Management of invasive melanoma


Background
Maximising survival for patients with invasive melanoma hinges on early diagnosis of primary melanoma and appropriate management. Despite well-documented guidelines, many patients with melanoma have not been managed ideally.

Objective
The aim of this paper is to identify suboptimal aspects of melanoma management.

Discussion
Delayed or erroneous diagnosis is more likely to occur when a shave or punch biopsy is used to obtain histopathology. Wherever feasible, local excision with a narrow margin is the preferred biopsy choice for a suspected melanoma. The Breslow thickness of the primary melanoma remains the greatest predictor of outcome. Ulceration is associated with a poorer prognosis. Most invasive melanomas are managed with a margin of ≥10 mm of normal tissue. Patients who have developed one primary melanoma are at high risk of a second tumour. Ongoing management includes regular lifelong skin checks. Targeted approaches to improve occupational or lifestyle exposure to ultraviolet radiation are useful. Imaging is largely used when metastases are suspected on the basis of clinical symptoms or signs.

The two key steps in maximising survival of melanoma remain early diagnosis followed by excision of the tumour with a wide margin. Several medications have recently been shown to improve survival in patients with metastatic melanoma, including those with nodal spread. In this paper, we discuss the optimum approach to the biopsy of a suspected melanoma and the subsequent appropriate surgical margins of clearance for therapeutic excision. Investigations following diagnosis and follow-up procedures are outlined. The discussion also describes the circumstances in which referral for consideration of medication is indicated.

Biopsy technique
In nearly all cases, the appropriate technique to diagnose a suspected melanoma is by excising the entire apparent lesion with a narrow margin, typically 2–3 mm.

Wide excision prior to definitive histopathologic diagnosis is not recommended, as the appropriate margin of clinical clearance depends on the histopathologic details, which will be detailed later in this paper.

Partial biopsies are not recommended and should be reserved for circumstances in which complete excisional biopsy is impracticable. The most common scenario in which a partial biopsy may be necessary is when the patient has a large brown macule on the head, neck, hands, feet, anterior legs or genitalia. When a partial biopsy is chosen, a deep shave biopsy down to reticular dermis and involving all pigmented tissue for thin tumours, or a punch biopsy >6 mm in diameter (to below the level of the dermis) for thicker tumours, is preferable. Small punch biopsies are especially at risk of diagnostic pitfalls.

Partial biopsies are associated with an increased risk of missed, delayed or under-diagnosis. The thickest portion of the melanoma may not be sampled or the small specimen biopsied may not be representative of the lesion as a whole. An Australian study based in Melbourne identified the large risk associated with partial biopsies. On multivariate analysis, Ng et al found that the false diagnosis risk associated with a shave biopsy was 4.5 (P = 0.002) times that expected with local excision. A punch biopsy has a 14.7 (P <0.001) relative risk increase of incorrect diagnosis. Concern was further heightened when Ng et al identified the risk of an adverse event due to misdiagnosis associated with a punch biopsy. This odds ratio was 13.2 (P <0.001) times that of complete excision. In the past, up to 27% of melanomas in Australia were diagnosed through partial biopsy. We would hope that in 2019 that percentage is substantially smaller.

It was once thought that partial biopsy of a suspected melanoma might provoke spread of the tumour. This concept has been studied and has since been
Risk factors for worsened prognosis

A large prospective study of 2001 patients with primary melanoma identified histopathologic features associated with a poorer prognosis. Breslow thickness was the single most predictive feature of a worsened prognosis. Breslow thickness is the measurement in millimetres of the thickest portion of the melanoma from the granular layer of the epidermis to the deepest level of tumour extension into (or beyond) the dermis. The death from melanoma hazard ratio (DMHR) was shown to be 1.59 per mm of Breslow thickness ($P < 0.001$). Having a positive sentinel node has a DMHR of 2.40 ($P < 0.001$). Note that sentinel node hazard is positive versus negative, not per mm. Ulceration has a DMHR of 1.79 ($P = 0.002$). Melanoma located on the trunk also has a significantly increased DMHR on a multivariate analysis (DMHR of 1.91, $P = 0.002$).

Importantly, many other aspects were not shown to statistically increase the risk of death from a particular melanoma. These include gender, and other anatomic locations. Clark level also made no statistical difference to outcome on multivariate analysis. Indeed, Clark level is no longer considered a feature of a melanoma worthy of comment on a pathology report. Risk factors for melanoma survival are summarised in Table 1.

Margins of clearance

An invasive melanoma is defined as any melanoma growing into the dermis. Invasive melanoma with a Breslow thickness up to 1 mm needs wide local excision with a 10 mm clinical margin. Invasive melanomas between 1 mm and 4 mm in Breslow thickness can also be managed with a 10 mm clinical margin, though more concerning tumours in this thickness bracket need consideration of a 20 mm margin of clinically unaffected skin. These considerations include ulceration, poorly differentiated tumours, spindle cell melanoma or tumours with substantial mitotic figures. Poorly differentiated tumours are those for which the originating cell type is difficult to determine because of loss of cell differentiation features. Invasive melanomas >4 mm in Breslow thickness merit 20 mm clinical margins. These margins have recently been updated for Australian practice in the Medical Journal of Australia.10

Melanoma in situ margins

Melanoma in situ (MIS) is melanoma confined to the epidermis, with no invasive dermal involvement. MIS has traditionally been managed with a 5 mm margin of clearance. This recommendation has recently changed. It is now recommended that a 5–10 mm clinical margin clearance be effected for patients with MIS.10 The suggestion for wider margins follows concerning recurrence rates when MIS was treated with only 5 mm margins.11,12 Shining a Wood’s lamp on MIS in a darkened room may accentuate subclinical tumor extension and reduce the likelihood of incomplete excision.13 Dermoscopy may assist delineating the tumour margin beyond changes seen only with the naked eye;14 however, evidence that this improves outcomes is lacking. Confocal microscopy is emerging as a promising tool that may assist to diagnose MIS when used in conjunction with dermoscopy.15 No studies have confirmed that the combined approach improves the sensitivity or specificity of diagnosis when compared with dermoscopy alone.

Does location change the margin?

Anatomic location does not alter margin recommendations for primary invasive melanoma. In Australia, it has been concerning that many patients with primary melanoma do not have the melanoma excised with the required margins of clearance. This most often occurs when the melanoma location is on the face.4,16 Indeed, only one-third of patients in New South Wales and Victoria were shown to have been treated with appropriate margins based on national guidelines.4,16 Patients with non-facial tumours were more likely to be overtreated, receiving margins beyond those required for optimum outcomes. Physicians treating more than 30 new patients with melanoma annually were shown to perform better at managing melanoma in line with guidelines.16

Does subtype change the margin?

Approximately 58% of new cutaneous melanoma diagnoses in Australia are

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<th>Table 1. Factors of a new melanoma that alter melanoma-specific survival, based on multivariate analysis</th>
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<td><strong>Factors that worsen survival</strong></td>
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<td>Metastases</td>
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<td>Breslow thickness of primary tumour</td>
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<td>Primary tumour located on the trunk</td>
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When is a sentinel node biopsy required?
Sentinel node biopsy (SNB) became popular in the 1990s. It was theorised that only patients who were identified as having proven lymph node metastases would receive block dissection of their nodes. However, a long-term prospective randomised controlled trial showed that patients treated in such a manner had no survival benefit over patients managed by observation alone. Therefore, an SNB is not required in the management of any melanoma. The procedure can be used as a ‘staging or prognostic test’ to determine likelihood of survival, as identified previously in this article under ‘Risk factors for worsened prognosis’. For this reason it is recommended that SNB be discussed with patients who have melanoma. The complication rate associated with SNB is approximately 10%. We have previously written of our concerns that some patients with melanoma are being offered SNB when there is no apparent benefit relative to risk of harm. Concerns regarding the link between some studies of new medications and nodal surgery have been described. Patients should not be required to have additional surgery that does not improve their survival in order to enter a trial for a medication that might improve their survival.

Investigations following diagnosis
In the hands of an experienced clinician, ultrasonography of the nodal basin combined with fine needle aspiration (FNA) can identify early melanoma involvement in lymph nodes. Other investigations are typically undertaken on the basis of symptoms or signs that suggest secondary disease may be present.

In 2005, it was understood that no specific investigations were helpful following the diagnosis of primary melanoma. However, at that time there were no known pharmaceutical approaches shown to prolong survival of patients with melanoma. That situation has changed. We now have options for managing melanoma metastases.

Many patients with stage III melanoma may have asymptomatic metastatic disease that can be detected with imaging prior to the development of clinical features. However, we do not yet know whether there is benefit from treating such asymptomatic patients early, compared with waiting until symptoms arise. Early detection of secondaries may or may not alter the efficacy of newer treatments. The role of earlier imaging in asymptomatic patients is of uncertain benefit.

When is medication indicated?
There are now several medications of benefit in managing patients with melanoma. Two main groups of medications now commonly in usage are:

- programmed cell death medications, including nivolumab and pembrolizumab
- BRAF inhibitors, including dabrafenib and vemurafenib, usually combined with MEK inhibitors.

These medications have been shown to prolong life in patients with metastatic melanoma, including those with nodal metastases. In 2019, patients with metastatic disease require referral to a medical oncologist familiar with the current usage of these and other medications.

Follow-up appointments
Patients with melanoma require lifelong follow-up. In the past, patients were discharged from follow-up five years after diagnosis if no evidence of recurrent disease was present. A recent study in California showed that 7.9% of melanoma survivors developed a second primary melanoma during follow-up. A Dutch study showed a cumulative 5–10-year risk of a second primary melanoma of 4.6%. An Australian study has shown that 11.3% of patients with MIS developed a second primary cancer, including the risk of further melanoma.

While follow-up appointments frequently involve a check of the original surgical site and regional nodes for evidence of recurrence and metastasis, many do not include a full skin examination to check for second primary melanoma. A full skin examination is a vital part of routine melanoma follow-up. These checks could occur at least six-monthly for five years and at least annually thereafter. It is vital that the members of the treating team agree who will undertake these tasks, so that there is no presumption that the full check will be done at the melanoma unit or in the general practice setting, when in fact no one may be checking the patient’s skin. Patients that have many naevi, especially when dysplastic naevi are present, should be considered for ongoing skin checks with clinicians highly skilled in dermoscopy.

Whole body photography
Because many patients with melanoma have multiple other pigmented growths, including atypical naevi, it can be difficult to assess whether a lesion is static or evolving. This has created an established role for whole body skin photography at follow-up visits. Whole body skin photography can be undertaken with underwear in place unless there are pre-existing naevi beneath underwear requiring documentation. These images assist the clinician to identify new and changing lesions on follow-up. Early second melanomas can be detected with subtle changes in follow-up when these photographs are available for comparison.

Sun exposure advice
As with management of any patient who has sun exposure conditions, melanoma management includes advice on lifelong...
sun protection and ultraviolet (UV) radiation minimisation. Cumulative sun exposure is a risk factor for further melanoma in patients with a history of primary melanoma.\textsuperscript{28} Advice will ideally include discussion of wearing wide-brimmed hats, long-sleeved clothing, sunglasses and specialised sun-protective hats and clothing; seeking shade and avoiding outside exposure in the middle of the day is recommended. Patients often need help understanding that current glass technology can provide effective UVB and UVA protection.\textsuperscript{31} The Australian population-based Nambour study identified clear melanoma protective benefit in the intervention group who applied sunscreen twice daily when compared with the discretionary use of sunscreen displayed by control subjects.\textsuperscript{32}

Sun protection and avoidance after the diagnosis of melanoma remains critical.\textsuperscript{33} Many patients with melanoma are occupationally exposed to solar UV radiation. For these patients, the occupational therapist has a role in workplace assessments to coordinate safer workplaces and thereby reduce the patients’ further UV risk.\textsuperscript{33} Occupations involving arc welding are at particular risk of UV exposure, including to UVC.\textsuperscript{34} Delivering education could assist patients and their loved ones to undertake advice and precautions when engaging in occupations where UV exposure is high. Targeted advice can also be geared to recreational UV exposure, such as home gardening.\textsuperscript{35} Patients may need to find modifications to continue to enjoy their recreations in a safer manner.

**Psychosocial support**

There are many patients for whom the ‘m’ word brings psychological and social difficulties for themselves and their families.\textsuperscript{16} It is important for clinicians to consider the effects these important issues have and offer information on psychosocial support services when needed. Psychological support can be provided in the general practice setting, and melanoma units often have trained staff who are able to manage these aspects of patient care.

**Guidelines**

Until 2008, the National Health and Medical Research Council hosted and endorsed the development of quality melanoma guidelines for Australia and New Zealand. These were evidence-based and reliable. Unfortunately, considerable time has passed, and no updated, formal, evidence-based melanoma guidelines have been published in Australia. There is a largely an ad hoc set of documents that have been published online (eg those on Wikipedia). However, these guidelines are often not evidence-based, frequently internally contradictory and at times little more than the opinion of the authors. We look forward to the development of long-overdue new melanoma guidelines.

**Conclusion**

The key to maximising survival in melanoma hinges on early diagnosis followed by appropriate wide local excision. Medications are available for patients with metastatic disease. At present, SNB is not an integral part of managing primary cutaneous melanoma and should not become so unless and until a survival advantage is identified. To date, no survival advantage has been identified in large studies. When performed by an experienced clinician, ultrasonography with FNA can be reliable in detecting early nodal involvement.

**Key points**

- Excisional biopsy of the entire lesion is the preferred biopsy technique for melanoma.
- A wide margin excision of the primary melanoma is required subsequent to diagnosis.
- Melanoma spread to nodes or elsewhere can be managed with medication.
- Ultrasonography with FNA can diagnose nodal involvement as an alternative to SNB.
- Lifelong follow-up with skin checks is needed for patients with melanoma.
- Targeted sun protection advice can help prevent a second primary tumour.

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Competing interests: None.

Funding: None.

Provenance and peer review: Commissioned, externally peer reviewed.

**References**


