Routine usage of sentinel node biopsy in melanoma management must cease

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Sentinel lymph node biopsy (SNB) was first popularized in the 1990s because it might save lives. The multicenter selective lymphadenectomy trial (MSLT) demonstrated that SNB and subsequent completion lymphadenectomy (CL) do not improve either five year\(^1\) or ten year\(^2\) melanoma specific survival.

SNB is expensive and can affect ongoing quality of life. Complication rates of 10\(^\%\)^3 can include anaphylaxis, persistent seroma\(^4\), lymphedema\(^4\), tattooing at primary site from dye\(^5\), mobility impairment\(^5\)\(^6\), recurrent infection\(^4\), chronic site pain\(^5\), joint pain\(^6\) and nerve damage\(^4\).

SNB is still offered because it can provide added prognostic information in a subset of melanoma patients. Even when the test is offered, it is important that those who are found to be SNB positive do not then progress to CL. SNB has a role as test but subsequent CL is disproven as a therapy.

Now melanoma patients are being urged to undergo SNB for inclusion in clinical trials. Our significant ethical concern is that high risk primary melanoma patients could be “den(ied) participation in clinical trials of potentially curative therapy”\(^7\) because they choose not to have a further surgical procedure that has no survival impact. Surely cancer patients should only be encouraged to undertake procedures and therapies that have a demonstrated therapeutic benefit.

Pathology assessment of excised melanomas alone provides an array of accurate mortality prognostic information. This includes; Breslow thickness (HR [hazard ratio] 1.59 per one mm increase\(^2\) (95\%CI 1.21 – 2.09), ulceration (HR 1.79\(^2\) (95\%CI 1.24 – 2.58), tumour site (trunk HR 1.91\(^2\) (95\%CI 1.26 – 2.88), vascular invasion, age (HR 1.01 per year\(^2\) (95\%CI 0.99 – 1.02) and mitotic activity (HR 1.039\(^8\)). SNB positivity\(^2\) is associated with a hazard ratio of 2.4 (95\%CI 1.61 – 3.56). It is yet to be demonstrated and seems implausible that SNB, requiring a separate surgical procedure, is necessary to identify patients for drug trials rather than an algorithm of all information obtained from excision alone.

When some current pharmaceutical trials were developed and commenced there were realistic prospects that SNB would be confirmed with a therapeutic benefit in its own right. Hence it was reasonable at that stage to select SNB for a role in identifying high risk melanoma patients for experimental drug trials. But the prospect of SNB having a therapeutic benefit ended when the MSLT final results were published in 2014.\(^1\) Two years after the final MSLT data, some current clinical trials continue to accept patients with early occult sentinel lymph node involvement but will not accept high risk
melanoma patients who choose not to have SNB. In addition they exclude some high risk patients with a false negative SNB.

Examples of such clinical trials include; NCT01682083, NCT01972347, and ACTRN12613000737730. These trials will accept very low risk patients with thin primary melanoma so long as they have a positive SNB. Alarmingly these trials also require patients to have CL. The patients must have major surgery that has been demonstrated to not significantly improve their survival in order to get a drug that might benefit their survival. This has major ethical issues for both current patients and future patients through applicability of study results.

We are concerned patients are encouraged or required to have SNB to enter trials\(^7\). If this is the key reason for the surgery, and not improved health outcomes, then health insurers, Governments and patients should be alerted to the ethical, equity and financial issues arising from such a clinical trial design.

If these trials demonstrate a benefit for the intervention, then applicability may be erroneously restricted to those having positive nodes. This could cement a clinical role for a procedure without proven survival value, and will thus have far-reaching ethical and resource allocation implications for future patients who may be able to benefit from new interventions. Patients who decline to have unnecessary surgery (SNB) could then be denied access to drugs that may be able to treat their disease.

Like other authors, we are concerned about inappropriate influence on our patients by practitioners with vested interests\(^9\). Any practitioner still routinely encouraging patients to have SNB and gaining financially from SNB has a conflict of interest. We are therefore concerned by the suggestion that, “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”\(^9\). We are similarly concerned by the suggestion that “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 . . .”\(^10\).

Any clinician managing melanoma should have adequate knowledge of all current forms of melanoma diagnosis and management, including skills in dermoscopy (as the highest risk to most patients is the development of a new primary melanoma,) knowledge of the current recommendations for surgical care and an awareness of current medical oncology and radiation oncology options.. To suggest that melanoma patients must have a discussion with practitioners having a SNB conflict of interest is clearly untenable. It is noted that many of the authors\(^9, 11\) to these suggestions appear to have such a conflict.

Indeed health economists must now reconsider whether limited public health resources should still be extended to SNB on melanoma patients. Those choosing to have the added prognostic advice can choose to incur the costs of such added information and accept the 10% adverse outcomes risk\(^3\).
Public funding currently spent on SNB could possibly now be better directed to provision of therapeutic agents such as pembrolizumab, ipilimumab, nivolumab, dabrafenib, trametinib and vemurafenib. These agents have demonstrated clear benefits for our metastatic melanoma patients

SNB is a disproven therapeutic procedure. If an intervention has the same long term survival prospects as observation then observation must be considered “standard of care”.

**Recommendations for recruitment in melanoma adjuvant therapy trials:**
- Patients without clinical nodal or distant metastatic disease should no longer be required to have SNB for recruitment.
- Patients choosing observation must be considered for entry into melanoma therapeutic trials.
- Ethical oversight of current studies should be advised the entry into clinical trials need not require the use of surgery that has no influence on survival.
- Instances where patients choosing observation are denied or would be denied trial entry should be formally reported to trial ethics committees.

References


Declaration: Author AD has experience with the SNB procedure, but chose to cease performing the operation when its usage became dubious. Author JD is a clinical researcher who does not manage melanoma