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CORRESPONDENCE

MSLT-I—response of clinical trial investigators

Mark B. Faries, Alistair J. Cochran and John F. Thompson

Three recent News & Views articles that were published back-to-back in the May 2014 issue of this journal[1–3] commented on the final analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I).[4] The authors of these articles recognized the size and quality of the trial and were unstinting in their praise of the late Donald Morton, who, with his colleagues, developed sentinel-lymph-node biopsy (SLNB) technique and led the trial from conception to completion. All the articles acknowledged the staging power of SLNB; the MSLT-I confirmed numerous prior reports demonstrating the pathological status of the sentinel node as the most important prognosticator for patients with intermediate-thickness melanomas.[4,5]

However, we strongly disagree with the commentary by Yang *et al.* (Why is sentinel lymph node biopsy 'standard of care' for melanoma? *Nat. Rev. Clin. Oncol.* **11**, 245–246; 2014)[1] who state that knowledge of nodal tumour status is not of critical value to patients with newly diagnosed melanoma. Such information enables patients to be considered for timely application of additional therapies, including completion lymph-node dissection and IFN-α-2b treatment. The limited clinical benefit of current 'standard' therapies does not devalue accurate staging. Rather, the toxicity and modest benefits of current adjuvant therapy make accurate staging and prognostic assessment more critical, not less. Furthermore, data from the influential EORTC study demonstrate that, in patients with stage III melanomas, only those with microscopic involvement at the time of SLNB derive benefit from adjuvant therapy with IFN.[6] Staging information is also required for enrolment in clinical trials of new treatments, but the suggestion that SLNB only be performed in the setting of an adjuvant therapy trial is impractical. Because only approximately 20% of patients with intermediate-risk melanomas have nodal metastases, adjuvant therapy trials would need to enrol five times the number of patients that is required currently, and could only accrue at trial centres. This factor would make completion of the trials virtually impossible.

Furthermore, the assertion of van Akkooi and Eggermont (MSLT-1—SNB is a biomarker, not a therapeutic intervention. *Nat. Rev. Clin. Oncol.* **11**, 248–249; 2014)[3] that SLNB is merely a biomarker is not supported by the trial data. Although points of controversy inevitably exist in interpretation of the MSLT-I results, that a substantial biopsy-associated reduction in the frequency of recurrence was observed in the SLNB arm is not in question.[4] Despite the fact that patients in the observation arm can undergo delayed node dissection upon recurrence, clearly they have a substantially greater disease burden and risk of greater morbidity than is associated with earlier, sentinel-lymph-node-guided dissection.[7] We are unaware of a biomarker test that directly improves disease-free survival and reduces morbidity.

The most-significant issue addressed in the News & Views articles[1–3] is the influence of early nodal surgery on survival. Two of the articles flatly conclude that the MSLT-I demonstrated no survival benefit from sentinel-node biopsy.[1,3] In fact, abundant evidence in the trial data indicates that early removal of nodal metastases results in a considerable improvement in long-term outcomes, including survival.[4]

The trial was insufficiently powered to fully address the primary end point of melanoma-specific survival among all randomized subjects, owing to the unexpectedly favourable outcomes among all the patients enrolled in the trial, and not as a result of failure to achieve the patient-accrual target. The low rate of mortality events meant that the observed hazard ratio (HR) of 0.84 in favour of the SLNB arm did not reach statistical significance ($P = 0.18$). Nevertheless, the degree of risk reduction observed was almost identical to the benefit attributed to early nodal surgery in previous trials of elective lymph-node dissection (HR 0.86).[8]

In retrospect, the challenge of examining survival is clear; 80% of the population of patients with intermediate-thickness melanoma had no nodal metastases,[4] and the survival of this group cannot be improved by early nodal excision. Using SLNB, accurate assessment of nodal tumour status is obtained with only the minor adverse effects of lymph-node biopsy. Hypothetically, an ideal study would examine treatment efficacy only in patients with nodal metastasis, analogous to studying HER2-targeted therapy in the subgroup of patients with HER2-positive breast cancer. However, nodal metastasis can only be identified by immediate surgery or during long-term follow-up assessments, and it is impossible to use this clinical characteristic prospectively to randomize patients. With completion of trial follow-up evaluations, however, the patients with node-positive disease could be identified and analysed retrospectively, and in this group the survival benefit of early removal of nodal metastasis was clear with a hazard ratio of 0.56 ($P < 0.01$) and an absolute survival benefit of more than 20% at 10 years.[4]

As the patients with node-positive disease were not identifiable before randomization, questioning whether bias was introduced that led to false-discovery of this significant difference in survival is reasonable. To address this concern, the cumulative rate of nodal metastasis was compared between the SLNB and observation arms. An early 'excess' of patients with node-positive melanoma in the SLNB arm was expected, because at the start of the study 15.8% of biopsied patients had SLN metastases, whereas none of the patients in the observation cohort had nodal recurrence (that is, clinically evident nodal metastasis) at that point in the trial.[4] Over time, the rates of nodal metastasis in the two arms of the study converged to become statistically indistinguishable.[4] The closing of the nodal metastasis event curves continued even at latest follow-up assessment,[4] suggesting that the minimal residual disease rate difference will eventually disappear. Thus, there is no analytical support from the trial data for the concept of 'false-positive' sentinel lymph nodes.

We understand that absence of a difference in the rates of nodal metastasis is insufficient to completely exclude possible 'ascertainment bias' resulting from different methods of discovery of nodal disease. For this reason, a sophisticated statistical methodology, latent subgroup analysis, was applied to the trial data.[9,10] This technique examines the entire study population (that is, not only patients with demonstrated nodal metastases, but also those without confirmed lymph-node involvement) and uses all pertinent available clinical information to conduct numerous simulations and determine any statistically significant therapeutic effect from the intervention. This analysis confirmed independent and clinical meaningful extensions of both disease-free and melanoma-specific survival in the patients who underwent SLNB: disease-free survival time was tripled ($P<0.001$) and the duration of melanoma-specific survival was doubled ($P=0.05$).[9,10]

Although a trial larger than the MSLT-I that could have shown a statistically significant therapeutic effect (even in a population diluted with 80% patients with node-negative disease) might have been methodologically 'ideal', such a trial is no longer a possibility. On the basis of the enormous and precise staging value of SLNB, its ability to enable early treatment of nodal disease and thereby decrease recurrence, and the observed decreased risk of melanoma-related death among SLN-biopsied patients with nodal metastases in the MSLT-I, it is highly unlikely that any ethics committee would permit the inclusion of a randomized observation cohort in future trials. That patients would accept such randomization is even less likely. In the absence of such a trial, the best information on this issue we will ever have comes from the MSLT-I, and the data argue strongly in favour of a therapeutic benefit for SLNB. As such, failure to offer this option to patients when clinically appropriate is, in our opinion, a grave therapeutic omission.

*Department of Surgical Oncology, The John Wayne Cancer Institute, Saint John's Health Center, 2200 Santa Monica Boulevard, Santa Monica, CA 90404, USA (**M.B.F.**).*
*Laboratory Medicine and Surgery, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA (**A.J.C.**).*
*Melanoma Institute Australia, 40 Rocklands Road, North Sydney, NSW 2060, Australia (**J.F.T.**).*
Correspondence to: M.B.F.
mark.faries@jwci.org

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Competing interests
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