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Multicenter Selective Lymphadenectomy Trial-I confirms the central role of sentinel node biopsy in contemporary melanoma management:

Response to 'No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the Multicenter Selective Lymphadenectomy Trial-I final report'

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In their title, Sladden, Zagarella, Popescu and Bigby claim to have undertaken a 'critical appraisal' of the published results of Multicenter Selective Lymphadenectomy Trial-I (MSLT-I).[1,2] It is therefore disappointing that it was not a more balanced commentary, and we are particularly concerned and surprised by their suggestion that the publication is deliberately deceptive. As we have previously reported extensive data from original research, we have experienced the kind of criticism that may be levelled at data that do not confirm the preconceptions of others. However, the suggestion by Sladden *et al*.[2] that the editors and reviewers of the *New England Journal of Medicine* are less than rigorous in their examination and evaluation of research findings is well beyond the typical scope of such an appraisal and, frankly, undermines these authors' credibility.

Sladden *et al*.[2] accuse the authors of the MSLT-I publication of 'spin', citing as evidence a lack of satisfactory emphasis on the survival comparison of the two arms of the trial. However, the result they seek to highlight is, in fact, the very first observation in our abstract of the lead article in the *New England Medical Journal*, a highly respected and influential medical publication. It is hard to imagine a more prominent position for it.

They also criticize the report for failing to present all data from a 20-year trial involving over 2000 subjects. It seems necessary to point out that publication-determined space limitations prevent inclusion of every data point and analysis from our study in a single

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manuscript. As they have chosen to ignore numerous other publications of trial results that bear on the issues they raise, we are happy to provide some relevant references for their consideration.

They state that the morbidity of sentinel lymph node biopsy and completion lymph node dissection has not been reported (but nevertheless claim that such morbidity is excessive and unjustifiable). Somehow they have failed to note prior reports of the morbidity of sentinel node biopsy in MSLT-I and the Sunbelt Melanoma Trial.[3–5] Both reports showed convincingly that sentinel node biopsy was related to low rates of generally mild and transient morbidity. Complete lymph node dissection has always carried a greater risk of short- and long-term morbidity despite continuing attempts to reduce such problems. Sladden *et al*. fail to appreciate that not performing sentinel lymph node biopsy does not decrease the likelihood of eventual complete node dissection. It merely delays the need for this surgery to a time when the volume of nodal disease has more than doubled, the risk of postoperative lymphoedema has nearly doubled and hospital stays are significantly lengthened. Disregard of these readily available earlier publications greatly weakens their claim to have undertaken a ‘critical appraisal’.

Sladden *et al*. consider that our report violates an alleged injunction of the National Cancer Institute (NCI) concerning the reporting of distant disease-free survival. As we have previously pointed out, the NCI clearly stated that such matters are not within their purview, and that they rely upon reviewers and editors of the publishing journal to adjudicate.[6] The editors and reviewers of our recent publication did not feel that distant disease-free survival was a sufficiently important endpoint to warrant displacement of other results in the limited space available. Nevertheless, the result they seek has been published and the outcomes favour the biopsy arm, albeit to a nonsignificant degree in an underpowered analysis.[6]

Sladden *et al*. state that they do not ‘believe’ that there is adequate evidence to support the prognostic value of sentinel lymph node status in intermediate-thickness melanomas. While they are free to believe whatever they choose, the prognostic significance of sentinel node biopsy in this setting is controversial in the same way as the evolution of species is controversial. The weight of evidence supporting the prognostic value of nodal tumour status is so heavily on one side that it seems truly odd to have to address the subject in a scientific publication, but we certainly can do so.

Sladden *et al*. cite three papers to support their beliefs.[7–9] The first is a Bayesian statistical analysis that identified only two studies considered ‘informative’ on the subject. We suggest that, with modest effort, additional relevant studies should have been identified, for example American Joint Committee on Cancer (AJCC) staging publications with a database of more than 30 000 patients, and multiple prospective clinical trials.[1,5,10] The second paper claims to be a ‘meta-analysis’ of the topic, but the methodological deficiencies of that publication are extreme and an embarrassment to the peer-review process. That study could identify only six papers examining the question, and astonishingly, prospective trial data were not included. The qualitative ‘sign test’ was applied, a statistical method that is inappropriate when quantitative data are available. Even ignoring that basic issue, the test was applied to such a small set of studies that it could not possibly have yielded a significant result. In other

words, even if every individual study showed strong prognostic value for sentinel node biopsy, this so-called ‘meta-analysis’ would be nonsignificant. The third study that was cited actually states that ‘SLN [sentinel lymph node] status combined with the clinico-pathologic features produced the best prediction or relapse and survival’.

As Sladden *et al*. feel ‘it is not clear whether sentinel node status is a better prognostic indicator than Breslow thickness and ulceration combined, and if so by how much’, we refer them to level I evidence from two prospective, multicentre clinical trials and multivariable analyses that address precisely that question. Both show virtually identical results, with one (the Sunbelt trial) showing a hazard ratio of 2.763 ($P < 0.0001$)[5] and the other (MSLT-I) showing a hazard ratio of 2.40 ($P < 0.001$).[1] In both trials nodal tumour status predictions were independent of Breslow thickness and ulceration. In both trials nodal tumour status provided the largest hazard ratio among all examined factors. A clearer, more consistent and more significant result would be hard to imagine.

They appear to question the value of reducing disease recurrences in patients with melanoma, which suggests that they may be unfamiliar with treating such patients. Their illustrative materials concerning survival are, at best simplistic, at worst misleading and support their passionate but data-less convictions. These cartoons are also seriously confusing (e.g. all of the curves appear to end in ‘Death’ at the right-hand side of the drawings). It appears they are suggesting that the only difference between the two arms of the trial is the timing of removal of nodal metastases, and that the two arms are therefore really the same. In this, they are partly correct. Indeed, much of the disease-free survival advantage was due to early removal of nodal metastases that could lead to recurrence; but that is precisely the point. Delaying treatment of nodal metastases did not change the proportion of patients with such disease. However, it did increase the extent of their disease, the morbidity of treating that disease, and the likelihood of dying of it.

The assertion that the experiences of the patients with nodal recurrence in the observation arm are the same as the patients with sentinel node metastases contradicts another of their ‘beliefs’ contained in the curious concept of ‘false-positive’ sentinel nodes. While errors in pathological diagnosis are possible, all sentinel lymph nodes from patients in MSLT-I were centrally reviewed by highly experienced melanoma pathologists to confirm the presence of melanoma cells and ensure quality control. This certainly contributed to the accuracy of identifying patients with nodal metastases and helped ensure that there was no detectable difference in the frequency of nodal metastasis between the two arms. Identification of ‘false-positives’ would require an imbalance in the frequency of nodal metastases, which was not found. The data of MSLT-I therefore provide no support for the theory of pathological false-positivity.

Sladden *et al*. consider that a specific examination of the subgroup of node-positive patients is ‘invalid’. However, from a biological standpoint, this comparison is the only subgroup analysis that makes sense. The treatment (lymphadenectomy) is targeted at lymph node metastases. Removal of tumour-free lymph nodes provides staging data, but cannot be therapeutic. Because four of every five patients in MSLT-I were node-negative and event rates were correspondingly low, the trial lacked the statistical power to demonstrate

significance for the 3.1% absolute improvement in survival seen in the sentinel node biopsy group at 10 years. Separating groups based on lymph node tumour status reveals the exact result expected for a targeted therapy: no effect on the group without the target but a 20.6% absolute survival benefit (44% relative risk reduction) in the node-positive group.

We fully understand the potential for bias in comparing groups that cannot be prospectively defined at randomization and went to great lengths to try to identify and account for any such bias. The latent subgroup methodology which causes Sladden *et al*. concern has been reviewed and published in well-regarded statistical journals and was specifically requested by the editors of the *New England Journal of Medicine* as it was the best way to provide a statistically valid comparison.[11,12] This methodology, and the computing power needed to perform it, were not available in 1992 when the trial was initiated. However, its novelty and complexity do not undermine its validity, particularly given the magnitude of the supporting evidence.

Reasonable people can differ on whether this trial provides ‘proof’ of a survival benefit. We feel that a large preponderance of the evidence from MSLT-I and a large volume of prior clinical data strongly favour a substantial survival benefit for node-positive patients, but some may feel that more evidence of that effect would be necessary for absolute proof. Such evidence is unlikely to be forthcoming. The obvious and clearly demonstrated benefits of this minimally invasive procedure for staging, determination of prognosis and regional disease control preclude any possibility of additional clinical trials evaluating the survival question. No responsible ethics board would sanction a study that denied sentinel lymph node biopsy to patients with intermediate-thickness melanomas. Nor would any reasonable, informed patient accept withholding of sentinel node biopsy.

The published data from MSLT-I now require more than ‘belief’ to justify denying patients access to sentinel lymph node biopsy. Failure to recommend this technique to appropriate patients with melanoma whose survival may depend on information obtainable only by sentinel lymph node biopsy raises important ethical questions that cannot be ignored.

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