Clinical practice guidelines for the diagnosis and management of melanoma

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What is the role of dermoscopy (and sequential dermoscopy) in melanoma diagnosis?

What investigations should be performed following a diagnosis of primary cutaneous melanoma?

What investigations should be performed when in transit and/or regional node disease is diagnosed?

Should all patients with a positive sentinel lymph node biopsy have a complete node dissection?

What is the appropriate treatment for macroscopic (i.e. detectable clinically or by ultrasound) nodal metastasis?

What staging examinations are indicated for Stage IV patients?

How should patients with thin, intermediate thickness and thick melanomas be followed after initial definitive treatment?

7 Diagnostic Investigations - Systematic Review Topics

FNA core biopsy

Lymphoscintigraphy

Mutation testing

Lymph node ultrasound

Chest x-ray

Abdominal ultrasound

MRI

CT and PET

Bone scan

Melanoma laboratory bloods

1 Foreword

1.1 Foreword

Melanoma is a disease that is particularly important in Australia and New Zealand. The incidence of melanoma in the USA is around one third of the rates in Australia and the UK has one quarter of the incidence rate.[1]

Melanoma is the fourth most common cancer in Australia with one in 14 males and one in 23 females expected to develop melanomas in their life time.[2] Its incidence has been increasing by 16% in males and 24% in females over the last decade. It is our second most prevalent cancer with around 38,000 people cured or alive with the disease in New South Wales alone.

We know that around 60% of adults in New South Wales get sunburnt every year and around 15% five or more times each year.[3]

Survival from melanoma measured five years after the diagnosis is high if caught early with 96% alive if localised but only 63% if melanoma had spread regionally.[2] Only 34% were alive at five years following a presentation with metastatic melanoma. Only 80% of melanomas are diagnosed when localised and this could be improved considerably. This data clearly provides a rationale for promoting early diagnosis with the rigorous application of appropriate treatment.

Overall results have changed only marginally over the last 25 years with five year survival improving from 88% in 1980 to 90% in 2004. However in world terms these outcomes are good with USA reporting 92% five year survival and the UK 82%.[4] Optimal management of each stage of disease offers hope that survival can improve further. Strict adherence to best practice guidelines as presented in this report is the key to such improvements in outcomes in the future.

The Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand provides the evidence for optimal care developed by an expert team. The widespread dissemination and use of these guidelines will lead to better outcomes for our patients. I commend them to you.

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Professor of Cancer Medicine, University of Sydney

1.2 References

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2 Summary of recommendations

For explanation of the different types of recommendations, see below.

You may also like to refer to the Appendix - Guideline development process for details on the levels of evidence and recommendation grades.

2.1 Recommendations

2.1.1 What are the clinical features of melanoma and how do atypical melanomas present?

Practice point

Melanomas are generally distinguished from benign lesions by their history of change and thick melanomas often do not conform to the 'ABCD' rule, but are Elevated, Firm and Growing. Therefore, careful history taking is important and any lesion that continues to grow or change in size, shape, colour or elevation over a period of more than one month should be biopsied and assessed histologically or referred for expert opinion.

Practice point
Suspicious raised lesions should be excised and not monitored.

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2.1.2 What type of biopsy should be performed for a pigmented lesion suspicious for melanoma?

Evidence-based recommendation	Grade
The optimal biopsy approach for a suspicious pigmented lesion is complete excision with a 2 mm clinical margin and upper subcutis.	**C**

Evidence-based recommendation	Grade
Partial biopsies may not be fully representative of the lesion and need to be interpreted with caution and in light of the clinical findings to minimise incorrect false negative diagnoses and understaging.	**C**

Evidence-based recommendation	Grade
In carefully selected clinical circumstances (such as large in situ lesions, large facial or acral lesions or where the suspicion of melanoma is low) and in the hands of experienced clinicians, partial incisional, punch or shave biopsies may be appropriate.	**C**

Practice point
It is advisable to discuss unexpected pathology results with the reporting pathologist.

Practice point
Punch biopsy should not be utilised for the routine diagnosis of suspected melanoma because this technique is associated with high rates of histopathological incorrect false negative diagnosis. Where a punch biopsy has been used for the diagnosis of a suspected BCC or SCC, and the diagnosis has been found to be melanocytic, then consideration should be given to excision of the entire lesion.

Practice point
The use of deep shave excision (saucerisation) should be limited to in situ or superficially invasive melanomas to preserve prognostic features and optimise accurate planning of therapy.

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2.1.3 When is sentinel lymph node biopsy (SLNB) indicated?

Evidence-based recommendation	Grade
Sentinel lymph node biopsy should be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node positive.	**B**

Practice point
Sentinel lymph node biopsy (SLNB) should be performed at the time of the primary wide excision.

Practice point
Sentinel lymph node biopsy (SLNB) should be performed in a centre with expertise in the procedure, including nuclear medicine, surgery and pathology to optimise the accuracy of the test.

Practice point

Patients being considered for sentinel lymph node biopsy (SLNB) should be given an opportunity to fully discuss the risks and benefits with a clinician who performs this procedure.

Practice point

A consideration of sentinel lymph node biopsy (SLNB) forms an important part of the multidisciplinary management of patients with clinically node negative cutaneous melanoma.

Practice point

Sentinel lymph node biopsy provides accurate staging of the lymph node basin by presenting a high-yield, low volume tissue sample for histopathological assessment. Not surprisingly, there is an increased rate of detection of micrometastatic disease when increasing numbers of sections are evaluated pathologically including when supplemented by immunohistochemistry for melanoma associated antigens. However there is no consensus as to the optimal number of sections that should be examined, the levels at which they should be cut from the paraffin block and which immunostains should be utilised.

Practice point

Sentinel lymph nodes (SLNs) should be removed intact, preferably with a thin rim of surrounding adipose tissue and be devoid of crush or diathermy artefacts that may complicate pathological assessment. The pathology request form should indicate the number of removed SLNs and their anatomical locations and the specimens clearly labelled. Any “second tier” lymph nodes or non-SLNs that have also been removed should be indicated as such on the request form and the specimens clearly labelled. The pathologist should slice the SLN using either the bivalving procedure along its longitudinal axis through the median plane or cut the SLN into multiple transverse slices using the “bread loaf” technique to make available the largest cut surface area of lymph node tissue for pathological examination. To identify low volume metastases, pathologists should examine multiple haematoxylin-eosin and immunohistochemically-stained sections from each SLN. Sections from each

Practice point
slice of all SLNs should be stained with both H&E and immunohistochemistry for melanoma associated antigens. HMB-45, S100, SOX10, Melan A and tyrosinase have all been utilised as immunohistochemical stains. As per AJCC guidelines, in patients with positive SNs, the single largest maximum dimension (measured in millimeters to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic melanoma deposit should be recorded in the pathology report. Routine frozen section examination of SNs from melanoma patients is not recommended.

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2.1.4 What are the recommended safety margins for radical excision of a primary melanoma (in situ)?

Evidence-based recommendation	Grade
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 5-10 mm (measured with good lighting and magnification) with the aim of achieving complete histological clearance. Melanoma *in situ* of non-lentigo maligna type is likely to be completely excised with 5mm margins whereas lentigo maligna may require wider excision. Minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**D**

Practice point
Excisions should have vertical edges to ensure consistent margins.

Practice point
For all melanomas, minimum clearances from all margins should be stated/assessed. When necessary, further excision should be performed in order to achieve the appropriate margin of clearance.

Practice point

Excision biopsy of the complete lesion with a narrow (2mm) margin is appropriate for definitive diagnosis of primary melanoma. Once the diagnosis of melanoma has been made, re-excision of the lesion (biopsy site) should then be performed in order to achieve the definitive, wider margins that are recommended in these guidelines.

Practice point

Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved or has been reached during the diagnostic excision. For body sites where there is particularly deep subcutis, it is usual practice to excise to a depth equal to the recommended lateral (radial) excision margins for that specific melanoma; in these cases it is not deemed necessary to excise right down to fascia.

Practice point

Where tissue flexibility is limited, a flap repair or skin graft may be necessary subsequent to an adequate margin of removal.

Practice point

Most primary melanomas can be treated as an outpatient under local anaesthesia or as a day-case.

Practice point

Patients should be informed that surgical excision may be followed by wound infection, bleeding, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar, dehiscence and the possibility of further surgery.

Practice point
Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin (e.g. LM) and those with difficult-to-define margins (eg amelanotic and desmoplastic melanomas). In these categories, the presence of atypical melanocytes at the margins of excision should be detected by comprehensive histological examination (including immunohistochemical staining) and followed by wider excision as appropriate. Alternatively, staged serial excision (also known as 'slow Mohs' surgery) may be utilised to achieve complete histological clearance of melanoma *in situ*/lentigo maligna. Pre-operative mapping of the extent of some lesions with confocal microscopy may be useful and is available in some centres. Referral to a specialist melanoma centre or discussion in a multidisciplinary meeting should be considered for difficult or complicated cases.

Practice point
Amelanotic melanoma can present significant difficulties for defining a margin with up to one third of subungual and nodular melanomas being non-pigmented. This may dictate choice of a wider margin, or further re-excision, where practicable.

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2.1.5 What are the recommended safety margins for radical excision of invasive melanomas?

Evidence-based recommendation	Grade
(pT1) melanoma < 1.0 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1 cm. Minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**B**

Evidence-based recommendation	Grade
(pT2) melanoma 1.01 mm–2.00 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm. Minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary;	**B**

Evidence-based recommendation	Grade
positive histological margins are unacceptable.	

Evidence-based recommendation	Grade
(pT3) melanoma 2.01 mm–4.00 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm. Minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary; positive histological margins are unacceptable. Caution should be exercised for melanomas 2.01–4.00 mm thick, especially with adverse prognostic factors, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours depending on the tumour site and characteristics, and prevailing surgeon/patient preferences.	**B**

Evidence-based recommendation	Grade
(pT4) melanoma > 4.0 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 2 cm. Minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**B**

Evidence-based recommendation	Grade
Acral lentiginous and subungual melanoma are usually treated with a minimum margin as set out above, where practicable, including partial digital amputation usually incorporating the joint immediately proximal to the melanoma.	**D**

Evidence-based recommendation	Grade
Excision margins might be modified to accommodate individual anatomic sites or functional considerations, but this practice would be based solely on case-series information, and individual factors, rather than RCT evidence which is currently lacking.	**D**

Practice point

Excisions should have vertical edges to ensure consistent margins.

Practice point

For all melanomas, minimum clearances from all margins should be stated/assessed. Consideration should be given to further excision if necessary because positive histological margins are unacceptable.

Practice point

Excision biopsy of the complete lesion with a narrow (2mm) margin is appropriate for the definitive diagnosis of primary melanoma. Once the diagnosis of melanoma has been made, re-excision of the lesion (biopsy site) should then be performed in order to achieve the definitive, wider margins that are recommended in these guidelines.

Practice point

Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved or has been reached during the diagnostic excision. For body sites where there is particularly deep subcutis, it is usual practice to excise to a depth equal to the recommended lateral (radial) excision margins for that specific melanoma; in these cases it is not deemed necessary to excise right down to fascia.

Practice point

Where tissue flexibility is limited, a flap repair or skin graft is often necessary subsequent to an adequate margin of removal.

Practice point

Most primary melanomas can be treated as an outpatient under local anaesthesia or as a day-case.

Practice point

Patients should be informed that surgical excision may be followed by wound infection, bleeding, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar, dehiscence and the possibility of further surgery.

Practice point

Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin (e.g. lentigo maligna) and those with difficult-to-define margins (e.g. amelanotic and desmoplastic melanomas). In these categories, the presence of atypical melanocytes at the margins of excision should be detected by comprehensive histological examination (including immunohistochemical staining) and followed by wider excision.

Practice point

Amelanotic melanoma can present significant difficulties for defining a margin with up to one third of subungual and nodular melanomas being non-pigmented. This may dictate choice of a wider margin, or further re-excision, where practicable.

Practice point

For patients with deeper invasive melanomas (> 1 mm thick), referral to a specialised melanoma centre or discussion in a multidisciplinary meeting should be considered to ensure that best practice is implemented and for the collection of national outcome data. This may present logistic difficulties in regional and remote areas, but input from a specialist melanoma centre.

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This guideline includes evidence-based recommendations (EBR), consensus-based recommendations (CBR) and practice points (PP) as defined in the table below. Recommendations and practice points were developed by working party members and sub-committee members.

Each EBR was assigned a grade by the expert working group, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence according to NHMRC Level and Grades for Recommendations for Guidelines Developers[1]

2.1.6 NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

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2.2 References

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2.1 Identification and management of high-risk individuals – Introduction

Intro required?

2.2 Genetic determinants of high risk

To be developed (non SR)

2.3 Validated models for overall measurements of high risk

Appendices

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2.4 Interventions that benefit those at high risk of new primary melanomas

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2.5 Clinical features of melanoma

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2.5.1 Introduction

Whilst there is evidence that early detection of superficial spreading melanomas has improved, with a corresponding reduction in both median tumor thickness and melanoma mortality from this subtype,[1] a number of studies have also shown an increasing or stable incidence rate of thick melanomas.[2][3][4][5][6][7] Nodular, desmoplastic and acral lentiginous melanomas are often diagnosed when they are much thicker lesions compared to superficial spreading melanoma.[8][9][3][4][6][10] This is in part due to their atypical clinical presentation. Improved diagnostic accuracy of these subtypes can significantly improve mortality from melanoma.

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2.5.2 Classification of melanoma

Melanoma is currently classified into subtypes; superficial spreading (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), acral lentiginous (ALM) and desmoplastic melanoma (DM), based on various morphologic and histologic characteristics.[11][12] SSM is the most common subtype accounting for approximately 55-60% of melanoma, and is characterised by a slow radial growth phase (months to years), (with pagetoid spread of atypical melanocytes within the epidermis, followed by invasion into the dermis. LMM accounts for approximately 10-15% of cases in Australia, occurring on sun damaged skin with a slow lentiginous (linear) proliferation of atypical melanocytes along the basal layer of the epidermis, commonly involving hair follicles and sweat ducts, which may be present for years prior to invasion. Acral lentiginous melanomas (which

make up only 1-2% of cases in Australia) arise on glabrous skin and also have a prominent lentiginous radial growth component, but appear not to be causally associated with sun exposure. NM accounts for 10-15% of cases and differs from the other main subtypes by being uniformly invasive (early vertical growth) with a lack of epidermal involvement (radial growth) beyond 3 rete ridges. Desmoplastic melanomas account for 1-2% of cases in Australia and are characterized by malignant spindled melanocytes with surrounding fibrous stroma. They can be difficult to diagnose both clinically and on histopathology.

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2.5.3 Clinical presentations of melanoma subtypes

As well as having distinct histopathology, melanoma subtypes differ in their clinical presentation.

2.5.3.1 Superficial spreading melanoma

SSM is more common in younger patients and tends to occur on the trunk of naevus prone individuals and has a strong relationship with intermittent sun exposure. It presents as an **A**symmetrical pigmented lesion with irregular **B**orders, **C**olour variation, typically of larger **D**iameter (the ABCD rule). Macroscopically, it tends to stand out as an 'ugly duckling'. Common specific dermoscopic features are branched streaks or pseudopods, blue-grey veil, multiple irregular brown dots or globules, regression features, inverse or broadened network and atypical/polymorphous vessels.

2.5.3.2 Nodular melanoma

Whilst NM account for only 10-15% of melanomas in Australia, they contribute disproportionately to melanoma deaths.[6] In contrast to SSM, NM does not conform to the ABCD rule, but is more often a symmetrical, dome shaped, hypomelanotic lesion. The EFG aide memoire reminds us that they are often Elevated, Firm and Growing.[13] NM may therefore mimic less malignant tumours such as basal or squamous cell carcinomas or angiomas. Many NM appear to the patient to be without pigment but closer inspection will reveal light pigmentation in some and focal pigmentation in others. Dermoscopy will show melanin pigment in 90% of NM although 27% in one large series were lightly or focally pigmented and 9.6% were completely amelanotic.[14] Dermoscopic features seen in other subtypes are less common, but, blue-white veil, blue areas, black areas, milky pink areas, atypical vessels, symmetry of pigment pattern and shape are more commonly identified.[14] NM is more commonly found on severely sun damaged sites such as the head and neck of older individuals and is less commonly associated with large numbers of naevi.[15] NM tend to exhibit more rapid vertical growth compared to SSM and LMM, and are much thicker at diagnosis.[16][4]

2.5.3.3 Lentigo maligna melanoma

Lentigo Maligna (in-situ disease) may be present for months to years before invasion occurs. These lesions usually present as an asymmetrical pigmented macule which may occasionally be amelanotic (pink). Dermoscopic clues can be subtle, and include asymmetrical perifollicular pigmentation, grey and black dots (annular granular structures) and rhomboidal structures.

LMM (invasive disease) typically occurs on the head and neck of older patients and is associated with other signs of chronic sun exposure, such as solar lentigines, solar keratoses and non-melanoma skin cancer.

2.5.3.4 Desmoplastic melanoma

Desmoplastic melanoma also typically occurs on chronically sun-damaged skin, typically the head and neck, including the lip, nose and ears. It may arise de novo, or in association with a pre-existing lentigo maligna. It is more often amelanotic, firm or scar like in appearance. Dermoscopy is less useful in diagnosing DM unless features of an associated radial growth phase melanoma are present.. It may be misdiagnosed as a dermatofibroma, scar or non-melanoma skin cancer.

2.5.3.5 Acral lentiginous and subungal melanoma

Acral lentiginous melanoma may arise de novo or from a pre-existing naevus and occurs more commonly on the sole than on the the palm. ALM may also arise from the nail apparatus (subungual or periungual melanoma). They may have a prolonged radial growth phase (similar to LMM) before becoming invasive. ALM typically presents with light asymmetric pigmentation, which may be patchy and often flat and can therefore be mistaken for a stain or bruise. Over 30% of cases are hypomelanotic.[17] It has a predominant parallel ridge pattern on dermoscopy. Occasionally ALM can be verrucous and, particularly if hypomelanotic, may mimic plantar warts or tinea infection. If pared down, an ALM would not show the typical pinpoint vessels of a wart.

Subungual melanoma typically presents as longtitudinal melanonychia (full length longitudinal brown to black pigment band arising from the nail matrix). This band typically broadens over time and dermoscopically one can observe streaks within the band with variable colour, thickness and spacing. Pigmentation of the proximal or lateral nail fold (Hutchinson’s sign) may be present (sometimes only observed dermoscopically). Growth of the tumour may cause nail dystrophy and eventual destruction of the nail plate. Subungual haematoma is a common differential diagnosis and may be distinguished by the presence of multiple reddish globules at the periphery of the pigmented area. These will grow out when observed over months. Bleeding within a tumour may occur, however, and the presence of subungal blood can not be used to rule out melanoma.[18] Hypomelanotic subungual melanoma may present as a nail dystrophy and readily be mistaken for nail trauma or infection.

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2.5.4 Atypical clinical features

Melanoma may not conform to the usual ABCD criteria. They may be symmetric, dome shaped and skin coloured. Any lesion that is **E**levated, **F**irm and **G**rowing over a period of more than one month should raise suspicion for melanoma.

Lack of pigment is significantly associated with poorer diagnostic accuracy.[19] Up to 20% of all melanomas are only partially pigmented (hypomelanotic), with true amelanosis much less common.[20][21] Nodular, desmoplastic and ALM subtypes are more commonly hypomelanotic (over 40% of cases) compared to SSM and LMM subtypes (approximately 10-25% of cases).[15][21][17] Hypomelanotic melanomas may mimic basal cell carcinoma clinically, with a slightly shiny surface and atypical vessels on dermoscopy. Other dermoscopic clues include scar-like depigmentation, inverse network, irregular blue grey dots, blue-white veil and milky pink areas.[20][22] Whilst dermoscopic sensitivity is around 90% for pigmented lesions, it is much lower for predominantly amelanotic lesions.

Tumor thickness is not necessarily related to diagnostic delay.[2][23][24][25] Whilst some melanomas grow slowly over a number of years, others will become thick and life- threatening over weeks to months. More rapid growth has been associated with NM and desmoplastic subtypes as well as amelanosis.[16][26][27][28] These subtypes are more common on chronically sun damaged skin, typically on the head and neck and predominantly in older males.[9]

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2.5.5 Dynamic features of melanomas

Perhaps the most helpful clinical feature of melanomas is that biologically significant melanomas are changing, regardless of their other clinical features. If these changes have been accurately perceived by the patient or there is photographic evidence to demonstrate stability or change, this may be very helpful in determining the right index of suspicion. Radial growth phase melanomas change in size, shape or colour and vertical growth phase melanomas change in elevation, ulceration and may bleed. A history of the duration of a lesion and any change within it is a minimum requirement for the assessment of any potential skin cancer.

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2.5.6 Evidence summary and recommendations

Evidence summary	Level	References
NM, ALM and desmoplastic subtypes more commonly present as thick lesions and improved diagnostic accuracy of these is therefore critical.	IV	[10], [6], [9], [7], [4], [3]
Nodular melanomas are associated with more rapid vertical growth compared to superficial spreading melanomas.	IV	[26], [16], [27], [28]
Up to 20% of all melanomas are amelanotic or only partially pigmented, with this being more common amongst NM, ALM and desmoplastic subtypes.	IV	[15], [17], [21]
Amelanosis/ hypomelanosis is significantly associated with poorer diagnostic accuracy.	IV	[19], [20]

Practice point

Thick melanomas often do not conform to the 'ABCD' rule, but are Elevated, Firm and Growing. Therefore, careful history taking is important and any lesion that continues to grow over a period of more than one month should be biopsied and assessed histologically or referred for expert opinion.

Practice point

Avoid 'monitoring' raised lesions.

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2.5.7 Conclusions

A thorough history of the lesion with regards to change in morphology and/or growth over time is important. As there is a narrow window of opportunity for both patients and doctors to detect rapidly growing lesions whilst they are still thin, an awareness of the 'atypical' features of melanoma is critical.

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2.5.3 Sequential digital dermoscopy imaging

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2.5.4 Automated instruments

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2.5.5 Confocal microscopy

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2.6 Biopsy of suspicious lesion

Contents

2.6.1 Background

Biopsy of a suspicious pigmented lesion aims to establish a diagnosis and to stage the tumour for planning definitive surgical therapy. In addition, an excisional biopsy may completely remove the tumour. Different methods of biopsy are variably effective in achieving these goals and it is important to choose the most appropriate method according to the aims of the biopsy, the site and size of the lesion, the index of suspicion for melanoma, the likelihood of invasive tumour, and patient factors including comorbidities, cosmesis and age.

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2.6.2 Summary of systematic review results

2.6.2.1 Complete excisional biopsies

2.6.2.1.1 Elliptical Excision and Primary Closure

The ideal method for skin lesions suspected of being melanoma is complete excision with a 2mm margin. An ellipse specimen should follow the lines of relaxed skin tension with the deep margin in subcutis. Primary closure is the preferred method of closure following excisional biopsy and skin flaps or grafts should be avoided because these may compromise the definitive re-excision.

Complete excision best facilitates accurate diagnosis and microstaging compared to partial biopsy techniques [1] .

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2.6.2.1.2 Deep Shave excision (Saucerisation) and punch excision

Deep shave excision (Saucerisation, scoop shave excision) and punch excision methods (e.g. 5 mm punch for a 3mm lesion) may also be used for complete excision but are more often associated with positive margins than elliptical excision and primary closure[2]. Deep shave excision may be defined as a shave excision that aims to completely remove the lesion both peripherally and in depth. However, skill and practice are required to perform the procedure effectively.

Attempts at deep shave excision will more often completely remove thin melanomas and are more likely to transect the tumour margins with increasing tumour thickness.[2][1] Transection of the tumour base will lead to loss of limited amounts of residual tumour that may be destroyed by inflammation and wound healing and may undermine the capacity to accurately assess tumour depth for prognostication, accurate staging and treatment planning.

Deep shave excision is becoming more widely used and in most recent studies was the dominant mode of biopsy for melanoma, particularly by dermatologists worldwide. Transection of the tumour base has been shown to be common with shave biopsy in recent studies (68%, 32%, 62%, 65%, 9%, 37% in studies from Egnatios,[3] Hieken,[4] Lowe,[5] Mills,[6] Mir[2] and Zager[7] respectively), though the extent to which these shaves were attempting to completely remove the tumour were generally not stated.

Deep shave excision has the advantages of being relatively speedy, inexpensive and requiring little equipment or staff assistance. The procedure thus allows the conduct of greater numbers of biopsies, including lesions with lower indices of suspicion. Delays are minimized in the conduct of biopsy procedures as many deep shaves are conducted as part of the consultation and do not require another appointment.

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2.6.2.1.3 Partial biopsies

Methods of partial biopsy that have been assessed include partial punch biopsy, shave biopsy and, to a lesser extent, incisional biopsy. At times partial biopsy may be the most appropriate mode of biopsy for large lesions, those on acral sites or other difficult locations where an excisional biopsy may have unwanted functional or cosmetic outcomes or in patients with significant comorbidities.

The most important outcome of a partial biopsy is accurate diagnosis. One large study has compared melanoma biopsy methods for the detection of melanoma.[1] This study showed that punch biopsy is associated with a false negative diagnosis rate of 23.3% compared with 4.5% for all shave biopsies and 1.7% for excisional biopsy. Adverse outcomes with persistence or progression of disease followed 11.6% of false negative diagnoses on punch biopsy and 1.7% following shave biopsy. Most of these false negative diagnoses and adverse outcomes would have been avoided if all lesions clinically suspected as melanoma that had then been shown to be melanocytic on biopsy had been immediately subjected to excisional biopsy. Most (78%) of incorrect diagnoses made on small punch biopsies were attributable to errors in histopathological interpretation and the remainder appeared to be due to sampling error. Partial biopsies may lead to pathological incorrect interpretation because it is not possible to assess important diagnostic criteria when the whole lesion is not available for assessment.

Accurate staging of the tumour on partial biopsy permits prognostication and planning of appropriate surgical therapy for the primary tumour. Understaging of melanoma as a result of partial biopsy has been examined in multiple studies. Increases in tumour thickness on assessment of residual melanoma in wide local excision (WLE) after a partial biopsy were shown in 31% of cases,[2] after 44% of shave and 38% of punch biopsies,[8] after 34% of punch and 13% of shave biopsies,[6] after 3.5% of shave biopsies[9] and after 13% of shave biopsies [10]. The variation may be explained by differing intentions on the part of the clinicians to partially or completely remove the tumour in the initial biopsy procedure.

Sufficient change in tumour thickness to upgrade the T-stage on WLE has been reported in 34% of punch biopsies and 19% of shave biopsies,[1] 2.5% of shaves,[9] 13% of shaves,[10] 8% of shaves and 23% of punches, [6] 11.7% of shaves and 7% of punches,[3] 7% of shave biopsies, 24% of punch biopsies, and 24% of incisional biopsies[4] and 3% of shaves.[7]

Upgrades to T-stages resulted in additional surgical therapy in 5% of shave biopsies, 4.7% of partial biopsies,[8] 3.3% of shaves [7] 2.1% of shaves and punches[9], 5% of shave biopsies, 18% of punch biopsies and 18% of incisional biopsies[4] and 5% of shave biopsies.[10]

Not all understaging of melanoma may be evident on the subsequent wide excision as diathermy used in the procedure or destruction of tumour by inflammation may destroy underlying tumour in the biopsy bed.

Deep shave excision (saucerisation) should be distinguished from superficial shave techniques which are generally used for partial biopsy. The latter are most appropriately applied to flat lesions that appear to be in situ. Shave biopsies of all types have been shown to be associated with very high rates of transection (64-65%) of the tumour base in some studies.[6][5] When shave excision is applied to thin melanomas (<1.0mm in tumour thickness), rates of base transection are much lower (9-21%)[2][9] with very few melanomas upstaged on WLE. Several studies have shown a relationship between base transection and increasing tumour thickness.[10][2][1] These studies do not distinguish attempts at deep shave excision from superficial shave for partial biopsy.

Survival and the performance and outcomes of sentinel node biopsy show no differences according to partial versus complete excisional biopsy type.[11][5][6][12][13][7]

There are no studies to date of the morbidity and cosmetic outcomes associated with different biopsy types.

All partial biopsies should include the most suspicious or invasive areas of the lesion. Dermoscopy or confocal microscopy may be helpful in targeting the most suspicious area.

It may be appropriate to indicate in the pathology report that a partial biopsy may not be fully representative of the lesion.

Partial biopsies are an important cause of litigation in the USA because of inadequate material being available for analysis by the pathologist.[14]

Naevoid melanomas and desmoplastic melanomas may be extremely difficult to diagnose histopathologically, particularly on a small biopsy.

It is important to consider the weaknesses of partial biopsies when interpreting the pathologist's report. If the result does not accord with the clinical impression or there is diagnostic uncertainty, an additional sample should be obtained, preferably by performing a complete excision. This is especially important when the histopathological diagnosis from a partial biopsy is of a melanocytic lesion.

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2.6.2.2 Clinical information for the pathology request to facilitate accurate histopathological diagnosis

All biopsy requests should include information on history of lesional changes, site of the lesion, age and gender of the patient and previous melanoma history. Any previous trauma or attempted therapeutic intervention to the lesion should be noted. If possible, the provision of clinical and dermoscopic images to the pathologist have been shown to enhance accuracy of histopathological diagnosis.[15]

The biopsy type and proportion of the lesion sampled should be indicated. Focally suspicious areas within a larger lesion can be indicated on a diagram or photograph or marked for the pathologist e.g. with superficial punch incision.[16]

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2.6.2.2.1 Indications for different modes of partial biopsy

Partial incisional or shave biopsies may be appropriate in the hands of experienced clinicians and in carefully selected clinical circumstances, such as large in situ or for large facial or acral lesions or where the suspicion of melanoma is low.

An incisional, partial **punch biopsy** provides dermis and often subcutis for assessment of tumour thickness but samples only a limited width of the lesion and is therefore prone to sampling error as well as diagnostic error. Punch biopsy should be avoided if there is any possibility of melanoma because of the high rates of false negative diagnosis demonstrated with partial punch technique. Multiple punch biopsies may reduce error in selected cases.

A **broad superficial shave biopsy** can provide a larger area of epidermis for histopathology and is often a useful diagnostic technique for large superficial lesions, but often fails to include sufficient dermis for the assessment of deeper parts of lesions with a significant dermal component. These biopsies may be considered for lesions that are likely to be confined to the epidermis (e.g. when attempting to differentiate in-situ melanoma from solar lentigo or seborrheic keratosis or a flat acquired melanocytic naevus). In order to maintain the integrity of the epidermis on the sample, at least papillary dermis must be present across the shave. Superficial shave biopsies taken through papillary dermis heal with little or no scar and are therefore suitable for use on the face. A photograph to identify the biopsy site should be used for superficial shave biopsies in cases for which it may not be possible to identify the biopsy site when it has healed.

Incisional biopsy removing as much of the lesion as is feasible or the most invasive or suspicious part can be a very useful method of partial biopsy in larger tumours.

Frozen section and cytological analysis are inappropriate for suspicious pigmented lesions, but may be of value (particularly fine needle biopsy cytology) when assessing potential metastases from a melanoma, for example, in a lymph node or subcutaneous tissue.

When clinical suspicion of malignancy is low and there is no elevation or induration to suggest possible invasive melanoma, short term observation for 3-6 months may be appropriate, preferably backed up by a dermoscopic image, a clinical image and an accurate description and measurement of the lesion.[17]

Referral to a specialist should be considered before biopsy for lesions in technically difficult anatomical locations (e.g. the eyelid) or where the operator is not confident in achieving an adequate sample or good cosmetic result. The specialist to whom the referral is being made should be advised directly of the degree of urgency.

Where clinical suspicion remains despite a negative pathology report following a partial biopsy, re-biopsy or excision should be performed. Even after complete excision, if the pathology result does not correlate with the clinical impression, discussion of the case with the pathologist is recommended. Review of the slides by a second pathologist may be appropriate if clinical suspicion remains or if there is diagnostic uncertainty.

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2.6.3 Evidence summary and recommendations

Evidence summary	Level	References
Partial biopsies versus completeness of excision Complete excision with a 2mm margin is the most reliable diagnostic biopsy method for skin lesions suspected of being melanoma.	III-2	[1]
Punch biopsy has been shown in one large study to be associated with high rates of false negative histopathological diagnosis of 23% and should be used with caution for melanocytic lesions.	III-2	[1]
Deep shave excision (saucerisation) is more likely to accurately stage the melanoma if it is in situ or superficially invasive.	III-2, IV	[1], [2], [10]
Partial biopsy has been shown to underestimate T-stage in 7-34% of punch biopsies and 3-19% of shave biopsies and provides insufficient information for appropriate surgical planning in 2-18% of punch biopsies and 2-5% of shave biopsies.	III-2, IV	[1], [6], [4], [8], [7], [10]
Survival and the performance and outcomes of sentinel node biopsy show no differences according to partial versus complete excisional biopsy type.	III-2, IV	[11], [5], [12], [13], [7]

2.6.3.1 Recommendations

Evidence-based recommendation	Grade
The optimal biopsy approach for a suspicious pigmented lesion is complete excision with a 2mm clinical margin and upper subcutis.	**C**

Evidence-based recommendation	Grade
Partial biopsies may not be fully representative of the lesion and need to be interpreted with caution and in light of the clinical findings to minimise incorrect false negative diagnoses and	**C**

Evidence-based recommendation	Grade
understaging.	

Evidence-based recommendation	Grade
In carefully selected clinical circumstances (such as large in situ lesions, large facial or acral lesions or where the suspicion of melanoma is low) and in the hands of experienced clinicians, partial incisional, punch or shave biopsies may be appropriate.	**C**

Practice point
It is advisable to discuss unexpected pathology results with the reporting pathologist.

Practice point
Punch biopsy should not be utilised for the routine diagnosis of suspected melanoma because this technique is associated with high rates of histopathological incorrect false negative diagnosis. Where a punch biopsy has been used for the diagnosis of a suspected BCC or SCC, and the diagnosis has been found to be melanocytic, then consideration should be given to excision of the entire lesion.

Practice point
The use of deep shave excision (saucerisation) should be limited to in situ or superficially invasive melanomas to preserve prognostic features and optimise accurate planning of therapy.

2.6.4 Conclusion

2.6.4.1 Issues requiring more clinical research

A better understanding of the role of deep shave excision (saucerisation) and superficial shave biopsy is needed.

Future studies are needed that clearly define the intention of the biopsying clinician to partially or completely biopsy each lesion. The index of clinical suspicion for each lesion would be helpful to further understand the intention of the clinician. Studies should include a clear description of the intended biopsy method to distinguish superficial shave biopsy from deep shave excision (saucerisation) and partial punch incision from punch excision. The presently available studies are retrospective and because they group attempts at partial or complete biopsy by different methods, results vary widely.

Studies that evaluate the morbidity and cosmetic outcomes associated with different biopsy types are also needed.

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2.7 Clinical information for the pathologist

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2.8 Definitive margins for excision of primary melanoma

Contents

2.8.1 Background

Surgery is currently the only potentially curative treatment for primary cutaneous melanoma. Standard treatment is wide local excision (WLE) of the skin and subcutaneous tissues around the melanoma with a safety margin. . The aim is complete excision of all *in situ* and invasive melanoma components. The purpose of the excision margin of additional tissue is to remove both the primary tumour and any melanoma cells that might have spread from the primary melanoma into the surrounding skin and subcutaneous tissue. If the malignant cells have spread no further, and are entirely included in the safety margin, the operation should prove to be curative.

Complete excision should be confirmed by histological examination of the excised specimen with special reference to the periphery. The in-situ component (which can be invisible), where present, often extends beyond the invasive melanoma, and complete excision of both is mandatory.

The width of excision margins is important because there could be trade-off between a better cosmetic result and poorer long-term outcomes if margins become too narrow.

The recommendations for the width of melanoma excision margins are based on the Breslow thickness of the primary melanoma at its thickest depth of invasion, as determined by histological assessment of the initial excision biopsy. In general, wider excision is favoured for tumours with a less favourable prognosis, such as increased Breslow thickness.

Surgical excision margins according to the tumour thickness have been assessed in six randomised controlled trials (RCTs) including a total of 4233.[1][2][3][4][5][6] All six RCTs assess width of excision but do not consider depth of excision. These RCTs compare narrow (1 to 2 cm) versus wide (3 to 5 cm) excision margins and assess outcomes including overall survival, melanoma specific survival and 'local recurrence', with median follow-up ranging from 5 to 16 years. However, definitions of 'local recurrence' are often inconsistent or unstated, and the impact on patient survival is unclear, so 'local recurrence' data must be interpreted with caution. In addition, the RCTs have been further assessed in six systematic reviews and meta-analyses.[7][8][9][10][11][12] There are also several published case series that provide further data. Unfortunately, the extent of surgical excision margins that should be used for a given thickness of melanoma and the magnitude of benefit of different margins remains unclear. This is because the trials use different criteria and 1 vs 2 cm margins have not been yet directly compared for all invasive melanomas to be conclusive to answer the question of what margin is minimal or optimal to be safe.

There are no RCTs which assess depth of excision. Recent studies suggest that excision of the deep fascia does not improve the outcome of melanomas thicker than 1 mm[13] or 2 mm[14] but results of these retrospective studies must be interpreted with caution. The depth of excision in usual clinical practice is excision down to but not including the deep fascia, unless the fascia is involved with tumour or is technically warranted.

However, in case of thick lesions, in the absence of a sufficient subcutis layer and in special areas where the deep fascia is less clearly defined, such as the face, neck and breast, the vertical excision margins require adaptation to the anatomic condition, for example down to the perichondrium on the ear.

Acral lentiginous and subungual melanomas are specific types of cutaneous melanoma that arise in the extremities/soles/palms and nail matrix respectively. Treatment of these melanomas for the most part has not been assessed in trials.

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2.8.2 Economic outcomes, patient preferences and adverse events

The available RCTs, systematic reviews and meta-analyses do not assess economic outcomes and patient preferences regarding width of excision. The Cochrane review does however state, "From the individual's point of view, when faced with a diagnosis of melanoma, the most important consideration is to make sure that it is removed with as much certainty as possible so that it is all gone! The size and depth of the excision should therefore err on the side of safety first. However, quality of life after surgery is an important consideration and unnecessary disfigurement should be avoided."

However, three trials, the Intergroup,[1] the UKMSG[6] and the 1992 Swedish Study,[4] do report adverse event outcome measures.[insert citations here]

The Intergroup trial[1] assessed skin grafting, hospital stay, wound infection rate, wound dehiscence (skin separation) rates:

- The rate of skin grafts was reduced from 46% with 4 cm surgical margins to 11% with 2 cm surgical margins ($P < 0.001$).
- For the study cohort as a whole, the hospital stay was reduced from 7.0 days for participants receiving 4 cm surgical margins to 5.2 days for those receiving 2 cm margins ($P = 0.0001$). This reduction in length of hospital admission was mainly due to the reduced need for skin grafting, since the hospital stay for those who had a skin graft was 3.5 days longer than that for those who had a primary wound closure (6.5 days versus 3.0, $P < 0.01$).
- There was no significant difference between wound infection rates (4.6% and 5.4%) between the two groups (4 and 2 cm margins respectively).
- There was no significant difference between wound dehiscence rates (4.2% and 4.6%) between the two groups (4 and 2 cm margins respectively).

The UKMSG trial[6] stated that the rate of surgical complications was 7.8% among participants with a 1 cm excision margin compared with 13.9% among those with a 3 cm excision margin ($P = 0.05$).

The 1992 Swedish Study[4] summarised their rates of primary closures, graft and flap between the two groups. Primary closure of the wound was possible in 319 patients (69%) in the 2-cm group compared with 173 (37%) in the 4-cm group. Split skin graft was used in 58 patients (12%) and 223 (47%), in the narrow and wide excision groups respectively. A surgical flap was used in 19 patients (4%) in the narrow excision group and 27 (6%) in the wide excision group.

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- Excision margins for invasive melanomas and melanomas at other sites

2.8.3 References

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2.8.4 Appendices

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2.9 Melanoma in situ

Contents

2.9.1 Background

As for invasive melanoma, the treatment for melanoma *in situ*, including lentigo maligna, is complete surgical excision with clear margins. For excision to be successful, a margin of clinically normal skin must be included because invisible tumour often exists at the margins.

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2.9.2 Evidence

There are no RCTs and limited case series data to help direct excision of melanoma *in situ*.[1] Given this lack of evidence, in 1992 consensus guidelines were published suggesting that 5 mm excision margins should be adequate for melanoma *in situ*. However, recent studies have shown that 5 mm margins are inadequate and lead to significant rates of disease recurrence, particularly for head and neck disease.

A large prospective study[2] assessed complete clearance of 1120 melanomas *in situ* excised by Mohs micrographic surgery with frozen-section examination of the margin.} Six millimetre margins were adequate for complete clearance in 86% of all tumours; 9 mm margins were adequate for complete clearance in 98.9% of all tumours. A 1.2 cm margin yielded 99.4% clearance, 1.5 cm margin yielded 99.6% clearance, and 3 cm margin yielded 100% clearance. The authors state that "the frequently recommended 5 mm margin for melanoma is inadequate. Standard surgical excision of melanoma *in situ* should include 9 mm of normal-appearing skin, similar to that recommended for early invasive melanoma". This study includes a mixture of cases of melanoma *in situ*, both lentigo maligna (LM) and non-lentigo maligna type, and it is possible that LM requires a wider margin than other melanomas *in situ*.

A retrospective review of 192 cases of melanoma *in situ*[3] found that LM required wider margins for complete excision than did non-lentigo maligna melanoma *in situ*.

In another retrospective study of 117 LM and lentigo maligna melanoma (LMM) cases treated with a staged margin-controlled excision technique,[4] the mean total surgical margin required for excision of LM was 7.1 mm and was 10.3 mm for LMM. Of the tumours diagnosed as LM on initial biopsy specimen, 16% were found to have unsuspected invasion. Total surgical margin was associated with initial clinical lesion diameter. The authors concluded that the standard excision margins for LM and LMM are often inadequate and occult invasive melanoma occurs in LM. Dermatoscopy and confocal microscopy may be useful in defining margins before excision of melanoma *in situ*.

A retrospective review of 343 cases of melanoma *in situ* on the head and neck treated by Mohs micrographic surgery[5] showed that 65% of cases were cleared by a 5 mm margin whilst 15 mm margins were needed to obtain a 97% clearance rate. The authors concluded that "melanoma *in situ* on the head and neck can spread significantly beyond the clinical margins and demonstrates the importance of confirming clearance histologically before closure procedures. Mohs surgery has the advantage of total margin evaluation and where available it may be reasonable to start with 5 mm margins. Where Mohs surgery is not a treatment option, the authors would advocate larger excision margins of ≥ 10 mm."

In a study of 51 cases of facial LM and thin (<1 mm) LMM, with LMM present in nine lesions (average Breslow depth, 0.65 mm),[6] peripheral margin control was performed with repeated margin excision until histological clearance of the lesion. Margins required for clearance of LM and LMM averaged 1.0 and 1.3 cm, respectively. No recurrences were identified with long-term follow-up. Immediate reconstruction was performed in all cases.

In another retrospective review of 293 cases of LM and LMM treated by geometric staged excision,[7] the mean margin to clearance after excision was 6.6 mm for LM and 8.2 mm for LMM. Of concern, 26.6% of LM would not have been adequately excised using traditional 5 mm margins. The rate of recurrence of after geometric staged excision was 1.7% with a mean of 32.3 months of follow up. A total of 11.7% of LMM was initially diagnosed as LM on biopsy, with the invasive component discovered only after excision.

Zitelli comments that "Many surgeons shudder at the thought of such wide margins on the head and neck, and therefore it is important to note that Mohs surgery using MART 1 immunostains offers a way to keep more narrow margins for the majority of patients yet still have the ability to identify the outlier patients with wide subclinical extensions of MIS. The importance of clearing MIS on the first procedure is that recurrence appears as invasive melanoma of 1-mm thickness in 23% of recurrences."[8]

Most international guidelines suggest 5 mm margins for melanoma *in situ*.[9][10] However, as discussed above, recent studies have shown that 5 mm margins are inadequate for many cases of melanoma *in situ* and may lead to significant rates of disease recurrence. The 2010 UK guidelines state 5 mm margins to achieve complete histological clearance.[11] The 2011 US guidelines go further recommending 5 mm-1 cm margins and state that "wider margins may be necessary for lentigo maligna subtypes".[12]

The BMJ Best Practice monograph on melanoma[13] states that “For melanoma *in situ* the recommended surgical margin is 0.5 cm. The 5-year survival is about 98%. No adjunctive or secondary treatment is necessary. Some studies have found that this margin will be inadequate in some (up to 50% of) cases of melanoma *in situ* and particularly lentigo maligna. Options for dealing with this include: (a) wide excision with 1-cm margin; (b) staged excision with careful margin assessment; and (c) Mohs surgery.”

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2.9.3 Evidence summary and recommendations

Evidence summary	Level	References
There is case series evidence suggesting that 5 mm margins are inadequate for many cases of melanoma *in situ* and may lead to significant rates of disease recurrence.	IV	[2], [3], [4], [5], [6], [7]

2.9.3.1 Recommendations

Evidence-based recommendation	Grade
After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 5-10 mm with the aim of achieving complete histological clearance. Melanoma *in situ* of non-lentigo maligna type is more likely to be completely excised with 5mm margins whereas lentigo maligna may require wider excision. A final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**D**

Practice point

Mohs surgery, using appropriate immunostains, is useful in achieving complete histological clearance of melanoma *in situ*/lentigo maligna.

Practice point

Geometric staged excision is also useful in achieving complete histological clearance of melanoma *in situ* /lentigo maligna.

Practice point

Excisions should have vertical edges to ensure consistent margins.

Practice point

For all melanomas, a final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary because positive histological margins are unacceptable.

Practice point

Excision biopsy of the complete lesion with a narrow (2–5 mm) margin is appropriate for definitive diagnosis of primary melanoma. Lesions excised with a margin less than those defined above should be re-excised to achieve these margins.

Practice point

Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved or has been reached during the diagnostic excision.

Practice point

Where tissue flexibility is limited, a flap repair or skin graft is often necessary subsequent to an adequate margin of removal.

Practice point

Most melanomas can be treated as an outpatient or day-case under local anaesthesia, unless nodal surgery is required.

Practice point

Patients should be informed that surgical excision may be followed by wound infection, bleeding, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar, dehiscence and the possibility of further surgery.

Practice point

Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin (e.g. lentigo maligna) and those with difficult-to-define margins (eg amelanotic and desmoplastic melanomas). In these categories, the presence of atypical melanocytes at the margins of excision should be detected by comprehensive histological examination (including immunohistochemical staining) and followed by wider excision.

Practice point

Amelanotic melanoma can present significant difficulties for defining a margin with up to one third of subungual and nodular melanomas being non-pigmented. This may dictate choice of a wider margin, or further re-excision, where practicable.

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2.9.4 References

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2.10 Invasive melanomas

Contents

2.10.1 Melanomas ≤ 1mm thick

There are no RCTs that specifically assess only melanomas less than 1 mm thick. However, three of the RCTs that assessed melanomas ≤ 2mm thick included 762 participants with melanomas ≤ 1mm thick. These were the French trial (159 participants),[1] 1982 Swedish trial (244 participants)[2] and the World Health Organisation (WHO) trial (359 participants).[3] No difference in mortality was found for wider excision (5 cm in the French study,[1] 5 cm in the 1982 Swedish study,[2] 3 cm in the WHO study[3]) compared with narrower excision (2 cm in the French study,[1] 2 cm in the 1982 Swedish study,[2] 1 cm in the WHO study[3]). Of note, only 185 participants (WHO trial[3]) were treated with a 1 cm excision margin.

A recently published case-control study of 11,290 patients with thin melanomas (≤ 1 mm thick) showed that local recurrence was associated with < 8 mm histologic excision margins (corresponding to < 1 cm margins in vivo), suggesting that a ≥ 1 cm clinical excision margin for thin melanomas reduces the risk of local recurrence.[4]

Therefore, there is only limited data on which to base clinical recommendations for excision margins for melanoma ≤ 1mm thick. However, a 1 cm margin is widely accepted as standard treatment for thin (< 1 mm) melanomas and most international guidelines recommend 1 cm excision margins for melanoma < 1 mm thick.

See the evidence based recommendation.

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2.10.2 Melanomas 1.01 mm–2.00 mm thick

Four RCTs assessed melanomas between 1 mm and 2 mm thick and included 1429 patients. These were the French trial (167 participants),[1] the 1982 Swedish trial (745 participants),[2] the WHO trial (245 participants)[3] and the Intergroup trial (272 participants).[5] None of these trials demonstrated a statistically significant difference in overall survival between the two groups that were treated with wide (5 cm in the French study,[1] 5 cm in the 1982 Swedish study,[2] 3 cm in the WHO study,[3] 4 cm in Intergroup study[5]) or narrow (2 cm in the French study,[1] 2 cm in the 1982 Swedish study,[2] 1 cm in the WHO study,[3] 2 cm in the Intergroup study[5]) excision. Of note, only 113 participants (WHO trial[3]) were treated with a 1 cm excision margin.

Three retrospective studies[6][7][8] have assessed the width of excision margins for melanomas ≤ 2 mm thick, but the magnitude of any potential associations is difficult to understand, due to the need for multivariate adjustment for confounding by other risk factors. A large single centre retrospective study of 2681 patients with melanoma ≤ 2 mm thick suggested that a 1 cm clinical margin was adequate for cutaneous melanomas ≤ 2 mm in thickness and does not impact local recurrence or survival.[6] In another large single centre retrospective study of 2131 patients with primary cutaneous melanomas 1.01-2.00 mm thick, pathologic excision margins of < 8 mm were associated with worse regional node recurrence-free survival and distant recurrence-free survival compared with margins ≥ 8 mm (corresponding to ≥ 1 cm surgical margins), but did not translate into a statistically significant difference in melanoma-specific survival.[7] In another retrospective single centre series of 576 patients with 1-2 mm thick melanomas, 1 cm margins were associated with a small increase in local recurrence compared with 2 cm margins but this did not impact on overall survival.[8]

Again, there are only limited data on which to base clinical recommendations for excision margins for melanoma 1.01 mm–2.00 mm thick. There is little data to help differentiate between 1 cm and 2 cm margins for these tumours. Most international guidelines recommend either 1 cm excision margins or 1–2 cm excision margins for 1.01 mm–2.00 mm melanoma.

See the evidence based recommendation.

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2.10.3 Melanomas 2.01 mm–4.00 mm thick

Three RCTs included participants who had melanomas between 2 and 4 mm thick and included 1516 patients. These were the Intergroup trial (190 participants),[5] the 1992 Swedish trial (666 participants)[9] and the United Kingdom Melanoma Study Group (UKMSG) trial (approximately 660 participants).[10] None of these trials demonstrated a statistically significant difference in overall survival between the two groups who were treated with wide (4 cm in the Intergroup study,[5] 4 cm in the 1992 Swedish study,[9] 3 cm in UKMSG study[10]) or narrow (2 cm in the Intergroup study,[5] 2 cm in the 1992 Swedish study,[9] 1 cm in UKMSG study[10]) excision.

The recently updated UKMSG trialshowed a statistically significant improvement in melanoma specific survival (MSS) in favour of wide excision compared with narrow excision (HR 1.24: 95% CI 1.01 – 1.53; p = 0.041) but no statistically significant difference in overall survival between the 2 groups (hazard ratio [HR] 1.14, 95% CI 0.96 – 1.36; p = 0.14).[10] It is difficult to interpret the implications of this modest improvement in MSS in the absence of any significant difference in overall survival. Of note, MSS and overall survival were both secondary outcomes in this study. MSS is a more difficult than overall survival to measure accurately because it relies on accurate information about cause of death. Given that a significant number of melanomas in the UKMSG study were thick melanomas over 4 mm, it is unclear whether this influenced the overall study results. In an accompanying editorial, it is suggested that “the excess nodal disease in the narrow margin group was indicative of poor prognostic disease before the intervention, rather than resulting from the narrow margin intervention itself”.[11]

In a large single centre retrospective review of 1587 patients with melanomas 2.01 mm–4.00 mm thick, a histopathologic excision margin of 8 mm or more (roughly equivalent to a ≥ 1 cm surgical margin) was associated with increased local and intransit recurrence-free survival and disease-free survival compared with a less than 8 mm margin.[12] Another retrospective single centre cohort study of 325 patients with melanoma > 2 mm thick evaluating 1 cm or 2 cm excision margins showed no significant differences in locoregional and distant metastasis, and disease-free and overall survival between the groups.[13]

Given there is no difference in overall survival when comparing 4 cm and 2 cm margins in the Intergroup study[5] and 1992 Swedish study,[9] it seems reasonable to conclude that in most cases there is no need to take more than 2 cm margins for thick melanomas. Indeed, there is no convincing RCT evidence that a margin greater than 2 cm offers additional benefit for the patient in terms of overall survival or ‘local recurrence’, irrespective of melanoma thickness. The clinical significance of the modest improvement in melanoma specific survival in the UKMSG trial[10] in the 3 cm excision group compared with the 1 cm excision group in the absence of benefit in overall survival remains unclear. On balance, given the available evidence, we continue to recommend 1-2 cm excision margins for melanomas of Breslow thickness 2-4 mm. This is unchanged from our 2008 recommendation.

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2.10.4 Melanomas > 4 mm thick

Approximately 240 participants in the UKMSG study had melanomas > 4 mm thick.[10] A further 270 participants in the 1992 Swedish Study had melanomas 4 mm or thicker.[9] In both of these studies there was no statistically significant difference in overall survival between the two groups who were treated with wide or narrow excision.[10][9] Within these two studies patients with melanomas > 4 mm were analysed as part of the entire cohort and not as separate groups so it is not known how well the overall results can be extrapolated to these thicker melanomas.[10][9]

In a retrospective study of 632 clinically lymph node negative patients with melanomas more than 4 mm thick, histopathologically determined primary tumour excision margins more than 16 mm (corresponding to 2 cm surgical margins) were associated with better local control compared with narrower margins.[14]

No RCT data exist that any margin wider than 2 cm (that is 3, 4, or 5 cm) would result in any superior disease-specific outcomes, but these wider margins are associated with increased surgical morbidity. Most international guidelines suggest an excision margin of 2 cm for thick tumours over 4 mm thick. Individual adverse prognostic melanoma characteristics may dictate more caution and wider excision margins as clinically appropriate, although RCT data is lacking.

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2.10.5 Melanomas at other sites

The six RCTs[5][3][2][9][1][10] included in our review do not adequately address the issues of melanomas in specific body sites, such as head and neck, distal extremities, hands and feet (including digits and subungual melanomas). For example, only the French study included melanomas on the head and neck and this involved only 16 participants.[1]

In special areas where the deep fascia is less clearly defined, such as the face, neck and breast, the vertical excision margins require adaptation to the anatomic condition, for example down to the perichondrium on the ear.

The morbidity (particularly 'cost' for reconstruction, complications or potential disfigurement) associated with wider excisions on the face is likely to be greater than for those on the trunk. For example, even 1 cm margins are potentially problematic in critical facial locations. For this reason, some experts have advocated narrower margins on the face but there are no RCT data to help determine the consequences on mortality or recurrence of these narrower margins. A few non-randomised trials suggest that excision margins on the head and neck can be safely reduced but the results must be interpreted with caution given the nature of the studies.

In a recently published study, 79 cases of primary, invasive head and neck melanoma were treated by wide local excision and followed prospectively for local recurrence.[15] Forty-two wide local excisions were performed according to current National Comprehensive Cancer Network (NCCN) practice guidelines and reduced margins were utilized in 37 cases to preserve critical anatomical structures such as the eyelid, nose, mouth and auricle. Reducing margins of wide local excision did not increase local recurrence rates as demonstrated by local recurrence-free survival (90.4% vs. 91.9%, P = 0.806) at 5 years follow-up, suggesting that excision margins may be safely reduced in melanomas in close proximity to structures of the head and neck, but this was a small non-randomised study.

In a retrospective study of 368 melanomas of the face, the authors suggest that reduced safety margins can be employed in melanomas of the face.[16]

A prospective study evaluated 161 patients with melanoma of the external ear. The median thickness of the tumours in the present study was 1.08 mm (mean 1.51 mm; range 0.18–8.50 mm), and the median excision margins were 11.0 mm (mean 12.61 mm; range 2.0–31.0 mm). The 3-year disease-specific survival rate was 98%, and the 3-year recurrence-free survival rate was 83%. The authors concluded that the use of micrographic surgery, made it possible to reduce the excision margins (median 5 mm vs. 10 mm) without an increased risk of recurrence.[17]

A retrospective chart review of 78 patients evaluated the prognostic variables and clinical ramifications of melanoma of the ear.[18] Melanoma thickness averaged 1.7 mm (range 0.2–7.0 mm). After a mean follow-up of 55.7 months, 10 patients (13%) had local recurrence, 9 patients (12%) had regional recurrence, and systemic metastases had developed in 17 patients (22%). The authors concluded that treatment of malignant melanoma of the external ear should follow current standard guidelines, which require wide local excision with negative margins.

Guidelines for wide excision of cutaneous melanomas according to Breslow thickness are impractical when considering melanomas arising on eyelid skin. A retrospective study of 56 patients with invasive cutaneous eyelid melanoma sought to determine whether excision margins influenced locoregional recurrence, and to identify prognostic factors for survival in these patients.[19] Local recurrence occurred in 12 patients (21%), nodal metastasis in 6 (11%) and distant metastasis in 2 (4%). Pathological margins > 2 mm from the in situ component of the tumour were associated with increased disease-free survival (P = 0.029) compared with margins ≤2 mm but there was no statistically significant benefit for a pathological margin > 2 mm from the invasive component. The results suggest that, as a minimum, an in vivo surgical margin of 3 mm (corresponding approximately to a 2 mm pathological margin after tissue fixation) is desirable for eyelid melanomas. The authors recommended a surgical excision margin of 3 mm for eyelid melanomas ≤ 1 mm in Breslow thickness but for melanomas > 1 mm in thickness, the current practice of aiming to achieve 5 mm margins would seem reasonable. Patients with lower eyelid melanomas warrant particularly close follow-up given their higher local recurrence rate.

Management of digital melanomas including the subset of subungual melanomas often includes partial amputation.[20][21] As with facial lesions, there are no RCTs available to help determine whether less aggressive surgery would be as effective. Achieving a balance between adequate melanoma excision with the most appropriate margins for the site and characteristics of the melanoma, while maintaining the optimal preservation of function would seem sensible.

See the evidence based recommendation.

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2.10.6 Evidence summary and recommendations

Evidence summary	Level	References
There is no convincing RCT evidence that a margin greater than 2cm offers additional benefit for the patient in terms of overall survival or 'local recurrence', irrespective of melanoma thickness.	I, II	[5], [3], [2], [9], [1], [10], [22], [23], [24], [25], [26], [27]
Furthermore, two RCTs show evidence that a margin greater than 1cm offers no survival advantage, although it is not clear whether a wider margin reduces the risk of 'local recurrence'.	II	[3], [28]
Systematic review indicates that there are currently inadequate data to confirm a mortality difference between wider and narrower excision for primary invasive melanoma.	I	[22], [23], [24], [25], [26], [27]
For acral lentiginous and subungual melanomas there are no RCTs or SRs to define excision margins. Data are from retrospective case studies. There is limited RCT data for head and neck melanoma with the majority of data also derived from retrospective case series. Excision margins might be modified to accommodate individual anatomic sites or functional considerations, but this practice would be based solely on case-series information, and individual factors, rather than RCT evidence which is currently lacking.	III-2, IV	[15], [16], [18], [19], [20], [21]

2.10.6.1 Recommendations

Evidence-based recommendation	Grade
(pT1) melanoma < 1.0 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1 cm. A final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**B**

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Evidence-based recommendation	Grade
(pT2) melanoma 1.01 mm–2.00 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm. A final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**B**

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Evidence-based recommendation	Grade
(pT3) melanoma 2.01 mm–4.00 mm After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 1–2 cm. A final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary; positive histological margins are unacceptable. Caution should be exercised for melanomas 2.01–4.00 mm thick, especially with adverse prognostic factors, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours depending on the tumour site and characteristics, and prevailing surgeon/patient preferences.	**B**

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Evidence-based recommendation	Grade
'(pT4) melanoma > 4.0 mm' After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be 2 cm. A final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary; positive histological margins are unacceptable.	**B**

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Evidence-based recommendation	Grade
Acral lentiginous and subungual melanoma are usually treated with a minimum margin as set out above, where practicable, including partial digital amputation usually incorporating the joint immediately proximal to the melanoma.	**D**

Evidence-based recommendation	Grade
Excision margins might be modified to accommodate individual anatomic sites or functional considerations, but this practice would be based solely on case-series information, and individual factors, rather than RCT evidence which is currently lacking.	**D**

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Practice point
Excisions should have vertical edges to ensure consistent margins.

Practice point
For all melanomas, a final assessment of excision margins should be made in the light of the histological margins. Consideration should be given to further excision if necessary because positive histological margins are unacceptable.

Practice point
Excision biopsy of the complete lesion with a narrow (2–5 mm) margin is appropriate for definitive diagnosis of primary melanoma. Lesions excised with a margin less than those defined above should be re-excised to achieve these margins.

Practice point

Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved or has been reached during the diagnostic excision.

Practice point

Where tissue flexibility is limited, a flap repair or skin graft is often necessary subsequent to an adequate margin of removal.

Practice point

Most melanomas can be treated as an outpatient or day-case under local anaesthesia, unless nodal surgery is required.

Practice point

Patients should be informed that surgical excision may be followed by wound infection, bleeding, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar, dehiscence and the possibility of further surgery.

Practice point

Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin (e.g. lentigo maligna) and those with difficult-to-define margins (e.g. amelanotic and desmoplastic melanomas). In these categories, the presence of atypical melanocytes at the margins of excision should be detected by comprehensive histological examination (including immunohistochemical staining) and followed by wider excision.

Practice point

Amelanotic melanoma can present significant difficulties for defining a margin with up to one third of subungual and nodular melanomas being non-pigmented. This may dictate choice of a wider margin, or further re-excision, where practicable.

Practice point

For patients with deeper invasive melanomas (> 1 mm thick), referral to a specialised melanoma centre should be considered to ensure that best practice is implemented and for the collection of national outcome data. This may present logistic difficulties in regional and remote areas, but specialist care is recommended.

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2.11 Sentinel node biopsy

Contents

2.11.1 Background

Sentinel lymph node biopsy (SLNB) is a minimally invasive surgical technique to identify low volume metastatic disease within the draining lymph node basin in patients undergoing treatment for primary melanoma. The technique was developed to identify patients with a positive draining nodal basin and thereby minimise the morbidity associated with elective lymph node dissection in patients who may not require this procedure. Numerous studies have consistently demonstrated that the status of the sentinel lymph node (SLN) reflects the status of the entire draining nodal basin.[1]

The technique of SLNB has been extensively described. Briefly, it involves pre-operative lymphoscintigraphy to identify the draining nodal basin for the anatomical location of the primary melanoma. This is followed by intraoperative intradermal injection of the melanoma site with patent blue dye. Intraoperative exploration through a small incision allows the identification of SLNs. A node is considered a SLN if it has tracer uptake and /or is stained blue. This dual modality approach allows the successful identification of a SLN in over 95% of patients.

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2.11.2 Summary of systematic review results

There have been numerous large studies published since the last guidelines regarding the role of SLNB in melanoma. The most important of these publications is the final report of the Multicentre Selective Lymphadenectomy Trial (MSLT-I).[2] This was a phase III randomised controlled trial comparing wide excision of the primary melanoma and regional nodal observation with wide excision and SLNB followed by immediate completion lymph node dissection (cLND) for patients with a positive SLNB. Patients in the observation arm underwent therapeutic lymph node dissection (tLND) if they developed clinical lymph node involvement. The study included 1661 patients and the main study population was the 1347 with melanoma of Breslow thickness between 1.2 and 3.5 mm.

The primary endpoint of the study[2] was melanoma specific survival (MSS) and the final report demonstrated no difference in MSS for patients with intermediate thickness melanoma between those in the SLNB group (10 year MSS =81.4%) compared with the observation group (10 year MSS = 78.3%) (HR for death=0.84; 95% CI 0.64-1.09; P=0.18). Furthermore, there was no difference in distant disease-free survival between the two groups (HR=0.89; 95% CI 0.70-1.13; P=0.34). A post-hoc latent subgroup analysis was developed in an attempt to estimate treatment effect for the subgroup of patients who were SLN positive (ie. at baseline in the biopsy arm and those who would have tested positive had SLNB been performed in the observation arm). This showed that patients with intermediate thickness melanoma and nodal metastasis had a 10-year MSS of 62.1% with lymphadenectomy compared to 41.5% with observation (HR for death=0.56; 95% CI 0.37-0.84; P=0.006).

Controversy lies in the validity of comparing two possibly biologically different groups. It is impossible to prove that all patients with micrometastases in the sentinel node would progress to clinically overt disease if left untreated. SLNB was positive in 16% of patients in the SLN arm and the estimated cumulative incidence of

nodal metastases at 10 years was 21.9% (adding patients with a false negative test) compared to an estimated cumulative incidence of nodal metastasis in the observation arm of 19.5% (ratio 1.12). This suggests a 12% greater rate of nodal metastases in the SLN arm relative to the observation arm which could be explained by over diagnosis of single cell deposits in the sentinel node which may never progress (false positive SLNB), or by late nodal recurrences still pending in the observation group, or this difference may simply be attributable to chance.

Evidence for a survival benefit from SLNB has been shown in a matched cohort study of 673 patients comparing melanoma-specific survival in the pre-SLN era with patients undergoing SLNB. This study demonstrated a survival advantage in the SLNB group (5 year MSS = 80.3% vs 84.8% p=0.049).[3] Similarly in a large single institution analysis comparing 2909 patients undergoing WLE and SLNB with 2931 patients undergoing WLE alone, a stratified univariate analysis demonstrated an improved melanoma specific survival for patients with melanoma 1-4 mm thick undergoing WLE + SLNB, however this benefit was not seen on multivariate analysis.[4]

In a multivariate analysis, the MSLT-I study showed that the status of the SLN was the strongest predictor of MSS (10 year MSS for SLN positive = 62.1% versus 85.1% for SLN negative [HR for death = 3.09; 95% CI 2.12-4.49; P<0.001]). Multiple retrospective cohort studies have confirmed on multivariate analysis that the status of the sentinel node is significantly associated with MSS and in all but one[5] the status of the SLN was the most significant predictor of MSS (HR 1.5-6.9).[6][7][8][9]

Many studies have described predictors of a positive SLN, the most consistent of these include tumour thickness, ulceration, primary location outside of HN, mitotic rate >0, decreasing age, nodular subtype and TIL grade[9][10]. Predictors of sentinel node involvement from 7,756 patients in the AJCC database are shown in Table 1.

2.11.2.1 Table 1. Clinical and pathological criteria predicting SLN metastasis by univariate logistic regression analysis (n = 7,756), Balch et al 2014

Source: Balch et al 2014[11] (**Note:** permission currently sought from journal)

SLNB is a minimally invasive day-surgery procedure which usually requires a general anaesthetic. Complication rates for SLNB vary from 5.9-13.8%[12][13] and are significantly lower than for completion or therapeutic lymphadenectomy. Complications predominantly consist of seroma and wound infections; these are usually mild, manageable and of limited duration. Complication rates are inversely correlated with procedure volume[13] .

The addition of SLNB to the management of patients with primary melanoma involves the upfront use of increased resources, which raises the question of additional cost. Morton et al performed a cost-effectiveness analysis incorporating direct Australian health care data.[14] This study found only a slight increase in cost ($24,045 compared with $23,182 per patient) but an increase in cost effectiveness given the improved disease free survival and the reduced morbidity of completion lymph node dissection compared to therapeutic lymph node dissection for patients with macroscopic nodal disease.

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2.11.2.2 Special situations

2.11.2.2.1 Thin melanoma

In thin melanomas (Breslow thickness <1 mm), the risk of a positive sentinel lymph node is low (<5%), however there are certain subgroups of patients at increased risk of nodal involvement. Predictors of a rate of SLN involvement of greater than 5% in melanoma less than 1 mm include Breslow thickness >0.75 mm combined with another high risk feature, such as ulceration, mitotic rate >1, Clark level IV or V or lymphovascular invasion.[15][16][17] As described for intermediate thickness melanoma, in patients with thin melanoma, SLN involvement is associated with significantly worse MSS.[15]

2.11.2.2.2 Thick melanoma

The risk of SLN involvement increases with Breslow thickness. The MSLT-1 study demonstrated a SLN positive rate of 33% in patients with thick melanoma. Whilst the status of the SLN remains the most significant predictor of outcome for patients with thick melanoma (HR 2.3), the procedure itself does not offer a survival benefit in this group.[18]

2.11.2.2.3 Desmoplastic melanoma

A positive SLN is found in 13.7% of patients with desmoplastic melanoma.[19] The rate of nodal involvement differs according to whether the melanoma is a pure or mixed DM, with much lower rates in pure DM.

2.11.2.2.4 SLN after prior wide excision

Wide local excision can interrupt lymphatic drainage patterns and therefore reduce the accuracy of SLNB. A number of studies have however demonstrated the feasibility of SLNB in patients with prior WLE.[20][21] Where possible SLNB should be performed at the same time as WLE.

2.11.2.2.5 Head and neck melanoma

There is increased complexity associated with SLNB in the head and neck region compared to other sites because of the anatomical proximity of the primary site to the sentinel node in addition to more complex lymphatic drainage patterns in the head and neck.[22] As such, SLNB in the head and neck is associated with a higher false negative rate.

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2.11.3 Evidence summary and recommendations

Evidence summary	Level	References
The status of the sentinel lymph node is the most significant predictor of melanoma-specific survival for patients with melanoma >1 mm Breslow thickness.	III-3, IV	[6], [7], [8], [9], [18]
Overall, for patients with melanoma >1 mm thick, sentinel lymph node biopsy followed by immediate completion lymph node dissection for a positive node does not prolong melanoma specific survival or overall survival compared with not performing sentinel node biopsy (nodal observation) and delayed lymph node dissection for clinically detected nodes.	II	[2]
For patients with intermediate thickness melanoma who harbour metastatic disease within the sentinel node, early intervention with sentinel lymph node biopsy may be associated with an increased melanoma specific survival compared with nodal observation.	III-2, III-3	[2], [3]
Complication rates for sentinel lymph node biopsy are low and are inversely related to procedure volume. The procedure should be performed in a centre with appropriate expertise. in particular for primaries arising in the head and neck.	III-3	[12], [13]

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2.11.3.1 Recommendations

Evidence-based recommendation	Grade
Sentinel lymph node biopsy should be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node positive.	**B**

Practice point
Sentinel lymph node biopsy (SNLB) should be performed at the time of the primary wide excision.

Practice point

Sentinel lymph node biopsy (SNLB) should be performed in a centre with multidisciplinary expertise in the procedure, including nuclear medicine, surgery and pathology to optimise the accuracy of the test.

Practice point

Patients being considered for sentinel lymph node biopsy (SNLB) should be given an opportunity to fully discuss the risks and benefits with a clinician who performs this procedure.

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2.11.3.2 Conclusions

Sentinel lymph node biopsy is primarily a staging procedure which provides the best means for prognostic stratification for patients with melanoma greater than 1 mm thick and for some patients with thin melanoma with high risk features. Given that SLNB provides the best stratification of outcome for patients with melanoma greater than 1 mm Breslow thickness, many clinical trials in the adjuvant setting use a positive SLNB followed by CLND as an eligibility criterion in the absence of clinically detectable nodes. As such, SLNB provides the opportunity for patients with microscopic nodal disease to be included in adjuvant clinical trials. The overall survival benefit of adjuvant therapies for patients with microscopic or macroscopic node positive disease is unknown at this stage however there a number of ongoing studies that will be reported in the near term.

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2.13.1 Primary desmoplastic neurotropic melanomas

Draft intro text here.

Michael Hughes.

See:

- What is the optimal management for primary desmoplastic neurotropic melanomas?
- What is the role of sentinel node biopsy for desmoplastic neurotropic melanomas?

2.13.2 Management of primary desmoplastic and neurotropic melanomas

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2.13.3 Sentinel node biopsy for desmoplastic melanoma

Appendices

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3 Melanoma in children

3.1 Management of MelTUMPs

PENDING :)

3.2 Sentinel node biopsy for MelTUMPs

3.3 Excision margins in MelTUMPs

3.4 Pregnancy following a diagnosis of melanoma

Intro to be inserted

See:

- Does pregnancy following diagnosis of melanoma affect prognosis?
- What is the optimal management for pregnant women with melanoma?

3.5 Management of pregnant women with melanoma

Content to be inserted.

3.5.1 References

3.5.2 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

3.6 Optimal management of pregnant women with melanoma

Content to be inserted.

3.6.1 References

3.6.2 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

3.7 Continuation of HRT or oral contraceptive pill

Content to be inserted.

3.7.1 References

3.7.2 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

3.8 Investigations and follow-up – Introduction

3.9 Patients with stage I and stage II melanomas

Systematic review in progress.

3.10 Patients with in-transit/regional node disease (stage III)

Systematic review in progress.

3.11 Patients with stage IV melanoma

Systematic review in progress.

3.12 Follow up after initial definitive treatment

Systematic review in progress.

3.13 Ideal frequency and duration of follow-up

Contents

3.13.1 Headings to be inserted

Draft content to be inserted

3.13.2 References

3.13.3 Appendices

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4 Treatment of satellite and in-transit metastases

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5 Treatment of macroscopic nodal metastases

Systematic review in progress.

5.1 Treatment of melanoma brain metastases

5.2 Systemic drug therapy for patients with brain metastases

COPY OF CONTENT UNTIL NEW CONTENT RECEIVED

5.2.1 Evidence from literature

Brain metastases are diagnosed in more than 50% of patients with advanced melanoma and are associated with a poor prognosis with a median OS of 2.8 to 4 months.[1][2] Phase III trials of effective drug therapies have excluded patients with active central nervous system (CNS) metastases, except for specifically designed phase II studies, summarised below. There were no new toxicities observed in this population of active melanoma brain metastases.

A phase 2 trial of the anti-CTLA-4 checkpoint inhibitor ipilimumab (10mg/kg for four doses) demonstrated an intracranial response of 16% (8/51) in neurologically asymptomatic patients (cohort A) but only a 5% (1/21) intracranial response rate in symptomatic (cohort B) patients requiring corticosteroids.[3]

In a small study patients with active melanoma brain metastases treated with the anti-PD-1 checkpoint inhibitor pembrolizumab, the intracranial response was 22% (4/18).[4] Similarly, in the larger randomised phase II Australian Brain Collaboration (ABC) study the intracranial response rate in asymptomatic patients with untreated brain metastases was 21% (5/25) with nivolumab monotherapy, but higher at 46% (16/35) with ipilimumab combined with nivolumab, and 56% for the combination when patients had no prior BRAF and MEK inhibitors.[5] The 12-month landmark PFS for each cohort was 20% and 53% respectively, with a plateau in the Kaplan Meier survival curve at approximately 6 months, raising the possibility that a significant proportion of patients may experience long-term disease control. A US single-arm study of the combination of ipilimumab and nivolumab in patients with asymptomatic melanoma brain metastases showed an intracranial response rate of 55% in the brain and a landmark 6-month PFS of 67%[6], although the burden of brain metastases in this trial was lower than that of the ABC trial (proportion of patients with > 3 brain metastases 21% versus > 4 brain metastases 46% in ABC).[5]

Phase II trials of BRAF inhibitor monotherapy for V600 mutant melanoma demonstrated an intracranial response of 39% for dabrafenib and 29% for vemurafenib as assessed by the investigators.[7][8] The combination the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib was assessed in a phase II trial of four different cohorts of V600 BRAF-mutation positive patients with active melanoma brain metastases.[9] The intracranial response rate was 58% in the largest cohort (n=76, cohort A), which included neurologically asymptomatic patients without previous local (brain) therapy. In contrast to the results with anti-PD-1-based immunotherapy, the PFS decreased over the first 12 months from 44% at 6-months to 19% at 12-months, suggesting that responses are short-lived as patients develop resistance.

As there are now many treatment options for the management of melanoma brain metastases, patients are strongly recommended to be discussed by an expert multi-disciplinary team of clinicians including a neurosurgeon, radiation oncologist and medical oncologist to determine the optimal combination or sequencing of both local (surgery and stereotactic radiosurgery) and systemic therapies. Whole brain radiotherapy is now rarely used, often reserved as last line palliative therapy.

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5.2.2 Evidence summary

Evidence summary	Level	References
Combined therapy with a BRAF inhibitor and MEK inhibitor induce an intracranial response of 58% in patients with asymptomatic untreated brain metastases whose melanoma has a V600E BRAF mutation.	III-1	[9]
Anti-PD-1 monotherapy in drug treatment naïve patients induces an intracranial response in at least 20% of patients with active melanoma brain metastases.	III-1	[4], [5]
Combined ipilimumab and nivolumab in drug treatment naïve patients induces an intracranial response in approximately 55% of patients with active brain metastases. (In drug-treatment naïve patients, phase II studies demonstrated a 56% and 55% intracranial response rate in the Australian Brain Collaboration and the CheckMate 204 studies, respectively, with a 6-month PFS rate of 53% and 67%, respectively). 41-Tawbi et al 2018, awaiting PMID	III-1	[5], [6]

Practice point
Drug therapy is active in untreated melanoma brain metastases, and can be considered as first line treatment (as an alternative to local brain therapy) in asymptomatic patients with multidisciplinary support with a radiation oncologist and neurosurgeon.

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5.2.3 References

1. ↑ Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. *Prognostic factors for survival in melanoma patients with brain metastases.* Cancer 2011 Apr 15;117(8):1687-96 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20960525.
2. ↑ Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, et al. *Determinants of outcome in melanoma patients with cerebral metastases.* J Clin Oncol 2004 Apr 1;22(7):1293-300 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15051777.
3. ↑ Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. *Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial.* Lancet Oncol 2012 May;13(5):459-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22456429.
4. ↑ [4.0] [4.1] Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. *Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial.* Lancet Oncol 2016 Jul;17(7):976-983 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27267608.
5. ↑ [5.0] [5.1] [5.2] [5.3] Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. *Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study.* Lancet Oncol 2018 Mar 27 Available from: http://www.ncbi.nlm.nih.gov/pubmed/29602646.
6. ↑ [6.0] [6.1] Tawbi HA-H, Forsyth PAJ, Algazi AP, Hamid O, Hodi FS, Moschos SJ, et al. *Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204.* J Clin Oncol 2017;35:(suppl; abstr 9507).
7. ↑ Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. *Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial.* Lancet Oncol 2012 Nov;13(11):1087-95 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23051966.
8. ↑ McArthur GA, Maio M, Arance A, Nathan P, Blank C, Avril MF, et al. *Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study.* Ann Oncol 2017 Mar 1;28(3):634-641 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27993793.
9. ↑ [9.0] [9.1] Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. *Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial.* Lancet Oncol 2017 Jul;18(7):863-873 Available from: http://www.ncbi.nlm.nih.gov/pubmed/28592387.

5.3 Surgical treatment of brain metastases

5.4 Radiotherapy for patients with brain metastases

5.5 Summary of recommendations and practice points

Summary of recommendations and practice points

5.6 Adjuvant systemic therapy – resected stage II and III melanoma

Tamsin we'll have to open the edit tab and populate the PICO field later. I can show you how :)

Reminder: the search key parameter is the name of the saved search from our PubMed account. It should be a unique name which represents the guideline, topic being covered and should easily identify the clinical question it is associated with.

Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search
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5.7 Systemic drug therapy – unresectable stage IIIC and IV melanoma

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5.8 Immunotherapy

Add content

5.9 Targeted therapies (MEK and BRAF inhibitors)

Add content

5.10 Chemotherapy

Add content

5.11 Summary of recommendations and practice points

Add content

5.12 Radiotherapy for distant metastases

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5.13 Radiotherapy following resection of involved lymph nodes

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6 Management of mucosal melanoma

Redirect to:

- Guidelines:Melanoma/Mucosal melanoma

7 Management of ocular melanoma

Intro to be inserted

8 Multidisciplinary care of melanoma patients

Content to be inserted.

8.1 References

8.2 Appendices

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8.1 Guideline development process

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8.1.1 Background

In 2014, Cancer Council Australia and Melanoma Institute Australia partnered as guideline developers and initiated the project to revise the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand . Due to the advancements in treatment options, the 2008 guidelines are no longer up to date. The evidence base and management of melanoma has significantly changed since 2008, particularly for the treatment of stage III and stage IV disease emerging over the past few years. Importantly, targeted and systemic therapy drugs are now registered for use within Australia and there are significant publications demonstrating the improvement for life expectancy in melanoma patients due to the improved treatment options.

Cancer Council Australia and Melanoma Institute Australia contributed in kind resources consisting of project staff, facilities, systems and travel budget to revise the 2008 guidelines. In 2015, Skin Cancer College Australasia joined the project and provided funding to enable employment of an additional full-time Project Officer in the Systematic Review team.

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8.1.2 Project governance, guidelines scope and guidelines development group

Cancer Council Australia and Melanoma Institute Australia appointed a small Management Committee that were members of the 2008 working party, to oversee the guidelines revision project (see membership). The Management Committee is responsible for the overall management and strategic leadership of the guidelines review process. This includes the establishment of the wider multidisciplinary guidelines working party and question-specific sub-committee members in consultation with the lead authors and the evaluation of declarations of interest and, if necessary, implementing management strategies for conflict/s of interest.

During a face-to-face meeting in November 2014, the Management Committee assessed the clinical questions addressed the 2008 guidelines and determined the priority clinical questions to be included in this revision. Twenty-three questions were identified to be of greatest importance, covering issues related to diagnosis, staging and management of cutaneous melanoma (see list of questions).

The Management Committee proposed lead authors for each included clinical question. The nominated individuals were invited to join the multidisciplinary working party (see membership table). In addition, the Management Committee identified and nominated two consumer representatives and two GP representatives to join the multidisciplinary working party.

In consultation with the question lead author, sub-committees consisting of members with relevant expertise and experience were established for each question (see membership table)

Declarations of interest were collected from all nominated members and evaluated (see COI register. All members were advised to update their declarations of interest over the course of the project and received reminders to review their declarations prior to every formal working party meeting.

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8.1.3 Guidelines development approach

The Management Committee agreed to use Cancer Council Australia's Cancer Guidelines Wiki Platform and approach to develop the guidelines. The Wiki Platform is web-based and supports all processes of guidelines development, such as the literature search, critical appraisal, data extraction, evidence assessment and summary processes, as well as content and recommendation development, online consultation, review and web publication. It is in line with the NHMRC guidelines requirements, designated standards of quality, process and grading system for recommendations.[1][2] An infrastructure is set in place to process literature updates and continuously update content as new evidence emerges and is reviewed.

The Development of Clinical Practice Guidelines using Cancer Council Australia's Cancer Guidelines Wiki Handbook[3] illustrates the steps in the development of Cancer Council Australia's web-based clinical practice guidelines. It provides information to assist working party members and staff members to develop concise clinical questions in PICO format, construct sound search strategies, systematically search the literature, critically appraise, summarise the evidence and formulate guidelines recommendations.

The Management Committee was approached by the German guidelines development group, which developed the guidelines "Malignant Melanoma S3-Guideline Diagnosis, Therapy and Follow-up of Melanoma"[4] in 2012 and adapted some sections from the 2008 Australian guidelines. The systematic review team assessed the German guidelines using the AGREE II assessment tool[5] and found the guidelines to be high quality. As many exhaustive systematic reviews were undertaken to answer critical clinical questions in the melanoma diagnosis and management guidelines, it was decided to adapt the German systematic reviews and update the literature searches, where possible, rather than undertaking new systematic reviews for the same clinical questions (see also 3b. If a relevant clinical practice guidelines was found and assessed as suitable for adaption). The data extractions and quality appraisals of any new studies will be shared with the German group.

Rather than waiting until systematic reviews and content for all included clinical questions have been finalised, the Management Committee agreed to publish finalised question content and the associated recommendations in stages. The group decided that it is important to publish content and results as soon as it is finalised by the working party to ensure that the medical community receives up-to-date information without any publication delay. Prior to publication, feedback would be sought from guidelines stakeholders about the clinical questions content (See also Public consultation).

The first set of completed draft contents is now being released for public consultation (refer to set of questions).

- What are the clinical features of melanoma and how do atypical melanomas present?
- What type of biopsy should be performed for a suspicious pigmented skin lesion?
- When is a sentinel node biopsy indicated?
- What are the recommended safety margins for radical excision of primary melanoma?

Subsequent clinical questions and associated recommendations will be published in 2016 and 2017.

The detailed steps in preparing the question content, conducting the literature searches, appraising the literature and formulating and grading recommendations, are outlined below.

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8.1.4 Steps in preparing clinical practice guidelines

For every clinical question the following steps were completed:

1. Develop a structured clinical question in PICO format

2. Search for existing relevant guidelines and systematic reviews answering the clinical question

3. Perform systematic review process, depending on if a relevant clinical practice guideline is identified or not

3a If no relevant clinical practice guideline was found	**3b If a relevant clinical practice guideline was found and assessed as suitable for adaption**
Developing the systematic review protocol and systematic literature search strategy for each PICO question Conducting the systematic literature search according to protocol Screening of literature results against pre-defined inclusion and exclusion criteria Critical appraisal and data extraction of each included article Create body evidence table of all included literature	Undertake systematic literature search update for the question of the existing clinical practice guideline Screening of literature update results against pre-defined inclusion and exclusion criteria Critical appraisal and data extraction of each new included article Update body evidence table of evidence review of existing guideline with new literature update results

4. Summarise the relevant data

5. Assess the body of evidence and formulate recommendations

6. Write the content narrative

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8.1.4.1 Step 1. Develop a structured clinical question

All included questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework (see Appendix 3). The lead authors provided the systematic review team with feedback to refine the PICO questions and inclusion and exclusion criteria for the systematic review.

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8.1.4.2 Step 2. Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse (http://guideline.gov/), the Guidelines Resource Centre (www.cancerview.ca) and the scoping search for the PICO question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption.

Full systematic reviews were then performed as outlined in Developing a systematic search strategy; Conducting the systematic literature search according to protocol; Screening of literature results against pre-defined inclusion and exclusion criteria; Critical appraisal and data extraction of each included article.

If an existing relevant guideline was identified, the guideline was assessed with the AGREEII assessment tool[5] to ensure the guideline is of high quality. The ADAPTE process was then followed.[6]

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8.1.4.3 Step 3. Perform systematic review process

8.1.4.3.1 Step 3a. If no relevant clinical practice guideline was found

8.1.4.3.1.1 Developing a systematic search strategy

For each PICO question, systematic literature search strategies were developed by the technical team. Searches were limited or widened as necessary according to the PICO structure using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic databases. The included standard databases searched were Pubmed, Embase, Trip database, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and Health Technology Assessment for all questions. The psychosocial questions also included CINAHL and PsycINFO databases to retrieve relevant literature.

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8.1.4.3.1.2 Conducting the systematic literature search according to protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[2] For each clinical question that required a systematic literature review, literature searches were conducted systematically from 2007 onwards. The following electronic databases were part of the systematic literature search strategy:

- **PubMed –** bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences.
- **EMBASE –** major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries.
- **Trip Database –** A medical database with focus on Evidence based medicine and clinical practice guidelines with content available from Cochrane and Bandolier.
- **Database of Abstracts of Reviews of Effects and Health Technology Assessment –** Contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services.
- **The Cochrane Database of Systematic Reviews**.
- **Cinahl –** Bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioral sciences, management, and education
- **Psychinfo –** Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the appendix of the clinical question.

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8.1.4.3.1.3 Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen – During the first screening round, the titles and abstracts of all retrieved literature were screened by one reviewer. All irrelevant, incorrect and duplicates were removed.

b) Second screen – A second screen was undertaken based on the full article. Two reviewers assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

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8.1.4.3.1.4 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria. For all quality assessment tools, see link to pdf.

Any disagreements were adjudicated by a third reviewer.

For all included articles, the relevant data was extracted and summarised in study characteristics and evidence tables. Each data extraction was checked by a second assessor. These tables are available in the appendix of each question

[include screenshot]

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8.1.4.3.2 Step 3b. If a relevant clinical practice guidelines was found and assessed as suitable for adaption

Undertake systematic literature search update for the question of the existing clinical practice guideline If an existing clinical practice guideline of high quality was found that directly addresses the clinical question to be reviewed, an update search of the original systematic literature search was performed covering the time period between the literature cut-off of the original review until now across all relevant databases (see also Conducting the systematic literature search according to protocol).

8.1.4.3.2.1 Screening of literature update results against pre-defined inclusion and exclusion criteria

All retrieved literature results from the update search were screened against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen – During the first screening round, the titles and abstracts of all retrieved literature were screened by 1 reviewer. All irrelevant, incorrect and duplicates were removed.

b) Second screen – A second screen was undertaken based on the full article. Two reviewers assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

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8.1.4.3.2.2 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria. For all quality assessment tools, see link to pdf.

Any disagreements were adjudicated by a third reviewer.

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8.1.4.4 Step 4. Summarise the relevant data

The study results, level of the evidence, risk of bias due to study design and the relevance of the evidence for each included study were summarised in a body of evidence table.

[include screenshot]

When a systematic review from an existing guidelines was updated to answer and develop recommendations for a clinical question, the new evidence was added to the existing body of evidence table. Where required, the levels of evidence were translated to the NHMRC levels of evidence. The NHMRC levels of evidence are outlined below:

Table 1 . Designations of levels of evidence according to type of research question (NHMRC, 2009)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
	A randomised	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,	A prospective	A	A randomised

II	controlled trial	among consecutive patients with a defined clinical presentation	cohort study	prospective cohort study	controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study

	Interrupted time series without a parallel control group				Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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8.1.4.5 Step 5. Assess the body of evidence and formulate recommendations

The body of evidence table for each clinical question was forwarded to the lead author for assessment. The lead author in collaboration with the systematic reviewer (who conducted the systematic reviews and extracted the data and performed risk of bias assessment) assessed the body of evidence and completed the evidence assessment matrix in regard to the volume of the evidence, its consistency, clinical impact, generalisability and applicability and developed evidence statements for each recommendation.

The process is described in NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2009).[7]

Following grading of the body of evidence and development of evidence statements, authors were asked to formulate evidence-based recommendations based on the results of the systematic review summarised in the body of evidence table. The method of grading recommendations is shown in Table 2.

Table 2: Grading of recommendations

Component of Recommendation	**Recommendation Grade**			
	A **Excellent**	**B** **Good**	**C** **Satisfactory**	**D** **Poor**
	one or more level I studies with	one or two level II studies with a low risk of bias	one or two level III	level IV studies, or

Volume of evidence [1**]	a low risk of bias or several level II studies with a low risk of bias	or a systematic review/several level III studies with a low risk of bias	studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level I to III studies /systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

[**]For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B!

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au /_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

The overall recommendations grade are shown in Table 3.

Table 3: Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

The NHMRC approved recommendation types and definitions are shown in Table 4.

Table 4: NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

In addition to developing evidence-based recommendations as a result of the systematic review for a clinical question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review or practice points, when a matter was outside the scope of the search strategy for the systematic review.

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8.1.4.6 Step 6. Write the content narrative

For each question, the assigned lead authors were asked to draft their guidelines chapter using the following format:

- Background to the clinical question, including its clinical importance and historical evidence, where relevant
- Review of the evidence, including the number, quality and findings of studies identified by the systematic review
- Evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- Evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- Discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- References.

The content draft was then reviewed by all sub-committee members. The draft documents underwent several iterations until agreement between the members of the sub-committee on these drafts was reached.

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8.1.5 Review of the draft chapters

Draft content was circulated to the working party. The whole group was asked to review the content and submit feedback. Members were asked to submit further suggestions on consensus-based recommendation and practice points.

A face-to-face meeting with all working party members was scheduled to review and finalise the draft content for public consultation. Prior to this meeting, the latest iteration drafts were circulated. All panelists were asked to review the content, individual recommendations and practice points in detail, identify and note any controversies and points to be discussed at the meeting. During the meeting, each recommendation and practice point was tabled as an agenda point. Each was reviewed and approved by consensus, which was reached by voting. The Chairperson nominated a particular recommendation/practice point to be reviewed and the panelists had the opportunity to discuss any issues and suggest revisions to recommendations and practice points. Each recommendation and practice point was approved once the eligible panelists reached consensus.

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8.1.6 Public consultation

The first set of completed draft clinical questions was sent out for public consultation from xxx to xx. Submissions were invited from the general public and professional societies and groups and other relevant stakeholders. Relevant professional societies and groups, consumer groups and other relevant stakeholders were contacted.

All feedback on the draft received during the consultation period in Australia will be compiled and sent to the relevant Question Specific Author Team to review their draft content, assessing and considering the submitted comments. Each additional submitted paper during public consultation will be assessed by the methodologist team against the review protocol.

Another meeting of the working party will be organised in order to review all public consultation comments and suggested amendments. Subsequent changes to the draft will be agreed by consensus, based on consideration of the evidence and, in the absence of evidence, expert opinion. The same consensus process that was followed during the face to face working party meeting prior to public consultation was followed again. All changes resulting from the public consultation submission reviews will be documented and made accessible once the guidelines are published.

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8.1.7 Dissemination and implementation

A multi-strategy approach will be followed for the dissemination and implementation of the guidelines, as this has shown to positively influence guidelines uptake.[8][9]

Once all clinical questions that are part of the guidelines revision are completed, the guidelines will be distributed directly to relevant professional and other interested groups and through meetings, national and international conferences, and other professional development and continuing medical education (CME) events. Local expert leaders will be identified and approached to facilitate dissemination and act as champions for the guidelines.

A significant effort will be made to have the guidelines introduced to senior undergraduate medical students and to encourage the relevant learned colleges to support the guidelines and to foster their integration into hospital and community practice through resident and registrar education activities.

The guidelines will be made available as online guidelines via the Cancer Council Australia Cancer Guidelines Wiki. The online guidelines version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. The Cancer Guidelines Wiki is a responsive website that is optimised for mobile and desktop access.

Interlinking and listing the guidelines on national and international guideline portal is also an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guidelines. The guidelines will also be listed on national and international guideline portals such as Australia’s Clinical Practice Guidelines Portal, Guidelines International Network guidelines library and National Guidelines Clearinghouse.

The Cancer Guidelines Wiki is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guidelines content with systems and web applications used in the Australian healthcare context. Use of the guidelines as part of core curriculum in specialty exams will be encouraged.

It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guidelines recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

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8.1.8 Future updates

The handbook Development of Clinical Practice Guidelines Using Cancer Council Australia's Cancer Guidelines Wiki. Handbook for section authors and the guideline working party. outlines Cancer Council Australia's guidelines updating processes. The incoming literature updates will continue to be monitored for each systematic review question. The Working Party will notify the Technical Team if any clinical question requires revision because new high level evidence has been published. External stakeholders are encouraged to use the comment feature and notify us of any new evidence for a specific topic.

8.1.9 References

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8.2 Working party members and contributors

Contents

8.2.1 Working party membership and contributors to guidelines and public consultation submissions received

8.2.2 Management Committee

Member name	Position
Professor John Thompson	Executive Director, Melanoma Institute Australia
Professor Michael Henderson	Professor of Surgery, University of Melbourne; Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC
A/Professor John Kelly	Dermatologist, Armadale Dermatology, NSW
Professor Georgina Long	Medical Oncologist and Associate Professor of Melanoma Biology and Translational Research, Melanoma Institute Australia and The University of Sydney, NSW

Member name	Position
A/Professor Susan Neuhaus	General Surgeon and Surgical Oncologist, Royal Adelaide Hospital; Clinical Associate Professor, University of Adelaide Department of Surgery; Associate Professor, Conflict Medicine, University of Adelaide, SA
Dr Annette Pflugfelder	PhD Student, Dermatology Research Centre, School of Medicine, The University of Queensland
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW
Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital, NSW
Jutta von Dincklage	Head, Clinical Guidelines Network

8.2.3 Membership: Multi-disciplinary Working Party

The Management Committee established a multi-disciplinary working party to develop these guidelines.

The multi-disciplinary Working Party consists of the Management Committee members, the lead authors for guideline sections, consumer representatives as well as the Cancer Council Australia Project team members.

Role	Member name	Specialty/position	State
Management Committee member, Chair of working party	Professor John Thompson	Executive Director, Melanoma Institute Australia	NSW
Lead Author	A /Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD	QLD
Lead Author	Dr David Gyorki	Consultant Surgeon, Peter MacCallum Centre	VIC
Management Committee member Lead Author	Professor Michael Henderson	Professor of Surgery, University of Melbourne; Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC	VIC

Role	Member name	Specialty/position	State
Lead Author	A /Professor Angela Hong	Radiation Oncologist, Melanoma Institute Australia; Clinical Associate Professor, Medicine, The University of Sydney	NSW
Lead Author	Dr Julie Howle	Clinical Senior Lecturer, Surgery, The University of Sydney	NSW
Lead Author	A /Professor T Michael Hughes	Associate Professor, Surgery, The University of Sydney; Surgeon, Sydney Adventist Hospital	NSW
Lead Author	Dr Craig James	Dermatopathologist, Adelaide Pathology Partners	SA
Lead Author	Professor Richard Kefford AM	Professor of Cancer Medicine, Macquarie University	NSW
Management Committee member Lead Author	A /Professor John Kelly	Dermatologist, Armadale Dermatology	NSW
Management Committee member Lead Author	Professor Georgina Long	Medical Oncologist and Associate Professor of Melanoma Biology and Translational Research, Melanoma Institute Australia and The University of Sydney	NSW
Lead Author	Professor Graham Mann	Chair, University of Sydney Cancer Research Network and Cancer SPARC Steering Committee; Co-Director, Centre for Cancer Research, Westmead Millennium Institute; Research Director, Melanoma Institute Australia, NSW	NSW
Lead Author	Dr Victoria Mar	Dermatologist, Armadale Dermatology, NSW	NSW
Lead Author	Professor Scott Menzies	The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital; Professor, Discipline of Dermatology, The University of Sydney	NSW
Lead Author	Professor Michael Millward	Professor of Clinical Cancer Research, The University of Western Australia; Consultant Medical Oncologist, Sir Charles Gardiner Hospital	WA

Role	Member name	Specialty/position	State
Lead Author	Dr Rachael Morton	Senior Research Fellow, Public Health, The University of Sydney	NSW
Management Committee member	A /Professor Susan Neuhaus	General Surgeon and Surgical Oncologist, Royal Adelaide Hospital; Clinical Associate Professor, University of Adelaide Department of Surgery; Associate Professor, Conflict Medicine, University of Adelaide	SA
Management Committee member	Dr Annette Pflugfelder	Research Higher Degree Student, The School of Medicine, The University of Queensland	QLD
Lead Author	Dr Robyn Saw	Senior Lecturer, Surgery, The University of Sydney; Surgical Oncologist; General Surgeon, Melanoma Institute Australia and Royal Prince Alfred & Mater Hospitals	NSW
Management Committee member	Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney	NSW
Lead Author	A /Professor Michael Sladden	Dermatologist, Tas Derm	TAS
Lead Author	Professor H Peter Soyer	Director, School of Medicine, University of Queensland	QLD
Lead Author	A /Professor Andrew Spillane	Associate Professor, Surgical Oncology, The University of Sydney	NSW
Management Committee member Lead Author	Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital	NSW
GP representative	Dr Margaret Hardy	General practitioner Gladesville Medical	NSW
GP representative	Dr Paul Fishburn	General practitioner	NSW

Role	Member name	Specialty/position	State
Consumer representative	Alison Button-Sloan	Consumer representative	VIC
Consumer representative	Clinton Heal	Consumer, CEO and Founder, Melanoma WA, 2011 WA Young Australian of the Year	WA
Management Committee member CCA Project Team Lead	Jutta von Dincklage	Head, Clinical Guidelines Network	NSW

8.2.4 Cancer Council Australia Project Team

Role	Member name	Specialty/position	State
CCA Project Team member	Laura Wuellner	Project Manager, Clinical Guidelines Network	NSW
CCA Systematic Literature Reviewer Team member	Lani Teddy	Project Officer, Systematic Literature Reviews, Melanoma Guidelines	NSW
CCA Systematic Literature Reviewer Team member	Lyndal Alchin	Project Officer, Systematic Literature Reviews, Melanoma Guidelines	NSW
CCA Systematic Literature Reviewer Team member (from April 2015-Apr 2016)	Jackie Buck	Project Officer, Systematic Literature Reviews, Melanoma Guidelines	NSW

8.2.5 Sub-committee membership for each guideline question

For each guideline question, the guideline question lead author under consultation with the Management Committee established a sub-committee with relevant expert members of the working party and co-opted additional external clinical experts as required.

The role of the sub-committee is to review the draft content for the guideline questions of the section before it is presented to the working party.

WHAT IS THE ROLE OF DERMOSCOPY (AND SEQUENTIAL DERMOSCOPY) IN MELANOMA DIAGNOSIS?
Question lead: Professor Scott Menzies

Sub-committee members	
Name	**Position/speciality**
Dr Alex Chamberlain	Dermatologist, The Alfred Hospital, VIC
A/Professor Pascale Guitera	Senior Research Fellow, Dermatology, The University of Sydney, NSW
Professor H Peter Soyer	Director, School of Medicine, University of Queensland, QLD

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WHAT TYPE OF BIOPSY SHOULD BE PERFORMED FOR A SUSPICIOUS PIGMENTED SKIN LESION?

Question lead: A/Professor John Kelly

Sub-committee members	
Name	**Position/speciality**
Dr Trevor Beer	Histopathologist, Clinipath Pathology, WA
Professor Diona Damian	Professor of Dermatology, The University of Sydney, NSW
Jonathan Ng	Honorary Research Fellow, Victorian Melanoma Service, The Alfred Hospital, VIC
Dr Joseph Ohana	GP, The Village Medical Practice, NSW
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW
Professor H Peter Soyer	Director, School of Medicine, University of Queensland, QLD

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WHAT ARE THE CLINICAL FEATURES OF MELANOMA AND HOW DO ATYPICAL MELANOMAs PRESENT?

Question lead: Victoria Mar

Sub-committee members	
Name	**Position/speciality**
Dr Alex Chamberlain	Dermatologist, The Alfred Hospital, VIC
Professor Stephen Lee AM	Professor of Dermatology, The University of Sydney, NSW
Dr Bill Murray	Head of Anatomical Pathology, Peter MacCallum Cancer Centre, VIC
A/Professor John Kelly	Dermatologist, Armadale Dermatology, NSW

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WHAT INVESTIGATIONS SHOULD BE PERFORMED FOLLOWING A DIAGNOSIS OF PRIMARY CUTANEOUS MELANOMA?

Question lead: Dr Rachael Morton	
Sub-committee members	
Name	**Position/speciality**
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Victoria Mar	Dermatologist, Armadale Dermatology, NSW
A/Professor Mark Smithers	Associate Professor, Department of Surgery, The University of Queensland, QLD
A/Professor Jonathan Stretch AM	Associate Professor of Melanoma and Skin Oncology, The University of Sydney, NSW

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WHAT ARE THE RECOMMENDED SAFETY MARGINS FOR RADICAL EXCISION OF PRIMARY MELANOMA?	
Question lead: A/Professor Michael Sladden	
Sub-committee members	
Name	**Position/speciality**
Dr Julie Howle	Clinical Senior Lecturer, Surgery, The University of Sydney, NSW
Professor Omgo Nieweg	Surgeon, Melanoma Institute Australia, NSW

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WHEN IS A SENTINEL NODE BIOPSY INDICATED?	
Question lead: Dr David Gyorki	
Sub-committee members	
Name	**Position/speciality**
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Victoria Mar Dermatologist	Armadale Dermatology, NSW
Dr Mark Hanikeri	Director, Western Australia Plastic Surgery Centre, WA
Dr Shahneen Sandhu	Medical Oncologist, Peter MacCallum Cancer Centre, VIC

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WHAT INVESTIGATIONS SHOULD BE PERFORMED WHEN IN TRANSIT AND/OR REGIONAL NODE DISEASE IS DIAGNOSED?	
Question lead: Dr Robyn Saw	
Sub-committee members	
Name	**Position/speciality**
Dr Andrew Haydon	Medical Oncologist, Alfred Hospital and Cabrini Health, VIC
Professor Grant McArthur	Head, Molecular Oncology Laboratory and Translational Research Laboratory, Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC
Dr Alex Menzies	Medical Oncologist, Royal North Shore Hospital, NSW
Dr John Spillane	General Surgeon, Epworth Eastern Consulting, VIC

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SHOULD ALL PATIENTS WITH A POSITIVE SENTINEL LYMPH NODE BIOPSY HAVE A COMPLETE NODE DISSECTION?	
Question lead: A/Professor Andrew Spillane	
Sub-committee members	
Name	**Position/speciality**
Dr Frank Bruscino-Raiola	Consultant Plastic Surgeon, Alfred Health, VIC
Dr David Gyorki	Consultant Surgeon, Peter MacCallum Centre, VIC
Dr Julie Howle	Senior Lecturer, Surgery, The University of Sydney, NSW
Dr Chris McCormack	Consultant Dermatologist, St Vincents Hospital Melbourne, VIC
A/Professor Mark Smithers	Associate Professor, Department of Surgery, The University of Queensland, QLD

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WHAT IS THE APPROPRIATE TREATMENT FOR MACROSCOPIC (I.E. DETECTABLE CLINICALLY OR BY ULTRASOUND) NODAL METASTASIS?
Question lead: Professor Michael Henderson
Sub-committee members

Name	Position/speciality
A/Professor T Michael Hughes	Associate Professor, Surgery, The University of Sydney; Surgeon, Sydney Adventist Hospital, NSW
A/Professor Mark Smithers	Associate Professor, Department of Surgery, The University of Queensland, QLD
A/Professor Andrew Spillane	Associate Professor, Surgical Oncology, The University of Sydney
Dr John Spillane	General Surgeon, Epworth Eastern Consulting, VIC

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WHAT STAGING EXAMINATIONS ARE INDICATED FOR STAGE IV PATIENTS?

Question lead:Professor Michael Millward

Sub-committee members

Name	Position/speciality
Dr Victoria Atkinson	Senior Staff Specialist, Princess Alexandra Hospital; Visiting Medical Oncologist, Greenslopes Private Hospital, QLD
Dr Michael Brown	Medical Oncologist, Royal Adelaide Hospital, SA
Dr Andrew Haydon	Medical Oncologist, Alfred Hospital and Cabrini Health, VIC
Dr Alex Menzies	Medical Oncologist, Royal North Shore Hospital, NSW

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DOES SYSTEMIC DRUG THERAPY IMPROVE PROGRESSION FREE AND/OR OVERALL SURVIVAL IN STAGE 3C UNRESECTABLE AND STAGE 4 MELANOMA?

Question lead: A/Professor Georgina Long

Sub-committee members

Name	Position/speciality
Dr Matteo Carlino	Medical Oncologist, The Crown Princess Mary Cancer Centre, Westmead, NSW
Professor Richard Kefford AM	Professor of Cancer Medicine, Macquarie University, NSW
Professor Grant	Head, Molecular Oncology Laboratory and Translational Research Laboratory, Co-Chair,

McArthur	Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC
Dr Alex Menzies	Medical Oncologist, Royal North Shore Hospital, NSW
Dr Mark Shackleton	Group Leader, Cancer Development and Treatment Laboratory, Peter MacCallum Cancer Centre, NSW

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HOW SHOULD PATIENTS WITH THIN, INTERMEDIATE THICKNESS AND THICK MELANOMAS BE FOLLOWED AFTER INITIAL DEFINITIVE TREATMENT?

Question lead: A/Professor Andrew Barbour

Sub-committee members

Name	Position/speciality
A/Professor Alexander Guminski	Associate Professor, Medicine, The University of Sydney, Medical Oncologist, Melanoma Institute Australia, North Shore Private Hospital, and Royal North Shore Hospital, NSW
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Professor Scott Menzies	The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital; Professor, Discipline of Dermatology, The University of Sydney, NSW
Dr Rachael Morton	Senior Research Fellow, Public Health, The University of Sydney, NSW

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WHO IS AT HIGH RISK OF MELANOMA?

Question lead: Professor Graham Mann

Sub-committee members

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Dr Anne Cust	Senior Research Fellow, Public Health, The University of Sydney, NSW
Professor Diona Damian	Professor of Dermatology, The University of Sydney, NSW
Professor H Peter Soyer	Director, School of Medicine, University of Queensland, QLD
Professor David Whiteman	Senior Principal Research Fellow and Head, Cancer Control, Queensland Institute of Medical Research Berghofer Medical Research Institute, QLD

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WHAT CLINICAL INFORMATION SHOULD THE CLINICIAN GIVE THE PATHOLOGIST TO AID DIAGNOSIS OF MELANOMA?	
Question lead: Dr Craig James	
Sub-committee members	
Name	**Position/speciality**
A/Professor Brendon Coventry	Associate Professor, Department of Surgery, The University of Adelaide; Senior Consultant Surgeon, Royal Adelaide Hospital, SA
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW
Professor Stephen Lee AM	Professor of Dermatology, The University of Sydney, NSW
Professor Catriona McLean	Director, Pathology Board, Monash University; Director, Anatomical Pathology, The Alfred Hospital, VIC

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HOW SHOULD LENTIGO MALIGNA BE MANAGED?	
Question lead: Professor H Peter Soyer	
Sub-committee members	
Name	**Position/speciality**
A/Professor Pascale Guitera	Senior Research Fellow, Dermatology, The University of Sydney, NSW
A/Professor Angela Hong	Radiation Oncologist, Melanoma Institute Australia; Clinical Associate Professor, Medicine, The University of Sydney, NSW
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW
A/Professor Jonathan Stretch AM	Associate Professor of Melanoma and Skin Oncology, The University of Sydney, NSW
Dr Geoff Strutton	Anatomical Pathologist, Princess Alexandra Hospital, QLD

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WHAT IS THE ROLE OF ADJUVANT INTERFERON IN PATIENTS WITH RESECTED STAGE 3 MELANOMA?	
Question lead: Professor Richard Kefford AM	
Sub-committee members	
Name	**Position/speciality**

Professor Catriona McLean	Director, Pathology Board, Monash University; Director, Anatomical Pathology, The Alfred Hospital, VIC

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DOES ADJUVANT RADIOTHERAPY OF THE LYMPH NODE "STATION"HAVE AN EFFECT ON OVERALL SURVIVAL OR RECURRENCE-FREE SURVIVAL IN PATIENTS WITH N+ RESECTED MELANOMA?

Question lead: Professor Graham Stevens

Sub-committee members

Name	Position/speciality
Professor Bryan Burmeister	Director, Radiation Oncology, Princess Alexandra Hospital, QLD
Dr Gerald Fogarty	Director, Radiation Oncology, Mater Hospital, NSW
Professor Michael Henderson	Professor of Surgery, University of Melbourne; Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC

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FOR PATIENTS WITH DISTANT METASTASES, WHEN IS SURGICAL THERAPY INDICATED?

Question lead: A/Prof Andrew Spillane

Sub-committee members

Name	Position/speciality
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Julie Howle	Clinical Senior Lecturer, Surgery, The University of Sydney, NSW

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WHAT RADIOTHERAPY IS INDICATED FOR PATIENTS WITH DISTANT METASTASES?

Question lead: A/Professor Angela Hong

Sub-committee members

Name	Position/speciality
Dr Gerald Fogarty	Director, Radiation Oncology, Mater Hospital, NSW
Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital, NSW

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SHOULD DESMOPLASTIC AND/OR NEUROTROPIC MELANOMAS BE TREATED DIFFERENTLY?	
Question lead: A/Professor T Michael Hughes	
Sub-committee members	
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Michael Foote	TBC
A/Professor John Kelly	Dermatologist, Armadale Dermatology, NSW
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW
A/Professor Jonathan Stretch AM	Associate Professor of Melanoma and Skin Oncology, The University of Sydney, NSW

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HOW SHOULD MELANOMA IN CHILDHOOD BE MANAGED?	
Question lead: Dr Robyn Saw	
Sub-committee members	
Name	**Position/speciality**
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Mark Hanikeri	Director, Western Australia Plastic Surgery Centre, WA
Dr Chris McCormack	Consultant Dermatologist, St Vincents Hospital Melbourne, VIC
Professor Richard Scolyer	Clinical Professor, Pathology, The University of Sydney, NSW

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HOW SHOULD MELANOMA IN PREGNANCY BE MANAGED?	
Question lead: Dr Julie Howle	
Sub-committee members	
Name	**Position/speciality**
A/Professor Kiarash Khosrotehrani	Clinical Scientist, Centre for Clinical Research, The University of Queensland, QLD
Dr Robyn Saw	Senior Lecturer, Surgery, The University of Sydney; Surgical Oncologist; General Surgeon, Melanoma Institute Australia and Royal Prince Alfred & Mater Hospitals, NSW

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HOW SHOULD SATELLITE AND IN TRANSIT METASTATIC DISEASE BE MANAGED?	
Question lead: Professor Michael Henderson	
Sub-committee members	
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Professor Diona Damian	Professor of Dermatology, The University of Sydney, NSW
Professor Omgo Nieweg	Surgeon, Melanoma Institute Australia, NSW
Dr Robyn Saw	Senior Lecturer, Surgery, The University of Sydney; Surgical Oncologist; General Surgeon, Melanoma Institute Australia and Royal Prince Alfred & Mater Hospitals, NSW
A/Professor Mark Smithers	Associate Professor, Department of Surgery, The University of Queensland, QLD
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8.2.6 Acknowledgement

Sincere thanks to Prof Ian Olver who initiated the Melanoma Guidelines Revision Project in collaboration with Melanoma Institute Australia in 2014 in his role as Chief Executive Officer, Cancer Council Australia. Since February 2015, he has been Director, Sansom Institute for Health Research.

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8.3 List of clinical questions

8.3.1 Draft Content

- What are the clinical features of melanoma and how do atypical melanomas present?
- What type of biopsy should be performed for a suspicious pigmented skin lesion?
- When is a sentinel node biopsy indicated?
- What are the recommended safety margins for radical excision of primary melanoma?

8.3.2 Currently in development

- What is the role of dermoscopy (and sequential dermoscopy) in melanoma diagnosis?
- Should all patients with a positive sentinel lymph node biopsy have a complete node dissection?
- What staging examinations are indicated for Stage IV patients?
- How should patients with thin, intermediate thickness and thick melanomas be followed after initial definitive treatment?
- What investigations should be performed following a diagnosis of primary cutaneous melanoma?
- What investigations should be performed when in transit and/or regional node disease is diagnosed?
- How should patients with thin, intermediate thickness and thick melanomas be followed after initial definitive treatment?

8.3.3 Systematic reviews yet to be completed

- Does systemic drug therapy improve progression free and/or overall survival in stage 3c unresectable and stage 4 melanoma?
- Who is at risk of melanoma?
- What clinical information should the clinician give the pathologist to aid diagnosis of melanoma?
- How should lentigo maligna be managed?
- What is the role of adjuvant interferon in patients with resected stage 3 melanoma?
- Does adjuvant radiotherapy of the lymph node "station" have any effect on overall survival or recurrence-free survival in patients with N+ resected melanoma?
- For patients with distant metastases, when is surgical therapy indicated?
- What radiotherapy is indicated for patients with distant metastasis?
- Should desmoplastic and/or neurotropic melanomas be treated differently?
- How should melanoma in children be managed?
- How should melanoma in pregnancy be managed?
- How should satellite and in transit metastatic disease me managed?

8.4 Declarations of interest register

Conflict of interest register