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Cutaneous melanoma: an updated SIGN Guideline

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Introduction

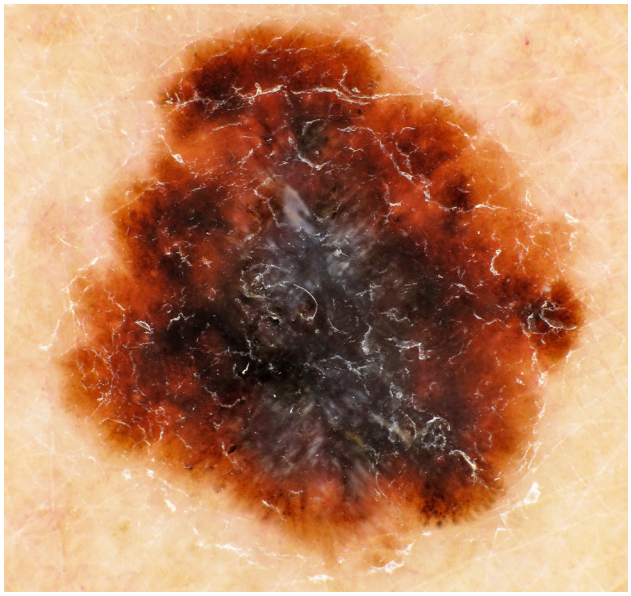
Cutaneous melanoma is a malignant tumour of cutaneous melanocytes. It has a complex aetiology, although the primary risk factor for development of melanoma is considered to be exposure to natural and artificial sunlight.[1] In Scotland, over the last decade, the incidence of melanoma has increased by 38% in men and 22% in women, with the most recent incident rates being 26 male and 21.3 female cases per 100,000 in 2013.[2] Melanoma is often curable by surgery if recognised and treated at an early stage but prognosis for patients with advanced melanoma remains poor. Recent years have seen considerable progress in the understanding of the molecular basis of melanoma which has led to the emergence of molecular therapies including BRAF inhibitors and novel immunotherapies that can improve outcomes.

The Scottish Intercollegiate Guidelines Network (SIGN) produce multidisciplinary, evidence-based clinical guidelines to reduce variation in practice across Scotland and improve patient outcomes. They are based on a systematic literature review and recommendations are explicitly linked to the clinical evidence.[3] *SIGN 146: Cutaneous melanoma* was published in January 2017.[4] It updates *SIGN 72* to reflect the most recent evidence. The main focus of the update is pathology, radiological and surgical staging, and management of advanced disease. Other sections of the guideline, which were not part of the evidence review, are reproduced verbatim from *SIGN 72*.

Melanoma diagnosis

The multidisciplinary team is crucial to the management of patients with cutaneous melanoma, and it is imperative that all patients are discussed in this forum. Clinicians should therefore be familiar with the 7 point or ABCDE checklist for assessing lesions (Tables 1 and 2),[5,6] and examine patients' skin with a dermatoscope when experienced in the use of this tool (Figure 1). The presence of any major feature in the 7-point checklist, or any of the features in the ABCDE system, is an indicator for referral. The presence of minor features should increase suspicion, as it is accepted that some melanomas will have no major features.

Figure 1 Dermatoscopic image of superficial spreading melanoma showing irregular pigmentation (reproduced with permission from Dr Susannah Fraser, NHS Fife)



GPs should be advised to urgently refer all patients with suspected melanoma, rather than carry out a biopsy in primary care. A good practice point identifies that targeted

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Table 1 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

education can enhance a health professional's ability to diagnose melanoma. This is applicable to both primary and secondary care. Following referral, a suspicious pigmented lesion should be excised with a 2 mm margin and a cuff of fat. If complete excision is not possible, an incisional or punch biopsy of the most suspicious area is advised; superficial shave biopsy is not appropriate.

Following diagnosis of melanoma, patients should receive verbal and written information, both about treatment options and support services available. After completion of treatment, patients with invasive melanoma should have a period of follow up, although melanoma in situ does not require follow up. This is an opportunity to examine the patient's entire skin, and also provide education in self-examination. Patients should also be offered psychological and emotional support, that can often be provided by trained nurses.

Surgical excision of primary melanoma

Once the diagnosis of melanoma has been established with an excision biopsy (or incisional biopsy), adequate wide local excision is the mainstay of treatment (in the absence of distant disease). The aim of wide local excision is to reduce the risk of local recurrence. Recommended clinical margins for varying stages of melanoma are given in Table 3. It should be acknowledged that compromise may be required at sites of aesthetic or functional importance but such decisions should be made within the context of the multidisciplinary team meeting.

Management of loco-regional lymph nodes

The presence or absence of nodal metastases is the most significant predictor of outcome in melanoma.[7] If there is palpable lymphadenopathy, fine needle aspiration cytology should be used to confirm the presence of metastases. Accuracy may be improved when this is performed under ultrasound guidance. An open biopsy is required if fine needle aspiration cytology is inconclusive or where doubt persists. Confirmation of metastatic melanoma in a palpable lymph node is an indication for radical dissection of that lymph node basin.

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. Biopsy of this node using the technique of sentinel lymph node biopsy can determine the presence or absence of metastasis within the regional lymph node basin.[8] It is a useful staging tool in melanomas > 1 mm thick, and in thick melanomas (> 4 mm) it can identify a subset of melanomas which are node negative and therefore offer a better prognosis. A completion lymphadenectomy (complete clearance of remaining lymph node basin) is often considered with a positive sentinel lymph node biopsy result despite lack of good quality evidence for any survival advantage. Tables 4 and 5 compiled by NICE are useful adjuncts to inform

Table 2 ABCDE lesion system

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

Table 3 Selected recommendations from *SIGN 146: Cutaneous Melanoma*[4]

Surgical excision
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
Sentinel lymph node biopsy
SLNB should be considered as a staging technique in patients with stage IB–IIC melanoma with a Breslow thickness of > 1 mm. It should not be offered to patients with IB melanoma where Breslow thickness is ≤ 1 mm.
Melanoma staging
Staging CT should be offered to patients with stage IIC or above melanoma.
Surveillance imaging
Routine surveillance imaging should not be offered to patients with stage I–IIB melanoma. Decisions on the use of routine surveillance imaging for patients with stage IIC–III melanoma should be made at a regional level after identifying and agreeing any additional imaging resources required, and considering other factors, including patient choice.
Management of advanced melanoma
Trametinib in combination with dabrafenib is recommended for patients with unresectable stage IIIC or stage IV melanoma with a *BRAF* V600 mutation.
Ipilimumab, pembrolizumab and nivolumab monotherapy or ipilimumab/nivolumab combination therapy are recommended for patients with unresectable stage IIIC and IV melanoma.

Table 4 Possible advantages and disadvantages of sentinel lymph node biopsy (reproduced with permission from NICE[9])

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

Table 5 Possible advantages and disadvantages of completion lymphadenectomy (reproduced with permission from NICE[9])

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

discussion with patients facing decisions about sentinel lymph node biopsy and lymphadenectomy, respectively.[9]

Melanoma staging

In the initial staging of melanoma, there is a lack of good quality evidence on who should undergo imaging, and with what imaging modality. Potential benefits of accurate staging need to be weighed against the potential disadvantages including radiation dose, false positives and incidental findings. Ultimately the higher the stage of disease based on primary excision, the more likely imaging is to find true distant disease, and the balance tips more towards performing imaging. Given the good prognosis, and therefore low incidence of distant disease in Stage I–IIB melanoma, the disadvantages of staging imaging were felt to outweigh the benefits for this group of patients. It was the consensus view of the guideline development group that patients with Stage IIC and III disease should be offered staging imaging with a CT with contrast of head, chest, abdomen and pelvis. The quality of the evidence did not support the routine use of PET/CT in the staging of melanoma and that PET/CT should be reserved for patients with indeterminate findings on CT or patients being considered for major surgical resection after discussion at the specialist multidisciplinary team meeting.

Surveillance imaging

Overall the evidence for surveillance method (including imaging modality), frequency and duration of surveillance in clinically relevant outcomes of interest, such as survival, is poor. This is demonstrated by the lack of a consensus approach from multiple different organisations and guidelines on this topic.[9,10] Although there are some arguments to support frequent surveillance imaging in terms of early detection of treatable metastatic disease, there are a number of potential disadvantages that need to be carefully considered, especially as it has not been shown to improve survival. Disadvantages include the discovery of incidental findings that are later found to be harmless, patient anxiety and radiation exposure from imaging.

It was the consensus opinion of the guideline development group not to offer routine surveillance imaging to patients with Stage I–IIB melanoma, as the disadvantages were felt to outweigh the benefits given the relatively low risk of recurrent disease. Given the lack of good quality evidence, a blanket recommendation on routine surveillance imaging could not

be made in patients with higher risk melanoma (stage IIC and III). It was therefore agreed that the decision on the routine surveillance imaging should be made on a regional level and take into account local resources. On an individual level, factors such as patient wishes after discussion of the advantages and disadvantages, stage of the original tumour and potential fitness for further treatment, should also be taken into account. Given the higher cost of PET/CT and its relatively limited availability, CT should be the imaging modality of choice for surveillance imaging if it is performed.

Management of advanced melanoma

Recent years have seen the development of several new treatment options for patients with advanced melanoma. Development of BRAF inhibitors (vemurafenib and dabrafenib) as single agents or in combination with a MEK inhibitor (cobimetanib and trametinib), and novel immunotherapies (ipilimumab, pembrolizumab and nivolumab) as single agents or in combination, all represent major advances for patients with advanced melanoma.[11–14] All of these treatments are associated with significantly improved outcomes, although the optimal choice, sequence and combination of therapies are still to be determined. Although durable responses to some of these agents are seen, it should be recognised that all of the novel immunotherapy agents are associated with a significant risk of autoimmune toxicity including colitis; early identification and treatment of auto-immune toxicity is important. It is now also recognised that there are several different genomic subtypes of melanoma but translating this increased understanding into the development of other new therapies for patients with melanoma remains under investigation.[15] A good practice point emphasises that 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 taking into account patient fitness, comorbidity, disease burden and overall aim of treatment.

Implementation and future work

Many specialties and professions are involved in the management of patients with melanoma and this guideline provides advice at all stages of the patient's pathway of care, from primary prevention to early recognition, treatment and follow up. The guideline is therefore intended to 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, GPs and patient support groups.

It should be acknowledged that given the selective nature of the update there remain important additional challenges and unanswered questions in the management of patients with melanoma, such as the role of vitamin D in melanoma development and prognosis and what is the optimal treatment pathway for patients with advanced melanoma. Nonetheless it is hoped that the guideline provides important education and practical advice on the management of patients at all stages of melanoma presentation and treatment.

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