THE AUSTRALASIAN COLLEGE OF DERMATOLOGISTS

Sentinel Node Biopsy in 2020

A Guide for Australian Dermatologists

January 2020

How does melanoma spread?

For patients with metastatic melanoma, approximately 63% will develop regional lymph node disease, 24% will develop direct haematogenous spread and 13% will develop satellite deposits as their first site of metastasis.[1]

In the Multicenter Selective Lymphadenectomy Trial (MSLT-I), of the 179 Sentinel Node (SN) positive patients, 69 (39%) died from melanoma. Of the 759 SN negative patients, 119 (15.6%) died from melanoma.[2]

What is a sentinel node (SN) biopsy?

SN biopsy is a staging procedure which provides prognostic information in addition to thickness, ulceration and other clinicopathologic prognostic factors.

It is performed at the time of definitive Wide Local Excision (WLE) to achieve 1–2 cm margin.

The procedure involves pre-operative lymphoscintigraphy using radiolabelled tracer, followed by intra-operative intradermal injection of blue dye at site of primary tumour to identify the first draining lymph node (i.e. the sentinel node).

Who should be considered for SN biopsy?

The generally accepted threshold of risk to consider SN biopsy is a 5% chance of finding a positive SN.

Discuss with patients if melanoma > 1 mm thick OR 0.8 – 1 mm if there are additional poor prognostic features (presence of mitoses, ulceration or lymphovascular invasion or < 40 years old).

Definitive surgery (WLE + SNB) should be performed in a timely manner (i.e. within 6 weeks), however there is no substantial evidence that time to definitive surgery will impact survival.

NB. Non-ulcerated tumours (< 2 mm), with a positive SN will be stage IIIA (see note re adjuvant therapy below).

Factors which may alter accuracy of SN mapping (i.e. increase false negative rate)

Site. Tumours of the head and neck have an increased false negative rate due to complex lymphatic drainage. However, given the low morbidity from SN biopsy in head and neck cases, the procedure is generally still recommended.

Previous WLE of the primary tumour (i.e. with 1 – 2 cm margin). SN biopsy may not be recommended in cases excised with an already significant margin, depending on lymphatic drainage pattern at the site. Importantly, a narrow excisional biopsy will *not* increase risk of false negative SN biopsy.

Flap closure following excisional biopsy of the primary tumour. SN biopsy may not be recommended as the flap closure may preclude accurate lymphatic drainage assessment.

Significant wound breakdown and/or infection following excision of the primary tumour. SN biopsy may not be recommended.

Estimating a patient's risk of sentinel node involvement

Table 1. Statistically significant predictors of sentinel node involvement and associated rates of involvement (N=7756)[3]

Variable	Percent of patients* with SLN involvement
Age (years)	
< 40	21.3
40 - 59	20.0
> 60	17.6
Gender	
Male	20.7
Female	17.7
Location	
Head and neck	15.5
Upper limb	15.1
Trunk	21.3
Lower limb	22.3
Thickness (mm)	
≤ 1.0	6.0
1.01 – 2.0	14.0
2.01 – 4.0	27.3
> 4.0	39.1
Ulceration	
Absent	15.6
Present	29.9
Lymphovascular invasion	
Absent	17.3
Present	47.2

*Patient data from AJCC melanoma database. All patients were Stage I and II, presented without clinical evidence of regional lymph node or distant metastases and underwent a lymphatic mapping and SN biopsy as part of staging workup.

Refer to Page 6 for useful links to risk prediction tools.

What are the advantages and disadvantages of SN biopsy?

Table 2. Pros and cons of SN biopsy

Pros	Cons
Improved staging and prognostic information - Performs better than ultrasound at finding small deposits in the LN	Requires a general anaesthetic
Access to adjuvant therapies	Short term risks - Infection - Seroma
Access to trials	Longer term risks - lymphoedema (6% overall MSLT-II, risk higher for groin compared to axilla or neck) False negative (4% trunk/limbs, 20% H+N)

Factors to consider for patient selection

Patient age/performance status. Is the additional prognostic information meaningful?

Patient co-morbidities. Anaesthetic risk, contraindications to adjuvant therapies e.g. autoimmune disease

Patient suitability. Would the patient be suitable for adjuvant therapies? An MDT discussion may be needed to determine this.

Patient choice and preference. Is the patient interested in prognostic information or adjuvant therapy? Are they willing to accept the short and long term morbidities associated with the procedure for prognostic information and/or the potential benefits of adjuvant therapy?

What if the sentinel node is positive?

Following results from MSLT-II, completion lymph node dissection is no longer recommended in the majority of cases as this does not provide a survival benefit.[4]

Patients should be referred to a Medical Oncologist for discussion of adjuvant therapy if:

- **Stage IIIA** - patients cannot access adjuvant immunotherapy on the PBS. They may self-fund immunotherapy, however this would require careful consideration and discussion of the potential benefits and risks with a Medical Oncologist
- **Stage IIIB/C/D** - patients will have access to adjuvant *immunotherapy* (e.g. 0.8 mm non ulcerated melanoma with 2 SN positive, or >1mm ulcerated melanoma with 1 SN positive are Stage IIIB)
- **Stage IIIB-D BRAF mutant** - patients will have access to adjuvant *targeted therapy* on the PBS
- **Stage IIIA BRAF mutant -** patients cannot access targeted therapy on the PBS. There will be a payshare arrangement from 1 January 2020. This would require careful consideration and discussion of the potential benefits and risks with a Medical Oncologist

NB: Staging in accordance with AJCC 8th Edition

Patients will have closer imaging surveillance (i.e. PET/CT + MRI brain) during follow-up.

There is mounting evidence that patients with low burden metastatic disease are more likely to respond to systemic therapies (i.e. this phenomenon is not explained by lead time bias), therefore accurate staging with more aggressive surveillance strategies in high risk (Stage IIC – III patients) have become standard of care.

What is the current data on adjuvant drug therapies?

Both adjuvant immunotherapy and targeted therapy in SN positive patients improves relapse free survival.

Table 3 shows an overview of Phase 3 clinical trial data as of January 2020. Note that the staging used in these trials was in accordance with the AJCC 7th Edition, whereas staging to determine PBS eligibility is in accordance with AJCC 8th Edition.

Table 3. Overview of Adjuvant Trial Data as of January 2020

Immunotherapy	Targeted therapy
Ipilimumab vs placebo[5,6] • Stage IIIA (> 1 mm), B, C (not in-transit) • Median OS follow up 6.9 years • OS benefit observed in the Ipilimumab group was durable with an 8.7% absolute difference at 7 years for OS (HR 0.73; 95% CI, 0.60 - 0.89; P = 0.002)	**Dabrafenib + Trametinib vs placebo**[7] • Stage IIIA (> 1 mm), B, C • 4 year RFS was 54% (95% CI, 49% - 59%) vs 38% (95% CI, 34% - 44%), (HR 0.49; 95% CI, 0.40 - 0.59) • Distant metastases free survival (HR 0.53; 95% CI, 0.42 - 0.67) • Estimated cure rate was 54% (95% CI, 49% - 59%) in the Dabrafenib + Trametinib arm compared with 37% (95% CI, 32% - 42%) in the placebo arm
Nivolumab vs Ipilimumab[8] • Stage IIIB, C, resected IV • Median 36 month follow up • RFS benefit HR 0.68; 95% CI 0.56–0.82; p < 0.0001	
Pembrolizumab vs Placebo[9] • Stage IIIA (> 1 mm), B, C • HR = 0.57 for recurrence or death, (CI 0.43 to 0.74; P<0.001) • 15 months follow up reported so far	

CI, confidence interval; HR, Hazard ratio; OS, overall survival; RFS, regression free survival

What if the sentinel node is negative?

Risk of disease recurrence is lower.[10] *Refer to AJCC 8th Edition survival figures*

Stage I-IIB patients would not routinely be offered surveillance imaging as there is no evidence that this will alter survival and risks, including false positive findings requiring further investigations, may outweigh benefits in this group.

Stage IIC patients may be offered surveillance imaging.

Stage IIB/C patients can access Stage II adjuvant immunotherapy trials (NB. other trials are likely in the future). Patients on trials may have imaging as per the trial protocol during follow-up.

Summary

For all SN biopsy eligible patients, careful discussion of the risks and benefits of the procedure is recommended.

SN biopsy is performed at the time of WLE.

SN positive patients are able to access adjuvant therapy to improve survival.

SN positive patients require increased surveillance intensity.

Future Directions

There is much interest in the development of additional biomarkers that will improve our ability to discriminate patients with low versus high risk of developing metastatic disease. None are currently recommended for clinical use in Australia.

It is hoped that validation and implementation of accurate biomarkers may make the SN biopsy procedure obsolete in the future, however, there is much work to be done before this becomes a clinical reality.

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The authors would like to declare the following interests:

VM: received honoraria from Merck-Sharpe-Dohme, Novartis and Bristol-Myers-Squibb. HPS: shareholder of MoleMap NZ Limited and e-derm consult GmbH, and undertakes regular teledermatological reporting for both companies; Medical Consultant for Canfield Scientific Inc.; Medical Advisor for First Derm, MetaOptima and Revenio. AH: Advisory Board member for Novartis, Merck-Sharpe-Dohme, Bristol-Myers-Squibb and Pierre Fabre; speakers Bureau for Novartis and Merck-Sharpe-Dohme. RPMS: received honoraria from Bristol-Myers-Squibb and involved in advisory boards for Novartis and Merck-Sharpe-Dohme.

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Further reading

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Outcome and risk prediction tools

http://www.melanomaprognosis.net

http://www.lifemath.net/cancer/melanoma/outcome/index.php

http://www.melanomarisk.org.au

https://www.mskcc.org/nomograms/melanoma/sentinel_lymph_node_metastasis