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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. However, the Multicenter Selective Lymphadenectomy Trial (MSLT) demonstrated that SNB and subsequent completion lymphadenectomy do not improve either 5-year[1] or 10-year[2] melanoma-specific survival.

Sentinel lymph node biopsy is expensive and can affect ongoing quality of life. Complication rates of 10%[3] can include anaphylaxis,[4] persistent seroma,[5] lymphoedema,[5] tattooing at the primary site from dye,[6,7] mobility impairment,[7,8] recurrent infection,[5] chronic site pain,[7] joint pain[8] and nerve damage.[5]

Sentinel lymph node biopsy is still offered because it can provide added prognostic information in a subset of patients with melanoma. But now patients with melanoma are being urged to undergo SNB for inclusion in clinical trials. Our significant ethical concern is that patients with high-risk primary melanoma could be 'den[ied] participation in clinical trials of potentially curative therapy'[9] because they choose not to have a further surgical procedure that has no survival impact. Surely patients with cancer should be encouraged to undertake procedures and therapies only when they have a demonstrated therapeutic benefit.

Pathological assessment of excised melanomas alone provides an array of accurate mortality prognostic information. Such prognostic information includes Breslow thickness [hazard ratio (HR) 1·59 per 1 mm increase, 95% confidence interval (CI) 1·21–2·09],[2] ulceration (HR 1·79, 95% CI 1·24–2·58),[2] tumour site (trunk HR 1·91, 95% CI 1·26–2·88),[2] vascular invasion, age (HR 1·01 per year, 95% CI 0·99–1·02)[2] and mitotic activity (HR 1·04).[10] 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 using 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 to have a therapeutic benefit in its own right. Hence it was reasonable at that stage to select SNB for a role in identifying patients with high-risk melanoma for experimental drug trials. However, 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 patients with high-risk melanoma 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 as long as they have a positive SNB. Alarmingly these trials also require patients to have completion lymphadenectomy. The patients must have major surgery that has been demonstrated not to improve their survival significantly, in order to get a drug that might benefit their survival. Requiring an ineffective survival intervention in order to enter a trial for a novel therapy has major ethical issues for both current patients and future patients through applicability of study results.

We are concerned that patients are encouraged or required to have SNB to enter trials.[9] If prospects of enrolment in trials are 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. We may find that we develop a cemented clinical role for a procedure without proven survival value, which 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'.[11] 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'.[12]

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 the current medical oncology and radiation oncology options. To suggest that patients with melanoma

must have a discussion with practitioners having an SNB conflict of interest is clearly untenable. It is noted that many of the authors[11,12] of 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 in patients with melanoma. 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.[2]

The 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 patients with metastatic melanoma.

Sentinel lymph node biopsy is a disproven therapeutic procedure. If an intervention has the same long-term survival prospects as observation, then observation must be considered the '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.
- Instances where patients choosing observation are denied or would be denied trial entry should be formally reported to trial ethics committees.

Conflicts of interest

A.D. has experience with the sentinel node biopsy procedure, but chose to cease performing the operation when its usage became dubious. J.D. is a clinical researcher who does not manage melanoma.

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