**Sentinel node biopsy now has limited role in melanoma management**

**Introduction:**

Sentinel lymph node biopsy (SLNB) became popular in managing melanoma once it became apparent that routine block nodal dissection for all melanoma patients was not helpful. Complication rates were high and the majority of melanoma patients had no nodal disease when the nodal basin was examined by pathologists.

The concept of SLNB is that blue dye and/or radioactive tracer is injected around the site of the primary melanoma on the skin. The dye/tracer finds its way through the lymphatic system to regional drainage lymph nodes. The initial node or nodes that demonstrates radioactive activity and/or blue colour change are then resected through a minimal incision site.

This node(s) is then examined for evidence of early melanoma metastasis. The concept was that if this node proved tumour positive, then and only then would the rest of the nodes in that nodal basin be removed. This concept meant that block nodal dissection was only undertaken on those selected patients who had demonstrated that they had disease worthy of such surgery. It was an exciting concept and most involved in managing melanoma expected melanoma patients would benefit.

Fortunately this idea was then subjected to a very large prospective randomized controlled trial (RCT) to determine whether the theoretical advantages would be realised. The study, known as the multicentre selective lymphadenectomy trial (MSLT), involved melanoma units throughout the world including several Australian melanoma units.

**10 year MSLT study now published:**

This large MSLT study of 2001 melanoma patients has now been published. In this RCT intervention patients had a SLNB and then if positive they progressed to regional completion lymphadenectomy (CL). Observation patients underwent delayed lymphadenectomy if nodal disease developed during observation. The primary hypothesis of the study was that intervention would improve 5 year and 10 year survival for melanoma patients.
**MSLT trial findings:** The primary end point was melanoma specific survival. On an intention to treat (ITT) basis, there was no 10 year melanoma specific survival benefit for intervention patients, 77% versus 76% observation.

For intermediate thickness melanoma patients, (Breslow 1.2 to 3.5 mm), 10 year survival was 81.4±1.5% in the intervention group and 78.3±2.0% in observation group, - not significant p = 0.1.

For patients with thick melanoma patients (Breslow over 3.5 mm) there was also no significant 10 year survival difference, with observation patients having a survival of 64.4±4.6% versus the intervention group at 58.9±4.1% - not significant p = 0.56.

As such there was a trend in favour of intervention in the intermediate group and against intervention in the thick melanoma group. Neither trend was statistically significant.

Overall the survival of all melanoma patients over 1.2 mm Breslow followed the following disease specific survival KM curve. There is not even a signal for a melanoma specific survival advantage at 10 years.

**Complication rate:** 10% for SLNB. Most complications are minor and transient including haematoma, wound infections and transient seroma. However, serious and prolonged complications can occur including nerve damage and lymphoedema.

The complication rate is 37% for those proceeding on to CL. These larger block nodal dissections have a greater risk of the more serious complications.

**Disease free survival:**

A secondary trial end point was disease free survival. Of those patients surviving, there was a greater likelihood of being disease free in SLNB group. Of patients with intermediate thickness melanoma, the difference was 65% versus 71% at 10 years. This difference was apparent at 2 years into follow up. There was a hope when this difference emerged early in the trial that by 5 years and then 10 years this disease free advantage would translate into a survival benefit. Now we know no such melanoma specific survival benefit occurs. As such, the continuing value of this secondary end point finding is unclear and difficult to interpret.
These figures INCLUDE regional nodes. This analysis has been criticised by London Professor of Surgical Oncology Meirion Thomas who pointed out; "In patients with intermediate thickness tumours, the most likely site of first recurrence is to the regional nodes. In the biopsy arm of MSLT, a prophylactic lymphadenectomy had been performed as part of trial protocol in SN-positive patients. Therefore, inevitably, there would be more nodal recurrence as site of first recurrence in the observation arm."

Distant disease free survival: This data compares disease but excludes regional nodes for reasons above. This was specifically designed prospectively as a trial secondary end point and yet data was not reported on ITT basis in the NEJM manuscript. – This remains unexplained and appears a curious omission from this manuscript.

Melanoma is different to most cancers. SLNB and subsequent CL may seem logical to both the surgeon and the patient but this disease behaves differently. When squamous cell carcinoma is present in nodes it could be negligent not to offer further dissection. Surgeons have partially learnt to think differently about melanoma but a further (evidence-based) leap of faith away from traditional paradigms is now required.

SLNB as a predictor of survival:

SLNB was confirmed as a major predictor of survival for those patients with a melanoma between 1.2 and 3.5 mm thick. Hazard ratio for SLNB “+” ve being 2.64, p<0.001. Overall survival in this Breslow range was 78% at 10 years. This can be refined to a 70% survival for SLNB “+”ve versus 90% if SLNB “-”ve. Many intermediate thickness melanoma patients may wish to know this added prognostic information.

Sentinel node biopsy provides additional prognostic advice for melanoma patients who choose to be tested.

The three other survival predictors highlighted in this study were Breslow thickness, (Hazard ratio of 1.62 per mm), ulceration (HR 1.4) and site being on the trunk (HR 1.42). Of course you don’t need an added operation with a complication rate of 10% to obtain Breslow thickness, site or presence of ulceration. Doctors can check for themselves how these three shape survival prospects for their specific melanoma patients at www.melanomaprosnosis.org

None out of Gender, Age or Clark level were predictive of survival.

Comment:

Like all RCTs, the key data is the analysis on an intention to treat (ITT) basis. Sub-group or exploratory analyses of the original data may provide novel insights, generate new questions or provide some data supporting causal relationships, but are potentially problematic, and they cannot alter the study’s findings regarding the studies primary hypothesis and aim and of course the result derived from the primary outcome measure.

An unexpected, unwanted or challenging result always generates knee jerk responses of:

i) “The original design was flawed"

ii) “Let’s look at subgroups to find support for what we know to be true”

iii) “Yes, but we have come a long way since this study was designed – today the result would be different"
Melanoma patients should no longer be routinely encouraged to have further lymph node resections if their sentinel node biopsy test is positive.

We have seen examples of all three knee jerk responses. Perhaps the most absurd example is claims the trial was insufficiently powered to find a difference. This was a large study on 2001 patients and was correctly powered to detect a clinically relevant difference in mortality at 10 years, yet didn’t even provide a signal suggesting advantage in SLNB. We have seen a flurry of attempts to describe unplanned analyses outside of the ITT basis.

One curious sub analysis finding is that considerably more nodal involvement occurred in the intervention group (19.9%) versus the observation group (17.4%). The intervention group data on nodal involvement is predominantly made up of all patients positive on SLNB (15.9%) along with patients that were biopsy negative but later developed nodal disease (4%). The unexplained variation in a well matched patient population suggests a prognostic false positive rate of 2.5% in the intervention arm. This unexplained variation can account for many other puzzling sub analyses.

We have also heard suggestions that SLNB is “improved” on the techniques known when recruitment commenced.

Summary:

SLNB is confirmed as a prognostic test but does not influence melanoma specific survival at 10 years. SLNB “+”ve patients SHOULD be carefully counselled regarding the risks and very limited benefit (if any) in proceeding to CL.

SLNB should not be regarded as “essential” or “standard of care” for melanoma patients.

SLNB should be discussed with intermediate thickness melanoma patients. This discussion is a part of the current Australia and New Zealand NHMRC guidelines for melanoma management. This data suggest the guideline remains correct. Note that “discuss” is not “offer” or “recommend”.

The discussion should include:

- SLNB does not alter survival prospects
- SLNB provides added accuracy to survival prognostic figures
  - 70% Vs 90% for melanoma between Breslow 1.2 to 3.5 mm.
- SLNB has 10% complication rate
- If positive no added treatment can be offered that has demonstrated survival benefits.
  - This includes no apparent survival benefit in proceeding to CL.
- SLNB “+”ve patients can be offered enrolment into further melanoma studies

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References: