Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

SIGN 146

Cutaneous melanoma

A national clinical guideline

First published January 2017
Revised August 2023

NHS SCOTLAND

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 has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2025 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2019 edition (www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk alongside the EQIA assessment of the manual. The full report in paper form and/or alternative format is available on request from the Healthcare Improvement Scotland Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our website www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

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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 seventh in men.[1] In Scotland, between 2007 and 2018, the incidence of melanoma in adults has increased by 6%, but mortality rates have decreased by 10–19.1% between 2008 and 2018.[1] The primary risk factor for cutaneous melanoma is exposure to natural and artificial sunlight.[2]

Although melanoma is the major cause of skin cancer mortality it is often curable by surgery if recognised and treated at an early stage. Increasing public and professional awareness of melanoma helps to promote early detection. In the last decade significant progress has been made in the management of patients with advanced melanoma. Molecular therapies (targeting serene/threonine-protein kinase B-RAF and mitogen-activated protein kinase (MEK)) and immunotherapies have resulted in significantly improved survival as well as durable disease control in some patients.

1.1.1 Updating the evidence

SIGN 146 was published in 2017 as a selective update to SIGN 72: Cutaneous melanoma, first published in July 2003. 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 146. The original supporting evidence was not reappraised by the current guideline development group.

2023 updates include:

- pathological reporting, in line with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th edition and the revised edition of the Royal College of Pathology dataset
- sentinel lymph node biopsy and completion lymphadenectomy
- advances in systemic anticancer therapies
- revised consensus-based guidance on follow-up surveillance
- other minor updates throughout to reflect current practice.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline provides advice on the management of adults with melanoma. It covers 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. The guideline does not cover management of children with cutaneous melanoma. Any cases of paediatric melanoma should be discussed with a paediatric oncology multidisciplinary team (MDT), ideally involving clinicians who have direct experience in the management of cutaneous melanoma.

1.2.2 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 or academic interests may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from these sources, 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 and academic 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 of declaration of interests forms 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 MA
- 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 MA. Such use should be supported by appropriate evidence and experience.[3]

"Prescribing medicines outside the conditions of their MA alters (and probably increases) the prescribers' professional responsibility and potential liability".[3]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[4]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need.
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed 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 (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[5]

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, all new formulations of existing 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.
- SMC advice relevant to this guideline is 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 Surgical management and staging

R **Sentinel lymph node biopsy should be considered as a staging technique in patients with IB-IIC melanoma with a Breslow thickness of >1mm.**

R **Consider sentinel lymph node biopsy for people who have melanoma with a Breslow thickness 0.8 mm to 1.0 mm and at least one of the following features:**

- **ulceration**
- **lymphovascular invasion**
- **a mitotic index of 2 or more.**

✓ While the above criteria have been shown to be the statistically significant thresholds for SLNB positivity in thin tumours, the likelihood of SLNB positivity in any individual is multifactorial. Outwith the above criteria, after consensus within the multidisciplinary team and careful discussion with the patient, SLNB may be considered in patients with thin melanomas (<1.0 mm) where the clinical team feel an individual patient's risk merits the procedure.

✓ Patients with resected stage IIB or IIC melanoma have the option of being considered for SLNB or proceeding directly to adjuvant immunotherapy, where appropriate *(see sections 7.2 and 12.4)*. These patients should be discussed on an individual basis by the multidisciplinary team.

R **Completion lymphadenectomy is not recommended for the majority of patients.**

2.2 Adjuvant treatment

R **In patients with completely resected stage IV melanoma, with or without BRAF mutation, nivolumab should be considered as adjuvant treatment.**

R **In patients with completely resected stage III melanoma without BRAF mutation, nivolumab or pembrolizumab should be considered as adjuvant treatment**

R **In patients with completely resected stage III melanoma with BRAF V600 mutation nivolumab, pembrolizumab or the combination of dabrafenib and trametinib should be considered as adjuvant treatment.**

R **In patients with completely resected stage IIB or IIC melanoma with or without BRAF mutation pembrolizumab should be considered as adjuvant treatment.**

2.3 Therapies for metastatic disease

R **In patients with untreated stage IV or unresectable stage III melanoma immunotherapy with checkpoint inhibitors are recommended as first-line treatment irrespective of BRAF status.**

R **Nivolumab plus ipilimumab should be considered for patients with untreated stage IV or unresectable stage III melanoma** (if suitable for them)**. If nivolumab plus ipilimumab is unsuitable or unacceptable** (for example, because of potential toxicity or patient choice)**, pembrolizumab or nivolumab monotherapy should be offered.**

R **Encorafenib plus binimetinib, or dabrafenib plus trametinib should be considered for patients with untreated stage IV or unresectable stage III melanoma with BRAF mutation if nivolumab plus ipilimumab, pembrolizumab or nivolumab monotherapy are contraindicated or it is predicted there is not enough time for an adequate immune response** (for example, because of high disease burden or rapid progression)**.**

2.4 Follow-up imaging

R **Routine follow up and imaging for patients with melanoma should be offered in line with the NHSScotland Cutaneous Melanoma National Follow-Up Guideline.**

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.[6]

Two systematic reviews focused on the relationship between patterns of sun exposure and risk of melanoma. The first was a high-quality review of case-control studies that concluded intermittent unaccustomed exposure was more important than age at sunburn.[7] 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.[8] 2++

The contribution of specific wavelength bands and the action spectrum for melanoma induction are unknown.[7] Sunburn is mainly due to UVB (280 to 320 nm) radiation, implicating ultraviolet B (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.[9]

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 (eg clothing, hats and opaque sunscreens) are likely to reduce the risk of melanoma. Sunscreen effectiveness is difficult to demonstrate for a number of reasons. Individuals at high risk are more likely to use sunscreen, although sunscreen use may be associated with greater sun exposure.[9,10] It may be that sunscreens offer a false sense of security and lead to increased time spent in the sun.[10,11] Most sunscreens offer greater protection from UVB, reducing the risk of sunburn, but not of exposure to UVA.[10,11] Some ingredients found in sunscreens may be carcinogenic.[10,11] 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.[10,11] 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.[10,11] 2++

There may be theoretical risks associated with sun avoidance,[12] 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 in Table 1 is based on the Australian guidelines on melanoma,[13] interpreted for the Scottish climate. 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[9]
• Use broad spectrum sunscreens with a minimum sun protection factor (SPF) of 30,[9] and 4 or 5 UVA stars,[14] in addition 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 11am and 3pm (eg 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.[15-20] 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. 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.[21,22] 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.[23] 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.**

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 they cannot accurately distinguish atypical moles from others.[24] 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.[25] 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.[26] 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.

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

R **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.**

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.[21]
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 3.6)*.[21]
Previous history of melanoma		Standardised incidence ratio range 4.5 to 25.6.[24]
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.[21]
Red or light-coloured hair[24]	1.4 to 3.5	

Risk factor	OR*	Information
Presence of actinic lentigines[24]	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.[25,26]
Unusually high sun exposure[24]	2.6	
Reported growth of a mole[24]	2.3	
Light-coloured eyes[24]	1.55 to 1.60	
Light-coloured skin[24]	1.40 to 1.42	
Skin that does not tan easily[24]	1.98	
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).[27,28]
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.[28] The validity of some risk factors, such as hair colour and sun exposure, is lower in the elderly.[21]

*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 two-fold (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.[29]

3.5 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% confidence interval (CI) 2.0 to 2.9) increased incidence of melanoma after transplantation.[30] A meta-analysis also found that inflammatory bowel disease was associated with a 37% increased risk of melanoma compared to the general population.[31] In addition, cohort studies have shown that patients with human immunodeficiency virus (HIV) have an increased risk of melanoma (standardised rate ratio of 2.6, 95% CI, 1.9 to 3.6),[32] patients with a history of non-Hodgkin Lymphoma (NHL) have a risk of subsequent melanoma that is increased 1.8 to 2.4 times,[33] and patients with chronic lymphocytic leukaemia (CLL) have an increased risk of 2.3 to 3.1 times that of controls.[34] 2++ 1- 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 (hazard ratio (HR) 1.5, 95% confidence interval 1.0 to 2.2).[35] A case-control study found that the 2-

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)[36] however, in a second cohort, the adjusted odds ratio was non-significant (OR 1.3, 95% CI, 0.6 to 2.7).[37] 2⁻

Several studies have investigated the relationship between immunosuppression and melanoma prognosis. A retrospective review of patients immunosuppressed after transplant found that those with thick melanoma (>3 mm) had a significantly poorer melanoma cause-specific survival rate.[38] A second retrospective review found that the outcome for patients with melanoma after transplant was significantly worse for those with tumours of Breslow thickness >2 mm.[39] A further retrospective review found that patients taking immunosuppressants at the time of diagnosis of melanoma had a higher mortality than controls (42% vs 23%, p=0.01) suggesting that immunosuppressive therapy may be associated with a more aggressive disease course.[40] There is limited data on the prognosis for patients who were diagnosed with melanoma before having a transplant.[30] 3 2++

Finally, a case series has described the spontaneous regression of advanced melanoma in patients on long-term azathioprine for autoimmune disease on withdrawal of the immunsuppression.[41] 3

✓ All patients with melanoma and a history of immunosuppression should have a multidisciplinary team approach to care. Minimising the immunosuppressive therapy should be considered where possible.

3.6 Genetics

It is estimated that 1–2% of melanomas are attributable to the inheritance of melanoma susceptibility genes.[28] Mutations in cyclin-dependant kinase inhibitor 2A *(CDKN2A)* are associated with an increased risk of melanoma.[27,28] Prevalence of *CDKN2A* in affected families varies between countries.[27,29,42] Cyclin-dependant kinase 4 *(CDK4)* has also been implicated but has a low prevalence worldwide.[27] 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).[43] 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.[28,29,42] 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.[42]

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.[44] People with mutations in *CDKN2A* may have a higher risk of smoking-related cancers and so should be advised to abstain from smoking tobacco.[45] 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. 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 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 (DM) is uncommon.

It is important to distinguish between pure and mixed subtypes of 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).[46] Similar figures were reported in another study, with 1/92 patients with pure DM having a positive SLNB compared with 7/39 patients with mixed subtype.[47] However, desmoplastic melanomas have been shown to have a higher rate of local recurrence (6–15%) than non-desmoplastic melanomas (<5%).[48] 3 4

4.1.6 Pigmented epithelioid melanocytoma

Pigmented epithelioid melanocytoma is rare. It should be considered an indolent type of melanoma where there is little incidence of systemic metastases despite frequent positive SLNB.[49-51] 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 3)* or ABCDE lesion systems *(see Table 4)* given below.[52,53] 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 Asymmetry in two axes
B	Irregular Border
C	At least two different Colours in lesion
D	Maximum Diameter >6 mm
E	Evolution/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.[19,54,55] 3

High-magnification dermoscopy is more sensitive than non-dermatoscopic diagnosis when used by clinicians with experience of the technique.[56,57] 1+

Training clinicians to be experts in handheld dermoscopy improves diagnostic accuracy but it may diminish the sensitivity of the diagnosis of non-expert or untrained dermatologists.[58-60] Observational studies have compared excision and pathological assessment to using other preoperative assessment methods of diagnosis including magnetic resonance imaging (MRI), high resolution ultrasound and digital imaging of possible melanomas.[58-64] These studies did not 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.[54,65-72] Significant delays (greater than 3 months) in diagnosis of invasive melanoma are usually patient rather than physician related.[54,65-72] 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.[70] 2+

Several studies showed longer delays in older patients,[19,67] in men, in rural versus urban dwellers and in those with plantar melanomas.[19,66]

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.[70,71] 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)*.[19] 3

Physician delay accounts for a very small part of the total delay in diagnosis.[54] Medical delays were shorter and the Breslow thickness was less when patients were seen by dermatologists as opposed to general practitioners.[54]

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 GPs after being given algorithms and cameras as aids to diagnosis.[73] 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.[74] 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.[75] 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.[76-80] 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.[78,81] 2+

Management of invasive LMM 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.[82] 2+

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

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

R **A superficial shave biopsy is inappropriate for suspicious pigmented lesions.**

✓ GPs should refer, via the urgent suspected cancer (USC) referral pathway, 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 *(see section 11.4)*.

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 based on standard surgical pathology textbooks.[83]

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)**.**

R **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)**, however they can be useful when the lesion is close to a polar margin.**
- **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, www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html.[84]

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 DM, 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[85] and has since been verified in many large scale studies of melanoma.[86-90] Breslow thickness is an important prognostic variable in primary cutaneous melanoma.[84] It is recommended that Breslow thickness is measured to the nearest 0.1 mm (ie one and not two decimal points). Decimal values ending in 1–4 should be rounded down, and those ending in 5–9 rounded up.[84] 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.[91] Ulceration has been shown to act as a prognostic variable after adjustment for other variables.[88,89] 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.[92] Some studies also show that increasing breadth of epidermal ulceration is associated with an increasingly unfavourable prognosis.[92] 2+

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

4.7.4 Mitotic rate

Mitotic index is no longer used to distinguish pT1a from pT1b melanomas.[93] Ulceration and Breslow thickness have been found to be stronger predictors of melanoma-specific survival.[93] Mitotic index remains a powerful prognostic feature at all Breslow thicknesses.[84]

The presence of dermal mitoses greater than or equal to 2 per square mm along with lymphovascular invasion can be criteria which determine whether a patient with pT1b melanoma is offered a sentinel node biopsy.[94] 4

R **Mitotic rate should be recorded in the pathology report for melanoma of any Breslow thickness.**

4.7.5 Lymphovascular invasion

Lymphovascular invasion (LVI) is a core dataset item from the RCPath and should be stated in the report. The presence of lymphovascular invasion correlates with a worse survival in patients with melanoma. It is important to exclude retraction artifact and it is not important to separate lymphatic or vascular invasion.[84] 4

4.7.6 Microscopic satellites/in-transit metastasis

A satellite is visible macroscopically and a microsatellite only microscopically. Microsatellites/satellites are defined by the 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.[95] Macrosatellite metastases are defined as discrete separate nodules within 2 cm of the primary tumour and are considered intralymphatic extensions of the primary tumour, whereas in-transit metastases are defined as any dermal or subcutaneous disease 2 cm or more from the primary tumour but not beyond the draining regional nodal basin.[93]

The presence of microsatellites (without lymph node metastases) upstages the melanoma to pN1c.[93] The RCPath supports the view that microsatellites do not have to be present within the lymphatic system.[84] 2++ 4

A systematic review found that the prognosis for patients with microsatellites is essentially identical to that for patients with macrosatellites.[96] 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.[97] 2++

A study of 140 patients with thick melanomas reported that the identification of vascular invasion was significantly correlated with the risk of metastasis but not with survival.[98] 2+

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** (8th edition) **and should be included in the pathology report. The defining criteria should be strictly adhered to and stated in the pathology report.**

4.7.7 Perineural invasion

The presence or absence of perineural invasion is a core data item in the RCPath melanoma dataset and should be included in the pathology report. The presence of perineural invasion correlates with a higher local recurrence rate.[84] 4

R **The presence or absence of perineural invasion should be included in the pathology report.**

4.7.8 Radial versus vertical growth phase

Tumour growth phase correlates strongly with clinical outcome.[89,99] A study of 501 patients with primary melanomas identified a subgroup of 122 with melanoma 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 1.0.[89] A second study evaluated 624 patients, of whom 161 had melanoma with radial growth phase characteristics only. None of the patients developed metastatic disease at long-term follow up (median 13.7 years).[99] The definitions of growth phase are discussed in more detail in the RCPath dataset.[84] 2++ 4

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

4.7.9 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,[89] the presence of an inflammatory response loses independent prognostic strength on multivariate modelling.[90] 2++

Tumour infiltrating lymphocytes are an AJCC prognostic item and are included in the RCPath dataset.[84]

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

4.7.10 Regression

It is unclear whether histological evidence of regression is associated with adverse or favourable outcomes. One large study identified tumour regression in the radial growth phase as a variable that retained predictive strength after multivariate analysis.[89] In a subsequent study of 1,042 patients the significance of tumour regression was subsumed by the other clinical and histological features studied.[90] 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.[100] 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 discussed by the MDT to determine whether the melanoma should be treated clinically as an upstaged lesion.[84] 4

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

4.7.11 BRAF status

✓ The *BRAF*, *NRAS* and *c-KIT* mutation status should be requested in all patients with stage IIB, IIC, III or IV melanoma and should be available to clinicians either on the pathology report or as a genetics report.

4.8 Specialist pathology reporting

Significant discrepancy exists between general pathologists and dermatopathologists, as well as between experts in pigmented lesion pathology, in the reporting of melanocytic tumours.[101-103] Both under- and overdiagnosis 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) and external quality assurance (EQA) activity is advisable.

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

4.9 Melanoma pathology report

Table 5 outlines the core features of a pathology report for invasive melanoma.

Table 5: Features of a melanoma pathology report[84]

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
	Margins, peripheral and deep
	Tumour stage (pT)
	Molecular studies requested (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.[104,105]

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:

- size of specimen in three dimensions
- the presence (and size) or absence of a macroscopic abnormality
- the presence or absence of a localisation marker
- matted nodes (stage pN3b).

The microscopic features which should be recorded include:

- the exact number of nodes identified in total within the specimen
- the number of nodes containing metastatic disease and whether the apical node is involved or not
- the presence or absence of extracapsular spread and
- whether the margin of the specimen is involved by tumour.[84]

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.[84]

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.[92,104,106] Nodes identified by lymphoscintigraphy (usually technetium-99) should be fixed in formalin for 24 hours to allow for radioactive decay.[84]

4

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.[84] In established units, alternative or EORTC-modified protocols are also acceptable outside EORTC clinical trials, provided that there is evidence of a positive detection rate approaching that of the EORTC protocol, that is an SLNB detection rate of around 25%.[84]

The sentinel lymph node report should identify macroscopic and microscopic features.

Macroscopic features which should be recorded include:

- dimensions of overall specimen
- the presence or absence of a macroscopic abnormality
- the presence or absence of dye in the tissue
- the presence or absence of a localising marker.

Microscopic features which should be recorded:

- the number of sentinel lymph nodes
- the number of nodes involved
- for each positive node:
  - the location and pattern of deposits
  - whether or not the deposits are subcapsular only
  - whether, if present, the parenchymal deposits are localised (≤3 deposits) or multifocal (>3 deposits)
- whether the tumour burden (maximum dimension of the largest tumour deposit) is <0.1 mm, 0.1–1.0 mm or >1.0 mm
- the presence or absence of extracapsular extension.[84]

Although immunohistocytology (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 AJCC8 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.[93]

The RCPath dataset states that a lymph node in which any metastatic tumour cells are identified either on haematoxylin and eosin stain or IHC should be regarded as positive.[84]

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 SLN using polymerase chain reaction (PCR) techniques cannot be recommended at present due to concerns regarding both sensitivity and specificity.[107]

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.[108-111] The safety of these narrower margins has been demonstrated in a series of studies.[112-115] 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.[116] A small number of patients with lesions thicker than 1 mm developed local recurrence.[117-119] 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.

Given the risk of invasion, lentigo maligna should also be surgically removed if the patient's comorbid status permits surgical intervention. Currently 5 mm surgical margins are recommended, although a case series reported that 26% of LM required greater margins to achieve clearance as atypical cells may extend beyond the visible edge.[120] There is limited evidence from case series that Mohs micrographic surgery (MMS) may reduce the size of the defect in LM.[121] For patients in whom surgery is not an option, there is some evidence for the use of radiotherapy and topical imiquimod for the treatment of LM.[111,120] Cryotherapy and topical-5-fluorouracil have also been used but there is no recently published evidence.[109,121] 1++ 3

Evidence-based recommendations on excision margins for melanoma can be found in the National Institute for Health and Clinical Excellence (NICE) guideline on assessment and management of melanoma.[57] 4

R

- **Consider a clinical margin of at least 0.5 cm when excising stage 0 melanoma.**
- **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.[108,110]

5.2 Staging melanoma

Melanoma should be staged using the tumour, node, metastasis (TNM) staging classification described by the AJCC8[114] and outlined in Tables 6 and 7.

Table 6: TNM staging categories for cutaneous melanoma[114]

T Classification	Thickness (mm)	Ulceration status/mitoses
T1	≤1.0	Unknown or unspecified
T1a	<0.8	Without ulceration
T1b	<0.8 0.8–1.0	With ulceration With or without ulceration
T2	>1.0–2.0	Unknown or unspecified
T2a	>1.0–2.0	Without ulceration

T2b	>1.0–2.0	With ulceration
T3	>2.0–4.0	Unknown or unspecified
T3a	>2.0–4.0	Without ulceration
T3b	>2.0–4.0	With ulceration
T4	>4.0	Unknown or unspecified
T4a	>4.0	Without ulceration
T4b	>4.0	With ulceration
N Classification	**No. of tumour-involved nodes**	**Presence of in-transit, satellite, and/or microsatellite metastases**
N1	1 tumour-involved node or in-transit, satellite, and/or microsatellite metastases with no tumour-involved nodes	
N1a	1 clinically occult (detected by SLNB)	No
N1b	1 clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2–3 tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumour-involved nodes	
N2a	2 or 3 clinically occult (detected by SLNB)	No
N2b	2–3, at least 1 of which was clinically detected	No
N2c	1 clinically occult or clinically detected	Yes
N3	≥4 tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumour-involved nodes or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastase	
N3a	≥4 clinically occult (detected by SLNB)	No
N3b	≥4, at least 1 of which was clinically detected, or presence of any number of matted nodes	No
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

M Classification	Site	Serum lactate dehydrogenase (LDH)
M1	Evidence of distant metastasis	Not applicable
M1a	Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node	Not recorded or unspecified (0) not elevated (1) elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified (0) not elevated (1) elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified (0) not elevated (1) elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified (0) not elevated (1) elevated

CNS – central nervous system

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Table 7: Anatomical and pathological staging for cutaneous melanoma[114]

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	-	-	IB	T1b	-	-
	T2a	-	-	IB	T2a	-	-
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	-	-	IIA	T3a	-	-
Stage IIB	T3b	-	-	IIB	T3b	-	-
	T4a	-	-	IIB	T4a	-	-
Stage IIC	T4b	-	-	IIC	T4b	-	-
Stage III	Any T	≥N1	M0	IIIA	T1a/b-T2a	N1a	M0
Stage III	Any T	≥N1	M0	IIIA	T1a/b-T2a	N1a	M0
				IIIB	T0	N1b-c	M0
					T1a/b-T2a	N1b/c	-
					T1a/b-T2a	N2b	-
					T2b-T3a	N1a-N2b	-
				IIIC	T0	N2b-c	M0
					T0	N3b-c	-
					T1a-T3a	N2c-3c	-
					T3b-T4a	Any N	-
					T4b	N1a-N2c	-
				IIID	T4b	N3a-c	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiological 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. Patients with pathologic Stage 0 or Stage IA melanoma are the exception; they do not require pathological 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 patients with melanoma.[113] 2++

The risk of developing nodal metastases increases with the thickness of the primary melanoma.[112,115] 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% incidence in melanomas more than 4 mm thick.[122,123]

Regional lymph node metastasis is associated with poor prognosis, survival being less than half that of patients without nodal involvement.[124-126] 2++

The number of involved nodes is of prognostic significance. Ten-year survival varies between 20% and 45% dependent on the extent of nodal involvement.[13,113,125,126]

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.[13,127] 4

✓ If there is palpable lymphadenopathy FNAC should be used to obtain cytological confirmation of metastases, with ultrasound if required.

✓ 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.[128,129] 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.[129]

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 Staging with sentinel lymph node biopsy

Sentinel lymph node biopsy is a key staging procedure in patients considered at risk of occult metastases, potentially upstaging these patients and making them eligible for consideration of adjuvant treatments. Sentinel lymph node prediction tools are available to avoid unnecessary SLNB, but further research into their accuracy is required before recommendations can be made on their use.

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.[130] Biopsy of this node can determine the presence or absence of metastasis within the regional lymph node basin and assist in staging patients at risk of metastatic disease.[131-133] 2++ 4

The standard for SLNB is a triple diagnostic approach of lymphoscintography, blue dye dermal infiltration and localisation using a hand held gamma probe *(see section 4.10)*.[130,134-138] Performing SLNB requires appropriate surgical expertise,[130] specialist nuclear medicine services and the availability of serial sectioning and immunohistochemistry techniques. It is therefore a costly procedure, and as it is invasive, potential risks also need to be considered (eg allergic reaction to dye, nerve damage and lymphoedema).[139] It should only be performed in patients at high risk of developing metastatic disease. 2+ 2++

Sentinel lymph node biopsy can determine the presence or absence of metastasis within the regional lymph node basin and it is a useful staging tool in melanomas >1 mm thick (stage IB-IIC).[87] In thick melanomas (>4 mm) it can identify a subset of melanomas that are node negative and therefore offer a better prognosis.[132] 2++ 4

Evidence identified in the NICE meta-analysis showed that melanomas with a Breslow thickness of ≤0.8 mm have a very low risk of SLNB positivity.[139]

The following risk factors were identified as having the highest risk of SLNB positivity:[139]

- ulceration had a two-fold risk compared to patients without ulceration (risk ratio (RR) 2.01, 95% CI 1.69 to 2.38; 26 studies)
- mitotic rate (RR 2.15, 95% CI 1.57 to 2.94; 25 studies).
- the presence of lymphovascular invasion (RR 2.24, 95% CI 1.67 to 2.99; 10 studies)

2++

The quality of the studies included ranged from high to low risk of bias.

A mitotic index threshold of >2 mitoses was found to provide greater accuracy than single mitosis, because of the difficulty in differentiating between one or no mitoses.[139]

Younger age (<55 years), a mitotic rate of 1 and a high Clark level (IV or greater) also showed a higher risk, but had a lower predictive accuracy than other factors. Clark level is no longer included in the core dataset. Tumour location was not found to be predictive of higher risk.[139] 2++

R **Sentinel lymph node biopsy should be considered as a staging technique in patients with IB-IIC melanoma with a Breslow thickness of >1mm.**

R **Consider sentinel lymph node biopsy for people who have melanoma with a Breslow thickness 0.8 mm to 1.0 mm and at least one of the following features:**

- **ulceration**
- **lymphovascular invasion**
- **a mitotic index of 2 or more.**

✓ While the above criteria have been shown to be the statistically significant thresholds for SLNB positivity in thin tumours, the likelihood of SLNB positivity in any individual is multifactorial. Outwith the above criteria, after consensus within the multidisciplinary team and careful discussion with the patient, SLNB may be considered in patients with thin melanomas (<1.0 mm) where the clinical team feel an individual patient's risk merits the procedure.

✓ Patients with resected stage IIB or IIC melanoma have the option of being considered for SLNB or proceeding directly to adjuvant immunotherapy, where appropriate *(see sections 7.2 and 12.4)*. These patients should be discussed on an individual basis by the multidisciplinary team.

See section 4.10 for pathological examination and reporting of therapeutic and sentinel lymph node dissection specimens.

5.3.3 Completion lymphadenectomy

The NICE systematic review identified two RCTs comparing completion lymphadenectomy to observation in patients with metastatic nodal disease detected by SLNB.[140] Completion lymphadenectomy (CLND) did not improve survival in either study (overall survival at 3 years adjusted HR 1.02, 90% CI 0.68 to 1.52 in the German Dermatologic Co-operative Oncology Group trial (DeCOG); melanoma-specific survival at three years adjusted HR 1.08, 95% CI 0.88 to 1.34 in the Multicenter Selective Lymphadenectomy Trial II (MSLT-II trial)).[140] Risk of lymphoedema was higher in the group who had surgery (24.1% versus 6.3% at 3 years).[140] NICE graded both studies as having a moderate risk of bias overall.[140] The protocols for each study relied on regular imaging for observation. This may be required for patients with a positive SLNB who fall below the threshold for adjuvant treatment. The DeCOG study excluded patients with head and neck metastases so the evidence for not performing CLND in these patients is less clear. **1++**

R **Completion lymphadenectomy is not recommended for the majority of patients.**

✓ There may be specific clinical cases where completion lymphadenectomy may be considered following multidisciplinary team discussion.

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, contrast-enhanced computed tomography (CE-CT), MRI and positron emission tomography–computed tomography (PET-CT)
- **Blood tests:** 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.[57] Consensus in the NICE guideline was that imaging for staging should be consistent with imaging for follow up.[57] The NHSScotland Cutaneous Melanoma National Follow-Up Guideline recommends patients with stage IIB disease and above should be offered imaging, with CE-CT of the head, chest, abdomen and pelvis.[141] 4

No RCTs comparing computed tomography (CT) and PET-CT for 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%).[142] 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[143] and specificity of 89% in patients with stage III disease.[144] 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, inform the consensus opinion of the guideline development group that its use should be restricted to patients with indeterminate findings on CE-CT or for those being considered for a major surgical resection.

R **Staging CE-CT should be offered to patients with stage IIB, IIC, III and IV melanoma.**

✓ Staging CE-CT should include head, chest, abdomen and pelvis. The neck should be included if primary drainage of the melanoma is into the head and neck.

✓ PET-CT should be considered for patients after discussion with the specialist multidisciplinary team. Clinical situations where CT-PET is generally considered include patients with indeterminate findings on CE-CT, patients who are being considered for major surgical resection, and patients with in-transit disease on the limbs.

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.[145,146] 4

Given that patients are likely to have a CE-CT of chest, abdomen and pelvis during staging of melanoma, and taking tolerability, cost and availability into consideration,[147] it is the consensus opinion of the guideline development group that CE-CT should be the first-line imaging modality for identifying brain metastases.

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

✓ MRI should be considered for patients after discussion with the specialist multidisciplinary team. Clinical situations where MRI may be considered include patients with indeterminate findings on CE-CT or patients being considered for locoregional treatment of brain metastases in order 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.[148,149] 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.[148,149] For patients with advanced disease, LDH is included in the AJCC classification system.[93] 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.[150] 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 resected stage II, III and IV 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 RCT 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 (HR 0.56, 95% CI 0.32 to 0.98, p=0.041) but no differences were noted for relapse-free or overall survival.[151] Adjuvant radiotherapy is known to be associated with a risk of both short-term (dermatitis) and long-term (lymphoedema) toxicity. A case series suggested a significant increase in morbidity including lymphoedema rate as a complication of adjuvant radiotherapy.[152] 1++ 3

R **Adjuvant radiotherapy for patients with completely resected stage IIIB or IIIC melanoma is not routinely recommended. It may be considered in individual patients following multidisciplinary team discussion of the risk of local recurrence and the benefits and risks of adjuvant therapy, including risk of significant adverse effects.**

7.2 Immunotherapy and targeted therapy

In a large multicentre RCT of adjuvant nivolumab versus ipilimumab patients with resected stage IIIB–IV disease showed a significant improvement in recurrence-free survival (RFS) with nivolumab (RFS at 4 years: 51.7% vs 41.2%, HR 0.71, 95% CI 0.60 to 0.86).[153] 1++

Adjuvant nivolumab is accepted for use by the SMC for patients with resected stage III–IV disease.

A large RCT of adjuvant pembrolizumab versus placebo showed a significant improvement in RFS in patients with resected stage IIIA–IIIC (HR 0.59, 95% CI 0.49 to 0.73) at 5 years.[154] 1++

Adjuvant ipilimumab alone (10 mg/kg) has been shown to have a significant survival benefit at 5 years compared to placebo in patients with stage IIIA (tumour deposit in lymph node >1.0mm) to IIIC disease (RFS 40.8% vs 30.3%, HR 0.76, 95% CI 0.64 to 0.89).[155] This was, however, at the expense of significant toxicity including 1.1% treatment-related deaths. 1++

Adjuvant ipilimumab 10mg/kg has been approved by the United States Food and Drug Administration but not submitted for approval in Europe.

For targeted therapy, an RCT of adjuvant dabrafenib plus trametinib versus placebo (Combi-AD) in patients with BRAF-positive resected IIIA (tumour deposit >1mm) to IIIC disease showed an improvement in RFS (5-year RFS 52% v 36%, HR 0.51, 95% CI 0.42 to 0.61) and overall survival (3-year overall survival (OS) 86% v 77%, HR 0.57, 95% CI 0.42 to 0.79).[156,157] 1++

In patients with resected stage IIB–IIC melanoma an RCT of adjuvant pembrolizumab versus placebo showed a significant improvement in RFS (HR 0.61, 95% CI 0.45 to 0.82).[158] 1++

Adjuvant pembrolizumab is accepted for use by the SMC for patients with resected stage IIB, IIC or stage III disease. Adjuvant dabrafenib in combination with trametinib is accepted for use by the SMC for patients with resected stage III disease.

R **In patients with completely resected stage IV melanoma, with or without BRAF mutation, nivolumab should be considered as adjuvant treatment.**

R **In patients with completely resected stage III melanoma without BRAF mutation, nivolumab or pembrolizumab should be considered as adjuvant treatment.**

R **In patients with completely resected stage III melanoma with BRAF V600 mutation nivolumab, pembrolizumab or the combination of dabrafenib and trametinib should be considered as adjuvant treatment.**

R **In patients with completely resected stage IIB or IIC melanoma with or without BRAF mutation pembrolizumab should be considered as adjuvant treatment.**

✓ For patients with stage IIIA disease with nodal metastasis 1 mm or less in diameter, the uncertainty of the individual risk/benefit ratio should be carefully discussed with the patient before deciding whether or not to have adjuvant treatment.

8 Management of advanced (unresectable stage III or IV) melanoma

8.1 Introduction

A range of treatment options for patients with advanced melanoma can be considered, including immunotherapy, BRAF and MEK inhibitors. 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[159] although translating this knowledge into 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 multidisciplinary team meeting in order to determine the optimal management strategy.

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

8.2 Systemic anticancer therapy

8.2.1 Immunotherapy

Several RCTs have demonstrated that immunotherapy with immune checkpoint inhibitors (ipilimumab, pembrolizumab and nivolumab) as single agents or in combination are effective in improving outcomes in patients with unresectable stage IIIC or stage IV melanoma.

A trial comparing ipilimumab to glycoprotein100 as second-line therapy in patients with unresectable stage III or IV melanoma found that ipilimumab was associated with improved OS of 10.1 months versus 6.4 months (HR 0.66; p=0.003).[160] 1+

Compared to chemotherapy as first-line treatment, nivolumab had a progression-free survival (PFS) of 5.1 versus 2.2 months, HR 0.43, 95% CI 0.34 to 0.56; 1-year OS of 72.9% versus 42.1%, HR 0.42, p<0.001.[161] A more recent analysis has confirmed a median OS of 37.3 months for nivolumab versus 11.2 months for dacarbazine (HR 0.5, 95% CI, 0.40 to 0.63, p<0.001).[153] 1+

Pembrolizumab was associated with improved 6-month PFS of 47.3% (2-weekly) or 46.4% (3-weekly) compared to 26.5% for ipilimumab, HR 0.58; p=0.001. Median PFS was 8.4 months for pembrolizumab versus 3.4 months in the ipilimumab group (HR 0.57, 95% CI 0.48 to 0.67, p<0·0001).[162] One-year OS was 74.1%, 68.4% or 58.2% respectively (HR 0.63, p=0.0005 for 2-weekly pembrolizumab; HR 0.69, p=0.0036 for 3-weekly pembrolizumab; RR was 33.7% versus 32.9% versus 11.9% (p<0.001 for both comparisons)).[163] More recent analysis has confirmed a median OS of 32.7 months for pembrolizumab and 15.9 months for ipilimumab (HR 0.73, 95% CI 0.61 to 0.88, p=0·00049). 1+

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).[164] Median OS was higher for the combination arm at 5 years, compared to 36.9 months in the nivolumab group and 19.9 months in the ipilipumab group, although formal analysis to compare the combination with single agent nivolumab was not possible due to the statistical design of the study.[165] 1+

A NICE network meta-analysis confirmed that the combination of nivolumab and ipilimumab is associated with the most favourable long-term survival, although it should be noted that that there are no head-to-head RCTs to confirm this statistically.[140] 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%).[160,161,163,165-167] All immunotherapy treatments can cause lifelong dependence on hormones and hormone dysfunction is not reversible.[165] 1+

Ipilimumab, pembrolizumab and nivolumab monotherapy (with restrictions), and nivolumab in combination with ipilimumab have been accepted for use by the SMC *(see section 12.4)*.

✓ When choosing systemic anticancer treatment for patients with untreated stage IV or unresectable stage III melanoma, treatment decisions should be based on the following factors:

- comorbidities and performance status
- risk of treatment toxicity
- whether potential treatment toxicity will be tolerated
- presence of symptomatic brain metastases
- tumour biology (for example, high disease burden, rapid progression, LDH level).

Treatment decisions should be made after a full assessment of the risks and benefits for the patient by the treating oncologist.[57]

R **In patients with untreated stage IV or unresectable stage III melanoma immunotherapy with immune checkpoint inhibitors is recommended as first-line treatment irrespective of BRAF status.**

R **Nivolumab plus ipilimumab should be considered for patients with untreated stage IV or unresectable stage III melanoma** (if suitable for the patient)**. If nivolumab plus ipilimumab is unsuitable or unacceptable** (for example, because of potential toxicity or patient choice)**, pembrolizumab or nivolumab monotherapy should be offered.**

8.2.2 BRAF and MEK inhibitors

BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) as single agents or in combination with a MEK inhibitor (cobimetanib, trametinib, binimetinib) are options for patients with advanced melanoma.

Two open label RCTs demonstrated that BRAF inhibitors improved response and 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.[168,169] Response is further improved with the combination of 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% vs 45-51% for BRAF inhibitors alone and PFS 9.3 to 11.4 months vs 6.2 to 8.8 months).[170-172] When compared to vemurafenib monotherapy a combination of encorafenib plus binimetinib had improved OS (33.6 months, 95% CI 24.4 to 39.2 vs 16.9 months, 95% CI 14.0 to 24.5 with vemurafenib).[173] 1- 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.[168,169,171,172] 1- 1+

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. The combinations of trametinib plus dabrafenib, and encorafenib plus binimetinib are accepted for use in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation *(see section 12.4)*. Economic modelling by NICE suggested that if there is insufficient time for an immune response due to high disease burden and/or rapid progression, encorafenib with binimetinib or dabrafenib with trametinib are the most suitable options.[140]

R **Encorafenib plus binimetinib, or dabrafenib plus trametinib should be considered for patients with untreated stage IV or unresectable stage III melanoma with BRAF mutation if nivolumab plus ipilimumab, pembrolizumab or nivolumab monotherapy are contraindicated or it is predicted there is not enough time for an adequate immune response** (for example, because of high disease burden or rapid progression).

8.3 Laser ablation

A carbon dioxide laser delivers short wavelength energy in a focused light beam to destroy tumour nodules. It can be applied under local anaesthetic, can be repeated and provides effective local disease control.[174-176] 4

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

✓ Laser ablation should be undertaken in a specialist setting by clinicians with experience of the technique and who are in a position to undertake appropriate post-treatment care or offer alternative treatments if laser ablation is not appropriate.

Other similar treatments are available and vary locally.

8.4 Electrochemotherapy

Electrochemotherapy (ECT) uses short electric pulses to increase the absorption of either intralesional or intravenous chemotherapy.[177] 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.[178,179] 1+

Meta-analyses report a high response rate to ECT in patients with cutaneous metastases.[177,178] 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).[178] ECT was well tolerated with 90% of patients reported to be amenable to further treatment if needed.[177] Minor side effects from treatment were muscle spasms, skin changes, nausea and fatigue.[179] 1+

Data on long-term survival or quality of life is limited.[179] No studies were identified comparing the efficacy of ECT with recently developed immunotherapies. 1+

No evidence on cost effectiveness of ECT was identified. 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.**

8.5 Radiotherapy

8.5.1 Radiosensitivity

There is evidence that melanoma cells in vitro have a spectrum of radiosensitivity and that melanoma should not be considered a uniformly radioresistant disease.[180] 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 use of large fraction sizes routinely.[180,181] 4 3

8.5.2 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.[182] There does not appear to be an advantage to using 20 Gy in four fractions over an 8 Gy single fraction.[183] Some patients may benefit from higher dose, fractionated regimens, although this has not been fully established.[184] 2+ 2++ 4

R **Single dose radiotherapy of a least 8 Gy may be considered for palliation of pain from bone metastases.**

8.5.3 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.[185-187] 3 4

The value of surgical intervention in such patients has been established.[186,188] Patients with symptoms of spinal cord compression should be referred urgently to an appropriate surgeon.[187]

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

8.5.4 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.[189] 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.[190] 4 2+

Postoperative radiotherapy has been used as adjuvant treatment following the resection of CNS disease. However, no survival benefit of postoperative radiotherapy has been demonstrated.[188,189] Radiotherapy without surgery, combined with corticosteroids appears to palliate the symptoms of some patients with inoperable cerebral metastases from melanoma but again there is no evidence of a survival benefit.[180,188,191] Radiosurgery (stereotactic radiotherapy) has been used to treat inoperable patients who are fit enough to undergo this procedure, and the results may be equivalent to radiotherapy alone.[192] 3

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.[193] 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 PFS.[194] 1+ 2+

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

R **Patients with good performance status, favourable response to corticosteroid treatment, absence of systemic disease and who have 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 *(see section 8.2)* or stereotactic radiotherapy.

8.6 Specialist palliative care

The GMC has stated that basic palliative care skills are required by every member of the medical profession.[195] Guidance and a training module is available from the Scottish Palliative Care Guideline,[196] Specialist palliative care is an integral component of the care of patients with advanced malignancy, required at varying times during their illness.

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 end of life care.

Three RCTs were identified that included all carcinomas, which, in the context of palliative care, are reasonable to relate to patients with melanoma.[197-199] 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.[197,199] The third RCT used place of death as the outcome measure in a study of 434 patients with incurable malignant disease.[198] 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 patients in the intervention group 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.[200] 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.**

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

9 Follow up

The purpose of the follow-up clinic is to:[141]

- manage and treat symptoms and complications
- encourage healthy lifestyle habits
- detect and treat recurrent disease
- provide information to support person-centred care, best delivered in the form of a holistic needs assessment and care plan, and a treatment summary.

There is little evidence to inform which patients should be followed up, by whom, or the frequency, method, or length of follow up, but a number of consensus guidelines have been produced.[201] Guidance for NHSScotland from the National Cutaneous Melanoma Follow-Up Short-life Working Group, based on the UK consensus-based position statement produced by Melanoma Focus has been approved by the cancer managed clinical networks across Scotland.[141,201] It recommends the schedule outlined in table 10.

Table 10: NHSScotland Cutaneous Melanoma National Follow Up Guideline surveillance schedule[141]

Stage	Risk	Clinical review	Imaging
IA	Low	Dermatology/surgical clinic Every 3–6 months for 12 months	-
IB-IIA	Low	Dermatology/surgical clinic Every 3–4 months for years 1–3 Every 6 months for years 4–5	-
IIIA with <1mm SLN deposit Also earlier stages where SLNB considered appropriate but unable to complete.	Low	Dermatology/surgical clinic Every 3–4 months for years 1–3 Every 6 months for years 4–5	Ultrasound of nodal basin (if available) Every 6 months for years 1–3 Annually for years 4–5 (if not having CLND and not having cross-sectional imaging follow up)
IIB, IIC, IIIA (with >1mm deposit), IIIB Also earlier stages with high-risk features (eg primary mitotic rate) *Patients on adjuvant treatment see below	Moderate	Dermatology/surgical clinic Every 3–4 months for years 1–3 Every 6 months for years 4–5 Annually for years 6–10	Baseline: CE-CT HCAP Years 1–3: 6-monthly CE-CT HCAP Years 4–5: Annual CE-CT HCAP (include neck in all CTs if primary drainage is into the head or neck)
IIIC *Patients on adjuvant treatment see below	High	Oncology and dermatology/ surgical clinics Every 3 months for years 1–2 Every 6 months for years 3–5 Annually for years 6–10	Baseline: CE-CT HCAP Years 1–3: 6-monthly CT HCAP Years 4–5: Annual CE-CT HCAP (include neck in all CTs if primary drainage is into the head or neck)

Stage	Risk	Clinical review	Imaging
IIID or fully resected IV *Patients on adjuvant treatment see below	Very high	Oncology and dermatology/ surgical clinics Every 3 months for years 1–2 Every 6 months for years 3–5 Annually for years 6–10	Baseline: CE-CT HCAP Year 1: 3-monthly CE-CT HCAP Years 2–3: 3–6 monthly CE-CT HCAP Years 4–5: Annual CE-CT HCAP (include neck in all CTs if primary drainage is into the head or neck) Note: brain imaging 6-monthly in years 1–3, unless resected brain metastases then MRI 3-monthly in year 1 and 3–6 monthly in years 2–3, and annual in years 4–5
Unresectable III/IV	Very high	Oncology clinic may need to be tailored to individual. Completed SACT: Every 3 months for years 1–3 Every 6 months for years 4–5 Annually for years 6–10	Baseline: CE-CT HCAP On SACT treatment: Years 1–2: CE-CT HCAP 3-monthly (brain imaging 6-monthly unless brain metastases) Years 3 and beyond: CE-CT HCAP 6-monthly End of treatment: If residual disease seen on CT or if disease only seen on PET** then PET followed by: Years 1–3: CT CAP months 3, 6, 12, 18, 24, 30, 36. Include 6-monthly CE-CT H Years 4–5: Annual CE-CT CAP include CT H at year 5 (include neck to all CTs if primary or metastases in the head or neck. If had SRS or brain surgery image with MRI to head)

CE-CT HCAP – contrast-enhanced computed tomography of the head, chest, abdomen and pelvis; CLND – completion lymphadenectomy; SACT – systemic anticancer therapy; SRS – stereostatic radiosurgery

*For patients on adjuvant systemic therapy, surveillance body scans are recommended every 3–4 months and head scans every 6 months whilst on treatment, and then as above after treatment, based on their stage.

**All PET-CTs should be considered on a patient-by-patient basis, ideally with MDT discussion.

The Scottish consensus guidance also recommends regular holistic needs assessments by a suitably trained person during follow-up care, to check on the patient's physical and mental wellbeing, and provide information on further support.[141] 4

R **Routine follow up and imaging of patients with melanoma should be offered in line with the NHSScotland Cutaneous Melanoma National Follow-Up Guideline.**

R **Patients should have a holistic needs assessment at regular intervals during follow up to support their physical and mental wellbeing.**

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 harmful for women with melanoma.

The prognoses of women with thickness-matched melanomas who became pregnant after apparently successful surgical treatment of AJCC stage I or II melanoma have been compared.[202-205] No difference in disease-free or OS is found between women who have, and women who have not, become pregnant after melanoma treatment. Prognosis is mainly dependent on tumour thickness.[202-205] 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.[206-208] 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.[204,205] 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.[209] 2++

There are no good data on prognosis for women who become pregnant having had a melanoma diagnosed and treated during a previous pregnancy. One study 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.[210] 4

✓ Women with a significant risk of recurrence (localised disease of ≥1 mm thickness) who wish to become pregnant after surgery for stage I or II melanoma should be advised to delay pregnancy for two years after surgery, 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.[211] Five large studies indicate that oral contraceptive use by women after surgery for stage I or II melanoma does not adversely affect their prognosis.[210,212-216] 2++

✓ Women who have had a melanoma treated should choose 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.[214,215,217-219] 2+

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

11 Provision of information

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 preventive measures.[220] 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.[221] A prospective cohort study in 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.[222] 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.

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

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

11.2 Communication

A Cochrane review, an RCT, three cohort studies and a survey were identified covering a wide range of issues related to communication skills, all demonstrating strongly that communication skills training for healthcare professionals is of lasting benefit.[223-228]

The following have been shown to be potentially effective communication tools or strategies: 1⁺ 2⁺ 3

- 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 should be provided in a format that meets the individual patient or carer's needs.

11.3 Patient support groups

Patients benefit from psychoeducational interventions provided in a structured group, facilitated by qualified personnel.[220-222,229] 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 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 development of locally produced information materials.

In primary care

- Explain fully the clinical features of melanoma and how (or why) they develop.
- Advise patients that they will be referred to a specialist and how long they should expect to wait for an appointment.
- Advise patients that removal or biopsy of the tumour may occur at the initial visit.
- 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 contact details.

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 particular treatment, eg flaps, grafts, complex reconstruction, sentinel lymph node biopsy.
- Explain what might be involved in recuperation and rehabilitation and realistic time scales 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 and getting to know their body, skin examination, checking lymph nodes
  - 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 whilst 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

Cancer Zone: www.nhsinform.scot/illnesses-and-conditions/cancer

The NHS inform Cancer Zone is full of practical and emotional support to help those living with cancer.

NHS inform A-Z article melanoma (skin cancer): www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/skin-cancer-melanoma

Info For Me

Caledonia House, Fifty Pitches Road, Cardonald Park, Glasgow G51 4EB

Telephone: 0800 22 44 88 (Monday to Friday 8am–6pm)

Email: nhs.inform@nhs24.scot.nhs.uk

Info For Me can help people find detailed information on different cancers, make their own customised cancer leaflet, find support groups and more, and is available within the Cancer Zone.

Local support groups and telephone helplines

Can be found by visiting the Support Service Directory on the NHS inform website.

Telephone: 0800 22 44 88 (8am–6pm)

www.nhsinform.scot/scotlands-service-directory

11.5.2 Organisations specific to skin conditions

British Association of Dermatologists

Willan House, 4 Fitzroy Square, London W1T 5HQ

Telephone: 0207 383 0266

Email: admin@bad.org.uk

Website: 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

Telephone: 020 7391 6341

Website: 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

Telephone: 0131 516 5481 (Monday to Thursday, 8.30am–3pm)

Email: scotland@changingfaces.org.uk

Website: 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)

MASScot – c/o SMITH 17 Cairnhill Road Bearsden Glasgow G61 1 AU

Telephone: 07738 231 260

Email: leigh@masscot.org.uk

Website: www.masscot.org.uk

MASScot is a Scottish charity run by volunteers who have experienced skin cancer. They provide local, qualified and insured therapists, 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

Telephone: 0141 337 8199

Email: info@cancersupportscotland.org

Website: 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

Telephone: 0300 123 1022 (Monday to Friday, 9am–5pm)

Website: 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

Telephone: 0808 808 00 00 (Monday to Sunday, 8am–8pm).

Website: www.macmillan.org.uk

Third floor, 132 Rose Street, Edinburgh. EH2 3JD

Telephone: 0131 260 3720

Email: bmunro@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

Telephone: 0300 123 1801

Email: enquiries@maggies.org

Website: www.maggies.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, Larbert, Kirkaldy, Dundee, Aberdeen and Inverness.

Marie Curie Cancer Care in Scotland

133 Balornock Road, Stobhill Hospital Grounds, Glasgow G21 3US

Telephone: 0131 561 3900

Email: supporter.relations@mariecurie.org.uk

Website: 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

Second floor, 93 Newman Street, London. W1T 3EZ

Telephone: 020 7612 0370

Email: hello@teenagecancertrust.org

Website: www.teenagecancertrust.org

Teenage Cancer Trust offers care and support, designed for and with young people. They provide information about living with cancer as a young person.

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 Cancer Alliance (NCA)

Room F185, Summerfield House, Aberdeen, AB15 6RE

Telephone: 01224 558579

Website: www.nhsscotlandnorth.scot/nca

South East Scotland Cancer Network (SCAN)

Waverly Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG

Telephone: 0131 465 7683

Website: www.scan.scot.nhs.uk

West of Scotland Cancer Network (WOSCAN)

Website: 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 resource impact analysis.

12.3 Auditing current practice

The cancer quality performance indicators (QPIs) were developed by Healthcare Improvement Scotland in collaboration with the three Regional Cancer Networks and the 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 Quality Performance Indicators.

12.4 Advice for NHSScotland from the Scottish Medicines Consortium

Dabrafenib is accepted for 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 (March 2015).

Full SMC advice: dabrafenib

Encorafenib in combination with binimetinib is accepted for use in NHSScotland for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/list prices that are equivalent or lower (February 2020).

Full SMC advice: encorafenib with binimetinib

Ipilimumab is accepted for use in NHSScotland for the treatment of advanced (unresectable or metastatic) melanoma in adults (April 2013 and November 2014).

Full SMC advice: ipilimumab

Nivolumab is accepted for use in NHSScotland as monotherapy for:

- the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (December 2018)

  Full SMC advice: nivolumab for lymph node involvement or metastatic disease

- the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilipumab (August 2016).

  Full SMC advice: nivolumab for previously untreated advanced melanoma

Nivolumab in combination with ipilimumab is accepted for use in NHSScotland for the treatment of adults with advanced (unresectable or metastatic) melanoma (November 2016).

Full SMC advice: nivolumab and ipilimumab

Pembrolizumab is accepted for use as monotherapy for:

- the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab (November 2015).

  Full SMC advice: pembrolizumab for previously untreated advanced melanoma

- the adjuvant treatment of adults with stage III melanoma and lymph node /involvement who have undergone complete resection (May 2019)

  Full SMC advice: pembrolizumab for resected stage III melanoma

- the adjuvant treatment of adults and adolescents aged 12 and over with stage IIB or IIC melanoma who have undergone complete resection (April 2023).

  Full SMC advice: pembrolizumab for resected stage IIB or IIC melanoma

Trametinib in combination with dabrafenib is accepted for use in NHSScotland for the first-line treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (September 2016).

Full SMC advice: trametinib with dabrafenib

Vemurafenib is accepted for restricted use as first-line treatment for patients with unresectable or metastatic melanoma with BRAF V600 mutation in December 2013.

Full SMC advice: vemurafenib

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 an Information Scientist. 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 Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

For the 2022 update the guideline development group considered the relevant evidence summaries produced by NICE, and searches for the remaining questions were conducted using Medline and Embase, for the years 2017–2022. The evidence identified was evaluated by a Health Services Researcher using standard SIGN methodological checklists.

13.1.1 Literature search for patient issues

At the start of the guideline development process, an Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to cutaneous melanoma. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Advisor 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 that 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 an 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:

- Studies into the benefits of vitamin D supplements for people with melanoma.
- Large studies on the behaviour of lentigo maligna and eventual risk of invasion.

- The behaviour of lentigo maligna melanoma compared 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.
- Studies of the validity and accuracy of sentinel lymph node prediction tools to determine who requires SLNB and to detect melanomas with negative, or low risk of SLNB, which progress to relapse with nodal or distant metastases.
- 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. The study could include 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 updated in 2023. The review history, and any updates to the guideline are 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, 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 2016 edition of SIGN 50, and the update in 2023 used the 2019 edition.

14.2 The guideline development group

Dr Ewan Brown (Chair)	Consultant in Medical Oncology, Edinburgh Cancer Centre, Western General Hospital, Edinburgh
Dr Stuart Ballantyne	Clinical Lead for Radiology, Gartnavel General Hospital, Glasgow
Ms Juliet Brown	Health 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, Lauriston Buildings, Edinburgh
Ms Elaine Fletcher	Specialist Registrar in Clinical Genetics, Western General Hospital, Edinburgh
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Mr Stephen Heller-Murphy	Programme Manager, SIGN
Dr Alex Holme	Consultant Dermatologist, Royal Infirmary of Edinburgh
Ms Frances Kelly	Lay representative, Wishaw
Dr Lucy Melly	Consultant Pathologist, Southern General Hospital, Glasgow
Mr Owen Moseley	Senior Health Economist, Healthcare Improvement Scotland
Dr Colin Moyes	Consultant Dermatopathologist, Southern General Hospital, Glasgow
Mr Omar Quaba	Consultant Plastic Surgeon, Ninewells Hospital, Dundee
Dr Sanjay Rajpara	Consultant Dermatologist, Aberdeen Royal Infirmary
Dr Alan Simms	Consultant Radiologist, St John's Hospital, Livingston
Ms Leigh Smith	Lay representative, Chair of Melanoma Action and Support Scotland
Ms Ailsa Stein	Programme Manager, SIGN
Dr Ashita Waterston	Consultant Medical Oncologist, The Beatson West of Scotland Cancer Centre, Glasgow

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Ms Juliet Brown	Information Scientist, Healthcare Improvement Scotland
Mr Iain Fiddes	Patient representative, Edinburgh
Dr Fiona MacDonald	Consultant Dermatologist, Royal Alexandra Hospital, Paisley
Mr Andy Malyon	Consultant Plastic Surgeon, Glasgow Royal Infirmary
Dr Lucy Melly	Consultant Pathologist, Queen Elizabeth University Hospital, Glasgow
Ms Eva Parkinson	Health Services Researcher, Healthcare Improvement Scotland
Dr Srikanth Puttagunta	Consultant Radiologist, Queen Elizabeth University Hospital, Glasgow
Dr Kaz Rahman	Consultant Plastic Surgeon, Aberdeen Royal Infirmary
Ms Ailsa Stein	Programme Manager, SIGN
Dr Lorna Thompson	Health Services Researcher, Healthcare Improvement Scotland
Dr Ashita Waterston	Consultant Medical Oncologist, The 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 Scotland 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

Karen Graham	Patient and Public Involvement Officer, SIGN
Domenico Romano	Publications Designer, Healthcare Improvement Scotland
Gaynor Rattray	Guideline Co-ordinator, SIGN

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

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 review

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
Professor Alan Denison	Consultant Radiologist, Summerfield House, Aberdeen
Dr Val Doherty	Dermatologist, Royal Infirmary of Edinburgh
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Mrs Kirsty MacFarlane	Principal Pharmacist, Scottish Medicines Consortium, Healthcare Improvement Scotland
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Dr Andy Affleck	Consultant Dermatologist and Mohs Surgeon, Ninewells Hospital, Dundee
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Mr John Scott	Consultant Plastic and Reconstructive Surgeon, Glasgow Royal Infirmary
Mrs Leigh Smith	Lay representative, Chair of Melanoma Action and Support Scotland, Glasgow
Mr Stuart Waterston	Consultant Plastic Surgeon, Ninewells Hospital, Dundee

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
Alan Timmins	Royal Pharmaceutical Society

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Professor Angela Timoney	Chair of SIGN; Co-Editor
Dr Antonia Torgersen	Royal College of Pathologists

Abbreviations

ALM	acral lentiginous melanoma
AJCC	American Joint Committee on Cancer
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
CE-CT	contrast-enhanced computed tomography
CI	confidence interval
c-KIT	receptor tyrosine kinase
CLL	chronic lymphocytic leukaemia
CLND	completion lymphadenectomy
CPD	continuing professional development
CrI	credible interval
CNS	central nervous system
CT	computed tomography
DeCOG	German Dermatologic Cooperative Oncology Group
DM	desmoplastic type melanoma
ECT	electrochemotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EQA	external quality assurance
FBC	full blood count
FNAC	fine needle aspiration cytology
GMC	General Medical Council
HCAP	head, chest, abdomen and pelvis
HEED	Health Economics Evaluation Database
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IARC	International Agency for Research on Cancer
IHC	immunohistochemistry
ISD	NHS Information Services Division
LDH	lactate dehydrogenase
LFT	liver function test
LM	lentigo maligna

LMM	lentigo maligna melanoma
LVI	lymphovascular invasion
MA	marketing authorisation
MEK	mitogen-activated protein kinase
MIA	melanoma inhibitory activity
MDT	multidisciplinary team meeting
MMS	mohs micrographic surgery
MRI	magnetic resonance imaging
MSLT-II	Multicenter Selective Lymphadenectomy Trial II
NCA	North Cancer Alliance
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NM	nodular melanoma
NRAS	neuroblastoma ras viral oncogene homolog
OR	odds ratio
OS	overall survival
PAS	patient access scheme
PCR	polymerase chain reaction
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
RFS	recurrence-free survival
RR	risk ratio
SACT	systemic anticancer therapy
SCAN	South East Scotland Cancer Network
SIGN	Scottish Intercollegiate Guidelines Network
SLN	sentinel lymph nodes
SLNB	sentinel lymph node biopsy
SMC	Scottish Medicines Consorium
SPF	sun protection factor
SRS	stereostatic radiosurgery
SSMM	superficial spreading malignant melanoma

TIL	tumour infiltrating lymphocytes
TNF	tumour necrosis factor
TNM	tumour, node, metastases
USC	urgent suspected cancer
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.

Section	Key question
3.5 **4.1**	**13.** What is the relationship between the immune system and melanoma? **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
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
5.3.2	**KQ1** ***(2023)*** In people with a diagnosis of a thin melanoma (Breslow thickness ≤1mm) undergoing SLNB which of the following predictors should be assessed for their relationship with positive SLNB result: • Breslow thickness (0.8-1.0mm versus <0.8mm) • mitotic rate (≥2 versus <2) • ulceration (present versus absent) • age (<45 versus ≥45) • lymphovascular invasion (present versus absent) • tumour location (head, neck or trunk versus extremities or other) Comparison: positive SLNB result Outcomes: accuracy for predicting SLNB result will be assessed using: • risk ratio • adjusted odds ratio
5.3.3	**KQ2** ***(2022)*** In people with a diagnosis of micrometastatic nodal disease (including aberrant lymph nodes) detected by sentinel lymph node biopsy what are the benefits and harms of completion lymphadenectomy? Comparisons: clinical observation or clinical follow up using imaging Outcomes: local recurrence, regional recurrence, all-cause and melanoma-related mortality (5 years, 10 years), health related quality of life, adverse events, long-term (including lymphoedema), short-term (surgical adverse events)

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 vs PET-CT, PET-CT vs no radiology, CT vs no radiology Outcomes: sensitivity, specificity, positive predictive value, false positive predictive value
6.1	**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
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
7.2	**KQ3 (2023)**	In patients with completely resected stage 2, 3 or 4 melanoma with a BRAF V600 mutation what is the efficacy of BRAF inhibitors? Interventions: dabrafenib, tramentinib Comparisons: observation, placebo Outcomes: overall survival (5 years, 10 years), progression free survival (5 years, 10 years), response rate, adverse effects
7.2	**KQ4 (2023)**	In patients with completely resected stage 2, 3 or 4 melanoma what is the effectiveness of immunotherapy as adjuvant therapy? Interventions: nivolumab, pembrolizumab, ipilimumab Comparisons: between therapies, interferon Alfa-2b, observation, placebo Outcomes: overall survival (5 years, 10 years), progression free survival (5 years, 10 years), response rate, adverse effects
8.2	**KQ5 (2023)**	What systemic anticancer therapies are effective in patients with advanced/metastatic disease? Patients with: a diagnosis of stage IV (or unresectable stage III) melanoma Interventions: • immunotherapies: - nivolumab - nivolumab + ipilimumab - ipilimumab - pembrolizumab

		• targeted therapy for BRAF-positive melanoma: - encorafenib + binimetinib - trametinib with dabrafenib - dabrafenib - vemurafenib Comparisons: any immunotherapies and targeted therapies, localised treatments for patients with locoregional disease. Between therapies. Outcomes: • rate of mortality and time to death • all-cause and melanoma-specific mortality; at 1, 2 and 5 years • progression free survival; at 1, 2 and 5 years • health related quality of life • serious adverse events • time on treatment • time to second treatment
8.4	**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

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