



# Clinical Practice Guidelines for the **Management of Melanoma** in Australia and New Zealand

Approved by



MELANOMA  
NETWORK



Evidence-based  
Best Practice  
Guideline





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## **Approval**

These guidelines have been developed by ACN and NZGG. Approval of the guidelines by the NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC and NZGG expect that all guidelines will be reviewed no less than once every five years. Readers should check with the Australian Cancer Network or NZGG for any reviews or updates of these guidelines.

## **Disclaimer**

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case.

The guidelines are designed to provide information to assist in decision-making. They are based on the best evidence available at time of compilation. The guidelines are not meant to be prescriptive.

## **Conflict of interest**

The development of these clinical practice guidelines has been undertaken by a non-remunerated working party of the Australian Cancer Network and NZGG, with further support from the Cancer Institute NSW, The Cancer Council Australia and the Clinical Oncological Society of Australia.

Some members have received sponsorship to attend scientific meetings, been supported in the conducting of clinical trials, or have been involved in an advisory capacity by pharmaceutical and biochemical companies. Others have special interests indicated in specific chapters.

## **Periodic updates**

New information arising in areas considered to be of importance will be posted periodically on the ACN ([www.cancer.org.au/clinical\\_guidelines](http://www.cancer.org.au/clinical_guidelines)) and NZGG ([www.nzgg.org.nz](http://www.nzgg.org.nz)) websites.

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# Foreword

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

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

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

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

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

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

**James F Bishop** AO MD MMed MBBS FRACP FRCPA  
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Professor of Cancer Medicine, University of Sydney

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# New Zealand foreword

*The New Zealand Cancer Control Strategy Action Plan* has specific actions for prevention, early detection and treatment goals that have supported the collaboration between Australia and New Zealand to develop this guideline.<sup>1</sup> The Early Detection Advisory Group (EDAG) recommendations<sup>2</sup> included development of a trans-Tasman management guideline that supports the recognition and management of melanoma in medical practice, and emphasises the importance of the promptness and accuracy of histological reporting. It is, therefore, pleasing that we can acknowledge the dedication of those who have contributed to the development of this guideline and the importance of this to support improved service delivery to those diagnosed with melanoma.

Malignant melanoma is an important health problem in New Zealand, with incidence and death rates being among the highest in the world. Melanoma is the fourth most common type of cancer registration for both males and females, with a total of 1896 new registrations and 249 deaths reported from the cancer registry in 2004.<sup>3</sup>

The age-standardised incidence rate for melanoma in New Zealand is approximately eight times higher in non-Māori than in Māori. However, between 1996 and 2001, the relatively small number of Māori cases had a significantly higher risk of being diagnosed at more advanced stages of disease spread than non-Māori.<sup>4</sup>

Analysis of New Zealand data on melanoma shows similar patterns to Australia, with the thickness of the lesion being the strongest predictor of prognosis; and in general, the thinner the lesion, the better the outcome.

Analysis of New Zealand data also shows that advanced age, non-European ethnicity and nodular and acral lentiginous types of melanoma are associated with thicker melanomas.

Implementation of these guidelines will provide challenges. However, alignment of practice with these guidelines will encourage improvements that lead to better outcomes. I encourage all those involved in the pathway of care for melanoma to continue collaboration for improvement of outcomes supported by this evidence-based guideline.

**John Childs** MBChB FRACP FRACR

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# Preface

Australia and New Zealand have the highest melanoma incidence rates in the world. Melanoma is therefore a major public health problem in both countries, with important social and economic implications. The high incidence rates are attributed to the high proportions of the population in both countries who are of Anglo-Celtic descent, and who are inevitably exposed to high levels of solar radiation from earliest childhood.

It is well known that in both Australia and New Zealand there are fairly wide variations in the treatment recommendations given to melanoma patients, and also in the quality of care that they receive. It is hoped that these Management Guidelines will assist in raising standards and producing greater uniformity of care by specifying evidence-based protocols for the prevention, diagnosis, treatment and follow-up of melanoma. The Guidelines were compiled by a multidisciplinary working party whose members devoted countless hours of their time to the task, mostly on a voluntary basis. All the available evidence was systematically collected and evaluated using a process approved by the Australian NHMRC and the New Zealand Guidelines Group, allowing levels of evidence to be documented and grades assigned for each recommendation that was made. Even when the available evidence had been carefully analysed, however, differing points of view were sometimes expressed by members of the working group. When this occurred an explanation of the reasoning that led to the recommendation through a consensus process was provided, as well as documentation of the level of evidence for the statement or recommendation.

The Guidelines are designed primarily to assist clinicians who care for patients with melanoma. However, it is expected that as well as being a best practice resource for doctors, they will also be useful for other health care professionals and for patients themselves, who may not only seek information but who may also require reassurance that the treatment they are receiving is evidence-based.

**John F Thompson** MD FRACS FACS  
Chair, Melanoma Guidelines Working Party



# Executive summary

- In 2002 reporting of melanoma to cancer registries in Australia and New Zealand revealed it to be the fourth most common cancer and ninth most common cancer causing death in Australia and New Zealand. These registries reported melanoma incidence rates in males and females that were substantially above those from all other reporting registries worldwide<sup>1</sup>
- Increasing mortality from melanoma in Australian and New Zealand men is a disturbing trend
- Exposure to ultraviolet (UV) radiation in sunlight is the primary cause of most melanoma
- Intermittent pattern of sun exposure is most frequently associated with melanoma
- Sun bed and tanning bed exposure is associated with a small increase in melanoma risk and may be more significant when exposure occurs before 35 years of age
- Brief periods of sun exposure are needed to maintain vitamin D levels
- In the absence of any substantial evidence as to its effectiveness in reducing mortality population-based screening cannot be recommended
- It is important for practicing clinicians to be aware of high-risk groups in the population and that those in such groups also be aware of their status and establish a surveillance program
- Early detection and diagnosis of melanoma is clearly important in sound management
- Doubt in diagnosis or where melanoma is highly suspected, referral to a specialist or biopsy is appropriate. A 2mm margin for the biopsy is adequate. Prophylactic excision of benign naevi is not recommended
- Diagnosis may be enhanced by clinicians trained in dermoscopy
- It is imperative that all biopsy material be submitted for histopathological examination
- Management of involved lymph nodes should be undertaken in specialist centres
- Following diagnosis of metastatic melanoma, no further investigations are required unless surgery is planned and the detection of additional sites of distant disease would result in a change in management
- Communication skills training should help promote patient-centred care, shared decision-making, empathy and support where desired
- Timing of referral for palliative care relates to the needs of the patient and family, not just the stage of the disease
- In treating specific populations, it is important to recognise cultural differences, particularly the final disposal of body parts after surgical removal in Māori and Pacific peoples. It is also good practice in physical examination to ensure that skin areas examined include periungual and subungual skin and soles of feet
- Patients with high risk primary melanoma, lymph node involvement and melanoma in unusual sites (eg. mucosal and disseminated melanoma) are best managed by multidisciplinary teams in a specialist or melanoma facility

- These evidence-based guidelines have been developed by a multidisciplinary volunteer working party. They are aimed at encouraging improved management through evidence-based decision-making
- Guidelines are guides not rules and they are not prescriptive in any way. A good approach is to be fully aware of appropriate guidelines before making final management decisions

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## Reference

1. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. The Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington (2008).



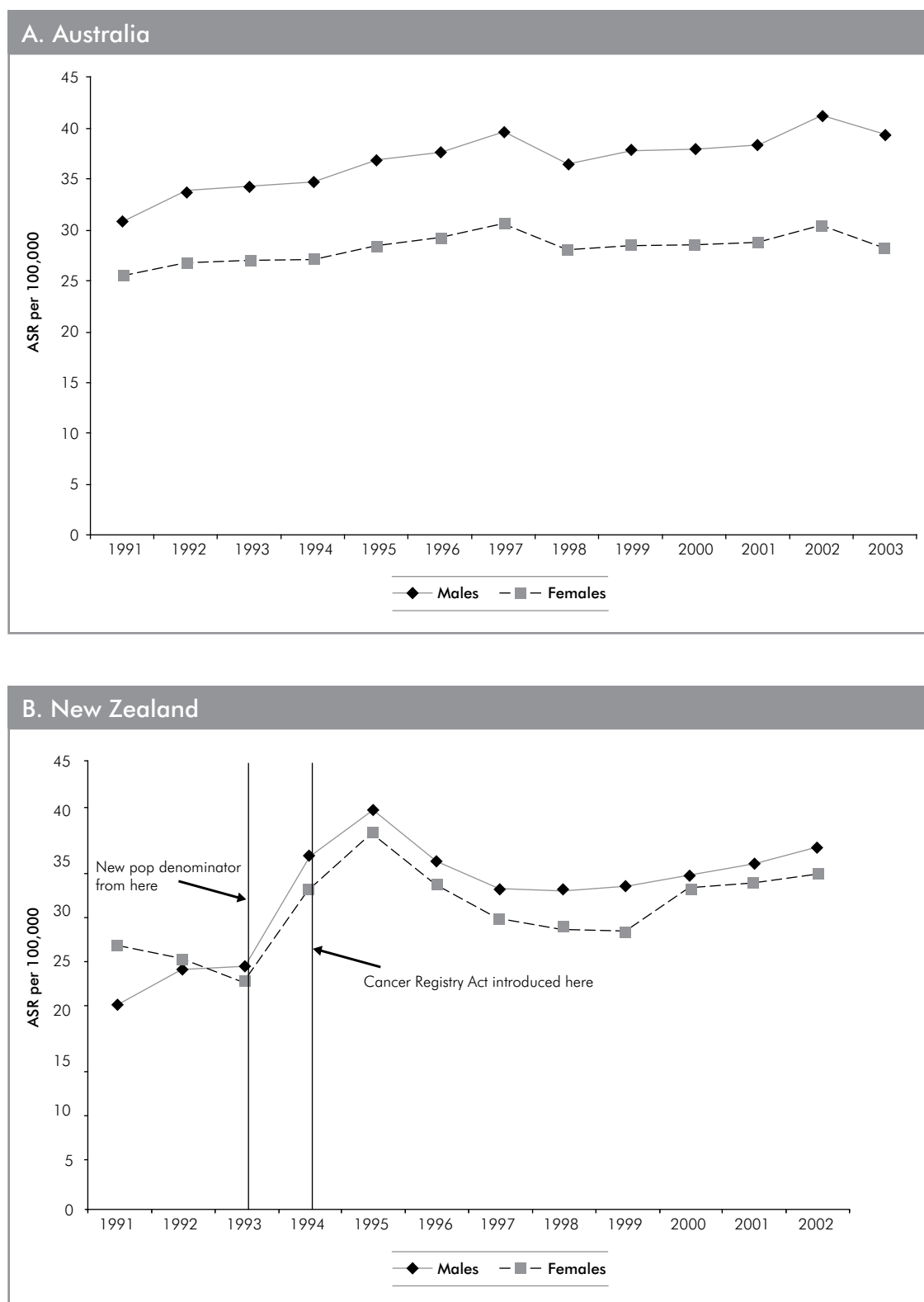
# Introduction

While melanoma is comparatively infrequent globally, it is an important contributor to the burden of cancer in Australia and New Zealand. Together, Australia and New Zealand contributed 6.4% of the cases and 3.2% of the deaths to the estimated global totals of 160,000 newly diagnosed melanomas and 41,000 deaths from melanoma in the year 2002.<sup>1</sup> While melanoma was the 18th most frequent among 25 specific categories of cancer (excluding nonmelanocytic skin cancers), and 22nd most frequent as a cause of cancer death, globally in 2002 it was the fourth most commonly diagnosed cancer and the ninth most common cancer causing death in Australia and New Zealand. Australian and New Zealand cancer registries reporting to the International Agency for Research on Cancer in 1997 (the most recent year for which data are publicly available) all had melanoma incidence rates in males and females that were substantially above those from all other reporting registries worldwide.<sup>2</sup>

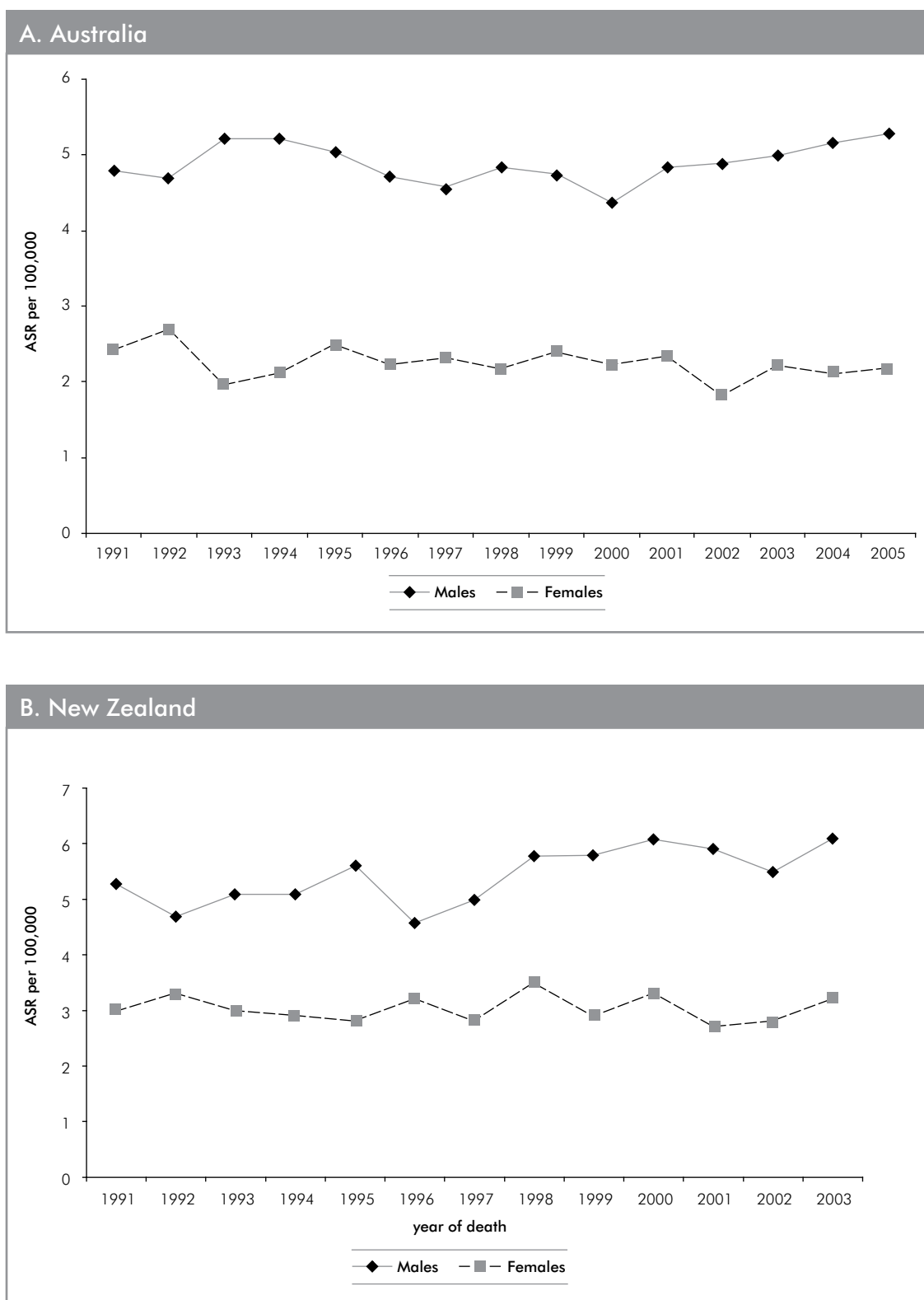
In spite of the high incidence of melanoma in Australia and New Zealand and the attention given to melanoma control in these countries, there is as yet limited evidence that their incidence rates are falling. For the period 1991–2003, incidence of melanoma in Australian males showed an upward trend; that for females, after increasing to 1997, remained steady (Figure 1A).<sup>3</sup> While corresponding patterns in New Zealand for the same period are somewhat complicated by an increase in completeness of cancer registration due to the passage of the Cancer Registry Act, 1993, the recent incidence trends are upwards in both sexes (Figure 1B).<sup>4</sup> Melanoma mortality shows a more encouraging picture in females, with the rates steady from 1991–2003 in New Zealand and falling a little in Australia to 2005; but in males, after initial periods of stability from 1991, rates now appear to be increasing in both countries (Figure 2).<sup>4,5</sup>

There is, though, some cause for hope, but also a warning note. An inspection of the incidence trends by age in Australia shows little evidence of any increase in incidence from 1991–2003 in any age-group under 45 years age.<sup>3</sup> The increases into the 1990s and 2000s have all been in older age groups and the older the age group the steeper the increase, particularly in men. Similar patterns by age are seen in the mortality trends, except that there was little upward trend in the 1990s in men up to 69 years of age and women up to 79 years of age, and there were downward trends in men up to 39 years of age and women up to 49 years of age.<sup>5</sup> It is reasonable to hope that these more favourable trends in younger age groups will extend to older age groups as the cohorts showing them age. However, there is an important exception to these patterns by age: reversal in previous flat or downward trends in most age-groups from 20–69 years of age have contributed to the increase in mortality in men that began in 2001, though it was driven mainly by continuing upward trends in the oldest men.

**Figure 1** Trends in the age-standardised incidence rates (ASR) of melanoma in Australia and New Zealand<sup>3,4</sup>



**Figure 2** Trends in the age-standardised mortality rates (ASR) of melanoma in Australia and New Zealand<sup>4,5</sup>



**Note:** Rates are standardised to the Segi World Population.

The increasing mortality from melanoma in Australian and New Zealand men is a disturbing trend. The continuing incidence increase could have contributed to it, but this may not be a sufficient explanation. Could it be due to poorer survival due, perhaps, to later diagnosis, poorer treatment or some other factor? There are published data on trends in melanoma survival in New South Wales (NSW), the most populous Australian State, covering cases incident from 1980–1998 and deaths occurring up to the end of 2000 (Table 1).<sup>6,7</sup> Five-year relative survival for men and women together increased in successive diagnosis intervals to 91.0% in the most recent interval (1994–1998). Five-year relative survival for men and women diagnosed between 1995 and 2006 in New Zealand was 90.5%. These data show no hint of a worsening in survival, but they would not be sensitive to a trend only in men and beginning with deaths in 2001. NSW cancer registry data on trends in the distribution of melanoma by thickness up to 2002 also show little evidence of an unfavourable trend (NSW Central Cancer Registry personal communication) that might cause increasing melanoma mortality.

The trend data reviewed above clearly indicate that Australia and New Zealand have some way to go before they have melanoma ‘under control’. These new guidelines will make an important and timely contribution to ensuring that melanoma control in our two countries is informed to the greatest degree possible by research evidence. The trend data also point, as will the guidelines themselves, to areas where research is required if we are to observe more favourable trends in melanoma than we have seen over the past ten or so years and in particular, during the period since the first Australian guidelines were published.

**Table 1** Trends in five-year relative survival from melanoma diagnosed in New South Wales, Australia, from 1980 to 1998<sup>6,7</sup>

Diagnosis interval*	Five-year relative survival %†
1980–1984	87.4%
1985–1988	89.2%
1989–1992	90.6%
1993–1996	90.9%
1994–1998	91.0%

\* Survival percentages are adjusted for age, sex and extent of cancer at diagnosis.

† Those diagnosed from 1980–1984 to 1993–1996 were followed-up for survival until the end of 1998; those diagnosed in the interval 1994–1998 were followed-up until the end of 2000.

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# Summary of clinical practice recommendations

These guidelines are intended for use by all practitioners and health workers who require information about management of patients with melanoma. They are wide-ranging in scope, covering prevention, screening, diagnosis and psychosocial matters as well as the clinical aspects of surgery, radiotherapy and chemotherapy.

The guidelines have been produced by a process of systematic literature review; critical appraisal and consultation encompassing all interested parties in Australia and New Zealand (see Appendix 2, p182).

This summary provides a list of the evidence-based recommendations detailed in the text of each chapter. It also provides a grade for each recommendation (A–D). The key references that underpin the recommendation are provided in the last column.

Each recommendation 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 supporting each recommendation.

## Grading of recommendations

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

## Good practice points

Good practice points are used when the conventional grading of evidence is not possible – these points represent the views of the Guideline Development Group.

## Levels of evidence

Table 2		Designations of levels of evidence according to type of research question			
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 clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>• non-randomised, experimental trial</li> <li>• cohort study</li> <li>• case-control study</li> <li>• interrupted time series with a control group</li> </ul>	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: <ul style="list-style-type: none"> <li>• non-randomised, experimental trial</li> <li>• cohort study</li> <li>• case-control study</li> </ul>
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>• historical control study</li> <li>• two or more single arm study</li> <li>• interrupted time series without a parallel control group</li> </ul>	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>• historical control study</li> <li>• two or more single arm study</li> </ul>
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
<b>Note:</b> Explanatory notes for this table are outlined in the methods handbook <sup>9</sup> available on request from the Australian Cancer Network or the New Zealand Guidelines Group.					



## Recommendations

Recommendations by chapter		Grade	Refs
<b>1</b>	<b>Prevention of melanoma</b>		
	1. Sunburn be avoided and UV protection (physical methods complemented by sunscreens) adopted	<b>B</b>	<b>2</b>
	2. Sunscreens be used to complement but not to replace physical methods of UV protection	<b>C</b>	<b>17, 19</b>
	3. Risks associated with exposure to tanning booths and sunbeds be explained	<b>C</b>	<b>8</b>
	4. As brief sun exposures are needed to maintain vitamin D levels, total lack of sun exposure is not advised without vitamin D supplementation	<b>C</b>	<b>10</b>
<b>2</b>	<b>Population screening for melanoma</b>		
	1. In the absence of substantive evidence as to its effectiveness in reducing mortality from melanoma, population-based skin screening cannot be recommended	<b>C</b>	<b>46</b>
<b>3</b>	<b>Identification and management of high-risk individuals</b>		
	1. Clinical assessment of future risk of melanoma take into account: <ul style="list-style-type: none"> <li>• person's age and sex</li> <li>• history of previous melanoma or non-melanoma skin cancer</li> <li>• family history of melanoma</li> <li>• number of naevi (common and atypical)</li> <li>• skin and hair pigmentation</li> <li>• response to sun exposure</li> <li>• evidence of actinic skin damage</li> </ul>	<b>B</b>	<b>1–6</b>
	2. 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	<b>C</b>	<b>8</b>
	<b>Good practice point</b> <ul style="list-style-type: none"> <li>• Prophylactic removal of non-suspicious lesions is not recommended since it is unlikely to increase survival and therefore may incur unnecessary procedures and give false reassurance as many new melanomas in high-risk individuals will occur outside pre-existing naevi</li> </ul>		

continued over...

Recommendations by chapter		Grade	Refs
<b>3</b>	<b>Identification and management of high-risk individuals</b> continued...		
	3. Screening for a genetic mutation such as the CDKN2A gene be contemplated only after a thorough clinical risk assessment (the patient is at personal high risk of melanoma), confirmation of a strong family history of melanoma (there is a significant probability of a family mutation), and appropriate genetic counselling	<b>C</b>	<b>9–14</b>
<b>4</b>	<b>Classification of melanoma</b>		
	1. That the current AJCC/UICC classification system be used for staging patients with melanoma	<b>B</b>	<b>3</b>
<b>5</b>	<b>Clinical diagnosis</b>		
	1. Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions	<b>A</b>	<b>21–30, 50</b>
	2. Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma	<b>B</b>	<b>34–37</b>
	3. Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma	<b>C</b>	<b>42–50</b>
	<b>Good practice points</b> <ul style="list-style-type: none"> <li>• Examination for melanoma detection requires examination of the whole skin surface under good lighting</li> <li>• A careful clinical history of specific changes in the lesion, any symptoms and their time course is critically important in assessing whether a lesion may be melanoma, particularly for melanomas that have absent or unusual clinical features for melanoma</li> <li>• Where there is a low index of suspicion for early, non-invasive melanoma a short period of observation aided by measurement, a clinical photo or dermoscopic imaging may be appropriate</li> <li>• All patients seeking advice about pigmented lesions be encouraged to regularly check their skin with the aid of a mirror or a partner and advised about the changes to look for in early melanoma</li> </ul>		

Recommendations by chapter		Grade	Refs
<b>6</b>	<b>Biopsy</b>		
	1. The optimal biopsy approach is complete excision with a 2mm margin and upper subcutis	C	1, 2, 3, 6
	2. Partial biopsies may not be fully representative of the lesion and need to be interpreted in light of the clinical findings	C	7
	3. Incisional, punch or shave biopsies may be appropriate in carefully selected clinical circumstances, for example, for large facial or acral lesions, or where the suspicion of melanoma is low	C	13–16, 18
	<b>Good practice point</b> <ul style="list-style-type: none"> <li>It is advisable to review unexpected pathology results with the reporting pathologist</li> </ul>		
<b>7</b>	<b>Histopathological reporting of cutaneous melanoma</b>		
	1. The essential components of a histopathological report: <ul style="list-style-type: none"> <li>Breslow thickness</li> <li>margins of excision (microscopic)</li> <li>mitotic rate/mm<sup>2</sup></li> <li>level of invasion (Clark)</li> <li>ulceration</li> </ul>	A	1–7
	2. The following components of a histological report are of prognostic or other value: <ul style="list-style-type: none"> <li>vascular invasion, local metastases, microsatellites and in-transit metastases, tumour-infiltrating lymphocytes, regression, desmoplasia, neurotropism, associated benign melanocytic lesion, solar elastosis, predominant cell type, histological growth pattern, growth phase and immunohistochemistry</li> </ul>	C	8–24
	3. Histological criteria, review of the primary melanoma and clinicopathological correlation be used for distinguishing between persistent primary melanoma and local metastasis	C	25–27
	4. The synoptic report be used in conjunction with, but not as a replacement for, the descriptive report	C	28, 29

continued over...

Recommendations by chapter		Grade	Refs
<b>7</b>	<b>Histopathological reporting of cutaneous melanoma</b> continued...		
	5. Pathology reports should include information from sentinel lymph biopsies, derived from multiple histological sections of sentinel nodes (including sections stained with H&E and immunohistochemically for melanoma-associated antigens including S-100)	<b>C</b>	<b>35–38</b>
	6. Non-sentinel lymph nodes should be carefully examined and reported	<b>D</b>	<b>39</b>
<b>8</b>	<b>Appropriate investigations</b>		
	1. Following the diagnosis of primary cutaneous melanoma (stage I, II) routine investigations are not required for asymptomatic patients	<b>D</b>	<b>1–9, 11–13</b>
	2. Routine investigations, including radiology, are not indicated for patients following the diagnosis of a positive sentinel lymph node in the absence of symptoms suggestive of metastatic disease	<b>D</b>	<b>3, 5–25</b>
	3. Following the diagnosis of locoregional melanoma, patients require a detailed history and physical examination. Investigations, including radiology, are indicated for symptoms suggestive of metastatic disease. CT scan of the chest, abdomen and pelvis or whole-body PET scan may be performed for the workup of otherwise asymptomatic patients prior to definitive therapy where the detection of occult metastatic disease would influence management	<b>D</b>	<b>3, 5–25</b>
	4. Patients suspected of having lymph node metastasis from cutaneous melanoma should undergo fine needle aspiration biopsy, with ultrasound or radiological guidance when required, to confirm the presence of stage III disease	<b>D</b>	<b>3, 5–25</b>
	5. Investigations, including serum LDH, CT, MRI, and/or PET scan, are indicated for symptoms suggestive of metastatic melanoma	<b>D</b>	<b>20, 24–31</b>
	6. Following the diagnosis of metastatic melanoma, no further investigations are required unless surgical therapy is planned and the detection of additional sites of distant disease would result in a change in management	<b>D</b>	<b>20, 24–31</b>

Recommendations by chapter		Grade	Refs
9	<b>Congenital melanocytic naevi</b>		
<b>Small and medium congenital melanocytic naevi</b>			
1. Prior to puberty, decisions regarding removal of these lesions be based on cosmetic considerations alone		C	3–6, 11, 13–17
2. Parents or patients be informed that the evidence regarding risk in adult life does not support routine prophylactic removal of these lesions		C	3–6, 11, 13–17
3. Patients report any suspicious changes in these lesions		C	3–6, 11, 13–17
4. Biopsy or removal of any lesions showing suspicious features be undertaken		C	3–6, 11, 13–17
<b>Large congenital melanocytic naevi more than 20cm in diameter</b>			
5. Lifetime surveillance be undertaken whether or not any surgery has been performed. This could include baseline photography and three-monthly evaluation for the first year of life, followed by six-monthly evaluation for the next three years, and then yearly evaluation		C	7–13, 17
6. Parents or patients report immediately any concerning changes that occur between follow-up visits		C	7–13, 17
7. Biopsies be undertaken immediately of any areas which show suspicious features		C	7–13, 17
<b>Good practice points</b>			
<ul style="list-style-type: none"> <li>All decisions regarding surgical management involve prolonged discussion with the parents, and later the patient, covering estimated risk of melanoma, what is involved in the surgery, the number and length of hospitalisations, possible morbidity of the procedures, and likely end cosmetic result</li> <li>MRI of the brain be undertaken in patients with large CMN in an axial distribution and those with multiple large scattered lesion, if the facilities are available. Some features of neurocutaneous melanosis, such as hydrocephalus, are amenable to treatment</li> </ul>			

Recommendations by chapter		Grade	Refs
<b>10</b>	<b>Lentigo maligna</b>		
	1. Biopsy is indicated for changing pigmented lesions on the face	<b>C</b>	<b>3, 6</b>
	2. Where lentigo maligna is histologically confirmed, complete excision is the preferred management	<b>C</b>	<b>5, 6</b>
	3. Radiotherapy is an alternative treatment option for patients where surgical excision is problematic or best avoided	<b>C</b>	<b>3–6</b>
	4. Cryotherapy is a form of treatment that may occasionally be useful in patients with severe comorbidities or in those in whom surgery is not a possible option	<b>D</b>	<b>6</b>
	5. Topical treatment modalities for lentigo maligna cannot be recommended at this time	<b>C</b>	<b>6</b>
	<b>Key point</b> <ul style="list-style-type: none"> <li>For some patients with lentigo maligna, observation for change utilising macroscopic and dermoscopic photography and measurement is an acceptable alternative to immediate excision, with a biopsy indicated for changing lesions</li> </ul>		
<b>11</b>	<b>Treatment of primary melanoma</b>		
	1. After initial excision biopsy; the radial excision margins, measured clinically from the edge of the melanoma, be: <ol style="list-style-type: none"> <li>(pTis) Melanoma <i>in situ</i>: margin 5mm</li> <li>(pT1) Melanoma &lt; 1.0mm: margin 1cm</li> <li>(pT2) Melanoma 1.0–2.0mm: margin 1–2cm</li> <li>(pT3) Melanoma 2.0–4.0mm: margin 1–2cm</li> <li>(pT4) Melanoma &gt; 4.0mm: margin 2cm</li> </ol>	<b>C</b> <b>B</b> <b>B</b> <b>B</b> <b>B</b>	<b>5, 13</b>
	2. <b>Caution</b> be exercised for melanomas 2–4mm thick, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2cm) for these tumours depending on tumour site and surgeon/patient preference	<b>B</b>	<b>5–7</b>
	3. <b>Acral lentiginous and subungual melanoma</b> 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	<b>D</b>	<b>1, 14–16</b>

continued over...

Recommendations by chapter	Grade	Refs
<b>11 Treatment of primary melanoma</b> continued...		
<p><b>Good practice points</b></p> <ul style="list-style-type: none"> <li>• Excisions should have vertical edges to ensure consistent margins</li> <li>• Caution be exercised for melanomas thicker than 2mm, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2cm) for thicker tumours depending on tumour site and surgeon/patient preference</li> <li>• Excision biopsy of the complete lesion with a narrow (2mm) margin is appropriate for definitive diagnosis of primary melanoma. Lesions excised with a margin less than those defined above should be re-excised as soon as practicable to achieve these margins</li> <li>• Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved</li> <li>• Where tissue flexibility is limited, a flap repair or skin graft is sometimes necessary subsequent to an adequate margin of removal</li> <li>• Treatment of most melanomas can be achieved on an outpatient or day-surgery basis, under local anaesthesia, unless nodal surgery is required</li> <li>• Melanoma (i) is a risk factor for new primary melanoma(s) and (ii) also has the potential to recur or metastasise. Patients should be appropriately managed and followed-up for these aspects, as discussed elsewhere in these guidelines</li> <li>• Patients should be informed that surgical excision may be followed by wound infection, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar and the possibility of further surgery</li> <li>• Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin 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. The possible use of staged Mohs excision has been proposed in such situations</li> </ul>		

continued over...

Recommendations by chapter		Grade	Refs
<b>11</b>	<b>Treatment of primary melanoma</b> continued...		
	<ul style="list-style-type: none"> <li>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</li> <li>For patients with deeper invasive melanomas (&gt; 1 mm thick), referral to a specialised melanoma centre should be considered to ensure that best practice is implemented and for the collection of national outcome data. This may present logistic difficulties in regional and remote areas, but specialist care is recommended</li> <li>The AJCC/UICC (2001)<sup>20-23</sup> system has been recommended for melanoma staging. Sentinel node biopsy (SNB) is an important prognostic factor for melanoma<sup>24</sup> but there is debate about its use in treatment.<sup>24-26</sup> SNB should be considered in patients with primary melanomas &gt; 1.2mm thick, who want to be as informed as possible about their prognosis. SNB should be performed before wider local excision</li> </ul>		
<b>12</b>	<b>Management of regional lymph nodes</b>		
	1. Patients with a melanoma greater than 1.0mm in thickness be given the opportunity to discuss sentinel lymph node biopsy to provide staging and prognostic information	<b>C</b>	<b>2, 4, 10, 12</b>
	2. SLNB be performed only following a full discussion of the options with the patient, in a unit with access to appropriate surgical, nuclear medicine and pathology services	<b>C</b>	<b>2</b>
	3. Patients who have positive sentinel lymph node biopsy be offered completion lymphadenectomy, or be referred to a specialist centre for discussion of further treatment options	<b>C</b>	<b>4</b>
	4. Therapeutic node dissection be offered to all patients with evidence of metastatic nodal disease after excluding stage IV disease using appropriate investigations	<b>C</b>	<b>16</b>

continued over...



Recommendations by chapter		Grade	Refs
12	<b>Management of regional lymph nodes</b> continued...		
	<p><b>Good practice points</b></p> <ul style="list-style-type: none"> <li>• A therapeutic node dissection includes a full levels (I to III) clearance in the axilla. A therapeutic neck dissection may include a superficial parotidectomy as clinically indicated</li> <li>• Patients with inguinal node metastases be considered for clearance of the intra-pelvic iliac and obturator nodes when the staging investigation demonstrates evidence of involvement</li> <li>• Elective clearance of the pelvic nodes be considered when there is gross macroscopic disease in the inguinal node field or there are three or more histologically positive nodes below the level of inguinal ligament</li> <li>• Patients with lymph node metastases be offered discussion with a multidisciplinary team with a view to enrolment in clinical trials</li> </ul>		
13	<b>Management of locoregionally recurrent melanoma</b>		
	1. Persistent melanoma be excised completely	C	1
	2. Adjuvant radiation therapy be considered for close or positive margins unsuitable for re-excision	C	2
	3. Local metastasis, in transit metastases and satellitosis may be managed using a variety of local treatments	C	3, 4
	4. Prophylactic isolated limb perfusion (ILP) is not recommended	A	5
	5. Recurrence on a limb with multiple or rapidly progressive lesions not suitable for local treatments is best managed with ILP using melphalan under hyperthermic conditions if technically possible	A	6
	6. ILI may be substituted for ILP	C	7
	7. Recurrence involving multiple or rapidly progressive lesions that are unsuitable for regional drug therapy be managed on an individual basis by a multidisciplinary team proficient in a range of local treatments	C	3, 4

continued over...

Recommendations by chapter		Grade	Refs
<b>13</b>	<b>Management of locoregionally recurrent melanoma</b> continued...		
In the context of locoregionally recurrent melanoma:		<b>D</b>	<b>9</b>
8. SLNB be considered if the nodal basin has not been dissected and if there is no clinical evidence of nodal involvement			
9. Lymph node dissection be performed for clinically involved nodes with no previous dissection, following confirmation of melanoma, preferably by fine needle biopsy		<b>C</b>	<b>2, 8, 9</b>
10. Postoperative adjuvant radiation therapy be considered for adverse pathological findings, though the value remains uncertain		<b>C</b>	<b>10</b>
11. Clinical recurrence in a previously dissected nodal basin be managed by excision if possible, followed by radiation therapy (unless given previously)		<b>C</b>	<b>2,10</b>
<b>14</b>	<b>Adjuvant systemic therapy of melanoma</b>		
1. Observation is acceptable management for patients with resected stage I–III melanoma		<b>B</b>	<b>1, 2</b>
2. These patients be considered for enrolment in clinical trials of adjuvant therapy. Sentinel lymph node biopsy is mandatory staging for the stratification of patients on adjuvant therapy trials. Trials of adjuvant therapy include an observation-only control arm		<b>B</b>	<b>1, 2</b>
3. Patients with high-risk disease be considered for adjuvant therapy with high-dose interferon-alpha		<b>B</b>	<b>1, 2</b>
4. Because the toxicity associated with high-dose interferon is considerable, the risks and benefits of therapy in individual patients be carefully reviewed before proceeding		<b>B</b>	<b>1, 2</b>
5. Patients be treated in an experienced medical oncology facility, monitored closely for toxicity related to treatment with interferon, and dose adjusted based on the degree of toxicity		<b>B</b>	<b>1, 2</b>

Recommendations by chapter		Grade	Refs
<b>15</b>	<b>Treatment of disseminated melanoma</b>		
	1. Patients with metastatic melanoma be referred for consideration of chemotherapy and/or palliative care to improve their symptoms	C	3, 6, 11, 12, 15, 16, 37
	2. Patients with localised symptoms from melanoma metastasis be referred for radiotherapy	C	18
	3. To improve survival, patients with limited or no extracranial disease and with favourable prognosis brain metastases be considered for surgical resection and if unresectable, for stereotactic radiosurgery. Patients with unfavourable prognostic metastases receive palliation with surgery, whole brain radiotherapy, chemotherapy, steroids or palliative care	C	19, 23, 28–30
	4. Patients with surgically operable metastases be considered for resection	C	36–45
<b>16</b>	<b>Psychosocial issues</b>		
	1. Structured psychosocial interventions, such as cognitive behavioural group therapy and psycho-education, as well as support groups, be made available to all patients with melanoma to improve their quality of life	B	8–12
	2. Communication skills training be provided to health professionals treating people with melanoma to assist them in effectively providing information, patient-centred care, shared decision-making where desired, empathy and support	C	8, 17, 20–23
	3. If the matter is raised, patients be advised that there is no known (or proven) link between psychosocial factors and survival outcome	C	1, 6, 27–33
	4. Patients be advised that individual or group psychosocial intervention may not improve their overall survival	C	4–7

Recommendations by chapter		Grade	Refs
<b>17</b>	<b>Palliative care</b>		
1. Palliative care specialists be included in the multidisciplinary melanoma treatment team to: <ul style="list-style-type: none"> <li>• provide assistance with symptom control</li> <li>• support melanoma patients and their families</li> <li>• when necessary, coordinate care of melanoma patients between settings</li> <li>• assist in clarifying goals of care</li> </ul>		<b>A</b>	<b>4, 5 11–14</b>
2. Referral for palliative care be based on the needs of the patient and family, not just the stage of the disease		<b>C</b>	<b>16–19, 23</b>
3. Patients and their families with complex needs including physical, psychosocial and spiritual domains be referred to a specialist palliative care team at any stage during the illness		<b>A</b>	<b>12–14, 22, 25, 29</b>
<b>18</b>	<b>Multidisciplinary care</b>		
1. Multidisciplinary care be considered throughout the management of patients with melanoma		<b>C</b>	<b>7</b>
<b>19</b>	<b>Follow-up</b>		
1. 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		<b>C</b>	<b>14–16</b>
2. Follow-up intervals are preferably six-monthly for five years for patients with stage I disease, three-monthly or four-monthly for five years for patients with stage II or III disease, and yearly thereafter for all patients. Ultrasound may be used in conjunction with clinical examination only in the follow-up of patients with more advanced primary disease. For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials		<b>D</b>	<b>20–25</b>
3. While it is important that clinicians weigh up the advantages and disadvantages of undertaking routine follow-up, individual patient's needs be considered before appropriate follow-up is offered		<b>C</b>	<b>6, 13, 26, 27</b>

Recommendations by chapter		Grade	Refs
<b>20</b>	<b>Clinical trials</b>		
	1. Patients can be informed that they are unlikely to be disadvantaged by participation in an RCT	<b>A</b>	<b>2</b>
	<b>Good practice point</b> <ul style="list-style-type: none"> <li>Given the lack of evidence in treating melanoma, patients be given the opportunity to enter clinical trials</li> </ul>		
<b>21</b>	<b>Treatment of desmoplastic melanoma</b>		
	1. Local wide excision for desmoplastic neurotropic melanoma conforms with the same margins as for other forms of cutaneous melanoma	<b>C</b>	<b>2</b>
<b>22</b>	<b>Mucosal melanoma</b>		
	1. The primary lesion for melanoma of the anorectal region should be managed by sphincter preserving complete local excision in most cases. APR is indicated only for patients with loco-regional disease whose primary tumour cannot be completely resected by a limited procedure	<b>D</b>	<b>2–14</b>
	2. Pelvic node failure as an isolated event is uncommon. Extended pelvic lymphadenectomy is not indicated	<b>D</b>	<b>2–14</b>
	3. There is no evidence to support elective (as compared to therapeutic) inguinal lymphadenectomy	<b>D</b>	<b>2–14</b>
	4. Sentinel node biopsy has been described in a small number of cases but there is no evidence to support its routine use at the present time	<b>D</b>	<b>2–14</b>
	5. The role for radiotherapy (RT) in patients with close/involved margins after wide local excision or abdomino perineal resection is unknown but it may be considered	<b>D</b>	<b>2–14</b>
	6. The care of patients with anorectal melanoma be undertaken by a multidisciplinary team experienced in the management of these patients	<b>D</b>	<b>2–14</b>
	7. Patients with mucosal melanoma of the head and neck are best managed by complete surgical excision. Radiotherapy has not been shown to be of benefit to patients who have undergone a complete resection but may be of benefit in patients who have residual disease	<b>D</b>	<b>17–22</b>

continued over...

Recommendations by chapter		Grade	Refs
<b>22</b>	<b>Mucosal melanoma</b> continued...		
	8. Patients be referred to a specialist unit with experience in head and neck melanoma	D	17–22
	9. Histologically confirmed melanoma of the vulva 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	D	23–30
	10. Patients with vulval melanoma be referred to a specialist unit with expertise	D	32
	<b>Good practice points</b> <ul style="list-style-type: none"> <li>Any suspicious lesions of the genital tract should be biopsied</li> <li>As there is a high incidence of systemic disease in these cases, a CT/PET scan is indicated prior to radical surgery</li> </ul>		
<b>23</b>	<b>Occult melanoma</b>		
	1. Patients with metastases and no obvious primary tumour be examined for primary melanomas in obscure sites. If none are found, assume that the primary melanoma has completely regressed	D	1, 2
<b>24</b>	<b>Ocular melanoma</b>		
	1. Ocular melanoma is a complex and uncommon form of melanoma that should be managed in specialised units where eye-conserving therapies are available	C	2
<b>25</b>	<b>Melanoma in children</b>		
	1. The pathology slides of all Spitz-like lesions in children suspected of being malignant be referred to histopathologists who are highly experienced in the differential diagnosis of such lesions	C	8–12
	2. 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	C	15–17, 21–26

Recommendations by chapter		Grade	Refs
<b>26</b>	<b>Melanoma in pregnancy (including hormone replacement therapy and oral contraceptives)</b>		
	1. Any naevus that changes during pregnancy and/or has other features suggestive of melanoma be investigated	<b>C</b>	<b>1–3</b>
	2. Melanoma in a pregnant woman be treated according to tumour thickness and ulceration, that is, as for a non-pregnant woman	<b>C</b>	<b>25</b>
	3. 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	<b>C</b>	<b>25</b>
	4. Sentinel node biopsy can be performed using only technetium in pregnant women	<b>B</b>	<b>5–8</b>
	5. Pregnant women with thicker melanomas and nodal metastases be treated in consultation with specialised centres	<b>C</b>	
	6. Hormone replacement therapy and oral contraceptives are not contraindicated in women who have or have not had melanoma	<b>C</b>	<b>32, 37–53</b>
<b>27</b>	<b>Prognostic factors and survival outcomes in cutaneous melanoma</b>		
<b>28</b>	<b>Complementary and alternative medicine</b>		
	1. Patients be encouraged to share with their treating clinician(s) their wishes to embark on either a complementary or alternative therapy	<b>C</b>	<b>1–8</b>
	2. There is no available evidence to recommend CAM over conventional therapy for adjuvant management of melanoma	<b>C</b>	<b>9</b>
	3. Patients are advised to discuss planned CAM therapy with their clinician, to ensure the safety of their action	<b>C</b>	<b>12, 13</b>
	<b>Key point</b> <ul style="list-style-type: none"> <li>• There is level IV evidence suggesting patients may derive emotional benefit from CAM therapy</li> </ul>		

Recommendations by chapter		Grade	Refs
29	<b>Melanoma in specific populations in Australia</b>		
<b>Good practice point</b> <ul style="list-style-type: none"> <li>When examining melanocytic lesions in non-Caucasians, it is important to keep in mind the possibility of melanoma. Furthermore, the skin areas examined should include the palms, periungual and subungual skin and especially the soles of the feet</li> </ul>			
30	<b>Melanoma in Māori and melanoma in Pacific peoples in New Zealand</b>		
<b>Good practice points</b> <ul style="list-style-type: none"> <li>Accurate ethnicity data be collected by all service providers</li> <li>Māori-specific cancer services or service components be provided where possible</li> <li>Health practitioners and others providing cancer care receive training and support in culturally competent, patient-centred care</li> <li>Health practitioners consult with Māori patients about final disposal of tissue or body parts surgically removed</li> </ul>			



# 1 Prevention

Exposure to ultraviolet (UV) radiation in sunlight is the primary cause of most melanomas.<sup>1</sup> Intermittent pattern sun exposure, such as recreational exposure, confers higher risks of melanoma than more continuous pattern sun exposure, such as occupational sun exposure.<sup>2,3</sup> Sun exposure in childhood appears to be associated with a higher relative risk of melanoma than is sun exposure in later life.<sup>3</sup> Childhood sun exposure is also associated with the development of melanocytic naevi (moles), which are a risk factor for melanoma.<sup>4</sup>

The UV wavelengths in sunlight that cause melanoma are not known; only a few studies on relevant animal models have been performed.<sup>5</sup> Solaria (tanning or sunbeds) emit mainly ultraviolet A (UVA) radiation. A review of the health effects of using solarium in an Australian context has recently been reported<sup>6</sup> and an Australian Standard for solarium for cosmetic use<sup>7</sup> has been produced. The later document suggests age restrictions for young people under 15 years, written parental permission forms for those under 18 years old and restrictions from use for those people with a type I skin (pale skin, with freckles and inability to tan).

From a systematic review and meta-analysis of 19 studies<sup>8</sup> there was a borderline significant but minor increase in relative risk (RR) of developing melanoma with 'ever use' compared with no use of sunbeds overall (RR 1.15; 95% CI 1.00–1.31). The increase in RR was greater and was significant, however, when restricted to studies of people exposed to sunbeds prior to 35 years of age (RR 1.75; 95% CI 1.35–2.26 from seven studies). Overall, in those eight studies where adjustment was made for confounders related to sun exposure and sun sensitivity, no firm conclusion about the association of melanoma and sunbed use could be reached (RR 1.19; 95% CI 0.33–4.30). In addition, when the data were limited to four studies with sufficient information about the amount of exposure from sunbeds, there was no clear dose–response relationship between sunbed use and melanoma. Problems with significant heterogeneity, which may be related to various factors, including differences in assumed lag-time, differences in exposures from earlier ultraviolet B (UVB)-rich versus later UVA-rich sunbeds and lack of control of certain confounders, make robust conclusions difficult at this time, though the data suggest that exercising caution with exposure to sunbeds early in life is warranted.

UVB radiation in sunlight is responsible for cutaneous production of the prohormone vitamin D, which is converted into the hormone 1,25-dihydroxyvitamin D (calcitriol). The skin is the main source of vitamin D in the absence of supplements, since natural food sources are very limited. Infants obtain vitamin D from trans-placental transport, depending on their mother's vitamin D status. Breast milk does not contain significant amounts of vitamin D.<sup>9</sup> Adequate vitamin D is essential for mineralisation of the skeleton and preservation of bone mass and is also important for muscle function and to reduce the risk of falls in older individuals.<sup>10,11</sup> There is increasing but not conclusive evidence that adequate vitamin D may reduce the incidence of and mortality from some internal cancers as well as the likelihood of some autoimmune diseases and other diseases such as hypertension and type 2 diabetes, and may increase innate immunity.<sup>10–12</sup> There is even increasing though low-level evidence that sun exposure and/or higher activity of the vitamin D system may reduce mortality from melanoma.<sup>13,14</sup>

Skin type, latitude, season, time of day, cloud cover and age will all affect synthesis of vitamin D.<sup>10</sup> Obesity will affect blood levels achieved. At present there are insufficient data to clearly recommend the duration, body surface area and frequency of sun exposure required to maintain adequate vitamin D levels. Continued exposure to sunlight causes vitamin D breakdown in the skin, so shorter exposures may be more efficient at maintaining vitamin D levels. Exposure to as little as one-third of a sunburning dose of UVB to 15–18% body surface (hands, arms and face or legs) can produce significant amounts of vitamin D.<sup>15</sup> This can be achieved for fair individuals in around 6–8 minutes just before 10am or just after 2pm in summer in most of Australia and New Zealand, but in winter takes around 30–50 minutes at these times in Southern parts of Australasia but still under 10 minutes in the North.<sup>9</sup> Although sunscreens reduce vitamin D synthesis in the laboratory,<sup>16</sup> there is conflicting evidence about whether they reduce vitamin D levels in practice.

Sunscreens have been shown to reduce the incidence of both premalignant skin lesions (actinic keratoses)<sup>17</sup> and squamous cell carcinoma.<sup>18</sup> As yet there is no conclusive evidence that sunscreens reduce the risk of basal cell carcinoma<sup>18</sup> or melanoma.<sup>19</sup> The level of protection provided by sunscreens is determined not only by their labelled sun protection factor (SPF) but also by the amount of product applied and its conditions of use. The effectiveness of sunscreens is dramatically reduced by inadequately applying product, failing to reapply product frequently, and loss of product through perspiration, swimming and friction from clothing. Skin damage can occur below the sunburn threshold<sup>20</sup> and sunscreens should not be used as a means of intentionally prolonging sun exposure.

The Cancer Council Australia, the Cancer Society of New Zealand and the Health Sponsorship Council of New Zealand recommend the following approach to sun protection.

1. Minimising direct sun exposure when the UV index<sup>i</sup> is 3 or greater through the use of shade, broad-brimmed or Legionnaire's-style hats, sunglasses that meet the Australia/New Zealand standard, and tightly woven clothing that covers the arms, legs and trunk (physical protection). This is particularly important during peak UVR periods. These occur in Australia between 10am and 2pm standard time and in daylight saving time between 11am and 3pm. In New Zealand the peak UVR period is between 11am and 4pm during daylight savings months.
2. Sunscreens should be used to complement physical sun-protection measures rather than as the sole or primary means of sun protection. Sunscreen should be used on exposed skin (such as the face) that cannot otherwise be fully covered. Broad-spectrum SPF30+ products (offering some protection from UVA as well as UVB) should be recommended, and should be applied before going outside and reapplied every 2 hours.

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i. The UV Index scale, found in the weather section of most Australian daily newspapers, provides a simple representation of solar UV levels. Each point on the scale is equivalent to 25 mW/m<sup>2</sup> of UV radiation. An index of 2 or less is considered low; 3–5 is moderate, 6–7 is high, 8–10 very high and 11 or higher represents extreme UV irradiance.

3. Correct application of sunscreens includes application of liberal amounts to clean, dry skin at least 20 minutes before going outside. It is recommended that an average-size adult use one teaspoon of product on each arm and leg, on the back and on the torso. Half a teaspoon should be applied to the face and neck including the ears and the back of the neck. Sunscreen should be reapplied every two hours.
4. Infants under six months of age should be kept out of the sun when the UV index is 3 or greater. If this is not possible, protection should include clothing and hats. Sunscreen should only be applied to areas such as the face, ears and hands if these areas cannot be protected with clothing or wraps. Infants of mothers with inadequate vitamin D levels, especially exclusively breast-fed infants of women who are dark skinned and/or wear clothing that covers most of the body, are likely to be vitamin D deficient and likely to need vitamin D supplementation.

Evidence summary	Level	Reference
Environmental melanoma risk is most strongly associated with an intermittent pattern of sun exposure, as in recreational exposure, and may be more potent in causing melanoma when received in childhood and adolescence than in later life	III-3	2
While robust conclusions are difficult at this time, the use of sunbeds and tanning booths is associated with a small increase in melanoma risk. This risk may be more significant when exposure occurs before age 35	II	8
Incidental brief sun exposures (for fair skinned individuals 6–8min in summer but 6–50min in winter depending on latitude) to around 15–20% body surface, most days are needed to maintain vitamin D levels, so total sun avoidance should not be practised without vitamin D supplementation	III-3	10
Although sunscreens can reduce the risk of some non-melanoma skin cancers, they have not conclusively been shown to reduce the risk of melanoma	III-3	17, 19

## Recommendations

	Grade
1. Sunburn be avoided and UV protection (physical methods complemented by sunscreens) adopted	<b>B</b>
2. Sunscreens be used to complement but not to replace physical methods of UV protection	<b>C</b>
3. Risks associated with exposure to tanning booths and sunbeds be explained	<b>C</b>
4. As brief sun exposures are needed to maintain vitamin D levels, total lack of sun exposure is not advised without vitamin D supplementation	<b>C</b>

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## 2 Population-based whole-body skin screening for melanoma

Survival from melanoma is strongly associated with depth of invasion. Early diagnosis of melanoma therefore appears essential and skin screening, defined as a visual inspection of the whole body, may be one method of achieving it. The US Preventive Services Taskforce in a 2001 review concluded, however, that there was insufficient evidence to recommend for or against routine skin screening for skin cancer.<sup>1</sup> Currently in Australia and in New Zealand,<sup>2</sup> The Cancer Council Australia and The Cancer Society of New Zealand does not recommend routine skin screening for average risk individuals, similar to the recommendations of the Royal Australian College of General Practitioners.<sup>3,4</sup> However, the American Cancer Society<sup>5</sup> supports regular screening on its own or linked to a general health check.

### 2.1 Proportion of population undergoing whole-body skin examination

Although there is no substantial evidence of its effectiveness, skin screening is being conducted in a significant proportion of the population. In most Australian studies, the twelve-month frequency of skin screening ranges from around 10–50% depending on the definitions of skin screening.<sup>6–10</sup> One large cross-sectional Australian study conducted in 1998 found 11% of participants reported having a whole-body skin screening examination in the previous twelve months, and 20% in the previous three years.<sup>6</sup> In this same study, some 45% intended to have a clinical skin examination within the next twelve months.<sup>11</sup> More recent data from Queensland indicates that 45% of men report ever having a whole-body skin screening examination by their doctor.<sup>12</sup> In a New Zealand population-based study carried out in 1993–1995, 40% of participants reported having a skin examination by their doctor in the previous five years, but only 5% reported a whole-body skin examination.<sup>13</sup> In overseas studies the frequency of skin screening ranges from 14–20%.<sup>14–17</sup>

Those attending a screening examination are more likely to have sun-sensitive skin, higher levels of education, and an increased awareness of skin cancer and perceived risk of skin cancer. An Australian study<sup>18</sup> found those aged 40–49 years, with fair skin, a previous history of non-melanoma skin cancer, or a concern about a suspicious spot or mole, were more likely to attend an open-access skin screening clinic. Men and women of all levels of education attended in essentially equal numbers, similar to results in a further Australian study.<sup>19</sup> In US national health surveys, both men and women were equally likely to report having a skin examination, with 60% stating the main reason for the examination was for routine screening. Additionally, 29% of those screened indicated they sought an examination due to concern about a specific lesion.<sup>14</sup> Analysis of data from open-access skin screening programs in the US show those attending the program were predominantly female and aged between 35 and 65 years. Approximately one-third reported a history of a spot or mole changing and 3% reported a personal history of melanoma.<sup>20</sup> Similar results have been seen in other overseas skin screening programs.<sup>21–23</sup> In the majority of studies,

following adjustment for confounders, analysis has shown the strongest predictors of attending a skin screening examination are a previous history of skin cancer, self-perceived susceptibility towards skin cancer, and a concern about a mole or spot.<sup>6,10,11,14,17–21,24–26</sup>

Evidence summary	Level	References
Studies are mostly descriptive and show both men and women attend skin examinations in similar numbers. Studies consistently report that those attending a skin screening examination are more likely to be at heightened risk of melanoma and/or have a high level of self-perceived risk	IV	6, 10, 11, 15, 18–21, 24, 26

## 2.2 Accuracy of whole-body skin examination by health professionals

Accuracy of clinical whole-body skin examination has been assessed in a number of studies conducted mainly within screening programs. Patients were self-selected in all studies, with some programs focussing on attracting participants with a number of risk factors for skin cancer (increased number of naevi, spot or mole of concern, sun-sensitive skin). The use of various screening definitions (whole-body, part-body, specific lesions only) has made comparisons across studies difficult. In most screening programs skin examinations have been conducted by dermatologists or other specialists, with only one study to date reporting on the clinical outcomes of a melanoma screening program where whole-body skin screening examinations were conducted by a general practitioner.<sup>27</sup>

In analysis of data from an Australian skin screening program the positive predictive value (PPV) for a diagnosis of melanoma was reported as approximately 11% where a whole-body skin screening examination was performed by a specialist.<sup>28</sup> One study in Queensland has examined the clinical outcomes of a screening program where a general practitioner has conducted whole-body skin examinations within a skin screening program. Of over 1300 lesions where a histological diagnosis was available, the PPV for a diagnosis of melanoma was 20.5% (based on 161 suspected melanomas and 33 confirmed on histology).<sup>27</sup> Similar values have been reported in a study of general practitioner screening for melanoma in individuals aged 50 years or more.<sup>29</sup> PPV values of 6–17% have been observed in programs where participants have self-selected on the basis of the presence of skin cancer risk factors and/or a suspicious skin lesion.<sup>30–32</sup> Analysis of the American Academy of Dermatology (AAD) skin screening program reported a PPV for a melanoma diagnosis of approximately 11%, which increased to 21.1% when analysis was restricted to men over the age of 50 years.<sup>33,34</sup> Similar results have been seen in other skin screening programs.<sup>35</sup>

Few studies have examined the sensitivity of the screening examination. Fritschi et al matched screening participants with a population-based cancer registry. Of 7436 skin screening examinations 23 melanomas were detected during screening and an additional 10 were false-negative screens giving sensitivity in the first year of 69.7% when body-site was ignored. Further analysis of this data two years after the original skin screening examination found an additional 15 melanomas and a subsequent decrease in sensitivity to 49% with increasing specificity.<sup>28</sup> A Queensland study<sup>27</sup> reported the specificity of a skin screening examination at 86% which compares favourably with screening programs for breast cancer, colorectal cancer

(faecal occult blood test) and prostate cancer (prostate specific antigen).<sup>36</sup> In a prospective Australian study of a sample of men and women aged 50 years and over, which was 'enriched' with patients with previously diagnosed suspicious pigmented lesions, general practitioners achieved sensitivity of 95% and specificity of 49% for detecting melanoma in men and women aged 50 years and over.<sup>29</sup> A small Dutch study followed-up, by record linkage, patients who had been screened negative by a dermatologist and reported data suggesting 100% sensitivity (lower 95% confidence bound 61%) for melanoma, though two melanomas diagnosed 30 and 33 months after screening were discounted as false negatives on the grounds they were 'not present or discovered at the screens'.<sup>37</sup> Studies that included only a follow-up of biopsied or excised lesions report sensitivities for diagnosing skin cancer ranging between 40% and 80% with associated high specificities.<sup>38–40</sup> However, in most of these studies accuracy for diagnosing melanoma is somewhat lower. The PPV for a diagnosis of melanoma within general practice has been reported to be between 20 and 40%.<sup>29,39,40</sup>

The yield of skin cancer screening programs for melanoma varies. Reported melanoma detection rates range between one and nine per 1000 individuals screened.<sup>22,27,32,33,41–43</sup> Higher yields of melanoma have been observed when analyses have been restricted to men 50 years and over.<sup>33,34,44,45</sup>

Evidence summary	Level	References
Most studies that have reported on the accuracy of a skin screening examination for detecting melanoma have been primarily descriptive and have reported on the outcomes of screening programs. In most studies screening was undertaken in the specialist setting (primarily dermatologists). Positive predictive values ranged from 6% to 20%	IV	22, 27–35, 37, 39, 45
One study examined the outcomes of screening when undertaken by a general practitioner within a melanoma screening program	IV	27

## 2.3 Thickness of melanoma detected through skin screening by health professionals

There is evidence that melanomas detected during a screening examination are thinner than melanomas not so detected. A large population-based study of 3772 melanoma cases in Queensland found lesions detected by a doctor during a whole-body skin examination were significantly more likely to be < 0.75mm in thickness<sup>46</sup> whereas melanoma detected incidentally were more likely to be thicker.<sup>46,47</sup> The authors of the Queensland study acknowledge, however, that it has not been shown that the increased detection of thin melanomas corresponds to a reduction in the incidence of thick melanoma and an improved survival.<sup>45</sup> In the AAD screening program, over 90% of melanomas detected were in situ or lesions ≤ 1.5mm in thickness. The proportion of lesions diagnosed less than 1.00mm in thickness during this screening program was significantly less than that found in a population-based register.<sup>20,33</sup> In an early detection campaign in Italy, Rossi and colleagues<sup>48</sup> found that 92% of melanomas diagnosed during the screening campaign were

less than 1.5mm and when compared to pre-campaign data, there was a significant trend towards thinner tumours ( $P < 0.02$ ). Similar results have been found in other studies.<sup>42,49–51</sup>

One issue for a skin screening program is whether such a program would result in diagnosis of melanomas that would not otherwise present clinically during the patient's life ('overdiagnosis').<sup>52</sup> A recent examination of trend data from Queensland found in situ melanoma has increased by 10.4% per year among men and 8.4% per year among women. Thin invasive lesions ( $< 1.00\text{mm}$ ) increased by 3.8% in men and 3.0% in women. While invasive melanomas ( $\geq 1.00\text{mm}$ ) were observed to increase by only 2.0% per year in men and 0.9% per year in women.<sup>53</sup> Increases of around 10% in rates of in situ lesions have been seen in other cancer-registry based data.<sup>54–56</sup> While trend data has consistently shown in recent years an increase in the detection of thin melanoma, this has not been accompanied by a subsequent decrease in thicker melanoma. It is known that the rate of melanoma progression can vary. Histological types such as nodular melanoma have a faster vertical growth phase while superficial spreading melanomas tend to have a longer radial growth phase. It is possible that aggressive lesions may be advanced at the time of detection. However, the future challenge is how to identify those lesions that do not threaten health or life; there is no known way of doing this at present. Further research is needed to investigate the impact of skin screening on melanoma incidence and survival.

Evidence summary	Level	References
Most studies, while descriptive, provide evidence that melanomas detected during a screening examination are thinner than those that present in other ways	IV	20, 33, 42, 47–50
One Australian case-control study has shown that melanomas detected during a skin screening examination performed by a doctor are significantly more likely to be $< 0.75\text{mm}$ than those found incidentally	III–3	46

## 2.4 Cost-effectiveness of population-based skin screening by health professionals

Currently there is no direct evidence showing that population-based screening for melanoma is effective in reducing melanoma morbidity or mortality. Thus studies examining the cost-effectiveness of skin screening to date have been based on theoretical models.

An Australian study in which the sensitivity of the screening examination was set at 60% and specificity at 98% estimated for bi-annual examination that the cost per life year saved was approximately \$12,000 for men and \$20,100 for women. Screening was estimated to be more cost-effective if conducted every five years (\$6,900 for men and \$11,100 for women) than more frequently.<sup>57</sup> Burton reported that the costs per life year saved where men were screened every two years by a general practitioner were \$12,137 and \$6,853 for screening every five years.<sup>29</sup> Using a number of assumptions, Freedberg<sup>58</sup> calculated a cost-effectiveness ratio of approximately \$36,450 per year of life saved with skin screening compared with no screening. Recent work using a US population estimated that screening once by a dermatologist at 50 years of age would cost US\$7,400 per year



of life saved.<sup>59</sup> These theoretical studies have concluded skin screening was reasonably cost-effective when compared with other cancer screening tests, particularly for men 50 years and over. The estimated costs of diagnosing and managing suspicious skin lesions detected during a population-based melanoma screening program have been assessed in an Australian study. The average cost to the health care system per referred patient was \$193, with the average cost per treated lesion calculated at \$118.<sup>60</sup> The study found that over 60% of costs were attributed to individuals 50 years or more.

Evidence summary	Level	References
Studies assessing the cost-effectiveness of skin screening are theoretical and based on statistical models that assume effectiveness. These studies have concluded that the cost-effectiveness of skin screening is comparable to that of other screening modalities, and that screening is more cost efficient when conducted in those $\geq 50$ years. A more thorough examination of the costs of screening to both the patient and the health system should be undertaken	IV	57–59

## 2.5 Effectiveness of whole-body skin examination by health professionals in reducing melanoma mortality

A recent examination of melanoma mortality data in Australia<sup>61</sup> shows a statistically significant decrease in mortality rates in both men and women younger than 55 years of age. Additionally, rates in those aged 55–79 are stable for both men and women. It is possible that this reduction is due to the beneficial effect of earlier detection although there has been no rigorous examination of the relationship between trends in indicators of earlier detection and trends in melanoma mortality.

Currently, no studies have been completed examining whether whole-body clinical skin examination reduces mortality from melanoma. Aitken et al aimed to examine the effectiveness of a community-based melanoma screening program by way of a randomised controlled community intervention study in Queensland.<sup>62</sup> The first (pilot) phase of this trial was conducted over a three-year period. The trial involved 18 communities (nine intervention and nine control) in rural and regional Queensland, with approximately 60,000 adults aged  $\geq 30$  years. The intervention included the provision of additional skin screening services in intervention communities. The rate of clinical skin examination increased significantly in intervention communities while remaining stable in the control group.<sup>63</sup> However, due to funding constraints, the full trial involving a total of 44 communities – some 500,000 adults – did not proceed, and the first phase of the study lacked power to examine for any changes in melanoma thickness or mortality.

Evidence summary	Level	References
No adequate randomised controlled intervention study has been conducted to see if whole-body skin examination is effective in reducing mortality from melanoma	n/a	n/a

Recommendation	Grade
1. In the absence of substantive evidence as to its effectiveness in reducing mortality from melanoma, population-based skin screening cannot be recommended	<b>C</b>

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# 3 Identification and management of high-risk individuals

About 3.3% of Australian women and 4.0% of men will develop melanoma at some time in their life, but individual risk varies widely about these averages. The aetiology of melanoma is now understood to involve both environmental and genetic factors and individual risk represents the sum of both types of influences.

It is reasonable to posit that successful and timely diagnosis of melanoma will be enhanced if clinicians are aware of high-risk groups in the population, and that people in these groups are aware of their status.

## 3.1 Strongest predictors of future cutaneous melanoma

The systematic meta-analyses of studies of melanoma risk factors between 1966 and 2002 by Gandini et al<sup>1–3</sup> provide the highest-level evidence available on risk associated with common and atypical melanocytic naevi, skin phototype and pigmentation, indices of sun exposure and family history of melanoma. Further systematic searches of the literature were undertaken for this review, but no studies identified since then warrant modification of their conclusions, which are summarised below and provide a basis for comprehensive clinical risk assessment.

## 3.2 Baseline risks due to age and sex

Clinical assessment of the probability that a patient is presenting with, or may develop, melanoma must start with their baseline risk due to the patient's age, sex and ethnicity.<sup>4–6</sup> Age is one of the strongest risk factors for melanoma, as with all cancer. For example, a 70-year-old Australian man is eight times more likely to develop melanoma in the next ten years (2.5% risk), and a 70-year-old woman three times more likely (1.0%) than is a 30-year-old man or woman (0.3%). In New Zealand a 70 year old man or woman is, respectively, more than ten times (2.2% risk) or four times (1.4%) more likely to develop melanoma in the next ten years than is a 30 year old man or woman (0.2% and 0.3% respectively). Ethnic origin is also a strong risk factor. For example, in Los Angeles County, USA, in 1993–1997, non-Hispanic whites were, on average, six times more likely to develop melanoma in a year than Hispanic whites, 19 times more likely than blacks, and 24 times more likely than people of East Asian origin living in the County.<sup>7</sup>

The potential to focus detection and prevention efforts where they will be most efficient is greatest where absolute risks are highest, namely in the elderly and in high-risk (relative risk at least five- to ten-fold) younger and middle-aged adults. While there are no widely accepted algorithms for clinical estimation of melanoma risk, many of the risk factors below can be considered as contributing independently in a global risk assessment. It is important to recognise which factors are capable of conferring high risk in their own right, as opposed to many of the best-known risk factors, which are relatively weak (two-fold relative risk).

### 3.3 Previous melanoma or other skin cancer

Retrospective large-scale studies in several cancer registries have shown that a history of previous melanoma is a powerful predictor of future melanoma, with estimated relative risks ranging above ten. The risk is highest in the first one to two years after diagnosis and may be partly accounted for by increased surveillance. A history of non-melanoma skin cancer or premalignant lesions such as actinic keratoses confers relative risks of around four-fold in meta-analysis.<sup>3</sup>

### 3.4 Melanocytic naevi

Melanoma risk increases with naevus count, whether counted over the whole body or restricted to one body site, such as the arms. Those with the highest counts ( $> 100$  naevi, whole body) had seven times (6.89; 95% CI 4.63–10.3) the risk of people with the lowest counts ( $< 15$  naevi) in meta-analysis.<sup>1</sup>

Total body counts of clinically atypical (dysplastic) naevi are strongly associated with melanoma risk, independent of the count of common melanocytic naevi. Those with the highest counts ( $> 5$  atypical naevi) had six times (6.4; 95% CI 3.8–10.3) the risk of those with no atypical naevi in meta-analysis.<sup>1</sup>

The thresholds that define high- and low-risk groups by naevus count in different population are not yet well defined.

### 3.5 Skin and hair colour, skin phototype and freckling

Meta-analyses of studies done mainly in populations of European origin show that light versus medium/dark skin colour, red-blond versus black hair, and blue versus dark brown eyes, confer risk increases of about two-fold. Similarly, a person with a Fitzpatrick phototype I (burn easily, never tan) is about twice as susceptible to melanoma as one with phototype IV (always tan, never burn), as are the most heavily freckled versus those without freckles.<sup>3</sup> These phenotypes are not independent of one another and while combinations may further increase risk, they do not multiply it.

The dramatic variation of melanoma incidence across ethnic groups is partly accounted for by these variations in skin type, though there are additional genetic (e.g. MC1R variation, see 3.9 *Genetic risk factors and testing*) and cultural/behavioural determinants (e.g. clothing and sun-seeking practices).

### 3.6 Sun exposure and its surrogates

Sun exposure is the main driver of melanoma incidence at the population level, with significant contributions made by total lifetime exposure, an intermittent pattern of exposure and exposure in childhood and adolescence (as indicated by the ambient solar UV irradiance at the place of residence). However, none of these exposures can be measured readily or retrospectively outside research settings and in any case, the relative risks for the highest categories of exposure, compared with the lowest, are rarely  $> 1.5$ . These low relative risks, however, may be due, at least in part, to inaccuracy in the



measures of exposure. Prior sunburns confer relative risks of up to 2.0 in meta-analyses.<sup>2</sup> However, such a history has limited clinical predictive value in regions such as Australia and New Zealand where the prevalence of sunburn is so high.

There are no reliable clinical surrogates for prior amount or pattern of sun exposure since they are all confounded by the effect of individual susceptibility to those endpoints. However, the presence of actinic damage is detectable clinically and confers a relative risk of 2.0 (95% CI 1.2–3.3).<sup>3</sup>

### 3.7 Family history of melanoma

One first-degree relative with melanoma approximately doubles melanoma risk in international meta-analyses (1.7; 95% CI 1.4–2.1).<sup>3</sup> Robust population-based estimates are not yet available in Australia and New Zealand on the risk conferred by additional affected relatives of different degrees of relationship, but data from other common cancers suggest that each close affected relative doubles the risk of that cancer. Relatives affected at an earlier age than average, or who have experienced more than one melanoma, further raise the likelihood that strong familial and genetic risk factors are present (see 3.9 *Genetic risk factors and testing*).

Evidence summary	Level	Reference
Major risk factors for melanoma are, for the most part, well characterised in population-based studies. They include patient age and sex; history of previous melanoma or non-melanoma skin cancer; family history of melanoma, including age of onset and multiplicity of any melanoma cases; the number of common melanocytic naevi; number of clinically atypical naevi; skin and hair pigmentation type and response to sun exposure; and evidence of actinic skin damage. Present alone or in combination, they can substantially increase risk	I	1–6

Recommendation	Grade
1. Clinical assessment of future risk of melanoma take into account: <ul style="list-style-type: none"> <li>• person's age and sex</li> <li>• history of previous melanoma or non-melanoma skin cancer</li> <li>• number of naevi (common and atypical)</li> <li>• family history of melanoma</li> <li>• skin and hair pigmentation</li> <li>• response to sun exposure</li> <li>• evidence of actinic skin damage</li> </ul>	<b>B</b>

## 3.8 Management of high-risk individuals

See Chapter 5.7 for detailed evidence and recommendations on early melanoma diagnosis.

The direct relationship between survival of patients with melanoma and lesion thickness (thicker lesions having a poorer prognosis) suggests that early detection of primary melanoma by regular review may decrease mortality from the disease. Regular skin examination can be done by the person himself or herself, perhaps aided by a partner or carer, or by a clinician. Both of these can be aided by total body photography, which provides a baseline that may aid recognition of new and changing lesions. The clinician examination can be aided by dermoscopy and short-term digital monitoring, in which suspicious lesions are photographed and reviewed at three months.<sup>8</sup> In individuals with multiple naevi there is no evidence that prophylactic removal of lesions that are not clinically suspicious reduces prospective risk of melanoma.

Prospective studies of high-risk groups have repeatedly demonstrated that the average thickness of melanomas detected is reduced under regular surveillance. Therefore, to the extent that the prognosis of primary melanoma is related to its thickness, surveillance may be inferred to benefit such patients. However, to date none of these studies have involved systematic comparisons of alternative methods or protocols of surveillance, and such studies are unlikely to be done. Recommendations can therefore only be based on expert opinion and comparisons with historical experience. A screening interval of six months is regarded as sound practice, provided that patients also self-screen in the interim.

Evidence summary	Level	Reference
High-risk individuals may benefit from regular clinical surveillance for new melanomas and education to self-screen, based on expert opinion. There is no evidence to compare the relative effectiveness of specific surveillance techniques in high-risk patients, as opposed to those at average risk	III-2	8

Recommendation	Grade
2. 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	C

## 3.9 Good practice point

- Prophylactic removal of nonsuspicious lesions is not recommended since it is unlikely to increase survival and therefore may incur unnecessary procedures and give false reassurance as many new melanomas in high-risk individuals will occur outside pre-existing naevi

### 3.10 Genetic risk factors and testing

Inherited mutations in the genes encoded by the CDKN2A locus, p16INK4A and p14ARF are strongly associated with melanoma risk, especially in the context of a family history of melanoma. The international GenoMEL consortium has systematically collated and synthesised evidence on the prevalence of these mutations in familial melanoma.<sup>9–11</sup> These studies have incorporated and superseded the data presented since 1993 by individual member groups and represent the highest level of evidence available about the prevalence of these mutations and the risk of melanoma associated with them.

There are important differences between countries in the contribution of CDKN2A mutations to familial risk of melanoma, and the international literature previously suggesting that 20–40% of familial melanoma kindreds carry CDKN2A mutations is now known to be an overestimate in the Australian context. Only 10% of clusters of three to four cases carry such mutations, but 25% of five-case clusters, for example. However, the number of relatives in the cluster who have had multiple primary melanoma, or early median age of onset among the relatives (e.g. < 40 years) strongly influences the chance of a mutation in a high susceptibility melanoma gene being present.<sup>10</sup>

Limited data exist on the prevalence of these mutations outside the context of familial melanoma in Australia. However rates of < 0.5% in melanoma cases, and 2% in large series of cases with a second primary, not selected for family history, have been reported.<sup>12,13</sup>

CDKN2A mutations do not confer a clinically recognisable phenotype on carriers. In particular, they do not directly cause atypical naevus syndrome, which appears to have complex genetic origins.

There is wide variation in estimates of risk conferred by carrying a CDKN2A mutation (penetrance) and strong evidence exists that it varies across different populations and is influenced by other independent risk factors for melanoma.<sup>9</sup> However, in the context of familial melanoma in Australia, estimates of risk conferred are in the range ten- to twenty-fold. In contrast, mutations detected in the absence of familial melanoma, for example in cases of multiple primary melanoma unselected for family history, appear to confer much lower risks: four- to five-fold.<sup>12</sup>

Because of these uncertainties about risk conferred, and the lack of evidence that individuals at high familial risk should be managed differently according to their mutation test results, current consensus recommendations from GenoMEL emphasise that clinical testing for CDKN2A mutations has a very limited role at present which is confined to highly selected, well-characterised melanoma families.<sup>14</sup>

Variation in the melanocortin-1 receptor (MC1R) gene is strongly associated with skin and hair pigmentation and also contributes to melanoma risk independent of these clinical features. Large studies in populations, as well as in the context of familial melanoma have given reliable estimates of the degree of melanoma risk conferred by the red-hair associated (RHC) subset of MC1R variants. Risks vary from around 2.0 per RHC allele in the population, to 3.0 in the context of familial melanoma. These risks are at least additive: carriers of two RHC alleles have risks four- to six-fold higher than those with no RHC alleles. These alleles also amplify the risk to carriers of CDKN2A mutations.<sup>15</sup> However, MC1R variants contribute to skin pigmentation, phototype and freckling and it is not yet clear how genetic testing of MC1R variants might be incorporated into clinical risk assessment independent of these other risk factors.

Evidence summary	Level	Reference
CDKN2A mutations cause high melanoma risk in the context of familial melanoma, though their prevalence is low, even in that setting	I	9–13
It is unclear at present whether individual risk management should be influenced by the results of genetic testing for CDKN2A mutations	IV	14

### Recommendation

	Grade
3. Screening for a mutation such as the CDKN2A gene be contemplated only after a thorough clinical risk assessment (the patient is at personal high risk of melanoma), confirmation of a strong family history of melanoma (there is a significant probability of a family mutation), and appropriate genetic counselling	<b>C</b>

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# 4

## Classification and staging of melanoma

A revised version of the internationally accepted classification and staging system for melanoma was published in 2002 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC).<sup>1,2</sup> The review was based on analysis of prognostic factors involving 17,600 patients from 13 cancer centres and organisations.

The AJCC Melanoma Staging Committee used the following guidelines to determine which criteria should be used in the tumour-node metastases (TNM) classification and the stage groupings:

- (i) The staging system must be practical, reproducible, and applicable to the diverse needs of all medical disciplines.
- (ii) The criteria must accurately reflect the biology of melanoma based on consistent outcome results of patients treated at multiple institutions from multiple countries.
- (iii) The criteria used must be evidence-based and reflect the dominant prognostic factors consistently identified in Cox multivariate regression analyses.
- (iv) The criteria must be relevant to current clinical practice and regularly incorporated in clinical trials.
- (v) The required data must be sufficiently easy for tumour registrars to identify in medical records to code staging information.

Major changes from the previous version of the AJCC/UICC melanoma classification and staging system included:

- (i) Melanoma thickness and ulceration but not level of invasion to be used in the T category (except for T1 melanomas).
- (ii) The number of metastatic lymph nodes rather than their gross dimensions and the delineation of clinically occult (i.e. microscopic) versus clinically apparent (i.e. macroscopic) nodal metastases to be used in the N category.
- (iii) The site of distant metastases and the presence of elevated serum lactic dehydrogenase to be used in the M category.
- (iv) An upstaging of all patients with stage I, II and III disease when a primary melanoma is ulcerated.
- (v) A merging of satellite metastases around a primary melanoma and in-transit metastases into a single staging entity that is grouped into stage III disease.
- (vi) A new convention for defining clinical and pathologic staging to take into account the staging information gained from intraoperative lymphatic mapping and sentinel node biopsy.

An extract from the 2002 AJCC classification and staging system is provided under section 4.1 *Extract from AJCC Cancer Staging Manual, 6th edition, 2002.*

The AJCC Melanoma Staging Committee reconvened in 2006 to begin preparation of the next version of the AJCC staging system, scheduled to become official with publication of the seventh edition of the AJCC Cancer Staging Manual which is expected to be published in late 2009 and will become operative in 2010.

Evidence summary	Level	Reference
Analysis of staging and survival data from 17,600 melanoma patients demonstrated the following results which informed the 2002 6th edition of the AJCC melanoma staging system. For primary tumours (T), the most powerful predictors of survival were thickness and ulceration. Level of invasion had a significant impact only within the subgroup of thin (< 1 mm) melanomas. Three independent factors for the classification of regional lymph nodes (N) were found to be the number of metastatic nodes, whether nodal metastases were clinically occult or clinically apparent, and the presence or absence of primary tumour ulceration. Finally, in the category of distant metastasis (M), nonvisceral metastases were associated with a better survival compared with visceral metastases. The results of this study were used to inform the 2002 edition of the AJCC/UICC melanoma staging system	II	3

Recommendation	Grade
1. That the current AJCC/UICC classification system be used for staging patients with melanoma	<b>B</b>

## 4.1 Extract from AJCC Cancer Staging Manual, 6th edition, 2002<sup>2</sup>

### Rules for classification

There should be histological confirmation of the disease. The following are the procedures for assessing T (Primary Tumour), N (Regional Lymph Nodes) and M (Distant Metastasis) categories, shown in Table 3.



**Table 3** Melanoma TNM classification

<b>T classification</b>	<b>Thickness</b>	<b>Ulceration status</b>
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Melanoma in situ	
T1	</= 1.0mm	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01–2.0mm	a: without ulceration b: with ulceration
T3	2.01–4.0mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration
<b>N classification</b>	<b>No. of metastatic nodes</b>	<b>Nodal metastatic mass</b>
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	1 node	a: clinically occult (microscopic) metastasis b: clinically apparent (macroscopic) metastasis
N2	2–3 nodes	a: clinically occult (microscopic) metastasis b: clinically apparent (macroscopic) metastasis c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic nodes	
<b>M classification</b>	<b>Site</b>	<b>Serum lactate dehydrogenase</b>
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastasis	Normal
M1c	All other visceral metastasis	Normal
	Any distant metastasis	Elevated

**Table 4** Stage groupings for cutaneous melanoma

	Clinical stage grouping			Pathologic stage grouping		
	T	N	M	T	N	M
O	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2b	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III	Any T	N1	M0			
	Any T	N2	M0			
	Any T	N3	M0			
IIIA				T1–4a	N1a	M0
				T1–4a	N2a	M0
IIIB				T1–4b	N1a	M0
				T1–4b	N2a	M0
				T1–4a	N1b	M0
				T1–4a	N2b	M0
				T1–4a/b	N2c	M0
IIIC				T1–4b	N1b	M0
				T1–4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	M1	Any T	Any N	M1

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# 5 Clinical diagnosis\*

## 5.1 How patients detect melanoma

About half of melanomas are detected by the patient and present with a history of a new and/or changing lesion.<sup>1,2</sup> It is important to pay close attention to any history of change, even if the lesion shows no typical clinical features of melanoma. While most are asymptomatic, there may be sensory changes (most commonly itch) that, if persistent, can be helpful in raising suspicion. Changes that are seen in an early melanoma include changes in size, shape or colour in a macular (flat) lesion and, as the melanoma invades more deeply in the dermis, raising up, bleeding or crusting. The time course of the change in melanoma is generally over months. Aggressive, rapidly growing melanomas are more often detected by patients and often present with a nodule, which may be red in colour or pigmented. Patients find changes more useful than atypical clinical features in distinguishing melanoma from benign lesions.<sup>3</sup> All patients seeking advice about pigmented lesions should be encouraged to regularly check their skin with the aid of a mirror or a partner and advised about the changes to look for in early melanoma.

## 5.2 How doctors detect melanoma

The melanomas detected by doctors may be found opportunistically at health examinations for other purposes or at skin examinations for the purpose of detecting skin cancer. Examination for melanoma detection requires examination of the whole skin surface under good lighting and dermoscopy provides increased diagnostic accuracy in experienced hands.

Most melanomas present with an initial flat phase (superficial spreading melanoma, lentigo maligna melanoma and acral lentiginous melanoma) and the features of these melanomas have been summarised by the ABCD(E) rule (Asymmetry, Border irregularity, Colour variation, large Diameter [and Evolution]).<sup>4</sup> Both ABCD(E) and the 7 point checklist<sup>5</sup> have been recommended for use by trained medical practitioners.

About 15% of melanomas present with a clinically predominant expansile nodule (nodular melanoma) and are symmetric nodules with a single colour that is often pink or red.<sup>6</sup> They are often misdiagnosed as non-melanoma skin cancer. These are generally growing rapidly and surgical excision is urgent. Nodular melanomas account for at least half of thick melanomas and are likely to make a disproportionately high contribution to mortality.<sup>7,8</sup> Greater awareness of this presentation is needed so that urgent therapy is more often instituted. Their appearances can be summarised by the acronym EFG (Elevated, Firm and Growing progressively).<sup>9</sup>

### 5.3 Clinical melanoma subtypes

The clinical subtypes of melanoma mentioned above were originally described by Dr Wallace Clark<sup>10</sup> and describe presentations of melanoma that have distinctive clinical, epidemiological and body site associations. The clinical aspects are summarised here.

**Superficial spreading melanoma (SSM)** is the most common subtype and is characterised by an initial flat phase that shows changes in size, shape or colour. SSM may occur as early as teenage years and mean age for SSM is in the 40s. Large numbers of melanocytic naevi and more than a few dysplastic naevi are strong risk factors. SSM is associated aetiologically with relatively small amounts of ultraviolet light exposure and has been linked to intermittent exposure and sunburns.

**Nodular melanoma (NM)** accounts for about 15% of melanomas overall, but for the majority of thick melanomas. It presents as a symmetrical, raised, firm, often uniformly coloured and frequently non-pigmented nodule that is enlarging and becoming more raised. Bleeding and crusting are common. NM occurs more often in older people, particularly men, and is more commonly seen on the head and neck than elsewhere.<sup>7</sup>

**Lentigo maligna (LM) and lentigo maligna melanoma (LMM, the invasive form of LM)** accounts for 10–15% of melanomas. It has an initial flat phase that may be prolonged. It presents as an atypical pigmented macule that is changing and has to be differentiated from seborrhoeic keratoses, solar lentigines and pigmented actinic keratoses. LM has been linked epidemiologically to large cumulative doses of UV light, has a strong predilection for the head and neck, and is more common in outdoor workers, in older people and in association with solar damage and non-melanoma skin cancer.<sup>11</sup>

**Acral lentiginous melanoma (ALM)** accounts for 1–3% of melanomas in Australia and occurs on the acral skin of the palms and soles. It presents with a flat phase with similar appearances and changes to SSM. ALM is more often light-coloured or pink.<sup>12,13</sup> Importantly, melanomas that appear relatively flat on the soles of the feet may have significant depth histologically. Although the epidemiology is not as well understood, this type of melanoma is at least equally common in people with dark skin and may have no relationship with UV exposure.<sup>12</sup>

**Subungual melanoma**, a variant of ALM, arises within the nail matrix and usually presents initially as longitudinal melanonychia (brown to black stripe throughout the full length of the nail). The differential diagnosis of longitudinal melanonychia includes naevi (moles) or lentigo in the nail matrix, ethnic-type pigmentation (seen with dark skin, often familial and affects multiple digits) and drug-induced pigmentation. The skin of the surrounding nail folds may be involved (Hutchinson's sign). Subungual haematoma is the most common differential diagnosis of subungual melanoma, however dermoscopic examination usually allows easy differentiation between these two diagnoses. Like ALM, subungual melanoma appears with a similar incidence in dark skin races and may not be related to sun exposure.<sup>13,14</sup>

**Desmoplastic melanoma** may arise within a lentigo maligna or present *de novo*. The latter presentation is typically as a firm, evenly skin-coloured or pink nodule that is progressively enlarging. The differential diagnosis includes dermatofibroma and hypertrophic scar.

Some melanomas are not easily classified into one of these categories and may have overlapping features.

## 5.4 Good practice points

- Examination for melanoma detection requires examination of the whole skin surface under good lighting
- A careful clinical history of specific changes in the lesion, any symptoms and their time course is critically important in assessing whether a lesion may be melanoma, particularly for melanomas that have absent or unusual clinical features for melanoma
- Where there is a low index of suspicion for early, non-invasive melanoma a short period of observation aided by measurement, a clinical photo or dermoscopic imaging may be appropriate
- All patients seeking advice about pigmented lesions should be encouraged to regularly check their skin with the aid of a mirror or a partner and advised about the changes to look for in early melanoma

## 5.5 Identification of the high-risk patient for prospective surveillance for melanoma

See Chapter 3 *Identification and management of high-risk individuals*.

## 5.6 Evidence-based assessment of aids to the clinical diagnosis of melanoma

### 5.6.1 Dermoscopy

Dermoscopy (surface microscopy, oil epiluminescence microscopy, dermatoscopy) 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.<sup>15–18</sup> Meta-analyses performed on studies in a variety of clinical and experimental settings have shown that using dermoscopy improves diagnostic accuracy for melanoma.<sup>19,20</sup> From a meta-analysis of nine level II diagnostic studies subject to varying degrees of verification bias performed prospectively in a clinical setting<sup>21–31</sup> 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 examination. 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 eye examination, but there was no evidence of an effect on specificity<sup>31</sup> (see Appendix 4). 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.<sup>22,23</sup>

While there are fewer studies on dermoscopy in general practice, all three that were undertaken in this context (one study with both general practitioners and inexperienced specialists or trainees)<sup>32</sup> show a consistently improved sensitivity for the diagnosis of melanoma or the identification of suspicious lesions requiring biopsy.<sup>21,32,33</sup> 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,<sup>34</sup> some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy.

### 5.6.2 Sequential digital imaging

Sequential digital dermoscopy imaging (SDDI) 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 digital monitoring (over a period of 1.5–4.5 months) for suspicious melanocytic lesions, and long-term monitoring for surveillance (usually at intervals of 6–12 months).<sup>35</sup>

Four level II studies that were conducted in a specialist setting show consistently that SDDI allows the detection of melanoma that lack dermoscopic evidence of malignancy.<sup>35–38</sup> In one prospective study of melanomas diagnosed by a variety of clinical means, 34% were detected using the changes detected by SDDI exclusively and were without dermoscopic features of melanoma.<sup>36</sup> Long-term digital monitoring is generally used in the surveillance of high-risk patients, usually with multiple dysplastic naevi. In contrast, short-term digital monitoring of individual suspicious naevi can be used in any patient setting. At this time diagnostic accuracy of the technique was not able to be assessed.

### 5.6.3 Automated instruments for the diagnosis of primary melanoma

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.<sup>39</sup> To date, only three instruments have had their diagnostic accuracy compared with a human diagnosis in the clinical field with a sample size that could allow some assessment of their application to the wider clinical arena.<sup>25,40,41</sup> The instruments showed a significantly inferior<sup>25,41</sup> or equivalent<sup>40</sup> specificity for the diagnosis of melanoma compared with specialists. In all studies sample sizes were not large enough to be able to detect potential differences in the sensitivity for melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field.

## 5.7 Total body photography for early melanoma diagnosis in high-risk subjects

Total body photography (TBP) is widely used in the follow-up of high-risk patients,<sup>42</sup> particularly those with large numbers of melanocytic naevi or dysplastic naevi. TBP has been recommended for the detection of new or changing pigmented lesions. Use of TBP is advocated in the follow-up of high-risk patients by the authors of most studies.<sup>43–50</sup> The technique has been said to reduce the need for unnecessary removal of benign lesions to exclude melanoma<sup>45,46</sup> and to increase the sensitivity and specificity of clinical examination for the detection of melanoma.<sup>46,47</sup> Several authors point out that TBP was the key factor in the detection of most melanomas in their high-risk populations.<sup>44–46,48</sup> Two authors referred to the role of TBP in enabling the detection of clinically subtle or undiagnosable melanoma.<sup>46,47</sup> No appropriately controlled or randomised study has been undertaken to confirm these observations in a high-risk population. Almost all melanomas are new or changing lesions and baseline images are helpful in identifying a new or changing lesion.

Evidence summary	Level	Reference
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	I	21, 22, 24–31
Dermoscopy has been shown to reduce the benign:malignant ratio of excised melanocytic lesions and reduce the number of patients referred for biopsy in a specialist setting	II	22, 23
Four level II studies show consistently that sequential digital dermoscopic imaging allows the detection of suspicious dermoscopic change in melanomas that lack dermoscopic evidence of melanoma at a particular time	II	35–38
To date only three automated instruments for the diagnosis of primary melanoma have been assessed against clinicians with a reasonable sample size in the clinical field. Here, instrument specificity was either inferior or equivalent to specialist diagnosis, and sample sizes were inadequate to assess differences in sensitivity	II	25, 40, 41
Eight level IV studies and one level III-3 study examined surveillance of high-risk subjects with total body photography but only one included a comparison arm (of lower-risk subjects). All studies on high-risk patients showed early melanoma detection and/or high melanoma incidence. All studies were designed to assess the outcomes of surveillance in high-risk groups rather than the value of TBP	IV	43–51

## Recommendations

	Grade
1. Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions	<b>A</b>
2. Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma	<b>B</b>
3. Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma	<b>C</b>

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# 6 Biopsy

The following is a discussion of the different forms of biopsy appropriate for suspicious pigmented lesions.

## 6.1 Complete excisional biopsies

The ideal method for skin lesions suspected of being melanoma is complete excision with a 2mm margin.<sup>1</sup> The National Comprehensive Cancer Network advises that the margin of normal skin should be no larger than 3mm to avoid interfering with subsequent lymphatic mapping<sup>2</sup> and Roberts et al 2002 suggest a margin of 2 to 5mm.<sup>3</sup> The ellipse specimen should follow the lines of relaxed skin tension with the deep margin in subcutis. Focally suspicious areas can be indicated on a diagram or marked for sectioning by the pathologist e.g. with ink, suture, superficial or punch incision. 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.

A retrospective analysis of 298 naevi which showed significantly different degrees of atypia in different zones of 36% of cases concluded that complete excisional sampling of atypical naevi is necessary.<sup>4</sup>

## 6.2 Partial biopsies

Partial biopsies of suspicious pigmented lesions have been shown to be less accurate (as measured by Breslow thickness) than subsequent wide local excision of suspicious melanocytic lesions or melanoma.<sup>5</sup> A retrospective review of 114 cases of lentigo maligna (with or without invasion) showed a higher risk of misdiagnosis with partial biopsy compared with excisional biopsy.<sup>6</sup> Farrahi et al and Karimipour et al found that 21% of 1783 melanoma patients undergoing various techniques of partial biopsy were upstaged on subsequent excisional samples (which showed significantly higher Breslow thickness).<sup>7</sup> They concluded that the smaller the percentage of lesion removed by biopsy, the greater the degree of inaccuracy was likely to occur. In a series of 46 partially biopsied pigmented lesions from actinically damaged skin, 40% of re-excisions revealed deeper invasion or diagnostic changes not seen on original biopsy, with 28% of these felt to be of prognostic or therapeutic significance. In 20% of cases, the initial biopsy did not identify invasion that was later seen on the excision sample.<sup>8</sup>

At times, complete excision is not practical for clinical, technical or other reasons, so partial biopsy may be necessary. This may be considered where the lesion is large or on a site where total excision may cause cosmetic or functional impairment, when there is a low index of clinical suspicion or significant comorbidities. All biopsies should include the most suspicious or invasive zones. The biopsy type and proportion of the lesion sampled should be indicated on the pathology request form. Careful planning of the biopsy site is essential and use of dermoscopy 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 US because of inadequate material being available for analysis by the pathologist.<sup>9</sup> They should only be performed by appropriately trained clinicians aware of the possible limitations of the technique. Evaluation of the subsequent excision specimen may be impaired by reparative changes, and accurate determination of Breslow thickness, regression or lymphocytic infiltration may be compromised.

A **punch biopsy** provides dermis for assessment of tumour invasion but samples only a limited breadth of large lesions and is therefore prone to sampling error. Multiple punch biopsies may minimise this source of error.

A **broad superficial shave biopsy (or curettage)** can provide a larger area of epidermis for histology, but often fails to include sufficient dermis for full assessment of invasion. These biopsies are therefore only suitable 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). 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 heal with little or no scar and are therefore suitable for use on the face.

**Deep shave biopsies** (saucerisation) include varying amounts of reticular dermis and may transect the base of a melanoma, impairing the assessment of Breslow thickness more often than with excisional biopsy. Any form of shave biopsy may incompletely sample the periphery of the lesion and samples can be difficult to orientate in the laboratory. Deep shave biopsies heal with a scar.

**Incisional biopsy** removing as much of the lesion as is feasible with primary closure can be a very useful method of partial biopsy.

In a retrospective analysis, excisional biopsy demonstrated better diagnostic accuracy than punch or shave biopsies, with deep shave (at least to mid dermis) favoured over punch biopsy.<sup>10</sup> In a study of dysplastic naevi (some of which were later diagnosed as melanoma on histology), 21 of 22 shave biopsies and 29 of 41 punch biopsies were concordant with the subsequent excision.<sup>11</sup> It should be noted that the type of shave used in this study was of the 'saucerisation' type, a style of shave biopsy that is not commonly used in many centres. A retrospective review of 223 cases of melanoma showed that shave samples generally gave the thinnest samples compared with punch or excisional biopsies, and that 50% of these shave biopsies showed at least one positive margin.<sup>12</sup> In Karimipour et al 2005, shave biopsy was less accurate in determining Breslow thickness.<sup>7</sup>

In a multicentre RCT of 2164 melanoma patients, Martin et al found that prognosis was not affected by previous incisional biopsy of the lesion.<sup>13</sup> A comparison of 265 melanomas sampled by incisional biopsy with 496 control melanomas not subjected to incisional biopsy did not show effects on prognosis, or on risk of recurrence.<sup>14</sup>

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, a better sample should be obtained, preferably by performing a complete excision.

The theoretical risk of melanoma dissemination by biopsy prior to excision has generally been rejected.

## 6.3 Alternative approaches

Frozen section and cytological analysis are inappropriate for suspicious pigmented lesions, but may be of value when assessing potential metastases from a melanoma, for example, in a lymph node.

When clinical suspicion of malignancy is low, observation may be appropriate, possibly backed up by dermoscopy, clinical photographs and an accurate description and measurement of the lesion. 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.

Where clinical suspicion remains despite a negative pathology report following a partial biopsy, rebiopsy 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 in some circumstances.

Evidence summary	Level	Reference
<b>Partial biopsies versus completeness of excision</b> Complete excision with a 2mm margin is the most reliable biopsy method for skin lesions suspected of being melanoma	IV	1, 3
One-third of atypical naevi show significantly different degrees of atypia in different zones indicating that complete excisional sampling of atypical naevi is necessary	III–3	4
Partial biopsy has been shown to be less accurate (as measured by Breslow thickness) than the subsequent wide local excision of suspicious melanocytic lesions or melanoma	III–3	5
Partial biopsies are an important cause of litigation because of inadequate material being available for analysis by the pathologist	IV	9
A retrospective review of 114 cases of lentigo maligna (with or without invasion) showed a higher risk of misdiagnosis with partial biopsy compared with excisional biopsy. In another study, 21% of partial biopsies were upstaged on subsequent excisional samples (which showed significantly higher Breslow thickness), with greater inaccuracy related to smaller percentages of lesion removed by biopsy	III–3	6, 7
In a series of 46 partially biopsied pigmented lesions from actinically damaged skin, 40% of re-excisions revealed deeper invasion or diagnostic changes not seen on original biopsy, with 28% of these felt to be of prognostic or therapeutic significance. In 20% of cases, the initial biopsy did not identify invasion that was later seen on the excision sample	III–3	8

continued over...

Evidence summary continued...	Level	Reference
Partial biopsies are an important cause of litigation because of inadequate material being available for analysis by the pathologist	IV	9
<b>Types of biopsies (punch, shave, incisional)</b> Excisional biopsy demonstrated better diagnostic accuracy than punch or shave biopsies. In a study of dysplastic naevi (some of which were later diagnosed as melanoma on histology), 21 of 22 shave biopsies and 29 of 41 punch biopsies were concordant with the subsequent excision. In a retrospective review, shave samples generally gave the thinnest samples compared with punch or excisional biopsies, and 50% of these shave biopsies showed at least one positive margin. In another study, shave biopsy was less accurate in determining Breslow thickness	III–3	
In a multicentre RCT, prognosis was not affected by previous incisional biopsy of the lesion	II	13
A comparison of melanomas sampled by incisional biopsy compared with melanomas not subjected to incisional biopsy did not show differences between prognosis, or on risk of recurrence	III–3	14

### Recommendations

	Grade
1. The optimal biopsy approach is complete excision with a 2mm margin and upper subcutis	<b>C</b>
2. Partial biopsies may not be fully representative of the lesion and need to be interpreted in light of the clinical findings	<b>C</b>
3. Incisional, punch or shave biopsies may be appropriate in carefully selected clinical circumstances, for example, for large facial or acral lesions, or where the suspicion of melanoma is low	<b>C</b>

## 6.4 Good practice point

- It is advisable to review unexpected pathology results with the reporting pathologist

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## 7

# Histopathological reporting of cutaneous melanoma

The aim of the histopathology report on primary cutaneous melanoma is to provide the clinician with the information necessary for the optimum management of the patient. The most important components of the report are the correct diagnosis of primary melanoma (refer Chapter 5 *Clinical Diagnosis*), the microscopic assessment of completeness of excision and the microscopic measurement of tumour thickness (Breslow), the single most important prognostic factor for primary melanoma.<sup>1</sup> Beyond these essential components, other features are usually included in the report, some probably with prognostic value, although less than that of tumour thickness, and others which may be more helpful for studies of epidemiology and pathogenesis, for example, associated benign melanocytic lesion, cell type, solar elastosis.

## A. Macroscopic description

- Dimensions of the specimen and the melanoma (in mm)
- Description of the melanoma: contour, profile, pigmentation, borders

## B. Microscopic

- Essential components
  - Diagnosis of primary melanoma
  - Breslow thickness, measured to the nearest 0.1 mm
  - Margins of excision in mm
    - (i) invasive melanoma: lateral and deep margins
    - (ii) *in situ* melanoma: lateral margins
  - Level of invasion (Clark)
  - Mitotic rate per mm<sup>2</sup>
  - Ulceration: presence and extent (in mm)
- Other components
  - Vascular invasion
  - Microsatellites
  - Lymphocytic infiltrate: presence and extent of tumour-infiltrating lymphocytes (TIL)
  - Regression: presence and extent; clearance from margins of excision
  - Desmoplasia: presence and extent (% of invasive component)
  - Neurotropism
  - Associated benign melanocytic lesion
  - Solar elastosis: degree of severity
  - Predominant cell type, for example, epithelioid, spindle cell, naevoid
  - Histological growth pattern
  - Growth phase: radial, vertical
  - Immunohistochemistry

## 7.1 Comments on the histopathological reporting of melanoma

**Assessment of completeness of excision:** The entire tumour should be embedded whenever practicable. The margins need to be carefully examined not only for the presence of invasive melanoma but also for *in situ* melanoma and other atypical melanocytic proliferation. In those cases where the borders of the lesion are very poorly defined, as in some cases of melanoma in severely sun-damaged skin, the entire periphery of the specimen may be embedded for histopathological examination. Mapped serial excision has recently been recommended for the treatment of lentigo maligna (LM) and lentigo maligna melanoma (LMM) as providing a more reliable assessment of excision than the arbitrary limits of 5mm for LM and 10mm for LMM on standard histological sectioning.<sup>2</sup>

**Level of invasion:** Level of invasion is now included in the AJCC Clinical Staging only in the PT1 category of tumours 1mm or less in thickness, on the basis that level of invasion is more likely to be of prognostic importance in thin melanomas.<sup>1</sup> Nevertheless, most clinicians expect level of invasion to be included in the report.

**Mitotic rate:** Some recent studies have suggested that mitotic rate (MR) is a more powerful factor than ulceration.<sup>3–6</sup> For consistency and reproducibility in assessing mitotic rate, counting needs to begin in a zone within the invasive tumour of obvious mitotic activity ('hot spot') and on an area of one square millimetre.<sup>7</sup>

**Ulceration:** Ulceration is an integral component of the AJCC/UICC staging system.<sup>1</sup> The standard method for measurement of tumour thickness in ulcerated lesions, however, may lead to an underestimate of thickness because the recommended measurement from the base of the ulcer to the base of the tumour makes no allowance for the amount of tumour lost through ulceration.

**Vascular invasion:** Vascular invasion as identified by the demonstration of melanoma cells within the lumina of blood vessels, and/or lymphatics, is an uncommon finding in the excision specimens of primary CM, but it is generally regarded as a marker of poor prognosis.<sup>8</sup> Extravascular migratory metastasis, also termed angiotropism in cutaneous melanoma, has recently been proposed as a means of metastasis and therefore may be an important prognostic factor.<sup>9</sup>

**Microsatellites, in-transit metastases, and local metastases (at the primary excision site):** These are probably biologically identical with the same prognostic implications. Microsatellites and in-transit metastases are included in the same prognostic group by the AJCC.<sup>1</sup> Correct classification of these tumours is important for accurate recording by cancer registries, for correlation with the initial method of treatment and for assessment of prognosis and clinical staging.

**Tumour-infiltrating lymphocytes (TIL):** The assessment of TIL by distribution and density is a subjective exercise and prone to inter-observer variation, although agreement may be improved by instruction.<sup>10</sup> Reports on the prognostic effect of TIL have varied; a recent study showed that TIL predicted sentinel lymph node positivity but were not an independent predictive factor for survival.<sup>11</sup>

**Regression:** Regression is recognised by apparent loss of invasive tumour with associated fibrosis, lymphocytes, melanophages, and increased vascularity. Regression at a lateral

excision margin is an indication for re-excision because it implies that there may be further melanoma in the skin beyond the visible margins. Reports on the prognostic impact of regression have produced conflicting results but some have indicated that regression is an important adverse prognostic factor in thin melanoma.<sup>12,13</sup>

**Desmoplasia:** Stromal desmoplasia underlying a melanoma should be examined for the presence of atypical spindle cells separated by collagen, as in *desmoplastic melanoma (DM)*. Extension of desmoplasia to the margins of excision is an indication for wider excision. Survival rates for patients with DM, with and without neurotropism, are similar to those for patients with other CM. A recent study reported that DM of 'pure' type (prominent desmoplasia throughout the invasive tumour) was associated with more favourable prognosis than DM of 'mixed' type (with partial desmoplasia).<sup>14</sup>

**Neurotropism:** Infiltration along nerve sheaths may be associated with an increased local recurrence rate.<sup>15</sup> Neurotropism is common in desmoplastic melanoma (desmoplastic neurotropic melanoma), but may occur in other forms of melanoma.

**Associated benign melanocytic lesion:** Although of no known prognostic value, the recognition of an associated benign melanocytic lesion is relevant to the pathogenesis of melanoma and may be important for epidemiologic and genetic studies.<sup>16,17</sup>

**Solar elastosis:** The relationship between patterns of sun exposure and site distribution of melanoma is fundamental to the understanding of the pathogenesis of melanoma. The reporting of solar elastosis as an index of prolonged sun exposure may be valuable, therefore, mainly for research purposes.<sup>16,17</sup>

**Predominant cell type:** Melanoma composed predominantly of spindle cells has been associated with a better prognosis than those composed of epithelioid cells in some studies, but this has not been a consistent finding.<sup>18</sup>

**Histological growth pattern:** The classification of melanoma by Wallace Clark et al<sup>19</sup> was widely accepted for many years on the basis of epidemiological studies that have indicated possible aetiological differences between some subtypes and on the didactic value of recognising a variety of growth patterns as an aid to diagnosis. This classification, however, has little if any prognostic value independent of tumour thickness, and its interpretation is very subjective and prone to inter-observer variation.<sup>20</sup> Recent epidemiological studies have emphasised the importance of site and different patterns of sun exposure as important determinants of melanoma growth patterns.<sup>16</sup> This concept is supported by recent genetic studies that have indicated distinct genetic pathways in the development of melanoma at different sites and with different levels of sun exposure, but which did not demonstrate any genetic features of a separate entity for nodular melanoma.<sup>17</sup>

**Growth phase:** The histological criteria for recognition of the growth phases are very subjective and prone to inter-observer variation.<sup>21</sup> The presence of vertical growth phase in thin tumours may be an indication of the possibility of metastasis from 'thin' melanoma.<sup>22</sup>

**Immunohistochemistry:** S100 protein is expressed by most melanomas; although not specific for melanocytes, its presence is especially helpful in assessing the extent of inconspicuous infiltration by spindle cell melanomas, especially desmoplastic melanoma. Immunostaining for HMB-45 is less likely to be helpful in these problem tumours but it may

be helpful in distinguishing between melanoma and atypical naevi, by virtue of retention of HMB-45 positivity in the deep component of melanoma, more so than in naevi. Melan-A (Mart 1) is a very helpful marker of melanocytes but it is not usually expressed by spindle cells, as in desmoplastic melanoma; MITF (microphthalmia transcription factor) is also a sensitive marker of melanocytic differentiation. Studies of cell kinetics in melanoma have produced conflicting results<sup>23</sup> but a recent report suggested that Ki67 expression (assessed by the MIB-1 antibody) is an independent prognostic factor for thin melanomas ( $\leq 1.00\text{mm}$  thick).<sup>24</sup>

**Primary melanoma versus metastatic melanoma:** The possibility of *metastatic melanoma* must be considered in cases where the tumour is located completely within the dermis and/or subcutis without either attachment to the epidermis or an intraepidermal component of atypical melanocytic proliferation<sup>25</sup> (see Table 5). *Epidermotropic* metastasis may mimic primary melanoma.

**Local recurrence** may be due to either persistence of incompletely excised primary melanoma or cutaneous metastasis. Clinically 'recurrent' melanoma in or adjacent to the scar or graft should be examined carefully for the histological criteria of persistent primary melanoma versus metastatic melanoma, and classified accordingly<sup>26</sup> (see Table 5). Persistent primary melanoma is most commonly the result of incomplete excision of *in situ* melanoma in sun-damaged skin, or diffusely invasive melanoma, for example, desmoplastic melanoma.<sup>26,27</sup> Clinicopathological correlation is important.

**Clinicopathological correlation:** The clinician and the pathologist should discuss any pathology report that does not accord with the clinical diagnosis. In cases of doubt, an expert opinion should be sought. Spitz naevi, for instance, usually have benign clinical features resembling haemangioma or pyogenic granuloma, whereas their histological features may lead to misdiagnosis as melanoma.

## 7.2 Pathology request form

The following clinical information needs to be provided on the pathology request form.

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Age and sex of patient

Anatomical site of melanoma

Clinical diagnosis

Description of type of specimen, for example, excision, biopsy (punch, incisional, shave)

Primary excision or re-excision. If re-excision, a copy of the previous report should be provided

History

- Present melanoma (duration, signs of malignancy, size of lesion)
- Previous melanoma(s)
- Family history
- Pregnancy
- History of lesional trauma, irritation or treatment with topical agent

Clinical photograph, if possible

Diagram of excision specimen with markers for orientation

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**Table 5** The histological features of persistent primary melanoma versus local metastasis of melanoma

	Persistent primary melanoma	Local metastasis of melanoma
<b>Epidermal component</b>	Usually present, with or without a dermal component	A. Absent in most cases B. Epidermotropism. The dermal component usually extends beyond a zone of epidermotropism when present. Sometimes the epidermotropic component is more extensive, simulating primary melanoma
<b>Dermal growth pattern</b>	The full range of patterns associated with primary melanoma: nodular, plaque-like, single cells, small groups of cells, diffuse, desmoplastic, neurotropic	A. Single or multiple symmetrical dermal and/or subcutaneous nodules B. Diffuse small groups and strands of atypical melanocytes (this pattern occurs in the smallest and presumably earliest metastases)
<b>Inflammation</b>	Lymphocytic inflammation usually present	Absent or sparse
<b>Vascular invasion</b>	Sometimes present	Present in many cases
<b>Mitotic rate</b>	Variable	High (usually > 6mm <sup>2</sup> )
<b>Cell type</b>	The full range of cell types seen in primary melanoma, frequently including a mixture of cell types	Usually monomorphic atypical melanocytic population of epithelioid, spindle or small (naevoid) cells
<b>Associated naevus</b>	Commonly present	Rare (coincidental)
<b>Necrosis</b>	Uncommon	Often present in the centres of the nodules
<b>Epidermal collarette</b>	Uncommon	Usually present when nodules of metastatic melanoma are in the superficial dermis
<b>Fibrosis</b>	Frequently present in zones of regression and in desmoplasia	Little or no fibrosis in the stroma of the tumour
<b>Scarring</b>	Present in the dermis and often also in the subcutis	Present when the metastasis occurs at the primary excision site

**Note:** In cases of persistent primary melanoma, histological review of the primary excision specimen confirms the presence of *in situ* or invasive melanoma (or both) at a margin of excision. Melanoma metastatic to the scar of primary excision shows the same features as distant cutaneous metastasis with the additional feature of scarring from the previous surgery.

## 7.3 Recommended terminology and synonyms for cutaneous melanoma

Recommended terminology	Synonyms
<b>Melanoma of common type</b>	
<b>Melanoma, <i>in situ</i></b>	Lentigo maligna (Hutchinson's melanocytic freckle) Superficial spreading melanoma <i>in situ</i> Acral lentiginous melanoma <i>in situ</i>
<b>Melanoma, invasive</b>	Lentigo maligna melanoma Superficial spreading melanoma Acral lentiginous melanoma Nodular melanoma  Unclassified melanoma
<b>Uncommon Variants</b>	
Desmoplastic melanoma	
<b>Others (controversial and provisional)</b>	
Malignant blue naevus (melanoma resembling or arising in a blue naevus)	
Melanoma in congenital naevus	
Minimal deviation (naevoid) melanoma	
Animal type melanoma (pigmented epithelioid melanocytoma)	
Primary dermal melanoma	

## 7.4 Format of the report

The format can be either descriptive or synoptic (tabulated). It is suggested that both formats may be used.

### 7.4.1 Descriptive

The descriptive report on CM needs to refer to all the histological features of possible importance for individual cases. The accurate description of atypical cytologic features and growth patterns provide the reader, either another pathologist or a clinician, with an insight into the reasons for the pathologist's decision to make the diagnosis of malignant melanoma. In particular, an accurate description in problem cases, such as spitzoid tumours, alerts the clinician to the difficulty in reaching a definitive diagnosis, suggesting that alternative diagnoses may be considered and that further opinion(s) should be sought. The synoptic report is not a substitute for the descriptive report – it should be an easily readable, succinct, appendage.

### 7.4.2 Synoptic

Synoptic reports present the histological features of the tumour in a tabulated form to provide essential information for the assessment of prognosis and the planning of treatment.<sup>28,29,30</sup>

The report should emphasise the most important components which are:

1. the correct diagnosis of primary melanoma
  2. Breslow thickness
  3. accurate assessment of margins of clearance of both invasive and *in situ* melanoma.
- In addition the synoptic report should include those histological features thought to be of prognostic importance, especially mitotic rate, ulceration and level of invasion and other features possibly relevant to the aetiology and pathogenesis of melanoma (see 7.4.3). Accurate synoptic reports are especially valuable for research data bases and cancer registries.

### 7.4.3 Example of a synoptic histopathology report

<b>Diagnosis: Melanoma, invasive</b>	
<b>Histological features</b>	
<b>Tumour thickness*</b>	<b>2.3mm</b>
<b>Margins of excision*</b>	
<b>A. Invasive component – nearest peripheral margin</b>	<b>3.7mm</b>
<b>B. <i>In situ</i> component – nearest peripheral margin</b>	<b>1.4mm</b>
<b>C. Deep margin</b>	<b>5.0mm</b>
<b>Mitotic rate (per mm<sup>2</sup>)*6</b>	
<b>Ulceration (diameter in mm)*</b>	<b>Present (2.0mm)</b>
<b>Level of invasion (Clark)*</b>	<b>4</b>
Vascular invasion	Absent
Microsatellites	Absent
Regression	Absent
Neurotropism	Absent
Desmoplasia (% of invasive tumour)	Absent
Solar elastosis	Present Severe
Tumour-infiltrating lymphocytes (TIL)	
• Distribution: focal or diffuse	Focal
• Density: sparse or dense	Sparse
Associated benign melanocytic lesion	Compound naevus
Predominant cell type	Epithelioid
Growth phase	
• Radial	Vertical
• Vertical	
Intraepidermal growth pattern (e.g. pagetoid, lentiginous, mixed)	Pagetoid
* Essential components.	



Evidence summary	Level	References
Breslow thickness, margins of excision (microscopic), mitotic rate, level of invasion, and ulceration are strong predictors of outcome for melanoma patients and so are regarded as essential components of a histopathological report	II/III-3	1-7
Microsatellites, in-transit and local metastases are uncommon but are strong predictors of outcome and should always be reported	II/III-3	1
Vascular invasion, although uncommonly recognised, is a marker of poor prognosis and should always be reported when present	II/III-3	8, 9
Other components, such as tumour-infiltrating lymphocytes, regression, desmoplasia, neurotropism associated benign melanocytic lesion, solar elastosis, predominant cell type histological growth pattern, growth phase and immunohistochemistry may be of prognostic or diagnostic importance or of value regarding aetiology and pathogenesis	II/III-3	10-24
The important distinction between persistent primary melanoma and local metastasis is made on histological criteria, review of the primary melanoma, and clinicopathological correlation	III-3	25-27
The descriptive and synoptic report remains essential. Although the demand for synoptic reports is increasing, their use remains optional	III-2	28, 29

### Recommendations

	Grade
1. The essential components of a histopathological report: <ul style="list-style-type: none"> <li>• Breslow thickness</li> <li>• margins of excision (microscopic)</li> <li>• mitotic rate/mm<sup>2</sup></li> <li>• level of invasion (Clark)</li> <li>• ulceration</li> </ul>	<b>A</b>
2. The following components of a histological report are of prognostic or other value: <ul style="list-style-type: none"> <li>• vascular invasion, local metastases, microsatellites and in-transit metastases, tumour-infiltrating lymphocytes, regression, desmoplasia, neurotropism, associated benign melanocytic lesion, solar elastosis, predominant cell type, histological growth pattern, growth phase and immunohistochemistry</li> </ul>	<b>C</b>

continued over...

**Recommendations** continued...

	Grade
3. Histological criteria, review of the primary melanoma and clinicopathological correlation be used for distinguishing between persistent primary melanoma and local metastasis	<b>C</b>
4. The synoptic report be used in conjunction with, but not as a replacement for, the descriptive report	<b>C</b>

## 7.5 Pathology report on sentinel and non-sentinel lymph nodes

The optimal histopathological protocol for examining sentinel lymph nodes (SLN) is unclear at present. The protocol must balance the accuracy of the result against the labour and costs involved. Most authorities recommend evaluation of multiple sections from each half of the SLN, including sections stained with haematoxylin-eosin (H&E) and sections stained immunohistochemically for melanoma-associated antigens (usually S100 and HMB-45 and/or MelanA and/or tyrosinase). It is unclear from the currently available evidence what is the most appropriate number of sections to examine, at what levels these should be cut from the tissue blocks and the most appropriate number and combinations of immunostains that should be assessed. A number of studies have assessed the detection rate of metastatic melanoma in SNs using different pathologic sampling protocols.<sup>31–34</sup> Most of these studies have shown that increased histopathological sampling of SLNs from melanoma patients detects more melanoma, although the extent of the increase in detection rates reported have differed in the various studies. Furthermore, the significance of small tumour deposits detected by extensive sampling remains unclear. Routine frozen section examination of SLNs from melanoma patients is not recommended.

The presence or absence of melanoma metastases should be documented in the histopathology report. Melanoma metastases should be distinguished from clusters of small banal naevus cells which are usually located in the capsule and radial trabeculae of lymph nodes.

Recent evidence suggests that the location and extent of tumour deposits within SLN provides important prognostic information.<sup>35–38</sup> If there are only a few metastatic cells in the subcapsular sinus of the SLN, the prognosis is relatively good and the chance of finding additional metastatic disease in a completion lymph node dissection CLND specimen is extremely small. If, on the other hand, there are multiple large foci of tumour, extending deeply into the central parenchymal part of the SLN, the prognosis is much worse, and the chance of finding metastases in non-SLNs in a CLND specimen is high. However, it remains unclear which correlate of tumour burden or combination of other factors best predicts a low probability of metastatic tumour being present in non-SLN and the likelihood of further recurrence and death from melanoma. More work is necessary to define optimally the most accurate and practical method of identifying patients who have a low probability of having metastatic tumour in non-SLNs and in using this information to direct further patient management. At present it is recommended that the size of the largest metastatic focus, the tumor penetrative depth (measured using a micrometer from the inner margin

of the node capsule to the deepest tumor cell within the SN) and the percentage nodal cross sectional area involved (as measured on the slides) be recorded in the pathology report. The role and significance of molecular assessment of SLN for low volume metastases of melanoma (primarily by RT-PCR) is currently being assessed.

Non-SLNs removed during the same operative procedure as SLNs should be examined and reported in a similar manner to lymph nodes removed in lymph node dissections specimens (see below).

Evidence summary	Level	References
The microanatomic location and micromorphometric features of metastases in SLN are, according to recent studies, of prognostic importance but the optimal protocol for examination of SLN requires further study	III–3	35–38
Reporting on lymph node dissection specimens requires the accurate assessment of the number of nodes involved by metastases, the extent of that involvement, and the presence of extranodal involvement	IV	39

### Recommendations

	Grade
5. Pathology reports should include information from sentinel lymph biopsies, derived from multiple histological sections of sentinel nodes (including sections stained with H&E and immunohistochemically for melanoma-associated antigens including S-100)	<b>C</b>
6. Non-sentinel lymph nodes should be carefully examined and reported	<b>D</b>

## 7.6 Pathology report on lymph node dissection specimens<sup>39</sup>

The specimen should be fixed in 10% buffered formalin for 24 hours prior to macroscopic examination. It should be dissected carefully and all lymph nodes present identified. All lymph nodes should be submitted in their entirety for microscopic examination, except that representative sections of macroscopically involved lymph nodes may be evaluated instead of the entire lymph node.

The histopathological report should indicate:

1. the number of lymph nodes found
2. the number of lymph nodes containing metastases
3. the size of any deposit of melanoma identified macroscopically.

If present, the following should be noted in the report:

1. the presence and size of aggregates of matted lymph nodes
2. the size of the largest metastasis
3. The presence and extent (in mm) of extranodal extension of tumour.

Other issues that need further consideration:

- minimal number of lymph nodes in regional clearance specimens from different sites
- definition and measurement of extent of extranodal spread.

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# 8 Appropriate investigations

## 8.1 Investigations following the diagnosis of primary melanoma

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of primary cutaneous melanoma. Specifically, there is no evidence about outcome (overall or relapse-free survival), with most studies assessing the accuracy of the investigations examined. The majority of studies are descriptive or observational, including one meta-analysis, two good-quality expert reviews and three good-quality clinical guidelines. There are no studies providing an economic evaluation.

### 8.1.1 Evidence statement

Investigations after the diagnosis of primary cutaneous melanoma are aimed at the detection of occult regional or systemic disease. The likely yield of such investigations for primary melanoma is directly proportional to the risk of metastatic disease. Hence the role of investigations following the diagnosis of primary melanoma might be stratified according to known prognostic factors, such as Breslow thickness. The first aim of detecting occult metastatic disease is to improve survival through an intervention or treatment that will change the natural history of the disease. However, there are no data to support the concept that the early detection of occult metastatic disease is associated with improved survival compared with later detection of symptomatic systemic disease. The second aim is to identify occult disease stage III or IV, not suggested by history and examination, which would result in a change in management.

The most accurate method for the identification of occult regional lymph node metastases is sentinel lymph node biopsy (SLNB) (see Chapter 12.1). In an attempt to avoid the morbidity of SLNB in patients with a negative SLNB, several radiological methods of regional lymph node assessment have been investigated. The meta-analysis by Bafounta et al<sup>1</sup> found that ultrasound examination of lymph nodes was consistently more accurate than palpation for the detection of lymph node metastases. Ultrasound can accurately detect lymph node metastases > 4.5mm in size.<sup>2,3</sup> However, prospective studies have shown that SLNB remains superior to ultrasound in the detection of occult regional lymph node metastases.<sup>2</sup> Similar prospective studies comparing the sensitivity and specificity of PET scan with SLNB as the reference standard found PET scan to be inferior to SLNB, with a sensitivity of 13% for PET scanning.<sup>4-6</sup> These studies also demonstrated significant false positive rates. No data regarding ultrasound or PET findings and survival were reported in these studies.

Elevated serum LDH has not been shown to be useful for the detection of occult metastatic disease in patients with stage I or II melanoma and the authors concluded that the routine use of serum LDH cannot be recommended.<sup>7</sup> Similarly, full blood count, serum electrolytes and liver function tests in combination with radiology, including CT scan, did not demonstrate any occult metastatic disease in a prospective study of 90 patients with primary melanoma.<sup>8</sup>

Four observational studies of low quality have investigated the yield of routine chest x-ray (CXR) for the detection of occult pulmonary metastases in patients with primary cutaneous melanoma and demonstrated true-positive rates of 0.0–0.1%.<sup>6–9</sup> Hence the routine use of CXR cannot be recommended. Similar findings have been demonstrated for CT scanning of the head, chest, abdomen and pelvis.<sup>8,10</sup> More recently, whole-body PET scanning has been investigated in two prospective non-randomised studies with comparable conclusions for patients with stage I or II cutaneous melanoma.<sup>6,11</sup> No sites of true-positive metastatic disease were demonstrated in any of the studies but both CT scanning and whole-body PET scanning yielded false positives.

In summary, the yield of any investigations for patients with stage I–II cutaneous melanoma is very low for the detection of occult stage IV disease. All of the investigational methods used are plagued by false positives and cannot be recommended. For the detection of occult stage III disease, the yields of ultrasound, CT scan or PET scan are inferior to SLNB and have been shown to be cost-inefficient.<sup>12</sup> There are no data regarding the utility of investigations with respect to outcome. Therefore, routine use of investigations for stage I–II cutaneous melanoma is not recommended. Radiological investigations may be routinely required for patients participating in clinical trials.

Evidence summary	Level	References
Regional lymph node ultrasonography is superior to palpation for the detection of regional lymph node metastasis	II	1
Both regional lymph node ultrasonography and PET scanning are inferior to sentinel lymph node biopsy for the detection of occult lymph node metastasis	III-2	2–6
The routine use of blood tests or radiological investigations, including chest x-ray, CT scanning, or whole-body PET scanning, rarely identifies occult stage IV disease in patients presenting with stage I or II cutaneous melanoma. The identification of false-positive metastatic disease is a consistently reported phenomenon for all reported investigations	III-2	3–9, 11–13

### Recommendation

	Grade
1. Following the diagnosis of primary cutaneous melanoma (stage I, II) routine investigations are not required for asymptomatic patients	<b>D</b>



## 8.2 Investigations following the diagnosis of locoregional disease

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of locoregional cutaneous melanoma. The majority of studies are descriptive or observational studies, with one meta-analysis, two good-quality expert reviews and three good-quality clinical guidelines. There are no studies providing an economic evaluation.

### 8.2.1 Evidence statement

As for patients with primary melanoma, the aim of routine investigations for patients with newly diagnosed locoregional melanoma is the detection of occult stage IV disease with a view to improving survival, changing management or providing more accurate prognostic information. There are no data that relate the use of investigations at the time of diagnosis of stage III cutaneous melanoma to outcome. Published studies to date have investigated the diagnostic yield of investigations in the detection of metastatic disease, with two studies examining the impact of investigations on management. Patients with stage III melanoma are essentially represented by three subgroups that will be considered separately: SLNB positive (microscopic stage III); clinically evident lymph node disease (macroscopic stage III); and in-transit metastases (stage IIIC).

For patients found to have positive sentinel lymph nodes, prospective cohort studies have investigated the role of routine CXR, CT scan of chest, abdomen and pelvis, and magnetic resonance imaging (MRI). The true-positive rate for these combined investigations was 0.5% and 1.9% for study groups of 185 and 270 patients respectively.<sup>14,15</sup> These results are similar to those for patients with stage I–II melanoma and do not include any outcome data.

The high probability of distant relapse for patients with macroscopic locoregional cutaneous melanoma has prompted the routine use of radiological investigations by many clinicians despite there being no evidence from randomised trials to support their use. Prospective cohort studies and non-randomised clinical trials assessing the role of CT scan in patients with stage III cutaneous melanoma without symptoms suggestive of metastatic disease have revealed true-positive rates of 0–26%, with most studies reporting rates < 10%.<sup>10,13,16–19</sup> False-positive diagnoses for metastatic disease remain problematic in these studies, with reported rates of 8–20%.<sup>10,16,18,19</sup> These studies do not include outcome data or whether the investigation altered management.

More recently, the role of PET scan has been investigated for patients with stage III disease at the time of diagnosis. These studies have generally shown PET scan to be superior to conventional imaging for the identification of unsuspected metastatic disease, except for the detection of small lung secondaries. However, false-positive diagnosis of metastatic disease remains in the order of 10%.<sup>20–23</sup> Three prospective studies have investigated the influence of PET scanning on management. These studies have reported that PET scan influenced clinical management by 22–49%.<sup>20,24,25</sup> However, all of these studies combined stage III patients with stage IV cutaneous melanoma patients and did not break down the results by stage, potentially limiting the applicability of the findings to patients with stage III disease.

In summary, the yield of routine CT or PET scanning for patients with stage III cutaneous melanoma is up to 20% for the detection of stage IV disease, although false positives remain a problem for all of the investigational methods used. For patients with newly diagnosed stage III disease where a potentially morbid treatment is planned that would be abandoned in the presence of metastatic disease, CT scan of the chest abdomen and pelvis or whole-body PET scan may be performed. No data exist for the role of investigations for patients with in-transit disease. Hence the recommendations for in-transit disease (as stage III disease) are the same as for macroscopic stage III disease. Routine radiological investigations may be required for patients with stage III disease considering entry into clinical trials.

Evidence summary	Level	References
The true-positive rate for routine radiological investigations for patients with positive sentinel lymph nodes is less than 2%	III-2	14, 5
The yield of routine CT or PET scanning for the detection of stage IV disease is up to 20% for patients with macroscopic stage III cutaneous melanoma. The false-positive rates for these investigations are in the order of 10%	III-2	10, 3, 5–23
For patients with stage III disease, the routine use of CT or PET scan may influence clinical management in up to 49% of patients	III-2	20, 24, 25

### Recommendations

	Grade
2. Routine investigations, including radiology, are not indicated for patients following the diagnosis of a positive sentinel lymph node in the absence of symptoms suggestive of metastatic disease	<b>D</b>
3. Following the diagnosis of locoregional melanoma, patients require a detailed history and physical examination. Investigations, including radiology, are indicated for symptoms suggestive of metastatic disease. CT scan of the chest, abdomen and pelvis or whole-body PET scan may be performed for the workup of otherwise asymptomatic patients prior to definitive therapy where the detection of occult metastatic disease would influence management	<b>D</b>
4. Patients suspected of having lymph node metastasis from cutaneous melanoma should undergo fine needle aspiration biopsy, with ultrasound or radiological guidance when required, to confirm the presence of stage III disease	<b>D</b>

## 8.3 Investigations following the diagnosis of metastatic melanoma

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of stage IV cutaneous melanoma. The majority of studies are descriptive or observational studies.

### 8.3.1 Evidence statement

The diagnosis of metastatic melanoma is made on the basis of investigations for symptoms or investigations as part of routine follow-up. Computerised tomography has been shown to be superior to chest x-ray alone in the diagnosis of pulmonary metastases, identifying 20% more metastatic lesions.<sup>26</sup> Recently, much attention has been focused on the utility of PET scanning in the diagnosis of metastatic melanoma. The sensitivity and specificity of PET scan for the detection of melanoma metastases are reported to be 85% and up to 97%, respectively.<sup>27,28</sup> However, the sensitivity of PET scan decreases to as low as 4% for lesions < 6mm in size.<sup>27</sup> Despite this limitation, PET scan is generally more sensitive than CT scan for the detection of metastatic melanoma at all sites, except for brain and possibly lung.<sup>29,30</sup> While the evidence suggests that PET is superior to CT with respect to the number of metastatic sites identified, once the diagnosis of metastatic melanoma has been established by conventional imaging techniques, the supplementary use of PET scan is of little value<sup>31</sup> unless the result would cause a change in management. Three studies have examined the influence of PET scan in addition to conventional imaging on the management of patients with stage IV melanoma who are planned to undergo metastasectomy.<sup>20,24,25</sup> In this setting, the additional use of PET scan influenced clinical management by 22–49%.<sup>20,24,25</sup> Pre-operative PET scan is associated with improved outcome after pulmonary metastasectomy by permitting the selection of patients without additional sites that are most likely to benefit from resection.<sup>32</sup>

Prospective and retrospective comparison studies of low quality have consistently shown contrast-enhanced MRI brain to be superior to computerised tomography for brain metastasis detection, anatomic localisation of lesions, and differentiation of solitary versus multiple lesions.<sup>33,34</sup> One retrospective study of patients with stage I–IV melanoma found that routine MRI only detected asymptomatic brain metastases in patients with known stage IV disease.<sup>35</sup> Overall, where the detection of asymptomatic brain metastases would impact on treatment strategy, more accurate and complete staging is achieved by MRI compared with CT brain.<sup>36</sup>

For patients in whom conventional imaging techniques yield equivocal results for metastatic melanoma, PET scan should be viewed as a complementary imaging technique.<sup>37</sup> Image-guided fine needle biopsy may be performed to establish the diagnosis of metastatic melanoma (see Chapter 12.2) where diagnostic doubt remains after imaging studies. Alternatively, clinical observation and serial imaging may be required to confirm the nature of lesions suspected to be metastatic melanoma. Serum LDH forms part of the current AJCC staging system for melanoma and may be measured, once the diagnosis of stage IV melanoma has been established by imaging and/or biopsy, to aid in the determination of prognosis (see Chapter 4 *Classification and staging of melanoma*).

Evidence summary	Level	References
Chest CT scan is superior to chest x-ray for the detection of pulmonary metastases	III-2	26
PET scan is generally more sensitive than CT scan for the detection of metastatic melanoma at all sites, except for brain, possibly lung, and lesions < 6mm in size	III-2	27–30
MRI brain is generally provides more accurate and complete staging compared with CT brain	IV	33–36
Once the diagnosis of metastatic melanoma has been established by conventional imaging techniques, the supplementary use of PET scan is of little value unless the result could cause a change in management	III-2	31
For patients with stage IV disease, the routine use of CT, MRI or PET scan may influence clinical management in up to 49% of patients	III-2	20, 24, 25

### Recommendations

	Grade
5. Investigations, including serum LDH, CT, MRI, and/or PET scan, are indicated for symptoms suggestive of metastatic melanoma	<b>D</b>
6. Following the diagnosis of metastatic melanoma, no further investigations are required unless surgery is planned and the detection of additional sites of distant disease would result in a change in management	<b>D</b>

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# 9

## Congenital melanocytic naevi

Congenital melanocytic naevi (CMN) are pigmented naevi which are present at birth. The term is usually restricted to naevocellular naevi and excludes other congenital melanocytic naevi such as blue naevi. The diagnosis of CMN is typically a clinical one but there are certain specific histological features seen in most but not all cases. The naevus cells in CMN characteristically involve the lower dermis, infiltrate in lines between collagen bundles and involve the skin appendages.<sup>1</sup> In some cases they extend deep into the subcutaneous fat and may involve fascia or even muscle.

CMN vary from small to giant-sized, covering over half the body surface. There are many and varied criteria for classification of the size of CMN including actual and predicted adult maximum diameter and percentage of body surface area involved by the lesion. The most universally accepted at present is that used by the New York University Registry.<sup>2,3</sup>

**Small:** Greatest diameter less than 1.5cm or predicted to reach that size in adult life

**Medium:** Greatest diameter between 1.5 and 19.9cm or predicted to reach that size in adult life

**Large:** Greatest diameter 20cm or more, or predicted to reach that size in adult life

### 9.1 Risk of melanoma in patients with congenital melanocytic naevi

#### 9.1.1 Small

An early histology-based study suggested that small CMN may be precursors for some cases of cutaneous melanoma developing in adult life,<sup>4</sup> but there have been no satisfactory studies to confirm or quantify the risk of malignancy in these lesions.

#### 9.1.2 Medium

The single prospective study of medium-sized (1.5–19.9cm in diameter) CMN<sup>5</sup> showed no development of melanoma in 227 subjects with 230 CMN followed for a median of 5.8 years to a median age of 19.1 years. Similarly, in a study of CMN of all sizes, no melanomas were observed (0.18 expected) in those 232 patients with CMN < 20cm in diameter.<sup>6</sup> However, individual case reports indicate that these lesions can, on rare occasions, be melanoma precursors.<sup>7</sup> As the few reported cases of melanoma in medium-sized CMN have occurred in adult life, very long-term studies would be required to accurately quantify the risk.

#### 9.1.3 Large

There are many studies which confirm the increased risk of melanoma in individuals with large CMN<sup>8–11</sup> but the estimated magnitude of the risk varies widely between retrospective and prospective studies, those from academic and non-academic centres, those from small and large series, and those using the NYU and other classifications of size.<sup>12</sup> Other probable confounding factors limiting the veracity of results include the effects of surgical intervention and non-surgical treatments, the fate of cases lost to follow-up

and histological misdiagnosis. Well-conducted prospective studies suggest the risk is in the order of 2–5%,<sup>3,12,13</sup> but an accurate answer will probably never be obtained.

The highest risk of developing melanoma in these patients is under the age of ten<sup>14</sup> and in particular, under the age of five.<sup>15</sup>

Other factors associated with increased risk are giant size, axial location on the trunk, and the presence of multiple satellite naevi beyond the main lesion.<sup>14</sup> These are also risk factors for neurocutaneous melanosis (NCN), the association of CMN with proliferation of melanocytes in the central nervous system (CNS),<sup>16</sup> and all patients with these features should have magnetic resonance imaging investigation. Multiple large scattered lesions are also a risk factor for NCN.<sup>16</sup>

Melanoma development in satellite lesions is exceptional but has been reported.<sup>17</sup>

It is important to appreciate that melanoma in patients with large CMNs occurs in areas other than the cutaneous naevus in approximately half the cases.<sup>13</sup> The commonest site of non-cutaneous melanoma in these patients is in the central nervous system. Patients with symptomatic NCN have more than a 50% risk of developing CNS melanoma.<sup>16</sup>

Evidence summary	Level	References
The risk of melanoma in patients with small and medium CMN has not been quantified with appropriate studies. Individual case reports, however, suggest that melanoma does occur in medium sized CMN, but rarely and only in adult life	IV	4–7, 12
Patients with large congenital melanocytic naevi (CMN) are at increased risk of development of melanoma both in the naevus and elsewhere. Well-conducted prospective studies suggest the risk is in the order of 2–5%, with most melanomas developing in the first decade of life	III-3	8–11

## 9.2 Approach to management of patients with congenital melanocytic naevi

Non-surgical techniques such as dermabrasion, laser therapy and chemical peeling may produce some cosmetic improvement but cannot be considered to reduce the risk of melanoma.<sup>18</sup>

In CMN, melanoma can occur in the deep dermis or below so in general, excision, if attempted, should be to the depth of the fascia. However even then, because of occasional even deeper involvement, recurrences can occur and the malignancy risk is not completely eradicated.

Because melanoma can occur in patients with large CMNs in sites away from the cutaneous naevus,<sup>12</sup> even complete surgical excision of the CMN cannot be said to have removed the risk of melanoma in patients with large lesions.

With giant lesions which have multiple satellites on the remaining skin, total removal is impracticable. Removal of the thickest and most infiltrated areas may be appropriate<sup>18</sup> and biopsy or removal of any areas showing concerning alteration is mandatory.



Patients with symptomatic neurocutaneous melanosis in whom there is a high mortality rate and a high risk of CNS melanoma<sup>16</sup> should be spared aggressive prophylactic surgery.<sup>18</sup>

The authors of a large systematic review<sup>8</sup> concluded '...there is no conclusive evidence in the existing literature that the complete excision of large congenital melanocytic naevi decreases the prevalence of melanoma'.

Several papers have compared the rates of development of melanoma in treated and untreated patients with large CMN respectively.<sup>3,13,17</sup> Melanoma development occurred more in untreated than treated patients. The findings are rendered very unreliable by the differences in patient selection and the lack of detail about patients subjected or not subjected to surgery respectively. It is likely that the treated lesions were smaller than the untreated lesions and therefore less likely to develop melanoma. Several of the untreated lesions in which melanoma developed were so large that treatment was not feasible.<sup>17</sup>

Evidence summary	Level	References
The evidence does not support routine prophylactic removal of small and medium CMNs	IV	3–6, 11, 13–17
In patients with large CMNs, prophylactic surgery may lessen the risk of melanoma in those individuals with more easily removable lesions, which will tend to be ones at the smaller end of the range. There is no evidence that surgery in patients with large (including very large and giant) CMNs reduces the risk of melanoma	IV	7–13, 17

## Recommendations

Small and medium congenital melanocytic naevi	Grade
1. Prior to puberty, decisions regarding removal of these lesions be based on cosmetic considerations alone	C
2. Patients and parents be informed that the evidence regarding risk in adult life does not support routine prophylactic removal of these lesions	C
3. Patients report any suspicious changes in these lesions	C
4. Biopsy or removal of any lesions showing suspicious features be undertaken	C
Large congenital melanocytic naevi (more than 20cm in diameter)	
5. Lifetime surveillance be undertaken whether or not any surgery has been performed. This could include baseline photography and three-monthly evaluation for the first year of life, followed by six-monthly evaluation for the next three years, and then yearly evaluation	C
6. Patients and parents report immediately any concerning changes that occur between follow-up visits	C
7. Biopsies be undertaken immediately of any areas which show suspicious features	C

### 9.3 Good practice points

- All decisions regarding surgical management involve prolonged discussion with the parents, and later the patient, covering estimated risk of melanoma, what is involved in the surgery, the number and length of hospitalisations, possible morbidity of the procedures, and likely end cosmetic result
- MRI of the brain be undertaken in patients with large CMN in an axial distribution and those with multiple large scattered lesion, if the facilities are available. Some features of neurocutaneous melanosis, such as hydrocephalus, are amenable to treatment

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# 10 Lentigo maligna

Lentigo maligna (Hutchinson's melanotic freckle) is a traditional term for atypical pigmented macular lesions on severely sun damaged skin, usually on the face of elderly patients. The histological diagnosis of lesions clinically suspicious of lentigo maligna may range from solar lentigo to *in-situ* melanoma (lentigo maligna pattern) or invasive melanoma (lentigo maligna melanoma).<sup>1,2</sup> While some authors regard lentigo maligna as referring only to melanoma *in situ*,<sup>2</sup> others distinguish between different phases of lentigo maligna as, respectively, a melanoma precursor and *in situ* melanoma.<sup>1</sup> The recommendations in this chapter refer to the treatment of both those lesions in which *in-situ* melanoma has been histologically confirmed and those lesions in which histological examination has shown junctional melanocytic proliferation lacking the criteria for *in-situ* melanoma.

The diagnosis of lentigo maligna and lentigo maligna melanoma can be suggested by clinical and dermoscopic features, however, biopsy and histological assessment is required to establish a definitive diagnosis<sup>3</sup> (see Chapter 5 *Clinical Diagnosis*). It is important that the potentially heterogeneous nature of the melanocytic proliferation in lentigo maligna is recognised and that any form of subtotal (shave, punch or incisional) biopsy may fail to include representative lesional tissue or identify a dermal invasive malignant component (lentigo maligna melanoma). For appropriate biopsy techniques see Chapter 6 *Biopsy*.

Clinical factors, including the age at presentation of the lesion, the rate of clinical change, identifiable changes in adjacent skin, anatomical site, and the patient's life expectancy and comorbidities, will all potentially impact on the way these lesions are managed clinically. When the clinical diagnosis of lentigo maligna is confirmed as *in-situ* melanoma by histopathological examination, complete excision is recommended. The recommended clinical margin of 5mm for melanoma *in situ* is an arbitrary figure which in diagnostically difficult cases may prove to be inadequate due to microscopic extension of the tumour to a lateral margin. A 5mm histological margin, however, should be adequate, but lesser margins may be acceptable according to certain clinical circumstances e.g. anatomical site. If invasive melanoma has occurred in the lentigo maligna, the recommended margins of excision are the same as those for other subtypes of invasive primary melanoma (refer to Chapter 11 *Treatment of Primary Melanoma*). Lentigo maligna melanoma on the face may not always be resectable with the recommended 1cm margin for technical or clinical reasons and a lesser margin may be acceptable. In these circumstances, the opinion of an appropriate reconstructive surgeon may be indicated to minimise the compromise between excision margins and cosmetic deformity.

Radiotherapy represents another potential treatment option for lentigo maligna, particularly where surgical margins are inadequate or surgery is not possible. No data from prospective or randomised trials on the efficacy of radiotherapy in the treatment of lentigo maligna are currently available and interpretation of the outcomes from the available literature is hampered by the heterogeneity of the treatments described and the relatively short

follow-up periods in these studies. However, they indicate that this is a convenient and well-tolerated therapy with a modest recurrence rate. Therefore, superficial x-rays or electron therapy can be considered as an alternative treatment of lentigo maligna for elderly or frail patients, particularly those with lesions that would require relatively extensive resections and complex reconstructions.<sup>4–6</sup> Cryotherapy has been used in clinical situations where there is impediment to surgery or significant comorbidity.<sup>6</sup> Cryotherapy is a destructive technique and it can be difficult to ensure effective removal of all melanotic cells at the site. The treatment should be employed with great caution.

To date, topical treatment modalities have not been satisfactorily evaluated and are associated with the hazard of being utilised in the management of lesions with an unrecognised component of dermal invasive melanoma.

Lentigo malignas on the face that are not suspicious of containing dermal invasive melanoma, and which cannot be definitively excised or treated with radiotherapy because of comorbidities, complexity of wound repair or patient age, may be considered for careful monitoring utilising macroscopic and dermoscopic photography. Biopsy is warranted if there is apparent change in size or pigmentation.

Evidence summary	Level	Reference
There are no prospective studies or randomised controlled trials available to form the basis of any recommendations for the management of lentigo maligna	IV	6
A biopsy is the best means of establishing the diagnosis of lentigo maligna, though interpretation of the histopathology may be difficult	IV	3, 6
Lentigo maligna can be treated by surgical excision with low rates of recurrence and is the treatment of choice for lentigo maligna melanoma	IV	6
Radiotherapy is useful in the management of lentigo maligna where surgical margins are inadequate or surgery is not possible	IV	3–6
Cryotherapy may be useful in the management of melanoma maligna where surgery is not possible or patient comorbidities are severe	IV	6
The evidence for the use of topical treatments for the treatment of lentigo maligna is currently inadequate	IV	6

**Recommendations**

	Grade
1. Biopsy is indicated for changing pigmented lesions on the face	<b>C</b>
2. Where lentigo maligna is histologically confirmed, complete excision is the preferred management	<b>C</b>
3. Radiotherapy is an alternative treatment option for patients where surgical excision is problematic or best avoided	<b>C</b>
4. Cryotherapy is a form of treatment that may occasionally be useful in patients with severe comorbidities or in those in whom surgery is not a possible option	<b>D</b>
5. Topical treatment modalities for lentigo maligna cannot be recommended at this time	<b>C</b>

**Key point**

- For some patients with lentigo maligna, observation for change utilising macroscopic and dermoscopic photography and measurement is an acceptable alternative to immediate excision, with a biopsy indicated for changing lesions

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# 11 Treatment of primary melanoma

The standard treatment for primary melanoma is wide local excision (WLE) of the skin and subcutaneous tissues around the melanoma. The aim is complete surgical excision of all in situ and invasive melanoma components. This should be confirmed by comprehensive histological examination of the entire excised specimen with special reference to the periphery. The *in-situ* component, where present, often extends beyond the invasive melanoma, and complete excision of both is mandatory.

The recommendations for minimum radial excision margins used for WLE have been based on the maximum Breslow thickness of the primary melanoma. This surgical (clinical) margin is measured clinically from the melanoma edge, using a ruler and marker pen, before the start of the operation. Margins should be measured **before** excision because specimen shrinkage after excision and during formalin fixation reduces the measured margin.

Treatment of the primary melanoma may differ for specific types and locations of melanoma such as desmoplastic, and neurotropic melanomas, mentioned also elsewhere in the guidelines. Acral lentiginous and subungual melanomas are specific types of cutaneous melanoma that arise in the extremities/soles/palms, and nail-beds, respectively.<sup>1</sup> These may require differentiation from haematomas and benign naevi using biopsy where appropriate. Local recurrence (persistence), local metastasis (including in-transit metastasis and satellitosis)<sup>2-4</sup> and distant spread of melanoma may need further assessment and treatment, as discussed elsewhere in the guidelines. (These definitions are listed in the glossary). 'Local recurrence' properly means persistence of residual primary tumour, whereas local metastasis, refers to tumour spread away from the primary site. However, these terms have sometimes previously not been differentiated in the literature.

## 11.1 Review of the evidence

There are three systematic reviews<sup>5-7</sup> and five randomised controlled trials (RCTs)<sup>8-13</sup> comparing different clinical excision margins in primary melanoma. The RCTs compare narrow versus wider excision margins and assess overall survival and 'local recurrence', with median follow-up ranging from 5 to 16 years. However, definitions of 'local recurrence' are often inconsistent, unclear, imprecise or not stated, and the impact on patient survival is unclear. Therefore, these 'local recurrence' data must be interpreted with caution.

Evidence from the currently available systematic reviews and RCTs indicate the following:

- ***in-situ* melanoma:** no RCTs are available for assessment
- **melanomas < 1 mm thick:** no RCT specifically assesses melanomas less than 1 mm thick. The French, Swedish and WHO RCTs investigated melanomas less than 2mm thick, which included melanomas < 1 mm thick. No difference in mortality was found for wider excision (5cm in the French study, 5cm in the Swedish study, 3cm in the WHO study) compared with narrower excision (2cm in the French study, 2cm in the Swedish study, 1cm in the WHO study)

- **melanomas 1–2mm thick:** the French, Swedish and WHO RCTs assessed melanomas less than 2mm thick, and 272 patients in the Intergroup study had melanomas between 1mm and 2mm thick. No statistically significant difference in overall survival was demonstrated between the two groups treated with narrow or wide excision
- **melanomas 2–4mm thick:** the Intergroup and the BAPS/MSG RCTs included melanomas between 2mm and 4mm thick. Again, there was no statistically significant difference in overall survival between the two groups treated with narrow or wide excision margins. However, numbers of patients and events were relatively small for statistical comparison
- **melanomas > 4mm thick:** only the BAPS/MSG RCT (~ 207 evaluable patients) had melanomas > 4mm thick, but was insufficient to permit meaningful analysis
- data on acral lentiginous and subungual melanoma are very limited, principally due to the lower incidence compared with other forms of cutaneous melanoma<sup>14–17</sup>
- acral lentiginous and subungual melanoma may be considered for ‘functional’ amputation, as limited studies show no statistical recurrence or survival differences over more radical amputation.<sup>14–17</sup> Radiotherapy or isolated limb infusion chemotherapy may be of use where surgery is limited or not possible.<sup>17,18</sup>

Evidence summary	Level	Reference
There is no convincing RCT evidence that a margin greater than 2cm offers additional benefit for the patient in terms of overall survival or ‘local recurrence’, irrespective of melanoma thickness	I	5–13
Furthermore, two RCTs show no evidence that a margin greater than 1cm offers any survival advantage, although it is not clear whether a wider margin reduces the risk of ‘local recurrence’	I	8, 9, 13
Systematic review indicates that there are inadequate data to confirm a mortality difference between wider and narrower excision for primary invasive melanoma	I	5–7
For acral lentiginous or subungual melanoma there are no RCTs or SRs to define excision margins. Data are from retrospective case studies	IV	14–17

Recommendations	Grade
1. After initial excision biopsy; the radial excision margins, measured clinically from the edge of the melanoma, be: <ol style="list-style-type: none"> <li>1. (pTis) melanoma <i>in situ</i>: margin 5mm</li> <li>2. (pT1) melanoma &lt; 1.0mm: margin 1cm</li> <li>3. (pT2) melanoma 1.0–2.0mm: margin 1–2cm</li> <li>4. (pT3) melanoma 2.0–4.0mm: margin 1–2cm</li> <li>5. (pT4) melanoma &gt; 4.0mm: margin 2cm</li> </ol>	C B B B B
2. <b>Caution</b> be exercised for melanomas 2–4mm thick, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2cm) for these tumours depending on tumour site and surgeon/patient preference	B
3. <b>Acral lentiginous and subungual melanoma</b> 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

## 11.2 Good practice points

- Excisions should have vertical edges to ensure consistent margins
- Caution be exercised for melanomas thicker than 2mm, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2cm) for thicker tumours depending on tumour site and surgeon/patient preference
- Excision biopsy of the complete lesion with a narrow (2mm) margin is appropriate for definitive diagnosis of primary melanoma. Lesions excised with a margin less than those defined above should be re-excised as soon as practicable to achieve these margins
- Depth of excision in usual clinical practice is excision down to but not including the deep fascia unless it is involved
- Where tissue flexibility is limited, a flap repair or skin graft is sometimes necessary subsequent to an adequate margin of removal
- Treatment of most melanomas can be achieved on an outpatient or day-surgery basis, under local anaesthesia, unless nodal surgery is required
- Melanoma (i) is a risk factor for new primary melanoma(s) and (ii) also has the potential to recur or metastasise. Patients should be appropriately managed and followed-up for these aspects, as discussed elsewhere in these guidelines
- Patients should be informed that surgical excision may be followed by wound infection, haematoma, failure of the skin graft or flap, risk of numbness, a non-cosmetic scar and the possibility of further surgery

- Some tumours may be incompletely excised despite using the above-recommended margins. These include melanomas occurring in severely sun-damaged skin 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)<sup>1</sup> and followed by wider excision. The possible use of staged Mohs excision has been proposed in such situations<sup>19</sup>
- 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
- For patients with deeper invasive melanomas (> 1 mm thick), referral to a specialised melanoma centre should be considered to ensure that best practice is implemented and for the collection of national outcome data. This may present logistic difficulties in regional and remote areas, but specialist care is recommended
- The AJCC/UICC (2001) system<sup>20–23</sup> has been recommended for melanoma staging. Sentinel node biopsy (SNB) is an important prognostic factor for melanoma,<sup>24</sup> but there is debate about its use in treatment.<sup>24–26</sup> SNB should be considered in patients with primary melanomas > 1 mm thick or Clark IV, who want to be as informed as possible about their prognosis. SNB should be performed **before** wider local excision.

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# 12 Management of regional lymph nodes in melanoma

All patients with invasive melanoma are at risk for metastasis to the regional lymph nodes. An important part of the follow-up protocol for these patients therefore involves careful examination of the lymph nodes at each follow-up visit. Lymph nodes containing metastatic melanoma often increase in size quickly, sometimes appearing overnight according to the patient. An involved node is usually non-tender and firm to hard in consistency.

The risk of metastasis to lymph nodes is directly related to the Breslow thickness of the primary melanoma.<sup>1</sup> Thus, metastases are rare for thin melanomas (< 0.75mm) and the risk for tumours 0.75–1.0mm thick is about 5%. Intermediate thickness melanomas (1–4mm) have a risk that starts at about 8% for 1mm tumours and this rises steadily to 30% with increasing depth. Melanomas thicker than 4.0mm have a risk of approximately 40% for nodal involvement, in addition to a high risk of systemic spread, but the involved regional nodes are usually not clinically apparent at the time of primary diagnosis.

## 12.1 Sentinel lymph node biopsy

Since the last publication of these guidelines, a significant body of evidence has accumulated regarding lymphatic mapping and sentinel lymph node biopsy (SLNB). A sentinel node is one that receives lymphatic drainage directly from the primary tumour site. Lymphatic mapping to determine the location of sentinel nodes involves the intradermal injection of a small dose of radioactive tracer at the primary tumour site. At the time of surgery, the surgeon injects patent blue dye adjacent to the primary tumour and identifies the sentinel node as 'hot and blue' through a small incision at the location indicated by the radiologist. The sentinel node is removed and sent for histological examination. Often there may be sentinel nodes in more than one lymph node field, particularly if the tumour is located along the central axis of the torso. Melanomas of the head and neck region regularly drain to more than one zone of the cervical node field.

Sentinel node biopsy can be technically demanding, particularly in the head and neck, and should not be undertaken without appropriate training in this technique.<sup>2</sup> Expert execution and interpretation of the pre-operative lymphoscintigraphy is crucial to the success of the procedure as the failure to correctly identify the sentinel node will be counterproductive to good management of the patient. Furthermore, the pathologist plays a big role in achieving accurate results from a SLNB. The reliability of sentinel node biopsy after prior wide excision is unknown but it may lead to the wrong lymph node being analysed. Patients who are being considered for sentinel node biopsy should be referred before wide local excision of the primary tumour site. If sentinel node biopsy is being considered it is important that lymphatic mapping be done prior to wide excision.

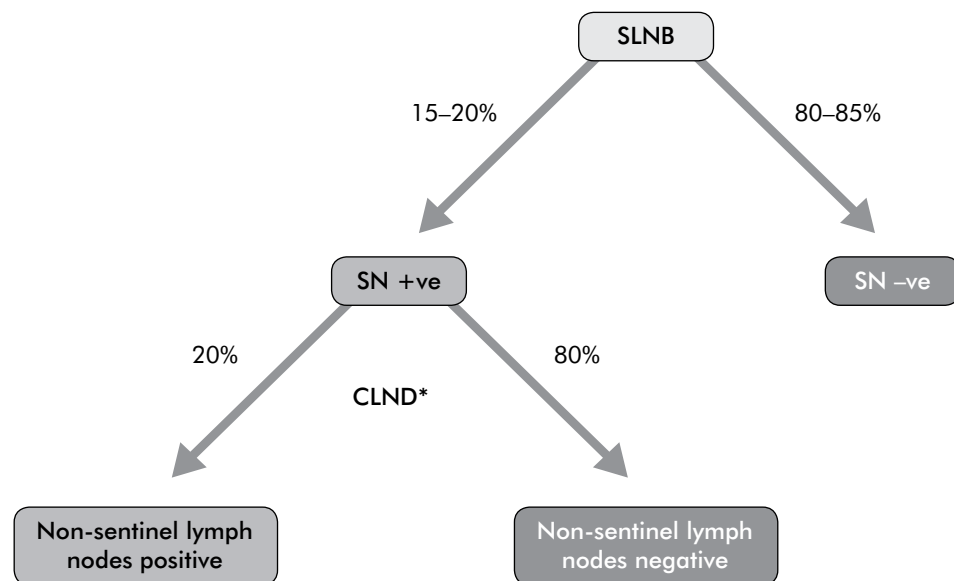
The status of the sentinel node reliably indicates the presence or absence of micrometastases in that node field and is the most accurate prognostic factor in primary melanoma added to the additional prognostic information from the primary lesion.<sup>3</sup> An international multicentre randomised controlled trial<sup>4</sup> (MSLT-1) was designed to assess the outcome of patients with occult metastases detected by SLNB compared with those who received wide local excision alone. The first Multicenter Selective Lymphadenectomy Trial (MSLT-1) randomised 1347 patients with intermediate thickness (1.2–3.5mm) melanomas to the primary aim strata; 1269 of these patients of these patients were evaluable because they accepted the assigned treatment (either wide excision plus post operative observation, with delayed completion lymph node dissection for clinically detectable nodal recurrence; or wide excision plus SLNB, with immediate completion lymph node dissection for sentinel node metastases. An additional 647 patients with lesions thinner than 1.2mm (low risk of nodal metastases) and thicker than 3.5mm (high risk of distant metastases at initial diagnosis ) were enrolled to evaluate surgical morbidity and accuracy of the procedure, but were considered unlikely to exhibit survival differences based on modelling from the John Wayne Cancer Institute's database.<sup>5</sup> In the primary aim group of patients with intermediate thickness melanomas (where the risk of a positive sentinel lymph node is 15–20%, Figure 3) the results of the third of five planned interim analyses were as follows; five-year melanoma-specific survival rates were similar in the two groups ( $87.1 \pm 1.3\%$  and  $86.6 \pm 1.6\%$ , respectively) (hazard ratio, 0.92; 95% CI, 0.67–1.25;  $P = 0.58$ ). The five year survival rate for sentinel node positive patients was  $72.3 \pm 4.6\%$  and  $90.2 \pm 1.3\%$  for node negative patients (hazard ratio for death, 2.48; 95% CI, 1.54–3.98;  $P < 0.001$ ). The mean estimated five-year disease-free survival rate was  $78.3 \pm 1.6\%$  in the biopsy group and  $73.1 \pm 2.1\%$  in the observation group (hazard ratio, 0.74; 95% CI, 0.59–0.93;  $P = 0.009$ ). The five-year survival was significantly higher in the group that underwent immediate lymph node dissection for a positive sentinel node compared to the group who underwent nodal observation and had delayed lymphadenectomy for clinically apparent nodal metastases ( $72.3 \pm 4.6\%$  vs.  $52.4 \pm 5.9\%$ ; hazard ratio for death, 0.51; 95% CI, 0.32–0.81;  $P = 0.004$ ). This statistic was not a primary outcome point in the original study design but it was a predetermined secondary outcome measure. The results of the interim analyses of this study and the interpretation of the data therein are still actively being debated.<sup>6</sup>

Preliminary information from the 4th interim analysis (median follow-up 59.5 months) confirms the results of the 3rd interim analysis and also shows a statistically significant lower rate of distant metastasis in the sentinel lymph node biopsy group (18.1% vs 21.2%) compared with wide local excision and observation.<sup>5</sup>

There is still no overall survival advantage shown at this time.



**Figure 3** Distribution of lymph node metastases for melanomas 1.2–3.5mm thick



\*CLND = completion lymph node dissection

Sentinel node biopsy should be discussed with patients who have a primary tumour 1.2–3.5mm thick. In addition, there are other patients with thinner tumours who are at particular risk of having a positive sentinel node. Therefore SLNB may be discussed with patients with melanomas 0.75–1.2mm thick based on the characteristics of the primary tumour, such as ulceration, Clark level (IV or V), or a high mitotic rate.<sup>7</sup> Where the true Breslow thickness cannot be determined, usually because the melanoma was diagnosed by shave biopsy, patients may also be offered SLNB. The risk of micrometastatic disease is inversely related to the patient's age and those younger than 35 years with a thin primary may benefit from sentinel node biopsy.<sup>8</sup> Patients with thick primaries (4mm or greater) are at substantial risk of developing disseminated metastatic disease. However, the status of the sentinel node in these patients is still the most important prognostic factor in this group of patients and biopsy may be recommended to assist in determining prognosis and to improve local disease control.<sup>9</sup>

Evidence summary	Level	References
Sentinel lymph node status provides accurate prognostic information for disease-free and overall survival for melanomas stage T1b <sup>10</sup> or greater	I	1, 3
To date, the MSLT-1 study shows no overall survival benefit	II	4, 5
Patients undergoing SLNB have a significantly lower rate of distant metastasis compared with wide local excision and observation	II	5
The interim results of the MSLT-1 study shows a potential survival benefit to patients with 1.2–3.5mm thick melanomas with positive sentinel lymph nodes who undergo immediate completion lymphadenectomy compared to those in the control group who undergo clinical observation and develop nodal recurrence	III-2	4
Sentinel node biopsy can be technically demanding and requires specialised expertise and resources	III-1	2

### Recommendations

	Grade
1. Patients with a melanoma greater than 1.0mm in thickness be given the opportunity to discuss sentinel lymph node biopsy to provide staging and prognostic information	<b>C</b>
2. SLNB be performed only, following a full discussion of the options with the patient, in a unit with access to appropriate surgical, nuclear medicine and pathology services	<b>C</b>

## 12.2 Therapeutic lymph node dissection

Therapeutic lymph node dissection is an operation involving the radical clearance of a lymphatic field and, in melanoma, is indicated for the presence of metastatic lymphadenopathy. Lymph node metastasis detected during clinical observation should be confirmed by guided fine needle biopsy of the suspicious node. Ultrasound imaging and guide FNB by a clinician experienced in the examination of lymph nodes may serve to increase the sensitivity of this procedure. A negative fine needle biopsy is not conclusive and should be repeated if the node remains clinically suspicious after a period of observation of one month. Only in centres where cytological diagnosis is unavailable, or if needle biopsy is unhelpful, is open biopsy recommended. If open biopsy is deemed necessary, the biopsy incision should be placed so that it can be easily excised in continuity with the lymph node field if radical lymphadenectomy is subsequently performed.

For patients with a positive SLN current practice is completion lymph node dissection.

However it is not known how to best manage patients with micrometastases detected by SLNB. This question is currently being investigated by MSLT-II, in which patients with histopathological or molecular (RT-PCR) evidence of tumour in the sentinel node are randomly assigned to receive completion lymph node dissection or observation.<sup>11</sup> MSLT-II is ongoing and the results are not yet available.

A systematic review of randomised controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence showed no significant overall survival benefit for patients undergoing elective lymph node dissection.<sup>12</sup> Therefore, except in rare circumstances, elective lymph node dissection is not recommended for melanoma patients.

Radical lymph node dissections for melanoma are relatively difficult operations and should be undertaken only by surgeons appropriately trained for the operation. There is a substantial risk of recurrence in dissected node fields in patients with clinically positive lymph nodes and only a thorough formal dissection will substantially lower the risk of recurrence in a dissected node field. A dissection can only be deemed thorough if it includes levels I–III in the axilla and a complete clearance of the femoral triangle nodes in the groin.<sup>7</sup> Extended procedures that include removal of the pectoralis minor muscle in the axilla and superficial parotidectomy in the neck should be considered. When dealing with lymphatic metastases in the groin, consideration should be given to the status of the ipsilateral external iliac and obturator nodes in the pelvis. Extension of the inguinal dissection to include the nodes in the pelvis, an ilio-inguinal dissection, may be indicated in the following circumstances: evidence of involvement of the pelvic nodes on staging investigations; gross clinical involvement or evidence of involvement in three or more nodes in the inguinal region; clinically suspicious nodes high in the groin.<sup>7,13</sup> Therapeutic neck dissection in melanoma patients carries a high risk of recurrence in the nodal field. This is a difficult operation, fraught with complications, and specific training is essential to achieve the optimal outcome. Even when surgeons with specific training undertake this dissection, the incidence of recurrence in the neck is considerable (up to 28%). Postoperative radiation therapy could be considered if the pathology report indicates matted nodes, extracapsular spread, and large size and/or large number of involved nodes.<sup>14,15</sup> (Refer to Chapter 13 *Management of locoregionally recurrent melanoma*).

All patients with positive lymph nodes are at high risk for systemic dissemination. It is therefore important to arrange consultation with a multidisciplinary melanoma treatment centre if possible.<sup>16</sup> Refer to Chapter 18 *Multidisciplinary care of melanoma*. Even where minimal involvement of the lymph nodes is found on node dissection, a referral of these patients to a melanoma centre may allow them to enrol or participate in clinical trials of adjuvant therapies. Refer to Chapter 13 *Management of locoregionally recurrent melanoma* for a discussion of the evidence regarding this treatment modality for lymph node metastases.

Evidence summary	Level	References
Elective lymph node dissection is not recommended, regardless of the Breslow thickness of the primary tumour	I	7, 12
Completion lymphadenectomy can result in complications in about a third of patients – most of these are minor but the rate of clinically significant lymphoedema following axillary or groin dissection is 5–10%	IV	2
All patients with positive lymph nodes are at high risk for systemic dissemination. It is therefore important to arrange consultation with a multidisciplinary melanoma treatment centre if possible	IV	16

### Recommendations

	Grade
3. Patients who have positive sentinel lymph node biopsy be offered completion lymphadenectomy, or be referred to a specialist centre for discussion of further treatment options	C
4. Therapeutic node dissection be offered to all patients with evidence of metastatic nodal disease after excluding stage IV disease using appropriate investigations	C

## 12.3 Good practice points

- A therapeutic node dissection includes a full levels (I to III) clearance in the axilla. A therapeutic neck dissection may include a superficial parotidectomy as clinically indicated
- Patients with inguinal node metastases be considered for clearance of the intra-pelvic iliac and obturator nodes when the staging investigation demonstrates evidence of involvement
- Elective clearance of the pelvic nodes be considered when there is gross macroscopic disease in the inguinal node field or there are three or more histologically positive nodes below the level of inguinal ligament
- Patients with lymph node metastases be offered discussion with a multidisciplinary team with a view to enrolment in clinical trials

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# 13 Management of locoregionally recurrent melanoma

Locoregionally recurrent melanoma refers to recurrence of melanoma in the anatomical region from the primary site to the regional lymph nodes, after apparently complete excision of primary melanoma. Locoregionally recurrent melanoma has a spectrum of presentations, temporally and anatomically. Anatomically, locoregional recurrence can be defined as:

- local recurrence at the primary excision site, being either:
  - re-growth of incompletely excised primary melanoma, involving the excision site scar or graft (persistent melanoma); or
  - local metastasis at the primary site.
- in-transit metastasis or satellitosis, due to lymphatic and/or haematogenous metastasis
- regional lymph node metastasis
- occurring in isolation or in association with disseminated disease.

These distinctions are important, as the intent of treatment and the prognosis differ greatly. Where possible, patients should be treated in conjunction with a specialist centre.

## 13.1 Persistent melanoma

The distinction between persistent melanoma and local metastasis is made histologically (see Chapter 7 *Histopathological reporting of cutaneous melanoma*). Persistent melanoma is a rare finding and should be excised completely.<sup>1</sup> There is no evidence indicating the superiority of any particular size of excision margin; margins used for the excision of primary melanoma should be considered. Adjuvant radiation therapy should be considered for close or positive margins unsuitable for re-excision, if normal tissue tolerances can be respected.<sup>2</sup>

Evidence summary	Level	References
Persistent melanoma should be excised completely	IV	1
For persistent melanoma which has been excised with close or positive margins, adjuvant radiation therapy reduces the risk of further recurrence	IV	2

### Recommendations

	Grade
1. Persistent melanoma be excised completely	C
2. Adjuvant radiation therapy be considered for close or positive margins unsuitable for re-excision	C

## 13.2 Local metastasis, in transit metastasis and satellitosis

Local metastasis, in transit metastasis and satellitosis are recurrences that generally occur in the lymphatic vessels more proximally towards the regional lymph nodes. Patients generally have a poor prognosis with frequent development of distant metastasis. The goal of treatment is maintenance of local control. There is a wide spectrum of clinical presentation and rate of disease progression.

Recurrent lesions may be managed by a variety of methods, including excision, cryotherapy, CO<sub>2</sub> laser, intralesional injection or application of drugs or immunomodulating agents, and radiation therapy.<sup>3,4</sup> There is no evidence that other local treatments are equivalent to excision where this is possible. Adjuvant radiation therapy should be considered for close or positive margins unsuitable for re-excision, if normal tissue tolerances can be respected.<sup>2</sup> There is no survival advantage for prophylactic regional drug therapy, although disease free survival is improved.<sup>5</sup> Slowly progressive lesions may be observed until they become symptomatic. There are few data comparing the efficacies of these modalities. These methods are of particular use when the disease progresses slowly.

Evidence summary	Level	References
Adjuvant regional drug therapy improves disease free interval but does not improve overall survival	II	5
For local metastasis, in transit melanoma and satellitosis, a range of local treatments have been reported as effective for local control, with no direct comparison to surgery	IV	3, 4

### Recommendations

	Grade
3. Local metastasis, in transit metastases and satellitosis may be managed using a variety of local treatments	<b>C</b>
4. Prophylactic isolated limb perfusion (ILP) is not recommended	<b>A</b>

The management of patients with multiple, rapidly growing or rapidly progressive lesions depends on the anatomical location. Involved limbs should be treated with regional drug therapy. Isolated limb perfusion (ILP) using melphalan under hyperthermic conditions is the standard, but involves a high level of technical skill and experience to minimise complications.<sup>6</sup> Isolated limb infusion (ILI), which is a simpler method of regional drug delivery, appears to provide a response rate and duration of response similar to that of ILP.<sup>7</sup> Response rates approaching 90%, including complete response rates of 60–70%, are routinely achieved with these methods, with low complication rates. Response rates may be sustained for periods approaching a year in approximately 50% of responders. The use of ILP or ILI obviates or delays the need for palliative amputation in most cases. ILI is the more common method in Australia.



Double ILP or ILI procedures are not associated with improved response rates or duration of response. However, further ILP or ILI following relapse is associated with response rates similar to those achieved with the initial ILP.

The use of drugs other than melphalan remains investigational. The addition of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) to melphalan does not significantly improve the response rate or duration of response compared with melphalan alone. However, there is some evidence that a second ILP using the combination of melphalan and TNF $\alpha$  may be of value following an initial ILP with a poor response.

Evidence summary	Level	References
Regional drug therapy using isolated limb perfusion (ILP) or isolated limb infusion (ILI) produces high overall, complete and durable responses Repeated ILP or ILI for recurrence in the same limb produce similar response rates to those achieved for the initial procedure ILP/ILI is technically challenging, with a documented incidence of serious complications	II	6, 7
ILI is a simpler alternative to ILP that may produce equivalent results	IV	7

### Recommendations

	Grade
5. Recurrence on a limb with multiple or rapidly progressive lesions not suitable for local treatments is best managed with ILP using melphalan under hyperthermic conditions if technically possible	<b>A</b>
6. ILI may be substituted for ILP	<b>C</b>

The management of extensive or rapidly progressive, in transit metastases unsuitable for regional drug therapy (e.g. proximal limb, trunk, head/neck) is difficult and must be individualised and discussed by a multidisciplinary team. Options include combinations of systemic drug therapies and local therapies.<sup>3,4</sup>

Evidence summary	Level	References
For recurrent melanoma with multiple and/or rapidly growing lesions which cannot be managed by regional drug therapy, a range of local treatments have been reported as effective for local control	IV	3, 4

**Recommendation**

- |   | Grade |
|---|-------|
| 7. Recurrence involving multiple or rapidly progressive lesions that are unsuitable for regional drug therapy be managed on an individual basis by a multidisciplinary team proficient in a range of local treatments | C     |

**Grade****C**

### 13.3 Regional lymph nodes

Regional lymph nodes should be considered in the management of locoregionally recurrent melanoma according to the following situations:

- **clinically uninvolved lymph nodes with no previous dissection:** SLNB has been suggested, although evidence for its value in this situation is lacking<sup>8</sup>
- **clinically involved lymph nodes with no previous dissection:** the nodal basin should be dissected, to improve local control.<sup>9</sup> The use of adjuvant postoperative radiation therapy remains controversial and must be decided in relation to its potential toxicity and other therapies. Postoperative radiation therapy could be considered if the pathology report indicates matted nodes, extracapsular spread, and large size and/or large number of involved nodes.<sup>2,10</sup> Although most evidence relates to the initial management of lymph nodes, extrapolation to the recurrent situation seems reasonable. No particular radiation treatment schedule has been found superior to other schedules
- **clinical recurrence in a previously dissected nodal basin:** further dissection should be performed if possible, with consideration of postoperative radiation (if not previously given).<sup>2,10</sup>

**Evidence summary****Level****References**

For patients without previous lymph node dissection, there is insufficient evidence to determine whether the information provided by SNB following locoregional recurrence of melanoma improves outcome	IV	8
The optimal management of clinically involved lymph nodes in a previously untreated nodal basin is lymph node dissection, which is superior to radiation therapy alone	IV	2, 9
Postoperative radiation therapy to a nodal bed may be effective in reducing the local recurrence rate when there are adverse pathological features	IV	2
The optimal management of recurrence in a previously dissected lymph node region is surgical removal of melanoma, followed by postoperative radiation therapy if this has not been delivered previously	IV	2

IV

8

IV

2, 9

IV

2

IV

2

## Recommendations

In the context of locoregionally recurrent melanoma:	Grade
8. SLNB be considered if the nodal basin has not been dissected and if there is no clinical evidence of nodal involvement	<b>D</b>
9. Lymph node dissection be performed for clinically involved nodes with no previous dissection, following confirmation of melanoma, preferably by fine needle biopsy	<b>C</b>
10. Postoperative adjuvant radiation therapy be considered for adverse pathological findings, though the value remains uncertain	<b>C</b>
11. Clinical recurrence in a previously dissected nodal basin be managed by excision if possible, followed by radiation therapy (unless given previously)	<b>C</b>

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# 14 Adjuvant systemic therapy of melanoma

Patients with resected AJCC stage IIC, IIB and IIIC disease are at high risk of dying of melanoma (< 50% ten-year survival) and should be considered for adjuvant systemic therapy. Those at intermediate levels of risk (stage IIA, IIB and IIIA) (51–64% ten-year survival) may be considered for clinical trials of adjuvant therapy. The only drug with demonstrated efficacy as adjuvant therapy for high-risk melanoma is interferon-alpha2b. No cytotoxic drug, other biological agent or vaccine has shown superiority over observation. Phase III clinical trials have compared high-dose (20 MU/m<sup>2</sup>), intermediate-dose (5–10 MU), intermediate-dose pegylated interferon, and low-dose (1–3 MU) regimens with observation. Multiple trials have shown that high-dose interferon improves relapse-free survival by approximately 10% at five years, but initially reported benefits in overall survival have disappeared with longer follow-up periods.<sup>1</sup> An individual patient data meta-analysis of ten of 13 observation-controlled trials of various dosing regimens showed a statistically significant benefit of interferon for event-free survival, and an absolute overall survival benefit of 3% (CI 1%–5%) at five years. In this meta-analysis there was no evidence of difference according to dose or duration of therapy. Individual phase III trials of intermediate and low-dose have not shown a clear advantage for interferon over observation.<sup>2</sup>

Long-term pegylated interferon improved four-year relapse-free survival by 7% but had no effect on distant metastasis-free survival or overall survival.<sup>3</sup> High-dose interferon-alpha remains the only FDA-approved systemic adjuvant therapy for melanoma. The toxicity of high-dose interferon-alpha is substantial but reversible, and requires experienced medical oncology management, aggressive supportive measures including the use of prophylactic antidepressants, and careful monitoring and dose-reduction strategies, particularly for hepatotoxicity.<sup>4</sup> Because of the toxicity of high-dose interferon and the uncertain and modest benefits of lower-dosing regimens, clinical trials of new adjuvant therapies are strongly encouraged and observation remains an appropriate comparator in phase III trials.

Evidence summary	Level	Reference
Adjuvant interferon-alpha therapy is the only drug with activity in the adjuvant systemic treatment of melanoma. It improves relapse-free survival by approximately 10% at five years and may have a small impact on overall survival. These benefits must be balanced against considerable, but rapidly reversible, toxicity	I	1, 2

**Recommendations**

	Grade
1. Observation is acceptable management for patients with resected stage I–III melanoma	<b>B</b>
2. These patients be considered for enrolment in clinical trials of adjuvant therapy. Sentinel lymph node biopsy is mandatory staging for the stratification of patients on adjuvant therapy trials. Trials of adjuvant therapy include an observation-only control arm	<b>B</b>
3. Patients with high-risk disease be considered for adjuvant therapy with high-dose interferon-alpha	<b>B</b>
4. Because the toxicity associated with high-dose interferon is considerable, the risks and benefits of therapy in individual patients be carefully reviewed before proceeding	<b>B</b>
5. Patients be treated in an experienced medical oncology facility, monitored closely for toxicity related to treatment with interferon, and dose adjusted based on the degree of toxicity	<b>B</b>

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# 15 Treatment of disseminated melanoma

The outcome for patients with stage IV melanomas is poor. The median survival is only six to nine months, with an estimated five-year survival of 5–10% depending on the prognostic factors, the site of metastasis, the number of metastatic sites, and elevated serum LDH levels.<sup>1,2</sup>

The standard chemotherapy has been single agent dacarbazine (DTIC) that has response rates reported at 5–20%, but only 5% are complete responses and of short duration.<sup>3,4</sup> Recently fotemustine was shown to produce higher overall response rate compared with dacarbazine, but with only a trend towards overall survival. Unlike DTIC and temozolomide, fotemustine is associated with higher risk of myelosuppression<sup>5</sup>.

The oral alkylating agent temozolomide has equivalent efficacy to dacarbazine (median survival 7.7 months versus 6.4 respectively).<sup>6</sup> Temozolomide resulted in better health-related quality-of-life outcomes than dacarbazine, both in functional improvements and decreased symptoms.<sup>7</sup>

Combination chemotherapy does not improve survival over single agents and may not improve palliation of more toxic than single agents.<sup>8</sup> For example, the Dartmouth regimen (cisplatin, carmustine, DTIC and tamoxifen) has a slightly increased response rate but there is no improvement in survival when compared to dacarbazine alone.<sup>4</sup> The combination of cisplatin and temozolomide did not improve the outcome compared to temozolomide alone.<sup>9</sup>

The addition of tamoxifen to chemotherapy is ineffective.<sup>10</sup> The biological agent interferon-alpha achieved single agent response rates around 15%, while IL2 phase II trials ranged between 3% and 50%.<sup>11,12</sup> Randomised trials of the combination showed no advantage over single agents.<sup>13</sup> Combining interferon-alpha with chemotherapy did not improve survival. IL2 was combined with dacarbazine only in phase II trials.<sup>14</sup> Similarly, adding interferon-alpha to temozolomide improved the response rate but did not translate into a survival advantage. Randomised studies of adding either or both interferon and interleukin to combination chemotherapy has not resulted in improved survival of patients with metastatic melanoma.<sup>15,16</sup> To date no other biological treatment, either vaccines or targeted therapies such as Bcl-2 antisense therapies, have been effective alone or demonstrated survival advantages in randomised trials which add them to chemotherapy.<sup>17</sup>

Radiotherapy can improve symptoms from the effect of local tumours. The sites commonly requiring treatment in melanoma are bone, brain, subcutaneous lesions, bulky lymph nodes, liver and adrenal metastases. Whilst many of these can be treated with short fractionation regimens such as 8 Gy in one fraction (bone metastases)<sup>18</sup> or 20 Gy in five fractions (brain metastases),<sup>19</sup> larger and bulky tumours such as those involving lymph nodes or widespread cutaneous deposits may require more lengthy schedules, such as 40 Gy in fifteen fractions or 45 Gy in twenty fractions.

## 15.1 Brain metastases

For patients who have brain metastasis with favourable prognostic signs including the presence of a single brain metastasis, no extracranial disease, good performance status (PS) and initial presentation with brain metastasis, resection seems to be better than WBRT.<sup>20</sup> Median survival ranges from 1.8 months to 10.5 months depending on prognostic factors.<sup>21</sup> Patients with multiple surgically accessible lesions and little or no extracranial disease may also have an improved prognosis when treated with resection. For patients with surgically inaccessible or multiple metastasis and medical comorbidities, SRS (stereotactic radio surgery) may offer better survival than WBRT.<sup>21–25</sup> Complete or partial response occurs in 55% of the patients and freedom from progression is achieved in 90–95% after SRS.<sup>26</sup> Median survival was better for a solitary lesion than multiple metastases.<sup>27</sup> The SIR score (Score Index for Radiosurgery) impacts on survival.<sup>28</sup> After surgery or SRS, adjuvant WBRT could improve local control but has no clear survival benefit.<sup>23,29,30</sup>

For poor prognostic patients, options include WBRT, chemotherapy, steroids or BSC (best supportive care). In one study WBRT alone had a median survival of 3.4 months compared to 2.1 months for BSC alone.<sup>22</sup> Steroids given 2–7 days prior to radiotherapy improved symptoms in 73% of the patients.<sup>31</sup> Surgery could be useful in relieving symptoms from large lesions.

The role of chemotherapy is mainly explored in small phase II trials. In a phase II trial of 151 patients, temozolomide had a response rate of 7% and stable disease of 29%, with an overall survival of 3.5 months in previously untreated patients.<sup>32</sup> Other agents studied were thalidomide, and docetaxel alone or in combination.<sup>33</sup> Two small phase II studies examined the role of radiotherapy concurrent with chemotherapy using temozolomide and fotemustine with MS of 8 months.<sup>34,35</sup> Avril reported RR of 5.9% for fotemustine, compared with DTIC in a phase III trial of metastatic melanoma where 18% of patients had brain metastasis.<sup>5</sup> Problems with phase II studies were illustrated by an Avril study in which the previously reported phase II response rate of nearly 30% was not replicated in this larger phase III study.

## 15.2 Surgery

In a phase III trial of adjuvant therapy, surgical resection of selected patients with metastatic melanoma in up to five sites leads to a five year survival of 42.5%.<sup>36</sup> Improvement in survival has been reported for metastasis to skin, subcutaneous soft tissue, distant lymph nodes, lung, brain, adrenal glands, liver and gastrointestinal system.<sup>37–44</sup> One of the most important prognostic factors for survival is the presence of a solitary metastasis.<sup>45</sup> Surgery for further recurrence can also be useful. In a small series, 20% of patients who underwent a second complete resection achieved a disease-free survival of more than five years.<sup>46</sup>



Evidence summary	Level	Reference
Single agent fotemustine, dacarbazine or temozolomide can be used for palliation of patients with disseminated melanoma	II	3, 6, 37
Biological agents such as interferon-alpha and interleukin-2 yield single agent response rates but do not improve survival alone or when added to single agent or combination chemotherapy. No vaccine has proven effective	II	11, 12, 15, 16
Radiotherapy is effective in providing relief of symptoms in patients with metastatic melanoma where metastases involve bone, brain, soft tissue, liver and adrenal	IV	18
Hypo-fractionated schedules may be more effective in soft tissue disease but not at all sites	IV	19
For good prognosis limited brain metastases with no extracranial disease, surgery improves survival compared to whole brain radiotherapy	IV	23, 24
For good prognosis surgically inaccessible brain metastases with no extracranial disease, stereotactic radiosurgery improves survival	IV	23–28
Surgery or radiosurgery for solitary or few brain metastases of any histology followed by whole brain radiotherapy is effective in reducing intracranial relapse but not improving overall survival	II	29, 30
Patients with resectable metastases have prolonged survival after resection. In patients with metastases limited to skin, subcutaneous tissue, distant lymph nodes, lung, adrenal gland liver, and/or gastrointestinal system, surgery can improve survival	IV	36–45

### Recommendations

	Grade
1. Patients with metastatic melanoma be referred for consideration of chemotherapy and/or palliative care to improve their symptoms	<b>C</b>
2. Patients with localised symptoms from melanoma metastasis be referred for radiotherapy	<b>C</b>
3. To improve survival, patients with limited or no extracranial disease and with favourable prognosis brain metastases be considered for surgical resection and if unresectable, for stereotactic radiosurgery. Patients with unfavourable prognostic metastases receive palliation with surgery, whole brain radiotherapy, chemotherapy, steroids or palliative care	<b>C</b>
4. Patients with surgically operable metastases be considered for resection	<b>C</b>

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# 16 Psychosocial issues in melanoma

Many people with melanoma and their carers face practical, emotional and psychological demands in addition to the physical effects of the disease and treatment. Challenges in melanoma include the existential fear faced by anyone with a diagnosis of a life-threatening disease,<sup>1</sup> pain and discomfort associated with treatment, and body image changes associated with disfiguring surgery. Patients with deeply indented scars, such as occur with skin grafting following removal of skin, subcutaneous and deep fascia, as well as those whose scars are longer than they anticipated, may be particularly distressed.<sup>2</sup>

While most studies have found that patients adjust well to melanoma in the long term, distress is common. In a prospective survey of 144 patients with stage I melanoma who did not relapse, 21% reported moderate to high levels of distress three months after excision, 26% at seven-month follow-up and 29% at 13-month follow-up.<sup>1</sup> The impact on families of those with melanoma is also considerable, as they share in the fears of relapse, the traumas of treatment and the sadness of late-stage disease.

Patients' psychosocial needs are significant, and frequently go undetected and unmet. Bonevski et al<sup>3</sup> assessed the perceived needs of a sample of patients attending the Newcastle Melanoma Unit. Patients reported the most unmet needs in relation to health information, psychological issues and melanoma-specific issues. The authors recommended that patient needs should be monitored routinely in oncology care so that groups of patients with specific needs could be identified.

## 16.1 Effect of psychosocial interventions in patients with melanoma

There are few studies exploring whether psychosocial interventions reduce psychosocial morbidity and unmet needs in patients with cutaneous melanoma or melanoma in specific sites and none which have explored interventions to reduce morbidity and unmet needs in carers of people with melanoma. Five randomised controlled trials have been conducted evaluating psychological interventions, two of high quality and three of medium quality.

1. Fawzy et al<sup>4-7</sup> conducted the first randomised controlled trial, on which they have reported to date the six-month follow-up for coping/immunological measures and ten-year follow-up for survival.

This was an American study of high quality. Eighty of 92 patients with stage I and II malignant melanoma approached agreed to participate and were randomised to standard care or a six-week structured group intervention incorporating health education, stress management, illness-related problem-solving skills and psychological support. One patient in the intervention group died and another was diagnosed with major depression and excluded, leaving 38. Ten dropped out of the control group and two had incomplete data, leaving 28. The experimental group was significantly older (mean age 46) than the control group (mean age 39). Psychometrically sound measures were used.

Immediately after the intervention (six weeks), intervention patients reported significantly more vigour ( $p=0.03$ , Profile of Mood States – POMS) and active-behavioural coping ( $p=0.0001$ ). At six months intervention patients were significantly less depressed, dejected, fatigued and confused, had more vigour ( $p=0.001$ ) and an overall better mood ( $p=0.006$ ). They continued to display more active-behavioural coping ( $p=0.0001$ ).

2. Fawzy et al<sup>8</sup> in a study of moderate quality randomised 61 consenting patients with stage I or II malignant melanoma to standard care or an intervention comprising an educational manual plus three hours of individual nurse teaching. Consent for randomisation was not sought, rather patients were offered either the control or intervention arm. Three subjects were lost to follow-up, all from the experimental arm. At baseline, intervention subjects had significantly higher Brief Symptom Inventory (BSI) scores and trends to more distress. At three months, total mood disturbance and fatigue were significantly lower in the intervention group ( $p<0.03$  for both), BSI somatisation was lower ( $p=0.05$ ) and intervention subjects were using less passive resignation coping ( $p=0.04$ ). Overall, there were less dramatic effects than observed in the earlier group study which involved more contacts for each patient (six rather than three) and group interaction.

3. Boesen et al<sup>9</sup> in a study of high quality reported a larger replication of the Fawzy et al<sup>4</sup> study with very minor modifications in a Dutch setting. Of 399 patients, 262 (66%) agreed to participate. Dropouts and exclusions resulted in 112 in intervention and 129 in the control group.

At six months there was a larger decrease in total mood disturbance (TMD) in the intervention group ( $p=0.04$ ) largely due to more vigour ( $p=0.003$ ) and less fatigue ( $p=0.04$ ). There was a greater effect on TMD for patients with higher TMD scores at baseline. The intervention group also used more active behavioural and active cognitive coping ( $p=0.0007$  and  $0.0002$ ). However there were no significant differences between the groups at 12 months. Thus this intervention does seem to have a medium-term impact on distress which is dissipated by 12 months.

4. Bares et al<sup>10</sup> conducted a small RCT of medium quality of cognitive-behavioural therapy for patients with heterogeneous melanomas who were reporting clinically significant levels of distress. The primary goal of the study was to conduct a cost-effectiveness analysis of the intervention above standard care, and the description of the methods was more detailed for that aspect than for the randomisation. Only 38 patients participated in the study, which was nonetheless able to report a significant reduction of distress at three months post intervention for the CBT group ( $p=0.005$ ). CBT was marginally more expensive (49c per minute) than the cost to nursing staff of dealing with distress-driven phone calls during standard care (41c per minute). However, the cost/benefit ratio (total costs/change in distress) was significantly lower for CBT. The cost to change distress in standard care was  $>\$402$  for a one-point change in standard care, versus \$7.66 for CBT. Including reimbursement for service in the analysis, CBT would generate \$1.16 per minute while standard care would cost the hospital \$0.40. Thus CBT is cost-effective.

5. Trask et al<sup>11</sup> conducted a small RCT of CBT of moderate quality using the same methods as Bares et al.<sup>10</sup> The sample size was somewhat higher ( $n=48$ ) and it is not clear whether the Bares sample was a sub-sample of this one, or a separate sample. In this study, however, there was no group effect for distress at two-month or six-month follow-up by intent to treat analysis, although a group effect for distress was detected at two months and a trend at six months when analysed by treatment received. In the ITT analysis at two months, State Anxiety was lower ( $p=0.02$ ) and aspects of QOL higher (e.g.  $p=0.008$  for general health) in the intervention group; at six months, anxiety was lower on the BSI ( $p=0.02$ ) and general health higher ( $p=0.05$ ). Thus even in this small sample, some important psychological outcomes were effected.

One non-randomised controlled study was reported by Rudy et al<sup>12</sup> of a peer telephone intervention for stage III and IV melanoma patients undergoing immunotherapy. The intervention was assessed after two phone calls had been made by volunteers. Questions were primarily qualitative, although intervention subjects ( $n=29$ ) did report significantly more providers of social support ( $p<0.05$ ) than control subjects ( $n=27$ ). Intervention subjects and peer providers reported that the intervention was effective.

One qualitative study has been reported<sup>13</sup> in which 26 patients with metastatic melanoma who were participating in an RCT of individual CBT versus relaxation training were interviewed about the benefits of therapy by a researcher blinded to allocation. Patients reported similar benefits regardless of allocation, which pertained to receiving patient-centred care from someone outside their family who they trusted and to whom they could speak openly. Thus non-specific therapist factors appeared to be more important than the actual therapy delivered.

Two psychiatric case reports<sup>14,15</sup> reported the benefits of: (a) supportive-expressive therapy and a focus on anxiety reducing techniques and (b) imagery in assisting patients with a poor prognosis.

In summary, all five RCTs produced evidence that psychological interventions can improve psychosocial outcomes for melanoma patients, including reducing general mood disturbance, distress and anxiety. The two studies of high quality reported large effects. Two of the studies of moderate quality reported small effects but their sample sizes were small, and one reported large effects despite a small sample size. Three of the studies targeting coping reported an increase in active coping or a reduction in passive coping in the intervention group. Qualitative studies supported a clinical benefit.

### 16.1.1 Educational interventions

Two non-randomised controlled studies evaluated educational interventions.

One study by Orringer et al<sup>16</sup> evaluated an educational intervention in a *non-randomised controlled trial* in which patients were allocated sequentially to receive or not to receive an educational video on melanoma before their first clinic visit. Patients in the intervention group were instructed to complete colour-coded questionnaires measuring knowledge, anxiety and distress immediately before and after viewing the video at home, while control patients completed the baseline measure at home and the follow-up measure after their

initial clinic visit. Knowledge improvement was significantly greater in the video group (who had unlimited time and were in their own space) but reduction in anxiety and distress was significantly higher in the control group, who had seen a doctor. It is hard to draw conclusions from this study given the methodological limitations.

In another study by Brandberg et al<sup>17</sup> stage I melanoma patients were offered an educational intervention. Interested patients were randomised to receiving the intervention before or after their post-surgical clinic visit. Patients not interested in education acted as controls. The allocation process was inconsistent, with some controls ending up in the post-visit education session, and some randomised to the pre-visit session ending up in the post-visit session. Analysis was not by intention to treat. Knowledge was higher in those who received the education session both at the pre-surgical clinic visit and six months later ( $p < 0.01$ ). Psychological variables were not affected by pre-visit versus post-visit receipt of education and a comparison with the control group was not provided. Thus few conclusions can be drawn from this study about the impact of the educational intervention on psychosocial outcomes.

### 16.1.2 Studies in cancers other than melanoma

The NICE guidelines (2006) recently reviewed evidence for the efficacy of psychosocial interventions in all cancer patients. Three systematic reviews or meta-analyses of good quality, four systematic reviews or meta-analyses of poor quality, four RCTs of poor quality and one observational study of fair quality were identified.

The majority of studies reported benefits, with few inconclusive studies. Benefits included both affective and physical improvements, improved coping and better understanding. The systematic review by Bottomley<sup>18</sup> suggested that structured interventions may offer more benefit than those of a purely supportive nature.

The most recent high-quality systematic review on this topic by Newell et al<sup>19</sup> reviewed 329 intervention trials, most of which were deemed of poor quality. The authors concluded: 'There is tentative evidence for a beneficial psychosocial effect arising from group therapy, education, counselling and cognitive behavioural therapy, all of which are believed to operate in the medium to long term.'

The Scottish Intercollegiate Guidelines Network (2003) concluded from the evidence that 'Health service patient support groups should be structured; facilitated by trained professionals and incorporate health education. Information on all patient support groups should be made easily available to patients'.

The UK guidelines (2002) do not review evidence of outcomes following psychosocial intervention, but recommend that patients with IIB or more advanced melanoma should be managed in a Cancer Centre by a multidisciplinary team which includes a counsellor, while all patients with metastatic melanoma should have access to a palliative care team offering psychosocial support.

The National Comprehensive Cancer Network (NCCN) guidelines do not review the evidence for psychosocial support but do recommend a structured follow-up program in part to provide ongoing psychosocial support (MS-8).



Evidence summary	Level	Reference
Overall, the evidence supports the provision of psychosocial interventions such as cognitive behavioural group therapy and psycho-education, as well as support groups, to assist patients with melanoma in optimally adjusting to and coping with their illness	I, II	8–12

Recommendation	Grade
1. Structured psychosocial interventions, such as cognitive behavioural group therapy and psycho-education, as well as support groups, be made available to all patients with melanoma to improve their quality of life	<b>B</b>

## 16.2 Communication strategies to reduce psychosocial morbidity and unmet needs in patients with melanoma

Two RCTs evaluated formal structured interventions by nurses<sup>8,17</sup> which reported small benefits in terms of increased knowledge,<sup>17</sup> less passive coping and reduced anxiety.<sup>8</sup> These studies provide some support for the role of members of the multidisciplinary team in delivering formal interventions.

One prospective cohort study<sup>20</sup> followed 133 patients with primary melanoma. Patients were interviewed about their experiences at diagnosis 3.8 months post diagnosis and psychological adjustment was measured at four and thirteen months. Large effect sizes were found for communication variables and patient satisfaction, anxiety and depression. In particular, getting full and clear information, having life expectancy discussed and receiving emotional support from their doctor influenced patients' psychosocial outcomes.

Three cross-sectional studies eliciting patient preferences<sup>21–23</sup> reinforced these messages, with patients expressing strong preferences for particular communication practices. Receiving the news face-to-face, not having another health professional present, and receiving assistance and support from the doctor were strongly endorsed. Butow et al (1996) reported a relationship between satisfaction with communication (particularly emotional support) recalled four years later and psychological adjustment reported three months after diagnosis.

In summary, there is preliminary support from one prospective study with very large effects sizes that communication from the multidisciplinary team has a significant impact on patient outcomes. Notably, prospective studies are the most feasible design for this research question, since randomising health professionals to provide different sorts of information to patients in different sorts of ways will rarely be acceptable, ethical or feasible. Patients have strong preferences for receiving full and clear information and emotional support from their doctor at the time of diagnosis.

**Studies outside of melanoma** have provided evidence for an impact of multidisciplinary team communication on patient outcomes. *The Psychosocial Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer*<sup>24</sup> quote a number of studies supporting the impact of empathy and clear information on patient recall, and psychological adjustment in the short and long term. A small number of large randomised controlled trials have shown that communication skills training can improve the communication skills of health professionals.<sup>25,26</sup>

Evidence summary	Level	Reference
There is a small body of evidence that the way the treatment team communicates with patients in providing information, empathy and support can influence patient satisfaction and adjustment in the long term	II, III-2	8, 17, 20–23
Communication skills training for all members of the treatment team is warranted	II, III-2	8, 17, 20–23

Recommendation	Grade
2. Communication skills training be provided to health professionals treating people with melanoma to assist them in effectively providing information, patient-centred care, shared decision-making where desired, empathy and support	C

### 16.3 Influence of patients' psychosocial characteristics on prognosis

Nine prospective cohort studies have explored the impact of psychosocial characteristics on outcome in melanoma. (One was a randomised controlled trial of a psychiatric intervention in which an analysis that controlled for group allocation explored the impact of baseline characteristics on outcome.<sup>6</sup>) Studies varied in the length of follow-up, the psychosocial variables measured and the potential confounders controlled for in the analyses. Only one explored outcomes in patients with metastatic melanoma.

**In early stage melanoma, three studies reported a null effect.** In the largest study with the longest follow-up (to 11 years), Bergenmar et al<sup>27</sup> followed 437 patients with localised cutaneous melanoma who had completed measures of anxiety and depression at their first follow-up after surgery. There was no relationship between baseline anxiety and depression and time to recurrence, although as mood can fluctuate, this is perhaps not surprising. Canada<sup>28</sup> followed 60 patients with stage I melanoma for ten years, and found no relationship between stable personality traits (extroversion, neuroticism, psychoticism) and time to recurrence. Finally, Gibertini et al<sup>29</sup> followed 75 patients for a brief period (unspecified in the paper) in which six of the cohort relapsed, and unsurprisingly observed no significant relationships between psychosocial variables and time to recurrence in univariate analysis.

**Three studies reported a weak effect.** Cassileth et al<sup>30</sup> followed 61 patients with cutaneous malignant melanoma (> 0.76mm thick) among a larger cohort of heterogeneous cancers for eight years. Patients had completed a number of psychosocial measures at baseline, including helplessness/hopelessness and effort needed to adjust to diagnosis. Some weak associations between psychosocial factors and time to recurrence were found in the melanoma group but they were inconsistent, depending on cut-off scores and sub-groups compared. The authors concluded that the data did not support a role for psychosocial factors.

Brandberg et al<sup>1</sup> followed 64 patients with stage I melanomas > 0.8mm. In contrast to the findings of Bergenmar<sup>27</sup> at two-year follow-up, baseline anxiety was significantly higher in those that recurred ( $p=0.05$ ) but there was no difference in the proportion scoring as a case on anxiety or depression at baseline. Perhaps the shorter follow-up time in this study meant that baseline measures of mood more accurately represented patients' prevailing psychological state before recurrence.

Fawzy et al<sup>6</sup> explored psychosocial predictors of time to recurrence in 68 patients with stage I or II malignant melanoma who had participated in a randomised controlled trial of a psychiatric intervention. Controlling for group allocation, and disease and demographic prognostic variables, at six-year follow-up higher baseline rates of total mood distress on POMS and higher baseline coping (active-behavioural) were associated with lower recurrence and death rates, and increase in active-behavioural coping over the study period was related to better survival ( $p=0.03$ ), with a trend apparent for recurrence ( $p=0.06$ ). Fawzy et al posited that the more distressed patients and those who tended to cope by taking active steps to solve problems, may have been more motivated to prevent recurrence by staying out of the sun and protecting their skin.

**Finally, two studies reported larger effect sizes.** In a large and well-conducted study, Brown et al<sup>31</sup> followed 426 patients with locoregional melanomas > 0.7mm for six years who were assessed for a range of psychological variables at diagnosis. In an analysis that controlled for all other prognostic demographic and disease variables, patients who at baseline used less avoidance ( $p=0.03$ ) and were more concerned about their disease ( $p=0.008$ ) had a greater time to recurrence, and there was a trend for patients who perceived the aim of treatment as cure ( $p=0.06$ ) to have longer time until recurrence. As in Fawzy et al (1993) these psychosocial variables might be related to active behaviours aimed at prevention, although this was not measured.

In one of the older studies, Rogentine et al<sup>32</sup> followed 64 patients for just one year, and found that patients who reported more difficulty in adjusting at baseline had a shorter time to recurrence ( $p<0.001$ ).

One study explored psychosocial predictors of time to death in late-stage melanoma. Butow et al<sup>33</sup> followed 125 patients with metastatic melanoma for six years. Controlling for other prognostic factors, patients who perceived the aim of treatment to be cure ( $p<0.001$ ), minimised their illness ( $p<0.05$ ), were more angry ( $p<0.05$ ), were married ( $p<0.01$ ), and who reported better QOL ( $p<0.05$ ) survived longer. Patients who believed treatment would lead to cure survived about twice as long (10.6 months) as those who did not (5.6 months).

### 16.3.1 Conclusions

As in all cohort studies, it is hard to interpret positive results as it is always possible that at baseline, patients were influenced by illness characteristics that were prognostic but not recorded in the traditional prognostic measures. The studies measured a wide range of psychosocial variables. Those which were found to be associated with outcome tended to reflect active coping styles or general distress. These may have promoted active lifestyle efforts to promote good health and avoid risk factors for melanoma, suggesting that increasing awareness of threat and mobilising active coping can assist survival.

The single study in metastatic melanoma reported large effect sizes and is intriguing. This study requires replication, perhaps with stronger measures.

Further research is required to establish if there is a link between psychosocial factors and outcome in melanoma.

Evidence summary	Level	Reference
There is inconclusive evidence that psychosocial factors influence outcome in melanoma	III-2	1, 6, 27–33

Recommendation	Grade
3. If the matter is raised, patients be advised that there is no known (or proven) link between psychosocial factors and survival outcome	C

## 16.4 Influence of psychosocial interventions on prognosis

Only one study has explored the impact of a psychosocial intervention on prognosis in melanoma.<sup>4,5</sup> All patients were analysed by intent to treat. Stage II patients were excluded, leaving 68 to analyse.

Immediately after the intervention there was a significant increase in one of the large granular lymphocyte sub-populations, CD8. There were no other significant changes.

At six months, the intervention group had an increased number of natural killer cells and an increased cytotoxicity, decrease in a major T-cell subpopulation-CD4 helper/inducer cells, and some increases in the percentage of larger granular lymphocytes. This was correlated with change in depression and anxiety.

At the six-year follow-up, 10/34 in the control group had died and three had local recurrences. In the intervention group 3/34 had died and four had recurrences.<sup>6</sup> Participation in the intervention lowered the risk of recurrence by more than 2.5, and decreased the risk of death sevenfold.

At ten-year follow-up, Fawzy et al reported that 11/34 control subjects had had recurrences and died and 3/34 had had recurrences and were still alive. In the intervention group, 9/34 had recurrences and died and two had recurrences and were still alive.<sup>7</sup> Univariate survival analysis showed non-significant differences between groups for recurrence

and survival. A multivariate cox regression analysis revealed a significant effect for the intervention on survival ( $p=0.05$ ) but not for recurrence. By ten years, participation in the intervention did not lower the risk of recurrence but decreased the risk of death threefold.

### Results in cancers other than melanoma

Few well-conducted RCTs have explored the impact of psychosocial interventions on cancer prognosis. Overall, the results have been equivocal. A recent systematic review concluded that there was insufficient evidence for a relationship between psychosocial interventions and survival of cancer, given methodological flaws and contradictory findings.<sup>34</sup>

Further research is required to establish the impact of psychosocial intervention on prognosis in patients with melanoma.

Evidence summary	Level	Reference
There is insufficient evidence that psychosocial intervention can impact on prognosis in patients with melanoma	II	4–7

Recommendation		Grade
4. Patients be advised that individual or group psychosocial intervention may not improve their overall survival		C

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# 17 Palliative care in melanoma

Palliative care as defined by the World Health Organization (WHO) is ‘an approach that improves the quality of life of patients and their families facing the problem[s] associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual’<sup>1</sup> (see also Appendix 6 *New Zealand palliative care definition*).

So defined, palliative care is applicable throughout the whole cancer illness.<sup>2</sup> The skills of palliative care specialists may be utilised by patients, their families and other clinicians, to assist in managing symptoms while patients are undergoing disease-modifying treatments. As the disease progresses, palliative care teams may provide continuing support aimed at maintaining or improving quality of life. Finally, palliative care teams may provide support for patients and their families at the end of life.

Any or all of these roles are highly applicable to patients with recurrent or metastatic melanoma, as these patients, many of whom are young, may have complex physical and emotional needs.<sup>3–5</sup> Stage IV melanoma has a propensity to metastasise widely so that affected people are particularly at risk for pain and fatigue.<sup>6,7</sup> As with other cancers, these and other symptoms tend to worsen as the individual’s condition deteriorates. Not only have people with melanoma been identified as being at risk of physical symptoms, but also of psychological concerns, particularly anxiety and mood disturbances.<sup>8</sup> Melanoma patients, in their last year of life, have been identified as a group who are at risk of deteriorating psychological functioning to a level where their ability to maintain their physical function is impaired.<sup>9</sup>

Palliative care is provided in a number of ways, with the majority of care coordinated by general practitioners and other members of the melanoma team. However, for patients and their families with more complex needs, more specialised care is needed.<sup>10</sup>

Integration of specialist palliative care into the melanoma multidisciplinary team allows partnerships between other health providers and specialists in palliative care (nurses, doctors, allied health) to be established and the individual needs of each patient to be considered. This allows specialist palliative care input to contribute to multidisciplinary care in a number of very positive ways and already evidence exists that the involvement of palliative care in the lives of cancer patients is beneficial. These benefits include improved symptom control and satisfaction with care, reduction of patient and family anxiety, reduction of time in hospital, and assistance in clarifying the goals of care.<sup>10–15</sup>

Evidence summary	Level	Reference
There are strong recommendations for the inclusion of palliative care specialists in the multidisciplinary care of skin cancer and melanoma patients in the UK and Scottish guidelines	I	4, 5
Palliative care services may assist advanced cancer patients and their families in improving symptom control, reducing anxiety and clarifying goals of care	I	12–14
Although this evidence relates to cancer in general, it is regarded as relevant and applicable	II	11

### Recommendation

	Grade
<p>1. Palliative care specialists be included in the multidisciplinary melanoma treatment team to:</p> <ul style="list-style-type: none"> <li>• provide assistance with symptom control</li> <li>• support melanoma patients and their families</li> <li>• when necessary, coordinate care of melanoma patients between settings</li> <li>• assist in clarifying goals of care</li> </ul>	<b>A</b>

## 17.1 Timing of referral for palliative care

Palliative care has often been linked to the very late stages of a terminal illness, with referrals for specialist palliative care advice occurring late in the disease trajectory,<sup>16–18</sup> but even at a late stage patients have gained benefit from palliative recommendations.<sup>19</sup> The WHO definition of palliative care indicates that palliative care referrals are appropriate at any stage of illness, even from diagnosis.

Although studies to address the timing of referral to palliative care specialists are limited, there is evidence that involvement of a palliative care team can improve symptom control, including pain, dyspnoea, anxiety, and spiritual wellbeing.<sup>11–14,19–22</sup> The timing of referral to a palliative care specialist should be dependent on the need for intervention for physical or psychological symptoms, not the stage of the illness.<sup>5,21,23</sup>

Evidence summary	Level	Reference
Referral for palliative care has often occurred in the very late stages of a terminal illness	III–3 IV	16 17, 18
Even with short involvement, patients gained benefit from palliative recommendations	IV	19
Timing of referral should be dependent on the need for intervention for physical or psychological symptoms	IV	23

### Recommendation

2. Referral for palliative care be based on the needs of the patient and family, not just the stage of the disease	<b>C</b>
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## 17.2 Patients and families who benefit from referral to specialist palliative care

Palliative Care Australia has described a population-based model for palliative care delivery ranging from primary palliative care to an interdisciplinary specialist palliative care team.<sup>10</sup> The New Zealand definitions of palliative care also recognise generalist and specialist palliative care. Generalist palliative care is provided as an integral part of standard clinical practice by health care professionals who are not specialist in palliative care (see also Appendix 6 *New Zealand palliative care definition*).

To define which patients and their families require specialist palliative care it is necessary to consider for each patient:

- the wishes and needs (current and future) of this patient
- the needs (current and future) of this family, including bereavement
- the needs and capabilities of the generalist palliative care providers.

Many advanced cancer patients are at risk of burdens from physical symptoms, particularly pain, respiratory problems, nausea and vomiting.<sup>24</sup> Cutaneous metastases in melanoma may present particular burdens including pain, bleeding and disfigurement. Regardless of the stage of illness, any patient with poorly controlled symptoms is appropriate to be referred for specialist palliative care.

Specialist palliative care teams in in-patient, out-patient or community settings can assist other medical teams in achieving better symptom management. Patients with cancer often express fear of progressive symptoms, and it is important to take these concerns seriously and to offer reassurance that every effort will be made to address these problems should they arise.<sup>11,14,20–22</sup>

The burden of psychological symptoms in patients with progressive disease may be high as well and should also prompt referral for palliative care. After referral, individuals are less likely to describe anxiety and they express greater levels of satisfaction with care.<sup>12,13,25</sup>

The WHO also asserts that the needs of the family must be considered. Families and other informal caregivers may need support to sustain their ability to offer care. Palliative care specialists may assist families in understanding the goals of care, reducing their anxiety and improving their satisfaction with caring.<sup>26,27</sup>

Many patients with cancer wish to remain home for as long as possible and the majority of patients would prefer to die there.<sup>28</sup> Patients and families who receive input from specialist palliative care teams show better outcomes in terms of the amount of time spent at home and an increased likelihood of dying where they wished.<sup>15,22,29</sup> This may be achieved with a reduction in overall costs compared with the costs of conventional care.<sup>13</sup>

Finally, referral to palliative care may assist in improving bereavement outcomes for the family. The support of palliative care services to allow an open awareness of impending death as the disease progresses is associated with increased satisfaction for families. This has been suggested as one way of assisting families in the time following the person's death.<sup>30</sup>

In conclusion, not all patients with melanoma will need specialist palliative care during their illness, but providers of generalist/primary palliative care should be able to recognise when specialist palliative care is required for more complex needs, and specialist palliative care support should be readily available to patients, families and generalist/primary providers.

Evidence summary	Level	Reference
Specialist palliative care can improve symptom control for patients	I	12, 13, 14, 22, 25
Specialist palliative care can assist families to provide care in the place of choice	I	22, 29

### Recommendation

	Grade
3. Patients and their families with complex needs including physical, psychosocial and spiritual domains be referred to a specialist palliative care team at any stage during the illness	<b>A</b>

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# 18 Multidisciplinary care of melanoma\*

Melanoma has a highly variable clinical course with individual patients requiring care from a range of disciplines during their cancer journey. The benefit of, and need for a multidisciplinary approach throughout the continuum of cancer care is identified in The New Zealand Cancer Control Strategy<sup>1</sup> and The New Zealand Cancer Control Strategy Action Plan 2005–2010.<sup>2</sup> Goal 3 mandates that the patient should have appropriate access to a multidisciplinary team approach throughout the continuum. In Australia and New Zealand, care of patients is delivered in settings ranging from large hospitals with specialist cancer services to primary care clinics. Multidisciplinary care of melanoma involves centralised, coordinated care of melanoma patients and multiple disciplines that usually attend one clinic.<sup>3</sup> This contrasts to an alternate model of care of sequential referral to particular disciplines. Typically, multidisciplinary clinics exist in large cancer treatment facilities and involve surgeons, dermatologists, pathologists, specialist nurses. Frequently, the multidisciplinary team also includes the important role of care coordinator as well as medical oncologists, radiation oncologists, palliative care physicians and psychosocial specialists. The patient's general practitioner is also a member of the team, and may play a number of roles, including referral for diagnosis, coordination of care and follow-up. While it may not be possible or practical for the general practitioner to attend multidisciplinary team meetings, it is essential that the general practitioner is kept informed about treatment decisions in a timely way.

## 18.1 Review of the evidence

There is strong support from expert bodies for multidisciplinary care of melanoma patients.<sup>4,5</sup> Although no data are available for assessment in melanoma, there is evidence in other cancers, notably breast cancer<sup>6</sup> that multidisciplinary care is associated with improved survival.

Multidisciplinary care of melanoma patients is more cost effective when compared to community-based care in a North American health care setting.<sup>7</sup> There is also evidence that the use of expertise in palliative care can improve quality of care for patients with advanced cancer including melanoma (see Chapter 17 *Palliative care in melanoma*).

Evidence summary	Level	Reference
Multidisciplinary care of melanoma patients is more cost effective than community-based care in a North American health care setting	III-2	7

Recommendation	Grade
1. Multidisciplinary care be considered throughout the management of patients with melanoma	C

\* Dr Grant McArthur received research support from Pfizer and Novartis, receives Honoraria from Novartis and is a consultant to Pfizer and Novartis.

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# 19 Follow-up

## 19.1 Introduction

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. The best guidelines available to date come from two systematic reviews of all the available reports on follow-up schedules.<sup>1,2</sup>

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 these ranges from 2–8%.<sup>1–3</sup> A second invasive melanoma is most commonly thinner than the initial primary melanoma and has a more favourable prognosis which does not adversely affect survival.<sup>1</sup> The rate of occurrence of a subsequent *in-situ* melanoma is about four times higher than the risk of a subsequent invasive melanoma,<sup>4</sup> but most series do not recommend follow-up for *in-situ* melanomas.<sup>5</sup>

## 19.2 Undertaking follow-up

Current guidelines world-wide do not specify where routine follow-up should take place or who should do it.<sup>6,7</sup> However, it is becoming accepted by most<sup>8–10</sup> but not all<sup>11–13</sup> 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.<sup>14</sup> World-wide the mean percentage is 62%.<sup>1</sup>

The UK Medical Research Council has designed a ‘framework for the design of an integrated follow-up program’.<sup>15</sup> 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. 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. 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<sup>6,16</sup> found that most considered routine follow-up worthwhile, with only a few considering that it was not. While favouring follow-up, more than half the patients in these studies reported anxiety before each visit.

Evidence summary	Level	Reference
There is a consensus that 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	14–16
Self-examination may be combined, if appropriate, with routine follow-up by the patient's preferred health professional	IV	14–16

Recommendation	Grade
1. 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	C

### 19.3 Follow-up intervals and tests

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. More frequent visits may also be warranted for AJCC stage I patients with many atypical naevi, a family history of melanoma, or those who have difficulty in performing self-examination. Six-monthly intervals for five years and yearly thereafter are probably appropriate for patients with stage I disease, and three-monthly or four-monthly intervals for five years and yearly thereafter (all with ultrasound examination of regional nodes) for patients with stage II and III disease. These intervals are based on the consistent observation that about 80% of recurrences develop in the first three years.<sup>4</sup> Lifetime surveillance has been recommended by some because recurrences as late as 46 years after excision of a primary melanoma have been recorded.<sup>17</sup> 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. Very few patients have metastases identified by the routine use of imaging techniques and blood tests.<sup>18,19</sup> 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.

Ultrasonography is a technique that is being used increasingly for higher-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. Most centres dealing with only a few melanoma patients lack experience as this technique has been used routinely for less than ten years.<sup>20–23</sup> There is a consensus of opinion that ultrasound is superior to

clinical examination of regional lymph nodes although its survival advantage is unproven.<sup>24</sup> A French group<sup>25</sup> obtained a sensitivity of 92.9% for ultrasound compared with only 71.4% for the clinical examination of regional lymph nodes. Their specificity was equally high for both procedures (> 98%). Despite this apparent superiority of ultrasound, very few patients actually 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. Thus in sum, in only 1.3% of patients was the use of ultrasound advantageous. 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.

Evidence summary	Level	Reference
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. Ultrasound, only if performed by experienced ultrasonographers, is a useful adjunct to clinical examination in the follow-up assessment of more advanced primary disease. No other tests have significant value in patients with localised disease	IV	20–25

Recommendation	Grade
2. Follow-up intervals are preferably six-monthly for five years for patients with stage I disease, three-monthly or four-monthly for five years for patients with stage II or III disease, and yearly thereafter for all patients. Ultrasound may be used in conjunction with clinical examination only in the follow-up of patients with more advanced primary disease. For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials	<b>D</b>

## 19.4 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.<sup>6,13,26</sup> 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.<sup>27</sup> 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.

Evidence summary	Level	Reference
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	6, 13, 26, 27

### Recommendation

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

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. However, 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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## 20 Clinical trials

The clinical trial is an instrument designed to assess the effectiveness of potentially new or altered interventions that involve a wide range of clinical activity.

Trials frequently involve drug therapy, but may address new devices, surgical procedures, treatment by external instrumentation (e.g. radiotherapy), or psychosocial aspects of clinical management.<sup>1</sup>

Commonly, the study question is whether a new treatment is better than the old one. It is customary to compare each new treatment group with a control group, the members of which must be offered treatment matching the best standard currently available for their consideration before joining the trial.<sup>1</sup>

The randomised clinical trial (RCT), which involves random allocation of patients to their treatment or control group, is becoming the 'gold standard' for assessment of new management processes.

Clinical trials involve significant funding and require the informed consent from patients and frequently, the involvement of a number of centres and health professionals to obtain an appropriate number of subjects to ensure sound statistical power.

The conduct of trials by cooperative groups of trialists is the most likely way to advance evidence-based medicine through well-designed protocols and rigorous evaluation.<sup>2</sup>

However, in our community some people are concerned about RCTs, believing that patients involved in such trials may be at risk from factors that would not occur in treatment outside a trial. On the other hand, others see participation in an RCT as being of benefit to the trial subject and probably an optimal way of receiving the best contemporary care and clinical oversight.

A recent Cochrane Review assessed the effect of participation in RCTs ('trial effects') independent both of the effects of the clinical treatments being compared ('treatment effects') and any differences between patients who participated in RCTs and those who did not.<sup>3</sup>

The outcome of this review led its authors to conclude that there is no greater risk from participating in RCTs than there is from being treated outside an RCT. The authors considered that the belief or assertion that results of RCTs cannot be applied to usual practice is challenged by the review.<sup>2</sup> This outcome would appear to provide a sound basis for clinicians to offer participation in RCTs to their patients.

Any uncertainty about the effects of treatment can best be resolved through a randomised trial as long as the eligibility criteria for the trial match the patient population seen in usual practice, or the trial treatment is applied only to patients who match the eligibility criteria.<sup>4</sup>

Evidence summary	Level	Reference
Outcomes for patients who participate in RCTs on average do not differ from those of patients who receive similar treatments and do not participate in a trial	I	2

Recommendation	
	Grade
1. Patients can be informed that they are unlikely to be disadvantaged by participation in an RCT	A

## 20.1 Good practice point

- Given the lack of evidence in treating melanoma, patients be given the opportunity to enter clinical trials

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## 21 Treatment of desmoplastic melanoma

Desmoplastic melanomas represent 1–3% of melanomas, occur in an older age group, and are more common on the head and neck.<sup>1,2</sup>

Histologically they are characterised by dermal spindle cells in a fibrous stroma. Compared to other melanomas, they present as thicker primary tumours and have an increased association with the lentigo maligna histogenetic subtype.<sup>1,2</sup> They are usually S100 positive on immunohistochemistry and often have a lymphocytic infiltrate. Nerve infiltration or neurotropism is found in 36–52%.<sup>1,2</sup> They are often amelanotic.<sup>2</sup>

When compared to melanomas of similar thickness, overall survival is no different.<sup>1,2</sup>

There is increased local recurrence when neurotropism is present.<sup>2</sup>

Recently desmoplastic melanomas have been further classified into ‘pure’, where greater than 90% of the melanoma is desmoplastic, and ‘mixed’, when less is present. There is some suggestion that the sentinel node biopsy procedure is less likely to be positive in the ‘pure’ subtype.<sup>1,3</sup> Multivariate analysis of variables affecting overall survival found Breslow thickness the most important indicator,<sup>1,2</sup> however, AJCC stage was also found to be a significant variable.<sup>1</sup>

Surgery is considered the treatment of choice for primary desmoplastic melanoma, with a minimum margin of one centimetre recommended.<sup>1–3</sup> Since these melanomas are more common on the head and neck, reconstruction by skin flap or skin graft is often required. The role of postoperative radiotherapy following excision of desmoplastic melanoma of the head and neck regions remains unclear.

Evidence summary	Level	Reference
Surgical treatment of primary desmoplastic melanoma has shown the most effective results to date	III–3	2

Recommendation	Grade
1. Local wide excision for desmoplastic neurotropic melanoma conforms with the same margins as for other forms of cutaneous melanoma	C

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## 22 Mucosal melanoma

Melanomas arising from mucosal surfaces are very rare tumours and can present formidable challenges for management of tumours which on the whole have a very poor prognosis. The recent finding that at least one third of mucosal melanomas over express the receptor kinase c-kit (compared to less than 5% of cutaneous melanomas) may have implications for treatment with imatinib.<sup>1</sup> Patients with mucosal melanoma should be strongly considered for referral to a major centre with experience in the management of these tumours.

### 22.1 Melanoma of the anorectal region

#### 22.1.1 Background

Anorectal melanoma (ARM) is a rare condition comprising less than 1% of anorectal tumours. The rate appears to be similar between patients of different racial and ethnic backgrounds. Median age of onset is approximately 60, with a slight female preponderance. The common presenting symptoms are haemorrhoidal-type bleeding, mass or discomfort. Most series report that at least a third of anorectal melanomas are excised with a preoperative diagnosis of haemorrhoids. The characteristic appearance is of a polypoid lesion, frequently ulcerated, although sessile and flat lesions are also encountered. The majority of lesions appear to arise around the dentate line or below from the anal canal. A small proportion of lesions appear to arise from the rectal mucosa just above the dentate line. Melanomas occurring in normal skin outside the anal canal should be considered as cutaneous melanoma and treated appropriately. Although microscopically it appears that the majority of anorectal melanomas contain melanin, at least a quarter and possibly a greater percentage do not contain obvious melanin macroscopically. Many anorectal melanomas do not have the typical dark appearance of cutaneous melanoma.

At least 20% of patients will present with regional lymph node metastases. Another 20–40% will present with distant metastatic disease. The average tumour size is in the order of 3–4cm and there is often associated in situ change. The standard AJCC/UICC staging for cutaneous melanoma is not appropriate for anorectal melanoma as most tumours are greater than 4mm in thickness. Tumour thickness has not been shown to be a reliable predictor of outcome. Neither has the presence of nodal metastases, histological subtype or gender.

Preoperative evaluation should include staging with a CT chest, abdomen and pelvis. A case can be made for PET scanning if available. Endoscopic ultrasound to assess the depth of penetration of the tumour to identify patients who may be suitable for a limited procedure has been evaluated in a small number of cases.

### 22.1.2 Management

Traditionally, abdomino-perineal resection (APR) has been recommended for the management of ARM. More recent studies have indicated that the much lesser procedure of complete wide local excision of the primary melanoma with sphincter preservation is an option for many patients. The results for all series published after 1990 that compare patients undergoing surgical management and report more than ten patients are shown in Table 6.<sup>2–14</sup> Most but not all studies show a higher rate of local control for patients undergoing APR, but in all but one study no advantage in survival was shown for either APR or local excision. This is an old study from Memorial Sloan Kettering Cancer Center, however a more recent study from the same institution reported very similar rates of local control and overall survival for the two procedures from 1984–2003, when the standard of care switched from APR to WLE (see Table 6). Approximately one third of patients with operable (non-metastatic) anorectal melanoma will require an abdominoperineal excision for complete resection of the melanoma to be accomplished. The extent of margins for either APR or WLE has not been evaluated, although Ward et al aim to achieve a 2cm margin.<sup>15</sup> Remarkably, the width of excision is uncommonly reported in the literature.

Patients with established nodal metastases at presentation should undergo lymphadenectomy at the time of the definite surgical procedure for local control. The commonest site of regional node failure is the inguinal region. High rates of pelvic lymph node involvement have been reported at the time of APR in one series, but are uncommon in other series when reported.

Overall survival is not strongly associated with the presence of regional node metastases, most likely reflecting the very high risk of distant metastasis. For this reason elective inguinal lymphadenectomy is of no value and is not indicated. Sentinel node biopsy has been successfully performed in a small number of cases with limited follow-up. In view of the lack of a relationship between outcome and lymph node status and lack of evidence supporting its role, SNB cannot be recommended. It is unlikely that there will ever be sufficient numbers for a comprehensive evaluation of the procedure.

Lymphadenectomy is indicated at the time of the definitive procedure for primary ARM with proven regional lymph node involvement.

Older anecdotal reports of radiotherapy following limited excision reported contradictory results, however a recent series of 23 patients treated by wide excision and postoperative radiotherapy (30 Gy in five fractions over 2.5 weeks to the primary tumour and draining lymphatic sites) was achieved with minimal toxicity, a local control rate of 74%, and a five-year actuarial survival of 31% after a median follow-up of 37 months.<sup>16</sup> Local control in this report is similar to patients undergoing APR.

The experience of ARM is that the overwhelming majority of patients with anorectal melanoma will die of the disease, with most manifesting evidence of distant disease within two years of diagnosis. The commonest sites of metastases are lung (over 50%) followed by liver, brain and gastrointestinal tract. Distant metastatic disease is generally managed similarly to metastatic cutaneous melanoma. Radiotherapy may have a role for palliation of local, regional or distant recurrence.

The overall survival for ARM is poor. Patients with disease confined to the anal canal have a five-year survival of approximately 35% and a median survival of approximately 30 months. Patients with regional disease at presentation have a median survival of 20 months, and patients with metastatic disease at presentation rarely survive 12 months.

Evidence summary	Level	Reference
The only data to support recommendations for surgical therapy are small retrospective cohort studies with the potential for considerable bias. Nevertheless the results from these studies are consistent. In summary, wide local excision in many but not all series is associated with a higher rate of local recurrence than APR, but overall no advantage for survival with APR over wide local excision has been shown (see Table 6). The very high rate of distant failure and poor overall survival appears to be independent of local recurrence	IV	2–14

### Recommendations

	Grade
1. The primary lesion for melanoma of the anorectal region should be managed by sphincter preserving complete local excision in most cases. APR is indicated only for patients with loco-regional disease whose primary tumour cannot be resected by a limited procedure	<b>D</b>
2. Pelvic node failure as an isolated event is uncommon. Extended pelvic lymphadenectomy is not indicated	<b>D</b>
3. There is no evidence to support elective (as compared to therapeutic) inguinal lymphadenectomy	<b>D</b>
4. Sentinel node biopsy has been described in a small number of cases but there is no evidence to support its routine use at the present time	<b>D</b>
5. The role for radiotherapy (RT) in patients with close/involved margins after wide local excision or abdomino perineal resection is unknown but it may be considered	<b>D</b>
6. The care of patients with anorectal melanoma be undertaken by a multidisciplinary team experienced in the management of these patients	<b>D</b>

Table 6 summarises papers published since 1990 that have treated more than ten patients with locoregional disease only at presentation. Figures refer to patients from these papers treated by APR or WLE only. Survival figures in some instances have been obtained from Kaplan Meier plots in the papers. In many cases formal statistical comparison of APR and WLE survival curves were not performed, but if the authors concluded that there was no difference in survival the result has been summarised as a non-significant result (NS). In most papers the local recurrence rate was expressed as a simple fraction rather than a product limit estimate.

**Table 6**

**Studies comparing Abdomino-pelvic resection and sphincter preserving wide local excision for patients with localised anal melanoma (more than 30 patients and published since 1990)**

Author	Year	Time period	Number of patients APR, WLE	Survival % 5 yr, or median (months)	Local recurrence APR, WLE
Goldman <sup>2</sup>	1990	1970–1984	15,18	12m 13m NS	4/15 9/12
Slingluff <sup>3</sup>	1990	1974–1989	24,12	8% 7% NS	50% 100%
Ross <sup>4</sup>	1990		14,12	19% 20% NS	4/14 7/12
Antoniuk <sup>5</sup>	1993	1951–1991	4,8	29m 22m NS	2/4 5/8
Brady	1990	1929–1993	43,14	25% 8% P<0.05	not available
Konstadoulakis <sup>6</sup>	1995	1975–1991	8,5	0% 25% NS	50% 22%
Roumen <sup>7</sup>	1996	1960–1995	18,16	25% 58% NS	1/8 12/16
Thibbault <sup>8</sup>	1997	1939–1993	26,11	25% 39% NS	10% 28% NS
Moozar <sup>9</sup>	2003	1980–1999		7m 12m NS	not available
Bullard <sup>10</sup>	2003	1988–2002	4,11	25% 64% NS	50% 18% NS
Weyandt <sup>11</sup>	2003	1992–2002	5,11	NS no info	1/5 5/8
Malik <sup>12</sup>	2004	1983–2001	9,10	25m 20m NS	not available
Pessaux <sup>13</sup>	2004	1977–2002	9,21	33 16 NS	2/9 10/21
Yeh <sup>14</sup>	2006	1984–2003	19,10	34% 35% NS	21% v 26% NS

## 22.2 Mucosal melanoma of the head and neck

### 22.2.1 Background

Mucosal melanoma of the head and neck is a very rare tumour accounting for less than 1% of all head and neck melanomas. The median age of presentation is approximately 60 with a slight male predominance. Approximately 60% occur in the sino-nasal region, with two-thirds arising obviously from the nasal cavity. Virtually all the remainder occur in the oral cavity, particularly the upper jaw, apart from a very small percentage found in the larynx.

Nasal melanomas present with nasal obstruction or bloody discharge similar to sinus melanoma. Oral melanoma may present with a mass, an area of pigmentation, bleeding, or loosening of teeth. The standard AJCC staging system is not appropriate for mucosal melanoma. Lymph node involvement is unusual at the time of presentation and does not commonly occur among patients who develop local recurrence or distant disease.

### 22.2.2 Management

Because of the rarity of this tumour, treatment guidelines are not well established and consideration should be given to referral to a unit with expertise in managing head and neck melanoma. Recommendations for treatment are based on a limited number of small retrospective case series<sup>17–22</sup> with considerable potential for bias.

Overall survival remains poor with reported rates of survival varying from approximately 20% to less than 5% at ten years. A high rate of early haematogenous dissemination and late presentation compared to cutaneous melanoma may explain these poor results.

Evidence summary	Level	Reference
Complete surgical excision is the fundamental surgical aim but may be difficult to achieve without a destructive or disabling procedure. The addition of radiotherapy to surgery has not been shown to improve either local control or survival, apart from one small study which found a small improvement in local control	III–3	17–22
Primary radiotherapy alone has been advocated, but to date the series comparing it with surgery with or without radiotherapy show poorer local control and survival	IV	19

### Recommendations

	Grade
7. Patients with mucosal melanoma of the head and neck are best managed by complete surgical excision. Radiotherapy has not been shown to be of benefit to patients who have undergone a complete resection but may be of benefit in patients who have residual disease	<b>D</b>
8. Patients to be referred to a specialist unit with experience in head and neck melanoma	<b>D</b>

## 22.3 Melanoma of the oesophagus

A very small number of oesophageal melanomas have been reported in the literature, but as the gastro-intestinal tract is a potential site for metastasis from cutaneous melanoma, the true nature of many lesions is debated. Many patients present with disseminated disease. Tumours are often large at presentation and tend to be located in the distal third of the oesophagus. The majority of patients are dead within twelve months. Radical resection can be considered in patients with limited disease.

## 22.4 Melanoma of the male genito-urinary tract

Melanoma of the male external genitalia and lower urinary tract is a very rare tumour. Many patients have been aware of a pre-existing pigmented lesion. Melanomas of the glans penis arise in glabrous skin (no hair follicles or sweat glands) and behave similarly to vulval melanoma. Wide excision rather than penectomy (radical or partial) is appropriate if possible. Lymphadenectomy is indicated for involved inguinal lymph nodes. Sentinel node biopsy has been reported but there is not sufficient evidence to make any recommendation. Overall survival is poor, with most patients dying within three years.

In contrast, melanomas of the skin of the penis and scrotum behave similarly to cutaneous melanoma, but presentation is often delayed and results poorer than seen with cutaneous melanoma. Wide excision is indicated rather than penectomy. Again, a role for SNB has not been established.

## 22.5 Vulval melanoma

Vulval melanoma is a very rare condition accounting for less than 1% of all gynaecological malignancies. In contrast to cutaneous melanoma, the incidence of vulval melanoma appears to be stable or decreasing. It is typically a disease of elderly females (median age at presentation late sixties). Most patients report the presence of a mass and/or bleeding, while pruritus and pain are less common symptoms at presentation.

The commonest histological subtypes are mucosal lentiginous melanoma or nodular melanoma. Many lesions are ulcerated and typically 2–4mm in thickness. The regional lymph nodes are involved in up to one third of patients at presentation, and up to 25% of patients present with distant disease.

The skin of the perineum varies from hair-bearing skin over the labia majora to glabrous (non-hair-bearing skin) in the inner vulva to the mucosa of the vaginal introitus. Up to one third of vulval melanomas arise on the labia majora and are characteristically flat, pigmented lesions, while more centrally-based lesions, which frequently involve the labia minora and clitoris, are characteristically nodular, and up to one third may be amelanotic. Clark micro-staging is of no value for lesions arising in the mucosa or glabrous skin and Breslow thickness has been variably reported but is of significance. Several staging systems have been proposed, including a simple clinical staging system (stage I, local disease only; stage II, spread to regional lymph nodes; stage III, metastatic disease), although in one more recent study the AJCC staging system for cutaneous melanoma was the only factor predictive of recurrence-free survival in a multivariate analysis.<sup>23</sup>

Similar to cutaneous melanoma, prognostic factors associated with outcome include tumour thickness, ulceration and nodal status. In several reports amelanosis and age are also related to outcome. Overall the prognosis of vulval melanoma is poor, with 50% of patients surviving five years. Five-year survivals may be as high as 70% for patients with thin lesions (< 1mm) but less than 20% for patients presenting with regional lymph node involvement.<sup>24</sup>

### 22.5.1 Surgical management

Surgery remains the mainstay of treatment for vulval melanoma. There are little prospective data and no randomised studies to guide management due to the rarity of the disease. The surgical approach has evolved from aggressive surgery, for example bilateral vulvectomy with inguinal lymphadenectomy, to more limited procedures due to the recognition that extensive procedures, while providing a higher rate of local control, do not impact on overall survival but cause considerably more morbidity.<sup>23,25–30</sup>

Superficial lesions, particularly those in a favourable position, may be treated effectively by wide local excision. Unfortunately central lesions involving clitoris and urethra, which are often thicker, may require more aggressive procedures to obtain complete excision.



There is little evidence on which to make recommendations for the width of excision but in principle, for thinner lesions, limited excision margins are appropriate. A Swedish collaborative study reported a series of 281 patients with lesions < 2mm thick. The local recurrence rate was 1.8% and was not affected by margin sizes of 1–2cm versus 5cm.<sup>30</sup>

Elective lymph node dissection has not been shown to improve outcome but is associated with considerable morbidity. Sentinel node biopsy has been reported in vulval melanoma but its role is yet to be clarified.<sup>31</sup> The role of adjuvant radiotherapy is unknown but may be considered where resection margins are less than optimal. Radiotherapy may have a role for the patient who is unable or unwilling to undergo a surgical procedure.

Recurrent disease is best managed surgically, however most patients with recurrence also manifest evidence of distant disease. Management of distant disease, which has a similar pattern to cutaneous melanoma, should be similar to the management of disseminated cutaneous melanoma.

Evidence summary	Level	Reference
There are no randomised data and little prospectively collected data on which to base recommendations for treatment. Most series are small, collected over long time periods and retrospective. There appears to be no survival advantage to radical procedures over wide excision with modest margins of 1–2cm. There is no survival advantage for prophylactic lymphadenectomy and although sentinel node biopsy has been performed successfully for vulval melanoma, there are little data on its efficacy or safety at the present time	IV	23–30, 32

Recommendations		Grade
9. Histologically confirmed melanoma of the vulva 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		<b>D</b>
10. Patients with vulval melanoma be referred to a specialist unit with expertise		<b>D</b>

## 22.6 Vaginal melanoma

Melanoma of the vagina and urethra is an extraordinarily rare condition. The lower third of the vagina is most commonly affected and patients invariably present with advanced disease. Complete surgical removal, if feasible, frequently requires a major exenterative procedure. The risk of local recurrence, regardless of the extent of surgery or treatment modality, for example RT, is very high and most patients succumb to a combination of locoregional and distant disease within a short time.

## 22.7 Good practice points

- Any suspicious lesions of the genital tract should be biopsied
- As there is a high incidence of systemic disease in these cases, a CT/PET scan is indicated prior to radical surgery

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## 23 Occult melanoma

Melanoma is among a number of cancers in humans where the primary tumour cannot always be found. In some patients the primary may be in an obscure site such as the eye, ear or the intestine, but in the majority it is likely that the primary tumour has been destroyed by the host's immune system via lymphocyte activation.<sup>1,2</sup> It is likely that total regression occurs in 10–20% of melanomas, though only those where there have been metastases are diagnosable (about 5% of melanomas). Partial regression of primary tumours is more common and is often reported on pathology reports (30–50%). Two recent studies have shown that those patients with metastases and an occult primary melanoma have a better prognosis than those with metastases and a known primary melanoma.<sup>3,4</sup> This suggests an intrinsically superior host tumour interaction in those with occult primary melanoma.

Evidence summary	Level	Reference
Patients with occult primary melanoma usually present with lymph node disease, a soft tissue metastasis, or widespread systemic disease, in the absence of a primary tumour and the diagnosis is made by pathological examination of the lymph node, or metastasis which shows the characteristics of melanoma. Such patients should be examined carefully to exclude the possibility of a hidden primary by examination of the eyes, inner ears and scalp, and possibly colonoscopy. The presenting lymph nodes or metastases should be treated appropriately regardless of the inability to detect the primary tumour and a PET scan should be performed	IV	1, 2

Recommendation	Grade
1. Patients with metastases and no obvious primary tumour be examined for primary melanomas in obscure sites. If none are found, assume that the primary melanoma has completely regressed	<b>D</b>

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## 24 Ocular melanoma

There are two primary types of ocular melanoma, uveal (choroid, iris and ciliary body) and conjunctival melanoma. Both types are uncommon.<sup>1</sup> 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.<sup>2</sup> Other forms of treatment include periodic observation, transpupillary thermotherapy, charged particle irradiation, local tumour resection, enucleation and exenteration. Despite this, the survival rate of uveal melanoma has not changed over a 25-year period.<sup>3</sup> This may well reflect an inability to prevent or treat metastatic disease.

Similarly for conjunctival melanoma, there has been a move to using eye-conserving treatment.<sup>4</sup> Local resection is well established and commonly used. Topical chemotherapy and radiotherapy may have a role, but it is yet to be defined. The management of ocular melanoma is complex and should be conducted in specialised units where eye-conserving therapies are available.

Evidence summary	Level	Reference
Eye-conserving therapies are available for ocular melanoma which results in similar rates of local control to enucleation	IV	2

Recommendation	Grade
1. Ocular melanoma is a complex and uncommon form of melanoma that should be managed in specialised units where eye-conserving therapies are available	C

**For those requiring further information on ocular and periocular melanoma, please refer to the comprehensive document accompanying these guidelines, which will be available on the website at [www.cancer.org.au/clinical\\_guidelines](http://www.cancer.org.au/clinical_guidelines) under the 'skin cancer' heading.**

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## 25 Melanoma in children

The current understanding of childhood melanoma is derived from the collective experience of many institutions and from data obtained from state and national registries, since no single institution has a large experience with this rare condition.

Different definitions of 'childhood' have been made. Studies reporting the experiences of individual centres have tended to merge all ages of young patients, often labelling those up to 20 years of age as 'childhood' cases. However, it seems more appropriate to separate the prepubertal cases from the postpubertal or adolescent ones, since melanoma incidence rises sharply around the time of puberty. Defining puberty is itself fraught with difficulty, particularly because of the rather indistinct transition to puberty in boys. A further problem is that most reports of childhood melanoma rely on data from registries, whether they be population-based or from hospitals, which almost invariably use age groups of 1–4, 5–9, 10–14 and 15–19 years. Thus 'puberty' is most likely to occur some time in the 10–14 year age group, after which age there is a sharp rise in incidence. To illustrate this point, melanoma before the age of 10 years occurred in only seven cases (all girls) registered in Australia in 2001 by the Australian Institute of Health and Welfare.<sup>1</sup> In the 10–14 year age group, six girls and six boys were registered. This rose to 38 girls and 39 boys in the 15–19 age group. In New Zealand between 1995 and 2006, 20 melanomas were diagnosed in children under the age of 15 years and 105 diagnosed in adolescents aged 15–19 years.<sup>2</sup>

### 25.1 Diagnosis

Transplacental transmission of melanoma, an exceedingly rare condition, was first reported in 1949<sup>3</sup> and there had been less than a dozen recorded cases up until 2005.<sup>4,5</sup> 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. Primary melanoma may also very rarely arise within a giant congenital melanocytic naevus, present in approximately 1 in 20,000 newborns.<sup>4</sup> The lifetime risk of malignant transformation in these giant naevi is between 2 and 20%.<sup>6</sup>

There is general agreement that because of the difficulty in differentiating benign from malignant melanocytic lesions in young adults, all histological slides should be reviewed by histopathologists highly experienced in the diagnosis of such lesions. Some melanocytic lesions are misdiagnosed as benign and only recognised as malignant when they recur. This was often the case in the past. More recently, on the other hand, there has been a tendency to over-diagnose prepubertal lesions as melanoma, thus ascribing malignancy to some lesions which have no malignant potential.<sup>7</sup> Nearly 60 years have elapsed since Sophie Spitz<sup>8</sup> reported a series of melanocytic lesions which behaved in benign manner but which shared many histological features with melanoma. Nevertheless, there are still no criteria that will definitively separate the two lesions, since each can simulate the other. Crotty et al<sup>9</sup> suggested that in some cases it may not be possible to give an unequivocal diagnosis. In such cases, the presence of deep and/or atypical mitoses is a strong indicator

of malignancy, as is positive staining with HMB45 (especially in the deep component). Even in these cases, a definite diagnosis may still not be possible and there is need to consider the balance of features in favour and against a diagnosis of melanoma. These cases should be completely excised and the patient carefully followed-up. Recently, attempts have been made to illustrate the problems associated with making this difficult diagnosis and criteria to differentiate benign from malignant lesions have been proposed.<sup>10–12</sup> Most pathologists claim that the histological features of melanoma in children are similar to those in adults. The only reports to the contrary, citing architectural and cytopathological differences, emanate from specialist referral centres where slides have been examined after the development of metastases<sup>13</sup> or in cases of advanced localised disease.<sup>14</sup> This underscores the problems associated with comparing results from population-based data with those from individual referral centres.

Evidence summary	Level	References
The differential diagnosis between Spitz naevi and spitzoid melanomas is a difficult one. Several attempts have been made to assist histopathologists make this distinction	IV	8–12

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

## 25.2 Treatment and survival

Irrespective of whether the source of data is population-based or from individual referral centres, the mainstay of treatment is surgical, as in adults. 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 arises in a giant naevus, a small congenital melanocytic naevus, a dysplastic naevus or de novo, surgical excision should be performed with the same excision margins recommended for adults with melanomas of similar thickness.

The largest number of children surveyed to date comes from the National Cancer Data Base in the United States, which draws its cases from hospital registries. Their most recent publication described the demographics and clinical presentation of melanoma in 3158 young patients aged 1–19 years between 1985 and 2003, and reports a high rate of metastatic disease in 289 children aged 1–9 years.<sup>15</sup> The possible explanations given for this are either (a) a delay in diagnosis due to a low awareness of the possibility of melanoma in such young patients, or (b) age-related differences in biological behaviour not yet understood, or (c) an overrepresentation of patients with more advanced disease in their hospital-based population.

This high metastatic rate and an advanced stage at first presentation has been reported by others, but most reports have emanated from specialist referral centres<sup>16,17</sup> rather than registries.<sup>18–20</sup> Nonetheless, the consensus is that despite this more common presentation of advanced disease, ultimate survival is similar to that of adults,<sup>15–17,20</sup> and it is generally agreed that sentinel node biopsy is warranted, no matter what age, in children with melanomas of appropriate thickness.<sup>21–23</sup> Although the number of children reported to have undergone sentinel node biopsy is so far quite small, rates of positivity range from 25% to over 60%.<sup>21–26</sup> This could be regarded as an extension into early childhood of the well-accepted fact that younger adult patients have a higher incidence of sentinel node positivity than adult patients.<sup>22,25,27,28</sup>

Additionally, in all series, surprisingly good survivals have been recorded following a positive sentinel node biopsy in children. For example, five-year disease-free survival of 83% after a positive sentinel node biopsy has been reported. This again reflects the paradoxical situation in which overall survival in adults is poorer than in younger patients despite a higher sentinel node positivity rate.

Authors are divided on the value of completion lymph node dissection in children, despite the harvesting of the occasional positive non-sentinel node, but generally there is agreement that such surgery should not be avoided in young children and the indications should be the same as in adults.

Thus in sum, sentinel node biopsy for children with intermediate- to high-risk disease is a useful adjunct in the treatment of melanoma in a paediatric population with frequently apprehensive parents. The use in children of high-dose interferon alpha-2b therapy has been described as being well-tolerated with less associated toxicity, both after resected high-risk melanoma<sup>29,30</sup> and after positive sentinel node biopsy.<sup>26</sup> However, the efficacy of high-dose interferon as an adjuvant therapy in children is poorly documented, since in most drug trials subjects < 18 years of age are excluded from participation.

Evidence summary	Level	References
Surgical excision of the primary melanoma should be performed with excision margins similar to those in an adult with equivalent disease. Sentinel node biopsy, completion lymph node dissection, or adjuvant therapy with high-dose interferon are all well tolerated by children. The indications for these therapies should be the same as in adults	IV	21–26
Survival in children with advanced disease is better than in adults with comparable disease	IV	15–17

### Recommendation

	Grade
2. 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	<b>C</b>

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# 26 Pregnancy and melanoma (including hormone replacement therapy and oral contraceptives)

## 26.1 Naevi and pregnancy

Pregnancy increases melanocytic activity, causing hyperpigmentation as observed in the linea nigra, chloasma and areolar pigmentation. There is little evidence that significant changes in naevi occur during pregnancy.<sup>1–3</sup> It is therefore recommended that any naevus that changes during pregnancy and has other features suggestive of melanoma should be investigated. An excision biopsy can be performed safely using local anaesthetic during pregnancy with the obstetrician's and patient's consent.<sup>4</sup>

Evidence summary	Level	Reference
Naevi do not usually undergo significant changes during pregnancy	III–3	1–3

Recommendation	Grade
1. Any naevus that changes during pregnancy and/or has other features suggestive of melanoma be investigated	C

## 26.2 Melanoma and pregnancy

Melanoma is the most common malignancy in women of 25–29 years and internationally, it has been estimated that about 35% of women with melanoma are of child-bearing age.<sup>9</sup> Malignancy in pregnancy is reported in 1 in 1000 gestations, with malignant melanoma 8% of the total (1970s data).<sup>10</sup> Incidence of melanoma during pregnancy is estimated at 1 per 40,000 pregnancies<sup>11</sup> or 2.6 to 2.8 per 1000 pregnancies.<sup>9,12</sup>

Pregnancy does not increase the subsequent risk of having melanoma.<sup>13</sup> and there is no increased risk of melanoma developing during pregnancy.<sup>14</sup>

There is no significant difference in survival in pregnant patients diagnosed with melanoma or stage I disease.<sup>15–24</sup> The prognosis of pregnant women with melanoma is still dependent on tumour thickness and ulceration status.<sup>25</sup>

Pregnant women who present with regional or metastatic melanoma do not appear to have a worse prognosis.<sup>26,27</sup>

The effect of previous pregnancy on the prognosis of women subsequently diagnosed with melanoma is conflicting. One study showed previously pregnant women had a superior survival advantage (in particular those with stage I disease or women older than 50 years).<sup>28</sup> In another study there was a more favourable prognosis associated with five or more prior pregnancies.<sup>29</sup> Other studies showed no effect of prior pregnancy on the prognosis of melanoma in stage I disease.<sup>19,30,31</sup> But one study of stage II patients,<sup>30</sup> showed a significantly lower survival rate for pregnant patients and parous women who had experienced activation of the lesion in previous pregnancies.

There appears to be no effect of subsequent pregnancy on the prognosis of melanoma.<sup>15,19</sup>

Evidence summary	Level	Reference
There appears to be no relationship between pregnancy and risk of, or survival from melanoma	III–3	25

Recommendation		Grade
2. Melanoma in a pregnant woman be treated according to tumour thickness and ulceration, that is, as for a non-pregnant woman		C

## 26.3 Pregnancy after the diagnosis of melanoma

There are no standard, defined guidelines for patients who wish to become pregnant after the diagnosis and treatment of melanoma, but the consensus is to recommend that women avoid pregnancy for two to five years after the diagnosis of high-risk melanoma, whether or not the melanoma occurred during pregnancy,<sup>32</sup> as most recurrences are diagnosed within this period. Those with < 0.5mm thick melanoma have a 1–3% risk of recurrence within five years, while those with > 4mm thick melanoma have a risk of recurrence of up to 50% within two years. However, it is not completely predictable who will develop recurrent disease and each patient should be approached individually, with the patient ultimately making her own informed decision.<sup>33</sup>

Recommendation		Grade
3. 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		C

## 26.4 Treatment of melanoma during pregnancy

The treatment of primary melanoma does not differ because a woman is pregnant. The status of the sentinel node is one of the most important prognostic indicators for patients with clinically localised melanoma.<sup>34</sup> Lymphoscintigraphy is probably



safe in pregnant women<sup>5-8</sup> and they may be offered a SNB using technetium after careful counselling about the safety and efficacy of this procedure.<sup>35</sup> The use of the patent blue V dye does have a 1% risk of an allergic reaction. Its safety in pregnancy is unknown. Its use is therefore not recommended in SNB in pregnant women. The timing of the surgery is important: near term, the clinician would probably defer treatment until after delivery, but if the melanoma is diagnosed in the first or second trimester the decision is more difficult.

These patients and pregnant patients with metastatic melanoma should probably be treated in the setting of a comprehensive cancer centre.

Evidence summary	Level	Reference
Sentinel node biopsy is safe using technetium only in pregnant women.	III-3	5-8

### Recommendations

	Grade
4. Sentinel node biopsy can be performed using only technetium in pregnant women	<b>B</b>
5. Pregnant women with thicker melanomas and nodal metastases be treated in consultation with specialised centres	<b>C</b>

## 26.5 Melanoma and hormone replacement therapy and the oral contraceptive pill

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.<sup>32,36-53</sup>

Age at menarche, age at menopause, or duration of menstrual life does not affect melanoma risk.<sup>32,37-40,46</sup>

Evidence summary	Level	Reference
The use of HRT or OCP does not affect the natural history of melanoma	III-3	32, 37-53
Age at menarche, age at menopause, or duration of menstrual life does not affect melanoma risk	III-3	32, 37-40, 46

### Recommendation

	Grade
6. Hormone replacement therapy and oral contraceptives are not contraindicated in women who have had melanoma	<b>C</b>

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# 27 Prognostic factors and survival outcomes in cutaneous melanoma

## 27.1 Prognostic factors

Clinical stage is the most important determinant of prognosis in melanoma. Patients with thin early-stage melanomas have an excellent prognosis in general, but even in these patients there is no certainty of cure. Prognosis is poorer with increasing stage, but some patients may survive for extended periods with known metastatic disease. The American Joint Committee on Cancer (AJCC) Staging system, validated in a series of 17,600 patients with melanoma, uses T (Primary Tumour), N (Regional Lymph Nodes) and M (Distant Metastasis) categories to predict survival outcome.<sup>1,2</sup> Despite the large number of established and putative prognostic factors in melanoma, accurate prediction of prognosis in an individual patient remains difficult.<sup>3</sup>

Key determinants of prognosis in localised melanoma (**stages I and II**) are Breslow thickness and ulceration.<sup>4</sup> Clark's level of invasion may have some value in thin melanomas, but this is controversial.<sup>5</sup> The importance of mitotic rate has been emphasised in a number of recent studies, and is one of the key prognostic determinants in thin melanomas in some series.<sup>6–12</sup> Most other suggested prognostic factors, including lymphocytic infiltration, regression, vascular invasion and cell type, are of lesser importance in the majority of studies, or findings are controversial and conflicting.<sup>5,6,8,13–17</sup> Pregnancy does not appear to significantly affect prognosis.<sup>18</sup>

Tumour growth phase has been shown to be poorly reproducible and of limited value, although it may assist in stratifying thin melanomas.<sup>6</sup> Histological subtype provides little prognostic information when Breslow thickness is considered, while pure desmoplastic melanomas may have a slightly better prognosis.<sup>19</sup>

Although many molecular and immunohistochemical studies have identified possible prognostic markers, multivariate analyses show that in general, these are no better than standard morphologic criteria.<sup>20</sup> In the future, gene expression profiling using cDNA-microarray analysis may be of value.<sup>21</sup> Serum markers such as S100 $\beta$  and melanoma-inhibiting activity protein can provide some prognostic information, but this is mostly relevant in monitoring treatment effects in advanced-stage melanoma.<sup>22</sup>

A number of prognostic models have been developed using a combination of clinical and pathological features. Some are complex and although they may show promise in whole populations, all suffer from the problem of limited predictive value for an individual patient.<sup>4</sup>

The site of a primary melanoma has been shown to have prognostic relevance in some studies, but not others, even when tumour thickness is controlled for in the analysis. In some series, tumours sited on the palms, soles and subungual regions have a worse prognosis. When controlled for thickness, ethnicity has been shown to be relevant in some populations, with African Americans having a somewhat worse outcome.

In **stage III** disease (regional metastases), the most important determinant of prognosis is the number of lymph nodes affected. The size of the metastases is also important, with clinically detected disease faring worse than that only identified microscopically. Ulceration of the primary tumour confers an adverse prognosis, and tumours in older patients, and those sited on the trunk, head and neck, may have a worse prognosis.

In **stage IV** (distant metastases), prognosis is worse, with increasing number of metastatic sites and with metastasis to viscera.<sup>23</sup> High serum lactate dehydrogenase (a marker of liver involvement) and poor performance status are associated with reduced survival.<sup>24</sup>

Approximately 5% of patients present with metastatic melanoma for which a primary cannot be identified. In these patients, the prognosis is much the same as that of patients with similar disease distribution associated with a known primary.<sup>4</sup>

Independent of the stage of disease, there are additional host-related factors that affect the prognosis of a melanoma patient. These include age, gender, and socioeconomic status. The risk of death due to melanoma is greater in older people (60+ years of age) than it is in younger people, and greater in men than in women.<sup>5,25–43</sup> However, there is only limited evidence that the probability of death due to melanoma is greater in people of lower socioeconomic status.<sup>30,34,46</sup>

**Table 7** Prognostic factors in melanoma

		Prognostic factor
Tumour-related	Key factors	TNM Stage
		Breslow thickness
	Generally considered to be of importance	Ulceration
		Mitotic rate
		Regression
		Clark's level (mainly of importance in thin melanomas)
		Lymphovascular invasion
	Of uncertain or disputed importance	Tumour infiltrating lymphocytes
		Growth phase
		Desmoplastic type
Host-related		Age
		Gender
		Site
		Raised serum LDH*
		Poor performance status*
* In stage IV disease		

## 27.2 Survival outcomes

The most recent comprehensive analysis of survival outcomes, based on the results of over 17,000 melanoma patients from several countries around the world, is reproduced below. This analysis was used to develop the 2002 AJCC melanoma staging system.<sup>2</sup>

The AJCC Melanoma Staging Committee reconvened in 2006 to begin preparation of the next version of the AJCC staging system, scheduled to become official with publication of the seventh edition of the AJCC Cancer Staging Manual which is expected to be published in late 2009.

**Table 8** Survival rates for melanoma TNM and staging categories

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. + Nodes	Nodal Size	Distant Metastasis	No. of Patients	Survival ± SE			
								1-Year	2-Year	5-Year	10-Year
IA	T1a	1	No	0	–	–	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1	Yes or level IV, V	0	–	–	1,380	99.8 ± 0.1	98.7 ± 0.3	90.9 ± 1.0	83.1 ± 1.5
IB	T2a	1	No	0	–	–	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	1.01–2.0	Yes	0	–	–	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	1.01–2.0	No	0	–	–	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	2.01–4.0	Yes	0	–	–	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	2.01–4.0	No	0	–	–	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	> 4.0	Yes	0	–	–	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	> 4.0	No	1	Micro	–	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	Any	No	2–3	Micro	–	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	Any	Yes	1	Micro	–	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	Any	Yes	2–3	Micro	–	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
	N1b	Any	No	1	Macro	–	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	Any	No	2–3	Macro	–	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	Any	Yes	1	Macro	–	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	Any	Yes	2–3	Macro	–	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	N3	Any	Any	4	Micro/Macro	–	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	Any	Any	Any	Any	Skin, SQ	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	Any	Any	Any	Any	Lung	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	Any	Any	Any	Any	Other visceral	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9
Total							17,600				

Reproduced from Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001; 19(16):3622–3634.

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## 28 Complementary and alternative medicine

Since the earliest of times, humans have endeavoured to enhance their physical and emotional wellbeing by selectively choosing botanicals, minerals and extracts of animal, avian and reptilian tissues, and physical measures such as massage. Powerful medical systems such as Ayurvedic and Traditional Chinese Medicine were developed from these essential ingredients.

Complementary and Alternative Medicines (CAM) are now being used more frequently in both general medical care and in association with cancer.<sup>1–3</sup> The increasing employment of CAM is due to clinicians perceiving some value in CAM therapy as outlined in a meta-analysis by Ernst, Resch and White.<sup>3</sup> After a wide literature search aimed at retrieval of all recent surveys (1983–2004) of CAM, the search was extended beyond the common databases. The overall results were highly heterogeneous. To achieve the aim of using a uniform grading system to determine whether physicians perceive CAM as useful and/or effective, six CAM experts (medical and non-medical) assessed 12 surveys using a scale of 0% (neither useful nor effective) to 100% (optimal usefulness and effectiveness). There was significant variability between the 12 surveys. Physicians rated CAM as moderately effective,  $46 \pm 16$  on the proposed scale, with younger physicians proving more accepting than their more experienced seniors. There was no trend to endorse CAM as useful or effective and the data do not confirm whether physicians see CAM as a non-specific powerful placebo or as specifically effective. The conclusion is that CAM may be useful but is in need of randomised controlled trials (RCTs) if it is to be further embraced.

Given the increasing patient interest in CAM it is proposed that clinicians pay more attention to accruing data that will provide reliable evidence and identify approaches that will ameliorate the patients' lot rather than do harm. Governments are alert to public need and demand and some, together with their instrumentalities, are seeking a better 'fit' for CAM in an environment of conventional therapy. Maha,<sup>4</sup> in a recent exploratory and qualitative paper outlining the views of academic doctors towards CAM and its role in the United Kingdom's National Health Service, concludes that while CAM is unlikely to be incorporated on a wholesale basis into NHS practice, it could be adopted and applied more widely to 'enhance overall quality of care and even increase doctors' fulfilment in their practice'.

Clinicians are very observant and must evaluate information both observed and provided. Some CAM modalities can be involved in situations where claims made for treatments lead to demand for their assessment. In just such a situation, an NIH Consensus conference<sup>5</sup> adjudged acupuncture to be effective in managing nausea and vomiting associated with chemotherapy and in controlling pain associated with surgery.

The consensus meeting also referred to a wide range of possibilities for the use of acupuncture as well as to the wide range of difficulty in conducting evidentiary-oriented studies.<sup>5</sup>

A major difficulty in evaluating CAM relates to the lack of a unifying definition for CAM, although Sollner<sup>6</sup> derives a useful approach from outlines suggested by Eisenberg<sup>7</sup> and Ernst and Cassileth.<sup>1</sup>

A review of CAM in PubMed leads to an extensive list of interventions, very few of which apply specifically to melanoma in a clinical sense. Among the modalities available are the following:

- music
- religion
- colour therapy
- relaxation
- acupuncture
- homeopathy
- massage
- hypnosis
- systematic management (vitamins, hormones, mistletoe)
- diet.

This list, which is not in itself exhaustive, clearly outlines the task ahead to properly evaluate each declension of CAM.

## 28.1 CAM – what patients find worthwhile

A significant number of patients employ CAM initiatives while undergoing conventional care.

Downer and colleagues<sup>8</sup> aimed to assess the CAM treatments most used in cancer and the motivation for using them. The study was conducted using a postal screening questionnaire and a semi-structured interview. Six hundred (600) unselected oncology patients were approached; 415 (69%) responded; 16% had used CAM in a variety of forms (see list above), with dietary therapies, however, often causing difficulties. Of the 48 patients (74%) interviewed, 36 (75%) commenced CAM during conventional therapy, 28 derived greater hope from CAM than from conventional therapy, and 20 were attracted to the holistic, non-toxic nature of the treatments. Twelve wanted therapies allowing greater involvement with their treatment, eight said the relationship with their doctor was important, while 12 were said to be incurable in spite of conventional treatment, prompting them to turn to CAM.

Patients using CAM tended to be younger, higher social class and female. Their satisfaction with CAM other than dietary therapies was high and they found psychological benefits, including hope and optimism.<sup>8</sup>

Another study by Sollner<sup>6</sup> examined CAM correlation with psychological disturbance, coping with illness and compliance with standard treatment. The study involved 172 participants answering 205 questionnaires, an 83.9% response rate, in which 24.4% used CAM and 31.4% showed interest in CAM. Logistic regression analysis observing demographic and psychological factors as independent variables provided three useful predictors: younger age ( $p=0.004$ ), progressive cancer ( $p=0.064$ ) and active coping ( $p=0.16$ ). CAM did not involve greater psychological disturbance, decreased psychological disturbance, decreased social support, or less trust in conventional medicine. CAM can be seen as prompting coping, and avoiding passivity and feelings of hopelessness (see also Chapter 16 *Psychosocial issues* and Chapter 17 *Palliative care*).

Evidence summary	Level	References
There are clear indications that patients embrace CAM for a range of physical and emotional reasons, with many hoping for cure, many hoping for help to cope, many looking to avoid passivity, and many wishing for their treating doctors' involvement in their care	IV	1–8

Recommendation	Grade
1. Patients be encouraged to share with their treating clinician(s) their wishes to embark on either a complementary or alternative therapy	C

## 28.2 Comparing CAM and conventional therapies for melanoma

Searches resulted in one randomised control trial in which melanoma is directly addressed in a selective treatment arm. Another trial in a systematic review of mistletoe<sup>6</sup> was not further considered due to methodological limitations.

The EORTC 18871/DKG 80-1 randomised phase III adjuvant trial<sup>9</sup> addresses evaluation of the efficacy and toxicity of low-dose recombinant interferon – alpha 2b (rIFN-alpha 2b) (IMU) or recombinant interferon gamma (rIFN-gamma) (0.2mg – given subcutaneously every other day for 12 months and compared with an untreated control group.

The German Cancer Society (DKG) added a fourth arm, using Iscador M on a special schedule (p=391). This popular mistletoe product is the CAM most widely used against cancer in Eastern Europe.

The study subjects were all high-risk melanoma patients who had either stage II (thickness > 3mm) and stage III patients (positive lymph nodes) without distant metastases. They were randomised and followed to first progression or death, and were subjects of an intention to treat analysis.

From 1988–1996, 830 patients were randomised into a four-arm trial. Stage II patients were treated by primary tumour resection with a > 2cm free margin and regional lymph node metastases were resected in the manner of Karakousis.<sup>10</sup> There were 423 patients in a three-arm EORTC trial and 407 in the DKG arm. Median follow-up was 8.2 years.

The disease-free interval rate at eight years was 32.4% and overall survival 40%. The 95% confidence intervals (CIs) for rIFN-alpha 2b versus control was 1.04 (0.84, 1.30), for rIFN-gamma CI versus control was 0.96 (0.77, 1.20), and for Iscador M versus controls CI was 1.32 (0.93, 1.87). For overall survival in the three arms, the CI was 0.96 (0.76, 1.21), 0.87 (0.69, 1.10) and 1.21 (0.84, 1.75) respectively. 'No adjustment for multiple comparisons was done. The trials were stopped once the planned sample size was reached to provide sufficient power to answer the IFN-question. To assess the efficacy of Iscador, it was impossible to continue the randomisation after an eight-year recruitment period. An interim evaluation at that time showed an approximately 10% lower two-year DFI (Disease Free Interval) rate in the Iscador® arm compared with the control group.'<sup>9</sup>

There was no clinical benefit for adjuvant treatment in this study with low-dose recombinant interferon, rIFN-alpha 2b or rIFN gamma or with Iscador M in high-risk melanoma patients. The data supported but did not prove a negative effect of mistletoe extracts in melanoma patients, since the observations did not reach significance.<sup>9</sup> There was no demonstrated efficacy in reducing toxicity of conventional therapy.

A retrospective study compared 153 white adult patients, aged 25–72 years, with superficial-spreading nodular melanoma to rates in the medical literature.<sup>11</sup> The patients were treated with Gerson's diet therapy – this is a lactovegetarian, low sodium, low fat and (temporarily) protein, high potassium, fluid and nutrients (hourly raw vegetable and fruit juices). Metabolism increased by thyroid hormone administration, calorie supply was limited to 2600–3200 calories/day. Coffee enemas as needed for pain and appetite. Comparison of conventional results from literature seem favourable, the number of patients is small, retrospective and non-randomised.

Evidence summary	Level	Reference
A well-conducted randomised phase III trial yielded no benefit for adjuvant treatment with low-dose recombinant interferon rIFN-alpha 2b or rIFN gamma or with Iscador M (mistletoe) in high-risk melanoma patients. The Iscador M arm of the trial was discontinued after eight years of recruitment, as interim review revealed approximately 10% lower two year DFI when compared to control groups	II	9
The evidence accrued on Iscador M supported but did not statistically prove a negative effect on patients with melanoma		

Recommendation	Grade
2. There is no available evidence to recommend CAM over conventional therapy for adjuvant management of melanoma	C

## Key point

- There is level IV evidence suggesting patients may derive emotional benefit from CAM therapy

## 28.3 Value for money and CAM therapies

No evaluations specific to melanoma were located. MacLennan, Wilson and Taylor<sup>12</sup> reported a 1993 survey on the use of CAM by a South Australian population aged 15 or over, and using correlations with demographics and medical variables, they extrapolated modelling of the costs to the Australian population in 1993 of \$621 million and for CAM therapists \$309 million. In 1992/1993 the Australian people spent \$360 million on CAM. Users of CAM were primarily post-menopausal females, of normal weight, better educated, more likely to be employed, and having greater alcohol intake than non-users.

A question is raised as to the size of expenditure in comparison to the paucity of sound safety and efficacy available for CAM products.

A further paper by MacLennan, Myers and Taylor<sup>13</sup> surveyed a similar population in South Australia and found the extrapolated cost of CAM and CAM therapists to be \$1.8 billion, falling from \$2.3 billion in 2000.

It was reported that CAM users had lower quality of life scores and that 57.2% did not inform their doctors of their use. Most believed the drugs were tested by The Therapeutic Goods Administration (TGA), but testing for safety and efficacy is not done at this time.

Evidence summary	Level	References
While the dollar value of CAM in Australia is large, there is little or no control of either product content or the clinical competence of CAM practitioners	IV	12,13

Recommendation	Grade
3. Patients are advised to discuss planned CAM therapy with their clinician, to ensure the safety of their action	C

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## 29 Melanoma in specific populations in Australia

Melanoma<sup>i</sup> develops in both Caucasian<sup>ii</sup> and non-Caucasian populations, although the incidence in non-Caucasians is lower than in Caucasians. Melanoma in non-Caucasians often presents in acral sites and in general, melanomas in non-Caucasians have a poorer clinical outcome. This, together with the growing proportion of non-Caucasians in the Australian population, highlights the need for awareness of melanoma in non-Caucasian groups.

### 29.1 Melanoma in non-Caucasians

#### 29.1.1 Incidence data: non-Caucasians (non-Indigenous)

World wide, the incidence of melanoma in non-Caucasians is lower than in Caucasians.

Selected figures from Asia reveal very low melanoma incidence rates (per 100,000):<sup>1</sup>

- Japan: 0.3–0.7 (male) and 0.3–0.5 (female)
- Hong Kong Chinese: 0.7 (male) and 0.6 (female)
- Philippines: 0.8 (male) and 0.6 (female)
- India: 0.4 (male) and 0.3 (female)
- Singapore: 0.5 (male Chinese), 0.3 (male Malay), 0.5 (female Chinese), 0.8 (female Malay).

In Australia, approximately 16% of the population identified their ancestry as non-Caucasian.<sup>2</sup> This percentage continues to increase due to trends in Australian immigration: the greatest change in migrant influx in the past 10 years has been the increased numbers from Southern and Central Asia as well as sub-Saharan Africa.<sup>3</sup>

This highlights the need for awareness and for strategies for the surveillance and management of melanoma in non-Caucasians.

Ethnic origin is a **major** factor in determining the risk of melanoma: the incidence of melanoma in various ethnic groups in the same region differs markedly from group to group.<sup>4</sup>

In Australia, the incidence of melanoma is considerably lower in non-Caucasian groups compared to the Australian-born population. Numerous studies have confirmed this for Asian and Middle Eastern migrants.<sup>5–8</sup>

Melanoma constituted about 8% of all registered cancers in the Australian-born during the period 1972–1990 in New South Wales (NSW), but accounted for less than 2% in most of the immigrant groups.<sup>5–7</sup>

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i The term melanoma in this chapter relates to cutaneous melanoma only.

ii The term 'Caucasian' generally denotes people of European descent with type I or type II coloured skin (i.e. Anglo-Saxon or Anglo-Celtic).

### 29.1.2 Incidence data: Indigenous communities in Australasia

#### Aboriginal data

There is a paucity of data relating to the incidence and key features of melanoma in Aboriginal communities in Australia. This is multifactorial:

1. there is often incomplete identification of Indigenous people
2. there is probable under-notification of cases in most cancer registries
3. the available data are from a relatively short period only
4. the Aboriginal population is a minority group<sup>iii</sup> and melanoma in Aboriginals is uncommon.

The available data reveal a low incidence of melanoma for Aboriginals in the Northern Territory: 5.6 (male) and 1.4 (female) per 100,000.<sup>iv,9</sup> A similarly low incidence was found in NSW: 2.3 (male) and 2.1 (female) per 100,000.<sup>10,11</sup> Melanoma comprised only 3% of all Indigenous cancer cases compared to 10% for the non-Indigenous population in NSW.

### 29.1.3 Non-Caucasian melanoma: distinguishing features

Non-Caucasians have a high proportion of melanomas in 'sun protected' skin regions. These include palms, subungual areas and in particular, soles.<sup>4,12–15</sup>

In the Japanese<sup>13</sup> and Hong Kong Chinese,<sup>16</sup> the commonest site for melanoma is the sole of the foot.

Non-Caucasian groups generally present with more advanced, thicker tumours at diagnosis and thus have a poorer prognosis. This is reflected in a higher overall mortality<sup>4,12,17</sup> which may be due to a low index of suspicion in relation to non-Caucasian melanoma and the fact that the more prevalent non-Caucasian sites such as the soles are not routinely included in mole checks.

World-wide, non-Caucasians have a much higher incidence of acral lentiginous melanoma (African American 60–72%; Asian 29–49%; Hispanic 20–34%, compared to Caucasians 2–8%)<sup>18</sup> in contrast with the superficial spreading melanoma subtype seen in two thirds of Caucasian melanomas.<sup>19</sup>

The incidence of non-Caucasian melanoma increases with advancing age.<sup>20</sup>

### 29.1.4 Conclusion

Melanoma does occur in non-Caucasians, even though it is a relatively uncommon cancer in these groups. In Australia, with the growing proportion of non-Caucasians in our population, both migrant and Australian-born, and the 'westernisation' of their life-styles, the issue of non-Caucasian melanoma is one of increasing significance.

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iii Population in 2001 estimated nationally at 460,000 (2.4% of the total population).

iv Note: there was only a small number of documented cases (< 10), hence the actual incidence values need to be interpreted with caution.

## 29.2 Good practice point

- When examining melanocytic lesions in non-Caucasians, it is important to keep in mind the possibility of melanoma. Furthermore, the skin areas examined should include the palms, periungual and subungual skin and especially the soles of the feet

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# 30 Melanoma in Māori and melanoma in Pacific peoples in New Zealand\*

## 30.1 Melanoma in Māori

### 30.1.1 Epidemiology

Melanoma is not a common cancer in Māori, with a total of 163 new cases of melanoma in Māori registered between 1995 and 2006.<sup>1</sup> In 2004 there were five new registrations and four deaths from melanoma in Māori men and 12 new registrations and two deaths in Māori women.<sup>2</sup> Although Māori have a very low registration rate of melanoma compared to the New Zealand population as a whole, they have a greater than expected number of cases with thicker lesions and more extensive disease at diagnosis.<sup>1</sup> Furthermore, although there are few melanoma diagnosed in Māori, there is a suggestion of poorer relative survival compared with non-Māori. The distribution of melanoma by body site is similar in Māori to the pattern seen in the New Zealand population overall, with the trunk and the leg the most common sites.

Factors that confer a higher individual risk for melanoma are detailed in Chapter 3.

### 30.1.2 Māori health: guiding principles

The principles of partnership, participation and protection are the basis of the special relationship between iwi and the Crown under the Treaty of Waitangi<sup>3</sup> and encourage working with iwi, hapū, whānau and Māori communities to develop appropriate services for Māori, and respect for Māori cultural concepts, values and practices within service provision.

### 30.1.3 Health perspectives

Māori comprise approximately 15% of the total New Zealand population<sup>4</sup> and are also a significant minority population in Australia. Although many Māori share cultural norms and distinct views of health, Māori are not a homogeneous group. Routine questioning about ethnic background offers an opportunity for the health practitioner to discuss individual cultural preferences.<sup>5</sup> Accurate and consistent gathering of ethnicity data is also important for service planning and evaluation, and should follow current protocols prepared for the health and disability sector by the Ministry of Health.<sup>6</sup>

Traditionally, Māori have a more holistic view of health than the general population. Māori traditional belief systems, such as views about reliance on the whānau (family), individual mana, death and dying, and practices associated with tapu/noa, continue to influence health behaviour and health preferences for many Māori.<sup>5</sup> Biopsies and other tissue sampling or surgery may raise particular issues for some Māori and preferred arrangements for final disposal of the material should be discussed.<sup>7</sup>

### 30.1.4 Access to cancer care services

Accurate information on Māori utilisation of cancer health care services is limited by poor gathering of ethnicity data.<sup>8</sup> Information on access to cancer care services from the point of view of Māori with cancer and their whānau is currently limited. This is an important information gap<sup>9</sup> and the focus of several current research initiatives.<sup>10</sup>

Barriers to health care access for Māori are recognised as multidimensional and as including health system and health care process factors (e.g. institutional values, workforce composition, service configuration and location), as well as patient factors (e.g. socioeconomic position, transportation, patient values).<sup>9,11</sup> Cost is a major reason given by Māori for not visiting a general practitioner when necessary.<sup>12,13</sup> Cancer care service providers have identified a lack of culturally responsive services and culturally competent health professionals as a barrier to Māori access to cancer treatment services in some areas, as well as a contributor to Māori underutilisation of palliative care services.<sup>9</sup> Māori with cancer and their whānau are reported by providers of services as having difficulty in negotiating the treatment system.<sup>9</sup> A report prepared for the Cancer Society of New Zealand, the country's major NGO provider of cancer support and rehabilitation services, also indicates reduced uptake of these services by Māori.<sup>14</sup>

### 30.1.5 Cancer care services for Māori

Available information indicates there are currently insufficient Māori-specific cancer services or service components to meet identified needs.<sup>8,9</sup> The policies or practices of mainstream cancer services often do not support a whānau-based approach to care, and physical facilities are often also inadequate for whānau participation.<sup>9</sup>

A recent review of community cancer care services in the Auckland area by Māori identified the need for a comprehensive kaupapa Māori community cancer service and for a whānau ora approach throughout cancer care.<sup>8</sup> Recommendations for existing cancer services included employing Māori staff (e.g. kaitiaki), including whānau throughout the cancer journey and meeting their needs for information and support. Appropriate delivery of information was also highlighted, with focus groups and key informant interviews identifying the preference for information to be presented 'straight up', in familiar surroundings, and with the support of kaitiaki wherever possible.

## 30.2 Good practice points

- Accurate ethnicity data be collected by all service providers
- Māori-specific cancer services or service components be provided where possible
- Health practitioners and others providing cancer care receive training and support in culturally competent, patient-centred care
- Health practitioners consult Māori patients about final disposal of tissue or body parts surgically removed

### 30.3 Melanoma in Pacific peoples in New Zealand

#### 30.3.1 Epidemiology

The term 'Pacific peoples' describes a diverse group of New Zealand-born individuals and migrants from South Pacific nations who identify with one or more of the Pacific Islands because of ancestry or heritage.

Melanoma is uncommon in Pacific peoples living in New Zealand, with only 39 cases of melanoma registered in this group between 1995 and 2006.<sup>1</sup> In 2004, four Pacific people were registered with melanoma and one died of the disease.<sup>2</sup> As with Māori, Pacific peoples have a greater than expected number of cases with thicker lesions and more extensive disease at diagnosis.<sup>1</sup> Pacific peoples also have a much higher proportion of acral lentiginous melanomas than other New Zealanders.<sup>1</sup> Acral lentiginous melanomas tend to occur on the soles of the feet, palms of the hand and under the nails in darker skinned people.

#### 30.3.2 Health perspectives

Traditionally, Pacific cultures are oriented towards the social group and concepts of health are holistic.<sup>15</sup> Some Pacific peoples use traditional methods of healing as well as Western medicine.<sup>16,17</sup> Christianity is a large part of many Pacific cultures and may influence health behaviour.<sup>15</sup> Although there are commonalities, each Pacific nation has its own particular cultural beliefs, customs, values and traditions.<sup>18</sup> Routine questioning about ethnic background offers the health practitioner an opportunity to discuss individual cultural preferences in relation to health care in addition to gathering appropriate ethnicity data.<sup>6</sup>

#### 30.3.3 Access to cancer care

Only limited information is available on Pacific peoples' access to cancer care and there is a need for better collection of ethnicity data by service providers.<sup>16</sup> Fono (meetings) held to discuss a cancer control strategy for New Zealand identified health professionals' lack of cultural competence as a barrier to early detection, diagnosis and treatment of cancer.<sup>16</sup> Fono also highlighted specific barriers to access to palliative care, including that the hospice setting was seen as a 'foreign' environment where visits by the extended family could be difficult.<sup>19</sup> Pacific families often chose to provide care for their dying family members at home and reported difficulty in accessing appropriate community-based information and support on issues such as medication use. Attitudes of health providers, including primary care, were often seen as unhelpful in this context.<sup>19</sup>

Pacific peoples are known to experience significant barriers to access both to and through the health system. They are more likely than other New Zealanders not to have seen a doctor even though they perceived a need to do so.<sup>20</sup> Barriers to accessing health care are often cost related<sup>21,22</sup> and include the location of services.<sup>22</sup> Other barriers include the lack of culturally appropriate services and the attitudes of health care workers.<sup>22</sup> Language is a barrier for some, in accessing both information about relevant services and information during their interactions with a health service.<sup>23</sup> Doctors responding to the National Primary Care Medical Survey rated 22% of Pacific patients attending primary care as not fluent in English.<sup>24</sup> Pacific peoples surveyed have indicated that the language used in health care interactions can pose a particular difficulty.<sup>23,25</sup>

### 30.3.4 Cancer care services for Pacific peoples

Further research on Pacific peoples' experience of and preferences for cancer care is needed. Participants attending fono on a cancer control strategy for New Zealand indicated a desire for more information on cancer prevention, and for their communities to have greater involvement in service development and delivery.<sup>16</sup> The need for information to be made available in all the main Pacific languages was also highlighted.

## 30.4 Good practice points

- Accurate ethnicity data be collected by all service providers
- Health practitioners and others providing cancer care receive training and support in culturally competent, patient-centred care

\* Dr Peter Jansen is a director of Mauri Ora Associates, a training and health research consultancy that has a focus on priority populations.

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# Appendices

- 1: Medico-legal considerations
- 2: Guideline development process
- 3: Working party membership and contributors to guidelines and public consultation submissions received
- 4: Dermoscopy versus naked eye examination for the diagnosis of melanoma
- 5: Recommended terminology and synonyms for cutaneous melanoma
- 6: New Zealand palliative care definition

# Appendix 1:

## Medico-legal considerations

### A1.1 Australia

While clinical management of melanoma is a major component of clinical care (see Introduction page xiii), it is the source of few medico-legal matters. This reflects well on the general clinical management of melanoma.

Figures obtained from a major medical defence organisation reveal that over a fifteen-year period (1990–2005) there were 47 civil and unlitigated claims. The majority of claims arose from failure to diagnose melanoma, particularly in cases which were brought to the clinician's attention (see Table A1).

The guidelines have evaluated evidence in chapters that outline diagnosis, including appropriate investigations and biopsy. There are also chapters on the individual forms of cutaneous melanoma, psychosocial aspects of the disease, and palliative care.

Paying attention to the evidence in these chapters when making decisions about the appropriate care program to follow should ensure optimal care and outcome. This approach should assist in meeting the highest level of medico-legal requirements.

Should a question arise that may lead to a legal claim, it is well to remember that apart from consideration of guidelines, appropriate professionalism reassures patients and should ensure appropriate information for patients through observing the following:

- courtesy
- discussing the program of investigation

**Table A1** Claims – National Medical Defence Organisation (1990–2005)\*

Reason for claim	Surgeons (8) <sup>†</sup>	Dermatologists (2)	GPs (44)
Total number of claims	7	2	38 <sup>‡</sup>
Failure to diagnose patient observed melanoma (delayed or missed)	3	1	32
Incorrect pathology report	2	1	5
Problems in surgical technique and treatment	2		3
Failure to inform patient of diagnosis			2
Failure to obtain pathology report			1
Delay in referral for definitive specialist treatment			1

\* 47 claims – 32 litigated civil claims, 15 unlitigated matters

<sup>†</sup> No claims 2000–2005

<sup>‡</sup> Six general practitioners involved in one claim

- discussing diagnosis and options of care
- clear communication
- compassion
- understanding
- skilful care.

Should there be any mishaps in care, the initial response by the clinician to a patient question should involve the process of open disclosure, which is clearly delineated in the National Open Disclosure Standard.<sup>1</sup>

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## Reference

1. National Open Disclosure Standard. Office of the Safety and Quality Council, Canberra website: [www.safetyandquality.org](http://www.safetyandquality.org)

## A1.2 New Zealand\*

New Zealand has a unique medico-legal system. Of particular note is that, as a general rule, patients in New Zealand cannot sue for treatment injuries (including delayed or missed diagnosis). Assistance is available from the New Zealand Accident Compensation Corporation for patients who are injured as a result of being treated by a registered health professional. Details of this assistance and the claim process are available at [www.acc.co.nz](http://www.acc.co.nz)

Accountability for negligence by medical professionals is achieved through the Health and Disability Commissioner process and through professional registration authorities under the Health Practitioners Competence Assurance Act 2003. The Health Practitioners Competence Assurance Act 2003 provides mechanisms for the registration, assessment and discipline of all registered health practitioners in New Zealand. All complaints about patient care are handled in the first instance by the Health and Disability Commissioner.

Clinicians' legal duties are set out in the Code of Health and Disability Services Consumers' Rights (available at [www.hdc.org.nz](http://www.hdc.org.nz)). The duties of particular relevance in the context of melanoma treatment are that services must be provided with reasonable care and skill, and comply with legal, professional, ethical and other relevant standards. Patients must be given all information that a reasonable patient, in his or her circumstances, would expect to receive. Clinicians need to communicate effectively with patients, in a form, language and manner that enables the consumer to understand the information provided. The Code also requires that clinicians openly disclose any unintended harm that occurs during treatment.

\* Prepared in consultation with the Office of the Health and Disability Commissioner, New Zealand.

## Appendix 2:

# Guideline development process

In 2005, the Australian Cancer Network (ACN) agreed to facilitate a revision of the 1999 *National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines for the Management of Melanoma* based upon advice from melanoma experts across Australia.

A multidisciplinary group comprising clinical experts, a consumer representative and an epidemiologist was convened to develop the guidelines. This group became known as the Guidelines Working Party. Experts from within or outside the Working Party were nominated to become chapter leaders or members of a chapter group. Further experts were added to the Working Party to lead a chapter group when additional topics were proposed at subsequent meetings. Members of the New Zealand Melanoma Reference Group also joined the Working party in 2006 and New Zealand melanoma experts were added as members of chapter groups.

In early Working Party meetings, it became apparent that the guideline development processes required by the NHMRC for national guidelines had changed somewhat since the last set of guidelines were developed. The processes had become much more scientifically rigorous and involved substantially more documentation of the development processes. In addition, several new questions were posed by clinicians in the Working Party that had not been addressed in the 1999 guidelines. In response, the Working Party decided to develop a new set of melanoma clinical practice guidelines incorporating the newer more rigorous processes and including additional topics, rather than just updating the previous guidelines.

The Australian Cancer Network (ACN) received a grant from the Cancer Institute NSW to assist in the development of the guidelines. The grant made it possible for the ACN to contract a consultancy group, the Sydney Health Projects Group at the University of Sydney, to assist in the development of project methods and to complete the searches for each chapter of the guidelines. Further assistance in the development of the guidelines was provided by staff of the NSW Melanoma Network and the New Zealand Guidelines Group. The whole process was monitored and assisted by a representative of the NHMRC Guidelines Assessment Register (GAR).

A brief overview of the methods undertaken to complete the melanoma guidelines is outlined in the next few pages. Further details of guideline development methods including the specific questions posed, search strategies, inclusion and exclusion criteria and literature appraisal templates for individual chapters are available on request from the Australian Cancer Network or the New Zealand Guidelines Group ([www.nzgg.org.nz](http://www.nzgg.org.nz)).

## A2.1 Development of methods handbook

A large number of publications have been produced by NHMRC on the development of guidelines.<sup>1–8</sup> These can be accessed at [www.nhmrc.gov.au/publications](http://www.nhmrc.gov.au/publications). The methods consultants recommended development of a summary handbook for the chapter leaders and their expert working groups to outline the major steps and expectations for the development process.<sup>9</sup> The handbook provides the definitions and protocols for developing research questions and search strategies, conducting searches and critical appraisal, summarising and assessing the relevant literature, and finally formulating the recommendations. The series of checklists and templates within the handbook were created to satisfy NHMRC legislative requirements and designated standards of quality and process. Copies of the handbook are available on request from the Australian Cancer Network or the New Zealand Guidelines Group ([www.nzgg.org.nz](http://www.nzgg.org.nz)).

## A2.2 Steps in the preparation of NHMRC clinical practice guidelines

All the chapter leaders and their expert working group went through the following steps to complete their recommendations. They received considerable assistance for the first four steps of this process from methods consultants, but the great majority of leaders completed their own critical appraisal and assessment of the body of evidence.

1. Structure the research question
2. Develop a search strategy
3. Search the literature
4. Select and sort the literature
5. Critically appraise and summarise each selected article
6. Assess the body of evidence and formulate recommendations

### A2.2.1 Structure the research question

All chapter leaders and their expert working group were asked to contribute key questions to be researched for this set of guidelines. Over 230 questions were submitted to the Working Party for consideration. The Working Party prioritised the questions for systematic review and decided upon a final list of about 70 questions.

All chapter leaders were asked to specify the purpose, scope and target audience for their questions and structure their question according to the PICO (populations, interventions, comparisons, outcomes) formula. Typically, chapter leaders achieved this and specification of a search strategy (see A2.2.2 below) during a 30–60 minute meeting with a methods consultant.

### A2.2.2 Develop a search strategy

A search strategy based on the PICO was developed for each research question. A generic search strategy for ‘melanoma’ was used by most chapter groups, and additional limits were imposed with regard to patients, interventions, comparisons, outcomes or other relevant aspects. Keywords were devised for each search following

discussion with the chapter leader(s) during the PICO process. Additional sources for keywords and MeSH or subject terms were determined by searching other relevant evidence-based clinical guidelines, systematic review articles, and literature pertaining to each question. These terms were then combined into a single systematic search strategy applied to all included electronic databases. For quality control, keywords, MeSH or subject terms, and searches were checked by other members in the chapter group, the University of Sydney's medical librarian, and an NHMRC representative.

### A2.2.3 Search the literature

NHMRC specifies that clinical practice guidelines be based on systematic identification and synthesis of the best available scientific evidence.<sup>1</sup> Literature searching was conducted systematically using electronic databases concluding mid-2006 to early-2007, such as:

- **Medline:** bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information, biomedicine, including the allied health fields, biological and physical sciences<sup>10</sup> <http://www.library.usyd.edu.au/databases/info/medline1.html>
- **EMBASE:** major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries<sup>10</sup>
- **PubMed:** database of bibliographic information, drawn primarily from MEDLINE and PreMEDLINE. In addition, for participating journals indexed 'selectively' for MEDLINE, PubMed includes all articles from that journal, not just those included in Medline<sup>10</sup>
- **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, behavioural sciences, management, and education<sup>10</sup>
- **Cochrane Library:** regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews<sup>10</sup>
- **AUSThealth:** contains nine databases, including the Australasian Medical Index, Australia's leading medical information resources, and DRUG, produced by the Alcohol and other Drugs Council of Australia – Australia's leading organisation representing the interests of the alcohol and other drugs field<sup>11</sup>
- **Clinical Evidence:** compendium of evidence on the effects of clinical interventions updated every six months published by the BMJ Publishing Group<sup>10</sup>
- **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.<sup>10</sup> Source material comes from a wide range of languages.

Search histories were dated, documented and are available on request from the Australian Cancer Network or the New Zealand Guidelines Group ([www.nzgg.org.nz](http://www.nzgg.org.nz)). The chapter leaders and the methods consultants were asked to provide details on the following:

- electronic databases searched
- terms used to search the databases
- search inclusion/exclusion criteria



- dates the search included
- abbreviations
- methods used to assess the quality of the search
- language
- study type.

In addition, chapter leaders and their expert groups were asked to hand search the reference lists at the end of their relevant articles to identify additional articles not identified through searches of the electronic databases. Finally, bi-annual meetings of the guidelines Working Party provided a forum for discussion and sharing of overlapping evidence, and/or discovery of unpublished literature and information from other key organisations.

#### **A2.2.4 Select and sort the literature**

The literature generated by the electronic database searches was appraised for relevance to each question. The following steps were taken to select and sort the literature:

1. review titles from the search
2. review abstracts
3. where uncertain about relevance, download full text of article
4. identify articles answering the questions and those useful for background information
5. obtain articles from the Internet, library or interlibrary loans
6. sort studies by type (e.g. interventions, prognosis, diagnosis)
7. sort studies by design (e.g. systematic review, randomised controlled trial, cohort, case control, case series, descriptive)
8. determine whether systematic reviews account for all preceding literature
9. prepare folders to file searches, background papers and reviewed articles for each question addressed
10. enter selected articles for review into the guideline master list
11. assess the quality of the search and the appraisal.

All articles emerging from this process as potentially relevant to a guidelines question were forwarded to the chapter leader for his/her consideration and for critical appraisal.

#### **A2.2.5 Critical appraisal and summary**

Relevant articles selected from the search were reviewed and summarised by the chapter leader. Each article was summarised in a template with headings such as the type of study, level of evidence, number and characteristics of patients, type of analysis, outcome measure and results. Each article was then critically appraised with respect to level of evidence, quality of evidence, size of the effect and relevance of the study, and documented in another template.

Details on the templates, rating systems, and criteria for the critical appraisal process, are outlined in the methods handbook<sup>9</sup> available on request from the Australian Cancer Network or the New Zealand Guidelines Group ([www.nzgg.org.nz](http://www.nzgg.org.nz)).

Levels of evidence<sup>1</sup>

Table A2		Designations of levels of evidence according to type of research question			
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 clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>• non-randomised, experimental trial</li> <li>• cohort study</li> <li>• case-control study</li> <li>• interrupted time series with a control group</li> </ul>	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: <ul style="list-style-type: none"> <li>• non-randomised, experimental trial</li> <li>• cohort study</li> <li>• case-control study</li> </ul>
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>• historical control study</li> <li>• two or more single arm study</li> <li>• interrupted time series without a parallel control group</li> </ul>	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>• historical control study</li> <li>• two or more single arm study</li> </ul>
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
<b>Note:</b> Explanatory notes for this table are outlined in the methods handbook <sup>9</sup> available on request from the Australian Cancer Network or the New Zealand Guidelines Group.					

### A2.2.6 Assess the body of evidence and formulate recommendations

The body of literature was assessed by each chapter leader with respect to the volume of the evidence, its consistency, clinical impact, generalisability and applicability. These aspects were graded and documented in a template.

Following grading of the body of evidence, chapter leaders were asked to formulate a recommendation that related to the summarised body of evidence. This recommendation also had to be graded as follows:

Grading of recommendations	
Grade	Description
<b>A</b>	Body of evidence can be trusted to guide practice
<b>B</b>	Body of evidence can be trusted to guide practice in most situations
<b>C</b>	Body of evidence provides some support for recommendation(s) but care should be taken in its application <sup>1</sup>
<b>D</b>	Body of evidence is weak and recommendation must be applied with caution

### A2.3 Writing the chapter

All the chapter leaders and their groups were asked to write their guidelines chapter using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references
- recommendation(s) and its grade
- references.

### A2.4 Review of the chapters

The body of evidence and recommendations for each chapter were reviewed by the Working Party and final recommendations agreed by consensus.

### A2.5 Public consultation

A complete draft of the guidelines was sent out for public consultation in Australia and New Zealand in October 2007. In Australia, the consultation process included soliciting public review of the document through advertisements in a range of newspapers. In New Zealand, the draft guideline was widely circulated to all individuals and organisations identified by the New Zealand Melanoma Reference Group as having a potential interest in the document. A large conference meeting was also organised for clinicians and other interested parties in February 2008 to outline the major recommendations in the guideline and to provide a forum for further discussion and debate.

All feedback received on the draft during the consultation period in Australia and New Zealand and from the conference meeting was reviewed by the Working Party and subsequent changes to the draft agreed by consensus.

## A2.6 Dissemination and implementation

The Australian Cancer Network will lead in disseminating the guidelines in Australia and the New Zealand Guidelines Group will oversee the dissemination and implementation of the guidelines in New Zealand on behalf of the Ministry of Health. In both countries this will include a campaign to raise awareness of the new guidelines, with organised media coverage through multiple outlets and an official launch. Widespread dissemination will be achieved through distribution to relevant professional and other interested groups directly and through meetings, conferences, and other CME events. A significant effort will be undertaken to have the Guidelines be introduced to senior undergraduate medical students and to encourage the relevant learned Colleges, which are bi-national (surgeons, radiation oncologists and pathologists), to support the Guidelines and to foster integration of the Guidelines into hospital and community practice through resident and registrar educational activity.

The scope of implementation activities will depend on funding available. 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 guideline recommendations. Implementation of the guideline will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer assisted decision aids and electronic decision support systems, and the creation of audit and other clinical tools.

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# Appendix 3:

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

### Management of Melanoma Guidelines Working Party

**Professor John Thompson (Chair)**  
Surgical Oncologist – Sydney

**Professor Bruce Armstrong**  
Epidemiologist – Sydney

**Dr Andrew Barbour**  
Surgeon – Brisbane

**Professor Ross Barnetson**  
Dermatologist – Sydney

**Ms Heather Beanland**  
Consumer – Melbourne

**Dr Trevor Beer**  
Histopathologist – Perth

**Dr Mary Brooksbank**  
Palliative care physician – Adelaide

**A/Professor Bryan Burmeister**  
Radiation Oncologist – Brisbane

**A/Professor Phyllis Butow**  
Psychologist – Sydney

**Dr Katherine Clark**  
Palliative care specialist – Sydney

**Dr Max Conway**  
Ophthalmologist – Sydney

**A/Professor Brendon Coventry**  
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Public consultation October 2007

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# Appendix 4:

## Dermoscopy versus naked eye examination for the diagnosis of melanoma

### A systematic review of statistical methods and results

See Chapter 5 *Clinical diagnosis* for the evidence developed in the chapter.

This extract is from a systematic review undertaken on dermoscopy compared with naked eye examination for melanoma diagnosis. The systematic review has subsequently been published: Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *Br J Dermatol*. 2008 Sep;159(3):669-76.

#### Inclusion criteria

The included level 2 diagnostic studies were those comparing diagnostic accuracy (sensitivity and specificity) of clinical examination with and without dermoscopy compared independent to a valid reference test (histopathologically diagnosis or diagnosis made by an expert in the field) on consecutive patients with a defined clinical presentation. All studies examined sensitivity and specificity for the diagnosis of melanoma except the randomised trial by Argenziano et al. which used as its end point all suspicious lesions identified by an expert. For this reason the meta-analysis was performed with and without this study (see below).

#### Statistical methods

Since a comparison of the diagnostic performance of two tests (eye only versus dermoscopy examination) was the major focus of the analysis, attention was restricted to 'paired' studies that directly compared the two tests using either a truly paired or randomised study design. Even though heterogeneity between studies is expected in underlying test performance because of differences in patient and/or design characteristics across studies, the test comparison should not be confounded by these factors because each study acts as its own control. Hence, the primary aim of the analysis was to assess the relative performance of the tests, rather than the diagnostic performance of each test separately.

Study specific estimates of sensitivity and specificity for the two tests were displayed in forest plots. The study specific estimates of sensitivity and specificity for each test were also represented in ROC space, with the two resulting points for each study joined by a line to highlight the pair of estimates for each study. The Hierarchical Summary

ROC (HSROC) method<sup>1,2</sup> was used to estimate a summary ROC (SROC) curve for each test, and the relative accuracy of the two tests. The HSROC method provides a statistically rigorous approach because it takes appropriate account of both the within and between study variability in the estimates of sensitivity and specificity through the inclusion of random study effects that allow for heterogeneity in underlying test accuracy and test positivity rate (a proxy for test threshold) between studies. The 'pairing' of results for sensitivity (and also specificity) for the two tests within each study was also taken into account in the analysis. A more detailed technical description of the HSROC model is provided in the appendix.

Because the primary purpose of the analysis was to compare test performance, a covariate for test type (eye examination versus dermoscopy) was included in the HSROC model to test for differences in the shape of the SROC, accuracy and positivity rates of the two tests. The diagnostic odds ratio (DOR), which takes account of both sensitivity and specificity and the trade-off between them, is used as the measure of test accuracy in the model. As the DOR increases, the ability of the test to discriminate between 'diseased' and 'non-diseased' improves. Since the modelling is performed in terms of the log DOR, the comparison of the accuracy of the two tests is expressed as the relative DOR (RDOR) which is multiplicative.

The model parameters for the HSROC model were used to obtain an expected operating point (average sensitivity and specificity) for each test. The summary estimates of the DOR, sensitivity and specificity for each test will be affected by patient and study design factors of the included studies. Nevertheless, the comparison between the DOR's (i.e. the RDOR) for the two tests, and the comparison of the expected operating points of the two tests does provide a basis for assessing whether there is evidence of a difference in diagnostic performance between the tests because the analysis is restricted to 'paired' studies only.

## Results

The forest plots shown in Figure 1 provide an overview of the study specific data and estimates of sensitivity and specificity for each of the nine studies included in the analysis. As can be seen from these plots, the study size varied markedly. For eye examination, sensitivity ranged from 0.43 to 1.0 compared with 0.79 to 1.0 for dermoscopy. Two studies (Carli<sup>4</sup> and Carli<sup>6</sup>) had a sensitivity of 1.0 for both tests, however the denominators were extremely small. For the remaining seven studies, the observed sensitivity was higher for dermoscopy than for eye examination alone. Specificity ranged between 0 (Carli<sup>6</sup>) and 0.99 for eye examination, and between 0.69 and 0.99 for dermoscopy. For seven of the studies, the observed specificity for dermoscopy was higher than or equal to specificity for eye examination.

Figure 2 provides a plot of sensitivity against 1-specificity for each test and study. The paired points for each study serve to illustrate the within study differences in sensitivity and specificity for the two tests. HSROC analysis showed no evidence that the underlying shape of the SROC curve differed between the two tests, indicating

that the RDOR does not depend on threshold. The overall RDOR was statistically significant, indicating higher accuracy for dermoscopy compared with eye examination alone. The diagnostic odds ratio was estimated to be 15.6 times higher for dermoscopy than for eye examination (95% CI 2.9 to 83.7;  $P=0.016$ ). This difference in accuracy of the tests is reflected in the separation between the estimated SROC curves shown in Figure 2. Summary estimates for both sensitivity and specificity were higher for dermoscopy than for eye examination, but the difference in specificity was not statistically significant (Table 1).

Removal from the analysis of two studies which had extreme values of sensitivity based on very small numbers of cases of disease (Carli<sup>4</sup> and Carli<sup>6</sup>) and also a large difference in specificity favouring dermoscopy (Carli<sup>6</sup>), resulted in a relative diagnostic odds ratio of 9.0 (95% CI 1.5 to 54.6;  $P=0.03$ ). The summary estimates for sensitivity were 0.69 and 0.87 for eye examination and dermoscopy respectively; and the corresponding estimates for specificity were 0.88 and 0.91. Removal of these two studies reduced the difference in expected specificity between the tests but had little effect on the expected sensitivities.

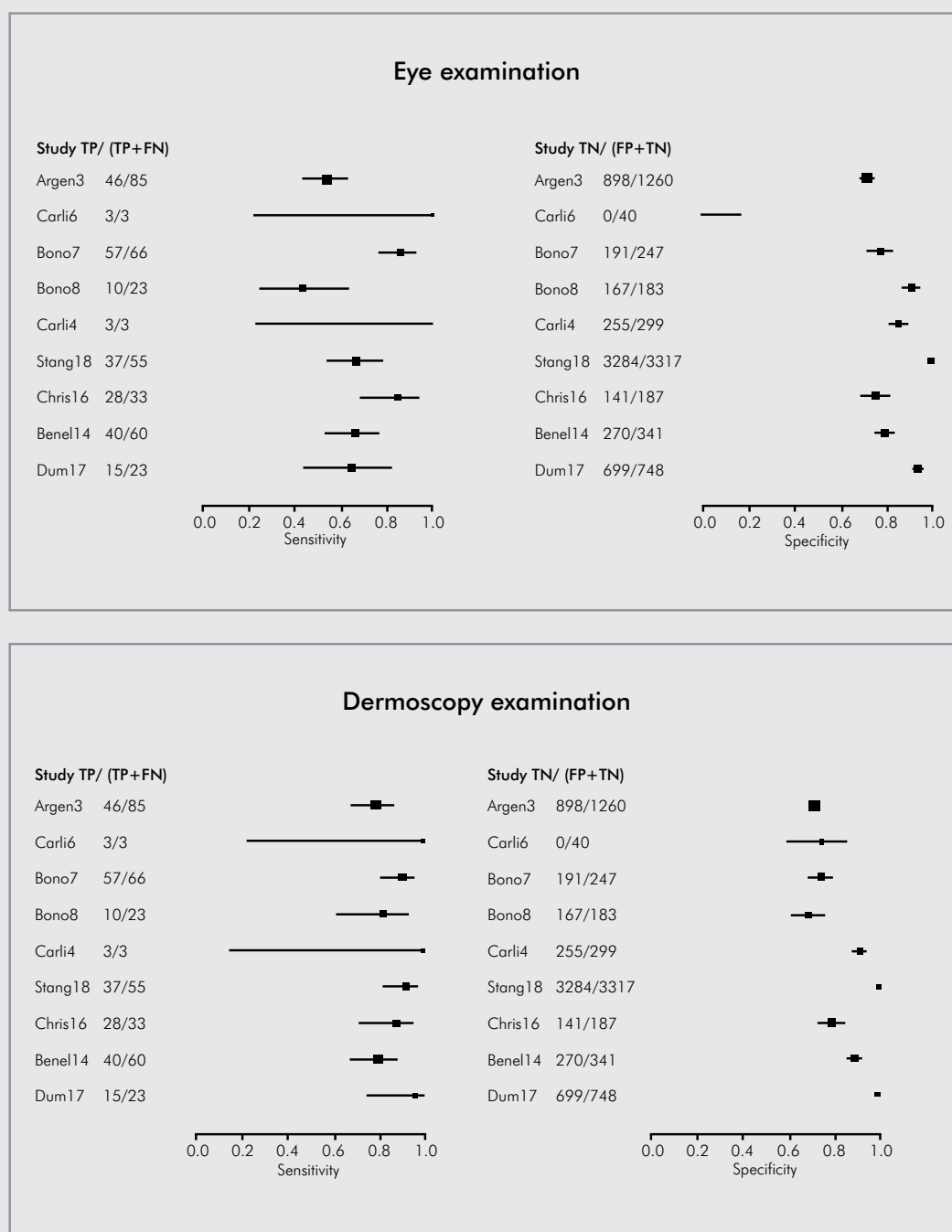
Since the randomised trial of Argenziano et al. in primary care had suspicious lesions requiring excision following expert evaluation as the endpoint, the overall HSROC analysis was repeated without this study. The omission of this study had a negligible effect on the overall model estimates.

Because estimates of sensitivity and specificity for some studies may be subject to verification bias, the positive predictive value (PPV) was also computed for each test within each study. This measure is less likely to be affected by verification bias as it computes the proportion of positive test results that are true positives. The PPV for eye examination ranged from 0.06 to 0.53 with a median of 0.36. The PPV for dermoscopy examination ranged from 0.07 to 0.81 with a median of 0.43. For seven of the nine studies, the PPV for dermoscopy was higher than the PPV for eye examination.

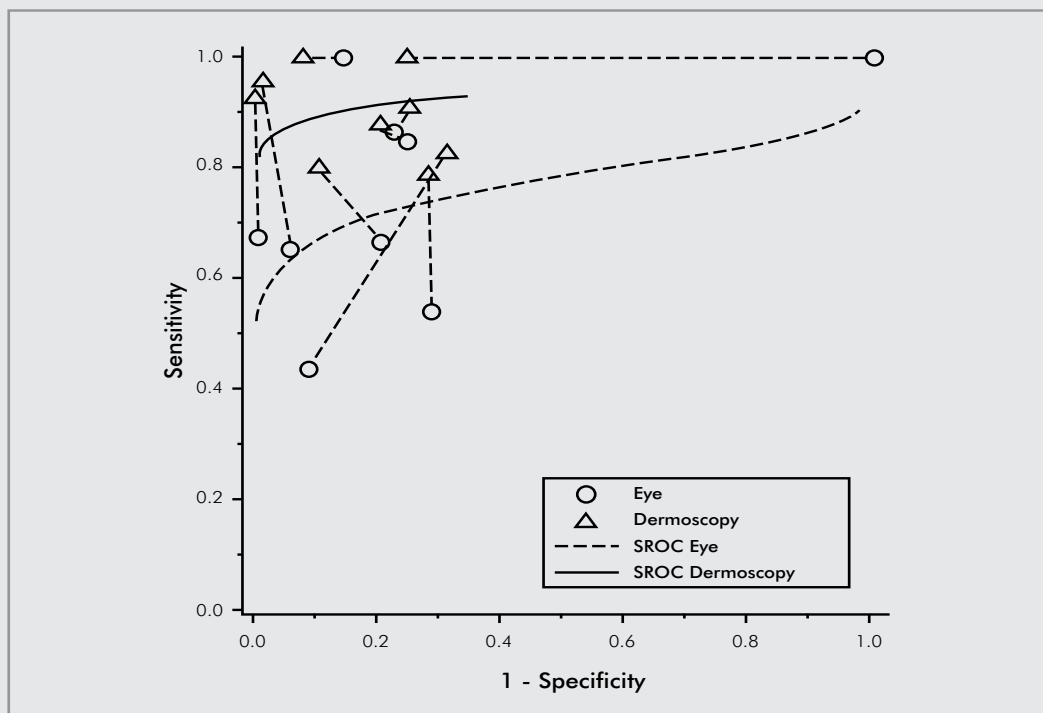
## Tables and figures

Test	Sensitivity (95% CI)	Specificity (95% CI)
Eye examination	0.71 (0.59, 0.82)	0.81 (0.48, 0.95)
Dermoscopy examination	0.90 (0.80, 0.95) $P=0.002$	0.90 (0.57, 0.98) $P=0.18$

**Table 1:** Summary estimates of sensitivity and specificity based on HSROC model



**Figure 1:** Study specific estimates of sensitivity and specificity and 95% confidence intervals



**Figure 2:** Plot of sensitivity against 1-specificity for each study and each test with the SROC for each test superimposed. (Note: The two estimates for each study are joined by a line.)

## Appendix

Heterogeneity in sensitivity and specificity across studies is common, and hence summary ROC analysis is the appropriate method of analysis for the meta-analysis of diagnostic accuracy studies. The expected trade-off between sensitivity and specificity within studies also means that separate pooling of sensitivity is not recommended. For these reasons, summary ROC analysis is the recommended method of analysis in the Cochrane draft handbook for diagnostic reviews.

The HSROC model used in this analysis takes account of the 'coupling' of sensitivity and specificity within studies as well as the within and between study variability in these measures of test accuracy. It is a more up-to-date and statistically more rigorous approach than the commonly used method of Moses et al.<sup>3</sup>

### HSROC model

The HSROC model is a two-level (multi-level) model that focuses on the estimation of a summary ROC curve. At the first level, the within study sampling error is taken into account by assuming a binomial error distribution for the sensitivity and 1-specificity for each study. Each study provides an estimate of test accuracy (log diagnostic odds ratio) and a proxy for threshold which are both taken to be random effects that follow a normal distribution at level two.



## Level 1

For each study ( $i, i = 1, \dots, k$ ) the number testing positive ( $y_{ij}$ ) for both the diseased ( $j=1$ ) and non-diseased ( $j=2$ ) groups is assumed to follow a binomial distribution  $B(\pi_{ij}, n_{ij})$ , where  $\pi_{ij}$  represents the probability of a positive test result in group  $j$ , and  $n_{ij}$  represents the number of subjects in group  $j$ ). The model takes the form  $\text{logit}(\pi_{ij}) = (0_i + \alpha_i \text{dis}_{ij}) \exp(-\beta \text{dis}_{ij})$  where  $\text{dis}_{ij}$  is coded as -0.5 for the non-diseased and 0.5 for the diseased;  $\theta_i$  are random effects for test threshold;  $\alpha_i$  are random effects for accuracy for each study; and  $\beta$  is a fixed effect for dependence between accuracy and threshold.

## Level 2

The  $\theta_i$  and  $\alpha_i$  are assumed to be normally distributed random effects, and the two distributions of random effects are assumed to be uncorrelated.

Test accuracy, threshold and the dependence between them (shape of the SROC) can be modeled as a function of study level covariates (e.g. test type) to assess whether test performance is associated with the covariate(s). The SAS procedure PROC NLMIXED can be used to identify the model that provides the best fit.<sup>2</sup> The parameter estimates of the final model are used to derive the SROC curve(s), expected operating point(s) and corresponding 95% confidence intervals.<sup>2</sup> In this analysis, the final model also included random study effects for the relative accuracy of the tests.

It is important to note that the HSROC model does not take into account the relative 'cost' of a false positive or a false negative. The purpose here is to assess the relative accuracy of the tests in terms of their ability to discriminate between 'diseased' and 'non-diseased' individuals. The results of the HSROC analysis can be used in conjunction with estimates of prevalence, costs etc to address such issues. However, this is beyond the scope of the analysis presented here.

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## Appendix 5:

### Recommended terminology and synonyms for cutaneous melanoma

Recommended terminology	Synonyms
<b>Melanoma of common type</b>	
<b>Melanoma, <i>in situ</i></b>	Lentigo maligna (Hutchinson's melanocytic freckle) Superficial spreading melanoma <i>in situ</i> Acral lentiginous melanoma <i>in situ</i>
<b>Melanoma, invasive</b>	Lentigo maligna melanoma Superficial spreading melanoma Acral lentiginous melanoma Nodular melanoma Unclassified melanoma
<b>Uncommon Variants</b>	
Desmoplastic melanoma	
<b>Others (controversial and provisional)</b>	
Malignant blue naevus (melanoma resembling or arising in a blue naevus)	
Melanoma in congenital naevus	
Minimal deviation (naevoid) melanoma	
Animal type melanoma (pigmented epithelioid melanocytoma)	
Primary dermal melanoma	

# Appendix 6:

## New Zealand palliative care definition

The following is reproduced from: Subcommittee, NZ Cancer Treatment Working Party. 26 February 2007.

### **New Zealand Palliative Care: A Working Definition**

#### **1. Preamble**

The NZ Palliative Care Strategy (2001) aims to set in place a systematic and informed approach to the provision and funding of palliative care services. Furthermore, any approach must address inequalities in palliative care. Current inequalities include access for Māori, Pacific peoples, isolated communities, children, the very old, those with non malignant disease, as well as those with special needs: asylum seekers/refugees, people in prison, and those with mental illness.

Fundamental to the strategy's success will be clarity around palliative care definitions. Definitions form the basis upon which a comprehensive, cohesive and effective palliative care service can be built and sustained. They help clarify core service components, elucidate structure, and promote understanding. They are also key components for national palliative care service specifications.

As a starting point for defining palliative care in a NZ context we have used the 2002 WHO palliative care definitions:

#### **Palliative care: World Health Organization Definition, 2002**

For Adults:

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patients' care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated

- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

For Children:

Palliative care for children represents a special, albeit closely related field to adult palliative care. WHO's definition of palliative care appropriate for children and their families is as follows (the principles also apply to other paediatric chronic disorders):

- Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease
- Health providers must evaluate and alleviate a child's physical, psychological and social distress
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited
- It can be provided in tertiary care facilities, in community health centres and even in children's homes

In applying the WHO definitions, New Zealand also needs to take into account the following:

1. The fundamental place of the Treaty of Waitangi and the principles of Partnership, Participation and Protection. In addition, we must acknowledge and include He Korowai Oranga (the Māori Health Strategy (2002)). Furthermore, acknowledgement of a holistic Māori philosophy/model, such as Te Whare Tapa Whā (four sided house) towards health/wellbeing is appropriate when applied to palliative care: Te Taha Tinana (physical health), Te Taha Hinengaro (psychological health), Te Taha Wairua (spiritual health) and Te Taha Whānau (family health).
2. Palliative care continues to evolve. Thus definitions need to be flexible enough to adapt to changes in society, disease and illness, and individual and society's expectations. Palliative care recognises and respects the rights of patients as detailed in the Code of Health and Disability Services Consumers' Rights.
3. Generalist Palliative Care will be available throughout the course of a life-limiting illness, with specialist palliative care provided on the basis of assessed need, rather than simply diagnosis or prognosis. Palliative care will also be available wherever the patient is – be that home, hospital, residential care, or hospice. Palliative care is centred on the patient and family / whānau. The level of palliative care support required for any individual, family or whānau is dynamic and varies during the course of illness (and into bereavement).

4. Palliative care services will acknowledge the diverse cultural beliefs, values and practices of patients and their families or whānau in contemporary New Zealand society.
5. Palliative care is best delivered through an integrated approach to care that recognises the roles and responsibilities of both palliative care generalists and specialists, in meeting palliative care need. This integrated model or framework of care delivery is essential for effective palliative care provision.
6. The patient's primary care team will continue to provide continuity of care through illness. Depending on need, the involvement of specialist palliative care may be episodic or continuous.
7. In the case of children and young people, palliative care will also be available on the basis of assessed need. Specialist palliative care will be provided in collaboration with formally trained or experienced paediatric healthcare professionals either community (eg GP, district nurse) or hospital based. In New Zealand, home is the preferred and usual location for palliative care for children and young people. It is recognised, however, that some children and young people spend long periods of time in tertiary hospitals far from the primary care team.

## 2. In detail

**Generalist palliative care is palliative care provided for those affected by life-limiting illness as an integral part of standard clinical practice by any healthcare professional who is not part of a specialist palliative care team. It is provided in the community by general practice teams, Māori health providers, allied health teams, district nurses, and residential care staff etc. It is provided in hospitals by general ward staff, as well as disease specific teams – for instance oncology, respiratory, renal and cardiac teams.**

Some of the generalist providers, e.g. general practice teams, will have ongoing contact with a family throughout and following illness. Others, such as district nurses or ward nurses will have episodic contact, depending on the needs of the patient and family.

Providers of generalist palliative care will have defined links with (a) specialist palliative care team(s) for the purposes of support and advice or in order to refer patients with complex needs. They will also have access to palliative care education to support their practice.

**Specialist palliative care is palliative care provided by those who have undergone specific training and/or accreditation in palliative care/medicine, working in the context of an expert interdisciplinary team of palliative care health professionals.**

Specialist palliative care may be provided by hospice or hospital based palliative care services where patients have access to at least medical and nursing palliative care specialists.

Specialist palliative care will be provided through accredited services (or organisations) that work exclusively in palliative care and meet specific palliative care standards as they are developed nationally. Specialist palliative care practice builds on the palliative

care provided by generalist providers and reflects a higher level of expertise in complex symptom management, psychosocial support, grief and bereavement. Specialist palliative care provision works in two ways:

1. Directly – to provide direct management and support of patients and families/whānau where more complex palliative care need exceeds the resources of the generalist provider. Specialist palliative care involvement with any patient and the family/whānau can be continuous or episodic depending on the changing need.

Complex need in this context is defined as a level of need that exceeds the resources of the generalist team – this may be in any of the domains of care – physical, psychological, spiritual, etc.

2. Indirectly – to provide advice, support, education and training of other health professionals and volunteers to support the generalist provision of palliative care provision.

### **Generalist/Specialist Integration**

**Generalist and specialist services need to be part of an integrated framework of care provision which may be facilitated through local and regional networks, with defined formal linkages to key services including community primary care, local acute hospitals, regional cancer centres, and other regional palliative providers.**

- Depending on the complexity of palliative care need, smaller specialist palliative care services will at times require input from a more comprehensive service with greater specialist resources which may be geographically distant. This must be readily available through defined linkages and processes.

**Therefore, the New Zealand definition of Palliative Care is:**

**Care for people of all ages with a life-limiting illness which aims to:**

1. **optimise an individual's quality of life until death by addressing the person's physical, psychosocial, spiritual and cultural needs.**
2. **support the individual's family, whānau, and other caregivers where needed, through the illness and after death.**

**Palliative care is provided according to an individual's need, and may be suitable whether death is days, weeks, months or occasionally even years away. It may be suitable sometimes when treatments are being given aimed at improving quantity of life.**

**It should be available wherever the person may be.**

**It should be provided by all health care professionals, supported where necessary, by specialist palliative care services.**

**Palliative care should be provided in such a way as to meet the unique needs of individuals from particular communities or groups. These include Māori, children and young people, immigrants, refugees, and those in isolated communities.**





# Abbreviations and glossary

## Abbreviations

<b>AJCC</b>	American Joint Commission on Cancer	<b>GP</b>	General practitioner
<b>ALM</b>	Acral lentiginous melanoma	<b>HPF</b>	High power field
<b>AMR</b>	Amrubicin	<b>HRT</b>	Hormone replacement therapy
<b>APR</b>	Abdomino perineal resection	<b>IARC</b>	International Agency for Research on Cancer
<b>ARM</b>	Anorectal melanoma	<b>ILI</b>	Isolated limb infusion
<b>ATBC</b>	Alpha-tocopherol beta carotene	<b>ILP</b>	Isolated limb perfusion
<b>BAPS</b>	British Association of Paediatric Surgeons	<b>KM</b>	Kaplan Meier
<b>BSC</b>	Best supportive care	<b>LD</b>	Limited disease
<b>BSI</b>	Brief symptom inventory	<b>LDH</b>	Lactate dehydrogenase
<b>Bx</b>	Biopsy	<b>LM</b>	Lentigo maligna
<b>CAM</b>	Complementary and alternative medicine	<b>LMM</b>	Lentigo maligna melanoma
<b>CBT</b>	Cognitive behavioural therapy	<b>LYS</b>	Life-year saved
<b>CD4</b>	Co-receptor for T cell receptor	<b>M</b>	Metastases
<b>CD8</b>	Co-receptor for T cell receptor	<b>MDC</b>	Multidisciplinary care
<b>CHART</b>	Continuous hyper-fractionated accelerated radiotherapy	<b>MDT</b>	Multidisciplinary team
<b>CI</b>	Confidence interval	<b>MM</b>	Melanoma
<b>CM</b>	Cutaneous melanoma	<b>MMC</b>	Mitomycin
<b>CMN</b>	Congenital melanocytic naevi	<b>MSG</b>	Melanoma study group
<b>CO2</b>	Carbon dioxide	<b>MR</b>	Mitotic rate
<b>CT</b>	Computed tomography	<b>MRI</b>	Magnetic resonance imaging
<b>CXR</b>	Chest x-ray	<b>MS</b>	Median survival
<b>DALY</b>	Disability adjusted life year	<b>MSLT-I</b>	International multicentre randomised controlled trial
<b>DFI</b>	Disease free interval	<b>N</b>	Regional lymph nodes
<b>DIF</b>	Diffuse interstitial fibrosis	<b>NCCN</b>	National Comprehensive Cancer Network
<b>DKG</b>	German Cancer Society	<b>NHMRC</b>	National Health and Medical Research Council
<b>ED</b>	Extensive disease	<b>OCA</b>	Vincristine, adriamycin and cyclophosphamide
<b>ELCAP</b>	Early lung cancer action project	<b>OCP</b>	Oral contraceptive pill
<b>FDA</b>	Food Drug Administration	<b>OR</b>	Odds ratio
<b>FDG-PET</b>	Fluoro-deoxy glucose PET	<b>PAM</b>	Primary acquired melanoma
<b>FNA</b>	Fine needle aspiration	<b>PE</b>	Cisplatin with etoposide
<b>FU</b>	Follow up	<b>PET</b>	Positron emission tomography
<b>G-CSF</b>	Granulocyte colony stimulating factor	<b>PI</b>	Cisplatin with irinotecan
<b>GM-CSF</b>	Granulocyte-macrophage colony stimulating factor	<b>POHEM</b>	Population health model

<b>POMS</b>	Profile of mood states	<b>T</b>	Primary tumour
<b>PS</b>	Performance status	<b>TIL</b>	Tumour infiltrating lymphocytes
<b>QOL</b>	Quality of life	<b>TMD</b>	Total mood disturbance
<b>RCT</b>	Randomised clinical trial	<b>TNF<math>\alpha</math></b>	Tumour necrosis factor $\alpha$
<b>RPA</b>	Recursive partitioning analysis	<b>TROG</b>	Trans-Tasman Radiation Oncology Group
<b>RR</b>	Relative risk	<b>Tx</b>	Therapy
<b>RRLCA</b>	Relative risk for lung cancer	<b>UICC</b>	International Union Against Cancer
<b>RT</b>	Radiotherapy	<b>USS</b>	Ultrasound study
<b>RTC</b>	Randomised controlled trial	<b>UV</b>	Ultraviolet radiation
<b>SLN</b>	Sentinel lymph node	<b>VA</b>	Visual acuity
<b>SLNB</b>	Sentinel lymph node biopsy	<b>WBRT</b>	Whole brain radiation therapy
<b>Solaria</b>	Tanning or sunbeds	<b>WHO</b>	World Health Organization
<b>SCLC</b>	Small cell lung cancer	<b>WLE</b>	Wide local excision
<b>SIR</b>	Standardized incidence ratios	<b>YLD</b>	Years lost due to disability
<b>SPF</b>	Sun protection factor	<b>YLL</b>	Years of life lost
<b>SRS</b>	Stereotactic radio-surgery		
<b>SVCO</b>	Superior vena cava obstruction		

## Glossary

<b>Actinic keratosis</b>	A precancerous condition. Consists of thick, scaly patches of skin. Also called solar or senile keratosis.
<b>Adjuvant therapy</b>	Additional treatment that is added to increase the effectiveness of the main treatment.
<b>Aetiology</b>	The cause or origin of disease.
<b>Allied health professional (AHP)</b>	One of the following groups of healthcare workers: physiotherapists, occupational therapists, art therapists, chiropodists/podiatrists, dieticians, drama therapists, music therapists, orthoptists, paramedics, prosthetists/orthotists, radiographers, speech and language therapists.
<b>Anaesthetic</b>	A drug that is taken to stop a person feeling pain during a medical procedure. A local anaesthetic numbs only a part of the body; a general anaesthetic causes a person to lose consciousness for a period of time.
<b>Atypical naevi</b>	A condition where a person has a number of moles that are generally larger than ordinary moles and have irregular and indistinct borders. Their colour is frequently not uniform and ranges from pink to dark brown; they are usually flat, but parts may be raised above the skin surface. If the condition runs in the family, it may be called familial dysplastic naevus syndrome.
<b>Autosomal</b>	Refers to a chromosome that is not involved in determining sex. If a disorder is autosomal it affects both males and females equally.

<b>Basal cell carcinoma</b>	A type of skin cancer that arises from the basal cells, small round cells found in the lower part (or base) of the epidermis, the outer layer of the skin.
<b>Benign</b>	Not cancerous; not malignant
<b>Biopsy</b>	Removal of a sample of tissue or cells from the body to assist in the diagnosis of a disease.
<b>Brachytherapy</b>	Radiotherapy delivered by a temporary or permanent implant of radioactive material into a tissue or organ.
<b>Breslow thickness</b>	A measuring scale of thickness for malignant melanomas, measured from the top layer of skin to the bottom of the tumour. The deeper the melanoma has grown, the more likely it is that some cells may have spread through the blood stream or lymphatic system.
<b>Cancer</b>	Growth of altered body cells that keep on growing and which is able to spread from where it started to another part of the body.
<b>Carcinoma</b>	Cancer of the skin tissue that covers all the body organs. Most cancers are carcinomas.
<b>Cells</b>	The 'building blocks' of the body. A human is made of millions of cells which are adapted for different functions. Cells are able to reproduce themselves exactly unless they are abnormal or damaged, as are cancer cells.
<b>Chemoprophylaxis</b>	The use of a drug or chemical to prevent future occurrences of a disease.
<b>Chemotherapy</b>	The use of drugs that kill cancer cells, or prevent or slow their growth.
<b>Clinical oncologist</b>	A doctor who specialises in the treatment of cancer patients, particularly through the use of chemotherapy, by may also use radiotherapy.
<b>Clinical oncology</b>	The specialist treatment of cancer patients, particularly through the use of chemotherapy, but may also be through the use of radiotherapy.
<b>Cohort studies</b>	Research studies in which groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it.
<b>Computed tomography (CT)</b>	An x-ray imaging technique.
<b>Cytopathologist</b>	A doctor who specialises in the study of disease changes within individual cells or cell types.
<b>Cytotoxic</b>	An agent that kills cells.
<b>Dermatologist</b>	A doctor who specialises in the diagnosis and treatment of skin disorders.
<b>Dermatology</b>	The specialist treatment of skin disorders.

<b>Dermatopathologist</b>	A pathologist with special training and expertise in the diagnosing of skin diseases.
<b>Dermatopathology</b>	The study of the pathology of skin.
<b>Dermoscope</b>	A tool like hand-held microscope used by doctors to view a mole or suspicious spot on living skin.
<b>Dermoscopy</b>	Observing the skin directly using a special magnifying lens, usually performed on a mole or suspicious spot on living skin.
<b>Dermis</b>	The lower or inner layer of the two main layers of tissues that make up the skin.
<b>Diagnostic radiographer</b>	The role of the diagnostic radiographer is to work closely with other specialists, to provide safe and accurate imaging examinations, to give patients information and support and to discuss possible side effects and care.
<b>Diathermy treatment</b>	The use of a direct current electrical apparatus to ablate skin cancer and related dysplasias.
<b>Distant spread</b>	See metastasis
<b>Ear, nose and throat (ENT)</b>	Diagnosis and treatment of diseases of the ear, nose and throat.
<b>Epidemiology</b>	The study of populations in order to determine the frequency and distribution of disease and to measure risks.
<b>Excision</b>	Removal of tissue by surgery.
<b>Fine needle aspiration cytology (FNA)</b>	The use of a fine needle to biopsy a tumour or lymph node to obtain cells for cytological confirmation of diagnosis.
<b>Hapū</b>	Sub-tribe
<b>Histology</b>	The study of body tissue and cells by examination under a microscope to find out what type of body tissue it is, or if a cancer, what type of body cells the cancer cells look like most.
<b>Histopathologist</b>	A doctor who specialises in examining tissue samples microscopically in order to make a diagnosis and ensure tumour excision is complete.
<b>Histopathology</b>	The study of microscopic changes in diseased tissues.
<b><i>In situ</i></b>	Localised and confined to one area; often used to describe a cancer that has not spread.
<b>Iwi</b>	Tribe
<b>Isolated limb infusion</b>	A technique that may be used to deliver anticancer drugs directly to an arm or leg. The flow of blood to and from the limb is stopped temporarily and anticancer drugs are injected directly into the blood of the limb. This allows the person to receive a high dose of drugs in the area where the cancer occurred.

<b>Isolated limb perfusion</b>	A technique in which blood vessel surgery is used to temporarily isolate the circulation of an arm or leg from the rest of the body. The blood is mixed with high doses of chemotherapy drugs, recirculated through a heart-lung machine, and heated for a period of time to enhance the drug's potency. The treated blood is recirculated to the affected limb.
<b>Kaupapa Māori</b>	Incorporating Māori culture and belief systems.
<b>Kaitiaki</b>	Carer
<b>Laser therapy</b>	The use of laser technology to ablate skin cancer and related dysplasias.
<b>Lentigo maligna</b>	Flat, mottled, tan-to-brown freckle-like spots with irregular borders, usually appearing on the face or other sun-exposed areas of older persons, which typically enlarge slowly for many years before cancer appears. Also known as Hutchinson's or melanotic freckle.
<b>Lesion</b>	An area of abnormal tissue.
<b>Local recurrence</b>	Local persistence of primary tumour due to incomplete excision.
<b>local metastasis</b>	Development of separate melanoma colonies due to lympho-vascular metastasis despite complete excision of the primary tumour; including 'in transit metastases' and 'satellitosis'.
<b>Lymphadenopathy</b>	Disease or swelling of the lymph nodes.
<b>Magnetic resonance imaging (MRI)</b>	A non-invasive method of imaging which allows the form and metabolism of tissues and organs to be visualised (also known as nuclear magnetic resonance).
<b>Malignant</b>	Cancerous. Malignant tumours can invade and destroy nearby tissue and spread to other parts of the body.
<b>Mana</b>	Power, respect, status
<b>Margin</b>	The edge or border of the tissue removed in cancer surgery.
<b>Maxillofacial</b>	The speciality that combines full surgical training with dental expertise for the treatment of diseases, injuries, tumours and deformities of the face and jaws.
<b>Medical oncology</b>	The specialist treatment of cancer patients through the use of chemotherapy and for some tumours, immunotherapy.
<b>Melanocyte stimulating hormone</b>	Melanocyte stimulating hormone is derived from the pituitary gland and keratinocytes amongst other cells and is capable of stimulating melanin production by melanocytes to increase pigmentation.
<b>Melanoma</b>	A form of skin cancer that arises in melanocytes, the cells that produce pigment.
<b>Meta-analysis</b>	The statistical analysis of the results of a collection of individual research studies in order to add the findings together.
<b>Metachronous</b>	At different times.

<b>Metastases</b>	Also known as ‘secondaries’. Tumours or masses of cells that develop when cancer cells break away from the original (primary) cancer and are carried by the lymphatic and blood systems to other parts of the body.
<b>Minimum dataset</b>	A widely agreed-upon and generally accepted set of terms and definitions making up a core dataset acquired for medical records and used for developing statistics for different types of analyses and users.
<b>Mohs surgery</b>	A surgical technique used to treat skin cancer. Individual layers of cancerous tissue are removed and examined under a microscope one at a time until all cancerous tissue has been removed.
<b>Morbidity</b>	A diseased condition or state.
<b>Mortality</b>	Either (a) the condition of being subject to death or (b) the death rate, which reflects the number of deaths per unit of population in any specific region, age group, disease or other classification, usually expressed as deaths per 1000, 10,000 or 100,000.
<b>Noa</b>	Ordinary, safe
<b>Neoplasm</b>	An abnormal mass of tissue that results from excessive cell division.
<b>Occupational therapist</b>	A health professional trained to help people who are ill or disabled learn to manage their daily activities.
<b>Oculoplastic surgeon</b>	A doctor who specialises in the restoration, reconstruction, correction or improvement of the shape and appearance of the eye.
<b>Odds ratio</b>	The ratio of a part to the remainder. It is used to express the chance that a particular outcome will occur.
<b>Oncologist</b>	A doctor who specialises in treating cancer.
<b>Oncology</b>	The study of the biological, physical and chemical features of cancers. Also the study of the causes and treatment of cancers.
<b>Palliative</b>	Anything that serves to alleviate symptoms caused by the underlying cancer but that is not expected to cure it.
<b>Palliative care</b>	Active, holistic care of patients with advanced, progressive illness that may no longer be curable. The aim is to achieve the best quality of life for patients and their families. Many aspects of palliative care are also applicable in earlier stages of the cancer journey in association with other treatments.
<b>Pathologist</b>	A doctor who examines cells and identifies them. The pathologist can tell where in the body a cell comes from and whether it is normal or a cancer cell. If it is a cancer cell, the pathologist can often tell the type of body cell from which the cancer developed. In a hospital practically all the diagnostic tests performed with material removed from the body are evaluated or performed by a pathologist.
<b>Perineural</b>	Around a nerve or group of nerves.
<b>Physiotherapist</b>	A specialist trained in using exercise and physical activities to condition muscles and improve level of activity.

<b>PICO</b>	Populations, interventions, comparisons, outcomes
<b>Plastic surgeon</b>	A doctor who specialises in surgery to correct damage to the skin. For example, reducing the amount of scarring or disfigurement that may happen because of surgery to treat a skin tumour.
<b>Positron emission tomography (PET)</b>	A highly specialised technique using a radioactive tracer to produce a computerised image of body tissues to find any abnormalities. PET scans are sometimes used to help diagnose cancer.
<b>Precancerous</b>	A term used to describe a condition that may (or is likely to) become cancer. Also called premalignant.
<b>Prognosis</b>	A prediction of the likely outcome or course of a disease, the chance of recovery or recurrence.
<b>Prognostic factor</b>	Patient or disease characteristics, for example age or co-morbidity, which influence the course of the disease under study.
<b>Protocol</b>	An agreed policy that defines appropriate action.
<b>Psychological</b>	Adjective of psychology, which is the scientific study of behaviour and its related mental processes. Psychology is concerned with such matters as memory, rational and irrational thought, intelligence, learning, personality, perceptions and emotions and their relationship to behaviour.
<b>Psychologist</b>	A specialist who can talk with patients and their families about emotional and personal matters, and can help them make decisions.
<b>Psychosocial</b>	Concerned with psychological influences on social behaviour.
<b>Radiologist</b>	A doctor who specialises in creating and interpreting pictures of areas inside the body. An interventional radiologist specialises in the use of imaging techniques to assist treatment, for example, the insertion of intravenous catheters.
<b>Radiology</b>	The use of radiation (such as x-rays) or other imaging technologies (such as ultrasound and magnetic resonance imaging) to produce images to assist in diagnosis and treatment of disease.
<b>Radiotherapy</b>	The use of radiation, usually x-rays or gamma rays to kill cancer cells and treat tumours.
<b>Randomised controlled trial (RCT)</b>	A type of experiment that is used to compare the effectiveness of different treatments. The crucial feature of this form of trial is that patients are assigned at random to groups that receive either the interventions being assessed or control treatments. RCTs offer the most reliable (i.e. least biased) form of evidence of effectiveness.
<b>Scintigraphy</b>	A diagnostic method. A radioactive tracer is injected into the body. The radiation it sends out produces flashes of light on a scintillator (instrument used to detect radioactivity), and they are recorded. Also called radionuclide scanning.
<b>Sensitivity</b>	The proportion of people with a disease who have a positive test for the disease.

<b>Sentinel (lymph) node biopsy</b>	Removal and examination of the sentinel node(s) (the first lymph node(s) to which cancer cells are likely to spread from a primary tumour). To identify the sentinel lymph node(s), the surgeon injects a radioactive substance or blue dye, or both, near the tumour. The surgeon then uses a scanner to find the sentinel lymph node(s) containing the radioactive substance or looks for the lymph node(s) stained with dye. The surgeon then removes the sentinel node(s) to check for the presence of cancer cells.
<b>Specificity</b>	The number of people without a disease who have a negative test. (A specific test will rarely misclassify people with a disease as being diseased).
<b>Supportive care</b>	Care that helps the patient and his or her family and carers to cope with cancer and its treatment and in the case of the family and carers, with bereavement. It aims to help the patient maximise the benefits of treatment and to provide the best possible quality of life.
<b>Surgical oncologist</b>	A doctor who specialises in using surgery to treat cancer.
<b>Synchronous</b>	At the same time.
<b>Systemic therapy</b>	Treatment that reaches and affects cells throughout the body rather than targeting one specific area; for example, chemotherapy.
<b>Therapeutic radiographer</b>	The role of the therapeutic radiographer is to work closely with other specialists, to deliver the radiotherapy as prescribed, to give patients information and support and to discuss possible side effects and care.
<b>Tapu</b>	Sacred, forbidden, special
<b>Topical therapy</b>	Treatment with drugs in a lotion, ointment or cream applied to the skin.
<b>Tumour</b>	A mass of excess tissue that results from abnormal cell division. Tumours perform no useful body function.
<b>Whānau</b>	Family, community
<b>Whānau ora</b>	Family wellness

Adapted from Appendix 6, *the Guidance on cancer services: Improving Outcomes for people with skin tumours including melanoma. The Manual*, February 2006. Developed by the National Collaborating Centre for Cancer (NHS).



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