Clinical practice guidelines for the diagnosis and management of melanoma

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1 Foreword

1.1 Foreword

Australia and New Zealand have the highest incidence of melanoma in the world, and comprehensive, up-to-date, evidence-based national guidelines for its management are therefore of great importance. Both countries have populations of predominantly Celtic origin, and in the course of day-to-day and recreational activities their citizens are inevitably subjected to high levels of solar UV exposure. These two factors are considered to be predominantly responsible for the very high incidence of melanoma (and other forms of skin cancer) in the two nations. In Australia melanoma is the third most common cancer in men and the fourth most common in women, with over 13,000 new cases and over 1,750 deaths each year. [1]

The purpose of evidence-based clinical guidelines for the management of any medical condition is to achieve early diagnosis whenever possible, make doctors and patients aware of the most effective treatment options, and minimise the financial burden on the health system by documenting investigations and therapies that are inappropriate. The first Australian guidelines for the management of melanoma were published in 1999 under the auspices of the Australian Cancer Network, whose CEO Professor Tom Reeve AC CBE encouraged and supported their development and promulgation. A multidisciplinary working party convened by Professor William McCarthy AM rigorously assessed all available evidence, and on this basis the guidelines received endorsement from the Australian National Health and Medical Research Council (NHMRC).[2] Within a few years

it was clear that updating of the guidelines was required, and another working party was assembled, with myself as chairman, to produce new evidence-based guidelines. On this occasion, New Zealand representatives were included in the working party, and the resulting guidelines published in 2008 were endorsed not only by the NHMRC in Australia but also by the New Zealand Melanoma Guidelines Group.[3] NHMRC endorsement was achieved once again because that body was satisfied that its required process for the development of evidence-based guidelines had been followed.

In 2014, with many further advances in melanoma diagnosis and management having been made, it was apparent that yet another revision of the Australian melanoma management guidelines was necessary. However, there was concern that the process used to develop the two previous sets of national guidelines would be too protracted and cumbersome in an era when rapid advances in management are occurring. Nor was any funding readily available to proceed along the same lines as previously, i.e. following the strict NHMRC requirements for the production of guidelines. A possible solution to the problem was proposed by Professor Ian Olver AM, then CEO of Cancer Council Australia. He suggested that using an electronic “wiki” platform, guidelines could be produced in a way that allowed individual sections to be updated as new evidence became available. This method had already been used successfully by Cancer Council Australia to produce national clinical practice guidelines for the management of lung cancer, sarcoma, and Barrett’s oesophagus.

The web-based wiki platform 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.[4] [5] 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 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 (P=Population, I=Intervention, C=Comparison, O=Outcomes), construct sound search strategies, systematically search the literature, critically appraise, summarise the evidence and formulate guidelines recommendations.

To develop the new management guidelines, Melanoma Institute Australia agreed to work in partnership with CCA using its wiki platform, with both organisations contributing to funding and providing in-kind resources. I took on the role of chairman, and a small management committee was appointed to oversee the guidelines revision process. Subsequently, a full multidisciplinary working party of individuals from all relevant disciplines was recruited, together with consumer representatives and members of the Cancer Council Australia Clinical Guidelines Network, headed by Ms Jutta von Dincklage (see full membership). The Skin Cancer College Australasia later joined the project and provided additional funding to enable employment of an additional full-time project officer in the systematic review team.

In November 2014, at an initial meeting of the guidelines working party, 23 questions were identified as being of greatest importance, covering issues relating to diagnosis, staging and management of cutaneous melanoma. These questions were then prioritised and work commenced immediately, with relevant evidence collected for each question then critically appraised by the systematic review team. Each publication bearing on the question

was structured according to the “PICO” format for the systematic review.[6] Small expert sub-committees, each headed by a lead author, were then given the task of formulating guidelines for the each clinical question and documenting the level of evidence supporting each recommendation. For matters outside the scope of the systematic review and when there was no good evidence available “practice points” were developed for inclusion in the guidelines (as in the two previously published Australian guidelines). Full details of the guidelines development process are given elsewhere.

An important contribution to the process of formal critical evaluation of available evidence, for which we are most grateful, was made by Professor Claus Garbe, Chairman of the German Dermatologic Cooperative Oncology Group (DeCOG) Committee on Guideline Development, who offered to let us use the systematic reviews that had recently been undertaken to produce updated German guidelines for melanoma management. These German guidelines had been published in 2013, so where the same questions were being considered, this greatly reduced the workload for the Australian systematic review team because they were able to limit update the systematic reviews with the publications that had appeared since 2012. In return, it was agreed that new data extractions and critical appraisals would be shared with the German group.

Made possible by use of the wiki platform, each chapter of the new Australian melanoma management guidelines will be published online when it is completed. After a draft has been prepared by each chapter group, it is released for public consultation, then finalised and approved for publication by the entire working group. At the time of preparing this Foreword the first four chapters have completed this process and are being published. They are:

- Type of biopsy
- Clinical features and atypical melanoma
- When is a sentinel node biopsy indicated?
- Recommended definitive margins for excision of primary melanoma

Subsequent chapters dealing with other important clinical questions will be published later, as they are completed and ratified by the working party, and chapters already published will be revised as relevant new evidence to guide management becomes available. These guidelines will thus be a living document, rather than a static printed publication that would inevitably be out of date within a very short time. It is hoped that wide dissemination of these guidelines and adherence to their recommendations will benefit melanoma patients in Australia by ensuring that they receive the most appropriate care.

Professor John Thompson AO

Chair, Melanoma Guidelines Working Party

1.1.1 Acknowledgments

The preparation of clinical guidelines of this nature involves a great deal of hard work by many people, and as Chair of the Working Party I acknowledge the contributions of all members of the group, particularly the chapter leaders. I also acknowledge those who undertook the arduous task of critical literature selection and appraisal, and the staff of the Clinical Guidelines Network of Cancer Council Australia, particularly its head Ms Jutta von Dincklage, who drove the project forward with great zeal and efficiency.

1.2 References

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6. ↑ Clinical Guidelines Network Cancer Council Australia. *Development of Clinical Practice Guidelines using Cancer Council Australia's Cancer Guidelines Wiki. Handbook for section authors and the guideline working party.* CCA Sydney; 2014 Available from: http://wiki.cancer.org.au/australiawiki/images/9/9b/CCA_Clinical_Practice_Guideline_Development_Handbook.pdf.

2 Summary of recommendations

This page provides a summary of the recommendations of the completed clinical questions published so far in the Melanoma guidelines. Other sections of the guidelines are currently in progress and will be published iteratively.

For explanation of the different types of recommendations, see NHMRC approved recommendation types and definitions below.

Refer to the Guideline development process for details on the levels of evidence and recommendation grades.

Jump to:

- Management of melanoma in children
- Management of melanocytic tumour of unknown malignant potential
- Management of melanoma in pregnancy
- Investigations and follow-up for melanoma patients
- Treatment of satellite and in-transit metastases
- Treatment of macroscopic nodal metastases
- Surgical therapy for patients with distant metastases
- Treatment approaches to brain metastases for patients with melanoma
- Systemic therapy
- Radiotherapy
- Management of mucosal melanoma
- Management of ocular melanoma
- Multidisciplinary care of melanoma patients
- NHMRC approved recommendation types and definitions

2.1 Identification and management of high-risk individuals

2.1.1 What are the genetic determinants of high risk for new primary melanoma?

Practice point

Clinical genetic testing for CDKN2A mutations and genetic counselling should be considered in individuals with a strong family history of melanoma (3 or more cases related in the first- or second-degree) where predictive features are present, such as multiple primary melanoma, early age of onset, or pancreatic cancer.

Practice point

Detection (genotyping) of melanoma susceptibility SNPs may have a future role in assessing and managing individual risk of melanoma.

2.1.2 What validated models integrate genetic and clinical risk factors into an overall measurement of high risk from new primary melanoma?

Evidence-based recommendation	Grade
Assess all patients for future risk of melanoma, using validated risk factors and a model that integrates personal risk factors into an overall index of risk.	**B**

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2.1.3 What interventions have been shown to provide clinical benefit in those assessed to be at high risk of new primary melanoma?

Evidence-based recommendation	Grade
Individuals at very high risk of melanoma and their partner or carer should be educated to recognise and document lesions suspicious of melanoma. These individuals should be checked regularly by a clinician with six-monthly full skin examination supported by total body photography and dermoscopy.	**C**

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2.2 Diagnosis

2.2.1 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.

2.2.2 What is the role of dermoscopy in melanoma diagnosis?

Practice point
Dermoscopy can also identify diagnostic features in non-pigmented (amelanotic) lesions.

Evidence-based recommendation	Grade
Clinicians who are performing skin examinations for the purpose of detecting skin cancer should be trained in and use dermoscopy.	**A**

2.2.3 What is the role of sequential digital dermoscopy imaging in melanoma diagnosis?

Practice point
Only flat or slightly raised lesions should undergo dermoscopy monitoring. Suspicious nodular lesions should not be monitored but should be excised.

Practice point
The interval for short-term monitoring is 3 months where any change leads to excision. Where lentigo maligna is in the differential diagnosis it is recommended an additional 3 months of monitoring performed, i.e. total of 6 months.

Practice point
The usual interval for long-term monitoring is 6-12 months. Unlike short-term monitoring, certain specific changes are required for excision to be indicated.

Evidence-based recommendation	Grade
To assess individual melanocytic lesions of concern, recommend the use of short-term sequential digital dermoscopy imaging (dermoscopy monitoring) to detect melanomas that lack dermoscopic features of melanoma.	**B**

Evidence-based recommendation	Grade
To assess individual or multiple melanocytic lesions in routine surveillance of high risk patients, recommend the use of long-term sequential digital dermoscopy imaging (dermoscopy monitoring) to detect melanomas that lack dermoscopic features of melanoma.	**B**

2.2.4 What is the role of automated instruments in melanoma diagnosis?

Evidence-based recommendation	Grade
There is insufficient evidence to recommend the routine use of automated instruments for the clinical diagnosis of primary melanoma. However, particularly when a benign measurement is found using the cited protocols of Nevisense™ and MelaFind™, this information may aid the clinician.	**D**

2.2.5 What is the role of skin surface imaging (total body photography) in the early diagnosis of patients at high risk of developing melanoma?

Evidence-based recommendation	Grade
Consider the use of total body photography in managing patients at increased risk for melanoma, particularly those with high naevus counts and dysplastic naevi.	**C**

Practice point
TBP allows monitoring of most of the skin surface, including most existing skin lesions. TBP should be the primary imaging intervention for early melanoma detection in patients at elevated risk who have high naevus counts or multiple dysplastic naevi.

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2.3 Biopsy

2.3.1 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.

2.3.2 What clinical information should the clinician give the pathologist to aid diagnosis of melanoma?

Practice point
It is advisable that as much relevant clinical information (Table 1) as possible be provided to pathologists to aid in the diagnosis of melanoma.

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2.4 Management of primary melanoma and lentigo maligna

2.4.1 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.

2.4.2 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; positive histological margins are unacceptable.	**B**

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.

2.4.3 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

Practice point
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 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.

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

Evidence-based recommendation	Grade
CLND is no longer the preferred treatment for patients with a positive SLNB. CLND or active surveillance are equivalent in terms of 3 year melanoma specific survival but CLND is more morbid.	**B**

Evidence-based recommendation	Grade
CLND offers high levels of immediate regional control for patients with positive SLNB however good regional control can be achieved with delayed CLND.	**C**

Practice point
To date there is no subgroup of patients for whom immediate CLND is likely to provide a clear benefit, however patients with a high risk of further non-SLN involvement and particularly those who are less likely to suffer significant morbidity from CLND may choose to have the procedure to reduce the risk of lymph node field relapse. A risk calculator for defining the likelihood of non-SLN involvement such as the N-SNORE (Murali et al. 2010) can be of assistance to more accurately estimate the probability of residual non-SN positive nodes.

Practice point
Close clinical and ultrasound surveillance using a protocol equivalent to that followed in MSLT-II and DeCOG-SLT of 3-4 monthly clinical examination and ultrasound of the regional lymph node field for 2 years and then the same at least 6 monthly for a total of 5 years, then annual clinical review is required if a patient with a positive SLNB chooses active surveillance.

2.4.5 What is the optimal management for primary desmoplastic melanomas?

Evidence-based recommendation	Grade
Desmoplastic melanomas and neurotropic melanomas should be excised with the same margins as would be performed on a non-desmoplastic/neurotropic melanoma of the same Breslow thickness.	**B**

Evidence-based recommendation	Grade
Adjuvant radiotherapy to the primary excision site should be considered for patients with desmoplastic or neurotropic melanoma for whom adequate (≥8mm) pathological resection margins cannot be achieved.	**C**

Practice point
It is important for all clinicians performing skin checks to be aware of DM and its often subtle clinical presentation.

Practice point
MRI and nerve biopsy should be considered for patients with facial DM located close to named nerves.

2.4.6 What is the role of sentinel node biopsy for desmoplastic melanomas?

Evidence-based recommendation	Grade
SLNB should be considered for patients with DM, as it would be for non-DM. See When is a sentinel node biopsy indicated?	C

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2.5 Management of melanoma in children

2.5.1 How should melanoma in children be managed?

Practice point
The pathology slides of all Spitz-like lesions in children suspected of being malignant should be referred to histopathologists who are highly experienced in the differential diagnosis of such lesions.

Practice point
All facets of melanoma treatment and follow-up in adults may be integrated into the treatment and follow-up of children. Parents may be assured that survival in children is at least equivalent and probably better than it is in adults with the same stage of disease.

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2.6 Management of melanocytic tumour of unknown malignant potential

2.6.1 The role of sentinel node biopsy in the management of MelTUMPs (melanocytomas)

Evidence-based recommendation	Grade
The routine use of sentinel lymph node biopsy for MelTUMPs is not recommended. In the event of a positive node, its significance should be reviewed by a multidisciplinary melanoma team with expertise in such diagnostic dilemmas.	C

Evidence-based recommendation	Grade
Age should not be used to determine the prognosis of a patient with a MelTUMP.	C

Practice point
It is advisable to have pathologists with expertise in the examination of melanocytic lesions review the tumour slides to confirm or reject a suspected diagnosis of MelTUMP.

2.6.2 Excision margins for patients with MelTUMPs

Practice point
It is advisable to excise MelTUMPs with a 5mm clinical margin and ensure there is at least a 2mm histological margin.

Practice point
It is advisable to follow up patients for at least five years following a diagnosis of MelTUMP, given the uncertainty surrounding the diagnosis. Six-monthly follow-up is advisable for the first 2 years.

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2.7 Management of melanoma in pregnancy

2.7.1 Pregnancy following diagnosis of melanoma

Practice point
Regular skin examination should be performed in pregnant women so that suspicious lesions can be dealt with in a timely fashion.

Practice point
Women of childbearing age who are within five years of primary treatment of a high-risk melanoma should be fully informed of their prognosis when considering pregnancy.

2.7.2 Optimal management of pregnant women with melanoma

Evidence-based recommendation	Grade
Where possible, surgical procedures requiring general anaesthesia should be deferred to the second trimester.	**B**

Evidence-based recommendation	Grade
Where possible, radiotherapy should be postponed until the post partum period unless the tumour is not located near the uterus and appropriate shielding is used.	**B**

Evidence-based recommendation	Grade
Use of targeted therapies and immunotherapies should be avoided during pregnancy until there is more evidence regarding their safety in this situation.	**B**

Evidence-based recommendation	Grade
In pregnant women, sentinel node biopsy should be performed without the use of Patent Blue dye.	**B**

Practice point
The treatment of melanoma during pregnancy should be approached the same way as in other melanoma patients, but needs to take into account the stage of the pregnancy and the stage of the melanoma. These patients should be managed by an expert MDT with input from the obstetrician.

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2.8 Investigations and follow-up for melanoma patients

2.8.1 What investigations should be performed following a diagnosis of primary cutaneous melanoma for asymptomatic stage I and stage II patients?

Evidence-based recommendation	Grade
Chest x-ray imaging for initial staging should not be performed	**C**

Evidence-based recommendation	Grade
CT head, chest, abdomen and pelvis imaging are not recommended for initial staging in asymptomatic patients with stage IIB or IIC melanoma. In addition, there is no evidence to support CT imaging in Stage I and IIA melanoma.	**C**

Evidence-based recommendation	Grade
CT imaging for initial staging is not recommended for patients with stage I-II melanoma	**C**

Evidence-based recommendation	Grade
PET/CT imaging for initial staging is not recommended for patients with a thin, or intermediate Breslow thickness primary melanoma (Stage I-IIB).	**C**

Evidence-based recommendation	Grade
MRI imaging of the head, spine or extremities is not recommended for initial staging in patients with stage I or stage II melanoma.	**D**

Evidence-based recommendation	Grade
S100B, MIA and LDH or standard blood tests are not recommended at initial staging for diagnosis of metastatic melanoma.	**C**

Practice point
Low sensitivity, specificity, and accuracy for general laboratory profiles (S100B, MIA, LDH blood tests) make them ineffective in the detection of subclinical recurrence and their roles are yet to be defined.

2.8.2 What investigations should be performed when in-transit and/or regional node disease (stage III melanoma) is diagnosed?

Evidence-based recommendation	Grade
FNB, with or without ultrasound guidance can be used to confirm the diagnosis of lymph node or intransit metastatic melanoma	**B**

Evidence-based recommendation	Grade
Core biopsy can be used to confirm the diagnosis of lymph node or intransit metastatic melanoma	**C**

Evidence-based recommendation	Grade
Consider NOT performing PET/CT or CT in newly diagnosed sentinel node positive patients	**C**

Evidence-based recommendation	Grade
Perform a PET/CT scan for the initial staging of stage III melanoma patients with palpable	**B**

Evidence-based recommendation	Grade
nodal disease.	

Evidence-based recommendation	Grade
A brain scan (high resolution CT or MRI) should be added to a PET/CT scan to assess for the presence of brain metastases.	**B**

Evidence-based recommendation	Grade
Consider using an MRI scan rather than a CT scan to assess for the presence of brain metastases.	**B**

Practice point
Ultrasound may be used for identification of the extent of intransit and nodal disease, and also used to diagnose liver metastases.

Practice point
Other countries consider performing S100B in stage III patients with palpable nodal disease, but this is not PBS available in Australia.

2.8.3 What investigations should be performed when stage IV melanoma is diagnosed?

Practice point
Serum LDH level should be measured at the time of diagnosis of stage IV melanoma.

Evidence-based recommendation	Grade
Whole body PET scanning or PET/CT is required in patients diagnosed with stage IV melanoma if the result will change management.	**A**

Evidence-based recommendation	Grade
Brain imaging with contrast enhanced CT or MRI is appropriate in asymptomatic patients diagnosed with stage IV melanoma.	C

Practice point
Documentation of the presence/absence of activating V600 BRAF mutations in tumour tissue is required before commencing systemic therapy for stage IV melanoma.

2.8.4 Follow up after initial definitive treatment for each stage of melanoma

Evidence-based recommendation	Grade
Self-examination is recommended following definitive local treatment for melanoma patients of any stage.	C

Evidence-based recommendation	Grade
History and physical examination by a patient's preferred medical practitioner should be undertaken for the detection of early, treatable recurrence following definitive treatment of stage I to stage III melanoma.	C

Evidence-based recommendation	Grade
Routine blood or radiological investigations are not recommended for the follow-up of asymptomatic stage I to stage IIB melanoma patients after definitive local treatment.	C

Evidence-based recommendation	Grade
Routine radiological investigations every 3-12 months may be considered for the first three years of follow up after definitive local treatment of stage IIC and III melanoma where detection of recurrence would allow early commencement of systemic therapy. However, there are currently no high-quality data that early detection and treatment of recurrence improves survival.	C

Practice point
Skin self-examination by patients is essential and they should be taught the process. Routine follow-up by the patient's preferred health professional may be appropriate to emphasise sun smart behaviour and perform skin checks, especially in 'hard to see' areas.

Practice point
Routine radiological imaging PET/CT or CT may be considered for patients with stage IIC or III melanoma for the early detection of recurrence, particularly in the context of a clinical trial. However, patients should be counselled regarding the potential risks of false positives, anxiety, and the risks of radiation including thyroid cancer and cataracts.

2.8.5 Ideal settings, duration and frequency of follow-up for patients with melanoma

Evidence-based recommendation	Grade
Routine follow-up by the patient's preferred doctor may be appropriate to emphasise sun smart behaviour and perform skin checks.	**C**

Practice point
It may be beneficial for medical professionals conducting follow up examinations for melanoma patients to be familiar with skin examination and dermatoscopy.

Evidence-based recommendation	Grade
Risk adjusted follow up looking for recurrence based on stage at presentation should be considered over a time period of 5-10 years for stages I-II melanoma. For surgically resected stage III melanoma, the most intensive follow up should be for the first 3 years.	**C**

Evidence-based recommendation	Grade
Melanoma survivors should be made aware of their risk of developing further primary	**C**

Evidence-based recommendation	Grade
melanomas, and of the consequent need for careful lifelong skin surveillance.	

Evidence-based recommendation	Grade
Follow-up intervals: ■ Stage I: follow-up annually for 10 years ■ Stage IIA: every 6 months for 2 years, then annually for 8 years ■ Stage IIB and IIC: every 3 to 4 months for 2 years, every 6 months during year 3, then annually for 5 years. ■ Stage IIIA-C: every 3 months for 2 years, every 6 months during year 3, then annually for 5 years.	**C**

Evidence-based recommendation	Grade
While it is important that clinicians weigh up the advantages and disadvantages of undertaking routine follow-up, individual patient's needs should be considered before appropriate follow-up is offered.	**C**

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2.9 Satellite and in-transit metastases

2.9.1 What are the most effective treatments of satellite and in-transit metastases?

Evidence-based recommendation	Grade
Sentinel node biopsy provides important prognostic information and should be performed if surgical excision of in-transit recurrence is planned.	**C**

Evidence-based recommendation	Grade
Limited disease may be treated with topical diphencyprone otherwise isolated limb	**C**

Evidence-based recommendation	Grade
infusion may be appropriate.	

Evidence-based recommendation	Grade
Isolated limb infusion is preferred to isolated limb perfusion despite slightly reduced effectiveness because of less frequent and less severe toxicity and reduced resource utilisation.	**C**

Practice point
The role of surgery has not been evaluated prospectively but supported by limited poor quality retrospective evidence and current practice surgical excision of limited disease is appropriate. Repeat excision is appropriate for patients with limited disease.

Practice point
Radiotherapy is particularly valuable for palliation of larger symptomatic lesions.

Practice point
For patients with extensive, recurrent or progressive disease, systemic therapy (targeted and immune-therapies) is appropriate. Patients should be considered for trials. See Systemic therapy for stage 3C unresectable and stage 4 melanoma

Practice point
Sentinel node biopsy provides important prognostic information and should be considered for patients presenting with in-transit metastases who are to undergo complete surgical excision.

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2.10 Macroscopic nodal metastases

2.10.1 What is the appropriate treatment of macroscopic (i.e. detectable clinically or by ultrasound) nodal metastases?

Practice point
Patients with macroscopic nodal disease should have the diagnosis confirmed preoperatively by image guided fine needle aspiration cytology and undergo staging with whole body PET-CT and MRI brain or CT Brain, Chest Abdomen and Pelvis.

Practice point
Patients with a parotid lymph node recurrence should undergo a superficial parotidectomy and upper neck dissection (levels 1B, 2, 3, and upper 5 and possibly 1a).

Evidence-based recommendation	Grade
Complete lymphadenectomy is recommended for patients with palpable or imaging detected lymph node field recurrence.	**C**

Practice point
Complete lymphadenectomy results in improved regional control over lesser procedures.

Practice point
All patients with Stage III B/C disease should be presented at a multidisciplinary management meeting.

Practice point
These high risk patients should be offered the opportunity to enrol in systemic adjuvant or neoadjuvant therapy trials.

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2.11 Surgical therapy for patients with distant metastases

2.11.1 Recommended surgical approach to brain metastases in patients with advanced melanoma

Practice point

Brain metastases that are symptomatic or generate mass effect at presentation are best treated with surgery, which results in rapid relief of symptoms and maintenance of functional independence.

Practice point

Surgical resection of brain metastases provides safe, durable local disease control. The use of the operating microscope, neuro navigation and an en bloc resection technique are recommended. The integration of surgery with systemic therapy and radiotherapy should be discussed by a multidisciplinary team.

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2.12 Treatment approaches to brain metastases for patients with melanoma

2.12.1 Systemic drug therapy in the management of patients with advanced melanoma brain metastases

Practice point

Systemic drug therapy is effective 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 from a radiation oncologist and a neurosurgeon.

2.12.2 Recommended surgical approach to brain metastases in patients with advanced melanoma

Practice point
Brain metastases that are symptomatic or generate mass effect at presentation are best treated with surgery, which results in rapid relief of symptoms and maintenance of functional independence.

Practice point
Surgical resection of brain metastases provides safe, durable local disease control. The use of the operating microscope, neuro navigation and an en bloc resection technique are recommended. The integration of surgery with systemic therapy and radiotherapy should be discussed by a multidisciplinary team.

2.12.3 For patients with distant metastases (other than brain metastases), when is radiotherapy indicated?

Evidence-based recommendation	Grade
Stereotactic radiosurgery (SRS) should be considered for patients with single or a small number of brain metastases to maximise local control.	**C**

Evidence-based recommendation	Grade
For patients with multiple brain metastases, whole brain radiation therapy may provide some palliative benefits.	**C**

Practice point
All melanoma patients with distant metastases should be reviewed at a multidisciplinary team meeting to ensure optimal drug, surgery and RT treatment combination.

Practice point
Patients with single or a small number of brain metastases should be given the opportunity to discuss adjuvant radiotherapy to the surgical cavity and/or the whole brain.

Practice point
Patients with painful bone metastasis should be considered for short course of RT for pain relief.

Practice point
RT should be considered in patients with problematic skin, soft tissue or nodal metastasis that have not responded to systemic therapy.

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2.13 Systemic therapy

2.13.1 What is the role of adjuvant systemic therapy in patients with resected stage II and stage III melanoma?

Evidence-based recommendation	Grade
All patients with resected stage III melanoma should discuss the benefits, potential toxicities and out-of-pocket costs of adjuvant systemic therapy with an experienced melanoma medical oncologist who is part of a multidisciplinary melanoma team, including the role of clinical trials.	**C**

Evidence-based recommendation	Grade
Patients with BRAF V600E/K resected stage III melanoma may be considered for 12 months adjuvant treatment with combination dabrafenib/trametinib. Note: Adjuvant dabrafenib/trametinib is not TGA approved or PBS listed	**B**

Evidence-based recommendation	Grade
Patients with resected stage IIIB/C or IV melanoma may be considered for 12 months adjuvant treatment with nivolumab. Note: Adjuvant nivolumab is not PBS funded.	**B**

Evidence-based recommendation	Grade
Patients with resected stage III melanoma may be considered for 12 months adjuvant treatment with pembrolizumab. Note: Adjuvant pembrolizumab is not TGA approved or PBS funded.	**B**

Evidence-based recommendation	Grade
Patients for whom adjuvant nivolumab, pembrolizumab or dabrafenib/trametinib is not appropriate or is not available, routine follow-up may be appropriate. Patients may consider treatment with IFN-α after discussion with a medical oncologist regarding the associated toxicity and potential benefit.	**B**

Evidence-based recommendation	Grade
Ipilimumab is not recommended because it has inferior efficacy and greater toxicity than nivolumab.	**B**

Evidence-based recommendation	Grade
Outside of a clinical trial adjuvant systemic therapy is not recommended for patients with resected stage II melanoma.	**C**

Practice point
Patients should be treated in a medical oncology facility with a melanoma multidisciplinary team and experience in using immunotherapy and BRAF/MEK inhibitors.

Practice point
At present neither dabrafenib/trametinib or pembrolizumab are TGA approved for adjuvant therapy and neither dabrafenib/trametinib, nivolumab or pembrolizumab are PBS funded. As such, enrolment in a clinical trial should be discussed.

Practice point
There are no data comparing combination dabrafenib/trametinib and nivolumab/pembrolizumab in patients whose tumours are BRAF V600 mutant, as such individual patient discussions are required for patients whose tumours are BRAF mutant.

Practice point
For those with stage III melanoma not able to receive dabrafenib/trametinib, nivolumab or pembrolizumab (or a clinical trial), interferon may be considered, but given the minimal overall survival benefit and significant toxicity, routine follow-up is usually preferred. See How should patients at each stage of melanoma be followed after initial definitive treatment?

2.13.2 Summary of recommendations and practice points: Immunotherapy for melanoma

Evidence-based recommendation	Grade
Anti-PD-1 based immunotherapy should be considered for the first-line/upfront drug treatment for patients with unresectable stage III/IV melanoma.	**B**

Evidence-based recommendation	Grade
A BRAF inhibitor combined with a MEK inhibitor should be considered as first-line/upfront drug treatment for patients with V600 BRAF mutation positive melanoma.	**B**

Consensus-based recommendation

Consensus Statement: Anti-PD-1 based therapies versus combination BRAF inhibitor plus MEK inhibitor have not been compared head to head, see Practice Points 6, 7 and 10.

Practice point

Practice point 1 All patients with unresectable stage III/IV metastatic melanoma (especially patients with brain metastases) should be discussed at a multidisciplinary team meeting, and managed by medical oncologists who have expertise using targeted and immune therapies.

Practice point

Practice point 2 Clinical trials should be considered for all patients with unresectable stage III/IV metastatic melanoma.

Practice point

Practice point 3 All patients with unresectable stage III/IV metastatic melanoma should have molecular testing of their melanoma for the V600 BRAF mutation, including V600E, V600K, V600R, V600D and V600M. Methodology should be used to detect appropriate mutations and be performed in an accredited laboratory using appropriate controls.

Practice point

Practice point 4 Baseline PD-L1 expression on melanoma cells should not be used to select patients for anti-PD-1 therapy due to its low predictive value.

Practice point

Practice point 5 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. See the Brain metastases section.

Practice point

Practice point 6 Cross phase III trial comparisons of landmark survival analyses (progression-free and overall survival) suggest that more durable responses and possibly higher long-term landmark survival values may be achieved with anti-PD-1-based therapy compared with combined BRAF inhibitor and MEK inhibitor in the first-line setting.^

^Check PBS guidelines before prescribing any drug.

Practice point

Practice point 7 Anti-PD-1-based therapy should be administered as first-line therapy as opposed to following BRAF inhibitor-based therapy.

Practice point

Practice point 8 While not formally compared, there is no suggestion that there is a difference in efficacy or toxicity between pembrolizumab and nivolumab.

Practice point

Practice point 9 While not formally compared, there is no suggestion that there is a difference in efficacy between dabrafenib/trametinib, vemurafenib/cobimetinib or encorafenib/binimetinib combinations, but toxicity profiles are distinct.

Practice point

Practice point 10 The combination of ipilimumab and nivolumab causes immune-related side effects, inducing grade 3/4 drug-related toxicities in 59% of patients, including asymptomatic laboratory abnormalities. Disease factors that may be considered in the selection of patients for this combination regimen include: rapidly progressive melanoma, baseline serum lactate dehydrogenase (LDH) > upper limit of normal, mucosal melanoma, active brain metastases, BRAF mutation-positive melanoma and low PDL-1 expression on melanoma cells (assay as per CheckMate 067).

Practice point

Practice point 11 Ipilimumab (anti-CTLA-4 immunotherapy), alone or in combination with anti-PD-1 may be administered following progression on anti-PD-1 monotherapy.

Practice point

Practice point 12 Any patient on immunotherapy can develop an auto-immune toxicity directed of any organ (and this risk must be discussed with the patient), The common toxicities are fatigue, rash, itch, diarrhoea, thyroiditis and hepatitis. Although a rare toxicity, it is important to note hypophysitis (inflammation of the pituitary gland) with subsequent hypopituitarism may occur, especially in regimens containing anti-CTLA-4 (e.g. ipilimumab).

Practice point

Practice point 13 Anti-PD-1 monotherapy may be administered in selected patients with auto-immune diseases with careful monitoring and after discussion with the patient and relevant clinicians regarding the risk of a flare of the auto-immune disease, planned treatment of the flare, and risk of death from auto-immune disease or melanoma.

Practice point

Practice point 14 Toxicity to one class of checkpoint inhibitor (e.g. anti-CTLA-4, ipilimumab) does not preclude use of a separate class of checkpoint inhibitor (e.g. anti-PD-1).

Practice point

Practice point 15 BRAF inhibitor monotherapy is not a recommended alternative to BRAF inhibitor combined with MEK inhibitor. Absolute contraindications to MEK inhibitors are rare, and single agent BRAF inhibitors are inferior to the combination in both efficacy and toxicity.

Practice point
Practice point 16 Patients with serum lactate dehydrogenase >2 x upper limit of normal at baseline have shorter progression-free and overall survival for both immune and targeted therapies, thus patients should be appropriately followed up and counselled.

Practice point
Practice point 17 Chemotherapy and binimetinib (for NRAS mutant melanoma) can be considered only after progression on immune checkpoint and BRAF inhibitor-based therapy, if appropriate.

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2.14 Radiotherapy

2.14.1 For patients with distant metastases (other than brain metastases), when is radiotherapy indicated?

Evidence-based recommendation	Grade
Stereotactic radiosurgery (SRS) should be considered for patients with single or a small number of brain metastases to maximise local control.	**C**

Evidence-based recommendation	Grade
For patients with multiple brain metastases, whole brain radiation therapy may provide some palliative benefits.	**C**

Practice point
All melanoma patients with distant metastases should be reviewed at a multidisciplinary team meeting to ensure optimal drug, surgery and RT treatment combination.

Practice point

Patients with single or a small number of brain metastases should be given the opportunity to discuss adjuvant radiotherapy to the surgical cavity and/or the whole brain.

Practice point

Patients with painful bone metastasis should be considered for short course of RT for pain relief.

Practice point

RT should be considered in patients with problematic skin, soft tissue or nodal metastasis that have not responded to systemic therapy.

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2.15 Management of mucosal melanoma

2.15.1 Mucosal melanoma

Practice point

The primary lesion for melanoma of the anorectal region should be managed by sphincter preserving complete local excision in most cases. Abdominoperineal resection is indicated only for patients with loco-regional disease whose primary tumour cannot be resected by a limited procedure.

Practice point

The routine use of sentinel node biopsy is not recommended.

Practice point

Adjuvant or post-operative radiotherapy after wide local excision may be considered particularly for patients with close/involved margins.

Practice point

The care of patients with anorectal melanoma should be undertaken by a multidisciplinary team experienced in the management of these patients.

Practice point

Patients with mucosal melanoma of the head and neck are best managed by complete surgical excision. Adjuvant radiotherapy should be considered particularly for patients with close and or involved margins after surgical resection.

Practice point

Patients to be referred to a specialist unit with experience in head and neck melanoma.

Practice point

Radical resection can be considered in patients with limited disease.

Practice point

Wide excision is recommended rather than penectomy for melanoma of the glans penis, skin of penis and scrotum.

Practice point

The role of SNB is not established for melanoma of the glans penis, skin of penis and scrotum.

Practice point
Histologically confirmed melanoma of the vulva can be managed by wide excision with limited margins (1–2cm). Extensive lesions particularly those centrally located may require extensive/exenterative procedures. In the absence of proven regional lymph node spread lymphadenectomy is not indicated.

Practice point
Patients with vulval melanoma be referred to a specialist unit with expertise.

Practice point
Any suspicious lesions of the genital tract should be biopsied.

Practice point
As there is a high incidence of systemic disease in these cases, a CT or PET scan is indicated prior to radical surgery.

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2.16 Management of ocular melanoma

2.16.1 Ocular melanoma

Evidence-based recommendation	Grade
Ocular melanoma is a complex and uncommon form of melanoma that should be managed in specialised units where multidisciplinary ocular cancer services are available.	**C**

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2.17 Multidisciplinary care of melanoma patients

2.17.1 Multidisciplinary care in the management of melanoma

Recommendation	Grade
Multidisciplinary care should be considered in the management of all patients with stage III and stage IV melanoma.	**C**

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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]

2.18 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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2.19 References

1. ↑ National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers.* Canberra: National Health and Medical Research Council; 2009 Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

2.1 Identification and management of high-risk individuals – Introduction

2.1.1 Introduction

This chapter of the Guidelines considers the evidence underlying the identification and management of individuals at high risk of melanoma.

The Australian *Clinical Practice Guidelines for Management of Cutaneous Melanoma* (2010) recommended that people at high risk of melanoma have ongoing surveillance, and be educated about skin self-examination and appropriate sun protection. However, Australia has no population-based melanoma screening program, and neither the main observable risk factors, such as fair skin, sun-sensitivity and naevus (mole) count, nor the genomic variations that underlie them, are currently used systematically to stream high-risk individuals for targeted prevention, screening or early detection programs. A recent evidence synthesis for the US Preventive Services Taskforce concluded: “Future research on skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer”.[1]

The 2010 edition of these Guidelines highlighted the strong evidence that individual melanoma risk is influenced by a range of risk factors: some demographic (e.g. age, sex, geographic location), some marked by skin phenotype (e.g. pigmentation, melanocytic naevi), some only signalled by personal or family history of melanoma (e.g. a high-risk genetic background). It concluded that genetic testing of *CDKN2A* mutations had a role in highly selected familial melanoma kindred's. It provided guidance on the appropriate surveillance of individuals at high risk, from whatever cause.

In the current guideline, evidence and recommendations have been updated in three areas:

- the genetic basis of high melanoma risk,
- integrated risk assessment, considering all relevant risk factors, and
- evidence for benefit of identification and systematic surveillance of individuals at high risk of future melanoma.

Taken together, there is evidence that clinical practice should change in both the areas of risk assessment and surveillance.

This section covers the following questions:

- What are the genetic determinants of high risk for new primary melanoma?
- What validated models integrate genetic and clinical risk factors into an overall measurement of high risk from new primary melanoma?
- What interventions have been shown to provide clinical benefit in those assessed to be at high risk of new primary melanoma?

2.1.2 References

1. ↑ Wernli KJ, Henrikson NB, Morrison CC, Nguyen M, Pocobelli G, Blasi PR. *Screening for Skin Cancer in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.* JAMA 2016 Jul 26;316(4):436-47 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27458949.

2.2 Genetic determinants of high risk

Contents

2.2.1 Introduction

The current chapter updates the evidence regarding the genetic factors underlying individual risk of cutaneous melanoma.

2.2.2 Evidence reviewed

A non-systematic, expert review was undertaken to identify relevant published systematic reviews and meta-analyses on genetic determinants of high risk for new primary melanoma. This review of the literature since the 2008 Guidelines had two aims: to update the evidence of rare mutations that confer high risk of melanoma, and to highlight the new evidence that common variations in the genome collectively influence personal risk of melanoma.

2.2.3 Rare mutations associated with familial melanoma

These are carried by fewer than 0.1% of the population, cause large increases in personal melanoma risk, and are commonly signalled by a strong family history of melanoma.

The first germline (heritable) mutations found to confer high personal risk of cutaneous melanoma disrupt the two genes encoded by the CDKN2A locus (p16INK4A and p14ARF), or the CDK4 gene. These mutations are strongly associated with familial melanoma, albeit in a minority of cases, and are rare in melanoma cases that have not been selected for a strong positive family history of melanoma.[1] Since the 2008 Guidelines were prepared, several additional genes have been reported to be mutated in rare instances of familial cutaneous melanoma: BAP1, POT1, ACD, TERF2IP and TERT. A recent review[2] estimated that a combined total of 50% of dense melanoma kindreds internationally might include carriers of mutations in one of these seven genes, the vast majority in CDKN2A. However, this may be an overestimate for Australia, based on previous data showing that fewer than 20% of Australian kindreds with at least three cases of cutaneous melanoma carried CDKN2A mutations.[1]

The chance that a melanoma cluster is due to a family CDKN2A mutation increases with the number of relatives affected, the number who have had more than one primary melanoma, the earlier their age at diagnosis, and the number of relatives with pancreatic cancer. However these relationships are poorly quantified as yet. In the only population-based study to date, cases with first primary melanoma under the age of 40yr had an average CDKN2A mutation prevalence of 2.3%: 1.4% (7/500) of those with no family history and 7.3% (7/96) of those with at least one affected relative.[3] Better knowledge of the prevalence and predictors of family CDKN2A mutations in Australia would improve selection of families for genetic testing. Current recommendations regarding genetic testing in familial melanoma are still valid, but will need modification as the specific predictors of CDKN2A mutation in Australia become better defined.[1] Appropriately selected genetic testing has potential benefits, including facilitating prevention and early detection in mutation carriers. (see What interventions have been shown to reduce the risk of death from melanoma in those assessed to be at high risk of new primary melanoma?). The additional risk of melanoma that is conferred by a CDKN2A mutation is well known, averaging 20% by age 50 and 52% by age 80 in Australia.[4] This risk information should be used to guide genetic counselling of carriers of these mutations.

Because of their rarity, there is no case for routine testing for mutations in genes other than CDKN2A in Australian familial melanoma, however panel and whole-genome sequencing analysis may in time make this cost-effective outside research settings. A germline BAP1 mutation should be considered if the family includes BAP1 associated cancers such as renal cancer, mesothelioma and meningioma, or if the melanomas have BAP1-associated clinical and histologic features[5]; however, these features are only weakly predictive of the presence of germline BAP1 mutation. Paradoxically, such families have not been found to include cases of uveal (ocular) melanoma, whereas familial uveal melanoma alone is strongly associated with BAP1 mutations.

2.2.3.1 Non systematic review evidence summary and recommendations

Evidence summary	Level	References
A proportion of familial cutaneous melanoma (defined as clusters of several cases all	III-3	

Evidence summary	Level	References
related to each other), is accounted for by germline mutations in the CDKN2A gene and, rarely, the BAP1, POT1, ACD, TERF2IP and TERT genes		[4], [2]

Practice point

Clinical genetic testing for CDKN2A mutations and genetic counselling should be considered in individuals with a strong family history of melanoma (3 or more cases related in the first- or second-degree) where predictive features are present, such as multiple primary melanoma, early age of onset, or pancreatic cancer.

2.2.4 Common genomic variants

Here we refer to genetic variations carried by at least 1% of the population, and which for most people are the main drivers of melanoma risk, together with sun exposure.

In the last edition, evidence was presented to show that a significant proportion of melanoma risk in the population is due to common variations in the MC1R gene, which contribute to skin pigmentation and sun sensitivity.[1]

Since the last edition, extensive evidence has accumulated from genome-wide association studies (GWAS) of case-control cohorts that common variations in many other genes contribute to risk of cutaneous melanoma and other skin cancers. These data will deepen and extend in years to come, expanding the number of genes known to influence melanoma risk, and better estimating the degree of risk that each confers. These gene variations are typically single-nucleotide polymorphisms (SNP), and they may or may not have readily-identifiable functional consequences. However, many of them are responsible for the common, clinically detectable risk factors for melanoma, namely skin pigmentation, sun sensitivity and increased naevus count.

The key evidence identified by the expert panel comprised the systematic review by Gerstenblith (2010)[6], and meta-analyses by Antonopoulou (2015)[7] and Law (2015)[8]. The meta-analysis by Law and colleagues focuses exclusively on genome-wide analyses, including data from 11 reported GWAS studies and additional datasets comprising a total 15,990 cutaneous melanoma cases and 26,409 controls, some from Australia.[8] Its findings include all but one positive finding from Antonopolou, are consistent with the earlier systematic review by Gerstenblith, and as the highest-powered such study to date, its results will be summarised here to represent the state of the field.

Twenty loci are now unequivocally associated with susceptibility to cutaneous melanoma (reaching $P < 5x10-8$, genome-wide) and are listed here by chromosome (Ch): (Ch 1) ARNT, PARP1; (Ch 2) CYP1B1, CASP8; (Ch 5) TERT, SLC45A2; (Ch 6) CDKAL1; (Ch 7) AGR3; (Ch 9) CDKN2A, RAD23B; (Ch 10) OBFC1; (Ch 11) CCND1, TYR, ATM; (Ch15) OCA2; (Ch 16) FTO, MC1R; (Ch 20) ASIP; (Ch 21) MX2; (Ch 22) PLA2G6. Five of these genes are in

regions known to be related to pigmentation, three are in nevus-related regions and four are in regions related to telomere maintenance. For the other eight it is unclear what mechanisms may mediate their effect on melanoma susceptibility. These 20 genetic loci are estimated to account for 19.2% of the increased risk exhibited by relatives of melanoma cases. Of this total, about a quarter is due to MC1R variants alone, due to their high prevalence (10-15%) and moderate effect on risk (1.7-fold). A rare variant in the MITF gene, present in about 0.7% of the population, was also found to increase risk by a comparable amount to MC1R.[9]

Further melanoma risk loci will be confirmed as larger GWAS cohorts are assembled, and the proportion of melanoma in the population that is attributable to genetic background will continue to increase. There is preliminary evidence that testing of these SNP may have a future role in clinical practice, however few studies have assessed their contribution to risk in multivariate analysis with clinical variables (see What validated models integrate genetic and clinical risk factors into an overall measurement of high risk from new primary melanoma?).

2.2.4.1 Non systematic review evidence summary and recommendations

Evidence summary	Level	References
Common variations (SNPs) in at least twenty genes influence melanoma risk in the population, accounting for about 20% of the excess risk to relatives of melanoma cases	IV	[7], [8]

Practice point
Detection (genotyping) of melanoma susceptibility SNPs may have a future role in assessing and managing individual risk of melanoma.

2.2.5 Issues requiring more clinical research study

If gaps in the evidence are identified during the evidence review, please note areas for further research including a brief description. Genetic testing of familial melanoma kindreds in Australia needs to be informed by better estimates of the prevalence and predictors of CDKN2A mutation.

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2.3 Validated models for overall measurements of high risk

Contents

2.3.1 Introduction

Melanoma risk factors such as skin pigmentation, naevus number and genetic loci are not independent of each other. Optimal clinical risk assessment needs a combination of these measurements that most reliably discriminates people with a high likelihood of future melanoma from those at lower risk. Such measures could inform and motivate preventive behaviours and provide a basis for targeted interventions to improve early detection in the population.

2.3.2 Systematic review evidence

Vuong *et al* (2014) and Usher-Smith *et al* (2014) conducted systematic reviews of 28 and 25, respectively, multivariable risk prediction models for incident primary melanoma reported to 2013, and concluded they achieved fair to very good discrimination (AUROC).[1][2] For example, Vuong *et al* (2014) assessed 19 eligible studies, which yielded two to 13 predictors; the most common were the presence of nevi, skin type, freckle density, age, hair colour and sunburn history. Only four studies in the two reviews had included genetic factors. Very few studies validated performance in an external dataset and calibration performance was only reported in two studies. Most base studies had used case-control design and therefore have a moderately high risk of bias. Three studies identified high risk individuals using absolute risk cutoffs, which are likely to have greater intelligibility for patients and clinical utility than relative risks.[3][4][5] However, relative risks can also be important for targeting sun protection interventions towards younger people at high relative risk, but low absolute risk.

The systematic review conducted for this guidelines process identified a further nine eligible studies[6][7][8][9][10][11][12][13][14] that reported discrimination, six[7][12][9][8][11][14] of them reporting calibration. Three of these studies included genetic factors.[7][12][9] Three studies conducted substantial external validation, including in cohort studies, however genetic factors were only assessed via family history.[8][11][14] Discrimination was, in general, high; the models validated externally and were well calibrated. Australian data have been extensively used to generate and validate the models and these outcomes are therefore highly suitable to inform Australian clinical practice.

One limitation in the evidence is that very few studies have externally validated the effect of introduction of measured genetic factors on risk discrimination. Two Australian studies[7][15], one measuring genotypes at MC1R and other melanoma susceptibility SNPs, and these modestly improved the discrimination and calibration of a base clinical model. A second limitation is that the lists of clinical risk factors studied and validated may not yet be complete, and further factors may improve future models. Finally, there is a need for suitable on-line tools to support melanoma risk assessment using these better-performing, systematic techniques (see Melanoma risk calculator).

In summary, there is high level evidence that integrated assessment of personal risk factors for cutaneous melanoma, whether self-measured or clinically assessed, stratifies the population by future likelihood of melanoma more reliably than less systematic methods. Data are emerging that measured genetic risk can improve the performance of these models, but this requires further validation.

2.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Integrated assessment of personal risk factors for cutaneous melanoma, whether self-measured or clinically assessed, effectively stratifies the population by future likelihood of melanoma.	III-3	[1], [2], [8], [11], [14]

Evidence-based recommendation	Grade
Assess all patients for future risk of melanoma, using validated risk factors and a model that integrates personal risk factors into an overall index of risk.	**B**

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

Contents

2.4.1 Introduction

See Diagnostic aids for melanoma for detailed evidence and recommendations on early melanoma diagnosis, which has been shown to be effective in detecting subsequent melanomas at an early stage, and is therefore inferred to reduce mortality.

There is variation among international guidelines about how best to identify and manage high-risk patients.[1] The 2010 Australian guidelines recommended surveillance intervals should be based on assessment of the level of future risk of melanoma, and on the basis of expert opinion have recommended that individuals at high risk of melanoma and their partner or carer be "educated to recognise and document lesions suspicious of melanoma, and to be regularly checked by a clinician with six-monthly full body examination supported by total body photography and dermoscopy as required".[2] Randomised comparisons of alternative screening methodologies and intervals have not been done, and are unlikely ever to be.

2.4.2 Systematic review evidence

The systematic review searched for studies in which a surveillance protocol reported key outcomes of incidence and thickness of prospectively detected melanoma, from which benefits to mortality and morbidity could be inferred. Two studies have reported the incidence and characteristics of melanomas detected prospectively in cohorts selected for high future risk of melanoma, using a systematic protocol of examination.[3][4] In Spain[3] and Australia[5] digital dermoscopy with reference to total body photography was used at average six-monthly intervals to monitor cohorts of individuals at high risk, defined by multiple criteria: increased numbers of atypical naevi, or a strong family history, or presence of a strong melanoma-predisposing mutation. Both studies were therefore of individuals at very high risk of melanoma, comprising less than 1% of the population. In a further French study conducted in primary care[4], the only entry criterion was increased risk based on age, and no systematic protocol of examination was followed.

Over a median eight years follow-up the Spanish study[3] identified 98 melanomas in 78 patients in a cohort of 618, at a ratio of excised benign:malignant melanocytic lesions of 10.7:1 and median Breslow thickness of 0.5 mm. The Australian study[5] reported results after median 3.5 years follow-up, identifying 61 melanomas in 48 patients of a cohort of 311, at a ratio of excised benign:malignant (including *in situ*) melanocytic lesions of 4.4:1 and the median Breslow thickness was in situ. Both studies therefore report *prima facie* evidence of clinical benefit to those screened, but the results of Moloney 2014, also suggested there was potential for significant cost-benefit, due to the very low ratio of benign:malignant lesions excised.[5]

In the Moloney *et al* (2014) cohort,[5] microcosting analyses were therefore performed and were compared with costs of usual care using the *45 and Up* study cohort (2008).[6] These comparisons confirmed a significant cost-benefit for the structured surveillance protocol.[7] Specialised surveillance was both less expensive and more effective than standard care. The mean saving was A$6,828 per patient, and the mean quality-adjusted life-year gain was 0.31.[7] The main drivers of the differences were detection of melanoma at an earlier stage resulting in less extensive treatment and a 70% lower annual mean excision rate for suspicious lesions in specialized surveillance compared with standard care.The results were robust when tested in sensitivity analyses.[7] These data have not yet been replicated elsewhere but expansion cohorts are under study. A critical factor for exploration in future research is the extent to which reduced rates of excision can be sustained in all clinical practice contexts in which such individuals are under surveillance. Finally, these outcomes confirm that a structured approach to both clinical assessment of future risk of melanoma, and to surveillance, stand to deliver real benefits to patients and the health care system more broadly. It is not yet known whether these cost-effectiveness advantages apply to patients at less extreme levels of risk.

In summary, a structured surveillance protocol, using six-monthly full skin examination, supported by dermoscopy with reference to total body photography provided clinical benefit to individuals at very high risk of melanoma, and according to Australian data does so at significant cost-benefit.

2.4.3 Evidence summary and recommendations

Evidence summary	Level	References
A structured surveillance protocol of full skin examination using dermoscopy, supported by total body photography, provides clinical benefit to individuals at very high risk of melanoma by detecting incident melanomas at an earlier stage, and according to Australian data is cost-effective.	III-3	[3], [5], [7]

Evidence-based recommendation	Grade
Individuals at very high risk of melanoma and their partner or carer should be educated to recognise and document lesions suspicious of melanoma. These individuals should be checked regularly by a clinician with six-monthly full skin examination supported by total body photography and dermoscopy.	**C**

2.4.4 Issues requiring more clinical research study

In principle, randomised controlled trials of alternative surveillance protocols are needed, but are unlikely, for ethical reasons, ever to be done. The surveillance protocols trialled so far in very high-risk individuals should be tested in individuals at high, but lower, levels of risk.

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2.5 Clinical features of melanoma

Contents

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 masquerade 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, and symmetry of pigment pattern 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 clinically as a dermatofibroma, scar or non-melanoma skin cancer. Recurrence at the site of a previous biopsy diagnosed as benign on histopathology (e.g. as dermatofibroma, neurofibroma, scar) is not an uncommon presentation of DM as the histopathology can be difficult in some cases, particularly with partial biopsy. Review of previous pathology can be helpful where there is clinical suspicion.

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 melanoma). They may have a prolonged radial growth phase (similar to LMM) before becoming invasive. ALM typically presents with light asymmetric macular pigmentation, which may be patchy and therefore 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. 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.

2.5.3.6 Spitzoid melanoma

Spitzoid melanoma is at the malignant end of the spectrum of melanocytic lesions which includes Spitz naevus and atypical Spitz tumour. The typical benign Spitz naevus occurs in the young (usually <20) presenting as a pink dome-shaped symmetrical papule with a well defined border (10% are pigmented). Atypical Spitz tumour and spitzoid melanoma tend to present as larger lesions, often asymmetrical with more irregular border and surface, and pink to variegated, at any age but usually >10.[19][20] Spitz type lesions are defined by their histomorphology with large epithelioid and/or spindling melanocytes. Pathological assessment of these tumors is challenging and expert histopathological review should be considered prior to definitive surgical management. Partial biopsy is particularly unreliable with Spitz lesions. As yet there are no definitive molecular markers to assist diagnosis but this area is developing.

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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.[21] Up to 20% of all melanomas are only partially pigmented (hypomelanotic), with true amelanosis much less common.[22][23] 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][23][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.[22][24] 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][25][26][27] 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][28][29][30] 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 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.	III-2, III-3, IV	[10], [6], [9], [7], [4], [3]
Nodular melanomas are associated with more rapid vertical growth compared to superficial spreading melanomas.	III-3, IV	[28], [16], [29], [30]
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], [23]
Amelanosis/hypomelanosis is significantly associated with poorer diagnostic accuracy.	III-2, III-3	[21], [22]

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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2.5.7 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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2.5.8 References

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2.5.9 Appendices

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2.5.1 Diagnostic aids for melanoma

Introduction

There are many instruments available to aid the diagnosis of primary melanoma of the skin. We have reviewed the main techniques that have an adequate literature to propose recommendations, but understand that a variety of devices have not been reviewed.

This section covers the following questions:

- What is the role of dermoscopy in melanoma diagnosis?
- What is the role of sequential digital dermoscopy imaging in melanoma diagnosis?
- What is the role of automated instruments in melanoma diagnosis?
- What is the role of confocal microscopy in melanoma diagnosis?
- What is the role of skin surface imaging (total body photography) in the early diagnosis of patients at high risk of developing melanoma?

2.5.2 Dermoscopy

Contents

2.5.2.1 Background

Dermoscopy (dermatoscopy, surface microscopy, epiluminescence microscopy) is a technique that uses a hand-held magnifying device combined with either the application of a liquid between the transparent plate of the device and the skin, or the use of cross-polarised light. This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye.[1][2][3][4]

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2.5.2.2 Summary of systematic review results

Meta-analyses performed on studies in a variety of clinical and experimental settings have shown that using dermoscopy improves diagnostic accuracy for melanoma.[5][6] From a meta-analysis of nine level II diagnostic studies subject to varying degrees of verification bias performed prospectively in a clinical setting[7][8][9][10][11][12][13][14][15][16] the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 (95% CI 2.9–83.7) times higher for dermoscopy compared with naked eye (clinical) examination.[17] Importantly, the meta-analysis was restricted to studies that directly compared the two methods within each study. Sensitivity of dermoscopy was 18% (95% CI 9%–27%; P=0.002) higher than for naked eye examination, but there was no evidence of an effect on specificity (9% higher for dermoscopy; P=0.18).[17] Subsequent to this meta-analysis one level II study has been published in a primary care setting showing results consistent with the meta-analysis (42% increase in sensitivity and 5% increase in specificity with dermoscopy compared to naked eye).[18] However, there was a significant improvement in the confidence of diagnosis of both true melanoma (17% increase) and true non-melanoma (16% increase) with dermoscopy. In a further randomized clinical trial in primary care of both pigmented and non-pigmented lesions the odds ratio for a correct diagnosis in the dermoscopy compared to naked eye group was 1.51 (95% CI:0.96-2.37, p=0.07). Again, consistent with the meta-analysis, the effect was greater for the diagnosis of melanoma (61.5% sensitivity using dermoscopy versus 22.2% for naked-eye).[19]

Specificity can also be examined by its effect on excision rates of benign lesions, which was not addressed in the meta-analysis. Two such studies suggest reduced rates of excision of benign lesions using dermoscopy (reduced benign to malignant ratio of excised lesions and reduction of patients referred to biopsy) and provide indirect evidence for improved specificity in a specialist setting.[8][9] The addition of dermoscopy to naked eye (clinical) examination has also been shown to reduce excisions of benign pigmented lesions in high-risk patients in a specialist setting[20] and routinely managed pigmented lesions in primary care.[18][19]

While there are fewer studies on dermoscopy in primary care (general practice), all five that were undertaken in this context (one study with both general practitioners and inexperienced specialists or trainees)[21] show a consistently improved sensitivity for the diagnosis of melanoma or the identification of suspicious lesions requiring biopsy.[7][18][19][21][22] It should be noted that all the studies cited were undertaken by clinicians with some training in dermoscopy (restricted to lectures or reading material in some studies). For this reason, and based on other evidence where lack of training can lead to a reduction of diagnostic accuracy[23] some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy.

Practice point
Dermoscopy can also identify diagnostic features in non-pigmented (amelanotic) lesions.

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2.5.2.3 Evidence summary and recommendations

Evidence summary	Level	References
From a meta-analysis of nine level II studies prospectively performed in a clinical setting, the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 times higher for dermoscopy compared with naked eye examination. Sensitivity of dermoscopy was 18% (95% CI 9%–27%; P=0.002) higher than for eye examination, but there was no evidence of an effect on specificity. Two subsequent level II studies showed results consistent with the larger meta-analysis.+	I, II	[7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19]
Dermoscopy has been shown to reduce the benign:malignant ratio of excised melanocytic lesions and reduce the number of patients referred for biopsy in both specialists and primary care.+	II	[8], [9], [18], [20]

+The studies were classified as III-2 according the NHMRC 2009 levels and grade of evidence. Using the Grade approach, the studies were then upgraded to level II if the only criteria not meeting level II was the pathologist was not blinded to clinical information of the patient/lesion since it is established that clinical information is required for an accurate pathological diagnosis of melanocytic lesions.

2.5.2.3.1 Recommendations

Evidence-based recommendation	Grade
Clinicians who are performing skin examinations for the purpose of detecting skin cancer should be trained in and use dermoscopy.	**A**

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2.5.2.5 Appendices

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2.5.3 Sequential digital dermoscopy imaging

Contents

2.5.3.1 Background

Sequential digital dermoscopy imaging (SDDI) or dermoscopy monitoring involves the capture and assessment of successive dermoscopic images, separated by an interval of time, of one or many melanocytic lesions to detect suspicious change.

This is performed in two settings: short-term dermoscopy monitoring (over a period of 3 months) for suspicious melanocytic lesions without evidence of melanoma, and long-term monitoring for surveillance (usually at intervals of 6–12 months).[1][2] Long-term monitoring is generally used in the surveillance of high-risk patients, usually with multiple dysplastic naevi. In contrast, short-term monitoring of individual suspicious naevi can be used in any patient setting (eg. mildly atypical lesions with a patient history of change or moderately atypical lesions with a patient history of no change).

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2.5.3.2 Summary of systematic review results

In one study the sensitivity for the diagnosis of melanoma using short-term dermoscopy monitoring was 94% (excluding lentigo maligna which requires longer interval monitoring) and the specificity 84%.[3] For long-term monitoring, three studies have shown a high specificity (95-96%) for the diagnosis of melanoma, but the sensitivity was not evaluated.[4][5][6]

Four level II studies[1][4][7][5] with more recent cohort studies[3][8] all conducted in a specialist setting show consistently that SDDI allows the detection of melanoma that lack dermoscopic evidence of malignancy. Furthermore, the impact of routinely using SDDI has been shown in multiple studies to be high in regards to the proportion of melanomas detected by the technique. In three studies (two prospective observational trials[4][9] and one retrospective cohort[10]) of moderate-high risk patients in a specialist setting, SDDI allowed the

detection of 34-61% of the patients' melanomas, in two studies (one prospective observational trial[11] and one retrospective cohort[8]) in routine dermatological practice between 12-55% of melanomas detected and in 52% in a self-referring dermoscopy telemedicine setting (retrospective study).[12] Short-term SDDI allowed the detection of 33% of the patients' melanomas in a clinical trial of primary care physicians[13], however routine long-term SDDI of multiple naevi in lower risk patients is less efficacious.[14][15][16] Finally, SDDI has been shown in two prospective observational trials in both a specialist (both short and long-term monitoring)[11] and primary care setting (short-term monitoring)[13] to significantly reduce the benign:melanoma excision ratio and the number of excised benign melanocytic lesions.

Practice point

Only flat or slightly raised lesions should undergo dermoscopy monitoring. Suspicious nodular lesions should not be monitored but should be excised.

Practice point

The interval for short-term monitoring is 3 months where any change leads to excision. Where lentigo maligna is in the differential diagnosis it is recommended an additional 3 months of monitoring performed, i. e. total of 6 months.

Practice point

The usual interval for long-term monitoring is 6-12 months. Unlike short-term monitoring, certain specific changes are required for excision to be indicated.

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2.5.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Four level II studies and more recent cohort studies show consistently that	II, III-	[1], [4], [7], [5]

Evidence summary	Level	References
sequential digital dermoscopic imaging (SDDI) allows the detection of suspicious dermoscopic change in melanomas that lack dermoscopic evidence of melanoma at a particular time.	2	[3], [8]
The routine use of SDDI in both specialist and primary care allows the detection of a significant proportion of patients' melanomas. Long-term SDDI of multiple naevi in lower risk patients, while allowing detection of melanoma, is less efficacious.	II, III-2	[13], [4], [8], [10], [9], [11], [14], [15], [16]
SDDI has been shown to reduce the benign:malignant ratio of excised melanocytic lesions and reduce the number of patients referred for biopsy in both specialists and primary care.	II	[13], [11]

2.5.3.3.1 Recommendations

Evidence-based recommendation	Grade
To assess individual melanocytic lesions of concern, recommend the use of short-term sequential digital dermoscopy imaging (dermoscopy monitoring) to detect melanomas that lack dermoscopic features of melanoma.	**B**

Evidence-based recommendation	Grade
To assess individual or multiple melanocytic lesions in routine surveillance of high risk patients, recommend the use of long-term sequential digital dermoscopy imaging (dermoscopy monitoring) to detect melanomas that lack dermoscopic features of melanoma.	**B**

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2.5.3.4 References

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2.5.3.5 Appendices

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2.5.4 Automated instruments

Contents

2.5.4.1 Background

An automated diagnostic instrument is defined as one that requires minimal or no input from the clinician to achieve a diagnosis. Each automated instrument offers different technology with differing diagnostic ability. Guidelines for assessing such instruments have been published.[1] To date, only 2 studies have been reported comparing clinician diagnosis or management with machine diagnosis with an adequate sample size to assess both specificity and sensitivity for the diagnosis of melanoma.[2]

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2.5.4.2 Summary of systematic review results

The MelaFind™ system, a digital multispectral image analysis device for the use on suspicious pigmented melanocytic lesions, was directly compared to specialists' diagnosis in a prospective multicentre clinical trial.[3] Here, lesions were recruited (analysed) if they were scheduled for biopsy, usually because of clinician concern. The measured sensitivity of MelaFind™ was 98.4% (125 of 127 melanomas; 95% lower confidence bound 95.6%) which achieved the pre-trial primary aim and had a superior specificity (9.9%) to clinicians' (3.7%); p=0.02.

The Nevisense™ system, an electrical impedance device for the use on lesions, irrespective of pigmentation, where a diagnosis of melanoma needs exclusion, underwent a prospective multicentre clinical trial in a specialist setting.[4] The observed sensitivity of Nevisense™ was 96.6% (256 of 265 melanomas; 95% lower confidence bound 94.2%) with an observed specificity of 34.4%. Again, lesions were recruited if they were scheduled for biopsy, but a direct comparison with the recruiting clinician's diagnosis was not performed.

In both of the above systems high false positive rates with the highly prevalent seborrhoeic keratoses may cause a significantly poorer specificity when used by non-experts in the field. This has yet to be investigated. Indeed, currently there is no data on the use of these instruments in clinical trials in a primary care setting.

The effect of adding the MoleMate™ system, a digital image analysis device, to suspicious pigmented lesions in primary care, was assessed in a multicentre randomised clinical trial.[5] The primary endpoint was the effect of the device on the proportion of appropriately referred lesions, where the secondary care experts decided to biopsy or monitor, which did not differ significantly between those lesions being measured by the device (56.8% 130/229) or not (64.5% 111/172); p=0.12. The proportion of benign lesions appropriately managed and the percentage agreement with an expert decision to biopsy or monitor also did not significantly differ between use and non-use of the device. 18/18 melanomas were appropriately referred in the intervention group and 17/18 in the control group.

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2.5.4.3 Evidence summary and recommendations

Evidence summary	Level	References
To date, only 2 studies have been reported comparing specialist clinician diagnosis with an automated machine diagnosis with an adeqaute sample size to assess both specificity and sensitivity for the diagnosis of melanoma.	II	[2], [3]

2.5.4.3.1 Recommendations

Evidence-based recommendation	Grade
There is insufficient evidence to recommend the routine use of automated instruments for the clinical diagnosis of primary melanoma. However, particularly when a benign measurement is found using the cited protocols of Nevisense™ and MelaFind™, this information may aid the clinician.	**D**

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2.5.5 Confocal microscopy

2.5.5.1 Reflectance confocal microscopy

In vivo reflectance confocal microscopy (RCM) is a non-invasive technique that allows examination of the skin with cellular resolution. A systematic literature search up to 24 December 2015[1] identified a total of 21 studies involving 3108 patients with a total of 3602 lesions included in the per-lesion analysis: The pooled results for sensitivity and specificity were 93.6% (95% CI: 0.92-0.95) and 82.7% (95% CI: 0.81-0.84) respectively for the diagnosis of malignant lesions. Positive likelihood ratio and negative likelihood ratio were 5.84 (95% CI: 4.27-7.98) and 0.08 (95% CI: 0.07-0.10) respectively. Subgroup analysis showed that RCM had a sensitivity of 92.7% (95% CI: 0.90-0.95) and a specificity of 78.3% (95% CI: 0.76-0.81) for detecting melanoma. A systematic review by the Cochrane Collaboration[2] compared the diagnostic accuracy of RCM and dermoscopy for cutaneous melanoma; reviewing 19 study cohorts (up to August 2016) with 2838 lesions (including 658 with melanoma); this provided 67 datasets for RCM and 7 for dermoscopy. The meta-analysis found RCM to be more accurate than dermoscopy in studies of participants with any lesion suspicious for melanoma and in participants with lesions that were more difficult to diagnose (equivocal lesion populations). For example, assuming a fixed sensitivity of 90% for both tests, specificities were 82% for RCM and 42% for dermoscopy for any lesion suspicious for melanoma (9 RCM datasets; 1452 lesions and 370 melanomas). The authors conclude that RCM may reduce the number of people receiving unnecessary surgery by up to three-quarters compared to dermoscopy. Selective participant recruitment, lack of blinding of the reference test to the RCM result, and differential verification were limitations. It was noted that studies may not have been representative of populations eligible for RCM, and test interpretation was often undertaken remotely from the patient and blinded to clinical information.

Lesions located on the head and neck, lesions in areas chronically damaged by sun-exposure[3][4], lesions dermoscopically demonstrating regression[5] and amelanotic tumors[6][7] represent the best indications for the use of RCM. It could be particularly useful to assess lentigo maligna margins.[4]

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2.5.6 Skin surface imaging (total body photography)

Contents

2.5.6.1 Introduction

Early detection of melanoma is critical as thinner primary tumours are associated with enhanced survival.[1] Therefore, strategies to improve early detection are important to reduce melanoma-related mortality.

Total body photography (TBP) describes the use of clinical photography to provide a photographic record of patients' entire skin surface.[2][3] TBP typically includes 12-24 baseline photographs of the skin surface.[4][5][6][7][8] Each view may be defined by easily located anatomical reference points.[5][4] TBP provides a comparative reference point for subsequent examinations and its value derives from the knowledge that melanomas are new or show varying rates of progressive, unremitting change, while the great majority of benign naevi appear stable.[5]

Primary cutaneous melanomas may arise de novo or in association with a pre-existing melanocytic naevus, with the majority arising as de novo lesions.[9][10][11][12][13] TBP facilitates the detection of de novo melanomas which will be identifiable as new lesions arising on normal skin, as well as melanoma presenting as morphologic change in pre-existing melanocytic lesions.

Newness or change in a lesion may be helpful in arousing suspicion of lesions that might not otherwise be suspicious for melanoma (see clinical featues of melanoma), while photographic evidence of the skin surface to demonstrate stability avoids the need for unnecessary biopsies. TBP is undertaken as a baseline record and only needs to be updated when a significant number of changes have occurred, generally every five to ten years. This interval may be shorter in young patients, especially those younger than 30 years, who more frequently develop new and changing benign naevi.[5]

The use of TBP has previously been demonstrated to aid in the early diagnosis of melanoma in high risk patients, particularly in those with a high naevus count or multiple atypical naevi.[14][15][4][3][5][16] Previous research has demonstrated that the use of TBP reduces unnecessary excision of benign lesions[4][3] and increases the sensitivity and specificity of melanoma detection in clinical examination.[3] Not all changed lesions need to be excised. Those that show benign clinical and dermoscopic features can be safely observed. If at any point, there is clinical or dermoscopic evidence for melanoma, excision is recommended.[3] A recent Australian study evaluated the cost-effectiveness of skin surveillance through a specialised clinic for high risk patients, which used both total body photography and digital dermoscopy.[17] This study determined that specialised surveillance through a high risk clinic was both less expensive and more effective than standard care, with melanoma detected at an earlier stage and with few excisions performed.[17]

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2.5.6.2 Systematic review evidence

More recent studies have confirmed that TBP reduces the biopsy rate of benign naevi and improves diagnostic accuracy of melanoma in high risk patients.[18][6] High risk patients include those with high naevus counts, multiple atypical naevi and high rates of personal and family history of melanoma.

Recent studies have focused on the use of multimodal surveillance methods to aid in early melanoma detection. The "two-step method of digital follow up," coined by Salerni and colleagues, describes follow up with TBP and sequential digital dermoscopy imaging (SDDI).[19] For a detailed discussion on the role of SDDI in melanoma diagnosis, we refer readers to the chapter in the current guidelines entitled, What is the role of sequential digital

dermoscopy imaging in melanoma diagnosis?. Several authors have advocated that a multimodal approach with the combination of TBP and SDDI provides optimal surveillance in high risk patients and may assist with early melanoma diagnosis.[20][21][6][22][23] Melanomas diagnosed by TBP and SDDI have been demonstrated to be thinner compared to those diagnosed by traditional diagnostic methods.[23] As survival is strongly related to Breslow thickness, the combination of TBP and SDDI may confer a survival advantage to patients at high risk of developing melanoma.

TBP has the advantage of monitoring patients' entire skin surface, rather than a subset of individual lesions. TBP may therefore reveal interval change in pre-existing lesions that were not initially suspicious or atypical on clinical or dermoscopic examination, and as such were not included for SDDI, as well as detecting de novo lesions.[22] A retrospective cohort study determined that a third of melanomas diagnosed during follow up of high risk patients corresponded to lesions that were not under digital dermoscopic surveillance.[22]

An Australian study aimed to assess the impact of TBP and SDDI on melanoma detection in an extreme high risk cohort of patients.[6] In their population, 38% of melanomas were diagnosed either exclusively or aided by TBP, highlighting the value of TBP in melanoma diagnosis.[6]

While SDDI alone is a sensitive tool for detecting subtle dermoscopic change in naevi over time, it is necessarily limited to detecting change in a subset of pre-existing naevi that are under dermoscopic surveillance. A group of investigators evaluated the use of TBP in high risk patients in the context of their prior experience with SDDI in a similar patient population.[24] Monitoring high risk patients with TBP was associated with lower biopsy rates and lower naevus-to-melanoma ratios among biopsied lesions compared to SDDI.[24] TBP was found to have a higher rate of melanoma detection than SSDI and to be a more time-efficient approach.[24]

It is clear that TBP and SDDI provide different evidence for the detection of change in melanoma surveillance and therefore should be applied for different but overlapping indications. TBP provides global imaging evidence and will permit identification of most new or changed lesions wherever these might occur on the skin surface. TBP is particularly suited to patients at elevated risk with high naevus counts and multiple dysplastic naevi. SDDI fulfils a different need for monitoring of one to many individual flat lesions of concern that lack diagnostic clinical or dermoscopic features of melanoma (see: What is the role of sequential digital dermoscopy imaging in melanoma diagnosis?).

One study examined the efficacy of face to face examinations supported by TBP and SDDI compared with teledermatology for both applications.[25] This study was conducted in a high risk population using expert dermatologists. Teledermatology proved equally effective in this study.[25]

There remain no randomised controlled studies that have specifically evaluated the role of TBP in the early diagnosis of melanoma. Indeed, many experts feel that it would not be ethical to randomise high risk individuals to not having TBP.

All of the abovementioned studies were conducted in extreme or high risk cohorts of patients. These techniques are untested in lower risk populations and may not have the same value.

It is well-established that skin self-examination is important in early melanoma detection. The availability of TBP for the patients to use in self-examination may increase their capacity to identify significant change and be reassured about stable lesions. A recent study by Secker et al 2016[26] has demonstrated that less than a third

of high risk patients found TBP useful for skin self-examination and none of the five melanomas noticed by patients in the study of Moloney et al. were found using TBP.[6] Those patients in which TBP was found useful was associated with having received instructions on how to perform skin self-examination and confidence at detecting changing moles.[26] This study highlights the importance of promoting a more active role in skin surveillance by patients. Provision of education to patients on the technique of skin self-examination should be a priority for general practitioners and specialists involved in the care of melanoma patients.

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2.5.6.3 Evidence summary and recommendations

Evidence summary	Level	References
Five level III-2 studies have demonstrated that a multimodal approach with the combination of total body photography and sequential digital dermoscopy imaging provides effective surveillance in high risk patients and may assist with early melanoma diagnosis.	III-2	[20], [21], [6], [19], [23]
Two level IV studies have demonstrated that total body photography may reduce the number of naevus biopsies and improve diagnostic accuracy in high risk melanoma patients.	IV	[18], [24]

Evidence-based recommendation	Grade
Consider the use of total body photography in managing patients at increased risk for melanoma, particularly those with high naevus counts and dysplastic naevi.	**C**

Practice point
TBP allows monitoring of most of the skin surface, including most existing skin lesions. TBP should be the primary imaging intervention for early melanoma detection in patients at elevated risk who have high naevus counts or multiple dysplastic naevi.

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2.5.6.3.1 Issues requiring more clinical research study

High-quality prospective studies are required to further investigate the role of TBP in early melanoma diagnosis and its impact on melanoma-related outcomes. In spite of the difficulties of a randomised trial of TBP in high risk patients with high naevus counts, a randomised trial in a large cohort of lower risk individuals would be justifiable. Research is needed to elucidate the optimal risk thresholds for the introduction of both TBP and SDDI to surveillance programs.

Further research should also be directed at assessing the performance of new methods of skin imaging, such as three dimensional imaging, automated detection of change in lesions, teledermatology using TBP and self-assessment of melanocytic lesions using telephone apps.

Total body photography also has the potential to aid skin self-examination by consumers, yet evidence to date would appear to indicate limited impact from uptake by consumers. An important area for future research might be to explore barriers and determinants of skin self-examination and to investigate appropriate methods of educating and empowering consumers with respect to the use of total body photography.

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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 2 mm 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 3 mm 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. The technique requires careful lesion selection and expertise in conduct to avoid base transection, a serious and too frequently evident drawback with use of this method. In general the technique should be limited to non-palpable lesions. If a clinician cannot be confident of complete removal of the deepest part of the lesion a full excisional biopsy should be undertaken.

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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 after 3.5%-44% of shave and 34%-38% of punch biopsies.[8][6][9][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 7%-34% of punch biopsies and 3%-19% of shave biopsies.[1][9][10][6][3][4][7]

Upgrades to T-stages resulted in additional surgical therapy in 3.3%-5% of shave biopsies,[7] and 18% of punch biopsies.[4][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 (<1.0 mm 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 than if it is more deeply 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 18% of punch biopsies and 3-5% 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]

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.

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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2.6.6 Appendices

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2.7 Clinical information for the pathologist

Contents

2.7.1 Introduction

The accuracy of any histopathology report is at least partly dependent on the amount of tissue provided and the availability of relevant clinical details. Some of this clinical information may be received in generic pathology request forms, however, there is also specific additional information required by the pathologist for the accurate diagnosis and optimal reporting of primary cutaneous melanoma.

2.7.2 Evidence

Most of the evidence about the clinical information that the clinician should provide to the pathologist to aid in the diagnosis of melanoma is derived from review articles and opinion pieces. There is a paucity of evidence correlating the clinical details provided and the accuracy of pathological diagnosis of melanoma (and melanocytic lesions) linked to clinical follow up data. No randomised trials exist and the recommendations below are all based on level IV evidence.

2.7.2.1 Primary melanoma specimens

A number of studies have demonstrated that the interobserver reproducibility of pathological diagnosis of melanocytic tumours is increased when clinical information is provided to the pathologist.[1][2] Furthermore, it has also been shown that the histopathological diagnosis may change when appropriate clinical information is provided.[1]

Clinical information that may assist pathologists when interpreting specimens of possible melanoma include: patient age, sex, ethnicity, tumour site, specimen laterality, specimen type, specimen orientation (if appropriate), history of the current lesion (duration, history or duration/tempo of change, clinical features suspicious for malignancy, size of lesion and ulceration), presence of any clinically or dermatoscopically suspicious areas focally within the lesion (including the presence of regression), interpretation of dermoscopy, confocal microscopy or other imaging findings, copies of (or access to) any relevant clinical photographs or prior pathology reports, relevant melanoma risk factors (including number of previous melanomas, presence of dysplastic nevi, total number of naevi, family history of melanoma or dysplastic naevus syndrome and personal history of nonmelanoma skin cancer), history of concurrent or recent pregnancy, details of previous primary melanoma (at this or any other site), evidence and sites of metastatic disease, serum LDH level (when distant metastatic disease is present), and whether this is a new primary melanoma or a recurrence of a previous melanoma, if known (Table 1).

Clinical factors relevant to diagnosis include patient age and sex, and the site of the lesion.[3] The diagnostic significance of any atypical pathological feature varies with the age of the patient and the site of the lesion. For example, the presence of some mitotic activity within a Spitz naevus in a preadolescent child would be compatible with this diagnosis, however, the same frequency of mitoses in an elderly patient would usually signify melanoma.[4][5][6]

Naevi occurring on certain sites (including the palms, sole, fingers and toes, flexural sites, genitalia, breast, and ear) often display irregular architecture (i.e., asymmetry, single-cell growth, focal pagetoid migration) that would be considered evidence favouring melanoma in melanocytic tumours occurring on other sites.[3][7][8]

It is particularly important that clinicians record factors that may induce atypical pathological features in melanocytic naevi (e.g., previous biopsy, trauma, surface irritation, pregnancy, topical treatment, recent prolonged sunlight exposure, laser or radiation therapy) and that may lead to an overdiagnosis of melanoma.[9][10]

Following lesional trauma, biopsy, irritation or topical treatment, melanocytic naevi may display many histopathological features that commonly occur in melanomas (including pagetoid epidermal invasion, cytological atypia, occasional dermal mitotic figures and HMB45 positivity).[11][10] Such regenerating naevi have been termed ‘pseudomelanomas’ and are prone to overdiagnosis as melanomas.[12] Changes typically occur within 6 months of a previous injury, and the pathological changes are usually confined to the area affected by the inciting agent. This may be a “portion” of a naevus in the case of trauma/irritation/biopsy, but it may also be the entire lesion in the case of topical treatment (or even trauma/irritation). Since the histological changes of

naevi or melanoma recurring after trauma may be very similar, it is essential that the previous biopsy and, if available, any relevant clinical and dermoscopic photographs, be reviewed. Another important consequence of trauma is that it may result in ulceration. Therefore, in most cases of re-excision of melanoma it is difficult to determine if such ulceration is “spontaneous” and should therefore be considered as a negative prognostic factor, or if it is not “spontaneous” and should therefore be ignored (see also section below on evaluation of re-excision specimens).[13]

Excision specimens should be oriented if the status of specific surgical margins is critical in determining the need for, or the extent of, further surgery. Specimen orientation may be indicated with marking sutures or other techniques. If a specimen is oriented, the orientation should be indicated on the specimen request form (and this may be facilitated by the use of a diagram or provision of a photographic image).

Any clinically or dermoscopically identified suspicious areas should be examined histopathologically, because they may represent melanoma. As an example, a long-standing lesion with a recent change in colour or texture may suggest a melanoma developing within a pre-existing naevus. Such areas should be identified, documented and marked for sectioning (e.g., with a suture or by superficially scoring the epidermis and superficial dermis around the area of concern, using a suitably-sized punch or other technique[14]) to allow identification at the time of processing the specimen and assessing the slides.

Clinical findings and/or the results of diagnostic imaging (e.g., dermoscopy or confocal microscopy) and/or a diagram should be included with the clinical request form if this information is likely to be useful to direct the pathologist to areas of particular clinical concern in the specimen, or to improve clinicopathological correlation. Photographic images can also be helpful when assessing clinically or dermoscopically heterogeneous lesions to direct the pathologist to areas of particular clinical concern.

If there is a discrepancy between the clinical features and the pathological interpretation, the clinician and pathologist should discuss the case and seek to determine the cause of the discrepancy. If a reason for the discrepancy cannot be determined, it may be appropriate for the pathologist to consider whether additional sections of the specimen should be examined to ensure that the reason for the discrepancy is not related to non-representative sampling. If the specimen is a partial biopsy and a clinicopathological discrepancy exists, consideration should be given to whether an excision biopsy should be performed. When there is difficulty in resolving the reason(s) for any discrepancy, it may be appropriate to consider referring the case to a pathologist with special expertise in the interpretation of melanocytic tumours.[15]

2.7.2.2 Table 1. Clinical information that may aid pathologists in the diagnosis of melanoma of the skin

Clinical Factor	Information required	Comments
	Type of specimen: ■ Not provided ■ Excision ■ Punch	

Clinical Factor	Information required	Comments
Specimen type	■ Incision ■ Shave ■ Curette ■ Re-excision Other	If 'other' is selected, record the other specimen type.
For re-excision specimens	Previous laboratory Previous laboratory accession number Findings in previous biopsy	A copy of, or access to, the pathology report for the previous biopsy or excision is often the most practical method to provide the required information. Alternatively important findings of the previous biopsy may be provided on the pathology request form.
Specimen laterality	Left/right	Example
Example	Example	
Clinical diagnosis or differential diagnosis	Text	
History of current lesion	Text	Duration, history or duration/tempo of change, size of lesion and ulceration
The history and timing of lesional trauma, biopsy, irritation or treatment with topical agent, laser or radiation therapy	Details	Many histopathological features that commonly occur in melanomas may occur in naevi that have undergone trauma, previous biopsy, irritation or topical treatment. These naevi may be overdiagnosed as melanoma unless the clinical context is known to the pathologist.
A past history of melanoma?	Details	Site, thickness, timing, treatment, previous metastasis
Evidence of current or previous metastatic disease?	Yes/no	If yes, when and where and consider recording the serum LDH for patients with stage IV disease
Other relevant history	Text	Family history of melanoma or dysplastic naevus syndrome, current or recent pregnancy
Details of specimen orientation		A diagram or clinical photograph may assist
Any clinically or dermatoscopically suspicious areas?	Yes/no	A diagram or clinical photograph may assist

Clinical Factor	Information required	Comments
Clinical or other relevant diagnostic imaging results		
New primary melanoma or recurrence	■ New primary ■ Recurrence – local ■ Recurrence – intransit metastasis (between primary site and regional node field) ■ Recurrence – regional ■ Recurrence – distant	

2.7.2.3 Melanoma wide excision specimens

When a diagnosis of melanoma is established, it usually requires a re-excision to ensure that the entire lesion is removed, primarily with the intention of reducing the risk of local recurrence. It is important that it is communicated to the pathologist whether or not the melanoma was reported to be completely excised originally, and whether it had unusual features, such as a desmoplastic component or neurotropism[16][17] because in many laboratories this will alter how the specimen is sampled for microscopic examination. Knowledge of the presence of a Spitziod, naevoid or heavily pigmented component in the prior biopsy may aid pathological interpretation of re-excision specimens, particularly if incompletely excised in the prior biopsy. Provision at, or access to a copy of the previous pathology report can facilitate optimal communication. If the melanoma includes a desmoplastic component or shows neurotropism, the entire scar area should be sampled and placed in tissue blocks for microscopic examination. The evaluation of surgical margins and identification of residual desmoplastic melanoma in re-excision specimens can be very difficult and the use of immunohistochemical stains such as S100 and SOX10 may be very helpful in distinguishing melanoma cells from scar tissue.

2.7.2.4 Sentinel lymph node biopsy specimens

A sentinel lymph node is defined as any regional lymph node receiving direct drainage from a primary tumour site and is usually the first site of regional metastasis.[18] The presence of sentinel lymph node metastasis is an adverse prognostic factor in melanoma.[19] Sentinel lymph nodes from melanoma patients are usually examined pathologically with multiple sections and multiple immunostains from each block of tissue.[20] To facilitate such a detailed pathological examination, it is important that sentinel lymph nodes are clearly identified both on the pathology request form and on the label of the specimen container.

2.7.2.5 Evidence summary and practice points

Evidence summary	Level	References
There is consensus that clinical factors are relevant to the pathological diagnosis of melanoma (and other melanocytic tumours) and indeed may alter the pathological diagnosis	IV	[21], [22], [23], [24], [25], [1], [26], [21], [27], [28], [29], [30], [31], [32]

Practice point
It is advisable that as much relevant clinical information (Table 1) as possible be provided to pathologists to aid in the diagnosis of melanoma.

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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 wider excision 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. When present, the in-situ component (which may not be apparent macroscopically), 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 patients.[1][2][3][4][5][6] All six RCTs assess width of excision but do not consider depth of excision. These RCTs compare narrow (1–2 cm) versus wide (3–5cm) 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, no RCT has yet addressed the most important question of 1cm vs 2cm surgical margins for intermediate thickness (≥1mm to 4mm) and thick (>4mm) melanomas in terms of clinical outcome (recurrence and survival) which is what is required to answer the question of whether 1 cm margins are adequate and safe for treatment of all melanoma Breslow thicknesses. In addition, 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. True local recurrence is development of melanoma associated with the scar. In addition, the RCTs have been further assessed in six systematic reviews and meta-analyses where a primary melanoma has been previously excised.[7][8][9][10][11][12] Re-occurrence of melanoma close to but away from the previous primary melanoma excision scar typically represents lymphatic metastasis also termed "local satellitosis". These different situations have been often combined inappropriately as "local recurrence". There are also several published case series addressing excision margins 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 because the trials use different criteria other than 1cm vs 2cm margins to directly compare invasive melanomas.

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 1mm[13] or 2mm[14] but results of these retrospective studies must be interpreted with caution because accurate data collection is often difficult. 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. Similarly, 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.

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 to assist in decision making. Case series data offers the best quality data currently to help guide treatment approaches.

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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.” An optimal safe balance is therefore is desirable to achieve survival and quality of life.

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.

These data reflect practices at the times that the studies were conducted, using wide excision margins (4-5 cm margins). With the narrower margins used in current practices (1-2 cm) these outcome data, such as lengths of hospital stay, may be different.

This section covers the following questions:

- Excision margins for melanoma in situ
- Excision margins for invasive melanomas and melanomas at other sites

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2.9 Melanoma in situ

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2.9.1 Background

As for invasive melanoma, the treatment for melanoma *in situ*, including lentigo maligna (LM), is complete surgical excision with clear margins. For excision to be successful, a margin of clinically normal skin must be included because macroscopically invisible tumour often exists at the margins. Use of magnification, bright light and possibly Wood's lighting or confocal microscopy for preoperative marking are useful methods for improving the accurate definition of detectable 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 might be inadequate in some situations and can lead to significant rates of disease recurrence, particularly for head and neck disease.

In many cases, in-situ melanoma margins can be accurately determined pre-operatively by careful examination and an adequate margin of ≥ 5mm can be confirmed by pathology. In some cases Mohs surgery or staged serial excision may have a role, but the accuracy is lesion dependant and operator dependant. Unfortunately Mohs surgery currently is not universally available or affordable in Australia. Most international guidelines suggest 5 mm margins for melanoma in situ.[2][3] The BMJ Best Practice monograph on melanoma[4] states that “For melanoma in situ the recommended surgical margin is 0.5 cm. 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.” The 2010 UK guidelines state 5 mm margins to achieve complete histological clearance.[5] The 2011 US guidelines go further recommending 5 mm-1 cm margins and state that "wider margins may be necessary for lentigo maligna subtypes".[6]

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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 often adequate to treat melanoma *in situ.* However, in some cases of melanoma *in situ* 5mm margins are inadequate and may lead to significant rates of disease recurrence.	IV	[7], [8], [9], [10], [11], [12]

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 (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

Practice point

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.

2.9.3.2 Supplement. Moh's surgery and staged serial excision

A large prospective study[7] 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 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*[8] 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,[9] 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[10] 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),[11] 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,[12] 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.”[13]

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2.9.5 Appendices

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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.

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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 the clinical outcomes (local recurrence and survival) for 1 cm and 2 cm excision 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.

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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 UKMSG trial "found a greater risk of locoregional recurrence when melanomas that were at least 2 mm thick were excised with a 1 cm margin, rather than a 3 cm margin (hazard ratio 1.26; 95 percent confidence interval, 1.00 to 1.59; P=0.05)". However, it should be noted that this combined outcome measure of locoregional recurrence was defined only after the trial had been commenced (that it, locoregional recurrence was not predefined in the study protocol).

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 melanoma specific survival in the absence of any significant difference in overall survival. Of note, melanoma specific survival and overall survival were both secondary outcomes in this study. Melanoma specific survival is more difficult than overall survival to measure accurately because it relies on accurate information about cause of death. A significant number of melanomas in the UKMSG study were thick melanomas over 4 mm, which may have 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" which might be an explanation of the significant difference in locoregional recurrence. It should also be noted that sentinel node biopsy was not used in the UKMSG trial and it is not known how this might have altered locoregional recurrence and the survival outcome in that study.

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.[11] 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.[12]

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 until more robust data is available. This is unchanged from our 2008 recommendation. However, we recognise that in certain areas of the body (eg face) and in the frail, excision margins greater than 1cm may not be possible.

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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.[13]

No RCT data exist to show 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. 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. There are no RCT data that demonstrate whether narrower excision margins impact on mortality or recurrence rates in head and neck melanoma.

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.[14] 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 excision margins can be employed in melanomas of the face.[15]

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.[16]

A retrospective chart review of 78 patients evaluated the prognostic variables and clinical ramifications of melanoma of the ear.[17] 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.[18] 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.[19][20] As with facial lesions, there are no RCTs available to help determine whether less aggressive surgery would be as effective. Management involves 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.

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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 2 cm 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], [21], [22], [23], [24], [25], [26]
Furthermore, two RCTs show evidence that a margin greater than 1 cm offers no survival advantage, although it is not clear whether a wider margin reduces the risk of 'local recurrence'.	II	[3], [27]
Systematic review indicates that there are currently inadequate data to confirm a mortality difference between wider and narrower excision for primary invasive melanoma.	I	[21], [22], [23], [24], [25], [26]
For acral lentiginous and subungual melanomas there are no RCTs or systematic reviews 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	[14], [15], [17], [18], [19], [20]

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. Minimum clearances from all margins should be stated /assessed. 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. Minimum clearances from all margins should be stated /assessed. 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. 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**

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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. Minimum clearances from all margins should be stated /assessed. 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, 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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2.10.8 Appendices

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2.11 Sentinel node biopsy

Contents

2.11.1 Background

Sentinel lymph node biopsy (SLNB) is a 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 as a staging procedure 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 as measured by elective lymph node dissection.[1] The recently revised AJCC staging system (8th edition) requires a SLNB for patients with primary melanoma greater than 1mm in thickness in order to perform microstaging of the lymph node basin and accurately allocate a pathological disease stage.[2]

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. SLNs are carefully examined pathologically to identify metastasis.

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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).[3] 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 rate of SLN involvement in the SLNB arm was 16% and of those patients with a negative results, the rate of subsequent nodal relapse (false negative SLNB) was 4.8%.[3]

The reported primary endpoint of the study[3] 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.*

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[4] the status of the SLN was the most significant predictor of MSS (HR 1.5-6.9).[5][6][7][8]

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.[8][9] Predictors of sentinel node involvement from 7,756 patients in the AJCC database are shown in Table 1.

Table 1. Statistically significant predictors of sentinel node involvement and associated rates of involvement (total 7756 patients from Balch et al.)

Variable	% patients with SLN involvement
Age	
<40 years	21.3
40-59 years	20.0
≥60 years	17.6
Gender	
Male	20.7
Female	17.7
Location	
Head/neck	15.5
Upper extremity	15.1
Trunk	21.3
Lower extremity	22.3
Tumour thickness	
≤ 1.0	6.0
1.01-2.0	14.0
2.01-4.0	27.3
>4.0	39.1
Ulceration	
Absent	15.6
Present	29.9

Clark Level	
I/II	4.5
III	11.9
IV	21.5
V	33.9
Lymphovascular Invasion	
Absent	17.3
Present	47.2

Source: Balch et al 2014[10]

SLNB is a surgical procedure which usually requires a general anaesthetic. Complication rates for SLNB vary from 5.9-13.8%[11][12] 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.[12]

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 with the outcome data from the MSLT-1 study.[13] 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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2.11.2.1 Special situations

2.11.2.1.1 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.[14][15][16] As described for intermediate thickness melanoma, in patients with thin melanoma, SLN involvement is associated with significantly worse MSS.[14]

2.11.2.1.2 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 melanomas. 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.[17]

2.11.2.1.3 Desmoplastic melanoma

A positive SLN is found in 13.7% of patients with desmoplastic melanoma.[18] The rate of nodal involvement differs according to whether the melanoma is a pure or mixed DM, with much lower rates in pure DM.

2.11.2.1.4 Atypical spitz naevi and spitzoid melanoma

Atypical spitz naevi are more commonly seen in younger patients, SLNB can be positive in these patients however this does not reflect malignancy nor is it a predictor of outcome, therefore SLNB is not recommended. By contrast, spitzoid melanoma is a subtype of melanoma and therefore these guidelines apply.

2.11.2.1.5 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 demonstrated that SLNB is feasible after prior WLE, but it may be inaccurate.[19][20] Where possible SLNB should be performed at the same time as WLE.

2.11.2.1.6 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.[21] 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	[5], [6], [7], [8], [17]
Overall, for patients with melanoma >1 mm thick, sentinel lymph node biopsy followed by immediate completion lymph node dissection for a positive node does	II	[3]

Evidence summary	Level	References
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.		
For patients with intermediate thickness melanoma (1.2-3.5 mm thick) 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	[3]
Complication rates for sentinel lymph node biopsy are low. The procedure should be performed in a centre with appropriate expertise as complication rates are inversely related to procedure volume - this particularly applies to primaries arising in the head and neck.	III-3	[11], [12]

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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

Practice point

each SLN. Sections from each 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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2.11.3.1 Conclusions

Sentinel lymph node biopsy is primarily a staging procedure which provides the best means of prognostic stratification for patients with melanoma greater than 1 mm thick and for some patients with thin melanoma with high risk features. Recently published data demonstrate that adjuvant systemic therapy for patients with resected stage III disease has a major impact in extending patient relapse-free survival and overall survival. This benefit has been shown for both immunotherapy[22][23] and molecular targeted therapy (for patients harbouring a BRAF mutation)[24] and includes patients with SLN- positive disease (link to systemic therapies chapters to be added once published). While these drugs are not currently subsidised in Australia on the PBS, SLNB provides patients with the necessary information to be aware of their recurrence risk and to seek access to adjuvant therapies where available.

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Summary of systematic review results: *A Cochrane review has been performed regarding the use of SLNB for melanoma (Kyrgidis *et al*). This review has not been cited in the evidence as the NHMRC recommendations for developers of guidelines suggest that a "systematic review should consist of at least two studies" (p. 16).[25] The paper by Kyrgidis *et al* only cites a single study, the MSLT-1 study[3] which is extensively discussed in the guidelines.

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2.11.5 Appendices

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2.12 Complete node dissection

Contents

2.12.1 Background

In the past most melanoma patients with lymph node involvement presented with clinically apparent disease for which therapeutic lymph node dissection (TLND) was and remains the standard treatment recommendation. Prior to the development of sentinel lymph node biopsy (SLNB), other patients, especially those treated in specialised melanoma centres, at moderate and high risk for lymph node involvement, would undergo elective lymph node dissection (ELND). Since the introduction of SLNB, ELND should no longer be performed. Depending on referral patterns in an area, around half the patients identified as having metastatic nodal disease are being diagnosed with microscopic disease by SLNB.[1] Overall around 16% of patients with intermediate thickness melanomas and 33% with thick melanomas have a positive SLNB (see SLNB chapter).[2]

Consistent with the intervention arm of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), completion lymph node dissection (CLND) has, until recently, been recommended for patients with a positive SLNB. However, from as early as 2004 the question of whether CLND is necessary was addressed by the MSLT-II [3] and from 2006 by the DeCOG-SLT study[4]. In both these clinical trials, patients with a positive SLNB were randomised to immediate CLND versus active surveillance. Active surveillance was defined as 3-4 monthly clinical and ultrasound monitoring for at least 2 years then at least 6 monthly clinical and ultrasound assessment until 5 years, followed by annual review. In the event of isolated nodal relapse delayed CLND was done. In MSLT-II when CLND was done for a positive SLNB the incidence of further disease in the non-sentinel lymph nodes (non-SLNs) was 11.5% but, depending on the circumstances (patient factors, tumour factors and sentinel lymph node tumour burden factors), retrospective literature suggests that the rate of non-SLN positivity can range from 3% to 66.7%.[5][6][7] The presence of non-SLN involvement is associated with a worse prognosis.[5]

2.12.2 Practice-changing randomised controlled trials

The overwhelming evidence from the publication of the interim results of these two RCTs is that for patients with a positive SLNB there is no melanoma-specific survival benefit associated with the early removal of non-SLNs by CLND compared to active surveillance and CLND only if isolated regional relapse occurs.[3][4] The MSLT-II[3] and DeCOG-SLT[4] studies also reported equivalent median 3-year melanoma distant metastasis-free and overall survival. The two trials showed that those patients with residual disease in the regional lymph node field benefited in terms of improved immediate regional cancer control. However, all patients having CLND are exposed to the risk of morbidity that can compromise quality of life (QOL). Possible complications of CLND include wound healing problems, cosmetic issues, sensory and motor neural disruption, fibrosis and tightness, limitations in range of movement and lymphoedema, which is more common after CLND in the groin than axilla.[8]

2.12.2.1 Possible limitations of the MSLT-II and DeCOG-SLT data

Although these studies are highly supportive of the safety of avoiding CLND, the interpretation and application of these results should take into account a number of factors including the fact that they are both reporting interim results, with quite short median follow-up periods (43 months for MSLT-II, 35 months for DeCOG-SLT) and the final results may possibly be somewhat different.[3][4]

Regarding DeCOG-SLT other limitations include the study not meeting the recruitment target, a lower than predicted event rate, recruiting only 39% of the eligible patient population, the fact that that around two-thirds of the patients had SLN deposits ≤1 mm, the exclusion of head and neck primary melanomas, and the fact that around 60% of patients received adjuvant interferon, which may delay recurrence.[4]

Regarding MLST-II it is unclear how many patients who were eligible for the study were offered randomization but 38% of screened patients declined randomization, only 18-19% of patients had more than 1 sentinel node involved, and similar to DeCOG-SLT only 1/3 of patients had a sentinel node tumour burden >1 mm.[3]

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2.12.3 Summary of systematic review results

2.12.3.1 Cancer control

Two RCTs have shown that patients with a positive SLNB who have immediate CLND have equivalent 3 year survival to those who have active surveillance. CLND after a positive SLNB has reduced rates of subsequent lymph node field relapse. Both MSLT-II and DeCOG-SLT are supportive of active surveillance as a strategy.[3][4]

The patients not undergoing CLND in DeCOG-SLT and MSLT-II had a standardised active surveillance protocol, described above.

Prior to the publication of these two RCTs[3][4] the best available evidence in support of the prior recommendation for CLND was the MSLT1[2], which found that patients who had a positive SLNB and CLND had a 20% improvement in 10 year melanoma-specific survival (MSS) compared to patients who did not have SLNB but later relapsed in the regional lymph node field and then had a therapeutic LND (TLND).[2] However, these comparator groups were not randomised and the data did not indicate whether SLNB alone was sufficient to gain that potential benefit (which was the question addressed in MSLT-II).

A number of previous retrospective studies, some analysing a prospective data base, also supported the safety of a strategy of close observation after a positive SLNB.[9][10][11][12][13][14] Other retrospective data have been published which was interpreted by authors to be consistent with a role for immediate CLND over the delayed CLND strategy, but the comparisons were acknowledged as biased as the delayed CLND patients all had residual disease whereas most (70-80%) of the immediate CLND patients had no residual regional disease identified.[15][1]

2.12.3.2 Morbidity and QOL

Morbidity varies depending on the CLND lymph node region. The most significant morbidity following CLND is lymphoedema and MSLT-II reported lymphedema occurred in 24.1% of the patients in the dissection group and 6.3% in the active surveillance group.[8] DeCOG-SLT reported grade 3 or 4 adverse events in 14% of CLND patients.[4] Generally speaking, the morbidity of neck and axillary dissection is less than that of groin CLND. Immediate CLND is less morbid than TLND.[8][16]

2.12.3.3 Conclusion

Active surveillance is an acceptable treatment recommendation for patients with positive SLNB. Patients can be reassured that careful observation with serial clinical examination and ultrasound surveillance undertaken by an ultrasonographer appropriately trained and experienced in the examination of lymph nodes for metastatic malignancy will offer equivalent survival rates to immediate CLND. Immediate CLND reduces the risk of lymph node field relapse, but there is a risk of significant morbidity.

However, depending on patient preferences, the likelihood of having further regional disease, the probability of the patient having long-term morbidity from CLND and future further evidence from the final results of the MSLT-II and DeCOG-SLT studies, CLND may still have a role in selected patients after a positive SLNB.

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2.12.4 Evidence summary and recommendations

Evidence summary	Level	References
Patients with a positive SLNB who have immediate CLND have no improvement in 3 year melanoma-specific survival compared to those who have active surveillance.	II	[3], [4]

Evidence summary	Level	References
CLND reduces the risk of early lymph node field relapse compared with an active surveillance strategy after a positive SLNB.	II	[8], [3], [4]
Patients having CLND have significantly greater surgical morbidity than those having active observation.	II	

Evidence-based recommendation	Grade
CLND is no longer the preferred treatment for patients with a positive SLNB. CLND or active surveillance are equivalent in terms of 3 year melanoma specific survival but CLND is more morbid.	**B**

Evidence-based recommendation	Grade
CLND offers high levels of immediate regional control for patients with positive SLNB however good regional control can be achieved with delayed CLND.	**C**

Practice point

To date there is no subgroup of patients for whom immediate CLND is likely to provide a clear benefit, however patients with a high risk of further non-SLN involvement and particularly those who are less likely to suffer significant morbidity from CLND may choose to have the procedure to reduce the risk of lymph node field relapse. A risk calculator for defining the likelihood of non-SLN involvement such as the N-SNORE (Murali et al. 2010) can be of assistance to more accurately estimate the probability of residual non-SN positive nodes.

Practice point

Close clinical and ultrasound surveillance using a protocol equivalent to that followed in MSLT-II and DeCOG-SLT of 3-4 monthly clinical examination and ultrasound of the regional lymph node field for 2 years and then the same at least 6 monthly for a total of 5 years, then annual clinical review is required if a patient with a positive SLNB chooses active surveillance.

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2.12.5 Issues requiring more clinical research study

The following issues require further clinical research:

1. Although the 2017 Nivolumab vs Ipilimumab and the Dabrafenib / Trametinib combination vs observation clinical trials of adjuvant systemic therapy mandated CLND for patients with a positive SLNB this was because these trials commenced before MSLT-II reported its results.[17][18] It can be fairly hypothesised, but remains unproven, that there would be even fewer indications for CLND when effective adjuvant therapies are widely available.
2. Therapies that improve control of the regional lymph node field but are less morbid than surgery would be desirable for those patients at higher risk of regional failure and should be investigated. These may include targeted or immune-modulating adjuvant systemic therapies as mentioned above, but may also include local therapies.
3. To date there are no good data assessing the quality of life implications of avoiding CLND and the anxiety of knowing that there is a higher rate of regional failure when CLND is not performed. The physical consequences of CLND are clear but the psychosocial implications of CLND and of not having CLND are undefined.

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2.12.7 Appendices

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2.13 Treatment for lentigo maligna

Contents

2.13.1 Introduction

Lentigo maligna (LM), historically known as Hutchinson's melanotic freckle, is a subtype of melanoma in situ characterised by atypical intraepidermal melanocytes that usually occurs in sun damaged skin. If left untreated LM can develop into invasive melanoma, term lentigo maligna melanoma (LMM), which shares the same prognosis as other types of invasive melanoma. LM usually occurs in the elderly population and is most commonly found on the head or neck region on severely sun damaged skin. However particularly in Australia, LM is occasionally found on the trunk and extremities. The diagnosis of LM is based on clinical and dermoscopic features, and confirmed through biopsy and histopathological assessment. The most effective treatment of LM is complete surgical excision with at least 5mm margins, however the often sensitive anatomical location of the lesion, the age of the patient and size of the lesion can present challenges for surgical intervention. There are multiple non-surgical treatment alternatives currently used including radiotherapy, cryotherapy, laser ablation, and topical immunomodulatory therapies such as imiquimod. These procedures have the advantage of reduced morbidity and cosmetic impact, however they have not achieved the same level of complete clearance and recurrence rates over surgical removal of lesions.[1]

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2.13.2 Systematic review evidence

To date there have been no randomised controlled trials that have compared the outcomes of surgical and non-surgical treatment methods for LM. One RCT on the off-label use of Imiquimod, 5% cream with vs without Tazarotene, 0.1% gel for the treatment of LM has been published by Hyde et al (2012).[2] This study concluded that the complete response rate of LM may be improved with the combined use of tazarotene with imiquimod, however it did not report statistically significant results. A Cochrane Systematic Review was conducted by Tzellos et al (2014)[3] to compare all treatments of LM, though only the aforementioned Imiquimod trial met the RCT inclusion criteria. The Cochrane review further concluded that whilst the addition of tazarotene to imiquimod as an adjuvant therapy may increase inflammatory response, it also may result in early cessation of treatment due to treatment-related side effects.

Three cohort studies[4][5][6] comparing the outcomes of conventional excision vs staged or Mohs micrographic surgery were identified for this review. Conventional excision has historically been the treatment method of choice when achieving 5mm margins LM location is not complicated by anatomical site of the LM. However, the studies reviewed suggested that 5mm margins, originally recommended by the National Institutes of Health (NIH) consensus statement in 1992, may be inadequate due to indistinct peripheral tumour borders often associated with LM, attributing to reported recurrence rates of between 6% and 20%[4][5][6] As a result, Mohs micrographic surgery (MMS) has become increasingly used as a surgical method for LM removal. Mohs micrographic surgery has the advantage of intraoperative assessment of tumour margins, conserving the amount of healthy tissue removed and furthermore achieving lower recurrence rates (0.5% to 6.3%).[6][7] The primary disadvantage of MMS remains the reliance on frozen sections and immunohistochemical staining for the challenging visualisation of epidermal melanocytes. However, techniques such as Slow MMS that use paraffin-embedded sections have been shown to improve the visualisation of melanocytes.[5] Slow MMS or Delayed Reconstruction After Primary Excision (DRAPE) involves leaving an open wound with regular dressings while a carefully oriented FFPE sample is assessed and a pathology report issued. If close or positive margins are encountered, these can be re-excised. A definitive reconstruction is delayed until a satisfactory excision margin is achieved.

In addition to the 2014 Cochrane Review described above, three other systematic reviews were identified that assessed outcomes of non-surgical therapeutic treatment of LM.[8][9][1] Mora and Tio both assessed outcomes for patients treated with imiquimod by reviewing 45 and 41 studies, respectively. Both authors concluded that while surgical removal remains the gold standard for the treatment of LM, imiquimod is a potential option for those patients not eligible or willing to undergo surgery and/or radiotherapy. Both reviews also recommended an intensive treatment regime of greater than 60 applications, with a frequency of six to seven applications per week. The clearance rates reported by Mora and Tio were 76–77% for histopathological clearance and 78% for clinical clearance, although these reviews were hindered by varying treatment protocols, short-term follow-up, and risk of publication bias in the case reports reviewed. In the systematic review by Read et al (2016),[1] three non-surgical methods were evaluated; radiotherapy, imiquimod and laser therapy. Read et al evaluated 29 studies and likewise concluded that while surgical removal of LM remains the preferred treatment; radiotherapy and imiquimod are both alternative treatment options, with radiotherapy achieving superior complete response rates and fewer recurrences than imiquimod. Read et al also reported that the evidence available for the effective use of laser therapy was weak. A cohort study published by Hedblad and Mallbris (2011)[7], describes the treatment of LM and early LMM with superficial energy radiotherapy in 593 patients. The study assesses

outcomes for three types of managements including primary treatment with radiotherapy; partial surgical removal followed by radiotherapy; and radical surgical excision followed by postoperative radiotherapy as a recurrence prophylactic, with reported complete clearance rate of 83%, 90% and 97%, respectively. While radiotherapy has the advantage of being non-invasive, easy to perform, is well tolerated and is associated with positive cosmetic outcome, it does not achieve the same clearance and recurrence rates as surgical excision. Lee et al (2011)[10] conducted a retrospective review comparing outcomes in treating LM though surgical excision, radiotherapy and carbon dioxide laser ablation. The authors found lower recurrence rates with surgical excision and carbon dioxide laser ablation, however the results were not statistically significant. Carbon dioxide laser ablation may have a role in treatment of LM when standard treatments are refused or unsuitable, however there is currently only weak evidence of its efficacy.

All publications reviewed resolved that the surgical removal of LM remains the reference standard treatment, however there remains a lack of quality evidence available to infer the most effective non-surgical treatment. Currently a multi-site, multi-country RCT (RADICAL) is underway by ANZMTG to compare outcomes of radiotherapy vs Imiquimod for complex LM where surgery is not suitable or refused. This trial is expected to produce a strong level of evidence that may influence future guidelines for the non-surgical treatment of LM.

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2.13.3 Evidence summary and recommendations

Evidence summary	Level	References
There have been no RCTs to date comparing the efficacy of all lentigo maligna (LM) treatments.	N/A	
Mohs micrographic surgery (MMS) has shown to improve complete clearance rates and reduced recurrences over conventional surgical removal of LM.	III-2	[6], [4], [5]
Superficial radiotherapy is a suitable alternative to surgical excision of LM or as adjuvant therapy after surgical excision especially for treatment of large lesions.	III-1	[7]
Radiotherapy has shown to have superior complete clearance rates and few recurrences over imiquimod therapy for LM.	IV	[1]
The addition of tazarotene to imiquimod as an adjuvant therapy can increase the inflammatory response for LM.	IV	[2]
There is currently a lack of sufficient evidence available to determine the efficacy of laser therapy.	III-1, IV	[10], [1]

Practice point
Diagnosis of lentigo maligna should be obtained by biopsy and histopathology.

Practice point
Considering the risk of lentigo maligna evolving into invasive melanoma is low and generally takes many years, it may be more appropriate in very elderly patients, or those with significant comorbidities, to monitor the lesion over time (watchful waiting). If significant clinical or dermoscopic changes are detected, a biopsy in suspicious areas to confirm invasive disease should be performed.

Evidence-based recommendation	Grade
Complete surgical removal of lentigo maligna lesion with 5-10mm margins is the preferred management, when possible.	**C**

Evidence-based recommendation	Grade
When surgical removal of lentigo maligna is not possible or refused, radiotherapy is recommended.	**C**

Evidence-based recommendation	Grade
When both surgery and radiotherapy of lentigo maligna are not appropriate or refused, imiquimod is recommended.	**D**

Evidence-based recommendation	Grade
Cryotherapy is not recommended for the treatment of lentigo maligna.	**C**

Evidence-based recommendation	Grade
Laser therapy is not recommended for the treatment of lentigo maligna.	**C**

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2.13.4 Issues requiring more clinical research study

It is recommended that further RCTs on LM patients are performed. Currently a multi-site, multi-country RCT (RADICAL) is underway by ANZMTG to compare outcomes of radiotherapy vs Imiquimod for complex LM where surgery is not suitable or refused. This trial is expected to produce a strong level of evidence that may influence future guidelines for the non-surgical treatment of LM.

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2.13.6 Appendices

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2.13.1 Primary desmoplastic neurotropic melanomas

2.13.1.1 Desmoplastic melanoma

Desmoplastic melanoma (DM) is a rare sub-type of melanoma (1–4% of primary cutaneous melanoma) that may be difficult to recognise, both clinically and pathologically, and behave differently compared to non-desmoplastic melanoma (non-DM).[1][2][3][4][5] As a consequence, the guidelines for the management of non-DM may not be directly applicable to DM and special consideration of this sub-type is warranted.

Conley et al first described desmoplastic melanoma in 1971.[6] It has been characterised histologically by variably pleomorphic, spindle-shaped cells with associated collagen production/stromal desmoplasia. The cells resemble fibroblasts as would be found in scar tissue.[1]

DM usually present as a firm plaque, nodule or thickening that is often not pigmented.[7] There may be little or no change in the appearance of the overlying epidermis. The often unremarkable appearance leads to delayed diagnosis in many cases.[8][9] As a result of the later presentation, the mean and median thickness of DM is close to 4.0mm (2.0 mm- 6.5mm) in many reported series.[1][2][3][4][8][10][11][12][13][14][15][16] The vast majority of DM are Clark level IV or V.

DM are strongly associated with sun-exposure and most frequently arise in the head and neck region.[1][11][12][3][17][15][16] In a large study of scalp melanomas, 29% were desmoplastic.[18] DM have been shown in all published series to be more common in males (M:F 2:1). Patients with DM are generally older at presentation than patients with non-DM. The DM median age is 60–70 years whereas non-DM is 50 years.[1][19][11][12][2][3][4][13][15][16][14][20]

In 2005, it was proposed that DM should be further sub-classified into pure DM (pDM) and mixed DM (mDM) on the basis that the subclasses have differing clinical behaviour.[21][22][23] Pure DM have been defined as those with 90% or more desmoplastic component while mixed DM were defined as those with greater than 10% and less than 90% desmoplastic component. pDM account for close to 50% of all DM.[12][2][3][4][13][16][14] In a review of 252 DM, Murali et al showed pDM to differ significantly from mDM in location, Clark level, Breslow thickness, mitotic rate, perineural invasion and locoregional recurrence rate (4% vs 12%).[14] A lower rate of distant metastasis with pDM and better survival[21][23][12][4] has been demonstrated in some series while not in others.[11][14]

Reflecting the role of sunlight exposure in the aetiology of melanoma, cutaneous melanoma is known to have the highest number of mutations of any cancer.[24] Recent evidence indicates that desmoplastic melanoma has the highest mutation burden of any melanoma.[25] Similarly the driver mutations events associated with desmoplastic melanoma differ from those more commonly seen in other types of cutaneous melanoma. Common mutations in desmoplastic melanoma include: NF1, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, MET, TERT, NFKBIE, NRAS PIK3CA PTPN11.[25]

An important histological feature of DM is a propensity for neurotropism. This subtype is referred to as desmoplastic neurotropic melanoma (DNM). Neurotropism was first described by Reed and Leonard in 1979[26] and further defined by Chen et al and Varey et al[1][27] with the following characteristics 1) tumour extension along nerves perineurally or endoneurally; 2) formation within the tumour of structures resembling nerves; 3) a change in the morphology of the tumour cells to resemble neural tissue. This is seen in 30–60% of DM[28][21][11][2][3][17][13][16][14] and may be more frequently found in pDM. Occasionally named nerves can be involved, an issue that can be particularly troublesome with cranial nerves and their branches due to extension towards the base of the skull.[11]

2.13.1.2 Neurotropic melanoma

Importantly, up to 30% of neurotropic melanomas arise in non-desmoplastic melanomas.[27] However, neurotropic melanoma has rarely been discussed in the literature outside the setting of DNM. Varey et al (2017) reported 191 such cases (28%), with the remaining 480 cases of neurotropic melanoma being DNM (72%).[27] The overall incidence of non-DM neurotropic melanoma is unknown, but likely to be less than 1% of all melanomas. There is some evidence to suggest that there may be also be a higher incidence of neurotropism in acral lentiginous melanoma (ALM), possibly up to 8% cases.[29][30] A study by Scanlon et al (2014) of 32 NM cases found that only 34% were DNM, with 22% ALM (acral lentiginous melanoma) and 41% superficial spreading or nodular.[29] A study of ALM by Nagore et al (2008) found neurotropism to be present in 2 of 25 cases (8%), compared to 8 of 549 (1.5%, p=0.014) other melanoma subtypes (superficial spreading, nodular and lentigo maligna, but excluding DNM).[30]

See:

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

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2.13.2 Management of primary desmoplastic and neurotropic melanomas

Contents

2.13.2.1 Introduction

Initial reports of desmoplastic melanoma (DM) highlighted a very high risk of local recurrence (LR) ranging from 25% to 60%[1][2][3][4] and suggested the need for more aggressive local treatment with wider margins and use of adjuvant radiotherapy (RT) to reduce the risk of local recurrence.[5] More contemporary studies do not show such an alarming rate of local recurrence. Nevertheless, the LR rate for DM in these studies (6–15%)[6][7][8][9][10][11] is higher than for non-DM (<5%).[8] The high rate of LR does clearly relate to incomplete or close resection in a significant portion of the study groups.[7][10][12] Neurotropism has not been demonstrated to be an independent significant risk factor for LR in most studies,[5][7][10][13][2][14][3][12] including non-DM.[12][15] The reported relationship of histological sub-type of DM (pDM vs mDM) to risk of LR is variable with some studies showing pDM to carry a higher risk of LR compared with mDM[16][13] while no difference in risk has been shown in others.[7][17]

2.13.2.2 Systematic review evidence

2.13.2.2.1 Excision margin for desmoplastic and neurotropic melanoma

There are no clinical trials that examine the appropriate clinical or histological margin to minimise the risk of local recurrence.

Maurichi et al (2010)[16] demonstrated higher LR in pDM ≤2mm resected with a 1cm margin compared with a 2cm margin (40% vs 18.5%). This was a retrospective study of prospectively collected data with no randomisation of treatment. The varying excision margins were due to a change in management policy. The overall LR rate in this study (19%) was higher than in more recent studies,[6][8][11] the reasons for which are unclear.

Local recurrence as the initial site of recurrence is associated with a high rate of development of distant metastases. Guadagnolo et al (2014)[7] reported 19 of 130 patients (15%) with DM to develop LR as first site of recurrence. Fifteen of the 19 (60%) patients developed distant metastases. Maurichi et al (2010)[16] reported subsequent distant relapse in 22 of 37 (59%) patients with LR.

Varey et al (2017) showed no difference in LR rates between DM and non-DM when neurotropism was present. There was a significant relationship between inadequate margins (<2mm vs ≥8mm) and LR for all neurotropic melanomas.[12]

Local recurrence is strongly related to involved definitive resection margins.[6][7][10][12]

In conclusion, there is no evidence to suggest that excision margins for DM or NM should be any different to those recommended for all other cutaneous melanomas.

2.13.2.2.2 Adjuvant radiotherapy following excision of desmoplastic and neurotropic melanoma

There are no published randomised controlled trials addressing the potential benefit of adjuvant RT for DM or NM.

Varey et al (2017)[12] showed in a study of 671 neurotropic melanomas, of which 72% were DM, that RT (given to 82 patients) halved the risk of local recurrence if microscopic margins were less than 8mm. There was no difference between DNM and non-DNM in response to RT.

Guadagnolo et al (2014)[7] showed a significant reduction in LR with adjuvant RT in 130 patients with DM. On subset analysis of this non-randomised study, no benefit was observed with RT for patients with either; 1) definitely no evidence of neurotropism or; 2) mDM .

Oliver et al (2016)[8] showed better local control in the small subset of patients that received adjuvant RT. There was 0% LR in 10 with surgery and RT vs 12% LR in 78 with surgery only.

Strom et al (2014)[10] reported on 277 patients with median follow-up of 43 months. The overall LR rate was 13%. There was a definite benefit for RT if resection margins were involved (5-year actuarial local control 89% vs 18%, p=0.003) and improved LR rates with RT for head and neck primaries with negative margins (local control 95% vs 76%, p=0.03). It was concluded that two subsets of patients with DM and clear resection margins could safely have adjuvant RT omitted: 1) non head and neck site and ≤4mm thick; 2) no neurotropism and ≤4mm thick.

Chen et al (2008)[6] reviewed 128 patients with DNM. Twenty-seven patients received adjuvant RT, 26 with primaries in the head and neck region and often with an excision margin <5mm. Local control rates in the RT group were similar to the surgery only group. It was concluded that adjuvant RT appears to produce local control rates similar to those produced by adequate surgical excision when the latter cannot be achieved.

2.13.2.3 Evidence summary and recommendations

Evidence summary	Level	References
Desmoplastic melanomas have a higher rate of local recurrence than non-desmoplastic melanomas.	IV	[6], [7], [8], [9], [10], [11]
Neurotropism does not significantly affect the risk of LR in DM.	IV	[5], [7], [10], [13], [2], [14], [3], [12]
Involved or close resection margins significantly increases the risk of local recurrence of DM and NM.	IV	[7], [10], [12]

Evidence-based recommendation	Grade
Desmoplastic melanomas and neurotropic melanomas should be excised with the same margins as would be performed on a non-desmoplastic/neurotropic melanoma of the same Breslow thickness.	**B**

Evidence summary	Level	References
Adjuvant radiotherapy to the primary excision site of desmoplastic and neurotropic melanoma reduces the risk of local recurrence when the resection margins are involved or deemed inadequate.	IV	[7], [10]
Patients with DM and disease free resection margins can safely have adjuvant RT omitted if – 1) non head and neck site and ≤ 4mm thick; 2) no neurotropism and ≤ 4mm thick.	IV	[10]

Evidence-based recommendation	Grade
Adjuvant radiotherapy to the primary excision site should be considered for patients with desmoplastic or neurotropic melanoma for whom adequate (≥8mm) pathological resection margins cannot be achieved.	**C**

Practice point
It is important for all clinicians performing skin checks to be aware of DM and its often subtle clinical presentation.

Practice point
MRI and nerve biopsy should be considered for patients with facial DM located close to named nerves.

2.13.2.4 Issues requiring more clinical research study

A higher level of evidence on the role of adjuvant RT to the primary site after complete excision of desmoplastic and neurotropic melanoma is needed. There is an ongoing randomised controlled trial on the role of RT in neurotropic melanoma in the head and neck region.

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2.13.2.6 Appendices

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2.13.3 Sentinel node biopsy for desmoplastic melanoma

Contents

2.13.3.1 Introduction

Regional lymph node involvement rates have been reported to be lower in all desmoplastic melanomas (DM) and, as a result, recommendations pertaining to sentinel lymph node biopsy (SLNB) for the staging of primary cutaneous melanoma may not be applicable. This may particularly be the case for pure DM (pDM) whereas mixed DM (mDM) regional lymph node metastasis rates approach those of non-DM.

2.13.3.2 Systematic review evidence

Dunne et al (2016)[1] published a systematic review of 16 case series that reported the sentinel node status in patients with DM. The results for the 1519 patients showed a positive sentinel node rate for all DM of 6.5%. This compares with an expected rate of 15–20% for non DM. The rate was significantly lower for pDM (5.4%) compared with mDM (13.8%). The reviewers concluded that SLNB should be considered for patients with mDM, as it would be for non-DM, but not for pDM.

2.13.3.3 Evidence summary and recommendations

Evidence summary	Level	References
A systematic review of 16 case series comprising results for 1519 patients showed a positive sentinel node rate for all DM of 6.5%. This compares with an expected rate of 15–20% for non DM. The rate was significantly lower for pDM (5.4%) compared with mDM (13.8%).	III-1	[1]

Evidence-based recommendation	Grade
SLNB should be considered for patients with DM, as it would be for non-DM. See When is a sentinel node biopsy indicated?	**C**

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2.13.3.5 Appendices

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3 Melanoma in children

Contents

3.1 Background

Melanoma in children and adolescents is rare. Although melanoma occurring in adults has many similar features there is enough variance in presentation and behaviour to warrant a separate guidelines section on childhood and adolescent melanoma (CAM).[1]

Different definitions of ‘childhood’ have been used. Studies reporting the experiences of individual centres have often merged all ages of young patients, some labelling those up to 20 years of age as ‘childhood’ cases. However, for these guidelines, it was considered more appropriate to separate patients into two groups, those under and those over 10 years old, since melanoma incidence rises sharply around the time of puberty.

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3.2 Epidemiology

Melanoma remains rare in childhood and uncommon in adolescent groups, however, it is the second most common cancer in adolescents and young adults. Australian and international databases report the incidence of childhood and adolescent melanoma to be approximately 0.5–0.6 per 100,000 per year.[2][3][4]

A systematic review indicated that paediatric melanoma (<10 years of age) represents 1–3% of all paediatric malignancies and accounts for 1–4% of melanoma cases across all ages.[5]

There are conflicting reported data on the incidence trends for paediatric melanoma, with different studies reporting stable, increased or decreased in rates.[6][7][8][9] Several factors that might contribute to these differences in incidence trends have been suggested, such as potential under-reporting in registries, and misclassification of atypical nevi in prepubertal children.[10] From birth the incidence rate of melanoma increases with age, especially once adolescence is reached.[3][7][11]

It has been suggested that the change in the observed incidence of childhood and adolescent melanoma, particularly the latter, may be attributable to sun-related behaviour.[12] Countries that have established sun protection programs in recent decades, such as Sweden,[13] the USA[4][8] and Australia,[14] are starting to report a decreased incidence.

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3.3 Pathology and aetiology

There are three major subtypes of melanoma occurring in children and adolescents:

- Spitzoid subtype (see Clinical features of melanoma)
- congenital naevus-associated subtype
- conventional (adult) subtype.

Spitzoid tumours are histological subtypes of melanocytic lesions that are more commonly seen in children and young adults. These lesions can be difficult to assess in terms of their malignant potential. Spitzoid tumours can be benign, malignant or of uncertain malignant potential (see Management of melanocytic tumour of unknown malignant potential).

Most melanomas occurring in prepubescent children (less than 10 years of age) are predominantly of the Spitzoid type (also termed malignant Spitz tumour).[15] This subtype displays much histological overlap with atypical Spitzoid tumours which can be difficult to distinguish from melanoma.[16] Some of these melanomas are associated with chromosomal translocations involving ALK, ROS1, NTRK1/3 or MET.

An infrequently encountered subtype of melanoma occurring in prepubescent children is that associated with the presence of a large/giant congenital naevus.[17] These melanomas tend to be aggressive[18] and they commonly contain NRAS mutations. This subtype, although uncommon, is disproportionately observed in prepubescent children compared to adolescents or adults.

Most melanomas occurring in adolescent children are conventional or adult subtypes of melanoma. They display histological features reflecting this, share molecular features with melanomas occurring in adult patients, and are commonly associated with BRAFV600E mutations.[19] An ultraviolet mutation signature is identified in conventional-type melanomas occurring in adolescent patients. Most paediatric melanomas develop sporadically (de novo) without a known underlying condition or genetic predisposition such as a germline mutation in the melanoma susceptibility gene Cyclin D Kinase 2 A(CDKN2A).[20][21]

Ultraviolet light exposure plays a significant role the development of in a large proportion of CAM.

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3.4 Clinical features

Melanomas in children and adolescents (CAM) as described above can present as a typical adult type melanoma, or in conjunction with a CMN or as a Spitzoid lesion.

Cordoro et al[22] found that 60% of children aged <10 years and 40% of adolescents presenting with melanoma did not meet the traditional ABCDE criteria. This resulted in frequent delayed diagnosis. Given that CAM are more likely to present in an atypical manner, then a modified version of the ABCDE criteria can be applied. CAM often presents as amelanotic, symmetrical lesions with regular borders, uniform colour and diameters of ≤6mm. It has been proposed the following criteria be included as they are more specific to CAM:

- A = amelanotic
- B = bleeding, bump
- C = colour uniformity
- D = de novo, any diameter
- E = evolution of mole.[22][23]

Using the ABCDE criteria in conjunction with dermoscopy improves diagnostic accuracy in childhood melanoma.[24]

Patients with conditions such as xeroderma pigmentosum, familial atypical mole-melanoma syndrome, >100 melanocytic naevi, atypical melanocytic naevi and those with genetic predisposition to melanoma are more prone to developing CAM.[25][26] Immunosuppressed patients may also be at increased risk.

CAM may be associated with thicker tumours and higher rates of lymph node metastasis when compared with melanoma in adults. Despite this, survival rates are similar to those seen in adults with melanoma. CAM patients have a higher risk of recurrence and melanoma deaths more than five years after initial diagnosis, hence long term follow up is necessary in these patients.[27][28]

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3.4.1 Genetic predisposition to melanoma

Most cases of melanoma are considered to be sporadic, however melanoma susceptibility is increased in individuals with inherited mutations in the CDKN2A or CDK4 gene (see Genetic determinants of high risk for new primary melanomas).

Routine genetic testing of patients is not recommended[29] however, referral to a genetics service should be considered if there is a significant family history of melanoma or where a genetic predisposition to melanoma is suspected. It is recommended that patients thought to be at increased risk should have regular clinical examinations and optimise their sun protection.

Primary melanoma may also uncommonly arise in a congenital melanocytic naevus (CNM). The incidence is low, of the order of 1–2%, however it greatly varies according to the severity of the congenital phenotype. Those at increased risk include patients with giant CNM, >40cm projected adult size and accompanied by multiple smaller CNM. A substantial proportion of cases of primary melanoma develop in the central nervous system rather than the skin. The presence of congenital neurological abnormalities on screening MRI in the first 6 months of life has been shown to correlate with an overall increased incidence of melanoma of 12%.[30]

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3.4.2 Transplacental transmission of melanoma

Transplacental transmission of melanoma, an exceedingly rare condition, was first reported in 1949 and there had been less than a dozen recorded cases up until 2005. This rarity is due to the fact that even within the small subset of women with placental involvement of metastatic melanoma, the risk of transmission to the foetus is only about 17%. Nearly all affected infants died within 18 months.[31][32][33]

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3.5 Diagnosis

Where a lesion is suspected of being a melanoma then an excisional biopsy with narrow margins is recommended. Partial biopsies may lead to sampling errors and misdiagnosis. Lesions with Spitzoid characteristics can be especially difficult to categorise as benign or malignant and any melanoma diagnosis should be referred to a pathologist with particular expertise in this field.[16][34]

Atypical spitzoid lesions that have uncertain malignant potential are more likely to metastasise to a sentinel lymph node. However, a positive sentinel node due to an atypical Spitzoid lesion of uncertain malignant potential rarely translates into an adverse effect on an individual's survival. Unless the lesion is a definite Spitzoid melanoma, sentinel node biopsy should avoided.[35]

Practice point

The pathology slides of all Spitz-like lesions in children suspected of being malignant should be referred to histopathologists who are highly experienced in the differential diagnosis of such lesions.

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3.6 Treatment and survival

The mainstay of treatment for melanoma in children, as in adults, is surgical. There is a need to integrate recent advances in the management of adult patients into the paediatric population, recognising that the relative rarity of melanoma in childhood precludes prospective trials of treatment and survival in children. Once the diagnosis of melanoma is established, whether it has arisen in a giant naevus, a small CNM, a dysplastic naevus or de novo, surgical excision should be performed with the same excision margins recommended for adults with melanomas of similar thickness. Freemyer et al[36] reported significantly improved survival for CAM patients who received care at a specialised melanoma treatment centres even when controlling for stage of disease at presentation.

Sentinel node biopsy should be considered in CAM using the same criteria as for adult melanoma.

Children and adolescents with melanoma have higher rates of SLN metastases (25–60%) than adults with comparable melanomas.[37][38][39][40][41]

Despite the higher incidence of nodal metastases, survival is equal to or better than what is reported for adults. However, long-term follow-up is necessary in this population since recurrences and deaths are often seen beyond 5 years.[27][42][28][43]

Sentinel node biopsy has been shown to provide prognostic information in children but there is no evidence yet of a direct survival advantage[44][45]. It is reported to be well tolerated in this group.[40] No difference was found in overall survival (OS) in patients <10 years of age who were node-positive versus node-negative. In patients <10 years of age, sentinel node biopsy and completion lymph node dissection are not associated with increased OS. In adolescents, nodal positivity is a significant negative prognostic indicator (hazard ratio 4.82, 95% confidence interval 3.38–6.87).[45]

Recent data from the MLST-2 study indicate that observation, rather than completion lymph node dissection, is appropriate in patients with a positive sentinel node.[46] However, these patients require close follow-up as per stage III disease guidelines dictate. Completion lymph node dissection should be carefully evaluated in CAM patients as it is associated with significant complication rates.[47]

Follow-up of CAM patients should follow adult guidelines. Special consideration should be given to the frequency of any investigations involving ionizing radiation. Consideration of the principles of “image gently” should be considered.[48]

There is currently no consensus on the management of inoperable stage III or stage IV CAM patients and no studies have been undertaken in these age groups. The use of high-dose interferon alpha-2b therapy in children has been found to be well-tolerated with less associated toxicity, both after resected high-risk melanoma and after a positive sentinel node biopsy.[49][50] However, interferon has been superseded with the introduction of immunotherapies and targeted therapies for melanoma in the adult population and this will most likely occur in the CAM group. This management is best delivered under the guidance of a multidisciplinary team specialised in childhood malignancy and melanoma management.

Melanoma susceptibility is increased in individuals with inherited mutations in the CDKN2A or CDK4 gene. However, most cases of melanoma are sporadic.[21][20] Routine genetic testing of patients at risk is not recommended due to lack of definitive evidence. It is recommended that patients thought to be at increased risk should have regular clinical examinations and optimise their sun protection.

Practice point

All facets of melanoma treatment and follow-up in adults may be integrated into the treatment and follow-up of children. Parents may be assured that survival in children is at least equivalent and probably better than it is in adults with the same stage of disease.

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3.7 Additional psychosocial considerations in children and adolescents

The impact of a malignant tumour diagnosis in paediatric patients, regardless of outcome, is psychosocially and physically profound. The family unit, patient, siblings, parents and occasionally grandparents all need to be considered when seeking to address the psychosocial functioning of the family.

Psychosocial effects can manifest as increased levels of depression, anxiety and concerns regarding mortality amongst all within the family unit.[51][52] A further layer of complexity, that sets a diagnosis in paediatric patients aside from adult patients, is the need to contextualise the diagnosis within a developmental stage. A child’s cognitive development determines the extent to which the young person can process the diagnosis.

Clinicians must be sensitive and adept at dealing with the natural transition of patients developmentally from childhood, to adolescence to young adulthood as these critical timepoints will herald a time to readdress disease knowledge and understanding with the possibility of further psychosocial support being required. Therefore, like the treatment of any childhood malignancy, international data would support the inclusion of psychosocial services to prevent long term emotional and behavioural problems amongst the family unit.[53]

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3.8 Melanocytic tumour of unknown malignant potential in children

See also Management of melanocytic tumour of unknown malignant potential (MelTUMP)

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3.1 Management of MelTUMPs

3.1.1 Introduction

Some cutaneous melanocytic lesions cause particular diagnostic challenges for pathologists as they have some features that do not typically fit with the diagnosis of a benign naevus, whilst also not fully reaching diagnostic criteria for melanoma.[1][2] This is especially the case in children and adolescents, because the lesions may have features that would usually be indicative of melanoma in adults but can be benign in children. Furthermore, as children transition through puberty to become adults, so the significance of these features changes. Such melanocytic lesions that are difficult to classify as either benign or malignant may be categorised using various terms, including 'borderline melanoma', 'minimal deviation melanoma', 'dermal based borderline melanocytic tumour', 'atypical cellular blue naevus', 'pigmented epithelioid melanocytoma', 'borderline deep penetrating naevus' or 'atypical Spitz naevus'. However, a commonly accepted term that encompasses all these is 'melanocytic tumour of uncertain malignant potential' (MelTUMP).[3] More recently, on the basis of accumulating clinical, histopathological, molecular and follow-up data, and as originally proposed by Zembowicz and Scolyer,[4] the World Health Organization Classification of Skin Tumours proposed the adoption of the term "melanocytoma" to encompass this group of intermediate/borderline tumours.[5]

3.1.2 Diagnosis

The diagnostic difficulties in correctly classifying MelTUMPs as either benign or malignant were investigated by a panel of 10 internationally recognised expert dermatopathologists, in a blinded study of 57 such cases with at least five years follow-up of all patients unless death occurred first.[1] The majority of the pathologists classified only 47% of cases with a favourable outcome as benign and 73% cases with an unfavourable outcome as malignant, whilst 16% of lesions were either unclassified by the majority or equally classified as benign and malignant. Of the 14 histological features assessed, only three were found to have prognostic significance: mitoses, an inflammatory reaction and mitoses near base of lesion, although only the latter was significant after correction for multiple hypothesis testing. The study also found that MelTUMPs with a favourable outcome had a significantly younger median age (23 years) than those with an unfavourable outcome (38.5 years), however, there were patients as old as 70 years with favourable outcomes and as young as 3 years with unfavourable outcomes, therefore patient age was not prognostic in the highly selected cases used in this study.

Since MelTUMPs are not a clearly defined entity, and the interobserver reproducibility of their diagnosis and classification is poor, incidence is likely to vary amongst pathologists, between centres and over time. Furthermore, pathologists may prefer to err on the side of caution and diagnose such lesions as melanomas, leading to an apparently decreased incidence of MelTUMPs and a corresponding improvement in outcomes.

Where a melanocytic tumour is assessed by a pathologist and there is uncertainty as to the diagnosis, it should be referred to a pathologist who is a recognised expert in the field of melanocytic lesions. In Australia, this is a Medicare rebatable consultation if the treating practitioner and the approved pathology practitioner who provided the original opinion on the patient specimen agree that a second opinion is reasonably necessary for diagnostic purposes. If the expert pathologist also has doubts as to whether the tumour is benign or malignant, it should be considered to be a MelTUMP.

Once a diagnosis of MelTUMP has been decided, appropriate management decisions must be made; including excision margins and whether to perform a sentinel lymph node biopsy.

This section addresses the following clinical questions:

- What is the role of sentinel node biopsy in the management of MELTUMPs?
- In patients with MELTUMPs, what excision margins are appropriate?

3.1.3 References

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3.2 Sentinel node biopsy for MelTUMPs

Contents

3.2.1 Background

Sentinel lymph node biopsy (SLNB) provides the most accurate staging for invasive melanoma and is therefore required for staging tumours greater than 1.0mm Breslow thickness according to the 8th edition of the AJCC system.[1] However, the role of SLNB in MelTUMPs has not been established and therefore a systematic review of the current evidence was undertaken.

3.2.2 Evidence

The systematic review found a total of 19 eligible studies: no randomised controlled trials, two prospective studies, 15 retrospective cohort studies, one case-control study and a systematic review.[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21]

The duration of follow-up was quite short in most of the studies, with an overall mean of 40 months. Because there were no randomised controlled trials, the reliability of the results is uncertain.

A total of 316 patients underwent sentinel node biopsy, with 112 found to have positive sentinel nodes, a rate of 35%. However, despite the high rate of sentinel node positivity in the MelTUMP patients, there was only one MelTUMP-related death reported[12] amongst all of the 112 patients with a positive node, a mortality rate of less than 1%. The patient who died had a diagnosis of a borderline deep penetrating naevus. For comparison, the rate of sentinel node positivity in the MSLT-1 study was 16% and the corresponding 5-year mortality rate for this group was 47%.[22]

The quality of the MelTUMP studies included did not permit a formal meta-analysis of the results, however, it is clear that the prognostic significance of a positive sentinel node biopsy is qualitatively very different between melanomas and MelTUMPs. Consequently, there is little prognostic utility in performing sentinel lymph node biopsy for MelTUMPs.

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3.2.2.1 Evidence summary and recommendations

Evidence summary	Level	References
Sentinel lymph node biopsy has a highly variable positivity rate in MelTUMPs, but a high mean rate of around 35%. However, positivity does not appear to correlate with melanoma recurrence or death.	III-1, III-2, III-3	[2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13],

Evidence summary	Level	References
		[14], [15], [16], [17], [18], [19], [20]

Evidence-based recommendation	Grade
The routine use of sentinel lymph node biopsy for MelTUMPs is not recommended. In the event of a positive node, its significance should be reviewed by a multidisciplinary melanoma team with expertise in such diagnostic dilemmas.	**C**

Evidence summary	Level	References
Most lesions classified as MelTUMPs behave as benign lesions, particularly in young patients.	III-2	[21]

Evidence-based recommendation	Grade
Age should not be used to determine the prognosis of a patient with a MelTUMP.	**C**

Practice point
It is advisable to have pathologists with expertise in the examination of melanocytic lesions review the tumour slides to confirm or reject a suspected diagnosis of MelTUMP.

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3.2.3 Issues requiring more clinical research study

Longer term follow-up of patients with MelTUMPs, particularly those who have had a positive sentinel node biopsy, would be useful to fully determine its clinical significance. Additional studies with molecular characterisation of lesions are necessary to determine whether there are distinct disease entities within the category of MelTUMP and how to distinguish them from bona fide naevi and melanomas.

Go to:

- Melanocytic tumours of uncertain malignant potential
- In patients with MELTUMPs, what excision margins are appropriate?

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3.2.4 References

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3.3 Excision margins in MelTUMPs

Contents

3.3.1 Background

Performing a wide local excision of a completely excised melanoma reduces the risk of local recurrence and may improve melanoma-specific survival. However, the amount of normal tissue that needs to be removed in order to reduce the risk of local recurrence to an acceptable level is uncertain, although the lack of benefit of wider margins over narrower ones in most studies has led to a move towards narrower margins for primary melanomas over the last two decades.[1][2][3][4][5][6][7][8][9]

Today a maximum margin of 2cm is recommended for thick tumours and 1cm for thin tumours.[10] MelTUMPs are generally well circumscribed, therefore unlikely to have microsatellites that will be removed by using a wider excision margin. However, in contrast to invasive melanomas, there has been an increase in the recommended margins for in situ melanoma from 0.5cm to 0.5–1.0cm, with the aim of ensuring complete histological clearance in order to minimise the local recurrence risk;[10] this is most relevant to the lentigo maligna subtype of in situ disease in which tumour margins are often hard to define.

Since there have been no trials of adequate margins for MelTUMPS, the evidence that exists on this topic was systematically reviewed.

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3.3.2 Systematic review evidence

In patients with MELTUMPs, what excision margins are appropriate?

Only three retrospective cohort studies were found that met the criteria for inclusion in the systematic review.[11][12][13]

One study of naevi and melanomas in children had only three lesions (described as atypical Spitz naevi) that would be regarded as MelTUMPs.[11] The excision margins used were 2mm and there were no reported recurrences, however, the duration of follow-up was not stated.[11]

One study included 28 MelTUMPs (all described as atypical Spitz naevi) diagnosed by a single dermatopathologist.[12] The clinical data were obtained from questionnaires sent to the referring dermatologists for the cases. Of the 28 lesions, 19 (68%) were completely excised with the initial biopsy (size of margins not reported). Seven of the nine lesions incompletely excised on biopsy had a wider excision of up to 5mm achieving, a mean margin of 2.2mm (range 0.75–5.0mm), and two patients were simply observed. However, follow-up data was available for only 38% of all patients (89) and the mean duration of follow-up was only 2.8 months, making interpretation of the adequacy of excisions impossible.

One study included 43 patients with an unspecified mix of MelTUMPs.[13] Margins of excision were available for 33 patients: 11 had excision biopsy alone, 10 had a 5mm wide local excision, 10 had a 10mm wide local excision and one had a 20mm wide local excision, whilst one patient had a shave biopsy and 2mm wide local excision. Follow-up data were available for only 29 patients, of whom 2 (4%) had a recurrence, but further details were not provided.[13] The adequacy of excisions in this study could not be determined.

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3.3.2.1 Evidence summary and recommendations

Evidence summary	Level	References
There is insufficient evidence to recommend the optimal excision margins for MelTUMPs.	III-2	[11], [12], [13]

Practice point
It is advisable to excise MelTUMPs with a 5mm clinical margin and ensure there is at least a 2mm histological margin.

Practice point

It is advisable to follow up patients for at least five years following a diagnosis of MelTUMP, given the uncertainty surrounding the diagnosis. Six-monthly follow-up is advisable for the first 2 years.

3.3.2.2 Notes on these recommendations

A reasonable interval for follow-up visits would be six-monthly for the first two years, reducing to yearly thereafter if no concerns however there is no evidence to support this and this guidance has been developed by consensus.

3.3.3 Issues requiring more clinical research study

Longer term (at least five years) follow up of patients with MelTUMPs needs to be undertaken with reference to the excision margins and clinical outcome in order to determine what is an adequate margin.

Go to:

- Melanocytic tumours of uncertain malignant potential
- The role of sentinel node biopsy in the management of MelTUMPs (melanocytomas)

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3.3.5 Appendices

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3.4 Pregnancy following a diagnosis of melanoma

3.4.1 Background

Melanoma is the most common malignancy in women of reproductive age[1] and an estimated 35% of women with melanoma are of child-bearing age. The incidence of melanoma during pregnancy in NSW was estimated at 51.8 per 100,000 maternities in 2008.[2]

Melanoma is rare during pregnancy, and there is a paucity of evidence concerning its treatment and prognosis in pregnant patients.

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3.4.2 Prognosis of melanoma diagnosed during pregnancy

There have been a number of studies investigating the prognosis of melanoma diagnosed in pregnancy, but they have had conflicting results. Most have been retrospective cohort or case control studies. The definition of pregnancy-associated melanoma has differed amongst studies, with some including women who were up to 5 years post-partum. Some studies did not control for risk or prognostic factors such as sun exposure and tumour thickness, and mortality was often calculated as overall mortality rather than disease-specific mortality.

Older studies did not show that melanoma during pregnancy had an adverse impact on survival.[3][4][5][6][7][8][9][10][11][12][13][14][15][16] A 2014 Swedish cohort study also found no difference in melanoma-specific mortality in melanoma associated with pregnancy compared with melanoma occurring in women of childbearing age who were not pregnant.[17] This contrasts with another nationwide cohort study from Norway which showed an increased mortality for melanoma occurring during pregnancy.[18] In a review of nine retrospective cohort studies and two population-based studies, Byrom et al reported that pregnancy-associated melanoma had a 56% increased risk of mortality compared to melanoma in women of childbearing age who were not pregnant.[19] Another meta-analysis of 15 studies found that pregnancy-associated melanoma had a 17% higher mortality and a 50% higher recurrence rate than melanoma not associated with pregnancy.[20] A small retrospective study of patients with retinal melanoma found no association between pregnancy and survival.[21]

There is conflicting evidence regarding the prognosis of melanoma occurring in pregnancy.

Topics in this section cover:

- Pregnancy following diagnosis of melanoma
- Optimal management of pregnant women with melanoma
- Discontinuation of hormone replacement therapy or oral contraceptive pill

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3.4.3 References

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3.5 Management of pregnant women with melanoma

Contents

A systematic review was performed to answer the following question: '*Does pregnancy following a diagnosis of melanoma affect prognosis?*

3.5.1 Evidence summary and recommendations

There is little information in the literature regarding the effect of subsequent pregnancy on the prognosis of melanoma. A systematic review and meta-analysis in 2015 evaluated the effect of pregnancy following diagnosis and treatment of melanoma. There were only five eligible studies identified for inclusion in the

analysis, 2 population cohort studies and 3 retrospective clinical cohort studies, with these studies suggesting that the risk of mortality from melanoma did not increase in a subsequent pregnancy.[1] Older studies have shown that pregnancy does not increase the subsequent risk of having melanoma,[2] with no increased risk of melanoma developing during subsequent pregnancy.[3] Moreover, women with higher parity have a reduced risk of melanoma.[2] There appears to be no effect of subsequent pregnancy on the prognosis of melanoma.[4][5]

Evidence summary	Level	References
Pregnancy-associated cutaneous melanoma may have an increased risk of mortality.	III-3	[6], [7]
Pregnancy occurring following treatment of melanoma does not appear to increase the risk of recurrence.	III-3	[1]

3.5.1.1 Note on recommendations based on this evidence

No direct recommendations were formulated based on this evidence because it serves to describe prognosis, not to evaluate the effects of interventions to manage prognosis.

Practice point
Regular skin examination should be performed in pregnant women so that suspicious lesions can be dealt with in a timely fashion.

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3.5.1.2 Recommendations

There are no standard guidelines for patients who wish to become pregnant after the diagnosis and treatment of melanoma. It has been recommended that women avoid pregnancy for two to five years after the diagnosis of high-risk melanoma, whether or not the melanoma occurred during pregnancy,[8] as most recurrences are diagnosed within this period. However, recurrence is not always predictable and factors such as the age of the patient and the features of the melanoma need to be taken into account when pregnancy is contemplated following treatment of melanoma.

Practice point

Women of childbearing age who are within five years of primary treatment of a high-risk melanoma should be fully informed of their prognosis when considering pregnancy.

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3.6 Optimal management of pregnant women with melanoma

Contents

A systematic review was performed to answer the following question: *What is the optimal management of pregnant women with melanoma?*

3.6.1 Investigations during pregnancy

3.6.1.1 Biopsies

Biopsies under local anaesthesia can be safely performed during pregnancy.[1]

3.6.1.2 Imaging

The effects of radiation on the foetus are dose dependent and include death, malformation, poor cognitive development and an increased risk of malignancy.[2]

Where possible, CT scans, PET scans and bone scans should be avoided due to the risks associated with irradiation.[3] Chest X-rays may be performed using abdominal shielding and ultrasound may be used to evaluate the abdomen if required.[3]

MRI scans should be avoided in the first trimester due to the theoretical risks of foetal heating/cavitation and gadolinium should not be used in pregnant women as it may be teratogenic.[3]

3.6.2 Treatment options during pregnancy

3.6.2.1 Surgery

Surgical procedures requiring general anaesthesia can be safely performed at any time during pregnancy, but there is a slightly higher risk of miscarriage in the first trimester, so they should be deferred to the second trimester where possible.[4] Such procedures should be discussed in a multidisciplinary setting, and involve input from the anaesthetist and obstetrician.

3.6.2.2 Radiotherapy

Radiation can cause foetal malformation, foetal death, mental retardation and can increase the risk of childhood cancer and leukaemia. These effects are dose dependent, and also depend on the age of the foetus and the extent of the radiotherapy field. The threshold dose associated with foetal malformations is 0.1-0.2 Gy, which is generally not reached in curative treatments, provided the tumour is not near the uterus and lead shielding is used.[4][3] Radiotherapy should be avoided during pregnancy unless there is an urgent clinical need or the tumour located away from the uterus and shielding is used.[4][3]

3.6.2.3 Systemic therapy

There is no evidence regarding the safety of targeted therapies such as BRAF inhibitors and MEK inhibitors or immunotherapies such as ipilimumab or PD-1 inhibitors during pregnancy. Therefore the use of such agents should be avoided during pregnancy.[4]

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3.6.3 Management of early stage melanoma during pregnancy

3.6.3.1 Primary melanoma

The treatment of primary melanoma should not differ because a woman is pregnant. Biopsies and wide local excision may be safely performed for management of melanoma in pregnant women.[1]

3.6.3.2 Sentinel lymph node biopsy

Pregnancy is not a contra-indication to sentinel lymph node biopsy. However, the use of Patent Blue dye should be avoided due to possible teratogenicity and the small risk of anaphylaxis. SLNB can be performed safely in pregnant patients, and lymphoscintigraphy using Technetium99 may be safely used for pre-operative lymphoscintigraphy.[3]

As is the case for women who are not pregnant, sentinel node biopsy should be offered to pregnant patients whose melanoma is >1mm in Breslow thickness and discussed in those whose melanoma is >0.75mm with other high risk pathological features outlining specific risks and benefits (see Sentinel node biopsy).

3.6.3.3 Management of stage III disease

The timing of surgical treatment of metastatic nodal disease will depend on the trimester of pregnancy. If possible, surgery should be scheduled after the first trimester given the small increase in the risk of miscarriage associated with general anaesthesia. However, the risks versus the benefits of a significant delay in surgery should be discussed with the patient before a decision is made.

3.6.3.4 Management of stage IV disease

The treatment options for systemic disease will depend on the site and number of metastases, and the stage of pregnancy.

Surgery may be of benefit for the treatment of isolated or a small number of metastases (see surgical approach to stage IV disease and surgical approach to brain metastases).

As noted above, radiotherapy may be used for the treatment of isolated metastases or brain metastases (see radiotherapy approach to stage IV disease and radiotherapy approach to brain metastases).

There is no evidence regarding the safety of targeted therapies such as BRAF inhibitors and MEK inhibitors or immunotherapies such as ipilimumab or PD-1 inhibitors during pregnancy. Therefore the use of such agents should be avoided during pregnancy.[4]

In patients with stage IV disease, there is a very small risk of metastasis to the placenta and foetus, so at the time of delivery, the placenta should be assessed histologically for metastatic disease.[5]

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3.6.4 Evidence summary and recommendations

Evidence summary	Level	References
Surgical procedures requiring general anaesthesia should be deferred to the second trimester where possible.	N/A	[4]
Radiotherapy may cause foetal malformation, foetal death and increases in risk of childhood cancer and leukaemia and should be avoided during pregnancy unless there is an urgent clinical need or the tumour is located well away from the uterus and shielding is used.	N/A	[4], [3]
The safety of targeted therapies or immunotherapies is unclear, and their use should be avoided during pregnancy.	N/A	[4]
Sentinel node biopsy is safe in pregnant women if the use of Patent Blue dye is avoided.	III-3, N/A	[3], [6], [7], [8], [9]

Evidence-based recommendation	Grade
Where possible, surgical procedures requiring general anaesthesia should be deferred to the second trimester.	**B**

Evidence-based recommendation	Grade
Where possible, radiotherapy should be postponed until the post partum period unless the tumour is not located near the uterus and appropriate shielding is used.	**B**

Evidence-based recommendation	Grade
Use of targeted therapies and immunotherapies should be avoided during pregnancy until there is more evidence regarding their safety in this situation.	**B**

Evidence-based recommendation	Grade
In pregnant women, sentinel node biopsy should be performed without the use of Patent Blue dye.	**B**

Practice point

The treatment of melanoma during pregnancy should be approached the same way as in other melanoma patients, but needs to take into account the stage of the pregnancy and the stage of the melanoma. These patients should be managed by an expert MDT with input from the obstetrician.

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3.6.5 References

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3.6.6 Appendices

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3.7 Continuation of HRT or oral contraceptive pill

Contents

3.7.1 Non-systematic review evidence

A non-systematic literature search review was performed to answer the following question: *Should hormone replacement therapy or oral contraceptive pill be discontinued upon development of melanoma?*

Most of the data regarding the risk of melanoma associated with use of the oral contraceptive pill (OCP) or hormone replacement therapy (HRT) is based on epidemiological studies.

One cohort study found there was an increased risk of melanoma in women taking the OCP, and but no increase in the risk of melanoma in those who were not currently taking the OCP, but had done so in the past. However this study did not control for confounding factors such as sun exposure.[1] In contrast, a case-control study found that there was no association between OCP use and melanoma, but an increased risk of melanoma in those who had used HRT[2] and another large cohort study found no association between use of the OCP and melanoma.[3]

A randomised controlled trial involving over 27,000 women that compared the incidence of melanoma in post-menopausal women in those taking HRT and those who did not take HRT, found that the use of HRT did not affect the incidence of melanoma[4] and, furthermore, several meta-analyses and literature reviews found that use of the OCP or HRT was not associated with an increased risk of melanoma.[5][6][7][8][9][10]

The use of HRT and the OCP does not influence the prognosis of melanoma.[11]

Evidence regarding the use of the OCP and HRT and the risk of melanoma is insufficient to demonstrate an association.

There is no convincing evidence that either hormone replacement therapy (HRT) or the use of the oral contraceptive pill (OCP) affects the natural history of melanoma.[12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30]

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3.7.2 Evidence summary and practice points

Evidence summary	Level	References
The use of HRT or the OCP does not affect the natural history of melanoma.	III-3	[12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30]
The use of HRT or the OCP does not increase the risk of melanoma	III-3	[4], [5], [6], [7], [8], [9], [10]
The use of HRT or the OCP does not influence the prognosis of melanoma	III-3	[11]

Practice point
HRT and the OCP are not contraindicated in women who currently have or have had melanoma.

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3.8 Investigations and follow-up – Introduction

3.8.1 Background

Investigations for patients with any stage of melanoma are undertaken to determine the exact stage of the disease (whether melanoma has recurred locally or distant metastases have developed), to allow planning of the most appropriate treatments, and to permit patients to be given the best estimate of their prognosis. Investigations such as imaging and blood tests may be required for initial staging and may also be repeated as a part of a follow-up program after definitive surgical treatment.

The assessment of whether investigations should be performed can be measured in various ways; diagnostic accuracy, cost, morbidity and ease of performing the investigation. Diagnostic accuracy can be measured as being lesion based or patient based. Lesion based diagnostic accuracy assesses the number of metastatic lesions identified by an investigation and determines the specificity and sensitivity of the test. Patient based diagnostic accuracy assesses whether the investigation resulted in a treatment change for the patient.

The literature available to assess the various investigations has been poor and heterogeneous with small numbers, methodological deficiencies, inadequate descriptions of the patient group studied, whether they were of a retrospective or prospective design, the inconsistent availability of a diagnostic gold standard (biopsy or surgical pathology) and in particular for tests assessing diagnostic accuracy, not assessing both lesion based and patient based measures. This has resulted in wide ranges in sensitivity and specificity, and an inability to compare between studies. The recommendations in these sections should be considered in the light of these deficiencies.

Staging and follow up investigations, especially imaging, have previously been assessed in an era when treatment options for distant metastases were very limited. In recent years, substantial advances in systemic treatment with small molecule and immune checkpoint inhibitors have revolutionised treatment of advanced melanoma and resulted in high response rates and potential long term remissions see Systemic drug therapy. Currently available data indicate that both these types of systemic therapy are more likely to result in long term remissions when used when the amount of metastatic disease is low (measured by number of metastatic disease sites, level of LDH, presence of brain metastases, patient performance status etc). Therefore, follow up of patients at risk of developing recurrent or metastatic melanoma needs to considered in this context.

3.8.1.1 Follow-up

Ideally, routine follow-up in melanoma patients should be conducted in a cost-effective manner that has been scientifically proven to be beneficial. Unfortunately, however, guidelines for follow-up are typically based only on opinions of experts around the world as there have been no valid randomised trials comparing different follow-up schedules and patient survival. Previous guidelines on diagnosis, therapy and follow-up of melanoma[1] and systematic reviews of follow-up schedules were reviewed for these guidelines.[2][3] This section will focus on the follow up of asymptomatic patients with stages I-III melanoma after definitive treatment and not patients with stage IV disease. The reason for this is that patients with stage IV melanoma can be considered in one of two groups for the purposes of follow up: under active treatment where follow up with the treating doctor, including investigations, is aimed at determining treatment efficacy; or patients who are not undergoing active therapy either due to disease volume too limited to be considered for active therapy or those undergoing supportive care. The latter group may have follow up or investigations on an individual basis at the discretion of the patient and the treating doctor. Follow up of stage IV melanoma patients is considered in Systemic drug therapy.

The main purpose of follow-up is to detect recurrences quickly so that early treatment can be undertaken. This assumes that earlier treatment is likely to result in improvements in regional disease control, quality of life and survival. Therefore, follow-up should be mainly prognosis-oriented but should also include the detection of new invasive primary melanomas. The reported incidence of new primaries ranges from 2–8%.[2][3][4] The rate of second primary invasive melanomas is relatively constant over twenty years of follow-up at 6.01 per 1,000 person-years indicating a high, constant lifetime risk of second primary invasive melanoma.[5] This risk does not diminish over time and does not differ significantly between patients first diagnosed with lentigo maligna, in situ

melanoma or invasive melanoma. The risk is even higher for patients with a parental history of melanoma.[6] A second invasive melanoma is most commonly thinner than the initial primary melanoma and has a more favourable prognosis.[7] However, a Queensland population-based study of 32,238 patients found that the hazard ratio of death within 10 years from melanoma was two times higher for those with two melanomas and nearly three times higher when three melanomas were diagnosed compared with people with a single melanoma.[8] In general, subsequent primary invasive melanomas are more likely to occur at the same body site as the initial invasive or in situ melanoma.[9] The rate of occurrence of a subsequent in-situ melanoma is about four times higher than the risk of a subsequent invasive melanoma,[10] but most series do not recommend follow-up for in-situ melanomas.[11]

This section covers the following questions:

- What investigations should be performed following a diagnosis of primary cutaneous melanoma for asymptomatic stage I and II patients?
- What investigations should be performed when in transit and/or regional node disease (stage III melanoma) is diagnosed?
- What investigations should be performed when stage IV melanoma is diagnosed?
- Follow up after initial definitive treatment for each stage of melanoma
- Ideal settings, duration and frequency of follow-up for patients with melanoma

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3.9 Patients with stage I and stage II melanomas

Contents

3.9.1 Introduction

Investigations for patients with clinical stage I/II melanoma are undertaken to determine prognosis and identify early metastatic disease in the regional lymph nodes (stage III) or distant organs (stage IV). Investigations such as diagnostic imaging, ultrasonography, skin examination and blood tests are conducted for initial staging and also as a part of a follow-up program after definitive surgical treatment. Sentinel node biopsy, is also undertaken for staging and prognostic purposes, however for discussion of this procedure we refer readers to the specific guideline for use of sentinel node biopsy in staging cutaneous melanoma.

The main purpose of follow-up is to detect recurrences early so that early treatment can be undertaken. This assumes that earlier treatment is likely to result in improvements in regional disease control, quality of life and survival. Therefore, follow-up should be mainly prognosis-oriented but should also include the detection of new invasive melanomas. The reported incidence of new primaries ranges from >0.5% to 5% annually dependent on risk features.[1][2] A second invasive melanoma is most commonly thinner than the initial primary melanoma and has a more favourable prognosis that does not adversely affect survival.[3] The rate of occurrence of a subsequent in-situ melanoma is about four times higher than the risk of a subsequent invasive melanoma[4], but most series do not recommend follow-up for in-situ melanomas.[5]

After systematic review of the literature (2012-2016) including previous melanoma guidelines, we considered the evidence base for the use of diagnostic tests for initial staging and follow-up. NHMRC levels of evidence (I-IV) were assigned to each evidence summary statement and recommendations were formed and graded with regard to consistency, clinical impact, generalisability, and applicability for the Australian context. Investigations reviewed in this chapter include chest x-ray, computed tomography (CT) imaging, positron emission tomography (PET)/CT imaging, ultrasonography, and S 100B, MIA, LDH blood tests. Additional experimental investigations identified through our systematic search, are discussed in the section for further research.

The evidence below is a summary of the key findings of test accuracy and clinical usefulness for each diagnostic investigation. We report sensitivity and specificity, positive and negative predictive values where available as the main test performance characteristics for the index test compared to the referent (gold) standard. For follow-up, the proportion resulting in a change in management and/or a change in morbidity and mortality are presented if known. The evidence and recommendations for optimal follow-up settings, duration and frequency are discussed in a separate chapter (see following section)

Nearly all studies for initial staging and follow-up were retrospective in design, at high risk of bias and of NHMRC level III or IV (lower quality) evidence. Several follow-up studies grouped stage II and III patients making ascertainment of benefits or harms from diagnostic investigations difficult. All included results are for stage I/II patients unless otherwise indicated.

3.9.2 Investigations for stage I and stage II melanoma in patients with a negative sentinel node

3.9.2.1 Imaging

3.9.2.1.1 Chest x-ray (CXR) for initial staging

There was only one new study published since 2012. This retrospective study investigated use of pre-operative imaging for 546 clinically node negative cutaneous melanoma patients undergoing sentinel lymph node biopsy. In total 409/546 (75%) had an imaging study: 383 (70%)had a CXR, 53 had CT scans (10%; included 43 CT chest, 34 CT abdomen/pelvis, 2 CT head, 4 CT neck), 25 PET scans (5%), 20 MRI scans (4%; included 18 head MRI, 1 extremity MRI and 1 spine MRI), and 2 people had extremity X-rays (0.4%).[6] Of the 383 people who had CXR, three had positive findings, all of which were false positives (all had negative chest CT scans; false positive rate 0.8%, true positive rate 0%). The 380 negative results were all true negatives. Pre-operative imaging for detection of metastases was not recommended.

Given the limited number of new studies on CXR, a review of the recommendations from previous guidelines was warranted.[3] Among 17 studies, CXR detected stage IV metastatic disease in a few patients; however the test results did not change clinical management, and did not improve overall survival. CXR had a false positive rate of between 2-71%, and a true positive rate of 0%.[7] The evidence base for guidance on use of CXR consisted of small observational studies, with no RCTs, with medium to high risk of bias (NHMRC level of evidence III-2 to IV).

3.9.2.1.2 Chest x-ray (CXR) during follow-up

The use of routine chest X-ray exams for the detection of small pulmonary metastases has been investigated. However, false-positive and false-negative findings are frequent. The sensitivity of chest X-ray is poor with reports varying from 7.7% to 48%. A large study of 1969 patients with stage I-III melanoma undergoing routine follow up found that only 10/204 relapses were discovered by chest X-ray: the majority (7/10) of which were observed in patients with stage III disease.[8] A large prospective study of 1 235 patients found that only 0.9% of chest X-rays identified pulmonary metastases, less than 10% of which were amenable to resection, with a false positive rate of 3.1%.[9] A cost-effectiveness analysis using data from the Roswell Park Cancer Institute and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program found that the cost of CXR screening per quality-adjusted life year was $165,000, respectively, in 1996 US dollars.[10] Based on these findings, the investigators suggested reducing the frequency of screening CXR.

3.9.2.1.3 Computed tomography (CT) imaging for initial staging

One retrospective study of 172 patients with clinically stage IIB or IIC melanoma evaluated the use of CT of the head, chest, abdomen and pelvis for initial staging.[11] In total 75 patients had 104 CT scans for initial staging, with 8 positive results, of which 6 were false positives and two true positives in one patient with metastatic disease, and one patient with a secondary non-melanoma cancer.

3.9.2.1.4 Computed tomography (CT) imaging during follow-up

No new studies of CT surveillance of asymptomatic patients treated for stage I/II melanoma were identified. Existing guidelines and prior studies report little benefit in terms of early detection of metastatic disease, a change in clinical management, improved survival, or cost-effectiveness.[12][13]

3.9.2.1.5 Positron emission tomography (PET) or computed tomography (PET/CT) imaging for initial staging

One retrospective study among 106 patients with head and neck primary melanoma, clinically negative nodal disease and negative CT, evaluated the use of FDG-PET for initial staging.[14] In total 47 patients had FDG-PET, with 10 positive results, of which 8 were false positives and two true positives in patients with secondary non-melanoma cancers. Of the 37 patients with a negative FDG-PET, 33 results were true negatives and four were false negatives in patients with occult nodal disease. FDG-PET was found to have no clinical utility in this patient population.[14]

Five new studies using PET/CT were identified, including one systematic review[15], two primary studies assessing detection of nodal disease[16][17] and four assessing detection of distant metastases.[15][17][18][19] In one retrospective study of 149 patients undergoing pre-operative PET/CT imaging for clinically stage I/II melanoma of at least 1 mm thickness, 41 had positive findings, 35 were false positives and 6 were true positives (metastatic involvement of lymph node confirmed histologically; false positive rate 85%, true positive rate 15%).[18] There was no clinical utility associated with PET/CT above and beyond SNB: false positives led to unnecessary invasive procedures, and true positives yielded no further information to the SNB. The authors concluded pre-operative PET/CT was of limited benefit in staging clinical stage I/II patients.[18] Another study compared sensitivity and specificity of PET/CT versus high resolution ultrasound for the identification of metastatic involvement of sentinel lymph node.[16] The sensitivity, specificity, PPV and NPV of PET/CT were 0%, 100% (95%CI 91.6–100.0), 0% and 71.1% (95% CI 58.6–81.2) respectively. The authors concluded high resolution ultrasound was better value than PET/CT in preoperative identification of positive SLNs. A second retrospective study of 77 clinically stage I/II melanoma patients aimed to identify a threshold thickness for the primary melanoma, above which PET/CT might be useful.[19] All but 1 of the 11 patients with positive PET/CT findings had melanomas ≥5mm (only 5 positive PET/CT results were confirmed true positives histologically: 4 lymph node metastases, 1 distant metastasis). Four of the 11 patients with positive PET/CT (36%), and 5 of 66 patients with negative PET/CT (8%), died from melanoma. It was unclear whether the PET/CT results influenced clinical management.[19]

In general, against a histopathology reference standard PET/CT generally had moderate to low sensitivity and higher specificity. High false positive rates including detection of benign lesions and other cancers led to additional investigations including invasive procedures.[15][18] Some melanoma metastases were missed on PET /CT being detected clinically within 6 months of the index scan,[17] or detected with SNB.[14]

3.9.2.1.6 Positron emission tomography (PET) or computed tomography (PET/CT) imaging during follow up

A recent systematic review by Danielson et al[20] of 7 studies was undertaken to assess the diagnostic value of PET as a tool for surveillance in the regular follow-up program of asymptomatic cutaneous malignant melanoma patients. The majority of the 739 patients in the studies were stage IIB and III. The authors concluded that the mean sensitivity of PET was 96% (95% CI: 92-98) and the specificity was 92% (95% CI: 87-95). Overall, PET has a high diagnostic value. However, there were no data available to demonstrate better survival outcomes for patients as a result of routine PET surveillance.[20]

3.9.2.1.7 Magnetic resonance imaging (MRI) for initial staging

The retrospective study of 546 patients discussed above under CXR also included MRI scans used for initial staging in 20 patients (4%; included 18 head MRI, 1 extremity MRI and 1 spine MRI).[6] The one positive MRI test result was a false positive in a patient with a benign thyroid nodule. The 19 negative results were all true negatives.

3.9.2.1.8 Magnetic resonance imaging (MRI) for during follow-up

Cerebral metastases are more readily detected by magnetic resonance imaging (MRI) than by CT or FDG-PET/CT. [21], however no new studies published since 2012 of MRI follow-up of stage I/II patients were identified.

3.9.2.2 Blood tests

3.9.2.2.1 S100B, MIA, LDH blood tests for initial staging

Two small studies were identified assessing the diagnostic accuracy of either p-proteasome, MIA, S-100B, or LDH for melanoma metastases.[22][23] In the first study of 53 clinical stage I-II melanoma patients, 68 stage III-IV patients and 40 healthy volunteers, plasma samples were obtained before definitive surgical excision or treatment and followed for a median of 17 months. Reference standard positive patients were a mixture of patients with clinical stage III/IV disease at the outset and patients with clinical stage I/II who then developed metastases during follow-up (detected through clinical examinations and imaging tests). Likewise reference standard negative patients were a mixture of healthy volunteers and patients with clinical stage I/II disease who did not develop metastases during follow-up. Within the limitations of the substantial spectrum bias arising from the selection of the study population which was not limited to asymptomatic stage I/II patients, the area under the receiver operating curves (ROC) for p-proteasome and S100B were the highest (0.81,and 0.82 respectively), whereas LDH and MIA showed lower values (0.79, and 0.72 respectively).[22] In the second study, of 87 stage I/II patients, 71 stage III/IV patients and 50 healthy volunteers, serum concentrations were measured before

surgery.[23] The reference standard was again a composite of clinical exams and imaging tests to define whether or not the patient had stage III/IV disease at either the outset or during a median of 32.8 months follow-up. The authors reported that a cut-off value for MIA of 9.4 ng/ml, had 77% sensitivity and 94% specificity for the detection of stage IV disease. Among the 87 patients with stage I/II disease after imaging, 66% of those with MIA serum values greater than 9.4 ng/mL developed regional or distant metastases during follow-up , while 5% of those with values below this threshold developed metastases.[23]

3.9.2.2.2 Standard blood tests for initial staging and follow-up (e.g. electrolytes, urea, creatinine, liver function tests [LFTs], full blood count [FBC])

Evidence from previous guidelines states the routine use of standard blood tests rarely identifies occult stage IV disease in patients presenting with stage I or II melanoma and is not recommended. See [ANZ Melanoma guidelines]. These tests are not new and were therefore outside the scope of the current systematic review and guideline.

3.9.2.2.3 S100B, MIA, LDH blood tests during follow-up

As a tumour marker, S100B displays a sensitivity of 86–91 %, specificity[24][25] and may portend recurrence, however there are no data demonstrating superior survival outcomes for patients undergoing routine S100B testing in follow up. The use of serum LDH or melanoma-inhibitory activity (MIA) protein in follow up for the detection of asymptomatic melanoma recurrence has been reviewed by Fields and Coit.[26] Abnormal blood tests were rarely the first sign of metastases. Low sensitivity, specificity, and accuracy for general laboratory profiles make them ineffective in the detection of subclinical recurrence and their roles are yet to be defined.

3.9.3 Investigations for stage I-II patients with no sentinel node biopsy (ie. declined or patient unfit)

3.9.3.1 Ultrasonography for initial staging

For situations where SLNB has been declined or is not possible for technical reasons or patient co-morbidities, ultrasound monitoring may be considered, however 4 studies have shown poorer accuracy (both sensitivity and specificity) compared to SLNB[27][28][29][30], and so the latter is preferred whenever feasible (see chapter on SNLB). No studies were identified in patients who were not eligible for SLNB.

In three of the studies assessing ultrasonography against a reference standard of SNLB, the sensitivity of ultrasound ranged from 13% to 71%; the specificity from 57% to 97%[27][28][29]; and in two studies the positive predictive value ranged from 37% to 97%, while the negative predictive value ranged from 13% to 84%.[27][29] In one study that assessed a particular ultrasound characteristic (the echo free island) the sensitivity was 11%, the specificity 98%, the positive predictive value was 50% and the negative predictive value was 80%.[30]

One small study compared high resolution ultrasound (HRUSS) with PET/CT against a reference standard of SNB in 20 patients with clinically stage I/II disease.[16] HRUSS correctly identified two of 12 patients with positive SLNs whereas PET/CT imaging identified none; both imaging tests correctly identified all 12 patients with negative SLNs.[16]

3.9.3.2 Ultrasonography during follow-up

The usefulness of ultrasonography for follow-up of patients treated for Stage I/II melanoma depends entirely on the technical skill and experience of the personnel involved. There is a consensus of opinion that ultrasound is superior to clinical examination of regional lymph nodes, although its survival advantage is unproven.[31] A prospective cohort study of 373 patients with a primary tumour Breslow thickness of ≥1.5mm[32], reported a sensitivity of 93% for ultrasound compared with only 71% for the clinical examination of regional lymph nodes. Their specificity was equally high for both procedures (>98%). Despite the superiority of ultrasound, very few patients actually benefited from the addition of ultrasound to clinical examination. The reasons cited for this were that although ultrasound was useful in the earlier detection of regional disease or avoidance of unnecessary surgery in 7% of patients, 6% had deleterious effects such as unnecessary stress caused by repetition of ultrasounds for benign lymph nodes or useless removal of benign lymph nodes.[32] Thus in sum, in only 1% of patients was the use of ultrasound advantageous.

3.9.3.3 Ultrasound +/- Fine needle aspiration (FNA) +/- core biopsy for initial staging

One prospective study assessed whether the combination of ultrasound and fine needle biopsy could be used as a ‘triage’ test for SLNB in 107 asymptomatic patients with clinically stage I/II melanoma.[33] Using this test strategy, only two patients had final positive results, of which one could not be confirmed on histopathology (possible false positive) and the other was confirmed (true positive). Of the 105 patients who were negative on ultrasound +FNA, 36 were false negatives (nodal metastases found on SLNB), and 69 were true negatives.

3.9.3.4 Ultrasound +/- Fine needle aspiration (FNA) +/- core biopsy during follow-up

FNA is the current standard method to confirm the presence of suspected nodal metastases for lymphadenopathy identified after definitive local treatment of cutaneous melanoma.[34][35] Ultrasound guidance should be used as the diagnostic yield is superior, particularly for small lymph nodes <10mm in size. Core biopsy has higher sensitivity and specificity compared with FNA and should be considered where FNA is negative but clinical suspicion remains high. There is no role for routine lymph node biopsy during follow up of asymptomatic patients.[36]

3.9.4 Other investigations during follow-up

3.9.4.1 Skin Self-Examination

A review of 9 clinical practice guidelines by Marciano et al (2014)[37] reveals consensus that patients should be taught skin self-examination; this was based on retrospective evidence from several studies that recurrences were commonly first detected by patients. For this recommendation, 4 guidelines varied in evidence content while 5 guidelines provided consensus opinion only. Education on sun-smart behaviour was recommended by 4 guidelines.[37]

Successfully implementing self-examination requires patient education on whole-body skin examination with particular attention given to melanoma surgical scars and the corresponding lymphatic drainage areas for in-transit and lymph node recurrence. Patients should also be given education regarding symptoms that may warrant further investigation, such as pain, fatigue, weight loss, nausea and vomiting, dyspneoa, and headache. In addition, the use of brochures or videos, and the engagement of relatives in the education process may be helpful.[38][39][40] Randomized controlled trials do not exist. In Australia, patients themselves detect up to 75% of recurrences, while in other countries this can be as low as 20%.9-13 These data highlight the fact that even with education, there are great differences in patients' individual ability to detect recurrences.[40]

3.9.4.2 History and physical examination during follow-up

There is general consensus that the most cost-effective component of a strategy resulting in the detection of the majority of recurrences is careful history taking and physical examination. The detection of distant metastases in patients with early localised disease is unusual.

As with self-examination, history and physical examination include specific history taking, a full skin examination looking for new primaries, palpation of melanoma surgical scars, and lymphatic drainage areas for in-transit and lymph node recurrence. Apart from patient self-detected relapses, most relapses and secondary melanomas are detected during physical examinations.[41][42] In a large prospective study12, roughly 50 % of recurrences were identified by history taking/physical examination, 80 % of which were local recurrences, in-transit metastases, and regional lymph node metastases.[41] Indeed, the vast majority of operable recurrences (96%) are those detected by physical examinations.14 In summary, history and physical examinations for patients with stages I–III melanoma are the most effective procedure for early recurrence detection.[43][8]

3.9.5 Evidence summary and recommendations

Evidence summary	Level	References
Chest x-ray for initial staging produces high rates of false positive and incidental findings.	III-2	[6], [3], [7]
Chest x-ray can detect stage IV disease occasionally; however knowledge of these	III-2	[3]

Evidence summary	Level	References
results was not shown to change management, and did not improve overall survival.		

Evidence-based recommendation	Grade
Chest x-ray imaging for initial staging should not be performed	**C**

Evidence summary	Level	References
No studies of CT imaging for stage I or stage IIA patients were identified. CT imaging for initial staging of patients with stage IIB and IIC melanoma detects more false positives than true positives. Diagnostic accuracy is greater in symptomatic rather than asymptomatic patients.	IV	[11]

Evidence-based recommendation	Grade
CT head, chest, abdomen and pelvis imaging are not recommended for initial staging in asymptomatic patients with stage IIB or IIC melanoma. In addition, there is no evidence to support CT imaging in Stage I and IIA melanoma.	**C**

Evidence summary	Level	References
PET/CT demonstrates a moderate to low sensitivity and a high specificity.	III-2	[14], [17], [18], [15]
High false positive rates including detection of benign lesions and other cancers may lead to unwanted additional investigations including invasive procedures.	III-2	[18], [15]
PET/CT accuracy may be improved when used among patients with a higher risk of metastases (i.e. with thick primary melanomas)	III-3	[19]

Evidence-based recommendation	Grade
CT imaging for initial staging is not recommended for patients with stage I-II melanoma	**C**

Evidence-based recommendation	Grade
PET/CT imaging for initial staging is not recommended for patients with a thin, or intermediate Breslow thickness primary melanoma (Stage I-IIB).	**C**

Evidence summary	Level	References
There are few data regarding MRI for initial staging. MRI may lead to additional investigations for false positive results, without any identification of true positive cases in stage I/II patients.	IV	[6]

Evidence-based recommendation	Grade
MRI imaging of the head, spine or extremities is not recommended for initial staging in patients with stage I or stage II melanoma.	**D**

Evidence summary	Level	References
Blood tests – S100B, p-proteasome, MIA, LDH. P-proteasome and S100B showed good predictive ability for identifying metastatic disease, and this was superior to either MIA or LDH, however the studies were subject to several biases. In one study MIA was predictive of melanoma recurrence at 6 months in two thirds of pre-operative stage I/II patients using a cut-off value of 9.4 ng/mL.	III-3	[22], [23]
There is insufficient evidence to recommend routine measurement of S100B in asymptomatic patients at primary diagnosis of melanoma. There is insufficient evidence to determine whether MIA is as sensitive as S100B and therefore cannot be recommended. Serum LDH is not recommended. No evidence was identified supporting the use of standard blood tests (e.g. electrolytes, urea, creatinine, LFTs, FBC) in initial staging or follow-up of Stage I/II melanoma.		[3]

Evidence-based recommendation	Grade
S100B, MIA and LDH or standard blood tests are not recommended at initial staging for diagnosis of metastatic melanoma.	C

Practice point
Low sensitivity, specificity, and accuracy for general laboratory profiles (S100B, MIA, LDH blood tests) make them ineffective in the detection of subclinical recurrence and their roles are yet to be defined.

3.9.6 How should patients at each stage of melanoma be followed after initial definitive treatment

How should patients at each stage of melanoma be followed after initial definitive treatment?

3.9.7 What is the ideal setting, duration and frequency of follow-up for melanoma patients?

What is the ideal setting, duration and frequency of follow-up for melanoma patients?

3.9.8 Issues requiring more clinical research study

Should liquid biopsy be performed following a diagnosis of primary cutaneous melanoma for asymptomatic Stage I and II patients?

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3.9.10 Appendices

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

Contents

3.10.1 Introduction

Stage III melanoma is defined as the presence of nodal metastatic disease and/or the presence of intransit /satellite/microsatellite metastasis. Investigations are required to confirm the diagnosis of stage III disease as well as to assist in determining accurately the extent of disease. Accurate assessment is crucial in determining management and prognosis. Patients with isolated stage III melanoma are usually treated with surgical resection in the first instance. However, if widespread metastatic disease is identified, the treatment plan will be completely different.

3.10.2 Investigations to diagnose stage III disease

3.10.2.1 Clinically node-negative patients

Should be investigated as per the question What investigations should be performed following a diagnosis of primary cutaneous melanoma for asymptomatic stage I and stage II patients?"

3.10.2.2 Palpable disease

3.10.2.2.1 Lymph node disease

i. Fine needle biopsy (FNB)

There are no prospective studies to define the accuracy of FNB in the diagnosis of metastatic melanoma in a mass (lymph node or subcutaneous or internal nodule). However, a systematic review of 10 retrospective studies has been performed.[1] This has found the overall diagnostic accuracy of FNB for metastatic melanoma is high, with a sensitivity and specificity of 0.97 and 0.99 respectively. The authors also suggest because of its low procedural cost, minimal risk of harm to the patient, and rapid turnaround time, FNB allows treatment decisions to be expedited.

False negative results occur more commonly in axillary specimens, which can be offset by increasing the number of needle passes. Other causes of a false negative result include obesity, difficult areas for aspiration (deep inguinal lymph nodes), superficial subcutaneous lesions associated with fibrosis or a previous scar, enlarged lymph nodes with only small focal deposits of metastatic melanoma or poor circumscription of the suspicious lesion. The most common cause of a false-negative result in FNB was an inadequate specimen, and the most common cause of a false-positive result was the presence of a second malignancy.

FNB can be palpation-guided or ultrasound (US)-guided. Meta-regression analysis found no difference in accuracy between palpation-guided and US-guided FNB (P = .75). Diagnosis of lesions <10mm in diameter appears to have a slightly less sensitivity (~0.94) but an unchanged specificity.

FNB morbidity was negligible (<0.002%). Data obtained from studies of other cancers suggest seeding of tumour cells along the needle tract is a rare event.

FNB retrieved material is suitable for assessment for BRAF mutation status, being successful in >90% of cases.[2][3][4]

Evidence summary	Level	References
Sensitivity and specificity for FNB of a mass confirming melanoma is 0.97 and 0.99 respectively	II	[1]
FNB can be performed by clinical palpation or with ultrasound guidance	II	[1]
FNB retrieved material is suitable for BRAF mutation analysis in >90% cases	III-1	[2], [3], [4]

Evidence-based recommendation	Grade
FNB, with or without ultrasound guidance can be used to confirm the diagnosis of lymph node or intransit metastatic melanoma	**B**

ii. Core biopsy

There is only one study assessing the role of core biopsy in melanoma lymph node metastases.[5] This showed a sensitivity 97.9% and specificity 100%, which is very similar to FNB. There are no comparative studies between core biopsy and FNB for melanoma, but the studies in other cancers suggest that FNB should be the preferred initial test as it is less expensive, may not require local anaesthesia and is associated with little patient discomfort. Core biopsy should be used if FNB is unable to provide an adequate diagnosis or to avoid a surgical excision which may be more morbid. Core biopsy retrieved material can also be used for assessment of mutation status, and may in fact be more successful than FNB retrieved material due to the increased volume of tissue available for testing.

Evidence summary	Level	References
Core biopsy can be used to confirm the diagnosis of stage III melanoma with a sensitivity of 97.9% and specificity of 100%	III-2	[5]

Evidence-based recommendation	Grade
Core biopsy can be used to confirm the diagnosis of lymph node or intransit metastatic melanoma	**C**

3.10.2.2.2 Intransit disease

Histological diagnosis of the presence of intransit/satellite disease can be obtained by any type of skin biopsy (shave, punch or excision) or even FNB if it is bulky. This tissue would then also be available for mutational testing if clinically appropriate.

3.10.3 Investigations following the diagnosis of stage III disease

Accurate assessment to identify the presence of occult systemic metastatic disease is particularly important for patients following the diagnosis of stage III melanoma as it directly affects clinical management and prognosis.

The assessment of whether investigations should be performed can be measured in various ways; diagnostic accuracy, cost, morbidity and ease of performing the investigation. Diagnostic accuracy can be measured as being lesion based or patient based. Lesion based diagnostic accuracy assesses the number of metastatic lesions identified on an investigation and determines the specificity and sensitivity of the test. Patient based diagnostic accuracy assesses whether the investigation resulted in a treatment change for the patient.

The literature available to assess the various investigations has been particularly poor and heterogeneous with small numbers, methodological deficiencies, inadequate descriptions of the patient group studied, whether they were of a retrospective or prospective design, the inconsistent availability of a diagnostic gold standard (biopsy or surgical pathology) and in particular for tests assessing diagnostic accuracy, not assessing both lesion based and patient based measures. This has resulted in wide ranges in sensitivity and specificity, and an inability to compare between studies. The following recommendations should be taken in the light of these deficiencies.

3.10.3.1 PET/CT and CT

The present standard for PET imaging in cutaneous melanoma is combined PET/CT imaging, using [18F] Fluorodeoxyglucose (FDG). Prior to 2005 positron emission tomograph (PET) scans only were used, instead of PET/CT scans. The addition of low dose CT to a PET scan provides clinically important anatomical detail (Von Shulthesss 2006) and attenuation correction of PET data by CT can also reduce scanning duration by 20–30% (Buck 2010). This guideline will therefore only assess studies using PET/CT scans.

The sensitivity of PET/CT is dependent on the size of the lesion, its anatomical location, and its rate of FDG uptake per volume unit of tissue. Tumour deposits less than 3 to 5mm in diameter are unable to be detected by PET/CT scans.[6]

The brain is not well imaged with PET/CT scans and consideration should be given to imaging the brain separately with CT or MRI.[7][8]

i. The role of PET/CT in SNB positive patients

The role of PET/CT in SNB positive patients has been investigated in 5 retrospective studies. The yield of cross-sectional imaging in detecting occult metastases ranged from 0.5 to 3.7% (Holtkamp 2017).[9][10][11][12]

Evidence summary	Level	References
The yield of PET/CT and CT in detecting occult metastases ranges from 0.5 to 3.7%.	III-2	[9], [10], [11], [12]

Evidence-based recommendation	Grade
Consider NOT performing PET/CT or CT in newly diagnosed sentinel node positive patients	**C**

ii. The role of PET/CT in clinically palpable nodal disease

Six systematic reviews have been performed to assess the role of PET/CT in clinically palpable nodal metastatic melanoma.[13][14][15][16][17][18] Five of the systematic reviews showed that the diagnostic accuracy of PET/CT is better than conventional CT. However, the only one of the systemic reviews that limited the review to prospective studies[17] did not come to this conclusion. The reviews found the sensitivity of PET/CT ranged from 68% to 87%, and the specificity from 92% to 98% for lesion based analysis. CT scans had a lesser sensitivity (42-28%) but comparable specificity to PET/CT. However, CT scans showed a higher predictive value for liver and lung lesions.[19]

Two prospective trials and a systematic review have shown a change in treatment occurred in 19% to 35% of stage III patients after the use of PET/CT scans.[20][21][18]

The cost effectiveness of imaging for stage III melanoma has been assessed in three studies.[19][22][23] One study[22] showed that staging with radiography (chest x-ray) is the least cost-effective option, resulting in greater costs than CT alone, and fewer accurate diagnoses. PET/CT incurs a greater incremental cost compared to CT alone, but achieves a more accurate diagnosis of metastatic disease, particularly for lung lesions.[19][22][23] Authors suggest that the cost benefit of PET/CT over CT alone depends on a health system's priorities and willingness-to-pay.

Evidence summary	Level	References
A PET/CT scan has a higher sensitivity compared to conventional CT in identifying metastatic lesions in Stage III melanoma patients with palpable nodal disease. The specificity of the 2 investigations is similar.	II	[13], [14], [15], [16], [17], [18]
A CT scan has a higher predictive value than a PET/CT scan in identifying metastases to the liver and lung.	II	[19]

Evidence summary	Level	References
A treatment change occurs in 19-35% of stage III patients after the use of a PET/CT scan.	II	[20], [21], [18]
PET/CT is more costly than CT alone, but achieves a more accurate diagnosis of extent of metastatic disease.	II	[19], [22], [23]

Evidence-based recommendation	Grade
Perform a PET/CT scan for the initial staging of stage III melanoma patients with palpable nodal disease.	**B**

Evidence-based recommendation	Grade
A brain scan (high resolution CT or MRI) should be added to a PET/CT scan to assess for the presence of brain metastases.	**B**

3.10.3.2 MRI

The accuracy of whole body MRI appears to be less than that of PET/CT scans. It is also limited by its contraindications (the presence metal implants), long scan times, reduced diagnostic accuracy in the detection of lung nodules, high inter-reader variability and cost.[24][25][26][27]

MRI is superior to CT and PET/CT when examining the neural system, in particular, for cerebral metastases. MRI is undoubtedly superior for lesion detection, anatomic localisation and differentiating between single and multiple lesions[28], but there are no studies specifically related to melanoma metastases, and MRI is more costly than CT.

Evidence summary	Level	References
Whole body MRI is not as accurate as PET/CT in stage III melanoma patients with palpable nodal disease.	II	[24], [25], [26], [27]
An MRI scan is superior to a CT or PET/CT scan in identifying cerebral metastases.	N/A	[28]

Evidence-based recommendation	Grade
Consider using an MRI scan rather than a CT scan to assess for the presence of brain metastases.	**B**

3.10.3.3 Ultrasound

Ultrasound may be used to identify the extent of intransit and nodal disease, and also to diagnose liver metastases.

Practice point
Ultrasound may be used for identification of the extent of intransit and nodal disease, and also used to diagnose liver metastases.

3.10.3.4 S100B, LDH and MIA in locoregional melanoma

It is difficult to compare the studies investigating the value of any of these blood markers in patients with melanoma, because groups of patients with different stages of disease have been studied and several different assays and cut-off points have also been employed resulting in different recommendations at different institutions.

Even a meta-analysis of S100B levels of stage I to stage IV melanoma patients did not separately assess stage III patients. It still showed that an elevated level of S100B signified poor prognosis at whatever stage.[29] Two studies have analysed the value of S100B in patients with palpable nodal disease and found that an elevated S100B preoperatively was associated with poorer disease-free survival[30][31] and with increased tumor size[31]. Henry et al showed S100B could discriminate stage III patients before and post lymphadenectomy (p .0.007), but did not separately assess the role of S100B in stage III survival (Henry 2013).

LDH and MIA do not appear to have a role in the assessment of stage III disease.

S100B and MIA blood tests are currently not PBS available in Australia.

Evidence summary	Level	References
Elevated S100B may correlate with poorer disease free survival, increased tumour	III-1	

Evidence summary	Level	References
size and presence of systemic metastatic disease in patients with palpable nodal disease		[31], [30]
LDH and MIA are not useful in stage III disease	III-1	[30]

Practice point

Other countries consider performing S100B in stage III patients with palpable nodal disease, but this is not PBS available in Australia.

3.10.4 How should patients at each stage of melanoma be followed after initial definitive treatment

How should patients at each stage of melanoma be followed after initial definitive treatment?

3.10.5 What is the ideal setting, duration and frequency of follow-up for melanoma patients?

What is the ideal setting, duration and frequency of follow-up for melanoma patients?

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3.10.7 Appendices

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3.11 Patients with stage IV melanoma

Contents

3.11.1 Introduction

A diagnosis of stage IV (M1) melanoma can occur in differing clinical scenarios. Principally these are:

1. presentation with symptoms/signs of metastatic (stage IV) disease in a patient with no prior history of primary melanoma

2. presentation with symptoms/signs of metastatic disease (stage IV) in a patient with a prior history of a primary melanoma
3. discovery of asymptomatic metastatic disease (stage IV) in a patient being followed up following a prior diagnosis of 'high risk' stage II or stage III melanoma
4. discovery of asymptomatic metastatic disease (stage IV) as an incidental finding during investigation of an unrelated condition.

In (1) by definition, a histological diagnosis will have been obtained. In (2) histological confirmation that the metastatic malignancy is melanoma is essential to rule out alternative primary sites and to obtain tissue for molecular analysis. For patients in scenarios (3) and (4) where stage IV disease is found on imaging, histological confirmation is required particularly for patients with a long interval from the previous melanoma diagnosis, where the imaging appearance is atypical for melanoma metastases (e.g. a speculated lung lesion with intra-thoracic nodes), and where the stage IV lesion is solitary. The biopsy technique chosen (FNA, core biopsy, excision) should be performed to obtain enough tissue for molecular studies.

Appropriate investigations for individual patients with stage IV melanoma will be related to that patient's symptoms, findings on physical examination, medical history and co-morbidities. Other baseline investigations may be necessary for specific treatment options (e.g. endocrine tests for patients having immunotherapy). The recommendations in this chapter are however applicable to all patients with stage IV melanoma.

3.11.2 Systematic review evidence

A systematic review was undertaken to identify relevant evidence regarding investigations for stage IV melanoma. Several diagnostic accuracy studies were identified examining different types of investigations.

3.11.2.1 Sub-staging

Under the AJCC Staging Manual 8th Edition, stage IV melanoma is subdivided into:

- Stage M1a – skin, soft tissue including muscle and/or non-regional lymph nodes
- Stage M1b – lung metastases with or without M1a sites of disease
- Stage M1c – metastases to other non-central nervous system visceral sites with or without M1a or M1b sites of disease
- M1d – metastases to CNS with or without M1a, M1b, or M1c disease.

Additionally, each subdivision above is further divided by the LDH level, with (0) denoting LDH not elevated and (1) denoting LDH elevated. Sub-staging is essential to provide a more accurate prognosis and to determine treatment options. Serum LDH level is required for sub-staging and is an essential test when stage IV melanoma is first diagnosed.

Practice point
Serum LDH level should be measured at the time of diagnosis of stage IV melanoma.

3.11.2.2 Imaging – PET, PET/CT

Imaging for patients with stage IV melanoma requires, at minimum, a contrast enhanced CT of chest/abdomen /pelvis and/or a whole body PET scan with concurrent low-dose CT or combined PET/contrast enhanced CT scan. Comparative studies of these imaging modalities are based on both stage III and stage IV patients.[1][2] Systematic reviews show PET and PET/CT are superior in detecting sites of metastatic disease[3][4], and will therefore be preferred in most patients. However there are no randomised trials and in the absence of these, it must be realised the endpoint of diagnostic accuracy does not necessarily lead directly to better patient outcomes. Studies have described potentially beneficial outcomes based on changes to management plans, particularly where the proposed treatment is surgical[1][2] Where CT scanning has shown widespread metastatic disease and findings on PET will not change the planned management approach, metabolic imaging can be omitted.

Evidence summary	Level	References
Systematic reviews show superior diagnostic accuracy of whole body PET scanning and PET/CT scanning over CT scanning in stage IV melanoma.	II, III-2	[3], [4]
Whole body PET scanning or PET/CT can lead to beneficial changes to patient management.	II, IV	[1], [2]

Evidence-based recommendation	Grade
Whole body PET scanning or PET/CT is required in patients diagnosed with stage IV melanoma if the result will change management.	**A**

3.11.2.3 Imaging – MRI

Staging of melanoma with whole body MRI was been reported to have higher diagnostic accuracy than CT scanning in study of test accuracy[5] and comparable to PET or PET/CT in another study of test accuracy[6] but this is unlikely to be widely utilised. MRI scanning may be helpful in clarifying otherwise indeterminate liver lesions.[7]

3.11.2.4 Imaging – brain metastases

Neither whole body PET or PET/CT can reliably detect brain metastases. Because melanoma has a high rate of brain metastases developing during the course of stage IV disease, some guidelines have recommended routine brain imaging with contrast enhanced CT or MRI at initial presentation in all stage IV melanoma patients who do not have neurological symptoms or signs.[8] This also reflects the approach taken in most Phase III trials

evaluating targeted or immune-based treatments for stage IV melanoma. Only one recent comparative study (697 patients) has reported the incidence of asymptomatic brain metastases in stage IV patients – 12% using contrast enhanced CT scanning.[9] Although a higher number would likely have been detected using MRI, the clinical utility of detecting small brain metastases detectable only by MRI is unclear particularly with the increasing use of active systemic treatments as initial treatment of brain metastases from melanoma rather than brain directed RT.

Evidence summary	Level	References
One comparative study reported asymptomatic brain metastases on contrast enhanced CT in 12% of patients at diagnosis of stage IV melanoma.	III-2	[9]

Evidence-based recommendation	Grade
Brain imaging with contrast enhanced CT or MRI is appropriate in asymptomatic patients diagnosed with stage IV melanoma.	**C**

3.11.2.5 Molecular analysis

All patients with stage IV melanoma must have documentation of the presence or absence of activating V600 BRAF mutations prior to commencing systemic treatment because of the availability of targeted treatments for patients with these mutations. Analysis of BRAF mutation status can be performed on FFPE tumour tissue using a variety of techniques either as a single BRAF analysis or as part of multi-gene mutation panel assessment in accredited molecular pathology laboratories. The most recently obtained tumour biopsy should be used for analysis, preferably a direct biopsy from a site of stage IV disease or prior stage III disease. Use of a primary melanoma for analysis is not recommended, especially if there is a long time interval between the primary and the diagnosis of stage IV melanoma.

The most common activating V600 mutation, V600E, can be detected in tumour tissue using immunohistochemistry, but this method will miss other potentially targeted inhibitor-sensitive mutations so is of value only if positive.

BRAF gene mutations can be detected in tumour DNA from peripheral blood samples, but at present this technique has a high false-negative rate and is not recommended for routine use.

Practice point

Documentation of the presence/absence of activating V600 BRAF mutations in tumour tissue is required before commencing systemic therapy for stage IV melanoma.

3.11.3 How should patients at each stage of melanoma be followed after initial definitive treatment

How should patients at each stage of melanoma be followed after initial definitive treatment?

3.11.4 What is the ideal setting, duration and frequency of follow-up for melanoma patients?

What is the ideal setting, duration and frequency of follow-up for melanoma patients?

3.11.5 References

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3.11.6 Appendices

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3.12 Follow up after initial definitive treatment

Contents

3.12.1 Systematic review evidence

A systematic review was performed for the following question *How should patients at each stage of melanoma be followed after initial definitive treatment?*. The review did not identify any randomised trials. The recommendations are based on level III and IV evidence.

3.12.1.1 Self-examination

A review of nine clinical practice guidelines by Marciano et al (2014)[1] reveals consensus that patients should be taught skin self-examination and education, which was based primarily on consensus and/or clinical experience. For this recommendation, four guidelines varied in evidence content while five guidelines did not provide any evidence to support this. Education on sun-smart behaviour was recommended by four guidelines.[1]

Successfully implementing self-examination requires patient education on whole-body skin examination with particular attention given to melanoma surgical scars and the corresponding lymphatic drainage areas for in-transit and lymph node recurrence. Patients should also be given education regarding persistent symptoms that may warrant further investigation. In addition, the use of brochures or videos, and the engagement of relatives in the education process may be helpful.[2][3][4][5][6] Randomised controlled trials do not exist. In Australia, patients themselves detect up to 75% of recurrences, while in other countries this can be as low as 20%.[3][4][7][8][9] These data highlight that even with education, there are great differences in patients' individual ability to detect recurrences.[4] Self-examination is recommended following definitive local treatment for melanoma patients of any stage

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3.12.1.2 History and physical examination during follow-up

There is general consensus that the most cost-effective component of a strategy resulting in the detection of the majority of recurrences is careful history taking and physical examination. The detection of distant metastases in patients with early localised disease is unusual and hence a recurrence-risk adjusted approach should be undertaken with patients with higher disease stages undergoing more frequent follow up (see follow-up duration and frequency). For high-risk patients, the history should include questions regarding the existence of persistent symptoms that may warrant further investigation, such as pain, fatigue, weight loss, nausea and vomiting, dyspnoea and headache. Moreover, history and physical skin examination is important for the detection of second primary melanoma following the treatment of stage I/II melanoma.

As with self-examination, history and physical examination includes specific history taking, a full skin examination looking for new primaries, palpation of melanoma surgical scars, and lymphatic drainage areas for in-transit and lymph node recurrence. Apart from patient self-detected relapses, most relapses and secondary

melanomas are detected during physical exams.[8][10] In one large prospective study[8], roughly 50% of recurrences were identified by history taking/physical examination, 80% of which were local recurrences, in-transit metastases, and regional lymph node metastases.[8] Indeed, the vast majority of operable recurrences (96%) are those detected by physical examination.[10][11] In summary, history and physical examinations for patients with stage I to stage III melanoma are the most effective procedure for early recurrence detection.[12][13][11]

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3.12.1.3 Imaging techniques and blood tests during follow-up

Very few patients have metastases identified by the routine use of imaging techniques and blood tests.[14][15] There are no randomised trials indicating that such tests are of value and in any case it would be difficult to prove that the few who survive did so merely because they underwent these tests.

All current clinical guidelines recommendations are based on low-level evidence (case series, diagnostic accuracy or prognostic cohort studies). One guideline reports low yield and significant rates of false-positives, yet still recommends imaging in some cases. Two guidelines recommend using ultrasound in high-risk patients, while another two guidelines with similar evidence do not.[1]

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3.12.1.3.1 Ultrasonography during follow-up

Ultrasonography is a technique that is being used increasingly for high-risk patients with the goal of detecting regional lymph node metastases. However, its usefulness depends entirely on the technical skill and experience of the personnel involved. There is a consensus of opinion that ultrasound is superior to clinical examination of regional lymph nodes, although its survival advantage is unproven.[16] One group obtained a sensitivity of 92.9% for ultrasound compared with only 71.4% for the clinical examination of regional lymph nodes.[17] Their specificity was equally high for both procedures (>98%). Despite the superiority of ultrasound, very few patients benefited by the addition of ultrasound to clinical examination. The reasons cited for this were that although ultrasound was useful in the earlier detection of regional disease or avoidance of unnecessary surgery in 7.2% of patients, 5.9% had deleterious effects such as unnecessary stress caused by repetition of ultrasounds for benign lymph nodes or useless removal of benign lymph nodes. Therefore, the use of ultrasound was advantageous in only 1.3% of patients. Only from a large prospective randomised clinical trial could the efficacy of ultrasound be established, but this would be hardly feasible since about 3000 patients would have to be enrolled. Hence, the routine use of ultrasound in the follow-up of melanoma patients of any clinical stage cannot be recommended.

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3.12.1.3.2 Chest X-ray during follow-up

The use of routine chest X-ray (CXR) exams for the detection of small pulmonary metastases has been investigated. However, false-positive and false-negative findings are frequent. The sensitivity of CXR is poor with reports varying from 7.7% to 48%. A large study of 1969 patients with stage I to stage III melanoma undergoing routine follow up found that only 10/204 relapses were discovered by CXR: the majority (7/10) of which were observed in patients with stage III disease.[13] A large prospective study of 1,235 patients found that only 0.9% of CXRs identified pulmonary metastases, less than 10% of which were amenable to resection, with a false positive rate of 3.1%.[18] A cost-effectiveness analysis using data from the Roswell Park Cancer Institute and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program found that the cost of CXR screening per quality-adjusted life year was $165,000, respectively, in 1996 US dollars.[19] Based on these findings, the investigators suggested reducing the frequency of screening CXR.

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3.12.1.3.3 CT/MRI

Computed tomography and magnetic resonance imaging (MRI) are key investigations for the detection of suspected metastasis based on clinical, lab, or sonographic findings. In addition, they are useful in the monitoring treatment response for patients with stage IV disease.[20] It should be remembered that more than 50% of recurrences are detected by patients themselves or physical examination, hence the use of cross-sectional imaging screening should only be considered for patients at high of systemic recurrence.[2][21][8][22] Indeed, the detection rates for cross sectional imaging of asymptomatic distant metastases vary between 15 and 72%.[8][9][12][23] It should be noted that cerebral metastases are more readily detected by magnetic resonance imaging (MRI) than by CT or FDG-PET/CT.[24]

3.12.1.3.4 FDG-PET

Positron emission tomography (PET) utilises the uptake of radioactively labelled glucose in metabolically active areas to identify metastatic disease. PET scanning is usually combined with computed tomography in a PET/CT scanner, facilitating spatial mapping of metabolically active lesions thereby increasing the diagnostic utility.[25][26] PET/CT exams reveal a high sensitivity (80%) and specificity (87%) for the detection of distant melanoma metastases, compared with conventional CT (51% and 69%, respectively).[26] A recent systematic review by Danielson et al[27] of seven studies was undertaken to assess the diagnostic value of PET as a tool for surveillance in the regular follow-up program of asymptomatic cutaneous malignant melanoma patients. The majority of the 739 patients in the studies were stage IIB and III. The authors concluded that the mean sensitivity of PET was 96% (95% CI: 92-98) and the specificity was 92% (95% CI: 87-95). Overall, PET has a high diagnostic value. However, there were no data available to demonstrate better survival outcomes for patients

as a result of routine PET surveillance.[27] A small non-randomised study by Baker et al (2014)[28] in 38 asymptomatic stage IIIA melanoma patients examined the contribution of routine restaging PET/CT scans in detecting initial recurrence in routine follow-up. After median follow up of 27.5 months, there were 7 relapses: all in transit and regional nodes (n=3) were found by the patients; PET/CT detected 2 asymptomatic recurrences and MRI found 1.[28] There were no data provided to demonstrate whether early detection of asymptomatic recurrences improved survival.[28][11]

Recently, Australian investigators studied the utility of routine PET/CT for 170 patients with stage IIIA-C melanoma using schedules based on sub-stage-specific relapse probabilities.[11] Relapses were identified in 38% patients, of which 69% were asymptomatic. Positive predictive values of individual scans were 56–83%, while negative scans had predictive values of 89–96% for true non-recurrence. A negative PET at 18 months had negative predictive values (NPVs) of 80–84% for true non-recurrence at any time in the 47-month (median) follow-up period. Of relapsed patients, 33 (52%) underwent potentially curative resection was undertaken for 52% patients, although few patients (16%) remained disease-free after 24 months. While the NPV of a negative PET may be reassuring, these data do not conclusively demonstrate that survival was improved by routine PET /CT scanning.[11]

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3.12.1.4 Measurement of S100B serum levels during follow-up

Serum levels of S100B correlate with tumour load and the evidence has been reviewed previously.[20] In summary, increasing S100B levels over time may signify disease progression. However, delayed processing and warm storage temperatures of blood samples can result in falsely elevated levels. Thus, it is recommended to first repeat the test when elevated before undertaking investigations in search of regional nodal and distant metastases. As tumour marker, S100B displays a sensitivity of 86–91%, specificity[29][30] and its use has been recommended elsewhere.[20] While serum S100B levels may portend recurrence, there are no data demonstrating superior survival outcomes for patients undergoing routine S100B testing in follow-up. The use of serum LDH or melanoma-inhibitory activity (MIA) protein in follow-up for the detection of asymptomatic melanoma recurrence has been reviewed by Fields and Coit (2011).[31] Abnormal blood tests were rarely the first sign of metastases. Low sensitivity, specificity, and accuracy for general laboratory profiles make them futile in the detection of subclinical recurrence and their roles are yet to be defined. Hence, routine serum S100B, LDH or other blood testing for asymptomatic stage I to stage III melanoma patients cannot be recommended.

3.12.1.4.1 FNA, core biopsy and lymph node biopsy

FNA is the current standard method to confirm the presence of suspected nodal metastases for lymphadenopathy identified after definitive local treatment of cutaneous melanoma.[32][33] Ultrasound guidance should be used as the diagnostic yield is superior, particularly for small lymph nodes <10mm in size. Core biopsy has higher sensitivity and specificity compared with FNA and should be considered where FNA is negative but clinical suspicion remains high. There is no role for routine lymph node biopsy during follow-up of asymptomatic patients.[34] Routine ultrasound for clinically negative lymph node basins cannot be recommended.

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3.12.2 Evidence summary and recommendations

Evidence summary	Level	References
The majority of patients detect their own recurrence if they have received a thorough explanation of the signs and symptoms of recurrences and new primary melanomas.	IV	[7], [5], [6]
* History and physical examination are the most effective methods for the detection of early, treatable melanoma recurrence. ■ Ultrasound is most effective way to detect nodal recurrence. ■ FNA and core biopsy are accurate tests to confirm regional melanoma recurrence. ■ PET/CT is a useful test for the detection of melanoma recurrence during follow-up. ■ There are no data demonstrating superior survival outcomes as a result of routine imaging, even for patients at high risk of melanoma recurrence. ■ Low sensitivity, specificity, and accuracy for general laboratory profiles, S100, and MIA make them futile in the detection of subclinical recurrence and their roles are yet to be defined.	IV	[7], [5], [6]
Studies examining the benefit of routine cross-sectional imaging or blood tests over self-examination or physical examination alone include heterogeneous patients groups and are characterized by low evidence levels.	III-3, IV	[8], [9], [12], [13], [16], [17], [29], [30], [18], [23], [27], [28]

Evidence-based recommendation	Grade
Self-examination is recommended following definitive local treatment for melanoma patients of any stage.	**C**

Evidence-based recommendation	Grade
History and physical examination by a patient’s preferred medical practitioner should be undertaken for the detection of early, treatable recurrence following definitive treatment of stage I to stage III melanoma.	**C**

Evidence-based recommendation	Grade
Routine blood or radiological investigations are not recommended for the follow-up of asymptomatic stage I to stage IIB melanoma patients after definitive local treatment.	**C**

Evidence-based recommendation	Grade
Routine radiological investigations every 3-12 months may be considered for the first three years of follow up after definitive local treatment of stage IIC and III melanoma where detection of recurrence would allow early commencement of systemic therapy. However, there are currently no high-quality data that early detection and treatment of recurrence improves survival.	**C**

Practice point
Skin self-examination by patients is essential and they should be taught the process. Routine follow-up by the patient's preferred health professional may be appropriate to emphasise sun smart behaviour and perform skin checks, especially in 'hard to see' areas.

Practice point
Routine radiological imaging PET/CT or CT may be considered for patients with stage IIC or III melanoma for the early detection of recurrence, particularly in the context of a clinical trial. However, patients should be counselled regarding the potential risks of false positives, anxiety, and the risks of radiation including thyroid cancer and cataracts.

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3.13 Ideal frequency and duration of follow-up

Contents

3.13.1 Systematic review evidence

Two randomised studies were identified, Murchie et al[1] and the MELFO study[2] to answer the question *What are the ideal settings, duration and frequency of follow-up for patients with melanoma?*. The remaining studies are retrospective cohort studies of timing and patterns of recurrence.

3.13.2 Follow-up setting

Current guidelines world-wide do not specify where routine follow-up should take place or who should do it.[3][4] However, it is becoming accepted by most [5][6][7] but not all [8][9][10] that patients themselves rather than doctors are likely to detect their own recurrence. Those studies reporting a high patient-detection rate attribute this to patients receiving thorough explanations of the signs and symptoms of recurrences and new primary melanomas. Despite such explanations, it is obvious that the ability of individual patients to detect recurrence varies. Some can identify recurrences that are not discernible to doctors, while others can be unaware of a large tumour mass. The existence of these latter patients perhaps explains the reticence of some centres to forego routine follow-up.

In Australia, with its heightened awareness of the disease, up to 75% of patients detect their own recurrences.[11] World-wide the mean percentage is 62%.[12] The UK Medical Research Council has designed a 'framework for the design of an integrated follow-up program'.[13] One technique employed was to interview patients to determine their preferred follow-up requirements. Most supported follow-up by general practitioners, and felt that the main purpose of follow-up was reassurance that no recurrence was present.[13] However, there was concern over travelling times, costs, brevity of consultations, and poor continuity. Nearly all queried the

experience and skill of the general practitioners and said training would be vital, with rapid access to specialist advice if necessary. In the study by Murchie et al,[1] the goal of patient reassurance was achieved by general practitioners offering phone consultations, thus avoiding frequent follow-up exams. Total skin examination, instruction in self-examination and the provision of more information were seen as desirable at visits to general practitioners. Other studies assessing patients' opinions of the value of follow-up found that most considered routine follow-up worthwhile, with only a few considering that it was not.[4][14] While favouring follow-up, more than half the patients in these studies reported anxiety before each visit.

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3.13.2.1 Evidence summary and recommendations

Evidence summary	Level	References
There is consensus that follow up with a medical professional (GP, dermatologist, surgeon or medical oncologist) is beneficial for patients treated for melanoma in order to provide instruction for skin self-examination, examination for recurrence or new primary melanoma, and psychosocial support.	IV	[14], [13], [1], [4]

Evidence-based recommendation	Grade
Routine follow-up by the patient's preferred doctor may be appropriate to emphasise sun smart behaviour and perform skin checks.	**C**

Practice point
It may be beneficial for medical professionals conducting follow up examinations for melanoma patients to be familiar with skin examination and dermatoscopy.

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3.13.3 Follow-up duration and frequency

Standardized follow-up is considered an important component in the care of melanoma patients, aiming at early detection of recurrences and secondary melanomas. In the past, the choice of intervals between routine follow-up visits has been mostly arbitrary, but all suggested schedules have stipulated more frequent visits for patients with more advanced disease.[15] A systematic review by Cromwell et al[16] of current literature and consensus guidelines (n=104 studies) determined the variation in clinician practice patterns with respect to stage-specific

surveillance of melanoma patients by country and physician speciality. Surveillance recommendations varied according to disease stage, country of origin, and physician speciality, and were related to the frequency of examination and use of diagnostic imaging and laboratory tests. There was a general consensus among countries and specialities for annual surveillance, self-examination by all patients, and that patients with high-risk stage III disease require regular clinical examinations. Significant differences were noted in the surveillance practices among countries; the most significant of which noted to surveillance intervals following the treatment of stage I disease. Recommendations for surveillance intervals and diagnostic imaging and laboratory evaluations varied by speciality. The greatest variation was seen in the recommended frequency follow-up visits for patients with stage I disease, which ranged from 2 to 4 times per year.[17][8][4][16] However, a review of current melanoma follow-up care and treatment from various centres around Germany, by Livingstone et al[18], found that adherence to these guidelines is poor: 13% perform reviews more frequently than recommended, while 31% perform follow up less frequently.[18] Moreover, 150/668 patients underwent diagnostic imaging procedures, despite these not being recommended.[18] Similarly, an Australian case series of 3747 stage I and II melanoma patients found that only 34% of stage I patients and 14% of stage II patients had the number of follow-up visits recommended in the Australian and New Zealand guidelines (2008) at a melanoma centre.[19]

There is broad consensus for 5 or 10-year, risk-adapted follow-up with increasing intervals between exams over time. Understanding recurrence patterns and hazard rates provides a rational basis for the timing and duration of follow up aimed at detecting melanoma recurrence or new primary melanoma. Hazard rates for recurrences have been reviewed in the German Guidelines and reveal differences between stages I–III within the first year after primary diagnosis. At stage I, hazard rates remained consistently low over a 5-year period. At stages II–III, there was an increased recurrence risk in year 1–2, which, after 3 years, again approached the same hazard rate as stage I. The highest recurrence rates were observed at stage III within the first year, followed by an approximation to stage II.[8] A more recent analysis confirmed these findings.[20] Stage IA showed consistently low hazard rates during the entire follow-up period of 10 years. After a period of 10 years, hazard rates at stages IB–III converge with stage IA rates.[21] Analyses of stage I–II patients with negative sentinel lymph nodes after sentinel lymph node biopsy revealed recurrences in 8.9%–10.1%, 78 % of which occurred within 18 months.[22] Recently, a large case series from Duke University of 11,615 patients with primary melanoma, revealed that 4,616 (40%) had at least one recurrence during long-term follow-up.[23] The risk of overall recurrence peaked at 12 months, where subsequent metastases appeared at progressively shorter intervals, with the time to development of second and third metastases peaking at 6.2 and 2.6 months, respectively. The risk of recurrence decreased over time, but did not reach zero. The most common site of initial recurrence was distant skin or nodes (59%). The second most common site for metastases was other distant metastases (16.5%), followed by local skin (16.1%) and lung (8.4%). There was an association between survival and the initial site of recurrence; the best survival was associated with local recurrence follow by regional nodal recurrence.

Overall, studies in stage I–III disease show that 47% of recurrences occur within the first year after diagnosis, 32% within the second year [8] and 80% within the first 3years.[24][25][26][27][17][11][8] Median time to recurrence of locoregional or regional lymph node metastases is consistently earlier than distant metastases (approximately 24 months).[28] For stage IIIC, all metastases occurred within 24 months.[29] The risk for recurrence for all stages after 10 years decreases to approximately 1%.[20][30][17][11] These data suggest discontinuation of follow-up after 10 years is warranted. Shorter follow up duration of 5 years has been proposed by some groups.[11][31] However, 20% of recurrences may occur more than 5 years after primary diagnosis for stages I and II.

Follow up beyond 10 years has been advocated by some groups due to the ongoing increased risk of new primary melanomas that may even occur more than 30 years after the diagnosis.[32][33][34][35] However, most secondary melanomas occur within the first two years after the primary diagnosis of melanoma, with a marked drop in incidence thereafter suggesting little benefit for long-term extension of follow up.[32][34][36] Australian data demonstrate that patients who develop one melanoma are at substantially increased life-long risk of developing second primary melanoma. This most pronounced for patients initially diagnosed under the age of 65 years.[37] Patients with additional risk factors (dysplastic nevus syndrome, family history) should be provided access to long-term dermatologic exams in addition to regular follow-up for at least 5 years.

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3.13.3.1 Evidence summary and recommendations

Evidence summary	Level	References
The peak risk period for recurrence is the first 12-24 months after the treatment of stage I-III melanoma, the risk being lowest for stage IA and highest for stage III. At least 80% of recurrences occur with 3 years of diagnosis of primary melanoma, with less than 5% of recurrence occurring after 10 years. For primary melanoma, the majority of recurrences are locoregional or regional lymph nodes. For stage III melanoma, recurrence more than two years after complete surgical removal of disease is rare.	IV	[17], [11], [8], [20], [24], [25], [26], [27], [30], [31]
The risk for subsequent melanomas for melanoma survivors is approximately 5 times higher than the general population. The lifetime risk remains constant.	IV	[8], [20], [32], [35]

Evidence-based recommendation	Grade
Risk adjusted follow up looking for recurrence based on stage at presentation should be considered over a time period of 5-10 years for stages I-II melanoma. For surgically resected stage III melanoma, the most intensive follow up should be for the first 3 years.	**C**

Evidence-based recommendation	Grade
Melanoma survivors should be made aware of their risk of developing further primary melanomas, and of the consequent need for careful lifelong skin surveillance.	**C**

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3.13.4 Frequency of follow-up for melanoma patients

The issue of adequate follow-up intervals plays a crucial role as to the question whether specific workup for metastasis may be rationally employed to improve mortality, morbidity, and quality of life in affected patients. The assumed risk for recurrence at a given point in time represents an essential parameter in these considerations and has been reviewed in the German Guidelines.[38] Some authors have suggested that intensified follow-up might be reasonable, as long as 95% of expected metastases have not been detected.[29]

In general, cost-benefit analyses have to be taken into account as well when considering at what point the risk for metastasis warrants an intensified follow-up program. Present studies mainly consider the cost of various procedures for metastasis detection in various schedules and patient groups.[12][17][18] There are no explicit cost-benefit analyses with respect to time-related threshold values for recurrence risks. Basseres et al[10] showed that, in 66% of cases, the interval between detected relapse and the previous follow-up exam was up to 4 months.'[10] These data suggest that follow-up intervals in patient groups at significant risk for recurrence should not exceed 3–4 months, provided it is desirable to identify asymptomatic recurrence.[10] However, authors from the Melanoma Institute of Australia (MIA) analysed the time-course a predictors for recurrence among over 3000 patients with stage I-II cutaneous melanoma.[39] Using these data, they evaluated the potential delay in diagnosis of recurrence or second primary melanoma using two different follow-up schedules: first was the NHMRC 2008 guidelines schedule; and the second involved follow-up annually for 10 years (stage I); every 6 months for 2 years, then annually for 8 years (stage IIA); or every 4 months for 2 years, every 6 months during year 3, then annually for 5 years (stages IIB and IIC).[39] This study assumes detection rates of 75% by patients themselves. For every 1,000 patients, the second schedule required 3000 fewer visits and only a small number of patients would experience a delay in the detection of recurrence or new primary melanoma. This proposed less frequent and a stage-based follow up schedule is being prospectively evaluated in a randomised study: the Melanoma Follow Up (MELFO) trial.[2] One-year results were recently reported for 180 patients and found that the less frequent follow up group reported significantly less cancer-related stress response symptoms.[2] The recurrence rate was 9% in both groups, mostly patient-detected and not physician-detected while costs of 1-year follow-up were reduced by 45% in the less frequent follow up group.[2]

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3.13.4.1 Evidence summary and recommendations

Evidence summary	Level	References
Intervals between routine visits are mostly arbitrary. However, all studies stress that the more advanced the disease, the more frequent the visits need to be. The interval between follow up exams and recurrence are in the order of 4 months or less. No other tests have significant value in patients with localised disease. The available data suggest that less frequent follow up is not detrimental for overall survival.	IV	[40], [41], [42], [43], [44], [45]

Evidence-based recommendation	Grade
Follow-up intervals: ■ Stage I: follow-up annually for 10 years ■ Stage IIA: every 6 months for 2 years, then annually for 8 years ■ Stage IIB and IIC: every 3 to 4 months for 2 years, every 6 months during year 3, then annually for 5 years. ■ Stage IIIA-C: every 3 months for 2 years, every 6 months during year 3, then annually for 5 years.	**C**

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3.13.5 Value of follow-up

Some have questioned the value of any routine follow-up. Review of the advantages and disadvantages does not provide convincing evidence that regional control, quality of life or overall survival is increased through intense surveillance. Three studies showed no survival difference when comparing who detected recurrence.[9] [4][46] Even if patient survival were increased due to the metastases being detected by a doctor at a routine follow-up visit rather than by the patients themselves, it would be hard to prove that this occurred as a result of the follow-up. Interpretation of data would be thwarted by possible lead-time bias. This latter problem was one flaw of the sole prospective study to date that claimed to demonstrate the efficacy of routine follow-up.[47] The reasons for the lack of valid prospective randomised trials assessing the value of routine follow-up are numerous, but foremost among them may be patient reluctance to accept a 50% risk of being assigned to the arm not receiving ultrasound or other follow-up. Enrolment of large numbers of patients with monitoring in excess of 15 years would be required because any difference in end-points would be small. There would also be a problem in determining recurrence rate and survival in patients not receiving routine ultrasound or follow-up.

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3.13.5.1 Evidence summary and recommendations

Evidence summary	Level	References
There is a lack of valid prospective studies of the efficacy of routine follow-up. No study has demonstrated an improvement in survival due to intense routine surveillance. There may be some advantage in terms of patient reassurance and the detection of new melanomas	IV	[46], [4], [9], [47]

Evidence-based recommendation	Grade
While it is important that clinicians weigh up the advantages and disadvantages of undertaking routine follow-up, individual patient's needs should be considered before appropriate follow-up is offered.	**C**

3.13.6 Notes regarding the recommendations

The recommendations given above are based on the best evidence currently available, but it is acknowledged that this is low-level evidence. Individual patients may prefer more frequent follow-up for reassurance, while others may prefer less frequent follow-up because of the anxiety provided by the follow-up visits or the time and expense associated with attendance for follow-up. Routine radiological follow up for stage IIC and III melanoma may detect recurrence sooner, possibly leading to better outcome by allowing treatment with drugs, such as immunotherapy drugs, to start earlier. However, while early drug treatment of recurrent melanoma might improve survival, there is currently no evidence showing this. Thus, the recommendations are a reasonable compromise which, reinforced by good patient education, should ensure that most melanoma recurrences are detected promptly and new primary melanomas are diagnosed early.

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3.13.8 Appendices

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4 Treatment of satellite and in-transit metastases

Contents

4.1 Introduction

Traditionally, in-transit melanoma was defined as dermal or subcutaneous recurrence arising between the primary lesion and the draining lymph nodes and lesions within 2 cm of the scar were defined as satellite lesions although both are believed to represent arrest of tumour emboli in the dermal or subcutaneous lymphatics. In the new AJCC staging system, satellite or in-transit metastases are classified as N1,2,3c disease depending on the extent of lymph node involvement.[1]

Up to 10% of patients will develop in-transit metastases often as a first site of recurrence. The median time to presentation is approximately 12-18 months from time of definitive excision of the primary lesion.[2][3] The development of in-transit metastases is related strongly to advancing age, increasing tumour thickness, primary melanoma ulceration, mitotic rate and the presence of lymphovascular invasion as well as regional lymph node involvement (either clinically occult or apparent). Outcome is related to similar primary tumour characteristics, lymph node status and disease free interval.[2][4]

In a large Australian study of 505 patients with in-transit metastasis defined as more than 5 cm from the primary lesion, 190 had in-transit metastasis as a first presentation of recurrence. Eleven percent had a local recurrence prior to the in-transit melanoma, 42% developed regional recurrence at any time and 10% had a distant recurrence previously or concurrently with development of the in-transit metastasis.[3]

The extent of in-transit recurrence, the pace of disease and association with regional and distant spread is highly variable and makes the management of this condition difficult. The quality of evidence to guide management given the heterogenous nature of this condition is limited.

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4.2 Systematic review evidence

A systematic review was undertaken to identify evidence on effective treatments for satellite and in-transit metastatic melanoma. The evidence identified from the systematic review was low level; the highest level being level III-I. No high-level evidence was identified on which to base recommendations.

4.2.1 Sentinel node biopsy

Staging of patients with in-transit recurrence by sentinel node biopsy (SNB) is now incorporated in the new AJCC staging system and may be considered for patients undergoing surgical excision. Lymph node involvement detected either by clinical examination or SNB indicated poorer prognosis.[1] Five year survivals for patients with N1c (no lymph node involvement), N2c (one lymph node involved) and N3c (more than one node involved) were respectively 81%, 69% and 52%.[1] In a retrospective review, elective lymphadenectomy had no impact on outcome.[3]

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4.2.2 Local therapies

In addition to surgery other local therapies include laser destruction, injection of intra-lesional agents including BCG, Interleukin-2, PV-10 (rose Bengal 10%) and interferon alpha as well as a variety of topical agents including imiquamod and diphenylcyclopropenone (DCP). PV-10 followed by radiotherapy showed a complete response rate of 64% but time to in-field recurrence was short.[5] Currently only DCP is available for use in Australia. A small prospective nonrandomised study of 58 patients found a complete response rate of 22% and partial response rate of 39%[6] and treatment was well-tolerated.

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4.2.3 Isolated limb perfusion and isolated limb infusion

For patients with extensive in-transit recurrence, the standard of care has been isolated limb perfusion (ILP). This is a technically demanding procedure (the affected limb is isolated, maintained on a cardiac bypass machine and perfused with a heated chemotherapy solution (melphalan and actinomycin D). A complete and partial response rate of over 80% (73%-90%) was found amongst studies of ILP reporting more than 100 patients.[7][8][9][10][11][12][13][14][15][16]

Morbidity of moderate extent (Wiederbank acute limb toxicity score 3) is common (5-40%) as was severe skin and soft tissue compromise (Wiederbank acute limb toxicity score 4) 3-10%. Amputation due to severe limb toxicity occurs in 1%.[7][13][14][15][16][17] In view of the toxicity and resources necessary for ILP, Thomson and colleagues from the Melanoma Institute of Australia introduced isolated limb infusion (ILI).[18] This is a technically much easier procedure requiring far less resources and with reduced toxicity with Wiederbink acute limb toxicity scores of 3 (26- 39%) and 4 (3-13%).[7][12][19][20][21][22]

Isolated limb perfusion and ILI have not been formally compared. Non-randomised studies are not strictly comparable but indicate lower overall and complete response rates for ILI but with significantly reduced toxicity. The most mature data on ILI comes from the Melanoma Institute of Australia who reported a CR of 38% and a PR of 46%. Grouped data from other Australian centers report similar outcomes, CR 33% and PR 42%. Wiederbink acute limb toxicity Grade 3 and 4 was seen in 30% and median survival was 44 months (88 months in responders).[12][23]

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4.2.4 Systemic therapy

For patients with extensive and or recurrent disease, systemic therapy as for patients with disseminated disease may be appropriate. See Systemic therapy for stage 3C unresectable and stage 4 melanoma

4.2.4.1 Future developments

The role of newer strategies such as intralesionally delivered Talimogene laherparepvec a genetically modified oncolytic herpesvirus engineered to produce GM-CSF are yet to be determined in the current setting of active systemic drug therapies. The effectiveness of this strategy which leads to destruction of injected lesions as well as an immune-mediated tumoricidal effect on un-injected in-transit metastases as well as distant metastases offers the prospect of long term control.[24] Studies of combined Talimogene laherparepvec injected intra-lesionaly and PD-1 immunotherapy are currently underway.

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4.3 Evidence summary and recommendations

Evidence summary	Level	References
Topical diphenylcyclopropenone is easily administered and has limited toxicity. In up to 50% of selected patients may experience a local response.	III-2	[6]
Isolated limb infusion (ILI) provides high rates of objective response (approximately 80%) with limited toxicity. Limb toxicity with ILI is considerably less frequent and severe than with ILP.	III-2	[12]

Evidence-based recommendation	Grade
Sentinel node biopsy provides important prognostic information and should be performed if surgical excision of in-transit recurrence is planned.	**C**

Evidence-based recommendation	Grade
Limited disease may be treated with topical diphencyprone otherwise isolated limb infusion may be appropriate.	C

Evidence-based recommendation	Grade
Isolated limb infusion is preferred to isolated limb perfusion despite slightly reduced effectiveness because of less frequent and less severe toxicity and reduced resource utilisation.	C

Practice point
The role of surgery has not been evaluated prospectively but supported by limited poor quality retrospective evidence and current practice surgical excision of limited disease is appropriate. Repeat excision is appropriate for patients with limited disease.

Practice point
Radiotherapy is particularly valuable for palliation of larger symptomatic lesions.

Practice point
For patients with extensive, recurrent or progressive disease, systemic therapy (targeted and immune-therapies) is appropriate. Patients should be considered for trials. See Systemic therapy for stage 3C unresectable and stage 4 melanoma

Practice point

Sentinel node biopsy provides important prognostic information and should be considered for patients presenting with in-transit metastases who are to undergo complete surgical excision.

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4.4 Issues requiring more clinical research study

At the present time the role of systemic targeted and immune therapies for patients with melanoma is undergoing intense evaluation. The management of patients with in-transit recurrence will be directly impacted by these studies.

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5 Treatment of macroscopic nodal metastases

Contents

5.1 Introduction

At the time of writing of this guideline, surgery remains the standard of care for patients with symptomatic or imaging detected lymph node field relapse of melanoma. In a small proportion of patients (typically <5%), the extent of the disease is such as to preclude complete surgical resection. In this situation radiotherapy is an option, however systemic therapy with targeted therapies or immune checkpoint inhibitors are increasingly an option. The possibility of a neoadjuvant approach to these patients with extensive disease has been proposed but at the present time must remain an investigational approach.

Notwithstanding the enormous strides that have been made with targeted therapies and immune checkpoint inhibitors for patients with metastatic disease, there is currently no evidence that these agents have a definitive role in the management of patients with lymph node field relapse. Numerous studies investigating a role for these agents are currently underway and where appropriate patients should be referred for possible participation in these studies.

Even with the widespread use of sentinel node biopsy (SNB) approximately 50% of patients with Stage III disease present with symptomatic, usually palpable or imaging detected lymph node field recurrence.[1] These patients include those who did not undergo SNB, patients who had a false negative SNB and patients presenting with lymph node field relapse and no known primary lesion. Lymph node field recurrence is the commonest and usually first site of recurrence of melanoma in patients not undergoing a SLNB. Patients with thick melanomas who did not undergo a SNB have a median time to presentation with a lymph node field recurrence of 9 months and for patients with intermediate thickness melanoma and no sentinel node biopsy around 19 months. However lymph node filed recurrence many years after treatment of a primary lesion are a well-recognised but uncommon phenomenon.[1] Surgical management of patients presenting with macroscopic nodal disease results in a lymph node field results in long term control in nearly 50% of patients, however this varies widely depending on a number of factors including time since treatment of the primary lesion and features of the primary melanoma including thickness and ulceration.[1] The reported ten year survival of patients in the AJCC database is approximately 45% for patients with Stage III B disease (1-3 nodes involved)and approximately 25% for patients with Stage III C disease (more than 3 nodes involved).[2] As there is still a high risk of failure with surgical therapy there is great interest in the addition of effective systemic therapies to the management of these patients either in the adjuvant or neoadjuvant setting and clinical trials are currently underway.

The diagnosis should be confirmed pre-operatively preferably, by ultrasound guided fine needle aspirate (FNAC)) even for palpable lymphadenopathy rather than open biopsy (or core needle biopsy) which may potentially contaminate the operative site.

The risk for patients with clinical stage 3B/C disease of occult disseminated disease at presentation is approximately 20%. Preoperative staging preferably by PET-CT and MRI brain is therefore indicated.[3] Alternatively CT may be used. PET/CT however has superior sensitivity and specificity for staging compared to other imaging modalities. MRI brain is superior to standard CT brain.

Tumour markers (LDH, S100 etc) have not been shown to be particularly sensitive or specific in staging patients with stage III B/C disease nor useful in planning treatment or predicting outcome and are not recommended.

Practice point

Patients with macroscopic nodal disease should have the diagnosis confirmed preoperatively by image guided fine needle aspiration cytology and undergo staging with whole body PET-CT and MRI brain or CT Brain, Chest Abdomen and Pelvis.

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5.2 Systematic review evidence

Extensive observational data indicates surgical management of the lymph node field by radical lymphadenectomy results in long term control in up to 50% of patients.[2] There is limited data available as to the extent of the surgery. Limited and indirect evidence favours radical comprehensive surgical procedures over less aggressive approaches.[4] Special situations include patients presenting with lymphadenopathy and no prior history of a primary lesion (unknown primary). These patients achieve results comparable or better to those with a recognised primary lesion with standard surgical management.

5.3 Surgical treatment

Complete clearance of the involved lymph node field is indicated. There is little data available comparing radical clearance with lesser procedures. Higher rates of local recurrence and potentially worse survival have been noted following inadequate surgery.[4] In a number of retrospective studies, the adequacy of the surgical procedure as determined by the number of lymph nodes removed and performance of the surgery in a high volume institution were associated with reduced risk of lymph nodes field relapse and distant relapse.[5][6][7][8] More recently the Lymph Node Ratio (the number of involved to uninvolved nodes) has been shown to be related to both survival and regional recurrence presumably reflecting the completeness of the lymphadenectomy.[7][9][10][11]

5.3.1 Cervical lymphadenectomy

The surgical options for management of cervical lymphadenopathy include radical neck dissection (removal of all nodes in levels I-V including sterno mastoid muscle, accessory nerve and internal jugular vein), extended radical (includes a superficial parotidectomy in addition), modified radical neck dissection (removal of all nodes in levels I-V with preservation of all or some of sterno mastoid muscle, accessory nerve and internal jugular vein) or selective node dissection (removal of less than levels I-V usually with preservation of major structures). In addition resection of occipital/retro-auricular nodes is indicated for primary melanomas located behind the plane of the external auditory canal, patients who had lymphatic mapping to the area but no SLNB found or patients with involved lymph nodes in this region.

Patients with a parotid lymph node field recurrence have a risk of upper cervical lymph node involvement of up to 20%. Surgical management of parotid lymphadenopathy should include parotidectomy and an upper level cervical lymphadenectomy (levels 1B, 2, 3, and upper 5 and possibly 1a).

Practice point

Patients with a parotid lymph node recurrence should undergo a superficial parotidectomy and upper neck dissection (levels 1B, 2, 3, and upper 5 and possibly 1a).

In principle the sterno mastoid muscle, accessory nerve or internal jugular vein should only be removed if involved with tumour or to facilitate complete resection. The role of selective lymphadenectomy is undetermined. At present for limited volume disease it appears to offer similar rates of regional and distant control to more aggressive procedures however for patients with more extensive disease i.e. N2, N3 disease higher rates of local recurrence in particular have been noted.[12][13]

5.3.2 Axillary lymphadenectomy

The standard procedure for axillary lymph node involvement is a complete level 1-3 lymphadenectomy which may include resection of the pectoralis minor muscle (to facilitate clearance of the superior axilla), intercosto-brachial nerve(s) and usually medial pectoral nerve dependent on the extent of disease and body habitus. Less extensive procedures may be associated with higher rates of regional recurrence.[14]

5.3.3 Inguinal lymphadenectomy

The surgical management of inguinal lymph node field relapse is controversial with proponents arguing for inguinal lymphadenectomy or combined inguinal and pelvic lymphadenectomy.[15][16] Pre-operative staging should involve a CT scan or PET / CT scan of the inguinal and pelvic lymph node fields to exclude the presence of pelvic lymph node involvement as 25 to 50% of patients undergoing combined inguinal and pelvic

lymphadenectomy will have pelvic lymph node involvement.[15][17] Unfortunately the sensitivity and specificity of CT scanning in this situation is limited and there is limited data on the effectiveness of PET / CT scanning.[18] [15] Intraoperative assessment of the risk of pelvic lymph node involvement based on femoral canal or Cloquet's node status is unreliable. Tumour volume as determined by increasing number and size of inguinal nodes is associated with an increased risk of pelvic lymph node involvement but is of limited practical value for most cases.

Hesitation around recommending combined inguinal and pelvic lymphadenectomy reflects concerns about undertaking a more extensive and possibly more morbid procedure in the absence of a definite survival advantage. Unproven concerns about worse lymphoedema and poorer quality of life with the combined procedure has led most authorities to recommend inguinal and pelvic lymphadenectomy only for proven pelvic involvement or the presence of extensive inguinal disease. A prospective long term evaluation of symptoms, quality of life and limb volumes found no differences between inguinal and combined inguinal and pelvic lymphadenectomy. There is an ongoing randomised controlled trial evaluating the role of inguinal versus ilio-inguinal lymphadenectomy in this situation.[19] This study is a proof of principle study that less extensive surgery is safe when the PET / CT scan is negative in the pelvic area. It is a lead into other surgical extent de-escalation studies, especially relevant in the era of impending effective neoadjuvant and / or adjuvant therapy.

5.3.4 Unknown primary melanoma

In approximately 10-15% of patients with palpable lymphadenopathy the site of the primary lesion cannot be identified. Possible explanations include a regressed primary melanoma or a melanoma arising within the lymph node itself. A complete skin examination should be performed and the pathology of any previous skin lesions reviewed.These patients should be worked up and treated in a similar fashion to patients with a recognised primary lesion. The outcomes for these patients is at least as good as for patients with an identifiable primary lesion.[20][21][22][23][24][25]

5.3.5 Uncommon lymph node recurrences

Occasionally patients may present with disease in the epi-trochlear or popliteal fossae. Palpable disease in these lymph node fields may be associated with involvement of the inguinal or axillary lymph node fields and should be investigated prior to resection. In a small number of cases patients may present with disease just outside the axillary or inguinal lymph node fields. Consideration should be given to resecting the palpable recurrence, the adjacent lymph node field and the intervening tissue (in continuity resection).

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5.4 Adjuvant therapy

5.4.1 Adjuvant radiotherapy

Patients at high risk of lymph node field relapse after lymphadenectomy (at least 25%) include those with multiple nodes involved (1 parotid, >2 cervical or >3 axillary or inguinal), large lymph nodes (>3 cm) or extensive extra-capsular spread of tumour.[26] Adjuvant radiotherapy reduces the risk of lymph node field relapse by approximately 50% but does not improve survival. In addition radiotherapy is associated with worse long term regional symptoms and increased lymphoedema in the lower limb.[17] Patients who develop an isolated lymph node field relapse after lymphadenectomy alone can often be managed successfully by a combination of surgery and radiotherapy.[17][27]

5.4.2 Adjuvant systemic therapy

The use of adjuvant systemic therapies at the present time is highly controversial. Currently routine systemic therapy after lymphadenectomy cannot be recommended. Interferon alpha 2B (four week high dose induction therapy followed by 11 months maintenance therapy) is associated with a small improvement in survival (3% at five years) but with potential significant toxicity.[28] Initial results from a trial of ipilimumab (10 mg/kg) resulted in a modest improvement in survival but again at the risk of significant toxicity. Early data from a number of studies of BRAF and MEK inhibition and anti-PD-1 immunotherapy are encouraging but mature data is not yet available.[29][30][31]

5.5 Evidence summary and recommendations

Evidence summary	Level	References
Lymphadenectomy provides long term control in up to 50% of patients with Stage III B and III C disease.	II	[2]

5.5.1 Recommendations

Evidence-based recommendation	Grade
Complete lymphadenectomy is recommended for patients with palpable or imaging detected lymph node field recurrence.	**C**

Practice point

Complete lymphadenectomy results in improved regional control over lesser procedures.

Practice point

All patients with Stage III B/C disease should be presented at a multidisciplinary management meeting.

Practice point

These high risk patients should be offered the opportunity to enrol in systemic adjuvant or neoadjuvant therapy trials.

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5.7 Appendices

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5.1 Treatment of melanoma brain metastases

Melanoma has a high propensity to metastasise to the brain. Up to 50% of patients with stage IV disease will develop brain metastases during the course of their illness (25% of patients have them at initial diagnosis of stage IV)[1] and these are associated with a poor prognosis, with a median overall survival (OS) of 2.8 to 4 months.[2][3][4] Control of brain metastases is important since its progression often leads to deterioration in neurological function and quality of life and/or neurologic death.

This section covers the following:

- Role of systemic drug therapy in the management of advanced melanoma patient with brain metastases
- Surgical approach to brain metastases for patients with advanced melanoma
- Role of radiotherapy in the management of advanced melanoma patient with brain metastases
- Treatment approaches to brain metastases: Summary of recommendations

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5.2 Systemic drug therapy for patients with brain metastases

5.2.1 Evidence

What is the role of systemic drug therapy in the management of patients with advanced melanoma brain metastases?

Brain metastases are diagnosed in more than 50% of patients with advanced melanoma and are associated with a poor prognosis, with a median overall survival (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 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 progression-free survival (PFS) for the two cohorts were 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 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 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 was 21% versus 46% with >4 brain metastases 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 of 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 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, it is strongly recommended that patients be discussed by an expert multidisciplinary team of clinicians including a neurosurgeon, radiation oncologist and medical oncologist to determine the optimal combination or sequencing of both local therapy (surgery and stereotactic radiosurgery) and systemic therapies. Whole brain radiotherapy is now rarely used to treat brain metastases, usually reserved as last-line palliative therapy.

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5.2.1.1 Evidence summary

Evidence summary	Level	References
Combined therapy with BRAF and MEK inhibitors induces 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 56% and 55% intracranial response rates in the Australian Brain Collaboration and the CheckMate 204 studies, respectively, with 6-month progression-free survival rates of 53% and 67%, respectively).	III-1	[5], [6]

Practice point

Systemic drug therapy is effective 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 from a radiation oncologist and a neurosurgeon.

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5.2.2 References

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5.3 Surgical treatment of brain metastases

5.3.1 Evidence

What is the recommended surgical approach to brain metastases in patients with advanced melanoma?

Safe resection of brain metastases relates largely to their location within the brain. The vast majority of brain metastases occur in locations where the risk of new or worsening neurological deficit following surgery is low. However certain deep parts of the brain and brainstem remain inoperable areas. Apart from acute, life-threatening presentations, all other cases of melanoma brain metastases should ideally be discussed by a multidisciplinary team prior to embarking on treatment.

In 1990, Patchell et al conducted a randomised trial assessing surgery and whole brain radiotherapy versus whole brain radiotherapy alone for single brain metastasis.[1] The cohort consisted of 48 patients with different histologies (three patients with melanoma). They showed that the surgical resection group had significantly fewer local recurrences and significantly higher overall survival (40 weeks vs 15 weeks, $p<0.01$). The surgical group also remained functionally independent for longer (38 weeks vs 8 weeks, $p<0.005$). The authors of this landmark paper demonstrated that surgery is a valuable treatment modality for brain metastases of all histological subtypes. Since then, studies relating to surgical resection of brain metastases have been limited largely to retrospective cohorts, especially in the case of melanoma.

Local control rates after surgical resection in more contemporary surgical series have been in the order of 80–93%.[1][2][3][4][5] These studies advocate an en bloc resection technique, with mandatory use of neuro navigation. However, most patients in contemporary series were subject to multimodal treatment that undoubtedly contributed to the low recurrence rates.

Overall survival (OS) from the time of diagnosis of brain metastases has been steadily rising. In the current decade, patients who have had surgical resection of one or more lesions have a median OS of 13–16 months.[4]

Surgical morbidity and perioperative mortality have steadily declined over the last couple of decades. Perioperative mortality is currently approximately 2%, whilst the surgical complication rate is approximately 6–8%.[6]

In current clinical practice, new questions are emerging that are yet to be addressed. These include the optimal management of more complex patients who present with multiple brain metastases and/or leptomeningeal disease and determining the interaction of different modalities of treatment.

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5.3.2 Evidence summary and recommendations

Evidence summary	Level	References
Local control rates after surgical resection of melanoma brain metastases are very high, in the order of 80–93%	I, III-2	[1], [2], [3], [4], [5]
Surgery is highly effective in relieving symptoms and improving functional outcome.	I, III-2	[1], [7], [8], [9]
Perioperative surgical mortality is approximately 2% whilst complications occur in 6–8% of patients.	III-2	[6], [8]

Practice point

Brain metastases that are symptomatic or generate mass effect at presentation are best treated with surgery, which results in rapid relief of symptoms and maintenance of functional independence.

Practice point

Surgical resection of brain metastases provides safe, durable local disease control. The use of the operating microscope, neuro navigation and an en bloc resection technique are recommended. The integration of surgery with systemic therapy and radiotherapy should be discussed by a multidisciplinary team.

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5.4 Radiotherapy for patients with brain metastases

Contents

5.4.1 Evidence

When is radiotherapy indicated for patients with distant brain metastases?

5.4.1.1 Systematic review evidence

Clinical trials evaluating the use of radiotherapy (RT) in the management of metastatic malignancy have predominantly included multiple histological tumour types, including melanoma. The systematic review for these guidelines focused on studies that included patients with melanoma only.

5.4.1.1.1 Brain metastasis

The role of RT alone or in combination with other modalities in the management of brain metastases is complex, in view of the recent advances in systemic therapies that are effective in patients with brain metastases. Multidisciplinary team input is therefore required (see Treatment approaches to brain metastases).

There have been numerous studies on the role of RT in the management of melanoma brain metastases. Whilst there have been several randomised trials evaluating the role of stereotactic radiosurgery (SRS) and whole brain RT (WBRT) in the management of brain metastases, the number of patients with melanoma brain metastases in these studies was generally small. The systematic review focused on studies that included melanoma only (or mainly melanoma). The studies were all non-randomised and mostly retrospective series. For melanoma patients with single or a small number of brain metastases, SRS provides a high rate of local control, as for other malignancies.[1] At 6 and 12 months, the local control rates are about 80% and 60%, respectively, and the overall survival (OS) rates 70% and 15%.[2][3][4] The dose of SRS is dependent on the size of the metastasis and should be prescribed as per published protocols.[5] The addition of WBRT after SRS may improve intracranial control, but with no OS benefit. For patients with multiple brain metastases, WBRT may provide some benefit but its role has not been directly compared with systemic therapy or supportive care alone.

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5.4.1.2 Non-systematic review evidence

5.4.1.2.1 Adjuvant whole brain radiotherapy after local treatment of single or oligo brain metastases

A total of four randomised trials reported results for selected patients with up to four brain metastases (any histologies) treated with SRS alone versus WBRT and SRS.[6][7][8][9] The addition of WBRT to SRS significantly improved local control of the SRS-treated lesions as well as distant brain control. However, WBRT did not provide an OS benefit and was associated with a decline in neurocognitive function. In a randomised, phase III trial of SRS to the surgical cavity versus WBRT in patients with one resected brain metastasis, SRS was associated with a significantly shorter time to intracranial progression than WBRT (6.4 months vs 27.5 months, HR 2.45, $p<0.001$).[10] The cognitive deterioration-free survival was better with SRS to the cavity (3.7 months vs 3.0 months, $p<0.001$) and there was no difference in the OS between the 2 groups. Hippocampal avoidance WBRT using intensity modulated RT has been shown in one phase II study to lessen the effect of WBRT on neurocognitive function.[11]

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5.4.1.2.2 Adjuvant stereotactic radiosurgery to surgical cavity

In a randomised, phase III study it was shown that the addition of a SRS boost to the surgical cavity significantly improved the 12-month freedom from local recurrence rate compared with observation in patients with 1–3 completely resected brain metastases (72% vs 43%, HR=0.46, p<0.015).[12] The benefit was seen in all histologies including melanoma. There was no difference in OS between the two groups. Multiple retrospective studies of SRS to the surgical cavity after resection of melanoma metastases have shown local control rates exceeding 70%, which is similar to surgery with postoperative WBRT.[13][14]

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5.4.1.3 Evidence summary and recommendations

Evidence summary	Level	References
Stereotactic radiosurgery (SRS) for melanoma brain metastases achieves a high rate of local control.	III-2	[1], [3], [4], [15], [16]

Evidence-based recommendation	Grade
Stereotactic radiosurgery (SRS) may be considered for patients with single or a small number of brain metastases to maximise local control.	**C**

Evidence-based recommendation	Grade
For patients with multiple brain metastases, whole brain radiation therapy may provide some palliative benefits.	**C**

Practice point
There are no randomised controlled trials comparing surgery with SRS for local control and quality of life. Management of brain metastases should be discussed by a multidisciplinary team. Surgical resection of brain metastases is recommended for metastases in non-eloquent areas ≥1cm or symptomatic metastases. Stereotactic radiosurgery is recommended for small (<1cm, but maximum size to 3cm) or multiple metastases.

Practice point

All melanoma patients with brain metastases should be reviewed by a multidisciplinary team to ensure optimal combination and sequencing of systemic drug therapy, surgery and RT treatments.

Practice point

Patients with single or a small number of brain metastases should be given the opportunity to discuss the advantages and disadvantages of adjuvant radiotherapy to the surgical cavity and/or the whole brain after local treatment of the individual metastases.

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5.5 Summary of recommendations and practice points

Contents

5.5.1 Evidence summary: systematic drug therapy

Evidence summary	Level	References
Combined therapy with BRAF and MEK inhibitors induces an intracranial response of 58% in patients with asymptomatic untreated brain metastases whose melanoma has a V600E BRAF mutation.	III-1	[1]
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	[2], [3]
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 56% and 55% intracranial response rates in the Australian Brain Collaboration and the CheckMate 204 studies, respectively, with 6-month PFS rates of 53% and 67%, respectively).	III-1	[3], [4]

Practice point

Systemic drug therapy is effective 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 from a radiation oncologist and a neurosurgeon.

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5.5.2 Evidence summary: surgical approaches

Evidence summary	Level	References
Local control rates after surgical resection are very high, in the order of 80–93%	I, III-2	[5], [6], [7], [8], [9]

Evidence summary	Level	References
Surgery is highly effective in relieving symptoms and improving functional outcome.	I, III-2	[5], [10], [11], [12]
Perioperative surgical mortality is approximately 2% whilst complications occur in 6–8% of patients.	III-2	[13], [11]

Practice point
Brain metastases that are symptomatic or generate mass effect at presentation are best treated with surgery, with resultant rapid relief of symptoms and maintenance of functional independence.

Practice point
Surgical resection of brain metastases provides safe, durable local control. The use of the operating microscope, neuro navigation and en bloc resection technique are recommended. The integration of surgery with systemic therapy and radiotherapy should be discussed by a multidisciplinary team

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5.5.3 Evidence summary: radiotherapy

Evidence summary	Level	References
Stereotactic radiosurgery (SRS) to melanoma brain metastases achieves a high rate of local control.	III-2	[14], [15], [16], [17], [18]

Evidence-based recommendation	Grade
Stereotactic radiosurgery (SRS) may be considered for patients with single or a small number of brain metastases to maximise local control.	**C**

Evidence-based recommendation	Grade
For patients with multiple brain metastases, whole brain radiation therapy may provide some palliative benefits.	**C**

Practice point
There are no randomised controlled trials comparing surgery with SRS for local control and quality of life. Management of brain metastases should be discussed by a multidisciplinary team. Surgical resection of brain metastases is recommended for metastases in non-eloquent areas >= 1cm or symptomatic metastases. Stereotactic radiosurgery is recommended for small (< 1cm, but maximum size to 3 cm) or multiple metastases.

Practice point
All melanoma patients with brain metastases should be reviewed at a multidisciplinary team meeting to ensure optimal drug, surgery and radiotherapy treatment combination and sequencing.

Practice point
Patients with single or a small number of brain metastases should be given the opportunity to discuss the option of adjuvant radiotherapy to the surgical cavity and/or the whole brain after local treatment of the individual metastases.

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5.6 Adjuvant systemic therapy – resected stage II and III melanoma

Contents

5.6.1 Introduction

Despite adequate surgical treatment patients with resected stage II or III melanoma have a risk of both local and distant recurrence. The risk of relapse and death can be estimated based on tumour clinicopathological features, including but not limited to primary tumour Breslow thickness and ulceration, size and number of involved lymph nodes and the presence or absence of in-transit metastases (see What are the clinical features of melanoma and how do atypical melanomas present?) The purpose of adjuvant systemic therapy is to eradicate occult metastatic disease, thus reducing the risk of relapse and improving overall survival. In the setting of resected stage II or III melanoma, there have been randomised controlled studies (RCT) examining the role of, nivolumab, pembrolizumab, combination dabrafenib/trametinib, vemurafenib, ipilimumab, interferon-α, chemotherapy, vaccines and levamisole.

Randomised trials of chemotherapy, vaccines, levamisole and vemurafenib did not identify a survival benefit.[1] Ipilimumab and interferon-α (IFN-α) have both been shown to improve relapse-free and overall survival patients with resected stage III melanoma in RCTs (and meta-analyses for IFN), however the excessive toxicity of ipilimumab, and minimal overall survival benefit with interferon, mean that they are not considered standard therapy for most melanoma patients.

Recently, the initial results of three adjuvant RCTs of highly active drugs in metastatic melanoma, suggest that nivolumab, pembrolizumab and combination dabrafenib/trametinib are likely to soon replace other treatments as new standards of care.[2][3] These studies showed a significant improvement in relapse-free survival (RFS) (over ipilimumab for nivolumab and placebo for pembrolizumab and dabrafenib/trametinib), and mature analyses of overall survival are awaited.

Neither nivolumab, pembrolizumab nor combination dabrafenib/trametinib has been trialled in the setting of resected stage II melanoma and as such the activity of these agents in stage III cannot be extrapolated to patients with stage II melanoma. The nivolumab RCT[3] included patients with resected stage IV disease and it may be considered in patients considered for treatment after resection of stage IV disease (see For patients with distant metastases, when is surgical therapy indicated?)

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5.6.2 Systematic review evidence

Twenty-four RCTs and seven meta-analyses were identified examining the adjuvant treatment of resected stage II and III melanoma. The only agents to have been found to have benefit over placebo are pembrolizumab, ipilimumab, interferon-α-2b (IFN-α), pegylated interferon-α-2b (Peg IFN-α) and combination dabrafenib /trametinib. Nivolumab was shown to be superior to ipilimumab.

Of note a second adjuvant study in BRAF mutant melanoma (BRIM-8) has been undertaken which randomized patients to either single agent vemurafenib or placebo treatment for 1 year.[4] Preliminary results have been presented, however to date results have not been published (NCT01667419). Unlike the recent adjuvant drug trials, BRIM-8 included patients with resected stage IIC melanoma. This study did not meet its primary endpoint of improving RFS in patients with resected stage IIIC melanoma. In patients with resected stage IIC, IIIA and IIIB melanoma, RFS was greater in patients treated with vemurafenib vs placebo (HR 0.54; 0.0010), however this result was not considered statistically significant because of the prespecified hierarchical prerequisite for primary relapse free survival analysis in patients with resected IIIC disease.

5.6.2.1 Combination dabrafenib and trametinib in BRAF mutant melanoma

In patients with unresectable stage III and IV melanoma, whose tumours are BRAF V600 mutant, combination dabrafenib and trametinib improves survival compared with single agent dabrafenib or vemurafenib (see Does systemic drug therapy improve progression free, overall survival in unresectable stage IIIC and stage IV melanoma?) (which in turn improves survival over chemotherapy).[2] In the adjuvant setting, the double blind RCT Combi-AD included patients with resected stage III (AJCC IIIA, [sentinel node deposit >1mm diameter], IIIB and IIIC) BRAF V600E/K melanoma and randomised patients to 12 months of treatment with combination dabrafenib/trametinib or matched placebo.[2]

After a median follow-up of 2.8 years, dabrafenib/trametinib improved RFS over placebo; the 3 year RFS was 58% with dabrafenib/trametinib group versus 39% with placebo (HR 0.47; P<0.001).[2] Similarly, OS was improved; the 3-year OS rate was 86% versus 77%, respectively (HR 0.57; P = 0.0006). This OS result did not cross the prespecified interim analysis boundary, and the study is powered for a final survival analysis with further follow-up. The benefit of dabrafenib/trametinib was consistent across multiple subgroups tested, including mutation type (V600E vs V600K) and AJCC sub-stage (lymph node tumour burden and primary tumour ulceration status).[2]

Adverse events were reported in 97% of patients treated with adjuvant dabrafenib/trametinib versus 88% of patients on the placebo arm.[2] Grade 3/4 adverse events occurred in 41% of patients treated on the combination arm versus 14% on the placebo. Consistent with data from patients with advanced disease, the most common adverse events with dabrafenib/trametinib were pyrexia and fatigue, most commonly grade 1 or 2. In the dabrafenib/trametinib group 26% had adverse events leading to treatment discontinuation, 38% leading to a dose reduction and 66% leading to a dose interruption.[2] Back to top

5.6.2.2 Nivolumab

In patients with unresectable (metastatic) stage III or IV melanoma, nivolumab is associated with superior efficacy and improved safety as compared to ipilimumab. The double blinded phase III RCT CA209-238 included patients with resected stage IIIB/C or stage IV melanoma (AJCC 7th edition), randomised to 12 months treatment with either nivolumab (3mg/kg 2 weekly) or ipilimumab (10mg/kg) (see Does systemic drug therapy improve progression free, overall survival in stage IIIC unresectable and stage IV melanoma?).[3] The study cohort was predominantly resected stage III melanoma (81%), including 29% of patients with micrometastatic disease detected by sentinel lymph node biopsy.

At first analysis and after a minimum follow-up of 18 months, nivolumab was associated with an improvement in RFS; the 12-month RFS was 70.5% for with nivolumab and 60.8% with ipilimumab (HR 0.65; P<0.001).[3] Nivolumab was superior to ipilimumab across all subgroups including stage IIIB/C and stage IV disease, BRAF mutant and wildtype melanoma, and PD-L1 positive and negative subgroups. Initial data are too immature for an OS analysis.

Consistent with studies in the advanced setting, nivolumab was associated with a favourable safety profile compared with ipilimumab, and similar to that seen when used in the metastatic setting.[3] The rate of treatment related adverse events was 85.2% with nivolumab versus 95.8% with ipilimumab, and grade 3/4 toxicity was 14.4% versus 45.9%, respectively. There were two treatment-related deaths in the ipilimumab arm versus with no treatment related deaths in the nivolumab cohort.[3] Back to top

5.6.2.3 Ipilimumab

Ipilimumab was the first systemic therapy shown to improve overall survival in advanced melanoma.[5] The RCT, EORTC 18071, compared ipilimumab to placebo in resected stage III melanoma. Stage IIIA patients required sentinel nodal metastasis diameter >1mm, and patients with in-transit metastasis or prior adjuvant radiotherapy were excluded.[5] 951 patients were randomised one to one to ipilimumab (10mg/kg for 4 doses 3 weekly then a maintenance regime of 3 monthly for up to 3 years) or a matched placebo.[5]

Recurrence free survival (RFS), the primary endpoint, was improved in those treated with ipilimumab. Five-year RFS was 40.8% in the ipilimumab and 30.3% in the placebo arm (HR 0.76; P<0.001), and 5-year overall survival (OS) was 65.4% and 54.4%, respectively (HR 0.72; P = 0.001).[6] Subsequent therapy in those who recurred was roughly similar in both arms, but given the timing of the trial, only a small proportion of patients received BRAF /MEK inhibitors and anti-PD-1 therapy post-relapse.[6]

Ipilimumab had 54% grade 3/4 toxicity compared to 26% in the placebo arm, only a minority (40%) of patients received more than the four induction doses of ipilimumab, and only 13% received all three years of ipilimumab treatment. There were five treatment-related deaths ipilimumab arm, three related to colitis, one myocarditis and one Guillain-Barre syndrome. The general consensus among clinicians is that this treatment was associated with significant toxicity however there was no clinically significant difference in quality of life between both groups.[7]

Of note, the dose of ipilimumab used in this trial was higher (10mg/kg) than the TGA/PBS approved dose in the metastatic setting (3mg/kg), which is given without maintenance dosing. While a RCT in the metastatic setting has shown 10mg/kg to be more efficacious but also more toxic than 3mg/kg,[8] a subsequent RCT of adjuvant ipilimumab at 10mg/kg; 3mg/kg or high dose IFN (NCT01274338) should clarify the best dose of ipilimumab in this setting. However, given the superiority and favourable toxicity profile of nivolumab over ipilimumab (see above) the results of this subsequent study are unlikely to change practice. Back to top

5.6.2.4 IFN-α

Multiple randomised phase III trials have examined the role of IFN as an adjuvant treatment for the management of resected stage II and III melanoma.[9][1] Various dosing strategies have been examined including high-dose (20 MU/m2), intermediate-dose (5–10 MU), low-dose (1–3 MU) regimens and Peg IFN.

The results of the ECOG 1684 (E1684) study of high dose IFN-α (20MU/m2) 5 days a week for 4 weeks, followed by 11 months of maintenance treatment (10MU/m2 3 days a week) versus routine follow-up for the treatment of resected stage III melanoma led to the TGA approval and PBS listing of this regimen. The E1684 regimen improved relapse free survival (RFS, median 1.72 years compared with 0.98 years), with initial analysis suggesting an improvement in OS.[10] Subsequent analysis, including pooling data from E1684 and ECOG 1690 (E1690), treated with the same regimen, failed to confirm an improvement in OS.[11]

A meta-analysis of 17 RCTs found IFN-α improved RFS (HR = 0.83; P value < 0.00001).[9] Analysis from 15 of these studies identified an improvement in OS (HR = 0.91; 95% CI 0.85 to 0.97; P value = 0.003). This equates to an absolute improvement in OS of approximately 2–3%. Despite multiple studies examining different doses and durations of treatment no IFN regimen was found to be superior.[9]

There is conflicting evidence regarding the impact of the number and size of nodal melanoma burden on the efficacy of interferon. Patients with microscopic nodal disease benefited the most in the E1684 trial, whereas those with 2–3 positive nodes benefited in the E1690 trial, and those who were node-negative benefited in the E1694 trial.[10][12][13] A retrospective analysis of EORTC 18952 and 18891 suggested a greater benefit of IFN-α in those with ulcerated primaries.[14]

IFN-α treatment is associated with significant toxicity, which is reversible on cessation of treatment. Common toxicities include flu like symptoms (fevers, fatigue, myalgia), hepatotoxicity and depression.[15]

One study examined the role of IFN-α exclusively in resected stage II melanoma and reported OS, when adjusted for prognostic factors OS was significantly improved by treatment with IFN (HR 0.70; 95% CI 0.50-0.99, P=0.046).[16] Patients enrolled in this study did not undergo a sentinel node biopsy and as such, it is unclear if the results are applicable in the current era.

5.6.3 Overview of additional evidence (non-systematic review relevant literature)

5.6.3.1 Pembrolizumab

Like nivolumab, pembrolizumab is associated with superior survival and efficacy when compared to ipilimumab in patients with unresectable stage IIIC or stage IV melanoma (see Does systemic drug therapy improve progression-free, overall survival in unresectable stage IIIC and stage IV melanoma?). The double blind phase III RCT MK3475-054 included patients with resected stage III (AJCC 7th Addition IIIA, [sentinel node deposit >1mm diameter], IIIB and IIIC) melanoma and randomised patients to 12 months of treatment with pembrolizumab or matched placebo.[17]

After a median follow-up of 15.1 months, pembrolizumab improved RFS over placebo; the 12 month RFS was 75% with pembrolizumab versus 61% with placebo (HR 0.57; P<0.001). Pembrolizumab was superior to placebo across the all subgroups including AJCC substage, BRAF mutant and wildtype melanoma, and PD-L1 positive and negative subgroups. Initial data are too immature for an OS analysis.

The toxicity profile of Pembrolizumab was consistent with studies in the metastatic setting. The rate of treatment related adverse events was 77.8% with pembrolizumab versus 66.1% with placebo, and grade 3/4 toxicity was 14.7% versus 3.4%, respectively. There was one treatment-related death in the pembrolizumab arm due to myositis.

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5.6.4 Evidence summary and recommendations

Evidence summary	Level	References
Combination dabrafenib and trametinib treatment for one year in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC BRAF V600E/K melanoma improves RFS compared to placebo (HR 0.47; P<0.001).	II	[2]
Nivolumab for one year in resected IIIB, IIIC, IV melanoma improves RFS compared to ipilimumab (10mg/kg) (HR 0.65; P<0.001).	II	[3]
Pembrolizumab for one year in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC melanoma improves RFS compared to placebo (HR 0.57; P<0.001).	II	[17]
Ipilimumab (10mg/kg for 4 doses followed by 3 monthly maintenance treatment for 3 years) in resected IIIA (nodal deposit >1mm diameter), IIIB, IIIC melanoma improves RFS (HR 0.76, P<0.001) and OS (HR 0.72; P=0.001) compared to placebo.	II	[5]
Adjuvant IFN-α in resected stage II, III melanoma improves RFS (HR 0.83; P<0. 00001) and overall survival (HR 0.91; P=0.003) compared to observation.	I	[9]

Evidence-based recommendation	Grade
All patients with resected stage III melanoma should discuss the benefits, potential toxicities and out-of-pocket costs of adjuvant systemic therapy with an experienced melanoma medical oncologist who is part of a multidisciplinary melanoma team, including the role of clinical trials.	**C**

Evidence-based recommendation	Grade
Patients with BRAF V600E/K resected stage III melanoma may be considered for 12 months adjuvant treatment with combination dabrafenib/trametinib.	**B**

Evidence-based recommendation	Grade
Note: Adjuvant dabrafenib/trametinib is not TGA approved or PBS listed	

Evidence-based recommendation	Grade
Patients with resected stage IIIB/C or IV melanoma may be considered for 12 months adjuvant treatment with nivolumab. Note: Adjuvant nivolumab is not PBS funded.	**B**

Evidence-based recommendation	Grade
Patients with resected stage III melanoma may be considered for 12 months adjuvant treatment with pembrolizumab. Note: Adjuvant pembrolizumab is not TGA approved or PBS funded.	**B**

Evidence-based recommendation	Grade
Patients for whom adjuvant nivolumab, pembrolizumab or dabrafenib/trametinib is not appropriate or is not available, routine follow-up may be appropriate. Patients may consider treatment with IFN-α after discussion with a medical oncologist regarding the associated toxicity and potential benefit.	**B**

Evidence-based recommendation	Grade
Ipilimumab is not recommended because it has inferior efficacy and greater toxicity than nivolumab.	**B**

Evidence-based recommendation	Grade
Outside of a clinical trial adjuvant systemic therapy is not recommended for patients with resected stage II melanoma.	**C**

Practice point

Patients should be treated in a medical oncology facility with a melanoma multidisciplinary team and experience in using immunotherapy and BRAF/MEK inhibitors.

Practice point

At present neither dabrafenib/trametinib or pembrolizumab are TGA approved for adjuvant therapy and neither dabrafenib/trametinib, nivolumab or pembrolizumab are PBS funded. As such, enrolment in a clinical trial should be discussed.

Practice point

There are no data comparing combination dabrafenib/trametinib and nivolumab/pembrolizumab in patients whose tumours are BRAF V600 mutant, as such individual patient discussions are required for patients whose tumours are BRAF mutant.

Practice point

For those with stage III melanoma not able to receive dabrafenib/trametinib, nivolumab or pembrolizumab (or a clinical trial), interferon may be considered, but given the minimal overall survival benefit and significant toxicity, routine follow-up is usually preferred. See How should patients at each stage of melanoma be followed after initial definitive treatment?

5.6.5 The use of adjuvant systemic therapies in the Australian setting

At present, the only PBS-funded adjuvant treatment in Australia is IFN-α. Adjuvant IFN-α confers a small improvement in absolute OS but also has significant toxicity and as such for many patients the option of routine follow-up is considered favourable to IFN-α. Given the superiority of nivolumab over ipilimumab in the CA209-238 study, and the toxicity of ipilimumab, ipilimumab does not have a current role in the adjuvant treatment of melanoma in Australia, and is unlikely to have one in the future.

At present nivolumab is TGA approved but not PBS reimbursed and combination dabrafenib/trametinib and pembrolizumab are neither TGA approved or PBS reimbursed for the adjuvant treatment of resected melanoma. Enrolment in a clinical trial remains an alternative to routine follow-up for many patients. Self-funded adjuvant therapy is an option, however should be considered in the context of a multidisciplinary team involving a medical oncologist experienced in melanoma treatment.

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5.6.6 Appendices

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5.7 Systemic drug therapy – unresectable stage IIIC and IV melanoma

Contents

5.7.1 Introduction

The management of unresectable stage III and stage IV melanoma (metastatic or advanced melanoma) has been revolutionised with effective drug therapies that target either i) checkpoints on T-cells to induce T-cell mediated cancer-cell death or ii) the mitogen activated protein kinase (MAPK) pathway in melanoma cancer cells, particularly patients with V600 BRAF mutant melanoma. The former is referred to as immunotherapy and the latter as targeted therapy, these are discussed in more detail in their own sections (see bottom of this page). Whereas the 1-year overall survival (OS) was 25–35% for decades,[1] rapidly decreasing to <5% at 5 years, the 1-year OS is now 70–75% for both classes of systemic drug therapies. However, it is the longer-term control of advanced melanoma that is noteworthy, with landmark 3-year OS >60% for combination checkpoint inhibitor immunotherapy,[2] with maintenance of quality of life.[3]

Figure 1. Systemic drug therapy flowchart (click to enlarge)

Note: the options in the flowchart are not listed in order of preference.

5.7.2 Evidence

This section summarises the current highest level of evidence for the efficacy of these drug therapies in patients with advanced melanoma, as well as provide recommendations and practice points for clinicians treating these patients. With the variety of therapies available, as well as the available local therapies (surgery, radiotherapy, intralesional therapy [injection of a drug therapy directly into a melanoma metastasis] and experimental topical therapies), treatment algorithms must be considered carefully for each individual patient, including the choice of first-line drug therapy, the sequencing of therapies and the patient's eligibility for clinical trials. Due to the high incidence of brain metastases in patients with advanced melanoma, and the activity of systemic drug therapies in this patient population based on phase II trials, a separate section has been developed for these guidelines providing guidance and a summary of brain metastases evidence (see bottom of page). Given the increasing number of options and the complexity of the management of patients with advanced melanoma, it is strongly recommended that all patients be managed in the context of a multidisciplinary team of clinicians with experience in the management of melanoma. Specifically, patients requiring drug therapy should be managed by medical oncologists with expertise in managing associated toxicities

This section of the guideline does not provide evidence for drug therapy in metastatic uveal melanoma, and these patients should be considered for clinical trials given the lack of active drug therapies.

This section of the guideline is supported by evidence from a systematic review undertaken in March 2017. The systematic review addressed the research question: *Does systemic drug therapy improve progression free and /or OS in unresectable stage III and stage IV melanoma?* The systematic review included evidence published since 2010 and was limited to the inclusion of meta-analyses (of phase III randomised controlled trials [RCT]),

systematic reviews (of phase III RCTs), and individual phase III RCTs. The scope of the systematic review was limited to the mentioned criteria due to the large number of trials in this field. Additional evidence that was outside the scope the systematic review but considered important has been incorporated in the narrative section. Evidence included from outside the systematic review is identified with an asterisk (*) following the reference.

5.7.2.1 Drug therapies in patients with advanced melanoma

See the following sections:

- Immunotherapy
- Targeted therapies (MEK and BRAF inhibitors)
- Chemotherapy
- Immunotherapy: Summary of all recommendations and discussion

5.7.2.2 Systemic drug therapy in melanoma brain metastases

Systemic drug therapies are active in melanoma brain metastases. Management of melanoma brain metastases requires a multidisciplinary approach. Evidence for local therapies and systemic drug therapy in the management of brain metastases is covered separately, see the **Brain metastases** section.

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5.7.4 Appendices

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5.8 Immunotherapy

Contents

5.8.1 Systematic review evidence

Immunotherapy is now standard treatment for most patients with unresectable stage III and stage IV melanoma. Antibodies targeting the CTLA-4 and PD-1 checkpoints on activated T-cells have significant activity to shrink melanoma, and induce and durable responses and prolong survival. Immunotherapy is now considered first-line for most patients with unresectable stage III and stage IV melanoma.

Evidence included from outside the systematic review is identified with an asterisk (*) following the reference.

5.8.1.1 Ipilimumab

Three randomised controlled studies have been conducted with the anti-CTLA4 antibody ipilimumab. The first two showed a survival benefit for either ipilimumab monotherapy (3mg/kg) (HR 0.66 vs gp100 vaccine, median overall survival [OS] 10.1 months) or ipilimumab combined with DTIC (3mg/kg) (HR 0.72 vs DTIC, median OS 11.2 months). A third trial of ipilimumab at two doses (10mg/kg vs 3mg/kg) showed benefit with the higher dose (HR 0.84, median OS 15.7 months).

Toxicity is frequent with ipilimumab, but manageable, largely reversible and rarely fatal. Immune-related adverse events (irAE) occurred in 60% of patients on ipilimumab at 3mg/kg, and 15–20% had grade 3–4 toxicity.[1][2] Higher dosing of ipilimumab (10mg/kg) or in combination with chemotherapy (DTIC) resulted in greater toxicity (grade 3 in 34% and 42%, respectively) with no increase longer-term efficacy in the case of the DTIC combination, and insufficient increase in longer-term efficacy when balanced against toxicity for the 10mg/kg dose. As such these are not approved and should not be used in the clinic.[3][2]

A pooled analysis of approximately 1800 patients on ipilimumab trials demonstrated an OS plateau at approximately 20% at 3 years that persisted to 10 years.[4]*

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5.8.1.2 Anti-PD-1 antibodies, alone and in combination with ipilimumab

There have been three randomised phase III trials of the anti-PD-1 antibodies pembrolizumab and nivolumab in patients with advanced melanoma, demonstrating superiority over chemotherapy and ipilimumab monotherapy. Combination ipilimumab and nivolumab therapy appears more effective but more toxic than anti-PD1 monotherapy.

Nivolumab has been shown to be superior to chemotherapy (DTIC) in BRAF wild-type patients, with a higher response rate (40% vs 14%), and superior OS (HR 0.43, 1-year 73%, 2-year 58%).[5]* Nivolumab and pembrolizumab have each been proven to be superior to ipilimumab, with higher response rates, superior OS (HR 0.69 pembro vs ipi, HR 0.57 nivo vs ipi) and less toxicity (see below). In the pembrolizumab trial, treatment duration was two years and 91% of patients remain in disease control after a median of nine months follow-up time from cessation.[6]*

Combination ipilimumab (3mg/kg) and nivolumab (1mg/kg) has been studied in a single phase III trial of the combination versus nivolumab versus ipilimumab (CheckMate 067). While the trial was only powered to compare the nivolumab containing arms to ipilimumab, combination therapy had a numerically higher response rate (58% vs 44%) and numerically superior OS (HR 0.85, 3-year OS 58% vs 52%) than nivolumab. The greatest benefit of combination was seen in the PD-L1 negative, BRAF mutant melanoma and elevated LDH subgroups.

PD-1 antibodies as monotherapy were well tolerated, with grade 3+ irAEs occurring in approximately 15%, and only 4–8% of patients discontinued treatment for toxicity. In contrast, 55% had grade 3+ irAEs with combination therapy, and 36% discontinued due to toxicity. While there have been no trials comparing nivolumab and pembrolizumab, cross-trial comparisons suggest similar efficacy and toxicity. Studies exploring PD-1 antibodies in combination with lower doses of ipilimumab are underway in the hope that efficacy may be maintained with lower toxicity.

Trials using various cutoffs and scoring techniques demonstrate that PD-L1 expression does influence the response rate and PFS with PD-1 monotherapy, with higher expression correlating with higher efficacy.[7][8]* Negative staining does not preclude benefit and should not exclude patients from receiving PD-1 monotherapy. Early phase trials have demonstrated higher response rates and superior PFS when immunotherapy is used first-line compared to later lines,[9]* including in BRAF mutant patients. In contrast, BRAF inhibitors have been shown to have consistent response rates and PFS when used any line.[10][11]*

In patients who progress on PD-1 antibodies, ipilimumab and combination ipilimumab and nivolumab has been shown to have efficacy in retrospective series.[12][13]* Similarly, toxicity with one class of inhibitor does not preclude use of another, and selected patients with autoimmune disease have been shown to be safely treated with both ipilimumab or PD-1 antibodies as monotherapy.[14][15][16]*

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5.8.2 Evidence summary table

Evidence summary	Level	References
First-line/upfront anti-PD1 immunotherapy with nivolumab or pembrolizumab improves the progression-free survival (PFS) and overall survival (OS) compared with ipilimumab monotherapy, regardless of BRAF mutation status. First-line nivolumab improves the PFS and OS compared with dacarbazine chemotherapy (3-year landmark OS nivo vs chemo 56% vs 68%, HR 0.69 [95% CI 0.44–1.07]) in patients whose melanoma is BRAF wild-type.	II	[17], [18], [19]
First-line/upfront combined therapy with nivolumab and ipilimumab improves the response rate, PFS (3-year landmark PFS combi vs ipi 39% vs 10%, HR 0.43, p<0. 001) and OS (3-year landmark OS combi vs ipi 58% vs 34%, HR 0.55, p<0.001) compared with ipilimumab monotherapy, regardless of BRAF mutation status.	II	[17], [8]
First-line/upfront combined therapy with nivolumab and ipilimumab improves the response rate and PFS compared with nivolumab monotherapy 3-year landmark PFS combi vs nivo 39% vs 32%, HR 0.78 [95% CI 0.64–0.96]), regardless of BRAF mutation status of melanoma.	II	[17], [8]
Ipilimumab monotherapy or in combination with chemotherapy (dacarbazine) improves the PFS and OS compared with gp100 or dacarbazine, respectively. Ipilimumab at a dose of 10mg/kg improves the OS compared with ipilimumab at a dose of 3mg/kg.	II	[1], [3], [2]

Next section: Targeted therapies (MEK and BRAF inhibitors)

See the Summary of all recommendations section for all recommendations and practice points.

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5.9 Targeted therapies (MEK and BRAF inhibitors)

Contents

5.9.1 Introduction

The combination of a BRAF and MEK inhibitor are highly active in BRAFV600 mutant melanoma and, along with the checkpoint inhibitors targeting PD1 and CTLA-4, form the standard of care for BRAF-mutant melanoma.

Evidence included from outside the systematic review is identified with an asterisk (*) following the reference.

5.9.2 Systematic review evidence

5.9.2.1 BRAF-mutant melanoma

5.9.2.1.1 Single agent BRAF inhibitor

Two randomised phase III studies have compared the single agent BRAF inhibitors vemurafenib and dabrafenib to chemotherapy in treatment-naïve V600 BRAF-mutant positive patients. In the BRIM-3 study patients with BRAFV600E mutant melanoma were randomized to either vemurafenib 960mg twice a day or dacarbazine.[1] As compared to dacarbazine, vemurafenib was associated with an improvement in overall response rate (48% vs 5%, P<0.001), progression-free survival (PFS; median 5.3 vs 1.6 months, HR 0.26, P<0.001) and overall survival (OS; HR 0.37, P<0.001). Similarly dabrafenib 150mg bd improved the response rate (50% vs 6%) and PFS (median 5.1 vs 2.7 months, HR 0.30, p<0.0001) compared to dacarbazine.[2] Unlike the vemurafenib study, OS did not differ between the two arms of the study, a difference attributable to the dabrafenib study allowing cross-over for those who progressed on dacarbazine rather than any difference in efficacy between the drugs. The single agent study of dabrafenib BRAF inhibitors limited enrolment to patients whose tumours had a BRAFV600E mutation, whereas the vemurafenib study allowed any V600 mutation detected by the study screening test (which was design to be highly sensitive and specific for V600E). However both vemurafenib and dabrafenib are active in other BRAFV600 mutations, but not non-V600 mutations.[3]*

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5.9.2.1.2 Single agent MEK inhibitor

The MEK inhibitor trametinib was compared to decarbazine in a phase III study and improved both PFS (median 4.8 vs 1.5 months HR 0.45 P<0.001) and OS (HR 0.54, P=0.01).[4] Despite the positive study, single agent trametinib is not considered an appropriate treatment in BRAFV600 mutant melanoma given its inferior efficacy (response rate 22%) and toxicity compared with single agent BRAF inhibitor or combination BRAF/MEK inhibition (see below).

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5.9.2.1.3 Combination BRAF/MEK inhibition

Three published phase III studies have compared combination BRAF/MEK inhibition with single agent BRAF inhibitor.[5][6][7] Combination dabrafenib plus trametinib, as compared to dabrafenib plus placebo, improved the PFS (median 9.3 vs 8.8 months, HR 0.75, P = 0.03) and overall response rate (P = 0.002).[6] Similarly dabrafenib

and trametinib as compared with vemurafenib improved PFS (median 11.4 vs 7.3 months, HR 0.56, P<0.001) and OS (HR 0.69, P=0.005).[7] Combination vemurafenib and cobimetinib as compared with single agent vemurafenib improved the PFS (median 9.9 vs 6.2 months, HR 0.51, P<0.001)REF? 30 and OS (HR 0.70 p=0.005). In a pooled analysis[8]* of both the combination dabrafenib/trametinib phase III studies, the combination has a landmark 1-, 2- and 3-year PFS of 48%, 30% and 23%, respectively. Landmark OS at 1, 2 and 3 years was 74%, 53% and 44%, respectively.[8]*

Combination dabrafenib/trametinib and vemurafenib/cobimetinib despite not being compared directly are likely to have comparable efficacy, and there is no evidence that one combination can overcome failure of the other. A number of prognostic factors impact on duration of response and OS, a normal LDH and less than three organ sites involved is associated with a prolonged PFS.[9]* An elevated LDH, particularly one >2-fold upper limit of normal is associated with a shorter PFS and OS.[9]*

Combination dabrafenib/trametinib was associated with grade 3 or 4 adverse events in 35% of patients.[7] Combination vemurafenib/cobimetinib was associated with a 65% rate of grade 3 or 4 adverse events.[5][10] The two combinations have different toxicity profiles, vemurafenib/cobimetinib is associated with a risk of photosensitivity and hepatotoxicity (most commonly a transaminitis) while dabrafenib/trametinib commonly causes treatment related pyrexia syndrome. Over half of all patients treated with combination dabrafenib /trametinib will develop pyrexia syndrome defined as one or more of the following: fever (≥38°C); Chills/rigors /nightsweats; Flu-like symptoms. Initial management of pyrexia syndrome involves treatment interruption. In the setting of recurrent fevers, intermittent dosing and/or corticosteroids may be used.[11]

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5.9.2.2 MEK inhibition in NRAS mutant melanoma

The MEK inhibitor binimetinib was compared to dacarbazine in a phase III study in patients with NRAS Q61 mutant melanoma. Binimetinib was associated with an improvement in PFS (2.8 vs 1.5 months, HR 0.62, P<0.001).[12] There was no significant difference in OS (HR 1.00, P=0.50). Of interest the benefit of binimetinib appeared greatest in patients who received prior immunotherapy. MEK inhibitors are associated with a range of toxicities, including most frequently an acneiform rash, nausea and diarrhea, less commonly cardiac or ocular toxicities can occur.

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5.9.3 Evidence summary

Evidence summary	Level	References
TARGETED THERAPY: V600 BRAF Mutation-Positive Melanoma	II	[5], [6], [7], [9], [10], [13]

Evidence summary	Level	References
First-line/upfront combined therapy with a BRAF inhibitor and MEK inhibitor (dabrafenib + trametinib or vemurafenib + cobimetinib) improves the response rate, progression-free survival (PFS) and overall survival compared with BRAF inhibitor monotherapy in patients whose melanoma has a BRAFV600 mutation. ■ PFS: vemurafenib + cobimetinib vs vemurafenib, HR 0.58, p<0.0001; OS: vemurafenib + cobimetinib vs vemurafenib 48% vs 38% (2y), HR 0.70, p=0.005. ■ PFS: dabrafenib + trametinib + vs dabrafenib, HR 0.67, p=0.0004. ■ PFS: dabrafenib + trametinib + vs vemurafenib, HR 0.56, p<0.001; OS: dabrafenib + trametinib vs vemurafenib 28% vs 35%, HR 0.69, p=0.005.		
TARGETED THERAPY: Q61 NRAS Mutation-Positive Melanoma First- and second-line MEK inhibitor (binimetinib) improves the response rate and progression-free survival, but not the overall survival compared with dacarbazine chemotherapy in patients whose melanoma has an NRAS Q61 mutation. ■ PFS: binimetinib vs dacarbazine, HR 0.62, p<0.001; OS: binimetinib vs dacarbazine 60% vs 50%, HR 1.00, p=0.50	II	[12]

Next section: Chemotherapy

See the Summary of all recommendations section for all recommendations and practice points.

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5.9.4 References

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5.10 Chemotherapy

Evidence included from outside the systematic review is identified with an asterisk (*) following the reference.

5.10.1 Chemotherapy

The historical standard for chemotherapy is single agent dacarbazine (DTIC) but response rates are only 5–15%, with only 0–2% complete responses and most responses are of short duration.[1][2][3][4] Fotemustine and NAB-paclitaxel have slightly higher overall response rates compared with dacarbazine, but with no benefit in overall survival.[5][6]* Unlike other single agents used in melanoma, fotemustine is associated with a higher risk of myelosuppression (i.e. reduced bone marrow activity resulting in decreased production of red blood cells, white blood cells and platelets).[5]* The oral alkylating agent temozolomide has equivalent efficacy to dacarbazine (median survival 7.7 months vs 6.4, respectively).[7] Combination chemotherapy does not improve survival over that of single agents and increases toxicity.[8]* While it is recognised that chemotherapy is of palliative intent in patients with metastatic melanoma, there is no formal evidence that any form of chemotherapy improves duration or quality-of-life in this setting.

5.10.1.1 Evidence summary table

Evidence summary	Level	References
Single agent fotemustine, dacarbazine or temozolomide can be used for palliation of patients with metastatic melanoma in patients who have progressed on other drug therapies.	II	[1], [2], [3], [4], [7]

Next section: Summary of all recommendations: Immunotherapy chapter

See the Summary of all recommendations section for all recommendations and practice points.

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5.10.2 References

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5.11 Summary of recommendations and practice points

Contents

5.11.1 Summary of recommendations and practice points

This section includes all recommendations and practice points from the systemic therapies section of the guidelines.

Evidence-based recommendation	Grade
Anti-PD-1 based immunotherapy should be considered for the first-line/upfront drug	**B**

Evidence-based recommendation	Grade
treatment for patients with unresectable stage III/IV melanoma.	

Evidence-based recommendation	Grade
A BRAF inhibitor combined with a MEK inhibitor should be considered as first-line/upfront drug treatment for patients with V600 BRAF mutation positive melanoma.	**B**

Consensus-based recommendation
Consensus Statement: Anti-PD-1 based therapies versus combination BRAF inhibitor plus MEK inhibitor have not been compared head to head, see Practice Points 6, 7 and 10.

Practice point
Practice point 1 All patients with unresectable stage III/IV metastatic melanoma (especially patients with brain metastases) should be discussed at a multidisciplinary team meeting, and managed by medical oncologists who have expertise using targeted and immune therapies.

Practice point
Practice point 2 Clinical trials should be considered for all patients with unresectable stage III/IV metastatic melanoma.

Practice point

Practice point 3 All patients with unresectable stage III/IV metastatic melanoma should have molecular testing of their melanoma for the V600 BRAF mutation, including V600E, V600K, V600R, V600D and V600M. Methodology should be used to detect appropriate mutations and be performed in an accredited laboratory using appropriate controls.

Practice point

Practice point 4 Baseline PD-L1 expression on melanoma cells should not be used to select patients for anti-PD-1 therapy due to its low predictive value.

Practice point

Practice point 5 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. See the Brain metastases section.

5.11.1.1 Choice of first-line therapy

Practice point

Practice point 6 Cross phase III trial comparisons of landmark survival analyses (progression-free and overall survival) suggest that more durable responses and possibly higher long-term landmark survival values may be achieved with anti-PD-1-based therapy compared with combined BRAF inhibitor and MEK inhibitor in the first-line setting.^

^Check PBS guidelines before prescribing any drug.

Practice point

Practice point 7 Anti-PD-1-based therapy should be administered as first-line therapy as opposed to following BRAF inhibitor-based therapy.

Practice point

Practice point 8 While not formally compared, there is no suggestion that there is a difference in efficacy or toxicity between pembrolizumab and nivolumab.

Practice point

Practice point 9 While not formally compared, there is no suggestion that there is a difference in efficacy between dabrafenib/trametinib, vemurafenib/cobimetinib or encorafenib/binimetinib combinations, but toxicity profiles are distinct.

Practice point

Practice point 10 The combination of ipilimumab and nivolumab causes immune-related side effects, inducing grade 3/4 drug-related toxicities in 59% of patients, including asymptomatic laboratory abnormalities. Disease factors that may be considered in the selection of patients for this combination regimen include: rapidly progressive melanoma, baseline serum lactate dehydrogenase (LDH) > upper limit of normal, mucosal melanoma, active brain metastases, BRAF mutation-positive melanoma and low PDL-1 expression on melanoma cells (assay as per CheckMate 067).

5.11.1.2 Special notes

Practice point

Practice point 11 Ipilimumab (anti-CTLA-4 immunotherapy), alone or in combination with anti-PD-1 may be administered following progression on anti-PD-1 monotherapy.

Practice point

Practice point 12 Any patient on immunotherapy can develop an auto-immune toxicity directed of any organ (and this risk must be discussed with the patient), The common toxicities are fatigue, rash, itch, diarrhoea, thyroiditis and hepatitis. Although a rare toxicity, it is important to note hypophysitis (inflammation of the pituitary gland) with subsequent hypopituitarism may occur, especially in regimens containing anti-CTLA-4 (e.g. ipilimumab).

Practice point

Practice point 13 Anti-PD-1 monotherapy may be administered in selected patients with auto-immune diseases with careful monitoring and after discussion with the patient and relevant clinicians regarding the risk of a flare of the auto-immune disease, planned treatment of the flare, and risk of death from auto-immune disease or melanoma.

Practice point

Practice point 14 Toxicity to one class of checkpoint inhibitor (e.g. anti-CTLA-4, ipilimumab) does not preclude use of a separate class of checkpoint inhibitor (e.g. anti-PD-1).

Practice point

Practice point 15 BRAF inhibitor monotherapy is not a recommended alternative to BRAF inhibitor combined with MEK inhibitor. Absolute contraindications to MEK inhibitors are rare, and single agent BRAF inhibitors are inferior to the combination in both efficacy and toxicity.

Practice point

Practice point 16 Patients with serum lactate dehydrogenase >2 x upper limit of normal at baseline have shorter progression-free and overall survival for both immune and targeted therapies, thus patients should be appropriately followed up and counselled.

Practice point

Practice point 17 Chemotherapy and binimetinib (for NRAS mutant melanoma) can be considered only after progression on immune checkpoint and BRAF inhibitor-based therapy, if appropriate.

5.11.2 Considerations in making these recommendations

5.11.2.1 The use of adjuvant systemic therapies in the Australian setting

At present, the only TGA approved and PBS-funded adjuvant treatment of resected stage III melanoma (see What is the role of adjuvant systemic therapy in patients with resected melanoma?) in Australia is IFN-α. Adjuvant IFN-α confers a small improvement in absolute OS but also has significant toxicity and as such for many patients the option of routine follow-up is considered favourable to IFN-α. Given the superiority of nivolumab over ipilimumab in the CA209-238 study, and the toxicity of ipilimumab, ipilimumab does not have a current role in the adjuvant treatment of melanoma in Australia, and is unlikely to have one in the future. At present combination dabrafenib/trametinib (Combi-AD study, resected stage III melanoma), pembrolizumab (EORTIC 18071 study, resected stage III melanoma) and nivolumab (CA209-238 study, resected stage III and IV melanoma) are not PBS reimbursed for the adjuvant treatment of resected melanoma. Enrolment in a clinical trial remains an alternative to routine follow-up for many patients. Self-funded adjuvant therapy may be an option for some patients, however should be considered only in the context of a multidisciplinary team involving a medical oncologist experienced in melanoma treatment.

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5.11.3 Discussion

5.11.3.1 Issues requiring more clinical research study

There is no formal evidence comparing BRAF inhibitor-based targeted therapy versus immunotherapy in patients whose melanoma has a V600 BRAF mutation in the first-line/upfront setting.

5.11.3.2 Studies currently underway

There is a US intergroup study of dabrafenib/trametinib vs ipilimumab/nivolumab[1] and the Italian Sequential Combo Immuno and Target Therapy (SECOMBIT) Study (SECOMBIT).[2]

5.11.3.3 Future research priorities

Multiple combinations of immunotherapies, as well as immunotherapies combined with targeted therapies are underway in order to 1) look for effective combinations that are less toxic than the combination of ipilimumab and nivolumab and 2) target the 30% of patients with primary resistance to checkpoint inhibitors. One such combination that has completed phase III evaluation is pembrolizumab +/- an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor, which showed no response or survival benefit for the combination over pembrolizumab monotherapy.[3] Other examples include BRAF or MEK-directed targeted therapies combined with anti-PD-1 therapy or intra-lesional immunotherapies (e.g. TVEC) combined with anti-PD-1 therapies.

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5.11.4 References

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5.12 Radiotherapy for distant metastases

Contents

5.12.1 Introduction

Radiation therapy (RT) is an important cancer treatment modality that delivers high energy radiation to kill malignant cells by DNA damage. It is a useful treatment option for patients with metastatic melanoma. RT can provide beneficial palliation for metastatic disease such as cerebral metastases, bone pain, spinal cord compression and symptomatic soft tissue metastases. There is a general perception that melanoma is resistant to radiation based on in vitro data. However randomized clinical trials of fractionated RT have not demonstrated better outcomes with large fraction sizes and RT has been shown to be effective in controlling microscopic disease.[1][2]

Recent advances in RT treatment techniques have led to improved precision in treatment delivery, allowing higher dose within the target volume while sparing the surrounding normal tissue. Stereotactic radiosurgery (SRS) is the delivery of a single, very high dose of radiation using 3-dimensional coordinate system to a defined target and it is usually used in the treatment of brain metastasis. Stereotactic body RT (SBRT) uses similar setup as SRS but with hypofractionated (high dose per fraction in a few fractions) to any part of the body. Both deliver high, ablative doses that are effective in the control of metastases.[3]

5.12.2 Systematic review evidence

Clinical trials evaluating the use of RT in the management of metastatic malignancy predominantly include multiple histological types, including melanoma. The systematic review focused on studies that included patients with melanoma only.

5.12.2.1 Brain metastasis

Melanoma has a high propensity to metastasize to the brain. Up to 50% of patients with stage 4 disease will develop brain metastases during the course of their illness.[4] Control of brain metastasis is an important since progression of brain metastases often leads to deterioration in function and quality of life and/or neurologic death. The role of RT alone or in combination with other modalities in the management of brain metastases is complex with the recent advances in systemic therapies that are effective in brain metastasis. Multidisciplinary team input is therefore required (see Is multidisciplinary care of value in the management of melanoma?)

There have been numerous studies on the role of RT in the management of melanoma brain metastasis. Whilst there have been several randomized studies on the role of SRS and whole brain RT (WBRT) in the management of brain metastasis, the number of patients with melanoma brain metastasis in these studies was generally small. The systematic review focused on studies included melanoma only (or mainly melanoma).The studies were all non-randomised, mostly retrospective series. For patients with single or a small number of brain metastases, SRS provides high local control rate similarly to other malignancies.[5] At 6 and 12 months, the local control is about 80% and 60% and the overall survival is 70% and 15%.[6][7][8] The dose of SRS is dependent on the size of the metastases and should be prescribed as per published protocol.[9] The addition of WBRT after SRS may improve the intracranial control with no overall survival benefit. For patients with multiple brain metastases, WBRT may provide some benefit but its role has not been directly compared with systemic therapy or supportive care alone.

5.12.3 Evidence summary and recommendations

Evidence summary	Level	References
Stereotactic radiosurgery (SRS) to melanoma brain metastases achieves a high rate of local control.	III-2	[5], [7], [8], [10], [11]

Evidence-based recommendation	Grade
Stereotactic radiosurgery (SRS) should be considered for patients with single or a small number of brain metastases to maximise local control.	**C**

Evidence-based recommendation	Grade
For patients with multiple brain metastases, whole brain radiation therapy may provide some palliative benefits.	**C**

Practice point

All melanoma patients with distant metastases should be reviewed at a multidisciplinary team meeting to ensure optimal drug, surgery and RT treatment combination.

5.12.4 Non-systematic review evidence

5.12.4.1 Adjuvant WBRT after local treatment of single or oligo brain metastases

A total of four randomised trials reported on selected patients with up to 4 brain metastases (any histologies) treated with SRS alone versus WBRT and SRS.[12][13][14][15] The addition of WBRT when added to SRS significantly improved local control of the SRS treated lesions as well as distant brain control. However WBRT did not provide an overall survival benefit and was associated with a decline in neurocognitive function. In a randomised, phase 3 trial of SRS to surgical cavity vs WBRT in patients with one resected brain metastasis, SRS was associated with a significantly shorter time to intracranial progression than WBRT (6.4 months vs 27.5 months, HR 2.45, $p<0.001$).[16] The cognitive deterioration-free survival was better with SRS to the cavity (3.7 months vs 3.0 months, $p<0.001$) and there was no difference in the overall survival between the 2 groups. Hippocampal avoidance WBRT using intensity modulated RT has been shown in one phase 2 study to lessen the effect of WBRT on neurocognitive function.[17]

5.12.4.1.1 Adjuvant stereotactic radiosurgery to surgical cavity

A randomised, phase 3 study showed the addition of SRS boost to the surgical cavity significantly improved the 12-month freedom from local recurrence compared with observation in patients with 1-3 completely resected brain metastases (72% vs 43%, HR=0.46, $p<0.015$).[18] The benefit was seen in all histologies including melanoma. There was no difference in the overall survival between the 2 groups. Multiple retrospective studies of SRS to the surgical cavity after resection of melanoma metastasis have shown local control rates greater than 70 %, which is similar to surgery with postoperative WBRT.[19][20]

5.12.4.1.2 Bone pain and spinal cord compression

RT is effective in relieving pain from bony metastasis with complete pain relief in 23% and overall response rate of 60%.[21] A systematic review of 27 randomised trials including a variety of malignancies showed that a single fraction of 8 Gy was as effective as multiple fractions in relieving bone pain. However, patients who received a single fraction of RT were 2.6 times more likely to require retreatment with RT than those treated with multiple fractions of RT.

For patients with spinal cord or cauda equina compression, urgent RT is recommended for those who are not surgical candidates. Improvement in neurologic function is variable, and is dependent on the neurological function prior to treatment.[22]

5.12.4.1.3 Skin, soft tissue and lymph node metastases

Skin and soft tissue metastases (including in transit disease), and lymph node metastases can be problematic, causing pain, bleeding or compression of surrounding normal structures. RT frequently provides symptomatic benefit and prolonged local disease control. In a randomised study that examined the effectiveness of two different RT schedules in the treatment of metastatic disease in soft tissue and nodal region showed an overall response rate of 58.7% and complete response rate of 23.8% [2]. This type of treatment is generally well tolerated.

See in-transit metastatic melanoma

5.12.5 Practice points

Practice point
Patients with single or a small number of brain metastases should be given the opportunity to discuss adjuvant radiotherapy to the surgical cavity and/or the whole brain.

Practice point
Patients with painful bone metastasis should be considered for short course of RT for pain relief.

Practice point
RT should be considered in patients with problematic skin, soft tissue or nodal metastasis that have not responded to systemic therapy.

5.12.6 Issues requiring more clinical research study

Hippocampal avoidance WBRT: Randomised data are required to quantify the benefit of hippocampal avoidance whole brain radiation therapy in reducing effects on neurocognitive function. Best drug/RT combination and sequencing, response rate and toxicity: Future research should focus on the best combination RT and systemic therapy, especially immunotherapy, to understand the mechanism of synergy if any, the toxicty profile and ultimately to improve outcome.

5.12.6.1 Conclusions

Since the 2008 guideline was published, there have been major advances in systemic therapy for melanoma. The role of RT in combination with these newer systemic agents in patients with distant metastasis continues to evolve. With the prolongation of survival of patients with stage 4 melanoma, the delivery of RT needs to be carefully tailored to ensure long term symptom control with minimal acute and late toxicities.

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5.12.8 Appendices

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5.13 Radiotherapy following resection of involved lymph nodes

Contents

5.13.1 Introduction

Melanoma has had a reputation as a disease that is more difficult to control with RT than most other histological types. Therefore, the use of adjuvant radiotherapy (RT) following surgery for locally advanced melanoma has not been accepted as standard management in the same manner as other common cancer types. Numerous retrospective studies have addressed this issue in melanoma, with mixed results as to the benefit of adjuvant RT following therapeutic lymph node dissection. It is likely that selection bias and lack of generalisability have contributed to the variability of results. A randomised controlled trial (RCT) has helped to resolve the uncertainty.

Locoregional tumour recurrence is frequently associated with significant morbidity. However, the role of adjuvant RT must be considered in the era of effective systemic therapy, where longer survival is now possible and late complications of treatment may cause considerable morbidity.

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5.13.2 Systematic review evidence

5.13.2.1 Randomised controlled trial

A single RCT was identified comparing regional lymph node dissection alone with regional lymph node dissection followed by adjuvant RT.[1][2] A total of 217 patients who had undergone complete cervical, axillary or inguinal lymphadenectomy for metastatic melanoma in the regional lymph node basin were randomised to surgery alone (n=108) versus surgery followed by adjuvant radiotherapy (n=109). The criteria for eligibility included the number of involved nodes (any involved parotid node, two involved nodes in cervical or axilla, three involved nodes in groin), the size of involved nodes (≥3 cm in cervical node, ≥4 cm for axillary or inguinal nodes) and extracapsular extension.

Adjuvant RT consisted of a mildly hypofractionated schedule (48 Gray in 20 fractions). The endpoints were lymph-node basin relapse, overall survival, relapse-free survival, late toxicity and quality of life.[1][2]

Results were reported at 3 and 5 years. At 3 years there was a significant reduction in lymph node basin relapse (31% vs 19%, p=0.04) but no difference in overall survival or relapse-free survival.[1] At 5 years the cumulative incidence for isolated lymph node basin relapse as a site of first relapse was 8.3% for adjuvant radiotherapy and 23% for surgery alone (p=0.002).[2] There was no difference in overall survival.[2] Quality of life was the same in both groups, but late toxicity was increased in the adjuvant RT arm, particularly in field fibrosis and leg oedema following inguinal treatment.[2]

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5.13.2.2 Cohort studies

There were eight retrospective cohort studies identified comparing lymph node dissection alone with adjuvant RT.[3][4][5][6][7][8][9][10] The endpoints were generally the infield recurrence rates and overall survival. All cohort studies suffered from selection bias, as melanomas with high risk features and considered more likely to suffer locoregional relapse were considered for adjuvant RT. Surgical technique and RT doses and schedules varied between studies. The results varied greatly between studies, with conflicting conclusions regarding both the local control and possible survival benefits of adjuvant RT. As a result of these uncertainties, these retrospective cohort studies were disregarded in this guideline.[3][4][5][6][7][8][9][10]

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5.13.3 Evidence summary and recommendations

Evidence summary	Level	References
Adjuvant RT following therapeutic lymph node dissection decreased the risk of locoregional recurrence but did not improve survival compared with surgery alone.	II	[1]
Adjuvant RT following therapeutic lymph node dissection increased late toxicity, especially soft tissue fibrosis in the treated lymph node basin and leg oedema after groin irradiation.	II	[2]

Evidence-based recommendation	Grade
Adjuvant RT following regional lymph node dissection may be considered following histopathological identification of high risk features if potentially effective systemic therapy is not available.	**B**

Practice point
Patients at high risk of locoregional recurrence are also at high risk of distant metastases. The decision to recommend adjuvant RT should be made in a multidisciplinary forum where all options for further local and systemic therapy are addressed. In particular, the role of local treatments including adjuvant RT is changing rapidly as effective systemic therapies become available.

Practice point

Adjuvant RT may be considered also for (i) positive margins (ii) after therapeutic dissection where further surgical clearance is not feasible (eg parotid) and (iii) further recurrence after surgery.

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6 Management of mucosal melanoma

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7 Management of ocular melanoma

There are two primary types of ocular melanoma, uveal melanoma (arising in the iris, choroid and ciliary body) and conjunctival melanoma. Both types are uncommon.[1][2]

7.1 Treatment for ocular melanoma

For uveal melanoma, eye-conserving plaque radiotherapy is the most common treatment and results in similar rates of local control to surgery for most tumours.[1] Other forms of treatment include periodic observation, transpupillary laser thermotherapy (TTT), photodynamic therapy (PDT), charged particle irradiation, local tumour resection, enucleation and rarely exenteration.[1][3] Despite effective local treatment, the survival rate of uveal melanoma has not changed over a 25-year period.[1] This may well reflect an inability to prevent or treat metastatic disease. Uveal melanoma has a unique biomolecular signature which is quite distinct from that of cutaneous melanoma. While there have been significant improvements in molecular prognostic testing to sub-classify patients, to date, this has not translated into improvements in patient survival.[1][4]

Similarly for conjunctival melanoma, there has been a move to using eye-conserving treatment.[2][5] Local resection is well established and commonly used. Topical chemotherapy, cryotherapy and radiotherapy have a definite role as adjunctive treatments[2][5] Conjunctival melanoma has a biomolecular signature which is more similar to that of cutaneous melanoma (compared to uveal melanoma) and patients with advanced disease have had similarly good outcomes with targeted systemic treatment and immunotherapies.[6]

Periocular melanoma includes eyelid and orbital melanoma; both are rare conditions.

The management of ocular melanoma is complex and should be conducted in specialised units where eye-conserving therapies and dedicated pathology services are available for ocular melanoma.

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7.2 Evidence summary and recommendations

Evidence summary	Level	References
Eye-conserving therapies for ocular melanoma result in similar rates of local control to enucleation.	IV	[1]
The first surgery is most important. Inappropriate primary surgery results in upstaging of disease and a worse prognosis due to inadvertent tumour seeding	IV	[2], [5]

Evidence-based recommendation	Grade
Ocular melanoma is a complex and uncommon form of melanoma that should be managed in specialised units where multidisciplinary ocular cancer services are available.	**C**

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8 Multidisciplinary care of melanoma patients

Contents

8.1 Background

Patients with melanoma can experience very different clinical courses, with the requirements for appropriate treatment and support dependent on their stage of disease. The great majority present with early (stage I or stage II) melanoma and their care is usually provided by a general practitioner, a dermatologist or a surgeon, with critically important input from a pathologist. If sentinel node biopsy is undertaken, a nuclear medicine physician is also involved.

A much smaller group of patients present with or develop advanced (stage III and stage IV) melanoma and their care can involve further medical and allied health specialists – surgical oncologists, medical oncologists, radiation oncologists, specialty site surgeons (e.g. neurosurgeons, upper gastrointestinal tract surgeons), radiologists (both diagnostic and interventional), oncology nurses, physiotherapists, clinical trial staff, palliative care providers and psychologists. In some settings this care is provided in a sequential manner, where each specialty independently makes a recommendation but then interacts with other specialties, with written communication between care providers.

A more satisfactory alternative to this process for patients with stage III and stage IV melanoma is fully integrated multidisciplinary care, in which all involved specialists (including pathologists) meet to discuss treatment options and any uncertainties relating to their cases, share the latest evidence and consider patient suitability for clinical trials. The outcome of the multidisciplinary discussion can then be fed back to the patient directly, or via their primary care provider. This coordinated multidisciplinary approach has been shown to lead to more carefully considered care decisions, fewer missed opportunities for better care or clinical trial involvement, and greater collaboration across specialties. Multidisciplinary clinics tend to exist in large cancer treatment facilities and feasibility usually excludes attendance by general practitioners, however detailed information should always be fed back to primary care providers. Based on limited clinical trial evidence but many reported non-trial assessments and case series, it appears that, as would be expected, multidisciplinary clinics lead to better health outcomes for cancer patients and enhanced clinical trial recruitment.

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8.2 Evidence

Is multidisciplinary care of value in the management of melanoma?

Despite the absence of good quality randomised trials of multidisciplinary care in melanoma patients, there is strong support from expert bodies for a multidisciplinary approach.[1] This is largely based on extrapolation from non-trial data in other cancers, where it is associated with improved survival.[2][3]

Current guidelines for melanoma management in the United States[4] and Europe[5] do not include recommendations in relation to multidisciplinary care. Guidelines from the United Kingdom recommend referral to a multidisciplinary team for management of oligometastatic stage IV melanoma[6] but provide no evidence to support this recommendation.

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8.2.1 Evidence summary and recommendations

Evidence summary	Level	References
Multidisciplinary care improves quality of life in melanoma patients.	I, II	[7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]

Evidence-based recommendation	Grade
Multidisciplinary care should be considered in the management of all patients with stage III and stage IV melanoma.	C

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8.4 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 working party members and contributors). 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 clinical questions).

The Management Committee proposed lead authors for each included clinical question. The nominated individuals were invited to join the (see multidisciplinary working party). 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 multidisciplinary working party).

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 four sets of completed content and associated recommendations have been released for public consultation between 2016 and 2018. The full list of clinical questions shows those still in development.

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. 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, the Guidelines Resource Centre 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 the sections below (*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.[1] 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.

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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.

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:

8.1.4.4.1 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
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined	A prospective cohort study	A prospective cohort study	A randomised controlled trial

		clinical presentation			
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.

8.1.4.5.1 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	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	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.

8.1.4.5.2 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.

8.1.4.5.3 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

Each set of 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

This guideline is being developed in a staged process.

- The first set of draft clinical questions (Features of Melanoma, Biopsy, Sentinel Node Biopsy, Excision Margins) were made available on the wiki for public consultation from 14 May to 14 June 2016.
- The second set of draft clinical questions (Diagnostic aids for melanoma (Dermoscopy) and Confocal microscopy) were made available on the wiki for public consultation from 23 January to 17 February 2017.
- The third set of draft clinical questions (Investigations & follow-up; Identification & management of high-risk individuals; Total body photography; Clinical information for the pathologist; Lymphadenectomy; Radiotherapy for distant metastases) were made available on the wiki for public consultation from 15 September to 15 October 2017.
- The fourth set of draft clinical questions (Adjuvant radiotherapy [involved lymph nodes]; Systemic therapy, immunotherapy and targeted therapies; Satellite and in-transit metastatic melanoma; Lentigo maligna; Primary desmoplastic and neurotropic melanomas) were made available on the wiki for public consultation from 16 April to 16 May 2018.
- The fifth set of draft clinical questions (Ocular melanoma, Mucosal melanoma, Distant metastases and surgery, Multidisciplinary care, Pregnancy and melanoma and Treatment of brain metastases in advanced melanoma) were made available on the wiki for public consultation from 15 June to 16 July 2018.
- The sixth and final set of draft clinical questions (Melanocytic tumour of unknown malignant potential [MelTUMPs] and Melanoma in children) were made available on the wiki for publication consultation between 18 March to 16 April 2019.

During each public consultation period, 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 periods were compiled and sent to the relevant lead author (and subcommittee, when required) to review the draft content, assessing and considering the submitted comments. Any additional submitted paper during public consultation was assessed by the methodological team against the review protocol.

Wider Working Party review of the public consultation comments and suggested amendments was facilitated by email or teleconference. Subsequent changes to the draft were 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 by request 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.

8.1.7.1 Journal articles developed out of the guideline

Lead authors of the guideline will be encouraged to develop and submit articles out of their sections to promote usage of the guideline. Published articles are noted here: Journal articles developed out of the guideline.

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8.1.8 Future updates

The *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 Management Committee

Member name	Position
Professor John Thompson AO	Executive Director, Melanoma Institute Australia (until December 2016); Senior Surgeon, Melanoma Institute Australia; Professor of Melanoma and Surgical Oncology, The University of Sydney
Professor Michael Henderson	Professor of Surgery, University of Melbourne; Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC
Professor John Kelly	Dermatologist, Victorian Melanoma Service, Alfred Hospital, Melbourne

Member name	Position
Professor Georgina Long	Co-Medical Director, Melanoma Institute Australia (from December 2016); Medical Oncologist and Professor of Melanoma Medical Oncology and Translational Research, Melanoma Institute Australia and The University of Sydney, NSW
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	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); Clinical Professor, Pathology, The University of Sydney, NSW
Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital, NSW
Jutta Thwaites	Head, Clinical Guidelines Network (until November 2016)
Laura Wuellner	Acting Head, Clinical Guidelines Network (from November 2016)

For details of Working Party authorship and subcommittee membership, please see the membership for each guideline question.

8.2.2 Membership: Multidisciplinary Working Party

The Management Committee established a multidisciplinary working party to develop these guidelines (*denotes Management Committee member in the table below).

The multidisciplinary 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	Name	Specialty/position
Chair of working party*	Professor John Thompson AO	Executive Director, Melanoma Institute Australia (until December 2016); Senior Surgeon, Melanoma Institute Australia; Professor of Melanoma and Surgical Oncology, The University of Sydney, NSW
Lead Author	A /Professor Andrew	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD

Role	Name	Specialty/position
	Barbour	
Lead Author	Dr Matteo Carlino	Medical Oncologist Westmead and Blacktown Hospitals, Melanoma institute Australia Clinical Senior lecturer, University of Sydney, NSW
Lead Author	Dr David Gyorki	Consultant Surgeon, Peter MacCallum Centre, VIC
Lead Author*	Professor Michael Henderson	Professor of Surgery, University of Melbourne; Co-Chair, Melanoma and Skin Service, Peter MacCallum Cancer Centre, VIC
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	Professor Richard Kefford AM	Professor of Cancer Medicine, Macquarie University, NSW
Lead Author*	Professor John Kelly	Dermatologist, Victorian Melanoma Service, Alfred Hospital, Melbourne, VIC
Lead Author*	Professor Georgina Long	Co-Medical Director, Melanoma Institute Australia (from December 2016); Medical Oncologist and Professor of Melanoma Medical Oncology 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 MDI Co-Director, Centre for Cancer Research, Westmead Institute of Medical Research Chair, Research Committee, Melanoma Institute Australia, University of Sydney, NSW
Lead Author	Dr Victoria Mar	Dermatologist and Director, Victorian Melanoma Service, Alfred Health, Melbourne, VIC
	Professor	The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital;

Role	Name	Specialty/position
Lead Author	Scott Menzies	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
Lead Author	Dr Rachael Morton	Director of Health Economics, NHMRC Clinical Trials Centre, 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	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); 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
Lead Author*	Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital, NSW
GP representative	Dr Margaret Hardy	General practitioner Gladesville Medical, NSW

Role	Name	Specialty/position
GP representative	Dr Paul Fishburn	General practitioner, NSW
Consumer representative	Alison Button-Sloan	Patient advocate, VIC
Consumer representative	Clinton Heal	Patient advocate, CEO and Founder, Melanoma WA, 2011 WA Young Australian of the Year, WA
CCA Project Team Lead*	Jutta Thwaites	Head, Clinical Guidelines Network (until November 2016)
CCA Project Team Lead *	Laura Wuellner	Acting Head, Clinical Guidelines Network (from November 2016)

8.2.3 Cancer Council Australia Project Team

Role	Member name	Specialty/position
CCA Project Team member	Jutta Thwaites	Head, Clinical Guidelines Network
CCA Project Team member	Laura Wuellner	Project Manager, Clinical Guidelines Network (until November 2016); Acting Head, Clinical Guidelines Network (from November 2016 to January 2018)
CCA Project Team member	Katrina Anderson	Project Manager, Clinical Guidelines Network (from November 2016 to December 2017)
CCA Project Team member	Tamsin Curtis	Project Manager, Clinical Guidelines Network (from March 2018)
CCA Systematic Literature Reviewer Team member	Jackie Buck	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from project commencement until April 2016)
CCA Systematic Literature Reviewer Team member	Lani Teddy	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from project commencement until December 2016)
CCA Systematic Literature Reviewer Team member	Lyndal Alchin	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from project commencement until December 2016)
CCA Systematic Literature Reviewer Team		

Role	Member name	Specialty/position
member	Tamsin Parrish	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from June 2016 to December 2017)
CCA Systematic Literature Reviewer Team member	Meghna Kakani	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from January 2017 to December 2017)
CCA Systematic Literature Reviewer Team member	Cecilia Taing	Project Officer, Systematic Literature Reviews, Melanoma Guidelines (from January 2017)

8.2.4 Subcommittee membership for each guideline question

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

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

8.2.4.1 Identification and management of high-risk individuals

What are the genetic determinants of high risk for new primary melanoma? **What validated models integrate genetic and clinical risk factors into an overall measurement of high risk from new primary melanoma?** **What interventions have been shown to provide clinical benefit in those assessed to be at high risk of new primary melanoma?**	
Question lead: Professor Graham Mann	
Subcommittee members	
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
Dr Paul Fishburn	GP, The Village Medical Practice, NSW
Professor John	

Kelly	Dermatologist, Victorian Melanoma Service, Alfred Hospital, VIC
Dr Rachael Morton	Director of Health Economics, NHMRC Clinical Trials Centre, The University of Sydney
Dr Victoria Mar	Dermatologist and Director, Victorian Melanoma Service, Alfred Health, VIC

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8.2.4.2 Diagnosis

What are the clinical features of melanoma and how do atypical melanomas present?	
Question lead: Dr Victoria Mar	
Subcommittee members	
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
Professor John Kelly	Dermatologist, Victorian Melanoma Service, Alfred Hospital, Melbourne

What is the role of dermoscopy in melanoma diagnosis? **What is the role of sequential digital dermoscopy imaging in melanoma diagnosis?** **What is the role of automated instruments in melanoma diagnosis?**	
Question lead: Professor Scott Menzies	
Subcommittee members	
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

What is the role of confocal microscopy in melanoma diagnosis?	
Question leads: A/Prof Pascale Guitera	
Subcommittee members	
Prof Scott Menzies	The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital; Professor, Discipline of Dermatology, The University of Sydney, NSW
Dr Alex Chamberlain	Dermatologist, The Alfred Hospital, VIC

Prof H Peter Soyer	Director, School of Medicine, University of Queensland, QLD

What is the role of skin surface imaging (total body photography) in the early diagnosis of patients at high risk of developing melanoma?)	
Question leads: Professor John Kelly and Dr Nikki Adler	
Subcommittee members	
Dr Paul Fishburn	General practitioner
A/Prof Pascale Guitera	Senior Research Fellow, Dermatology,The University of Sydney
Clinton Heal	Patient advocate
Alison Button-Sloan	Patient advocate

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8.2.4.3 Biopsy

What type of biopsy should be performed for a pigmented lesion suspicious for melanoma?	
Question lead: Professor John Kelly	
Subcommittee members	
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	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); Clinical Professor, Pathology, The University of Sydney, NSW
Professor H Peter Soyer	Director, School of Medicine, University of Queensland, QLD

What clinical information should the clinician give the pathologist to aid diagnosis of melanoma?	
Question lead: Professor Richard Scolyer	
Subcommittee members	
A/Professor Brendon Coventry	Associate Professor, Department of Surgery, The University of Adelaide; Senior Consultant Surgeon, Royal Adelaide Hospital, SA
Professor Richard	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); Clinical

Scolyer	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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8.2.4.4 Management of primary melanoma and lentigo maligna

What are the recommended safety margins for radical excision of a primary melanoma (in situ) and radical excision of invasive melanomas?	
Question lead: A/Professor Michael Sladden	
Subcommittee members	
Dr Julie Howle	Clinical Senior Lecturer, Surgery, The University of Sydney, NSW
Professor Omgo Nieweg	Surgeon, Melanoma Institute Australia, NSW
A/ Professor Brendon Coventry	Surgeon, The University of Adelaide, Royal Adelaide Hospital

When is a sentinel node biopsy indicated?	
Question lead: Dr David Gyorki	
Subcommittee members	
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Victoria Mar	Dermatologist and Director, Victorian Melanoma Service, Alfred Health, VIC
Dr Mark Hanikeri	Director, Western Australia Plastic Surgery Centre, WA
Dr Shahneen Sandhu	Medical Oncologist, Peter MacCallum Cancer Centre, VIC

Should patients with a positive sentinel lymph node biopsy have a complete node dissection?	
Question lead: A/Professor Andrew Spillane	
Subcommittee members	
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

What are the most effective treatment/management interventions to improve outcomes in patients with lentigo maligna?	
Question lead: Professor H Peter Soyer	
Subcommittee members	
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	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); 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

What is the optimal management for primary desmoplastic and neurotropic melanomas? **What is the role of sentinel node biopsy for desmoplastic melanoma?**	
Question lead: A/Professor T Michael Hughes	
Subcommittee members	
Professor John Kelly	Dermatologist, Victorian Melanoma Service, Alfred Hospital, Melbourne
Professor Richard Scolyer	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); 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 David Gyorki	Consultant Surgeon, Peter MacCallum Centre, VIC
A/Professor Angela Hong	Radiation Oncologist, Melanoma Institute Australia; Clinical Associate Professor, Medicine, The University of Sydney, NSW
Dr Alex Varey	Staff Specialist, Department of Plastic and Maxillofacial Surgery, Westmead Hospital, Sydney, Australia

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8.2.4.5 Melanoma in children

HOW SHOULD MELANOMA IN CHILDHOOD BE MANAGED?
Question lead: Dr Chris McCormack

Subcommittee members	
Rachel Conyers	
Professor Richard Scolyer	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); Clinical Professor, Pathology, The University of Sydney, NSW
Friyana Bhabha	
Saxon Smith	

8.2.4.6 Management of melanocytic tumour of unknown malignant potential

HOW SHOULD MELANOCYTIC TUMOUR OF UNKNOWN MALIGNANT POTENTIAL (MELTUMP) BE MANAGED?	
Question lead: Dr Alex Varey	
Subcommittee members	
Name	**Position/speciality**
Professor Richard Scolyer	Conjoint Medical Director, Melanoma Institute Australia (from December 2016); Clinical Professor, Pathology, The University of Sydney, NSW
Professor John Thompson AO	Executive Director, Melanoma Institute Australia (until December 2016); Senior Surgeon, Melanoma Institute Australia; Professor of Melanoma and Surgical Oncology, The University of Sydney

8.2.4.7 Melanoma in pregnancy

HOW SHOULD MELANOMA IN PREGNANCY BE MANAGED?	
Question lead: Dr Julie Howle	
Subcommittee members	
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

8.2.4.8 Investigations and follow-up

WHAT INVESTIGATIONS SHOULD BE PERFORMED FOLLOWING A DIAGNOSIS OF PRIMARY CUTANEOUS MELANOMA FOR ASYMPTOMATIC STAGE I AND II PATIENTS?
Question lead: Dr Rachael Morton

Subcommittee members	
A/Professor Andrew Barbour	General Surgeon, Greenslopes Private Hospital, Princess Alexandra Hospital, QLD
Dr Victoria Mar	Dermatologist and Director, Victorian Melanoma Service, Alfred Health, VIC
A/Professor Mark Smithers	Associate Professor, Department of Surgery, The University of Queensland, QLD

WHAT INVESTIGATIONS SHOULD BE PERFORMED WHEN IN TRANSIT AND/OR REGIONAL NODE DISEASE (STAGE III MELANOMA) IS DIAGNOSED?	
Question lead: Dr Robyn Saw	
Subcommittee members	
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

WHAT INVESTIGATIONS SHOULD BE PERFORMED WHEN STAGE IV MELANOMA IS DIAGNOSED?	
Question lead:Professor Michael Millward	
Subcommittee members	
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

HOW SHOULD PATIENTS AT EACH STAGE OF MELANOMA BE FOLLOWED AFTER INITIAL DEFINITIVE TREATMENT? WHAT ARE THE IDEAL SETTINGS, DURATION AND FREQUENCY OF FOLLOW-UP FOR PATIENTS WITH MELANOMA?
Question lead: A/Professor Andrew Barbour
Subcommittee members

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
Wenyuan Liu	Dermatologist, Alfred Hospital, Peter MacCallum Cancer Centre, Victorian Melanoma Service, VIC
Professor Scott Menzies	The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital; Professor, Discipline of Dermatology, The University of Sydney, NSW
Dr Rachael Morton	Director of Health Economics, NHMRC Clinical Trials Centre, The University of Sydney

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8.2.4.9 Treatment for macroscopic nodal metastasis

WHAT IS THE APPROPRIATE TREATMENT FOR MACROSCOPIC (I.E. DETECTABLE CLINICALLY OR BY ULTRASOUND) NODAL METASTASIS?	
Question lead: Professor Michael Henderson	
Subcommittee members	
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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8.2.4.10 Treatment for satellite and in-transit metastatic melanoma

WHAT ARE THE MOST EFFECTIVE TREATMENTS FOR SATELLITE AND IN TRANSIT METASTATIC MELANOMA?	
Question lead: Professor Michael Henderson	
Subcommittee members	
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
Dr John Spillane	General Surgeon, Epworth Eastern Consulting, VIC

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8.2.4.11 Systemic therapy, immunotherapy and targeted therapies

WHAT IS THE ROLE OF ADJUVANT SYSTEMIC THERAPY IN PATIENTS WITH RESECTED STAGE 3 MELANOMA?	
Question lead: Dr Matteo Carlino	
Subcommittee members	
Dr Victoria Atkinson	Senior Staff Specialist, Princess Alexandra Hospital; Visiting Medical Oncologist, Greenslopes Private Hospital, QLD
Professor Georgina Long	Co-Medical Director, Melanoma Institute Australia (from December 2016); Medical Oncologist and Professor of Melanoma Medical Oncology and Translational Research, Melanoma Institute Australia and The University of Sydney, NSW
Dr Alex Menzies	Medical Oncologist, Royal North Shore Hospital, 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
Dr David Gyorki	Consultant Surgeon, Peter MacCallum Centre, VIC

DOES SYSTEMIC DRUG THERAPY IMPROVE PROGRESSION FREE AND/OR OVERALL SURVIVAL IN UNRESECTABLE STAGE II AND STAGE IV MELANOMA?	
Question lead: Professor Georgina Long	
Subcommittee members	
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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8.2.4.12 Radiotherapy

FOR PATIENTS WITH DISTANT METASTASIS (OTHER THAN BRAIN METASTASES), WHEN IS RADIOTHERAPY INDICATED?	
Question lead: A/Professor Angela Hong	
Subcommittee members	
Dr Gerald Fogarty	Director, Radiation Oncology, Mater Hospital, NSW
Professor Graham Stevens	Director of Radiation Oncology, Orange General Hospital, NSW

IS ADJUVANT RADIOTHERAPY OF VALUE FOLLOWING RESECTION OF INVOLVED LYMPH NODES?	
Question lead: Professor Graham Stevens	
Subcommittee members	
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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8.2.4.13 Surgical therapy for patients with distant metastases

For patients with distant metastases, when is surgical therapy indicated?	
Question lead: A/Prof Andrew Spillane	
Subcommittee members	
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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8.2.4.14 Treatment approaches to brain metastases in patients with advanced melanoma

What is the role of systemic drug therapy in the management of patients with advanced melanoma brain metastases?	
Question lead: Professor Georgina Long	
Subcommittee members	
A/Professor Angela Hong	Radiation Oncologist, Melanoma Institute Australia; Clinical Associate Professor, Medicine, The University of Sydney, NSW
Dr Brindha Shivalingam	Director of Neurosurgery, The Chris O'Brien Lifehouse; Consultant Neurosurgeon, Royal Prince Alfred Hospital and The Mater Hospital North Sydney
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 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 Mark Shackleton	Group Leader, Cancer Development and Treatment Laboratory, Peter MacCallum Cancer Centre, NSW

What is the recommended surgical treatment of brain metastases in patients with advanced melanoma?	
Question lead: Dr Brindha Shivalingam	
Subcommittee members	
Professor Georgina Long	Co-Medical Director, Melanoma Institute Australia (from December 2016); Medical Oncologist and Professor of Melanoma Medical Oncology and Translational Research, Melanoma Institute Australia and The University of Sydney, NSW
A /Professor Angela Hong	Radiation Oncologist, Melanoma Institute Australia; Clinical Associate Professor, Medicine, The University of Sydney, NSW

When is radiotherapy indicated for patients with distant brain metastases?
Question lead: A/Prof Angela Hong
Subcommittee members

Professor Georgina Long	Co-Medical Director, Melanoma Institute Australia (from December 2016); Medical Oncologist and Professor of Melanoma Medical Oncology and Translational Research, Melanoma Institute Australia and The University of Sydney, NSW
Dr Brindha Shivalingam	Director of Neurosurgery, The Chris O'Brien Lifehouse; Consultant Neurosurgeon, Royal Prince Alfred Hospital and The Mater Hospital North Sydney

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8.2.4.15 Mucosal melanoma

What is the appropriate treatment of mucosal melanoma?
Question lead: Professor Michael Henderson

8.2.4.16 Ocular melanoma

What is the appropriate treatment of ocular melanoma?	
Question lead: A/Prof Max Conway	
Subcommittee members	
Dr Michael Giblin	Clinical Senior Lecturer, Clinical Opthalmology & Eye Health, Central Clinical School
Dr Svetlana Cherepanoff	Consultant Pathologist & Leader, Ophthalmic Pathology Research Group, Brain and Mind Centre, The University of Sydney

8.2.4.17 Multidisciplinary care

IS MULTIDISCIPLINARY CARE OF VALUE IN THE MANAGEMENT OF MELANOMA?
Question lead: Prof John Thompson & Dr Gabrielle Williams

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8.2.5 Acknowledgement

Sincere thanks to Professor Ian Olver AM 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

Identification and management of high-risk individuals

- What are the genetic determinants of high risk for new primary melanomas?
- What validated models integrate genetic and clinical risk factors into an overall measurement of high risk from new primary melanoma?
- What interventions have been shown to provide clinical benefit in those assessed to be at high risk of new primary melanomas?

Diagnosis

- What are the clinical features of melanoma and how do atypical melanomas present?
- Diagnostic aids for melanoma
- What is the role of dermoscopy in melanoma diagnosis?
- What is the role of sequential digital dermoscopy imaging in melanoma diagnosis?
- What is the role of automated instruments in melanoma diagnosis?
- What is the role of confocal microscopy in melanoma diagnosis?
- What is the role of skin surface imaging (total body photography) in the early diagnosis of patients at high risk of developing melanoma?

Biopsy

- What type of biopsy should be performed for a pigmented lesion suspicious for melanoma?
- What clinical information should the clinician give the pathologist to aid diagnosis of melanoma?

Definitive margins for excision of primary melanoma

- What are the recommended safety margins for radical excision of a primary melanoma?
- What are the recommended safety margins for radical excision of invasive melanomas?
- When is a sentinel node biopsy indicated?

- Should patients with a positive sentinel lymph node biopsy have a complete node dissection?
- What are the most effective treatment/management interventions to improve outcomes in patients with lentigo maligna?
- Primary desmoplastic and neurotropic melanomas
  - What is the optimal management for primary desmoplastic and neurotropic melanomas?
  - What is the role of sentinel node biopsy for desmoplastic melanomas?

Melanoma in children

- How should melanoma in children be managed?

Management of melanoma in pregnancy

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

- Should hormone replacement therapy or oral contraceptive pill be discontinued upon development of melanoma?

Management of melanocytic tumour of unknown malignant potential

- What is the role of sentinel node biopsy in the management of MELTUMPs?
- In patients with MELTUMPs, what excision margins are appropriate?

Investigations and follow-up for melanoma patients

- What investigations should be performed following a diagnosis of primary cutaneous melanoma for asymptomatic stage I and II patients?
- What investigations should be performed when in transit and/or regional node disease (stage III melanoma) is diagnosed?
- What investigations should be performed when stage IV melanoma is diagnosed?
- How should patients at each stage of melanoma be followed up after initial definitive treatment?
- What are the ideal frequency and duration of follow-up for melanoma patients?

Treatment of satellite and in-transit metastases

- What are the most effective treatments of satellite and in-transit metastases?

Treatment of macroscopic nodal metastases

- What is the appropriate treatment of macroscopic (i.e. detectable clinically or by imaging) nodal metastases?

Surgical therapy for patients with distant metastases

- For patients with distant metastases, when is surgical therapy indicated?

Treatment approaches to brain metastases in patients with advanced melanoma

- What is the role of systemic drug therapy in the management of patients with advanced melanoma brain metastases?
- What is the recommended surgical treatment of brain metastases in patients with advanced melanoma?
- When is radiotherapy indicated for patients with distant brain metastases?
- Summary of recommendations and practice points

Systemic therapy for distant metastases

- What is the role of adjuvant systemic therapy in patients with resected stage II and stage III melanoma?
- Does systemic drug therapy improve progression-free and overall survival in unresectable stage IIIC and stage IV melanoma?
  - Immunotherapy
  - Targeted therapies (MEK and BRAF inhibitors)
  - Chemotherapy
  - Summary of recommendations and practice points

Radiotherapy

- For patients with distant metastases (other than brain metastases), when is radiotherapy indicated?
- Is adjuvant radiotherapy of value following resection of involved lymph nodes?

Mucosal melanoma What is the appropriate treatment of mucosal melanoma?

Mucosal melanoma What is the appropriate treatment of ocular melanoma?

Multidisciplinary care Is multidisciplinary care of value in the management of melanoma?

8.4 Declarations of interest register

Declaration of interest register

See also: A Code of Practice for Declaring and Dealing with Competing Interests

Last updated: 6 February 2019.