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Invasive melanoma management

Abstract

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

Objective We 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 should be our biopsy choice for a suspected melanoma. The Breslow thickness of the primary melanoma remains the single greatest predictor of outcome. Ulceration is associated with a worsened prognosis. Most invasive melanoma are managed with a margin of 10mm or more of normal tissue. Patients having suffered 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 are useful. Imaging is largely used when metastases are suspected based on clinical symptoms or signs.

Introduction

The two key steps in maximizing survival in melanoma remain early diagnosis followed by excision of the tumour with a wide margin. Recently several drug interventions have been shown to improve survival in patients with metastatic melanoma including those with nodal spread. 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. Further we discuss the circumstances where referral for consideration of drug interventions are 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 millimetres (mm).

Wide excision prior to definitive histopathologic diagnosis is not recommended as the appropriate margin of clinical clearance depends on the histopathologic details. (See margins of clearance below).

Partial biopsies are not recommended and should be reserved for circumstances where complete excisional biopsy is impracticable. The most common scenario where 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[1] or a punch biopsy greater than 6mm in diameter (to below the level of the dermis) for thicker tumours is preferable[2]. Small punch biopsies are especially at risk of diagnostic pitfalls.

(Figure 1. Large brown macule on right ear was confirmed as melanoma in situ on thick shave biopsy).

The concern with partial biopsies is missed, delayed or under-diagnosis, where the thickest portion of the melanoma is not sampled. An Australian study based in Melbourne identified the large risk associated with partial biopsies[3]. 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 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. It is known that in the past in Australia up to 27% of melanomas were diagnosed through partial biopsy[4]. We would hope that in 2019 that percentage is substantially smaller.

It was once thought that partial biopsy of a suspected melanoma might assist spread of the tumour. This concept has been studied and has been disproven.[5] The reason we avoid partial biopsies is not because of risk of spread, but for risk of an adverse patient outcome through diagnosis delay.[6]

Risk factors for worsened prognosis

A large prospective study of 2001 patients with primary melanoma identified histopathologic features associated with a poorer prognosis[7]. Breslow thickness was the single most predictive feature of a worsened prognosis. Breslow thickness is the measurement in mm 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 of ($p<0.001$). Note that sentinel node hazard is positive versus negative, not per mm.

Ulceration has a DMHR of 1.79 [7], ($p=0.002$). Melanoma located on the trunk also has a significantly increased a DMHR on a multivariate analysis, ($HR = 1.91$, $p=0.002$)[7].

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.[7] 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[8].

Margins of clearance

An invasive melanoma is defined as any melanoma growing into the dermis. Invasive melanoma with a Breslow thickness up to 1mm needs wide local excision with a 10mm clinical margin. Those between 1 - 4mm in Breslow thickness can also be managed with a 10mm clinical margin, though more concerning tumours in this thickness bracket need consideration of a 20mm margin of clinically unaffected skin. These considerations include ulceration, poorly differentiated tumours[9], spindle cell melanoma or tumours with substantial mitotic figures. Poorly differentiated tumours are those where the originating cell type is difficult to determine because of loss of cell differentiation features. Invasive melanomas greater than 4mm in Breslow thickness merit 20mm 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. Traditionally MIS has been managed with a 5mm margin of clearance. This recommendation has been

recently changed. It is now recommended that 5 to 10mm clinical margin clearance be effected for patients with MIS[10]. The suggestion for wider margins follows concerning recurrence rates when MIS is treated with only 5mm 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 in diagnosing MIS when used in conjunction with dermoscopy[15]. There are no studies confirming that the combined approach improves the sensitivity or specificity of diagnosis compared to 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 get the required margins of clearance. This mainly occurs when the melanoma location is on the face[4,16]. Indeed, only one third of patients in New South Wales and Victoria have been demonstrated 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 that required for optimum outcomes. Physicians treating more than 30 new melanoma patients 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 superficial spreading or of a non-specified subtype. Lentigo maligna subtype accounts for another approximately 22% of melanomas. The rest are primarily nodular (18%).[4] Nodular melanomas are a distinct biological entity[17] having an early vertical growth phase, meaning they develop a greater Breslow thickness faster.

Despite these differences, the margins of clearance remain the same in Australian and New Zealand guidelines along with most melanoma guidelines around the world[18].

When is a sentinel node biopsy required?

Sentinel node biopsy (SNB) became popular in the 90s. The theory was that by identifying patients who had proven lymph node metastases, only those patients would receive block dissection of their nodes. However, a long term prospective randomized controlled trial demonstrated that patients treated in such a manner had no survival benefit over patients managed by observation alone[7]. Hence 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 in "Risk factors for worsened prognosis" (above). For this reason it is recommended that SNB be discussed with melanoma patients[10]. The complication rate associated with SNB is around 10%[19]. We have written of our concerns that some melanoma patients are being offered SNB when there is no apparent benefit relative to risk of harm[20]. Concerns regarding the linkage between some studies of new drugs and nodal surgery has been described[21]. Patients should not be required to have added surgery that does not improve their survival in order to enter a trial of a drug that might improve their survival. We elaborate further on SNB in the "other article".

Investigations following diagnosis

In skilled hands, ultrasound of the nodal basin along with fine needle aspirate (FNA) can identify early melanoma involvement in lymph nodes[22]. We elaborate further in "other article". Other investigations are typically undertaken based on symptoms or signs suggestive that secondary disease may be present.

In 2005 it was understood that no specific investigations were helpful following the diagnosis of primary melanoma[23]. However, at that time there were no known pharmaceutical approaches shown to prolong survival in melanoma patients. That situation has changed. We now have options for managing melanoma metastases.

Many patients with stage 3 melanoma may have asymptomatic metastatic disease that can be detected with imaging prior to the development of clinical features[24]. However, we do not yet know whether there is benefit from treating such asymptomatic patients early, compared to 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[25].

When are drug therapies indicated?

There are now a number of drugs that have been shown to be of benefit in managing our melanoma patients. There are two main groups of drugs now commonly in usage.

1. Programmed cell death (PD1) drugs include nivolumab and pembrolizumab
2. BRAF inhibitors include dabrafenib and vemurafenib, usually combined with MEK inhibitors.

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

We elaborate further in "other article"

Follow up appointments

Melanoma patients require lifelong follow up. In the past, patients were discharged from follow-up 5 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[26]. A Dutch study showed a cumulative 5–10 year risk of a second primary melanoma to be 4.6%[27]. An Australian study has shown that 11.3% of MIS patients developed a second primary cancer, including the risk of further melanoma[28].

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[4]. A full-skin examination is a vital part of routine melanoma follow up. These checks could be at least six monthly for five years and at least annually thereafter. It is vital that the members of the treating team agree on 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 melanoma patients have multiple other pigmented growths, including atypical nevi, 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. This can be undertaken with underwear in place unless there are preexisting naevi requiring documentation beneath underwear. These images then assist the clinician in identifying 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[29].

Sun exposure advice

As with management of any patient suffering from sun exposure conditions, melanoma management includes advice on life-long sun protection and UV minimization. Cumulative sun exposure is a risk factor for further melanoma in patients with a history of primary melanoma[27]. Advice will ideally include discussion of wearing wide-brimmed hats, use of shade, avoiding outside exposure in the middle of the day, long sleeved clothing, specialized sun-protective hats and clothing and sunglasses. Patients often need help understanding that current glass technology can provide effective UVB and UVA protection[30]. The Australian population-based Nambour study identified clear melanoma protective benefit in the intervention group who applied sunscreen twice daily compared with the discretionary usage of controls[31].

Sun protection and avoidance after the diagnosis of melanoma remains critical[32]. Many of our melanoma patients are occupationally exposed to solar UV. For these patients, the occupational therapist has a role in work place assessments to coordinate safer workplaces reducing our patient's further UV risk[32]. Occupations involving arc welding are at special risk of UV exposure including to UVC[33]. 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[34]. Patients may need to find modifications to continue to enjoy their recreations, but 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[35]. Clinicians should 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 able to manage these aspects of patient care.

Guidelines

Up until 2008, the NHMRC 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 since, 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 on line here: https://wiki.cancer.org.au/australia/Guidelines:Melanoma

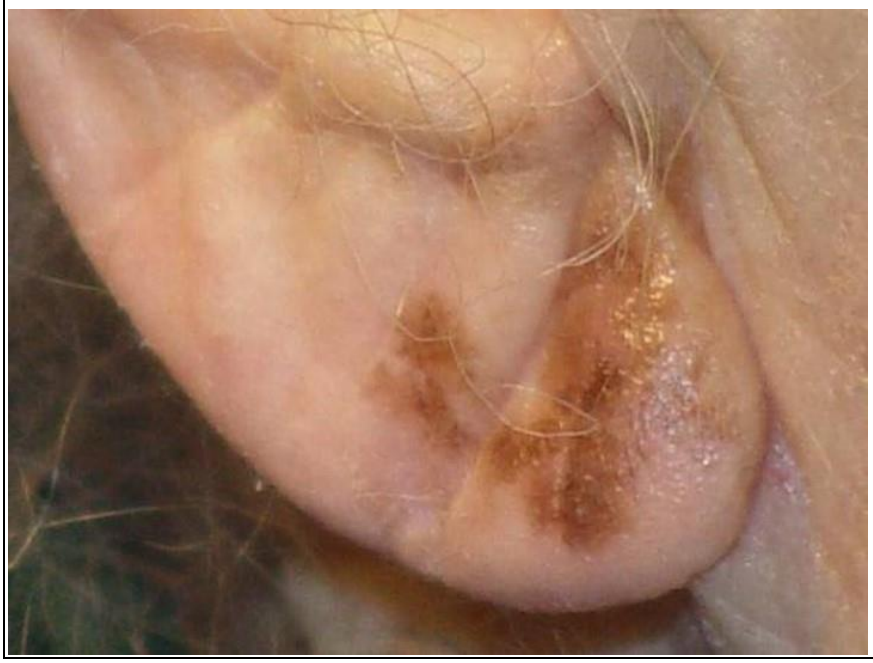
However, these suggested guidelines are often not evidence based, frequently internally contradictory and are at times little more than the opinion of the authors. We look forward to the development of long overdue new melanoma guidelines.

Conclusion

The key to maximizing survival in melanoma hinges on early diagnosis followed by appropriate wide local excision. Drug interventions are available for patients with metastatic disease. Sentinel node biopsy, at present, 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. Ultrasound with FNA can be reliable in detecting early nodal involvement in skilled hands.

Figure 1

This large pigmented macule on the ear was initially managed with a thick shave biopsy of the entire lesion to confirm diagnosis. The size and location were reasons local excision was not chosen to biopsy this melanoma.



Call out boxes

Key points when managing melanoma

1. Excisional biopsy of the entire lesion is the preferred biopsy technique
2. Wide margin excision of the primary melanoma is required subsequent to diagnosis
3. Melanoma spread to nodes or elsewhere can be managed with drugs
4. Ultrasound with FNA can diagnose nodal involvement as an alternative to sentinel node biopsy
5. Lifelong follow up with skin checks are needed for melanoma patients
6. Help prevent a second primary tumour with targeted sun protection advice

Which factors in a new melanoma alter melanoma specific survival (based on multivariate analysis)

Factors that worsen survival	**Factors that do not alter survival**
Metastases	Clark level
Nodal involvement	Gender

Breslow thickness of primary tumour	Incising into melanoma when effecting biopsy
Ulceration in primary tumour	Closure of defect technique
Primary tumour located on the trunk	Primary location on limbs or head and neck

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