recommended, while those who are SLN-negative can be told that no benefit is likely to be obtained from immediate CLND,

Dr. Coit similarly dismisses as ‘statistical gymnastics’ the reported results of the pre-planned subset analysis of the outcome of all patients who ultimately developed nodal metastases using the statistical technique of accelerated-failure-time latent-subgroup analysis. He resorts here to a

dialectical device rather than a reasoned scientific analysis. Most of us have difficulty understanding the theory of relativity but we do not dismiss it as ‘statistical gymnastics’ simply because we do not understand it. We leave technical analysis and determination of appropriateness and relevance to experts in the field. The statistical basis of latent subgroup analysis is certainly complex, but it has been accepted by the statistical community following rigorous peer review of Altstein’s landmark article as a valid method of dealing with the problem often encountered in medicine where a subgroup of patients in a clinical trial is able to be identified only after a period of follow-up (latency), whereas in other patients the subgroup can be identified immediately.^{5,6}

Although we hold strongly divergent views on some of the matters raised by Dr. Coit, we agree with other points that he raises and believe that we must base our ongoing discussions on data rather than speculative, armchair opinions. Importantly, we agree with him that Dr. Morton made enormous and unprecedented contributions to oncology in general, and melanoma in particular. Dr. Coit pays high tribute when he states that “while others have either analyzed retrospective series or criticized existing or proposed procedures, Dr Morton and his team conceived and completed two seminal international prospective randomized surgical trials (MSLT-I and MSLT-II) to rigorously and critically evaluate the role of SLNB in melanoma”. Dr. Morton was an academic giant, a surgical oncologist without peer, who made many important discoveries that have improved the lot of patients affected by melanoma.

Dr. Morton’s death has deeply affected and saddened his colleagues working on the problem of melanoma worldwide. His example should encourage us all to pursue with renewed vigor the rigorous, evidence-based approach to solving important clinical problems that he followed during his long and distinguished career. If Dr. Morton had still been with us, his response to Dr. Coit’s editorial and other commentaries on the MSLT-I results would probably have been along the same lines as ours, perhaps more strongly worded. He would undoubtedly have sought to use the invaluable data collected in MSLT-I to refute speculation and data-free opinions in ways that provide the greatest benefits to melanoma patients.

REFERENCES

1. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014;370:599–609.
2. Morton DL, Cochran AJ, Thompson JF. Authors’ response to a letter to the editor re: sentinel node biopsy for early-stage melanoma. *Ann Surg*. 2007;245:828–9.
3. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *J Clin Oncol*. 2012;30:2912–8.
4. Coit DG, Thompson JA, Andtbacka R, et al. Melanoma, version 4.2014. *J Natl Compr Canc Netw*. 2014;12:621–9.
5. Altstein L, Li G. Latent subgroup analysis of a randomized clinical trial through a semiparametric accelerated failure time mixture model. *Biometrics*. 2013;69:52–61.
6. Altstein LL, Li G, Elashoff RM. A method to estimate treatment efficacy among latent subgroups of a randomized clinical trial. *Stat Med*. 2011;30:709–17.