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 biospsy (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 MLST-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.

Samuel Zagarella FACD, Clinical Associate Professor of Dermatology, University of Sydney Medical School, NSW

Michael Sladden MRCP, Associate Professor, Department of Medicine, University of Tasmania, TAS

Catalin Popescu MD, Associate Professor of Dermatology, Carol Davila University of Medicine and Pharmacy, Romania

Peter Heenan FRCPath, FRCPA, Clinical Professor of Pathology, University of Western Australia, WA

Michael Bigby MD, Associate Professor of Dermatology, Harvard Medical School, Boston, MA

References

1. Spillane A, Read R, Thompson JF. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician 2015;44:604–06.
2. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Wellington: Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, 2008.
3. Sladden M, Foley P, Stanford D, Zagarella S, Reid C. Sentinel node biopsy: Not the standard of care for melanoma. J Am Acad Dermatol 2010;62:708–09.
4. Dixon A, Anderson S, Steinman H, et al. Sentinel lymph node biopsy now has a limited role in melanoma management. Aust Fam Physician 2014;43:479–80.
5. 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.
6. Sladden M, Zagarella S, Popescu C, Bigby M. No survival benefit for melanoma patients undergoing sentinel node biopsy: Critical appraisal of the multicenter selective lymphadenectomy trial-I final report. Br J Dermatol 2015;172:566–73.
7. McGregor JM, Sasieni P. Sentinel node biopsy in cutaneous melanoma: Time for consensus to better inform patient choice. Br J Dermatol 2015;172:552–54.
8. Mitra A, Conway C, Walker C, et al. Melanoma sentinel node biopsy and prediction models for relapse and overall survival. Br J Cancer 2010;103:1229–36.
9. Thomas JM. Prognostic false-positivity of the sentinel node in melanoma. Nat Clin Pract Oncol 2008;5:18–23.
10. Scoggins CR, Martin RC, Ross MI, et al. Factors associated with false-negative sentinel lymph node biopsy in melanoma patients Ann Surg Oncol 2010;17:709–17.
11. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: Accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005;242:302–13.

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.[3] 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.[5] 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.

John Azzopardi MMed (skin cancer) candidate, School of Medicine, University of Queensland, QLD

Simon Clark, Dermatopathologist, DHM Pathology – Skin Laboratory, Macquarie Park, NSW

Cliff Rosendahl, Capalaba General Practice, QLD; School of Medicine, University of Queensland, QLD

References

1. Spillane A, Read R, Thompson J. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician 2015;44:604–06.
2. 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.
3. Sladden M, Zagarella S, Popescu C, Bigby M. No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: Critical appraisal of the Multicenter Selective Lymphadenectomy Trial-I final report. Br J Dermatol 2015;172:566–571.
4. National Collaborating Centre for Cancer. Melanoma: Assessment and management of melanoma. London: NICE, 2015. Available at www.nice.org.uk/guidance/gid-cgwave0674/resources/melanoma-draft-guideline2 [Accessed 25 August 2015].
5. ClinicalTrials.gov. Multicenter Selective Lymphadenectomy Trial (MSLT). Washington, DC: US National Institutes of Health, 2015. Available at https://clinicaltrials.gov/ct2/show/NCT00275496?term=NCT00275496%26rank=1 [Accessed 23 August 2015].

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.[6] 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] The 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.

Andrew Spillane, Associate Professor of Surgical Oncology, University of Sydney; Surgical Oncology, Royal North Shore and Mater Hospitals, NSW

Rebecca Read, Poche Fellow in Melanoma and Surgical Oncology, Melanoma Institute Australia, NSW

John Thompson, Professor of Melanoma and Surgical Oncology, Melanoma Institute Australia, NSW

References

1. 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;30:2912–18.
2. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.
3. ClinicalTrials.gov. A study of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection. (COMBI-AD). Available at https://clinicaltrials.gov/show/NCT01682083 [Accessed 13 October 2015].
4. ClinicalTrials.gov. Efficacy study of ipilimumab versus placebo to prevent recurrence after complete resection of high risk stage III

melanoma. Available at https://clinicaltrials.gov/ct2/show/NCT00636168 [Accessed 13 October 2015].
5. ClinicalTrials.gov. Efficacy study of nivolumab compared to ipilimumab in prevention of recurrence of melanoma after complete resection of stage IIIb/c or stage IV melanoma (CheckMate 238). Available at https://clinicaltrials.gov/ct2/show/NCT02388906 [Accessed 13 October 2015].
6. Read RL, Pasquali S, Haydu L, et al. Quality assurance in melanoma surgery: The evolving experience at a large tertiary referral centre. Eur J Surg Oncol 2015;41:830–36.
7. Spillane A, Read R, Thompson. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician 2015;44:604–06.
8. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. NEJM 2014;370:599–609.

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.[1]

Melanoma is a major component of cancer mortality in Australia.[2] 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.[5] In recent years, new systemic therapies have resulted in an unprecedented improvement in survival for patients with the advanced disease.[6–8] 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.[9–11]

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.

Alexander M Menzies, Senior Research Fellow, Medical Oncologist, Melanoma Institute Australia, Royal North Shore Hospital and University of Sydney

Victoria G Atkinson, Medical Oncologist, Senior Staff Specialist, Princess Alexandra Hospital; Visiting Medical Oncologist, Greenslopes Private Hospital; Senior Lecturer, University of Queensland

Michael P Brown, Director, Cancer Clinical Trials Unit and Senior Medical Oncologist, Royal Adelaide Hospital; Clinical Professor in Medicine, University of Adelaide

Matteo S Carlino, Medical Oncologist, Crown Princess Mary Cancer Centre Westmead, Melanoma Institute Australia and University of Sydney

Jonathan Cebon, Professor, Medical Oncologist, Medical Director, Olivia Newton-John Cancer Wellness & Research Centre, Austin Health, University of Melbourne and LaTrobe University.

Alexander Guminski, Associate Professor, Medical Oncologist, Royal North Shore Hospital, Melanoma Institute Australia and University of Sydney

Richard F Kefford, Professor of Cancer Medicine and Head, Department of Clinical Medicine at Macquarie University; Honorary Professor in Medicine at University of Sydney; Co-Director of Research at Melanoma Institute Australia; Medical Oncologist at Crown Princess Mary Cancer Centre Westmead and Macquarie University Hospital

Georgina V Long, Associate Professor Melanoma Biology and Translational Research, Medical Oncologist, Melanoma Institute Australia and University of Sydney

Grant McArthur, Professor, Medical Oncologist; Director Melanoma and Skin Service, Peter MacCallum Cancer Centre; Lorenzo Galli Chair in Melanoma and Skin Cancers, University of Melbourne.

Catriona M McNeil, Clinical Associate Professor and Medical Oncologist, Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, Melanoma Institute Australia and University of Sydney

Michael Millward, Winthrop Professor and Cancer Council Professor of Clinical Cancer Research at University of Western Australia; Consultant Medical Oncologist at Sir Charles Gairdner Hospital

Shahneen Sandhu, Medical Oncologist, Melanoma and Skin Service, Peter MacCallum Cancer Centre

References

1. Spillane A, Read R, Thompson J. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician 2015;44:604–06.
2. Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. Cancer in Australia: An overview. Canberra: AIHW, 2008.
3. Azimi F, Scolyer RA, Rumcheva P, et al. Tumor-infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and survival in patients with cutaneous melanoma. J Clin Oncol 2012;30:2678–83.
4. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clinical Oncol 2009;27:6199–206.
5. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. New Engl J Med 2014;370:599–609.
6. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444–51.
7. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
8. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–32.

9. Garbe C, Hauschild A, Volkenandt M, et al. Evidence and interdisciplinary consense-based German guidelines: Diagnosis and surveillance of melanoma. Melanoma Res 2007;17:393–99.
10. Dummer R, Hauschild A, Guggenheim M, et al. Melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v194–97.
11. NCCN Clinical Practice Guidelines in Oncology. Melanoma. Version 3. 2015. Available at www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf [Accessed 13 October 2015].

Sentinel node biopsy in patients with intermediate and thick melanomas – A balanced view

We wish to comment on the recent articles regarding sentinel node biopsy (SNB) in melanoma patients,[1,2] and the letter by Zaggarella et al (*AFP* December 2015). The summary of the international Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) presented by Spillane, Read and Thompson (*AFP* August 2015)[2] represents an accurate assessment of the data. The 2014 final analysis article in the *New England Journal of Medicine*[3] confirms the prognostic and staging value of SNB for high-risk melanomas. It confirms that SNB is a minimally invasive diagnostic test, and as such it identifies patients who could benefit from early lymph node dissection to control regional disease, with lesser morbidity. In the current era of new systemic drug options for melanoma, it also identifies patients who could participate and benefit from adjuvant trials of systemic therapy.

Furthermore, SN mapping provides an opportunity to identify the site of the most likely nodal metastasis for a primary melanoma and represents an opportunity to evaluate the SN, whether by SNB or with serial ultrasound assessment.

As recommended in the *Clinical practice guidelines for the management of melanoma in Australia and New Zealand*,[4] 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.

Robyn Saw MS, FRACS, Senior Lecturer, University of Sydney; Head of Department Melanoma and Surgical Oncology Royal Prince Alfred Hospital; Melanoma Institute Australia, NSW

Christopher Allan MPhil, FRACS, Consultant Melanoma and Endocrine Surgeon, Mater Hospital Brisbane, QLD

Andrew Barbour FRACS, FACS, Upper GI/Soft Tissue Unit, Princess Alexandra Hospital and Head Surgical Oncology Laboratory, Discipline of Surgery, University of Queensland, QLD

Sydney Ch'ng PhD, FRACS, Associate Professor of Surgery, University of Sydney; Consultant Plastics and Head and Neck Surgeon, Royal Prince Alfred Hospital; Melanoma Institute Australia, NSW

Brendon J Coventry BMBS, PhD, FRACS, FACS, FRSM, Associate Professor of Surgery, University of Adelaide; Surgical Oncologist Royal Adelaide Hospital, SA

David Gyorki MD, FRACS, Herman Fellow in Clinical Cancer Research, Department of Surgery, University of Melbourne; Consultant Surgical Oncologist, Peter MacCallum Cancer Centre, VIC

Michael Henderson BMedSc, MD, FRACS, Professor of Surgery, University of Melbourne; Deputy Director Division of Cancer Surgery, Co-Head Skin and Melanoma Service, Peter McCallum Cancer Centre, VIC

Julie Howle FRACS, Clinical Senior Lecturer, University of Sydney; Head of Melanoma and Sarcoma Groups, Westmead Hospital, NSW

T. Michael Hughes FRACS, Surgical Oncologist; Associate Professor of Surgery, University of Sydney, NSW

Kenneth Lee FRACS, Consultant Plastic Surgeon, Royal Prince Alfred Hospital; Melanoma Institute Australia, NSW

Susan Neuhaus PhD, FRACS, Clinical Associate Professor Department of Surgery, University of Adelaide, SA

Christobel Saunders FRCS, FRACS, Winthrop Professor of Surgical Oncology, Head of Unit (General Surgery) School of Surgery, Fiona Stanley Hospital, Murdoch, WA; Harry Perkins Institute of Medical Research, WA

Kerwin Shannon FRACS, Consultant Head and Neck Surgeon, Royal Prince Alfred Hospital and Melanoma Institute Australia, NSW

Mark Smithers FRCS FRACS, Director, Upper GI/Soft Tissue Unit, Princess Alexandra Hospital and Mayne Professor, Head, Discipline of Surgery, University of Queensland, QLD

David Speakman FRACS, Consultant Melanoma and Breast Surgeon, Department of Surgical Oncology, Peter MacCallum Cancer Centre; Executive Director Clinical Services, Peter MacCallum Cancer Centre, VIC

John Spillane FRACS, Consultant Melanoma and Upper Gastrointestinal Surgeon, Department of Surgical Oncology, Peter MacCallum Cancer Centre, VIC

Jonathan Stretch DPhil(Oxon), FRACS, Associate Professor of Surgery, University of Sydney; Consultant Melanoma Plastic Surgeon, Royal Prince Alfred Hospital; Melanoma Institute Australia, NSW

References

1. Dixon A, Anderson S, Steinman H, Nirenberg A. Sentinel lymph node biopsy now has a limited role in melanoma management. Aust Fam Physician 2014;43:479–80.
2. Spillane A, Read R, Thompson JF. Sentinel node biopsy should be the standard of care for patients with intermediate and thick melanomas. Aust Fam Physician 2015;44:604–06.
3. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599–609.
4. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Wellington: Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, 2008.

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:
Email: afp@racgp.org.au
Mail: The Editor, *Australian Family Physician*
100 Wellington Parade
East Melbourne VIC 3002 Australia