Healthcare Improvement Scotland

SIGN

SIGN 146 • Cutaneous melanoma

A national clinical guideline

January 2017

Evidence

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R	For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For **'conditional'** recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

GOOD-PRACTICE POINTS

✓	Recommended best practice based on the clinical experience of the guideline development group.

NICE accredited
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NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2020 and is applicable to guidance produced using the processes described SIGN 50: a guideline developer's handbook, 2015 edition (www.sign.ac.uk/guidelines/fulltext/50/index.html). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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Scottish Intercollegiate Guidelines Network

Cutaneous melanoma

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Cutaneous melanoma, previously referred to as cutaneous malignant melanoma, is a malignant tumour of cutaneous melanocytes. In Scotland it is the fifth most common cancer in women and sixth in men.[1] In Scotland, over the last decade, the incidence of melanoma has increased by 38% in men and 22% in women, with the most recent incident rates being 26 male and 21.3 female cases per 100,000 in 2013. Mortality rates in men have been falling, but they have been rising for women at a lower rate than incidence. The most recent mortality rates are 4 men and 3.3 women per 100,000 in 2013.[1] The primary risk factor for cutaneous melanoma is considered to be exposure to natural and artificial sunlight.[1]

Although melanoma is the major cause of skin cancer mortality it is often curable by surgery if recognised and treated at an early stage. In recent years considerable efforts have been made to increase public and professional awareness of melanoma in order to promote early detection. In contrast, prognosis for patients with advanced melanoma remains poor although considerable progress has been made with the emergence of molecular therapies including BRAF inhibitors and novel immunotherapies which can lead to durable disease control in some patients.

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 72: Cutaneous melanoma, first published in July 2003, to reflect the most recent evidence.

Where no new evidence was identified to support an update or where a section was not updated, text and recommendations are reproduced verbatim from SIGN 72. The original supporting evidence was not reappraised by the current guideline development group.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

Many specialties and professions are involved in the management of patients with melanoma. This guideline provides advice at all stages of the patient's pathway of care, from primary prevention to early recognition, treatment and follow up. It does not address melanomas of non-cutaneous origin such as melanomas arising from mucosae, ocular melanomas and other rare non-cutaneous sites.

1.2.2 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

The following table shows which sections from each chapter have been updated and the extent of each update. Sections not listed below have been reproduced verbatim from SIGN 72.

1	**Introduction**	
1.1	The need for a guideline	Minor update
2	**Key recommendations**	**New**
3	**Prevention, surveillance and genetics**	
3.5	Genetics	Completely revised
4	**Diagnostics and prognostic indicators**	
4.1.5	Desmoplastic type melanoma	New
4.1.6	Pigment synthesising (animal type) melanoma	New
4.5	Biopsy of suspicious lesions	Minor update
4.6.1	Handling a suspected melanoma	Updated
4.7	Prognostic indicators/core microscopic dataset items	Updated

4.7.1	Histogenetic type	Completely revised
4.7.4	Mitotic rate	Updated
4.7.6	Microscopic satellites/in transit metastasis	Updated
4.7.8	Tumour infiltrating lymphocytes	Minor update
4.7.9	Regression	Updated
4.9	Melanoma pathology report	Updated
4.10	Pathological examination and reporting of therapeutic and sentinel lymph node dissection specimens	Completely revised
5	**Surgical management and staging**	
5.1	Wide local excision surgery for primary melanoma	Updated
5.2	Staging melanoma	Updated
5.3.1	Management of palpable lymph nodes	Updated
5.3.2	Management of non-palpable lymph nodes	Updated
6	**Further investigations and non-surgical staging**	
6.1	Imaging techniques	Completely revised
6.2	Laboratory investigations	Updated
7	**Adjuvant treatment of stage II and III melanoma**	
7.1	Adjuvant radiotherapy in resected stage III melanoma	New
7.2	Immunotherapy	Updated
7.3	Immunosuppression	New
8	**Follow up of patients with stage I, II and III melanoma**	
8.3	Timing and rate of recurrence	Updated
	Figure 1	New
8.4	Follow up	Completely revised
8.7.2	Surveillance imaging	Completely revised
9	**Management of advanced (unresectable stage IIIC or IV) melanoma**	
9.1	Introduction	New
9.3	Systemic therapy	Completely revised
9.5	Ablative therapies	Updated
9.5.2	Electrochemotherapy	New
9.6	Radiotherapy	Completely revised
10	**Melanoma in women**	
10.1	Pregnancy	Minor update
11	**Provision of information**	
11.2	Communication	New
11.4	Checklist for provision of information	Completely revised
11.5	Sources of further information	Updated

1.2.3 TARGET USERS OF THE GUIDELINE

The guideline should be of interest and relevance to primary care providers, dermatologists, surgeons, pathologists, medical and clinical oncologists, public health physicians, nurses, health promotion professionals, epidemiologists, radiologists, nuclear medicine physicians, general practitioners and patient support groups.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**.

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[2]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[1]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[3]

1.3.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

In addition, Healthcare Improvement Scotland reviews Multiple Technology Appraisals (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provides advice about their applicability in NHSScotland. If Healthcare Improvement Scotland advises that MTA guidance is applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

NICE MTAs deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

SMC advice and NICE MTA guidance relevant to this guideline are summarised in section 12.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 MANAGEMENT OF REGIONAL LYMPH NODES

R **SLNB should be considered as a staging technique in patients with stage IB-IIC melanoma with a Breslow thickness of >1 mm. It should not be offered to patients with IB melanoma where Breslow thickness is ≤1 mm.**

Patients should be given detailed verbal and written information regarding the possible advantages and disadvantages of the SLNB procedure to allow them to make an informed decision.

2.2 IMAGING TECHNIQUES

R **Staging CT should be offered to patients with stage IIC or above melanoma.**

✓ Staging CT should include head, chest, abdomen and pelvis. The neck should be included in patients with head and neck melanoma.

✓ PET-CT should only be considered for patients with indeterminate findings on CT or for patients who are being considered for major surgical resection, after discussion with the specialist multidisciplinary team.

2.3 SURVEILLANCE IMAGING

R **Routine surveillance imaging should not be offered to patients with stage I-IIB melanoma.**

Decisions on the use of routine surveillance imaging for patients with stage IIC-III melanoma should be made at a regional level after identifying and agreeing any additional imaging resources required, and considering other factors, including patient choice.

✓ CT should be used for surveillance imaging, if this is undertaken.

2.4 SYSTEMIC THERAPY

R **Trametinib in combination with dabrafenib is recommended for patients with unresectable stage IIIC or stage IV melanoma with a *BRAF* V600 mutation.**

Ipilimumab, pembrolizumab and nivolumab monotherapy or ipilimumab/nivolumab combination therapy are recommended for patients with unresectable stage IIIC and IV melanoma.

3 Prevention, surveillance and genetics

3.1 INTRODUCTION

Melanoma, especially when diagnosed at an advanced stage, can cause serious morbidity and may be fatal despite treatment. Prevention of the disease, or failing that, minimising its consequences by early detection, are key goals.

3.2 CAUSATION

A comprehensive review of evidence by the International Agency for Research on Cancer (IARC) has concluded that solar radiation is a cause of melanoma.[3]

Two systematic reviews focussed on the relationship between patterns of sun exposure and risk of melanoma. The first was a high-quality review of case-control studies which concluded that intermittent unaccustomed exposure was more important than age at sunburn.[4] The second study was a review of ecological and case-control studies and concluded that exposure to high levels of sunlight in childhood is a strong determinant of risk, but that exposure in adulthood also plays a part.[5] **2++**

The contribution of specific wavelength bands and the action spectrum for melanoma induction are unknown.[4] Sunburn is mainly due to ultraviolet B (UVB) (280 to 320 nm) radiation, implicating UVB as a contributing factor to the pathogenesis of melanoma. There is accumulating evidence for the role of ultraviolet A (UVA) (and sunbeds) in the pathogenesis of melanoma.[6]

3.3 PRIMARY PREVENTION

Primary prevention is defined as prevention targeted towards the general population.

There is indirect evidence that sun avoidance and other sun-protective measures (for example clothing, hats and opaque sunscreens) are likely to reduce the risk of melanoma. Sunscreen effectiveness is difficult to demonstrate for a number of reasons. High-risk individuals are more likely to use sunscreen, although sunscreen use may be associated with greater sun exposure.[6,7] It may be that sunscreens offer a false sense of security and lead to increased time spent in the sun.[7,8] Most sunscreens offer greater protection from UVB, reducing the risk of sunburn, but not of exposure to UVA.[7,8] Some ingredients found in sunscreens may be carcinogenic.[7,8] Case-control studies and clinical trials have shown no reduction or increase in melanoma incidence with broad-spectrum sunscreen use. Little is known about the potential long-term effects of sunscreen use.[7,8] Given these potentially adverse effects of sunscreens in relation to risk of melanoma, physical protection measures should be regarded as more important than sunscreen use.[7,8] **2++**

There may be theoretical risks associated with sun avoidance,[9] for example a lack of vitamin D, but the balance of evidence in terms of risks and benefits favours a cautious approach to sun exposure. In the absence of evidence to support recommendations about specific aspects of protection measures in Scotland, the advice below is based on the Australian guidelines on melanoma, interpreted in the light of the Scottish climate.[10] **4**

Table 1: Prevention of melanoma

- Use clothing as the primary means of protecting against the sun
- People of fair complexion should be especially careful about sun exposure
- Avoid using sun beds, tanning booths, and tanning lamps as an increased risk has been reported[6]
- Use broad-spectrum sunscreens with a minimum sun protection factor (SPF) of 30,[11] and 4 or 5 UVA stars,[12] as an adjunct to sun avoidance and other sun protective measures, providing this does not lead to increased time spent in the sun
- Avoid exposure to direct, intense sunlight, especially between 11 am – 3 pm (for example seek out shade)
- Provide children with appropriate sun protection for outdoor activities.

3.3.1 PUBLIC EDUCATION TO PROMOTE PRIMARY PREVENTION

As melanoma is potentially preventable, educating the general public is an important preventive measure. Six randomised controlled trials (RCTs) of interventions aimed at a variety of target groups including the general public, employees and school children were identified.[13-18] All interventions were in some part reliant on brochures and leaflets to deliver preventive information. Leaflets significantly increased short-term user knowledge of sun-awareness measures, and assisted in the early detection of melanoma. The tone of a leaflet or educational brochure is important when delivering health-promotion messages relating to sun awareness and should be non-alarmist.[14] **1+**

Two observational studies suggest that interactive computer-based educational packages may result in higher short-term knowledge gain (sun awareness) when compared to non-interactive packages.[19,20] A retrospective cohort study of French primary school children found that health-education programmes could improve the knowledge, attitude and behaviour of young children. Children with a fair complexion (the target of this campaign) showed the best improvement in their responses.[21] **2+**

Leaflets, brochures and educational packages can significantly influence increased short-term user knowledge of sun-awareness measures, and can assist in the early detection of melanoma. Insufficient evidence was identified to enable recommendations to be made about the style or content of leaflets and brochures.

R **Information on preventing melanoma should be provided to the general public through a variety of media and resources.**

Further resources can be found on the British Association of Dermatologists' website **www.bad.org.uk**.

3.4 SCREENING AND SURVEILLANCE

3.4.1 IDENTIFICATION OF INDIVIDUALS AT HIGHER RISK

A review of the literature on the reliability and usefulness of risk-assessment tools suggests that patients can count the number of moles 5 mm or larger in reasonable agreement with physicians, but that they cannot accurately distinguish atypical moles from others.[22] No longitudinal studies of the use of risk-assessment tools in primary care were identified. **2++**

A cross-sectional study that sent postal questionnaires to a random sample of households from a general practice population found that self assessment of risk was generally poor compared with the assessment of a dermatologist, suggesting that it might be very difficult to identify systematically a high-risk population suitable for screening.[23] **3**

An RCT carried out in 11 communities in Western Australia showed that targeted advertising can increase the yield of individuals with a higher prevalence of risk factors.[24] This may not be immediately transferable to Scotland, where disease prevalence is lower and baseline awareness may be lower. **1+**

3.4.2 RISK FACTORS

Risk factors for melanoma have been identified mainly from case control studies (*see Table 2*). The strength of a risk factor is usually expressed in terms of an odds ratio (OR). In the context of this guideline, the OR is the ratio of the odds in favour of exposure to a risk factor in people with melanoma to the odds in favour of exposure to the same risk factor among people who have not developed melanoma. For relatively rare diseases such as melanoma, the OR can be thought of as being equivalent to the relative risk, that is, the ratio of the incidence rate of melanoma among exposed individuals to the incidence rate among unexposed individuals. The higher the OR (or relative risk), the stronger the association between the risk factor and melanoma. This is important from the perspective of an individual, but from a public health perspective a lower OR for a commonly occurring risk factor may be more important than a higher OR for a risk factor which occurs rarely in the population.

Table 2: Established risk factors for cutaneous melanoma

Risk factor	OR*	Information
11–50 common moles >2 mm	1.7 to 1.9	The risk of melanoma rises with the number of common moles.[22]
51–100 common moles > 2 mm	3.2 to 3.7	
>100 common moles >2 mm	7.6 to 7.7	
Family history of melanoma	1.8	Melanoma in a first degree family member (parent, sibling or child of the patient; *see section 3.5*).[22]
Previous history of melanoma		Standardised incidence ratio range 4.5 to 25.6[268] (*see section 8.7*).
The presence of 1–4 atypical moles	1.6 to 7.3	Atypical moles: ill-defined or irregular border; irregular pigmentation; diameter >5 mm; erythema (blanchable in lesion or at edge); accentuated skin markings.[22]
Red or light-coloured hair[22]	1.4 to 3.5	
Presence of actinic lentigines[22]	1.9 to 3.5	Actinic lentigines: flat, brown skin lesions associated with acute and chronic sun exposure. No direct malignant potential.
Giant congenital melanocytic naevi ≥20 cm in diameter		Relative risk range 239 to 1,224 for extracutaneous as well as cutaneous melanoma.[269,270]
Unusually high sun exposure[22]	2.6	
Reported growth of a mole[22]	2.3	
Skin that does not tan easily[22]	1.98	
Light-coloured eyes[22]	1.55 to 1.60	
Light-coloured skin[22]	1.40 to 1.42	
Affluence		Relative risk approximately 3.0 for people residing in areas defined as Carstairs deprivation category 1 (least deprived) compared to Carstairs category 7 (most deprived).[271,272]
Female sex		Female:male ratio of age-standardised incidence rates is approximately 1.3:1.0.[271]
Age		Melanoma is rare in absolute terms in childhood and adolescence but risk begins to increase with age during adolescence, the elderly being at highest risk.[25] The validity of some risk factors, such as hair colour and sun exposure, is lower in the elderly.[22]

*OR = odds ratio. In some cases the range of ORs from more than a single study are given.

For example: a person with skin that does not tan easily has an approximately twofold (1.98 times) risk of developing melanoma compared to someone with skin that tans (after allowing for other risk factors). This is modest in comparison, for example, to the approximately 10-fold or greater risk of developing lung cancer in someone who smokes cigarettes compared to a person who has never smoked.[273]

R **Healthcare professionals and members of the public should be aware of the risk factors for melanoma.**

Individuals identified as being at higher risk should be advised about appropriate methods of sun protection, educated about the diagnostic features of cutaneous melanoma and encouraged to perform self examination of the skin.

3.5 GENETICS

It is estimated that 1–2% of melanomas are attributable to the inheritance of melanoma susceptibility genes.[25] Mutations in cyclin-dependant kinase inhibitor 2A (*CDKN2A*) are associated with an increase risk of melanoma.[25,26] Prevalence of *CDKN2A* mutations in affected families varies between countries.[26-28] Cyclin-dependant kinase 4 (*CDK4*) mutations have also been implicated but have a low prevalence worldwide.[26] In Scotland the prevalence of *CDKN2A* mutations in families with two or more first degree relatives affected by melanoma is approximately 22% (7 in 32 families).[29] Mutations in *CDKN2A* are also associated with a risk of pancreatic cancer in some families and therefore a family history of pancreatic cancer and melanoma may increase the likelihood of identifying a *CDKN2A* mutation.[25,27,28] **2++ 3 4**

A systematic review of clinical practice guidelines found that most guidelines do not cover genetic testing in their discussion, but where they do there is consensus that this should be offered in the context of genetic counselling.[28]

There may be additional benefits for patients to undergo genetic counselling for genetic testing as a higher compliance in self examination has been reported after genetic testing.[30] People with mutations in *CDKN2A* may have a higher risk of smoking-related cancers and so should be advised to abstain from smoking tobacco.[31] **1- 2+**

R **Genetic testing for mutations in *CDKN2A* should be offered to an affected individual who has a first degree relative affected by melanoma or pancreatic cancer.**

4 Diagnosis and prognostic indicators

The vast majority of melanomas are visible, if not to the patient, then at least to friends, family or health professionals. Members of the general public and health professionals should be aware of the signs suggestive of melanoma. In Scotland, melanomas occur more commonly in men than women. The most frequent site is the leg for women and the trunk in men. A small number of patients have occult primary lesions and present with metastatic disease. Up to ten percent of melanomas can be amelanotic (non-pigmented) or hypomelanotic, increasing diagnostic difficulty.

✓ All patients with a diagnosis of melanoma should be discussed at a specialist multidisciplinary team (MDT) meeting.

4.1 TYPES OF MELANOMA

Melanomas are subdivided into types on the basis of clinical features and pathology.

4.1.1 SUPERFICIAL SPREADING MALIGNANT MELANOMA

Superficial spreading malignant melanoma (SSMM) is the most frequently encountered type of melanoma; characteristically an asymmetrical pigmented lesion with variable pigmentation and sometimes an irregular outline. Patients may have noted growth, a change in sensation and/or colour, crusting, bleeding or inflammation of the lesion. The duration of the symptoms varies from a few months to several years.

4.1.2 NODULAR MELANOMA

The second most common type is nodular melanoma (NM). This usually has a shorter presentation and a greater tendency to bleed and/or ulcerate.

4.1.3 LENTIGO MALIGNA MELANOMA

The next most frequent is the melanoma that occurs most often in sun-damaged skin on the head and neck of older patients. This is the only type that has a clearly recognised and often lengthy pre-invasive (in situ) lesion termed lentigo maligna (LM) before progressing, in some instances, to an invasive lentigo maligna melanoma (LMM).

4.1.4 ACRAL LENTIGINOUS MELANOMA

Acral lentiginous melanoma (ALM) occurs on sites including the palms, soles and beneath the nails.

4.1.5 DESMOPLASTIC TYPE MELANOMA

Desmoplastic type melanoma is uncommon.

It is important to distinguish between pure and mixed subtypes of desmoplastic melanoma (DM). Pure DM is thought to be associated with a more favourable outcome and lower incidence of positive sentinel lymph node biopsy (SLNB) (2.2% versus 15.8% in mixed DM, and 17.5% in conventional melanoma).[32] Similar figures were reported in another study, with 1/92 patients with pure DM having a positive SNLB compared with 7/39 patients with mixed subtype.[33] However, a small single centre study described higher local recurrence rates in pure DM (28/118) compared with mixed DM (18/124).[34,35] **3**

4.1.6 PIGMENT SYNTHESISING (ANIMAL TYPE) MELANOMA

Pigment synthesising melanoma (also known as animal type melanoma) or low-grade hypermelanotic melanoma, is rare. It should be considered an indolent type of melanoma where there is little incidence of systemic metastases despite frequent positive SLNB.[36-38] **3**

4.2 CLINICAL DIAGNOSIS

Suspicious pigmented lesions are best examined in a good light with or without magnification and should be assessed using the 7-point checklist (*see Table 4*) or ABCDE systems (*see Table 3*).[39,40] The presence of any major feature in the 7-point checklist, or any of the features in the ABCDE system, is an indication for referral. The presence of minor features should increase suspicion. It is accepted that some melanomas will have no major features. **4**

Table 3: The 7 -point checklist lesion system

Major features	Minor features
• change in size of lesion	• inflammation
• irregular pigmentation	• itch/altered sensation
• irregular border	• lesion larger than others
	• oozing/crusting of lesion

Table 4: The ABCDE lesion system

A	Geometrical **A**symmetry in two axes
B	Irregular **B**order
C	At least two different **C**olours in lesion
D	Maximum **D**iameter >6 mm
E	**E**volution/change in lesion

Clinical diagnosis of melanoma is difficult and the accuracy of diagnosis may vary according to a clinician's level of experience, with reports of considerable variation in sensitivity from 50–86% and an inverse relationship between sensitivity and experience.[41-43] **3**

High-magnification dermoscopy is more sensitive than non-dermatoscopic diagnosis when used by clinicians with experience of the technique.[44 45] **1+**

Training clinicians to be experts in hand-held dermoscopy improves diagnostic accuracy but it may diminish the sensitivity of the diagnosis of non-expert or untrained dermatologists.[46-48] Observational studies have compared excision and pathological assessment to using other preoperative assessment methods of diagnosis including magnetic resonance imaging (MRI), high resolution ultrasound (US) and digital imaging of possible melanomas.[49-52] These studies failed to show significant benefit. **1+ 3**

R **Clinicians should be familiar with the 7-point or the ABCDE checklist for assessing lesions.**

✓ Assess all pigmented skin lesions that are either referred for assessment or identified during follow up in secondary or tertiary care, using dermoscopy carried out by healthcare professionals trained in this technique.

4.3 DELAY IN DIAGNOSIS

Nine observational studies exploring delay were identified.[41,53-60] Significant delays (greater than three months) in diagnosis of invasive melanoma are usually patient rather than physician related.[41,53-60] Delay was defined differently in each study, with some including both patient and physician components. **3**

All of the studies identified show inconsistency between Breslow thickness (*see section 4.7.2*) and delay, although melanomas diagnosed incidentally by health professionals were consistently thinner than those noted by patients themselves.[56] **2+**

Several studies showed longer delays in older patients,[42,58] in men, in rural versus urban dwellers and in those with plantar melanomas.[42,59] **2+**

There is inconsistency in findings regarding patients' knowledge of melanoma and delay. Two observational studies found that delay in presentation was shorter if the patient was aware of possibility of malignancy.[56,60] Conversely, another study found that delays were longer in those with greater knowledge, perhaps due to false reassurance caused by greater knowledge (*see section 3.4.1*).[42]

Physician delay accounts for a very small part of the total delay in diagnosis.[41] Medical delays were shorter and the Breslow thickness was less when patients were seen by dermatologists as opposed to general practitioners.[41] **3**

R **Health professionals should be encouraged to examine patients' skin during other clinical examinations.**

✓ Emphasis should be given to the recognition of early melanoma by both patients and health professionals.

4.4 EDUCATING HEALTH PROFESSIONALS ABOUT DIAGNOSIS

An Australian RCT demonstrated a decrease in the number of benign lesions excised by general practitioners (GPs) after being given algorithms and cameras as aids to diagnosis.[61] In an American RCT, the use of a booklet, magnifying and measuring tools and feedback sessions improved the ability of primary care residents to triage suspicious lesions.[62] **1+** **1–**

✓ Targeted education can enhance health professionals' ability to diagnose melanoma.

4.5 BIOPSY OF SUSPICIOUS LESIONS

The optimal specimen for full histological evaluation of a suspected melanoma is a complete excision with a 2 mm surround of normal skin and a cuff of fat.[63] This enables assessment of the entire lesion (*see section 5.1*). Elliptical excisions should be performed along the long axis in the line of a natural skin crease or longitudinally in limbs. The exact surgical margins of excision should be recorded on the operation note. **2+**

Non-excisional biopsy may lead to inadequate histology.[64-68] The least useful type of biopsy is the superficial shave variety. Two large studies demonstrate that non-excisional biopsy of the primary lesion has no effect on prognosis.[65,69] **2+**

Management of invasive lentigo maligna melanoma may have to be approached differently to superficial spreading melanoma. The frequently facial site and large diameter of such lesions may render full excision difficult or excessively destructive. In these instances incisional biopsy(s) of the most clinically suspicious areas are appropriate, but this may not detect all areas of invasion, and may underestimate depth.[70] **2+**

R **A suspected melanoma should be excised with a 2 mm margin and a cuff of fat.**

If complete excision cannot be performed as a primary procedure an incisional or punch biopsy of the most suspicious area is advised.

A superficial shave biopsy is inappropriate for suspicious pigmented lesions.

✓ GPs should refer urgently all patients in whom melanoma is a strong possibility rather than carry out a biopsy in primary care.

Newly-diagnosed patients should receive both verbal and written information about melanoma including the treatment options and support services available to them.

4.6 PATHOLOGICAL DIAGNOSIS

4.6.1 HANDLING A SUSPECTED MELANOMA

The volume of evidence addressing the handling of suspected melanomas is small. Recommendations on how to describe and select tissue blocks from a suspected melanoma are available from standard surgical pathology textbooks.[71]

Appropriate treatment, follow up and prognostication for patients with melanoma are entirely dependent on accurate pathological diagnosis and microscopic staging. The macroscopic description of the specimen, together with adequate and appropriate methods of block selection, is central to this process.

R

The macroscopic description of a suspected melanoma should:

- **state the biopsy type, whether excision, incision, or punch**
- **describe and measure the biopsy** (in mm)
- **state the size of the lesion in mm and describe the lesion in detail** (shape, pattern of pigment distribution, presence or absence of a nodular component and presence or absence of ulceration)
- **state the clearance of the lesion** (in mm) **from the nearest lateral margin and the deep margin.**

Selection of tissue blocks:

- **the entire lesion should be submitted for histopathological examination**
- **the lesion should be sectioned transversely at 3 mm intervals and the blocks loaded into labelled cassettes**
- **cruciate blocks should not be routinely selected** (they limit the assessment of low power architectural features such as symmetry)
- **cruciate blocks may be used to assess margins in very large LM excisions.**

A photograph of the macroscopic specimen may be of great value, especially if the precise origins of labelled blocks are drawn onto the photograph to permit exact orientation.

4.7 PROGNOSTIC INDICATORS/CORE MICROSCOPIC DATASET ITEMS

Histological reporting of primary cutaneous malignant melanoma and regional lymph nodes should follow the dataset produced by the Royal College of Pathologists (RCPath). The microscopic core items for the pathology report are summarised in this section. Further details are available from the RCPath dataset.[72]

4.7.1 HISTOGENETIC TYPE

The majority of studies do not demonstrate a significant association between histogenetic subtype and patient outcome in the common melanoma types when matched for Breslow thickness. However, in pigment synthesising melanoma and pure desmoplastic melanoma, histogenetic type does appear to play a role in determining the likelihood of recurrence.

✓ The histogenetic type should be included in the pathology report.

4.7.2 BRESLOW THICKNESS

A strong association between tumour thickness and prognosis was originally demonstrated by Breslow[73] and has since been verified in many large scale studies of melanoma.[74-78] Breslow thickness is the single most important prognostic variable in primary cutaneous melanoma.[72] It is recommended that Breslow thickness is measured to a minimum of one decimal place but to allow for accurate staging, two decimal places should be used in cases sitting close to the boundary between pT1/2, pT2/3, and pT3/4 as defined by the American Joint Committee on Cancer (AJCC) (*see Table 6*).[72,79]

2+ 2++ 4

R **An accurate measurement of the Breslow thickness should be included in the pathology report for any melanoma that has an invasive component.**

4.7.3 ULCERATION

A small study of 177 participants with melanomas of intermediate thickness (1.51 to 3.99 mm) identified epidermal ulceration as one of four variables that predicted visceral and bony metastases.[80] Ulceration has been shown to act as a prognostic variable after adjustment for other variables.[75,76] A study of 1,042 patients identified epidermal ulceration as a significant prognostic variable and this was incorporated into a mathematical model for predicting recurrence and survival at three, five and ten years.[74] Some studies also show that increasing breadth of epidermal ulceration is associated with an increasingly unfavourable prognosis.[74]

2+

R **The presence or absence of histological evidence of epidermal ulceration should be noted in the pathology report.**

4.7.4 MITOTIC RATE

The most recent AJCC guideline specifically uses the presence of mitotic activity in the dermal component of a melanoma to distinguish pT1a from pT1b tumours (*see Table 6*). Both the AJCC and RCPath provide guidance on how to measure and report mitotic rates. This should be documented as mitoses per square millimetre and should be recorded as a 0 or a whole number. The presence of any mitotic activity (irrespective of how many high-power fields have been used during the assessment) should always be given a figure of at least 1.[72,79]

2++ 4

R **Mitotic rate is used as a defining criterion for pT1b melanomas and should be recorded in the pathology report.**

4.7.5 LYMPHOVASCULAR INVASION

Lymphovascular invasion (LVI) is a core dataset item from the RCPath and should be stated in the report. It is important to exclude retraction artifact and it is not important to separate lymphatic or vascular invasion.[72]

4

4.7.6 MICROSCOPIC SATELLITES/IN-TRANSIT METASTASIS

Microsatellites are defined by AJCC as any discontinuous nest of intralymphatic metastatic cells greater than 0.05 mm in diameter that are clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm.[81] Macrosatellite metastases are defined as discrete separate nodules within 2 cm of the primary tumor and are considered intralymphatic extensions of the primary tumor, whereas in-transit metastases are defined as any dermal or subcutaneous disease 2 cm or more from the primary tumor but not beyond the draining regional nodal basin.[79]

The presence of microsatellites upstages a melanoma to pTN2c.[79] The RCPath supports the view that microsatellites do not have to be present within the lymphatic system.[72]

2+ 4

A systematic review found that the prognosis for patients with microsatellites is essentially identical to that for patients with macrosatellites.[82] There was no demonstrable difference in survival for patients with satellites compared to those with in-transit metastases.

1+

A prospective cohort study of 258 patients with clinical stage I melanoma found that 13 out of 14 patients with histological evidence of lymphatic invasion developed in-transit metastases after a median interval of 10 months and concluded that lymphatic invasion correlates strongly with early locoregional cutaneous relapse.[83] **2++**

A study of 140 patients with thick melanomas reported that the identification of lymphatic invasion was associated with an increased risk of metastasis but not with overall survival.[84] However, in a series of 17,600 patients the presence of microsatellites had a profound negative impact on prognosis and in the current AJCC staging system the presence of satellites upstages the tumour from I or II to IIIb or IIIc.[79] **2+ 4**

Identifying lymphovascular invasion and/or microscopic satellites confers considerable prognostic value. The presence of lymphatic invasion accurately predicts early cutaneous relapse and should be included as a stratification criterion for the selection of patients for adjuvant therapy. The histological identification of microsatellites also defines a subset of patients at much greater risk of relapse. The presence of microsatellites correlates strongly with occult metastatic disease in regional lymph nodes.

R **Identification of microscopic satellites upstages the pN status of melanoma according to the AJCC cancer staging manual** (7th edition) **and should be included in the pathology report. The defining criteria should be strictly adhered to and the presence or absence of microsatellites should be stated in the pathology report.**

4.7.7 RADIAL VERSUS VERTICAL GROWTH PHASE

Tumour growth phase correlates strongly with clinical outcome.[75,85] A study of 501 patients with primary melanomas identified a subgroup of 122 as being in radial growth phase only. No patients in this subgroup showed evidence of metastatic disease during a minimum follow-up period of 100 months. The OR for a patient with radial growth phase melanoma surviving for eight years was given as 1.0.[75] A second study evaluated 624 patients, of whom 161 had melanoma displaying radial only growth phase characteristics. None of the patients developed metastatic disease at long-term follow up (median 13.7 years).[85] The definitions of growth phase are discussed in more detail in the RCPath dataset.[72] **2++ 4**

R **The growth phase characteristics should be stated in the pathology report of all melanomas.**

4.7.8 TUMOUR INFILTRATING LYMPHOCYTES

The association between survival advantage and the presence of tumour infiltrating lymphocytes (TIL) within the vertical growth phase component is unclear. Although one study demonstrated a strong correlation,[75] the presence of an inflammatory response loses independent prognostic strength on multivariate modelling.[74] **2++**

TILs are an AJCC prognostic item and are included in the RCPath dataset.

✓ Tumour infiltrating lymphocytes are a core dataset item and should be recorded in the pathology report.

4.7.9 REGRESSION

There is an adverse association between histological evidence of regression and outcome, but the strength of this relationship is disputed.[74,75 86] One large study identified tumour regression in the radial growth phase as a variable that retained predictive strength after multivariate analysis.[75] In a subsequent study of 1,042 patients the significance of tumour regression was subsumed by the other clinical and histological features studied.[74] Extensive late regression might indicate that the melanoma has, at some time, been significantly thicker than it now appears. Tumours with this feature are liable to be understaged.[86] **2++ 2+**

If the zone of regression is deeper than the deepest melanoma cell then this should not alter the formal Breslow thickness; Breslow thickness should be measured to the deepest tumour cell as per the original definition. Regression is defined by the RCPath as variable destruction of melanoma cells, inflammatory response, fibrosis and melanin laden macrophages. The RCPath suggest that severely dysplastic nevi and in situ melanoma which show convincing features of established regression should be considered for MDT discussion.[72] **4**

R **If the presence or absence of regression is apparent it should be included in the pathology report.**

4.7.10 CLARK LEVEL

The Clark level has been replaced by mitotic index/count for defining pT1a and pT1b tumours in the 7th edition of the AJCC staging system (*see section 4.7.4*). In cases where there is no ulceration present and mitotic activity cannot be assessed, if the tumour has a Clark level of 4 or of 5 then the tumour is staged as pT1b according to the AJCC.[72,79] **2++ 4**

R **If the pT1a/pT1b status cannot be determined through the presence of ulceration and/or mitotic activity then a Clark level of 4 or 5 can be used to upstage the tumour. Clark level only need be documented in these cases.**

4.7.11 BRAF STATUS

✓ Serine/threonine-protein kinase B-Raf (BRAF) status should be requested in all patients with advanced disease and recorded on the pathology report *(see section 9.3.1)*.

4.8 SPECIALIST PATHOLOGY REPORTING

Significant discrepancy exists between general pathologists, dermatopathologists as well as between experts in pigmented lesion pathology, in the reporting of melanocytic tumours.[87-89] Both under- and over-diagnosis of malignancy is recognised and, for melanoma, there is poor agreement on the assessment of prognostic parameters. **2++**

✓ Pathologists responsible for reporting melanocytic lesions must be aware of the diagnostic pitfalls in this area. Participation in appropriate continuing professional development (CPD) activity is advisable.

Cases where significant diagnostic doubt exists should be referred for specialist dermatopathology opinion.

4.9 MELANOMA PATHOLOGY REPORT

Table 5: Core features of a pathology report for invasive melanoma

Clinical data/macroscopic description	Histological data
Clinical site	Histogenetic type
Specimen type	Breslow thickness
Size of specimen in three dimensions	Ulceration
Size of lesion in three dimensions	Mitotic index
Atypical features	Lymphovascular space invasion
	Microsatellites/in-transit metastatic cells
	Perineural invasion
	Growth phase
	Tumour infiltrating lymphocytes
	Regression
	Clark level (if pT1a/b staging not possible from mitotic index/ulceration)
	Margins peripheral and deep
	Tumour stage (pT)
	BRAF status (if applicable)

4.10 PATHOLOGICAL EXAMINATION AND REPORTING OF THERAPEUTIC AND SENTINEL LYMPH NODE DISSECTION SPECIMENS

Detailed protocols for dissection of therapeutic lymph node dissection specimens are available in standard textbooks of surgical pathology.[90,91]

The surgical report for completion and therapeutic lymph node dissections (*see section 5.3*) should identify both macroscopic and microscopic features.

Macroscopic features which should be recorded include:

- the size of the specimen in three dimensions
- the presence (and size) or absence of a macroscopic abnormality, and
- the presence or absence of a localisation marker.

The microscopic features which should be recorded include:

- the exact number of nodes identified within the specimen
- the number of nodes containing metastatic disease and whether the atypical node is involved or not
- the presence or absence of extracapsular spread, and
- whether the margin of the specimen is involved by tumour.[72]

4

When macroscopic examination reveals tumour within a node, a single block of tissue is sufficient to confirm the observation. Nodes that appear tumour free should be serially sliced (if large) and all of the tissue processed. Small nodes may be processed intact and levelled to ensure thorough examination.[72]

Sentinel lymph nodes (SLN) are processed using either lymphoscintigraphy and/or blue dye to trace the afferent lymphatic channels and node. Protocols giving further details are available.[91-93] Nodes identified by lymphoscintigraphy (usually technetium-99) should be fixed in formalin for 24 hours to allow for radioactive decay.[72]

When dye has been used, the sentinel node should be examined macroscopically to determine whether any staining has occurred. The node should then be processed according to the European Organisation for Research and Treatment of Cancer (EORTC) trial protocol.[72]

Additional information to be recorded in the pathology report for SLNs include dye observed in tissue (macroscopic) and the number of SLNs involved in the tumour and the location of deposit: subcapsular, parenchymal and/or extracapsular spread (microscopic).[72]

4

Although immunohistochemistry (IHC) facilitates the detection of melanoma in sentinel nodes, the possibility of false positive results, for example the misinterpretation of capsular naevus cells, remains. This can be minimised by careful evaluation of the immunochemical preparations in the context of the corresponding haematoxylin and eosin stained section. The AJCC (7th edition) considers it acceptable to diagnose nodal metastases solely on IHC staining for melanoma-associated markers in situations where corresponding atypical cells are not always seen on haematoxylin and eosin sections.[79]

Groups of sections at multiple levels throughout the sentinel node are sometimes examined, but there is no evidence that such rigorous sampling increases the diagnostic yield. Detecting melanoma cells in SLNs using polymerase chain reaction (PCR) techniques cannot be recommended at present due to concerns regarding both sensitivity and specificity.[94]

5 Surgical management and staging

5.1 WIDE LOCAL EXCISION SURGERY FOR PRIMARY MELANOMA

Historically very wide margins of excision were advocated in the management of melanoma. Appreciation of Breslow thickness as a prognostic indicator (*see section 4.7.2*) supports the concept of a conservative approach to surgery, with narrowing of the margins of excision.[101-104] The safety of these narrower margins has been demonstrated in a series of studies.[105-108] **1+ 3 4**

A comparison of 1 cm and 3 cm margins for tumours up to 2 mm thick found no overall survival difference between the two groups.[95] A small number of patients with lesions thicker than 1 mm developed local recurrence.[96-98] **1+ 3**

A 1 cm margin should therefore be adequate for melanomas less than 1 mm thick. For lesions 1–2 mm thick a width excision of 1–2 cm should be considered, in the context of a full clinical assessment.

Lentigo maligna, (a variant of melanoma in situ), should also be surgically removed, given the risk of invasion. Currently 5 mm surgical margins are recommended, although a case series reported that 26% of lentigo maligna required greater margins to achieve clearance as atypical cells may extend beyond the visible edge.[99] There is limited evidence from case series that Mohs micrographic surgery (MMS) may reduce the size of the defect in lentigo maligna.[100] For patients for which surgery is not an option, there is some evidence for the use of radiotherapy and topical imiquimod for the treatment of lentigo maligna.[99,101] Cryotherapy and topical-5-fluorouracil have also been used but there is no recently published evidence.[100,102] **1++ 3**

Evidence-based recommendations on excision margins for melanoma can be found in the NICE guideline on assessment and management of melanoma.[45] **4**

R

- **Consider a clinical margin of at least 0.5 cm when excising stage 0 melanoma.**
- **If excision for stage 0 melanoma does not achieve an adequate histological margin, discuss further management with the multidisciplinary team.**
- **Offer excision with a clinical margin of at least 1 cm to people with stage I melanoma.**
- **Offer excision with a clinical margin of at least 2 cm to people with stage II melanoma.**

The suggested width of excision at sites of aesthetic and functional importance requires clinical consideration and discussion with the MDT. The deep excision margin should incorporate adipose tissue down to, but not including, the deep fascia.[103,104] No evidence was identified on optimal timing of wide excision in patients with melanoma.

5.2 STAGING MELANOMA

Melanoma should be staged using the tumour, node, metastasis (TNM) staging classification described by the American Joint Committee on Cancer (AJCC)[105] (*see Tables 6 and 7*).

Table 6: TNM staging categories for cutaneous melanoma[105]

T Classification	Thickness (mm)	Ulceration status/mitoses
T1	≤1.0	a. w/o ulceration and mitosis <1/mm^2 b. with ulceration or mitosis ≥1/mm^2
T2	1.01–2.0	a. w/o ulceration b. with ulceration
T3	2.01–4.0	a. w/o ulceration b. with ulceration
T4	>4.0	a. w/o ulceration b. with ulceration
N Classification	**No. of metastatic nodes**	**Nodal metastatic mass**
N1	1 node	a. micrometastasis* b. macrometastasis**
N2	2–3 nodes	a. micrometastasis* b. macrometastasis** c. in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s) or satellite(s) with metastatic node(s)	Serum lactate dehydrogenase (LDH)
M Classification	**Site**	**Nodal metastatic mass**
M1a	Distant skin, subcutaneous or nodal met(s)	Normal
M1b	Lung metastases	Normal
M1c	All other visceral met(s) Any distant metastasis	Normal Elevated

* Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

** Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastases exhibits gross extracapsular extension.

Table reproduced with permission.

Table 7: Anatomical and pathological staging for cutaneous melanoma[105]

Clinical staging*				Pathological staging**			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥N1	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	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

** Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

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5.3 MANAGEMENT OF REGIONAL LYMPH NODES

Examination of the regional lymph node basin is an essential component of the clinical evaluation of melanomas (*see section 4.6.1*). The presence or absence of nodal metastasis is the most significant predictor of outcome in melanomas.[106] **2++**

The risk of developing nodal metastases increases with the thickness of the primary melanoma.[107,108] Metastasis to lymph nodes is rare in melanomas less than 1 mm thick. At least 25% of melanomas between 1.5 and 4 mm will have microscopic lymph node metastasis at the time of primary diagnosis and this rises to over 60% in melanomas more than 4 mm thick.[109,110]

Regional lymph node metastasis is associated with poor prognosis, survival being less than half that of patients without nodal involvement.[111-113] **2++**

The number of involved nodes is of prognostic significance. Ten-year survival varies between 20% and 45% depending on the extent of nodal involvement.[106,111,113,114]

5.3.1 MANAGEMENT OF PALPABLE LYMPH NODES

Fine needle aspiration/open biopsy

Patients with melanoma who have palpable lymph node(s) either at their first presentation or at a follow-up visit should have fine needle aspiration cytology (FNAC). If the first sample is unsatisfactory or negative with persistent suspicion, it should be repeated with ultrasound guidance, if required. If doubt persists an open biopsy can be performed.[114,115] **4**

✓ If there is palpable lymphadenopathy FNAC should be used to obtain cytological confirmation of metastases.

If open biopsy is undertaken the incision must be placed in the same line as for a potential radical lymphadenectomy.

Therapeutic lymph node dissection

Confirmation of metastatic melanoma in a palpable lymph node is an indication for radical dissection of that lymph node basin.

Therapeutic lymph node dissection is beneficial in controlling locoregional disease. The risk of recurrence in the dissected node field remains, particularly with head and neck melanomas.[116,117] **2++**

Head and neck melanomas have the most variable pattern of lymph node metastasis and require a variety of types of neck dissection that may include the parotid or the posterior occipital chain nodes.[117]

R **Therapeutic lymph node dissection requires complete and radical removal of all draining lymph nodes to allow full pathological examination.**

✓ Patients with a confirmed metastatic lymph node(s) should be radiologically staged prior to lymph node dissection.

Regional lymph node dissection carries a well defined and significant morbidity and should be undertaken only by surgeons with appropriate expertise.

Patients should be advised of the risk of lymphoedema following lymph node dissection. If lymphoedema occurs, patients should be referred to a lymphoedema specialist.

5.3.2 MANAGEMENT OF NON-PALPABLE LYMPH NODES

The high incidence of occult metastasis in clinically impalpable nodes has prompted surgeons to investigate regional lymph nodes.

Sentinel lymph node biopsy

The sentinel lymph node is defined as the first node in the lymphatic basin that drains the lesion and is the node at greatest risk for the development of metastasis.[118] Biopsy of this node can assist in staging patients at risk of metastatic disease.

The standard for sentinel lymph node biopsy (SLNB) is a triple diagnostic approach of lymphoscintography, blue dye dermal infiltration and localisation using a hand-held gamma probe.[118-123] Performing SLNB requires appropriate surgical expertise,[118] specialist nuclear medicine services and the availability of serial sectioning and immunohistochemistry techniques (see section 4.10). **2+**

Sentinel lymph node biopsy can determine the presence or absence of metastasis within the regional lymph node basin[124-126] and it is a useful staging tool in melanomas >1 mm thick.[78] In thick melanomas (>4 mm) it can identify a subset of melanomas which are node negative and therefore offer a better prognosis.[126] **2++ 4**

There are no randomised control studies addressing the most effective way of managing patients with a positive sentinel lymph node biopsy. All of the observational studies reviewed were retrospective, had very small numbers and had significant selection bias[127,128] **1+ 4**

People who choose to have SLNB may benefit from more accurate staging, giving a better indication of outcome (survival and risk of relapse). Table 8 outlines possible advantages and disadvantages of SLNB and may help inform discussion with patients on whether or not to proceed with SLNB.[45] **4**

Table 8: Possible advantages and disadvantages of SLNB [45]

Possible advantages	Possible disadvantages
The operation helps to find out whether the cancer has spread to the lymph nodes. It is better than ultrasound scans at finding very small cancers in the lymph nodes.	The purpose of the operation is not to cure the cancer. There is no good evidence that people who have the operation live longer than people who do not have it.
The operation can help predict what might happen in the future. For example, in people with a primary melanoma that is between 1 and 4 mm thick: • around 1 out of 10 die within 10 years if the sentinel lymph node biopsy is negative • around 3 out of 10 die within 10 years if the sentinel lymph node biopsy is positive.	The result needs to be interpreted with caution. Of every 100 people who have a negative sentinel lymph node biopsy, around 3 will subsequently develop a recurrence in the same group of lymph nodes.
People who have had the operation may be able to take part in clinical trials of new treatments for melanoma. These trials often cannot accept people who haven't had this operation.	A general anaesthetic is needed for the operation
	The operation results in complications in between 4 and 10 out of every 100 people who have it.

Table reproduced with permission.

R **SLNB should be considered as a staging technique in patients with stage IB-IIC melanoma with a Breslow thickness of >1 mm. It should not be offered to patients with stage IB melanoma where Breslow thickness is ≤1 mm.**

Patients should be given detailed verbal and written information regarding the possible advantages and disadvantages of the SLNB procedure to allow them to make an informed decision.

Completion lymphadenectomy

Current practice is to consider completion lymphadenectomy in patients with a positive sentinel lymph node. No good-quality evidence was identified to determine whether completion lymphadenectomy provides better survival than clinical observation with or without serial ultrasound. Additionally there is insufficient evidence to characterise pathological features of the positive sentinel lymph node to instruct the decision regarding further management.[128] **1+**

NICE compiled the following table to inform discussion with patients on whether to proceed with completion lymphadenectomy.[45] **4**

Table 9: Possible advantages and disadvantages of completion lymphadenectomy

Possible advantages	Possible disadvantages
Removing the rest of the lymph nodes before cancer develops in them reduces the chance of the cancer returning in the same part of the body.	Lymphoedema (long-term swelling) may develop, and is most likely if the operation is in the groin and least likely in the head and neck.
The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them.	In 4 out of 5 people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily.
People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. These trials often cannot accept people who have not had this operation.	There is no evidence that people who have this operation live longer than people who do not have it.
	Having any operation can cause complications.

Table reproduced with permission.

R **Patients with a positive sentinel lymph node should be offered appropriate counselling regarding the advantages and disadvantages of completion lymphadenectomy.**

✓ Following lymphadenectomy all patients should have access to specialist lymphoedema services.

6 Further investigations and non-surgical staging

Further investigation to determine precisely the extent of the disease is important in terms of prognosis, treatment, entry into clinical trials, research and audit.

Following pathological microstaging of a patient's melanoma (*see section 4.7*) the presence of metastatic spread can be determined using three techniques:

- **Surgical:** assessment of the impalpable node by sentinel node biopsy and of the palpable node (*see section 5*)
- **Imaging:** conventional radiography, ultrasound scanning (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET-CT)
- **Blood Tests:** routine haematology, tumour markers, liver function tests and lactate dehydrogenase (LDH).

6.1 IMAGING TECHNIQUES

6.1.1 CROSS SECTIONAL IMAGING

No good quality evidence was identified on which patients should undergo imaging as part of staging. Patients with stage IIC tumours have a worse prognosis compared to patients with other stage II tumours, with prognoses more comparable to stage III disease.[79] Stage IIC tumours are therefore treated like stage III tumours in two guidelines.[45,129] A guideline from NICE recommends that patients with stage IIC (without SLNB) and stage III disease should be offered CT imaging, due to the high risk of occult disease.[45] Guidelines from the British Association of Dermatology (BAD) advise against routine imaging for patients with stages I or II melanoma because of the low incidence of true-positive and high incidence of false-positive findings, with the exception of patients with high-risk primary melanoma.[130] **4**

It is the consensus opinion of the guideline development group that patients with stage IIC disease and above should be offered initial staging imaging.

No RCTs comparing CT and PET-CT in the staging of melanoma were identified. A meta-analysis of retrospective and prospective studies on the diagnostic accuracy of PET-CT and CT reported that PET-CT is the most sensitive and specific initial staging modality for the detection of distant metastases in patients with melanoma (sensitivity 80%, 95% credible interval (CrI) 53% to 93%; specificity 87%, 95% CrI 54% to 97% versus CT sensitivity 51%, 95% CrI 54% to 76%; specificity 69%, 95% CrI 30% to 92%).[131] Further systematic reviews found PET-CT to have a sensitivity of 68–87% and specificity of 92–98% in patients with stage III or stage IV disease[132] and specificity of 89% in patients with stage III disease.[133] Many of the included studies, however, were retrospective and of poor quality, with wide inclusion criteria and insufficient reporting of withdrawals. Several potential sources of bias were also identified including referral bias, verification bias and review bias. The studies reported on diagnostic accuracy but did not include patient relevant outcomes. **2^{++}** **2^{+}**

Whilst PET-CT would seem to have a higher sensitivity and specificity for the detection of metastases, the quality of the evidence does not support its routine use as a first-line imaging modality in the staging of melanoma. This, in addition to its relative cost and limited availability in Scotland,[134] inform the consensus opinion of the guideline development group that its use should currently be restricted to patients with indeterminate findings on CT or for those being considered for a major surgical resection.

R **Staging CT should be offered to patients with stage IIC or above melanoma.**

✓ Staging CT should include head, chest, abdomen and pelvis. The neck should be included in patients with head and neck melanoma.

✓ PET-CT should only be considered for patients with indeterminate findings on CT or for patients who are being considered for major surgical resection, after discussion with the specialist multidisciplinary team.

6.1.2 IDENTIFYING BRAIN METASTASES

No high-quality evidence was found on the optimal imaging modality for identifying brain metastases specifically in patients with melanoma. Evidence from reviews of studies of imaging on a variety of primary tumours suggest that contrast MRI is more sensitive than contrast CT in detecting brain metastases.[135,136] **4**

Given that patients are likely to have a CT of the chest, abdomen and pelvis during staging of melanoma, and taking tolerability, cost and availability into consideration (*see section 6.1.1*), it is the consensus opinion of the guideline development group that CT should be the first-line imaging modality for identifying brain metastases.

R **CT of the head with contrast should be used as the first-line imaging modality for identifying brain metastases.**

MRI of the head should be considered where CT findings are equivocal.

If patients are being considered for locoregional treatment of brain metastases, contrast MRI should be performed to identify further lesions which may alter management.

6.2 LABORATORY INVESTIGATIONS

Investigations such as full blood counts (FBC) and liver function tests (LFT) are not helpful in identifying asymptomatic patients with distant disease.[137,138] Elevated LDH in the absence of clinical symptoms or signs is the first indicator of stage IV disease in 12.5% of patients. By the time other blood parameters are significantly deranged, the patient will have other manifestations of metastasis.[137,138] For patients with advanced disease, LDH is now included in the AJCC classification system.[78] The evidence and availability of tumour markers such as S100 protein, melanoma inhibitory activity (MIA) protein and tyrosinase mRNA are limited. Investigating these markers is not routinely indicated.[139] **3**

R **Routine blood tests are not indicated in staging asymptomatic patients with melanoma, with the exception of LDH in patients with stage IV disease, which is part of routine classification.**

7 Adjuvant treatment of stage II and III melanoma

Pathological features of primary melanoma, particularly Breslow thickness and ulceration, make it possible to identify patients with stage II disease who are at high risk of local or systemic recurrence (*see section 4.7*). Once patients have had melanoma recurrence in the local regional lymph nodes (stage III disease), over 50% will subsequently develop further metastatic spread. These observations support attempts to identify adjuvant treatment such as chemotherapy, immunotherapy and radiotherapy, given after complete clinical surgical clearance of melanoma.

7.1 ADJUVANT RADIOTHERAPY FOR RESECTED STAGE III MELANOMA

A single randomised phase 3 trial comparing adjuvant radiotherapy and observation was carried out in 250 patients who had undergone complete lymphadenectomy and were thought to be at high risk of local recurrence. Risk of lymph node relapse was significantly reduced in the adjuvant radiotherapy group (hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.32 to 0.98, p=0.041) but no differences were noted for relapse-free or overall survival.[140] Adjuvant radiotherapy is known to be associated with a risk of both short-term (dermatitis) and long-term (lymphoedema) toxicity. Results from trials on long-term radiotherapy complications are awaited. A case series suggested a significant increase in morbidity including lymphoedema rate as a complication of adjuvant radiotherapy.[141]

1++
3

R **Consider adjuvant radiotherapy for patients with completely resected stage IIIB or IIIC melanoma after discussion of the risk of local recurrence and the benefits and risks of radiotherapy including risk of significant adverse effects.**

7.2 IMMUNOTHERAPY

7.2.1 INTERFERON

The observation that a large number of primary melanomas undergo partial regression and a small number of patients experience total regression of the whole melanoma has led to the concept of using either specific or non-specific immune stimulation as therapy for melanoma.

Adjuvant interferon alpha has been used in at least 10 large RCTs involving over 5,000 patients.[142-151] Interferon dosage, frequency and route of administration and total duration of therapy all varied, but no trial reported significant overall survival benefit for interferon-treated patients. Several of the larger studies do report longer disease-free intervals after surgery[145-147] but there is no evidence of a dose or duration of treatment effect. Toxic effects of interferon include extreme lassitude, muscle aches, headache, rigors, nausea, vomiting, and marrow toxicity, the latter being the cause of death in two patients in the first reported high-dose study.

1++

R **Adjuvant interferon should not be used for patients with AJCC stage II and III melanoma other than in a trial setting.**

A number of well-designed trials of adjuvant immunotherapy (including ipilmumab, nivolumab and pembrolizumab) are ongoing.

7.3 IMMUNOSUPPRESSION

Numerous studies have investigated the relationship between immunosuppression and melanoma incidence. A poor-quality systematic review of population studies found that compared to the general population, there is a 2.4-fold (95% CI, 2.0 to 2.9) increased incidence of melanoma after transplantation.[152] A meta-analysis also found that inflammatory bowel disease was associated with a 37% increased risk of melanomas compared to the general population.[153] In addition, cohort studies have shown that patients with HIV have an increased risk of melanoma (standardized rate ratio of 2.6 (95% CI, 1.9 to 3.6),[154] patients with a history of non-Hodgkin lymphoma (NHL) have a risk of subsequent melanoma that is increased 1.8 to 2.4 times,[155] and patients with chronic lymphocytic leukaemia (CLL) have an increased risk of 2.3 to 3.1 times that of controls.[156]

1-
2++
2+

Although iatrogenic immunosuppression has been associated with increased risk of malignancy there is little data that is specific to melanoma. A population-based cohort study found that patients with rheumatoid arthritis treated with tumour necrosis factor (TNF) inhibitors had an increased risk of melanoma compared with patients with rheumatoid arthritis not treated with TNF inhibitors (HR 1.5, 95% confidence interval 1.0 to 2.2).[157] A case-control study found that the use of TNF-alpha antagonists was independently associated with an increased melanoma risk in patients with inflammatory bowel disease (OR 1.9, 95% CI, 1.1 to 3.3)[158] however, in a second cohort, the adjusted odds ratio was non-significant (OR 1.3, 95% CI, 0.6 to 2.7).[159] **2**⁻

Several studies have investigated the relationship between immunosuppression and melanoma prognosis. A retrospective review of immunosuppressed transplant patients found that those with thick melanoma (>3 mm) had a significantly poorer melanoma cause-specific survival rate.[160] A second retrospective review found that the outcome for post-transplant patients with melanoma was significantly worse for those with tumours of Breslow thickness >2 mm.[161] A further retrospective review found that patients taking immunosuppressants at the time of diagnosis of melanoma had a higher mortality than controls (42% v 23%, p=0.01) suggesting that immunosuppressive therapy may be associated with a more aggressive disease course.[162] There is limited data on the prognosis for patients who were diagnosed with melanoma before having a transplant.[152] **3** **2⁺⁺**

A case-series has described the spontaneous regression of advanced melanoma in patients on long-term azothioprine for autoimmune disease on withdrawal of the immunsuppression.[163] **3**

✓ All patients with melanoma and a history of immunosuppression should have an MDT approach to care and minimising the immunosuppressive therapy should be considered where possible.

8 Follow up of patients with stage I, II and III melanoma

8.1 INTRODUCTION

The purpose of the follow up-clinic is to:

- provide reassurance and psychological counselling
- provide comprehensive information about all aspects of the patient's melanoma
- detect recurrent disease
- teach patients how to self examine for local and nodal recurrence
- detect new primary melanomas.

No RCTs on follow-up methods were identified. Eight retrospective studies[164-171] and one prospective cohort study[172] were identified highlighting the following issues:

- who should be followed up?
- how frequently should patients be followed up?
- for how long should patients be followed up?
- how are recurrences detected?

8.2 SITE OF INITIAL RECURRENCE

Large retrospective studies show that between 60% and 80% of first recurrences are local and/or nodal.[165-174] **4**

8.3 TIMING AND RATE OF RECURRENCE

The timing and rate of recurrence of melanoma is well recognised (*see Table 10*).[170,173] **3**

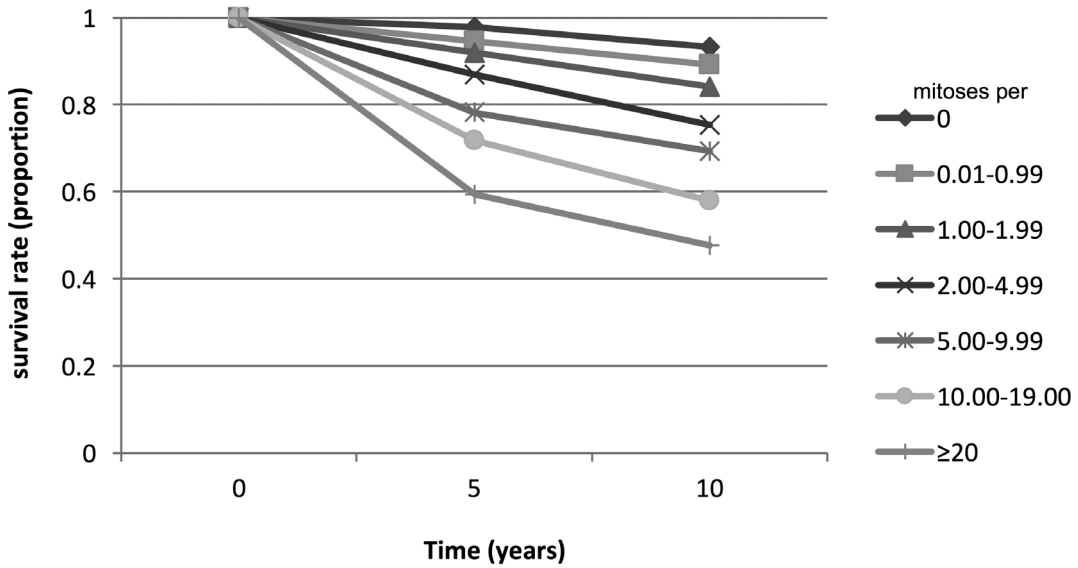
Table 10: Timing and rate of recurrence of melanoma

Tumour thickness	Recurrence rate	Median recurrence time
<1.5 mm	2–19%	25–32 months
>1.5 mm	47–66%	12–16 months

The annual risk of recurrence for tumours <1.5 mm thick remains <6% for the first five years dropping to under 1% for the next five years. Tumours >1.5 mm thick have a higher risk of recurrence in the first year, dropping to <2% after year five.[164,169,170] Overall most studies indicate that about 80% of recurrences occur within the first three years[164,173,174] but up to 16% of first recurrences have been reported to occur after five years[170] and late recurrence (more than ten years) is well recognised.[175-178] **3**

Increased mitotic rate has also been found to be associated with risk of recurrence and survival, (*see Figure 1 and section 4.7.4*). [179] **1+**

Figure 1: Five-and ten-year survival rates plotted against mitotic rate



8.4 FOLLOW UP

Current practice is that all patients with an invasive melanoma should have a period of follow up. Patients with completely excised melanoma in situ have no risk of recurrence.[164] **3**

✓ Patients who have had melanoma in situ do not require follow up.

Patients should be given information and education on personal regular skin surveillance and nodal disease.

Patients with an invasive melanoma should have a period of follow up.

The guideline published by NICE in 2015 on the management of melanoma recommends a standard follow-up system for the UK[45], based on the AJCC stage of a patient's melanoma at diagnosis (*see Table 11 and section 5.2*). **4**

Table 11: Follow up for patients with melanoma

Stage 0	No follow up after initial treatment, results and advice
Stage IA	2 to 4 reviews over a 12 month period then discharge with advice
Stage IB to IIC	Review every 3 months for 3 years then every 6 months for another 2 years
Stage III and over	Every 3 months for five to ten years

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8.5 PSYCHOLOGICAL AND EMOTIONAL SUPPORT

None of the studies identified explored patients' psychological and emotional needs when determining the frequency or length of follow up (*see section 11*).

✓ Follow-up frequency and duration should take account of patients' psychological and emotional needs.

8.6 SECOND PRIMARIES

Three retrospective studies found second primaries in 1.2%, 2% and 7% of their patients.[164,170,180] The timing of discovery ranged from synchronous with the initial melanoma to more than 10 years later. The second primaries were usually thinner. One paper estimated that the Scottish patients in their study had a 200-fold increase in risk of developing a second melanoma compared to the general population[180] (*see Table 2, section 3.4.2*). **4**

8.7 DETECTING RECURRENCES

Large retrospective studies have shown that 90% of recurrent disease in patients with stage I and II melanoma is detected solely by signs or symptoms noted either by the patient or the physician, with imaging techniques detecting the remainder.[165,167,168,181,182] Patients' own detection rates in between clinic visits are generally in the range of 33–72%[164,166,168,171,182,183] but in one study where patients with stage I-III melanoma were meticulously educated in self-examination techniques the rate of self detection rose to 100%.[184] The rate of self detection in one prospective trial was much lower at 17%.[183] Three retrospective studies indicate that the overall survival time is the same for patient-detected recurrences as for those detected in the clinic.[168,171,182] **3**

8.7.1 ROUTINE LABORATORY TESTS

Routine laboratory tests (full blood count and liver function tests) do not detect asymptomatic recurrent disease in patients with stage I-III melanoma.[137,165-167,184]

Lactate dehydrogenase is a marker of liver metastases and tumour burden in patients with stage IV disease that indicates a poor prognosis.[182,185,186] Two studies have looked at LDH as a first indicator of metastases. An elevated LDH was the first indicator in 12.5% of patients with stage III disease (with a sensitivity of 73%) when tested for every three months.[138] In a prospective cohort study of stages I-IV disease an elevated LDH was the first indicator in 2% of recurrences when patients were tested every 12 months (stages I and II melanoma) or every six months (stages III and IV melanoma).[172] **3**

8.7.2 SURVEILANCE IMAGING

Overall, the quality of evidence for the method (including imaging), frequency and duration of surveillance in patients with melanoma is very low in all clinical outcomes of interest.[45] This is demonstrated by the lack of a consensus on an approach to surveillance from a wide variety of different dermatological and oncological organisations.[187] **2++ 4**

A meta-analysis of prospective and retrospective studies addressing the diagnostic accuracy of imaging modalities for surveillance of patients with melanoma reported that PET-CT has the highest sensitivity and specificity for detecting distant metastases (sensitivity 86%, 95% CrI 76% to 93%; specificity 91%, 95% CrI 79% to 97%), compared to CT (sensitivity 63%, 95% CrI 46% to 77%; specificity 78%, 95% CrI 58% to 90%).[131] However, many of the included studies were retrospective and of poor quality with wide inclusion criteria and insufficient reporting of withdrawals. Several potential sources of bias were also identified including referral bias, verification bias and review bias. A further review of the role of PET-CT in the surveillance of patients with malignant melanoma found a sensitivity of 96% and specificity of 92%.[188] There was no direct comparison to CT. The authors criticised the lack of high quality prospective studies in this field and highlighted a number of possible biases in the studies, especially referral bias. Neither of these reviews included data on patient outcomes and the studies looked at diagnostic accuracy only. **2+ 4**

Whilst surveillance imaging has potential benefits, there are also considerable potential disadvantages that need to be taken into account. These are summarised in the NICE guideline on melanoma (*see Table 12*).[45]

Table 12: Potential advantages and disadvantages of surveillance imaging

Possible advantages	Possible disadvantages
If the melanoma comes back (recurrent melanoma), it is more likely to be detected sooner. It is possible that this could lead to a better outcome by allowing treatment with drugs (such as immunotherapy drugs) to start earlier.	Although early drug treatment of recurrent melanoma might improve survival, there is currently no evidence showing this.
Some people find it reassuring to have regular scans.	Some people find that having regular scans increases their anxiety.
	Scans expose the body to radiation, which can increase the risk of cancer in the future.
	Scans of the brain and neck increase the risk of developing cataracts.
	Scans of the chest cause a very small increase in the risk of thyroid cancer.
	Scans may show abnormalities that are later found to be harmless, causing unnecessary investigations and anxiety.

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It is the consensus opinion of the guideline development group that surveillance imaging should not be offered to patients with stage I-IIB melanoma as the potential disadvantages are felt, on balance, to outweigh the potential benefits.

Given the lack of good-quality evidence, recommendations on the routine surveillance imaging of patients with stage IIC-III melanoma cannot be made. It is suggested that decisions on the routine use of surveillance imaging should be made on a regional basis at the managed clinical network (MCN) level, Any additional imaging resources required for surveillance should be identified and agreed in advance. On an individual level, decisions about surveillance imaging also need to take account of other factors such as the stage of the primary tumour, potential fitness of the patient for further treatment, and the patient's views after discussion of the potential advantages and disadvantages of surveillance imaging.

As with initial staging, CT should be considered the investigation of choice for surveillance imaging, due to the poor quality of the evidence for the role of PET-CT in surveillance imaging and its higher cost and more limited availability (*see section 6.1.1*).

R **Routine surveillance imaging should not be offered to patients with stage I-IIB melanoma.**

Decisions on the use of routine surveillance imaging for patients with stage IIC-III melanoma should be made at a regional managed clinical network level after identifying and agreeing any additional imaging resources required and considering other factors, including patient choice.

✓ CT should be used for surveillance imaging, if this is undertaken.

9 Management of advanced (unresectable stage IIIC or IV) melanoma

9.1 INTRODUCTION

Recent years have seen the development of several new treatment options for patients with advanced melanoma including BRAF and mitogen-activated protein kinase (MEK) inhibitors and several novel immunotherapies. All of these treatments are associated with significantly improved outcomes although the optimal choice, sequence and combination of therapies are still to be determined. It is now also recognised that there are several different genomic subtypes of melanoma [189] although translating this increased understanding into the development of other new therapies for patients with melanoma remains under investigation.

✓ All patients with advanced melanoma should be tested for mutations in BRAF and have their management discussed at a specialist MDT in order to determine the optimal management strategy taking into account patient fitness, co-morbidity, disease burden and overall aim of treatment.

All patients with advanced melanoma should be offered the opportunity to participate in clinical trials.

9.2 SURGERY

Metastasectomy may be an option for patients with distant skin, node and visceral metastases. In subcutaneous metastases prevention of ulceration of superficial lesions is best prevented by resection when the lesions are at a size where skin closure is possible. Surgery of single or localised metastases has been shown to be associated with improved survival.190 The proportion of patients suitable for metastasectomy ranges from 10% to 25%.[191-193] Five-year survival of 14-33% was described in one retrospective review for those with distant subcutaneous and lung metastases respectively. This study showed prognostic significance for Breslow thickness, number of metastases and prior disease-free interval.[191]

✓ Metastasectomy should be considered in patients with stage IV disease

9.3 SYSTEMIC THERAPY

9.3.1 BRAF AND MEK INHIBITORS

Development of BRAF inhibitors (vemurafenib and dabrafenib) as single agents or in combination with a MEK inhibitor (cobimetanib and trametinib) represents a major advance for patients with advanced melanoma.

Two open label RCTs demonstrated that BRAF inhibitors (vemurafenib and dabrafanib) improved response and progression-free survival (PFS) compared to chemotherapy alone in patients with unresectable stage IIIC or stage IV *BRAF* mutation-positive melanoma with a response rate of 48% and 50% versus 5% and 6%; PFS 5.3 and 5.1 months versus 1.6 and 2.7 months respectively.[194,195] Response is further improved with the combination of a BRAF inhibitor (vemurafenib or dabrafenib) and a MEK inhibitor (cobimentinib or trametinib), with an improved response rate and PFS compared to a BRAF inhibitors alone (response rate 64–68% versus 45–51% for BRAF inhibitors alone and PFS 9.3 to 11.4 months versus 6.2 to 8.8 months).[196-198] **1⁻ 1⁺**

The toxicity profile for BRAF inhibitors compared to combination BRAF and MEK inhibitors is diverse: grade 3-4 toxicity rates range from 28–63% for BRAF inhibitor alone and 35–65% for combination therapy.[194-198]

Vemurafenib and dabrafenib are accepted for use by the SMC as monotherapy for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma as first-line therapy (*see section 12.4*). Trametinib in combination with dabrafenib is approved for use in the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.

R **Trametinib in combination with dabrafenib is recommended for patients with unresectable stage IIIC or stage IV melanoma with a *BRAF* V600 mutation.**

9.3.2 IMMUNOTHERAPIES

Development of novel immunotherapies (ipilimumab, pembrolizumab and nivolumab) as single agents or in combination represents a major advance for patients with advanced melanoma.

Several RCTs have demonstrated that novel immunotherapies are effective in improving outcomes in patients with unresectable stage IIIC or stage IV melanoma.

A trial comparing ipilimumab to glycoprotein100 (gp100) for second-line therapy found that ipilimumab was associated with improved overall survival (OS) of 10.1 months versus 6.4 months (HR 0.66; p=0.003). [199]

Compared to chemotherapy for first-line treatment, nivolumab had a PFS of 5.1 versus 2.2 months, HR 0.43, 95% CI 0.34 to 0.56; one-year OS was 72.9% versus 42.1%, HR 0.42, p<0.001.[200] **1+**

Ipilimumab has also been compared to nivolumab and pembrolizumab in RCTs.

Pembrolizumab (two-weekly or three-weekly) was associated with an improved six-month PFS of 47.3% (two-weekly) or 46.4% (three-weekly) compared to 26.5% for ipilimumab, HR 0.58; p,0.001; one-year OS was 74.1%, 68.4% or 58.2% respectively HR 0.63; p=0.0005 for two-weekly pembrolizumab, HR 0.69; p=0.0036 for three-weekly pembrolizumab; the response rate was 33.7% versus 32.9% versus 11.9% (p<0.001 for both comparisons).[201]

The combination of nivolumab and ipilimumab improved outcomes compared to ipilimumab or nivolumab alone (PFS 11.5 months (combination) versus 2.9 months (ipilimumab) versus 6.9 months (nivolumab), HR 0.42; p<0.001). This study also confirmed that the outcomes for nivolumab were significantly improved compared to ipilimumab; PFS 6.9 months versus 2.9 months, HR 0.57 (p<0.00001).[191] **1+**

All of the novel immunotherapy agents are associated with a significant risk of autoimmune toxicity including colitis. Grade 3–4 toxicity rates are generally lower with single agent nivolumab (11.7%) and pembrolizumab (10.1–13.3%), higher with ipilimumab (10–19.9%) and highest with the combination of nivolumab and ipilimumab (55%).[199-203] **1+**

While there is evidence of efficacy for novel immunotherapies, optimal choice, sequence and combination of therapies are still to be determined. Ipilimumab, pembrolizumab and nivolumab monotherapy and ipilimumab/nivolumab combination therapy have been considered and accepted for use by the SMC (with restrictions) (*see section 12.4*).

R **Ipilimumab, pembrolizumab and nivolumab monotherapy or ipilimumab/nivolumab combination therapy are recommended for patients with unresectable stage IIIC and IV melanoma.**

9.4 ISOLATED LIMB PERFUSION

Isolated limb perfusion (ILP) is a surgical technique that allows localised delivery of a high dose of chemotherapy (usually melphalan). Minimal systemic leakage occurs, confining toxicity to the limb. ILP has been used in two clinical situations:[204,205]

- adjuvant treatment for high-risk primary melanoma
- therapeutic treatment for major limb recurrence of melanoma.

Isolated limb perfusion is a significant surgical undertaking and should only be made available in centres where a high number of such operations are performed each year. One centre can provide this service for a population of approximately five million people.

✓ ILP should be performed in a specialist centre.

9.4.1 ADJUVANT TREATMENT

A prospective multicentre RCT involving 832 patients showed that prophylactic ILP with melphalan cannot be recommended in patients with a high-risk primary limb melanoma.[206] **1+**

✓ ILP should not be used as an adjuvant treatment.

9.4.2 THERAPEUTIC TREATMENT

A multicentre RCT[207] and reviews[208,209] suggest that hyperthermic ILP with melphalan alone or melphalan plus TNF alpha can produce a complete though short lived response rate ranging from 50 to 90% in patients with limb recurrence (in-transit metastases). **1+ 4**

✓ ILP is a treatment option for patients with bulky disease confined to one limb.

9.5 ABLATIVE THERAPIES

9.5.1 CARBON DIOXIDE LASER ABLATION

A carbon dioxide laser delivers short wavelength energy in a focussed light beam to destroy tumour nodules. It can be applied under local anaesthetic, can be repeated and provides effective local disease control.[210-212] **4**

✓ Carbon dioxide laser ablation can be considered for multiple lesions of trunk or abdomen and for limb disease.

Other similar treatments are available and vary locally.

9.5.2 ELECTROCHEMOTHERAPY

Electrochemotherapy (ECT) uses short electric pulses to increase the absorption of either intralesional or intravenous chemotherapy.[213] It can be used in patients who have had previous surgery, radiotherapy and isolated limb perfusion/infusion, and may provide further treatment options when others have been exhausted.[214,215] **1+**

Meta-analyses report a high response rate to ECT in patients with cutaneous metastases.[213,214] ECT had a complete response of 56.8% and, for complete response and partial response combined, an objective response of 80.6% in patients with melanoma compared to 8% and 19.9% for chemotherapy alone for all tumour types (with no significant difference found between tumour type).[214] ECT was well tolerated with 90% of patients reported to be amenable to further treatment if needed.[213] Minor side effects from treatment were muscle spasms, skin changes, nausea and fatigue.[215] **1+**

Data on long-term survival or quality of life is limited.[215] No studies were identified comparing the efficacy of ECT with recently developed immunotherapies. **1+**

No evidence on the cost effectiveness of ECT was identified. It is currently only available in one centre in Scotland: NHS Tayside. Delivery of ECT requires specialist equipment and training.

R **Electrochemotherapy should be considered as a treatment option for patients with cutaneous melanoma metastases after multidisciplinary team discussion and careful consideration of alternative systemic therapy options, or when other options have been exhausted.**

9.6 RADIOTHERAPY

9.6.1 RADIOSENSITIVITY

There is evidence that melanoma cells in vitro have a spectrum of radio sensitivity and that melanoma should not be considered a uniformly radio resistant disease.[216] Experimental studies have suggested that atypical, large radiotherapy fraction sizes may be more efficacious than standard treatments but at present there are no randomised trials to support the routine use of large fraction sizes.[216,217] **4 3**

9.6.2 BONE METASTASES

Studies looking at the treatment of bone metastases usually include only a small percentage of patients with melanoma. Recommendations have been extrapolated from the data available from studies of bone metastases from various tumour types. When using single fractions to palliate pain from bone metastases, an 8 Gy fraction is effective and provides superior pain relief to lower doses.[218] There does not appear to be an advantage to using 20 Gy in four fractions over an 8 Gy single fraction.[219] Some patients may benefit from higher dose, fractionated regimens, although this has not been fully established.[220]

2+ 2++ 4

R **Single-dose radiotherapy of a least 8 Gy may be an effective treatment for bone metastases.**

9.6.3 SPINAL CORD COMPRESSION

There is no clear evidence to support or refute the use of radiotherapy (in combination with other treatments) to alleviate the pain and neurological deficit associated with spinal cord compression caused by metastatic melanoma.[221,222]

3 4

The value of surgical intervention in such patients has been established.[222,226] Patients with symptoms of spinal cord compression should be referred urgently to an appropriate surgeon.[223]

✓ If a patient presents with spinal cord compression consideration should be given to available medical oncology options. *BRAF* testing should be considered if this has not already been done, and targeted *BRAF* therapy should be considered in new cases.

9.6.4 BRAIN METASTASES

Although central nervous system (CNS) involvement by melanoma is a common finding at autopsy, brain metastases are diagnosed in only approximately 10% of patients before death.[224] For cerebral metastases from all tumour types, good performance status, favourable response to corticosteroid treatment, and the absence of systemic disease are statistically significant predictive factors for a better survival.[225]

4 2+

Postoperative radiotherapy has been used as adjuvant treatment following the resection of CNS disease. However, no survival benefit from postoperative radiotherapy has been demonstrated.[224,226] Radiotherapy without surgery, combined with corticosteroids appears to palliate the symptoms of some patients with inoperable cerebral metastases from melanoma but there is no evidence of a survival benefit.[216,226,227] Radiosurgery (stereotactic radiotherapy) has been used to treat patients with inoperable disease who are fit enough to undergo this procedure, and the results may be equivalent to surgery alone.[228]

3

Two non-comparative studies were identified on BRAF inhibitors in patients with brain metastases,[229,230] which do not alter the current recommendation on the use of BRAF inhibitors (*see section 9.3.1*).

Two Cochrane reviews addressing brain metastases were identified. The first concluded that adding whole-brain radiotherapy (WBRT) to surgery or stereotactic radiosurgery (SRS) did not show a survival benefit over surgery or SRS alone.[231] The other concluded that there was low-quality evidence that adding upfront WBRT to surgery or SRS decreases any intracranial disease progression at one year but no clear evidence of an effect on overall and progression free survival.[232]

1+ 2+

R **Patients with good performance status, favourable response to corticosteroid treatment, absence of systemic disease and who harbour favourable CNS disease should be considered for surgical resection of their CNS disease.**

If surgery is not possible, patients should be considered for systemic therapy.

✓ All patients with brain-limited metastasis should tested for *BRAF* mutations and their management discussed at a neuro-oncology multidisciplinary team to determine the optimal choice of treatment including systemic or targeted therapy, surgery or stereotactic radiosurgery.

9.7 SPECIALIST PALLIATIVE CARE

The General Medical Council has stated that basic palliative care skills are required by every member of the medical profession.[233] Clinical Standards for the provision of both basic and specialist palliative care are available.[234] Specialist palliative care is an integral component of the care of patients with advanced malignancy, required at varying times during their illness. SIGN guideline number 106 (Control of pain in patients with cancer) covers pain control in patients with all cancers.[235]

Patients who develop metastatic melanoma require input from a number of agencies both within and outwith the health service. They may need rehabilitative, functional, social and/or financial support services, most of which are available in specialist palliative care settings, as well as in primary care and cancer centres. The evaluation of the effectiveness of specialist palliative care involves assessment of the different dimensions of care provided, such as pain and other symptom control, psychological care, care of the family and carers, rehabilitation and terminal care.

Three RCTs were identified that included all carcinomas, which, in the context of palliative care, are reasonable to relate to patients with melanoma.[236-238] The first two studies looked at the effect of co-ordinating all services available within the NHS, local authorities and the voluntary sector through the addition of nurse co-ordinators. A total of 203 cancer patients expected to live for less than one year were randomly assigned to either the intervention or the routine services group. Patients assigned to the intervention group spent fewer days in hospital, required fewer home visits and their family were less likely to feel angry about their relative's death.[236,237] The third RCT used place of death as the outcome measure in a study of 434 patients with incurable malignant disease.[238] The intervention group had inpatient and outpatient hospital services provided by the palliative medicine unit, the unit served as a link to community services, predefined guidelines maintained communication between services and community staff took part in an educational programme. Significantly more intervention group patients died at home and spent less time in nursing homes in their last months of life. **1+**

A systematic review of the effectiveness of specialist palliative care teams identified 18 studies, including five RCTs.[239] Specialist palliative care teams were associated with more time spent at home by patients, satisfaction of patients and their carers, symptom control, a reduction in the number of inpatient hospital days, a reduction in overall cost, and with the patient dying where they wished. **1+**

R **Patients with advanced melanoma require a co-ordinated multiprofessional approach with input from a specialist palliative care team.**

Patients with poorly controlled symptoms should be referred to specialist palliative care at any point in the cancer journey.

10 Melanoma in women

10.1 PREGNANCY

Pregnancy is frequently associated with increased activity of benign melanocytes leading to pigmentary changes. This has led to concern that pregnancy is deleterious for women with melanoma.

The prognoses of women with thickness-matched melanomas who embarked on a pregnancy after apparently successful surgical treatment of AJCC stage I or II melanoma have been compared.[240-243] No difference in disease-free or overall survival is found between women who have, and women who have not, become pregnant after melanoma treatment. Prognosis is mainly dependent on tumour thickness.[240-243] **2++**

There is no substantial evidence of an effect of pregnancy in women with stage III and IV melanoma, but as the prognosis for these groups is already poor, the possibility of a maternal death during pregnancy or when the child is an infant is high.

The placenta of an infant born to a mother with stage III or IV melanoma should be examined for the presence of melanoma metastases. If they are present there is a 20% risk of death of the baby from transplacental melanoma.[244-246] **3**

Women who develop melanoma during a pregnancy show a greater mean thickness of the primary lesion at the time of excision than age-matched non-pregnant women.[242,243] This suggests either delayed diagnosis or accelerated growth due to the hormonal and immunological environment of pregnancy. There is no evidence to support the suggestion that it is physiological for melanocytic naevi to change during pregnancy.[247] **2++**

There are no good data on prognosis for women who embark on a pregnancy having had a melanoma diagnosed and treated during a previous pregnancy. One paper reports that patients with stage I or II disease have no greater recurrence rate than non-pregnant age-matched controls but that those with nodal disease have significantly higher recurrence rates.[248] **4**

✓ Women with a significant risk of recurrence (localised disease of ≥1mm thickness) who wish to become pregnant after surgery for stage I or II melanoma should be advised to delay pregnancy for two years postsurgery, as the likelihood of recurrence is highest during this period.

Pregnant women who present with growing or changing pigmented lesions should be treated as non-pregnant women.

10.2 ORAL CONTRACEPTION AFTER MELANOMA TREATMENT

Meta-analysis provides no evidence that use of the oral contraceptive is a risk factor for melanoma.[249] Five large studies indicate that oral contraceptive use by women after surgery for stage I or II melanoma does not adversely affect their prognosis.[248,250-254] **2++**

✓ Women who have had a melanoma treated should select contraception in the same way as women who have not had a melanoma

10.3 HORMONE REPLACEMENT THERAPY AFTER MELANOMA TREATMENT

Five case controlled studies show no effect of hormone replacement therapy (HRT) as a risk factor for melanoma.[251,252,255-257] **2+**

✓ Women who have had stage I and II melanoma and who wish to take HRT should be treated as women who have not had melanoma.

11 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing melanoma with patients and carers and in guiding the production of locally produced information materials.

11.1 INFORMATION PROVISION

An RCT of patients with stage I melanoma suggests that a structured information programme to inform patients about melanoma progression and treatment options increased patients' knowledge of the disease, the risk factors involved and possible preventative measures.[258] The study reported no difference in psychological variables. A second RCT found that facilitated education programmes for patients with stage I and II melanoma, in which one element was an information programme about cancer recurrence, had a positive effect on coping behaviour and affective distress values.[259] A prospective cohort study with patients with metastatic disease found that those who understood the expected outcomes of their disease had higher quality of life scores and longer survival periods.[260]

1⁻ 1⁺ 2

The provision of information to patients increases their knowledge of the disease, can enhance coping behaviour and reduce levels of affective distress.

2⁺

R **Patients should receive targeted information throughout their journey of care.**

✓ Healthcare professionals working with cancer patients should have training in communication skills.

11.2 COMMUNICATION

A Cochrane review, an RCT, three cohort studies and a survey were identified that cover a wide range of issues related to communication skills, all demonstrating strongly that communication skills training for healthcare professionals is of lasting benefit.[261-266]

1⁺ 2⁺ 3

The following have all been shown to be potentially effective communication tools or strategies:

- health related quality of life measurements
- needs assessment tools
- recorded consultation
- audio of general information
- summary letter as follow up
- presence of support person
- actively encouraging questions and a question prompt list
- patient-held record.

R **Communication skills training should be provided across the multidisciplinary team.**

✓ Information needs should be resourced and provided using a variety of media, to meet individual patient/carer needs.

11.3 PATIENT SUPPORT GROUPS

Patients benefit from psychoeducational interventions provided in a structured group, facilitated by qualified personnel.[258-260,267] The studies suggest that facilitated groups can help patients cope better at all stages of their disease, increase knowledge levels and reduce affective distress.

1⁻

✓ 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.

11.4 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

In primary care

- Advise patients that removal or biopsy of the tumour may occur at the initial visit.
- Advise patients that it is appropriate to refer them to a specialist and how long they should expect to wait for an appointment.
- Explain how photo triage (if available) can be of benefit.

At the specialist clinic

- Explain to patients how a diagnosis will be reached including:
  - clinical examination
  - types of biopsy and the need for local anaesthetic
  - how, when and by whom biopsy results will be given.
- With any surgical procedure, whether small biopsy or large excision, explain about surgical complications which include: pain, swelling, bleeding, bruising, loss of function and unpredictable scarring, including keloid scarring.
- Advise patients about how long they should expect to spend at the hospital.
- Be clear about the time between biopsy results and treatment.
- Describe what treatments will be offered.
- Where possible, give patients written information about appointment waiting times and details of who to contact if appointment is not received within 2 weeks.

At the specialist clinic once the diagnosis is known

- Explain the nature of the patient's particular cutaneous melanoma in precise terms.
- Explain what further treatment options there are and which are appropriate for the patient.
- Explain whether any other tests are appropriate, such as scans.
- Give as much information as possible about the likely prognosis.
- Explain how the majority of melanomas arise.
- Where appropriate, explain that the patient's case will be referred to the MDT.
- Explain whether other specialists will be involved in the treatment, such as, plastic surgeons, oral and maxillofacial surgeons, oncologists, clinical nurse specialists, etc.
- Explain what might be involved in any one particular treatment eg flaps, grafts, complex reconstruction, sentinel lymph node biopsy.
- Explain what might be involved in recuperation and rehabilitation and realistic timescales for recovery (including scar potential and healing time, especially in visible areas).
- Try to give the patient some idea of the time to their definitive treatment, acknowledging that this might be difficult if other specialists are involved.

At follow up

- Discuss how well the treatment went and whether any further treatment is needed: surgery, radiotherapy or input from oncologists.
- Discuss the prognosis in light of the definitive treatment.
- Discuss the risk of recurrence and how the patient might detect this, and whether any tests are indicated to detect recurrence.
- Advise the patient about the likely length of follow up.
- Ensure patients are aware of the support available from a clinical nurse specialist and other health professionals eg Maggie's centres, MacMillan Cancer Support or camouflage clinic and refer if appropriate.
- Allow sufficient time to discuss the following with patients:
  - psychological adjustment after a diagnosis and treatment for skin cancer
  - anxiety and low mood
  - coping strategies
  - being visibly different/stigma
  - use of camouflage and cosmetics
  - assessment and management of lymphoedema for those patients at risk.
- Advise patients to bring a written list of questions or concerns. A proforma that addresses these aspects can focus the discussion time.
- Offer patient education about self care for example:
  - self checking, skin examination, checking lymph nodes and getting to know their body
  - what to look for, eg features of abnormal skin lesions and what actions to take if they are concerned (it is also useful to detect any other health issues that require medical assessment).
  - discuss prevention including:
    - use of high-factor sunscreen and protective clothing
    - the damaging effects of sun beds
    - the need for precautions while working and taking holidays in the UK.
- Provide patients with written information leaflets and advise them how they can access self-help groups (see *section 11.5*).

11.5 SOURCES OF FURTHER INFORMATION

11.5.1 GENERAL INFORMATION

NHS inform
A national health information service for Scotland.
Website: www.nhsinform.scot
www.nhsinform.scot/illnesses-and-conditions/cancer
The NHS inform cancer page is full of practical and emotional support to help you or someone you know who is living with cancer.

Skin cancer (melanoma)
www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/skin-cancer-melanoma
NHS inform can help you find detailed information on different cancers, make your own customised cancer leaflet, find support groups and more.

Care, support and rights
Information on accessing healthand care services can be found here.
Tel: 0800 22 44 88 (8am–10pm)
www.nhsinform.scot/care-support-and-rights/

11.5.2 ORGANISATIONS SPECIFIC TO SKIN CONDITIONS

British Association of Dermatologists (BAD)
Willan House, 4 Fitzroy Square, London W1T 5HQ
Tel: 0207 383 0266
Email: admin@bad.org.uk
www.bad.org.uk
One of the aims of the British Association of Dermatologists is to raise awareness of all aspects of skin disease. This charity provides a range of patient information leaflets.

British Skin Foundation
4 Fitzroy Square, London W1T 5HQ
Tel: 020 7391 6341
www.britishskinfoundation.org.uk
The British Skin Foundation supports research into skin conditions. It provides information on the treatment of skin cancers.

Changing Faces Scotland
Tel: 0845 4500 640 (Monday to Thursday, 8.30am-3pm)
Email: scotland@changingfaces.org.uk
www.changingfaces.org.uk
Changing Faces provide psychological support to people and families who are living with conditions, marks or scars that affect their appearance.

MASScot (Melanoma Action and Support Scotland)
A skin cancer charity
208 Clyde Street Glasgow G1 4JY,
Tel: 0141 221 9878
Email: info@masscot.org.uk
Charity number: SCIO 040286
www.masscot.org.uk
MASScot is a Scottish charity run by skin cancer patient volunteers. They provide qualified and insured therapists, near to you, free of charge. MASScot campaigns for improvements in prevention, detection and care, and works with primary and secondary schools to promote sun awareness. They aim to make the public aware of the dangers of sunburn.

11.5.3 ORGANISATIONS SPECIFIC TO CANCER

Cancer Support Centre, Cancer Support Scotland
The Calman Centre, 75 Shelley Road, Glasgow G12 0ZE
Freephone: 0800 652 4531
Tel: 0141 337 8199
Email: info@cancersupportscotland.org
www.cancersupportscotland.org
The Calman Cancer Support Centre provides emotional and practical support on a one-to-one basis and through community-based groups. It provides complementary and talking therapies to anyone affected by cancer.

Cancer Research UK
Angel Building, 407 St John Street, London EC1V 4AD
Tel: 0808 800 4040 (Monday to Friday, 9am–5pm)
www.cancerresearchuk.org
Cancer research UK funds research into cancer, campaigns on cancer issues and produces patient information leaflets.

Macmillan Cancer Support
89 Albert Embankment, London, SE1 7UQ
Tel: 0808 808 00 00 (Monday to Friday, 9am–8pm).
www.macmillan.org.uk
Third floor, 132 Rose Street, Edinburgh. EH2 3JD
Tel: 0131 260 3720
Email: pmather@macmillan.org.uk
Macmillan supports people with cancer and their families with specialist information, treatment and care.

Maggie's Cancer Caring Centres Scotland
The Gatehouse,10 Dumbarton Road, Glasgow G11 6PA
Tel: 0300 123 1801
Email: enquiries@maggiescentres.org
www.maggiescentres.org
Maggie's provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie's Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart. In Scotland there are Maggie's Centres in Glasgow, Airdrie, Edinburgh, Kirkaldy, Dundee, Aberdeen and Inverness.

Marie Curie Cancer Care in Scotland
133 Balornock Road, Stobhill Hospital Grounds, Glasgow G21 3US
Tel: 0131 561 3900
Email: supporter.relations@mariecurie.org.uk
www.mariecurie.org.uk
Marie Curie Cancer Care is dedicated to the cure of people affected by cancer and improving their quality of life through its caring services, research and education.

Teenage Cancer Trust
Third floor, 93 Newman Street, London. W1T 3EZ
Tel: 020 7612 0370
Email: hello@teenagecancertrust.org
www.teenagecancertrust.org

11.5.4 CANCER NETWORKS IN SCOTLAND

Scotland's cancer networks offer a range of support and advice to patients and families, including support groups and written information.

North of Scotland Cancer Network (NOSCAN)
Rosehill Annexe, Aberdeen Royal Infirmary Site, Cornhill Road, Aberdeen AB25 2ZG
Tel: 01224 552 745
www.noscan.scot.nhs.uk

South East Scotland Cancer Network (SCAN)
Pentland House, 47 Robb's Loan, Edinburgh EH14 1TY
Tel: 0131 465 7681
www.scan.scot.nhs.uk

West of Scotland Cancer Network (WOSCAN)
1st Floor, St Mungo Building, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF
Tel: 0141 211 1145
www.woscan.scot.nhs.uk

12 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

12.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

12.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

12.3 AUDITING CURRENT PRACTICE

The Cancer quality performance indicators (QPIs) have been developed by Healthcare Improvement Scotland in collaboration with the three Regional Cancer Networks (NOSCAN, SCAN and WOSCAN) and the NHS Information Services Division (ISD). QPIs will be kept under regular review and be responsive to changes in clinical practice and emerging evidence.

The overarching aim of the cancer quality work programme is to ensure that activity at NHS board level is focused on areas most important in terms of improving survival and patient experience whilst reducing variance and ensuring safe, effective and person-centred cancer care.

Further information on QPIs can be found on the Healthcare Improvement Scotland website www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis.aspx

12.4 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

In 2013 the SMC advised that ipilimumab is accepted for use in NHSScotland for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

In 2013 the SMC advised that vemurafenib is accepted for restricted use as first-line treatment of *BRAF* V600 mutation-positive unresectable or metastatic melanoma.

In 2014 the SMC advised that ipilimumab is accepted for use in NHSScotland for the treatment of advanced (unresectable or metastatic) melanoma in adults (first-line use).

In 2015 SMC advised that dabrafenib is accepted for restricted use as monotherapy treatment for adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation. It is restricted for use only in those patients who have received no prior therapy.

In 2015 SMC advised that it had approved pembrolizumab as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab

In 2016 SMC advised that it had approved nivolumab as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with nivolumab.

In 2016 SMC advised that it had approved trametinib in combination with dabrafenib for the first-line treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.

In 2016 SMC advised that nivolumab in combination with ipilimumab is accepted for the first-line treatment of adult patients with unresectable or metastatic melanoma.

13 The evidence base

13.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2004–2016. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

13.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with melanoma. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

13.1.2 LITERATURE SEARCH FOR COST-EFFECTIVENESS EVIDENCE

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2004–2016. Databases searched include Medline, Embase, NHS Economic Evaluation Database (NHS EED) and Health Economics Evaluation Database (HEED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per quality-adjusted life year (QALY).

13.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:

- Large studies on the behaviour of lentigo maligna and eventual risk of invasion
- A comparison of behaviour of lentigo maligna melanoma with superficial spreading malignant melanoma
- Large cohort studies on pure desmoplastic subtype biological potential compared to superficial spreading or mixed desmoplastic subtype, and for animal type versus superficial spreading
- Prospective study comparison of CT and MRI for identifying brain metastases in patients with melanoma
- RCTs on the efficacy of electrochemotherapy with immunotherapy versus immunotherapy alone
- An RCT of the role of regular surveillance imaging on the survival of patients with stage III melanoma compared to routine follow up including different imaging modalities and the optimal interval for imaging
- Trials on the sequencing of immune agents and targeted agents
- RCTs comparing the efficacy of combination BRAF inhibitors with novel immunotherapies
- RCTs on the efficacy of BRAF inhibitors after immunotherapy.

13.3 REVIEW AND UPDATING

This guideline was issued in 2017 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: sign@sign.ac.uk).

14 Development of the guideline

14.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk

This guideline was developed according to the 2015 edition of SIGN 50.

14.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Ewan Brown (*Chair*)	*Consultant in Medical Oncology, Edinburgh Cancer Centre, Western General Hopsital, Edinburgh*
Dr Stuart Ballantyne	*Clinical Lead for Radiology, Gartnavel General Hospital, Glasgow*
Ms Juliet Brown	*Evidence and Information Scientist, Healthcare Improvement Scotland*
Dr Richard Casasola	*Consultant Clinical Oncologist, Tayside Cancer Centre, Dundee*
Dr Mark Darling	*Consultant Dermatologist, New Victoria Hospital, Glasgow*
Ms Amanda Degabriele	*MacMillan Skin Cancer Clinical Nurse Specialist, Ninewells Hospital, Dundee*
Dr Robert Dickie	*General Practitioner, The Group Practice, Isle of Lewis*
Ms Sheena Dryden	*Clinical Nurse Specialist – Dermatology, NHS Lothian, Lauriston Buildings, Edinburgh*
Ms Elaine Fletcher	*Specialist Registrar in Clinical Genetics, Western General Hospital, Edinburgh*
Dr Susannah Fraser	*Consultant Dermatologist, Queen Margaret Hospital, Dunfermline and Victoria Hospital, Fife*
Mr Stephen Heller-Murphy	*Programme Manager, SIGN*
Dr Alex Holme	*Consultant Dermatologist, Royal Infirmary of Edinburgh*
Ms Frances Kelly	*Lay representative, Wishaw*
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Dr Colin Moyes	*Consultant Dermatopathologist, Southern General Hospital, Glasgow*
Mr Omar Quaba	*Consultant Plastic Surgeon, Ninewells Hospital, Dundee*
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Ms Ailsa Stein	*Programme Manager, SIGN*
Dr Lorna Thompson	*Health Services Researcher, Healthcare Improvement Scotland*
Dr Ashita Waterston	*Consultant Medical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Staff. All members of the SIGN Executive make yearly declarations of interest A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

Euan Bremner	*Project Officer*
Karen Graham	*Patient Involvement Officer*
Karen King	*Distribution and Office Co-ordinator*
Stuart Neville	*Publications Designer*
Gaynor Rattray	*Guideline Co-ordinator*
Dr Carolyn Sleith	*Evidence and Information Scientist, Healthcare Improvement Scotland*

14.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 72: Cutaneous melanoma, on which this guideline is based.

14.3 CONSULTATION AND PEER REVIEW

A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

14.3.1 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Ms Marissa Collins	*Researcher in Health Economics, Glasgow Caledonian University, Glasgow*
Professor Alan Denison	*Consultant Radiologist, Summerfield House, Aberdeen*
Dr Val Doherty	*Dermatologist, Royal Infirmary of Edinburgh, Edinburgh*
Mrs Wilma Ford	*MacMillan Skin Cancer Clinical Nurse Specialist, Southern General Hospital, Glasgow*
Dr Matthew Hough	*Consultant Plastic Surgeon, Ninewells Hospital, Dundee.*
Mrs Kirsty MacFarlane	*Principal Pharmacist, Scottish Medicines Consortium, Healthcare Improvement Scotland*
Dr Colin Malone	*Locum Consultant Dermatologist, Dumfries and Galloway Royal Infirmary*
Dr Megan Mowbray	*Consultant Dermatologist, Queen Margaret Hospital, Dunfermline*
Dr Lisa Naysmith	*Consultant Dermatological Surgeon, Royal Infirmary of Edinburgh*

Dr Marianne Nicolson	*Consultant Medical Oncologist, Aberdeen Royal Infirmary, Aberdeen*
Professor Mary Porteous	*Consultant Clinical Geneticist, Western General Hospital, Edinburgh*
Dr Charlotte Proby	*Professor of Dermatology, University of Dundee*
Dr James Vestey	*Consultant Dermatologist, Raigmore Hospital, Inverness*

14.3.2 PUBLIC CONSULTATION

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment.

14.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website www.sign.ac.uk.

Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Professor John Kinsella	*Chair of SIGN; Co-Editor*
Mr Alan Timmins	*Royal Pharmaceutical Society*

Abbreviations

ABCDE	Asymmetry, Border, Colours, Diameter, Evolution
AJCC	American Joint Committee on Cancer
ALM	acral lentiginous melanoma
BAD	British Association of Dermatologists
BCG	bacille Calmette-Guerin vaccine
BRAF	v-raf murine sarcoma viral oncogene homolog B gene or serine/threonine-protein kinase B-Raf
CDK4	cyclin-dependant kinase 4
CDKN2A	cyclin-dependant kinase inhibitor 2A
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CNS	central nervous system
CPD	continuing professional development
CR	complete response
CrI	credible interval
CT	computed tomography
DM	desmoplastic type melanoma
ECT	electrochemotherapy
EORTC	European Organisation for Research and Treatment of Cancer
FBC	full blood count
FNAC	fine needle aspiration cytology
GMC	General Medical Council
GP	general practitioner
gp100	glycoprotein100
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IARC	International Agency for Research on Cancer
IHC	immunohistochemistry
ILP	isolated limb perfusion
ISD	Information Services Division
LDH	lactate dehydrogenase
LFT	liver function test
LM	lentigo maligna
LMM	lentigo maligna melanoma
LVI	lymphovascular invasion

MA	marketing authorisation
MCN	managed clinical network
MDT	multidisciplinary team meeting
MEK	mitogen-activated protein kinase
MIA	melanoma inhibitory activity
MMS	mohs micrographic surgery
MRI	magnetic resonance imaging
MTA	multiple technology appraisal
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NM	nodular melanoma
NOSCAN	North of Scotland Cancer Network
OR	odds ratio
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PET-CT	positron emission tomography–computed tomography
PFS	progression free survival
QALY	quality-adjusted life year
QPI	quality performance indicator
RCPath	Royal College of Pathologists
RCT	randomised control trial
SCAN	South East Scotland Cancer Network
SIGN	Scottish Intercollegiate Guidelines Network
SLN	sentinel lymph nodes
SLNB	sentinel lymph node biopsy
SMC	Scottish Medicines Consorium
SPC	summary of product characteristics
SPF	sun protection factor
SRS	stereotactic radiosurgery
SSMM	superficial spreading malignant melanoma
TIL	tumour infiltrating lymphocytes
TNF	tumour necrosis factor
TNM	tumour, node, metastases
US	ultrasound
UVA	ultraviolet A
UVB	ultraviolet B
WBRT	whole-brain radiotherapy
WOSCAN	West of Scotland Cancer Network

Annex 1
Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
4.1	1.	What is the rate/risk of local recurrence and/or metastasis and survival in patients with desmoplastic melanoma or animal type melanoma compared to patients with superficial spreading? Comparison: superficial spreading Outcomes: local recurrence, metastasis, survival
5.3	2.	In which patients with melanoma is sentinel lymph node biopsy an effective tool for staging, predicting outcome or guiding treatment options? Patients with melanoma: a) <1 mm Breslow thickness with mitotic rate 1 or more b) intermediate thickness 1 mm to 3.5 mm c) thick melanoma >3.5 mm Interventions: SLNB (to exclude stage 3 disease) Comparisons: observation, clinical follow up, high definition ultrasound Outcomes: sensitivity/specificity for identification of microscopic metastases, overall survival (5 years, 10 years), disease free survival (5 years, 10 years),adverse events
5.3	3.	In patients with malignant melanoma who are SLNB+ what is the most effective management strategy? Interventions: completion lymphadenectomy (clearance/complete lymph node dissection) Comparisons: serial ultrasound, observation Outcomes: recurrence, overall survival (5 years, 10 years), disease free survival (5 years, 10 years), adverse events
4.1	4.	What evidence is there for treatment of lentigo maligna and lentigo maligna melanoma? Patients with: lentigo maligna, lentigo maligna melanoma Interventions: conventional surgery, Mohs micrographic surgery, radiotherapy, cryotherapy, imiquimod, 5-FU, observation Comparisons: conventional surgery, Mohs micrographic surgery, radiotherapy, cryotherapy, imiquimod, 5-FU, observation Outcomes: disease clearance/recurrence, development of invasive disease, adverse events, cosmesis, patient satisfaction.
6.1	5.	In patients with malignant melanoma, who should undergo radiology imaging as part of their initial staging investigations? Patients with: melanoma stage I-II, stage III Interventions: radiological staging Comparisons: between stage I-II and stage III Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value, patient anxiety, patient satisfaction

6.1	6.	What is the best radiology modality for systemic staging of patients with malignant melanoma? Interventions and comparisons: CT *v* PET/CT, PET/CT *v* no radiology, CT *v* no radiology Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value
6.1 9.6	7.	Is CT or MRI better for diagnosing brain metastases in patients with malignant melanoma? Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value
8.4	8.	What is the clinical and cost effectiveness of routine radiological follow up of patients with treated malignant melanoma? Patients with: treated malignant melanoma – stage IIb or greater Interventions: radiology follow up investigations at various intervals Comparison: clinical follow up only Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value, patient anxiety, patient satisfaction
8.7	9.	What is the best imaging modality for use in routine follow up for detection of recurrence in patients with malignant melanoma? Patients with: treated malignant melanoma – stage IIb or greater Interventions and comparisons: chest x-ray, CT, PET/CT, ultrasound Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value
9.5	10.	What is the clinical and cost effectiveness of electrochemotherapy (ECT) in the management of patients with melanoma skin metastases? Patients with: stage III/IV disease, cutaneous metastases Interventions: ECT Comparisons: isolated limb perfusion, laser, radiotherapy, surgery Outcomes: response rates, overall survival (5 years, 10 years), progression free survival (5 years, 10 years), adverse effects
9.3	11.	In patients with advanced melanoma (unresectable stage IIIC or stage IV) which is the most clinically and cost effective systemic therapy? Interventions: • BRAF inhibitors (vemurafenib, dabrafenib) • MEK inhibitors (trametinib, cobimetinib) • immunotherapy (ipilimumab, pembrolizumab, nivolumab, interferon interleukin-2) • chemotherapy (dacarbazine, paclitaxel, carboplatin) • cKIT inhibitors (imatinib) • combination treatment (eg vemurafenib/cobimetinib and dabrafenib/trametinib) Comparisons: chemotherapy, observation Outcomes: overall survival (5 years, 10 years), progression free survival (5 years, 10 years), response rate, toxicity

7.1	12.	In patients with completely resected stage III melanoma what is the benefit from adjuvant radiotherapy? Interventions: radiotherapy Comparison: observation Outcomes: overall survival (5 years, 10 years), progression free survival (5 years, 10 years), local recurrence, toxicity
7.3	13.	What is the relationship between the immune system and melanoma?

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