New treatment paradigms for clinically-apparent metastatic melanoma in regional lymph nodes.

Running title:

Melanoma regional lymph node management

Michael A Henderson, MD FRACS

Peter MacCallum Cancer Center Melbourne

Department of Surgery, University of Melbourne

John Spillane, MBBS, FRACS

Peter MacCallum Cancer Centre Melbourne

Department of Surgery, University of Melbourne

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/ans.15407](https://doi.org/10.1111/ans.15407)

T Michael Hughes, MBBS(Hons), FRACS

Sydney Adventist Hospital,

The University of Sydney

Andrew J Spillane, MD FRACS

Melanoma Institute Australia,

Royal North Shore Hospital

The University of Sydney

B Mark Smithers, MBBS, FRACS

Queensland Melanoma Project,

Princess Alexandra Hospital

University of Queensland

John F Thompson MD, FRACS

Melanoma Institute Australia,

The University of Sydney

Corresponding Author:

Michael A Henderson

Division of Cancer Surgery

Peter MacCallum Cancer Center

305 Grattan St

Melbourne 3000

Email: michael.henderson@petermac.org

Ph 03 8559 7666

None of the Authors are recipients of a research scholarship

Word Count: 1129 with acknowledgments; 1142 with reference

Tables / Figures: 0

Regional lymph node metastasis is the commonest form of first recurrence in patients with cutaneous melanoma. Sentinel lymph node biopsy (SNB) identifies clinically-occult lymph node metastasis in approximately 15% of patients with melanomas > 1mm in Breslow thickness (T2 -T4). However, despite the increasing use of SNB, clinically-apparent lymph node field metastasis remains a significant issue. It can occur in those who did not undergo a SNB, but can also be due to a false-negative SNB, or in patients who have had a positive SN removed, then progress during surveillance.

The purpose of this article is to highlight changes in the recommended management of clinically-involved regional lymph nodes in melanoma patients, as detailed in the recently-updated, evidence-based Clinical Practice Guidelines for the Management of Cutaneous Melanoma(1). These are available on the Cancer Council Australia website, and provide the references on which this article and all other sections of the guidelines are based. As new evidence is published the guidelines are updated, and should be consulted for up-to-date information.

The diagnosis of metastatic melanoma in clinically-suspicious lymph

nodes should be confirmed when possible by fine needle biopsy, if necessary using ultrasound guidance. Fine needle biopsy rather than open or core biopsy minimises the risk of tumour contamination of the lymph node field. Overall, the risk of synchronous metastatic disease at systemic sites being present at the time of diagnosis of involved regional nodes approaches 20%, justifying pre-operative staging. Whole body PET-CT and MRI of the brain are recommended, as they have superior sensitivity and specificity to CTs of the chest, abdomen, pelvis and brain. Serum tumour markers including LDH and S100 are of very limited value and are not recommended.

By itself, surgical management of regional lymph node recurrence results in long-term control in nearly 50% of melanoma patients. Unfortunately, the influence of the extent of surgery has not been extensively examined. However, retrospective reviews evaluating the minimum number of nodes removed and the completeness of surgery using the lymph node ratio (number of involved nodes to total number excised) have confirmed poorer outcomes with suboptimal surgery.

For involved cervical lymph nodes the options for surgical management include standard radical neck dissection (node levels I-V, plus sternomastoid muscle, internal jugular vein and accessory nerve), modified radical neck

dissection (levels I-V with preservation of major structures) and selective neck dissection (less than Levels I-V). For the majority of patients modified radical or selective neck dissection is appropriate. Patients presenting with parotid lymph node involvement require at least an upper neck dissection in addition to a superficial parotidectomy, in view of the approximately 20% risk of involvement in node levels I-III.

Axillary lymphadenopathy requires a complete dissection of levels I-III. This usually necessitates sacrifice of the intercostobrachial nerve, and in many cases the procedure is facilitated by division or removal of the pectoralis minor muscle.

For most patients with involved groin nodes, inguinal lymphadenectomy (resecting nodal tissue below the level of the inguinal ligament) is appropriate. However, ilio-inguinal lymphadenectomy should be considered for patients with a significant tumour burden, as up to 50% of these patients will be found to have occult pelvic lymph node involvement. For this reason patients with palpable inguinal lymph node involvement should have the pelvis imaged preoperatively.

In up to 15% of patients presenting with apparently metastatic melanoma in cervical, axillary or inguinal lymph nodes, the site of a primary lesion

cannot be determined. These patients should be managed in the same way as those with a known primary melanoma. They have outcomes at least as good as patients with a known primary.

Patients with multiple nodes involved in a lymphadenectomy specimen and those found to have significant extracapsular extension of tumour (> 2mm) have at least a 25% risk of regional recurrence, and an even greater risk of recurrence at systemic sites. Adjuvant post-operative therapies have therefore been used. Adjuvant radiotherapy reduces the risk of regional recurrence by 50% but has no impact on survival. Lymphoedema and ongoing regional symptoms are significantly more common in patients who receive radiotherapy following therapeutic groin or axillary dissections. Post-operative radiotherapy is therefore not recommended in most cases when the nodal tumour burden is low and there is no evidence of extra-nodal spread, as further isolated recurrence is uncommon and can generally be successfully managed by further surgery and radiotherapy.

Interferon alpha 2b was approved in Australia in 1997 for resected stage III melanoma, but due to limited efficacy and significant toxicity is no longer recommended. Based on the success in treating patients with metastatic disease by targeting either the mitogen activated protein kinase (MAP kinase)

pathway in patients with an actionable mutation of BRAF (e.g. V600E) or immune checkpoint inhibitor therapy, early results from several adjuvant studies indicate that these agents are likely to find a role in patients with high risk Stage 3 disease.

These trials have highlighted both the successes and difficulties associated with systemic adjuvant therapy. Immunotherapy with the anti-CTLA-4 immune checkpoint inhibitor ipilimumab improved median recurrence-free survival compared to placebo (26 versus 17 months) but at the cost of significant toxicity. Anti PD-1 blockade with either nivolumab or pembrolizumab also demonstrated improved outcomes (one-year recurrence-free survivals compared with placebo, 71% versus 61% and 75% versus 61% respectively). Early results of combined ipilimumab and nivolumab therapy resulted in even better outcomes but with greater toxicity than with either agent alone. Immune-related adverse events including colitis and pneumonitis are quite common and up to 2% of patients develop life altering toxicity including insulin-dependent diabetes and hypophysitis.

There are likely to be many changes in the approach to adjuvant systemic therapy over the years to come. There is also considerable interest in neoadjuvant (preoperative) systemic therapy rather than post-operative

adjuvant therapy, based on an improved understanding of melanoma tumour biology and immunology. Optimal surveillance strategies after potentially curative treatment for stage III melanoma are currently undefined, however, as tumour volume may influence response to treatment, PET-CT or CT imaging may be considered.

The management of melanoma patients with clinically-apparent lymphadenopathy is thus an increasingly complex and rapidly-moving field. Patients should therefore have the benefit of a high-level multidisciplinary team discussion, and strong consideration should be given to offering enrolment in clinical trials of both adjuvant and neoadjuvant therapies.

Acknowledgments:

Development of the new Clinical Practice Guidelines for the Diagnosis and Management of Melanoma was undertaken by Cancer Council Australia and Melanoma Institute Australia, and supported by the Skin Cancer

College Australasia and the Australasian College of Dermatologists. The authors thank the staff of the Cancer Council Australia Clinical Guidelines Network for their invaluable guidance and support. In particular we thank Tamsin Curtis for coordinating the melanoma guidelines revision process and Cecilia Taing for undertaking the systematic literature review that provided the evidence on which this article was based.

Disclosure statement: None of the authors have any conflicts of interest in this report.

References

1. Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma.

Retrieved 17 /07/2019, from

<https://wiki.cancer.org.au/australia/Guidelines:Melanoma>

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Henderson, MA;Spillane, J;Hughes, TM;Spillane, AJ;Smithers, BM;Thompson, JF

Title:

New treatment paradigms for clinically apparent metastatic melanoma in regional lymph nodes

Date:

2019-10-01

Citation:

Henderson, M. A., Spillane, J., Hughes, T. M., Spillane, A. J., Smithers, B. M. & Thompson, J. F. (2019). New treatment paradigms for clinically apparent metastatic melanoma in regional lymph nodes. ANZ JOURNAL OF SURGERY, 89 (10), pp.1187-1189. <https://doi.org/10.1111/ans.15407>.

Persistent Link:

<http://hdl.handle.net/11343/286458>