Sentinel node biopsy should not be the standard of care for patients with intermediate and thick melanomas

We wish to reply to the viewpoint by Spillane, Read and Thompson (AFP August 2015).1 The National Health and Medical Research Council (NHMRC) guidelines recommend that ‘patients with a melanoma greater than 1.0 mm in thickness be given the opportunity to discuss sentinel node biopsy (SNB) to provide staging and prognostic information’.2 However, the recommendation is only level C and therefore not a promotion. It is a huge and erroneous leap of faith to move from discussing SNB as a potential patient option to asserting that SNB should be ‘standard of care’. Based on current evidence, SNB should not be the ‘standard of care’.3,4

It is incomprehensible that the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I)5 would be used to promote SNB given the trial found no survival benefit of any kind for patients undergoing SNB for melanoma. Claims made in the final MSLT-I report regarding survival benefit or disease-free survival have been comprehensively and systematically criticised and found to be misleading.6 An accompanying editorial went even further, stating that ‘MSLT-I provides no evidence of improved melanoma-specific survival associated with sentinel node biopsy and elective lymph node clearance’ and ‘The claim that SNB prolongs disease-free survival is disingenuous’, and asking ‘How did they [MSLT-I report authors] get away with this?’7

Breslow thickness, ulceration, mitotic rate, vessel invasion, tumour site, age and sex are already available as useful prognostic indicators, not requiring a separate, invasive surgical procedure.8 It is doubtful that SNB adds much value over clinical staging for most patients, especially given the added cost of anaesthesia and an acknowledged 5–10% surgical morbidity.7

Finally, Spillane et al state the importance of SNB in the recruitment of patients for new drug trials. However, SNB is expensive, costing $15,000 per procedure in the US; has a high number of false positive (approximately 24%)9 and false negative (approximately 10%)10 results; and has significant morbidity (approximately 10% for SNB in MSLT-I, increasing to 37% for patients who proceeded to have complete lymphadenectomy).11 Using expensive and invasive screening tests to recruit patients into clinical trials is a paradigm shift in research methodology. SNB may not be the best criterion for trial recruitment.

In summary, SNB does not improve mortality, may not add much value over clinical staging for most patients, and has the added cost of anaesthetic and surgical morbidity. Based on current evidence, SNB should not be the standard of care for patients with melanoma.

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References

MSLT-I: Comparing apples to antelopes

We challenge the recent article by Spillane, Read and Thompson, ‘Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas’ (AFP August 2015).1

In the final trial report of sentinel-node biopsy versus nodal observation in melanoma (MSLT-I), Morton et al claimed that the 10-year melanoma-specific survival was significantly higher in the sentinel lymph node biopsy (SLNB) group than the control group for intermediate thickness melanomas.2 In fact, this statistical significance was only achieved by excluding patients lost to follow-up.2,3

Also, the definition of disease-free survival in the MSLT-I trial gave a fundamental ‘advantage’ to the treatment arm of the study.4 Patients in the SLNB group who had positive biopsies were
subjected to lymphadenectomy and were then declared ‘disease-free’ from the moment of treatment of this first metastasis. Patients in the control arm of the study were declared ‘diseased’ from the moment of their first metastasis and thereafter. Clearly, this limits the validity of the study’s conclusions because, arguably, it is like comparing apples to antelopes.

A recent assessment of SLNB in the draft UK guidelines for assessment and treatment of melanoma notes that the final MSLT-I report was of only moderate quality.4 Moreover, the authors made the point that it was seriously limited by ‘a risk of bias due to selective outcome reporting’. MSLT-I is indisputably a negative study because it failed to demonstrate a difference in overall survival between the treatment and control groups,2,3 this being the prospectively declared primary outcome of the study. A negative study is valid if the negative findings are reported. In this case these were not reported and nor was the ‘morbidity of procedures’, this being one of the prospectively declared secondary outcome measures.5

The role of SLNB in routine practice is not established as the standard of care. Although it may give limited prognostic information and eligibility for some trials, we strongly believe patients may be harmed by uncritical endorsement of the final report of the MSLT-I trial.

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Reply
We wish to comment on the use of sentinel node biopsy (SNB) in patients with clinically localised primary cutaneous melanomas in response to the opinions expressed in the letters from Zagarella et al and Azzopardi, Clark and Rosendahl. These opinions run contrary to the views of the vast majority of clinicians around the world who care for patients with melanoma, and are also at odds with the guidelines issued by the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO), the world’s largest and most respected medical oncology and surgical oncology societies, respectively.1

The referral of melanoma patients to a surgical oncologist enables a discussion of the potential benefits and risks of SNB. Pathological examination of sentinel nodes enables early identification of stage III melanoma, and is more significant in determining prognosis than any individual primary tumour characteristic, or any combination of them.2 Most patients want to know whether they have stage III disease and whether they might benefit from further treatment, particularly completion lymph node dissection. As well, SNB-positive patients have a poor prognosis, and consequently are eligible for enrolment in adjuvant systemic therapy trials today. These trials use agents that already have a proven benefit in the metastatic setting.3–5 Zagarella et al greatly overplayed the morbidity of SNB, which even if it occurs, is usually minor and short-lived. Within high-volume specialist melanoma units, complication rates are now very low.4 But in any case, potential morbidity can be more accurately discussed with the patient after clinical examination and pre-operative lymphatic mapping, when both patient-related and anatomical factors can be considered.

The viewpoint we presented recently in Australian Family Physician documents the compelling arguments for the use of SNB in patients with intermediate and thick melanomas.7 This issue should no longer be one of semantics over the validity of the peer-reviewed statistical technique that was used to compare non-randomised patient groups in the large MSLT-I trial. This was reported after rigorous peer review in the highly respected New England Journal of Medicine.8 To not refer patients for a discussion of SNB with a clinician who is skilled in the technique and in the management of patients with stage III melanoma is unacceptable because the existing, overwhelming evidence is that SNB is a safe, minimally invasive procedure that provides highly accurate staging and allows the identification of high-risk patients who could benefit from further therapy.

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5. ClinicalTrials.gov. Efficacy study of nivolumab compared to ipilimumab in prevention of recurrence of melanoma after complete resection of stage IIb/c or stage IV melanoma (CheckMate 238). Available at https://clinicaltrials.gov/ct2/show/ NCT02388906 [Accessed 13 October 2015].

**Sentinel node biopsy for melanoma: The medical oncology perspective**

We wish to comment on the recent article by Spillane, Read and Thompson (AFP August 2015) discussing the role of sentinel node biopsy (SNB) for intermediate and thick primary melanoma.

Melanoma is a major component of cancer mortality in Australia. In patients with clinically localised melanoma, sentinel node status is the strongest predictor of outcome, more important than any primary melanoma factors alone or in combination.3,4

SNB-positive patients (ie those with micrometastatic nodal disease) have up to a 50% chance of death within five years. In recent years, new systemic therapies have resulted in an unprecedented improvement in survival for patients with the advanced disease. The next phase of this revolution in patient care is to apply these drugs in the adjuvant setting to high-risk (node positive) patients, to increase the chance of long-term cure. At present, there is no effective adjuvant systemic therapy, but several adjuvant trials of new therapies highly active in the metastatic setting are open to node positive patients (including SNB positive). Given the poor prognosis of SNB-positive patients, enrolment in an adjuvant clinical trial is now the standard of care.

Nodal involvement also triggers more intensive surveillance for metastatic disease during follow-up. Although high-level evidence for surveillance of this high-risk group is lacking, this evidence may never be available because of the complexity of designing the necessary randomised clinical trials. However, increasing consensus opinion favours regular staging scans in node positive patients for the early years after diagnosis, when most recurrences occur.3–11

It concerns us that misinformation regarding SNB may deny patients, without their informed consent, accurate prognostic information for personal planning and follow-up, and deny participation in clinical trials of potentially curative therapy.

We hope that the vested interests of particular craft groups will not prevent or delay evaluation of new therapies that may substantially reduce mortality from this disease. We share the view of major national and international groups that SNB should be considered the standard of care for patients with intermediate or thick primary melanoma, to complete not only staging for prognosis, but also to enable access to clinical trials and, in the near future, standard therapy that is expected to improve survival.

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we believe that a full, balanced discussion of the advantages and disadvantages of SNB should be presented to all patients who could possibly benefit from the procedure, by a clinician who has experience both with the procedure and in melanoma management. Patients should not be denied informed choice or the opportunity to discuss options in the management of their melanoma.

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References


Erratum

Hope J, Keks N. Chronic schizophrenia and the role of the general practitioner. Aust Family Physician 2015;44:802-08.

Due to a production error, there was a misprint in Table 2. The dose of aripiprazole depot was incorrectly listed as 300–400 mg every 2 weeks. The correct dose is 300–400 mg every 4 weeks. The correction has been made to the HTML and PDF versions of this article.

We apologise for this error and any confusion this may have caused our readers.

Letters to the editor

Letters to the editor can be submitted via:

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