NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Melanoma: assessment and management

Draft for consultation, January 2022

This guideline covers the assessment and management of melanoma (a type of skin cancer) in children, young people and adults. It aims to reduce variation in practice and improve survival.

This guideline will update NICE clinical guideline NG14 (published July 2015).

Who is it for?

- Healthcare professionals in primary, secondary and tertiary care
- Commissioners and providers of NHS-funded healthcare services
- People with melanoma, their families and carers

What does it include?

- the recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the 2022 recommendations and how they might affect practice
- the guideline context.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

New and updated recommendations

We have reviewed the evidence on assessment, management and follow-up. You are invited to comment on the new and updated recommendations. These are marked as **[2022]**.

We have not reviewed the evidence for the recommendations marked **[2015]** (shaded in grey) and cannot accept comments on them. In some cases, we have made minor wording changes for clarification.

See update information for a full explanation of what is being updated.

Full details of the evidence and the committee's discussion on the 2022 recommendations are in the evidence reviews. Evidence for the 2015 recommendations is in the full version of the 2015 guideline.

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Stages of melanoma

The stages of melanoma referred to in this guideline are based on the 8th edition of the American Joint Committee on Cancer's AJCC cancer staging manual. Staging of primary melanoma can be carried out in 2 steps. The initial staging is based on the histopathological features reported by the pathologist looking at the microscopic sections of the tumour. The melanoma is staged as 0 to IIC, based on factors such as the thickness of the tumour and the presence or absence of ulceration.

In many hospitals in the UK, this first step is followed by the option of a second, which is a sampling of the lymph nodes most likely to contain secondary melanoma cells (sentinel lymph node biopsy). If a sentinel lymph node biopsy is performed and microscopic disease is detected, the melanoma becomes stage III. If no microscopic disease is detected, then the initial stage is used. Stage IV disease occurs when the melanoma has spread to distant parts of the body, such as the brain or lungs.

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Communication and support

1.1.1 Give people with melanoma accurate and easy to understand information (both written and spoken) in a sensitive and timely manner throughout their care, tailored to their needs and circumstances. Topics to discuss include:

- melanoma and different types of skin cancer
- treatment options, including the risks and benefits

- where the person's appointments will take place
- which healthcare professionals will undertake the person's care and how to get in touch with them
- expected waiting times for consultations, investigations and treatments
- preventing recurrence, and how to protect their skin from damage caused by exposure to the sun, while avoiding vitamin D depletion
- recognising signs and symptoms of suspicious skin lesions
- what to do if they have any concerns and how to re-access services
- local services and how to get in touch with them.

For more guidance on giving information to people and discussing their preferences, follow the recommendations on communication and patient-centred care in NICE's guidelines on patient experience in adult NHS services and shared decision making. **[2015]**

1.1.2 Discuss the psychological and emotional impact of melanoma with the person, ask whether they have any psychological or support care needs, and offer to carry out a holistic needs assessment. Topics to discuss include:

- their understanding of melanoma and its prognosis
- their specific concerns and preferences
- important values or personal goals for care and treatment
- risk of recurrence, metastatic spread or new primary cancers
- whether family members are at risk. **[2015]**

1.1.3 Explain to people with melanoma that they are welcome to bring a companion with them to appointments. **[2015]**

1.1.4 Ensure that each local skin cancer multidisciplinary team and specialist skin cancer multidisciplinary team has:

- at least 1 skin cancer clinical nurse specialist to provide people with information and support
- access to psychological support services for people with melanoma. **[2015]**

1.1.5 Ensure that healthcare professionals can support people with melanoma by attending training and being competent in:

- communicating complex and sensitive information clearly
- tailoring information and support to the person's individual needs and circumstances. **[2015]**

1.2 Managing vitamin D levels and concurrent drug treatment

1.2.1 Measure vitamin D levels at diagnosis in secondary care in all people with melanoma. **[2015]**

1.2.2 Give people whose vitamin D levels are thought to be suboptimal advice on vitamin D supplementation and monitoring in line with local policies and NICE's guideline on vitamin D. **[2015]**

1.2.3 Do not withhold or change drug treatment for other conditions, except immunosuppressants and immunomodulators, on the basis of a diagnosis of melanoma. For people on immunosuppressive or immunomodulatory treatments, seek advice from the person's specialist team, aiming to optimise quality of life while minimising the person's risk. **[2015, amended 2022]**

1.3 Assessing melanoma

Dermoscopy and other visualisation techniques

1.3.1 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. **[2015]**

1.3.2 Do not routinely use confocal microscopy or computer-assisted diagnostic tools to assess pigmented skin lesions. **[2015]**

Photography

1.3.3 For a clinically atypical melanocytic lesion that does not need excision at first presentation in secondary or tertiary care:

- use baseline photography (preferably dermoscopic) **and**
- review the clinical appearance of the lesion, and compare it with the baseline photographic images, 3 months after first presentation to identify early signs of melanoma. **[2015]**

Assessing and managing atypical spitzoid lesions

1.3.4 Discuss all suspected atypical spitzoid lesions at the specialist skin cancer multidisciplinary team meeting. **[2015]**

1.3.5 Make the diagnosis of a spitzoid lesion of uncertain malignant potential on the basis of the histology, clinical features and behaviour. **[2015]**

1.3.6 Manage a spitzoid lesion of uncertain malignant potential as melanoma. **[2015]**

Taking tumour samples for genetic testing

1.3.7 If targeted systemic therapy is a treatment option, offer genetic testing using:

- a secondary melanoma tissue sample if there is adequate cellularity **or**
- a primary melanoma tissue sample if a secondary sample is not available or is of inadequate cellularity. **[2015]**

BRAF analysis of melanoma tissue samples

1.3.8 Do not offer BRAF analysis of melanoma tissue samples from people with stage IA or IB primary melanoma at presentation except as part of a clinical trial. **[2022]**

1.3.9 Consider BRAF analysis of melanoma tissue samples from people with stage IIA or IIB primary melanoma. **[2022]**

1.3.10 Carry out BRAF analysis of melanoma tissue samples from people with stage IIC to IV primary melanoma. **[2022]**

1.3.11 When conducting BRAF analysis, consider immunohistochemistry as the first test for BRAF V600E, if available. **[2022]**

1.3.12 If BRAF V600E immunohistochemistry is negative or inconclusive, use a different BRAF genetic test. **[2022]**

For a short explanation of why the committee made these recommendations see the rationale and impact section on BRAF analysis of melanoma tissue samples.

Full details of the evidence and the committee's discussion are in evidence review A: genetic testing for melanoma.

1.4 Staging with sentinel lymph node biopsy and imaging

1.4.1 Do not offer imaging or sentinel lymph node biopsy (SLNB) to people who have stage IA melanoma. **[2022]**

1.4.2 Do not offer imaging before SLNB unless lymph node or distant metastases are suspected. **[2022]**

1.4.3 Consider SLNB for people who have melanoma with a Breslow thickness of 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. **[2022]**

1.4.4 Consider SLNB for people who have melanoma with a Breslow thickness greater than 1.0 mm. **[2022]**

1.4.5 For women who are pregnant, discuss the option of delaying SLNB until after the pregnancy is completed. **[2022]**

1.4.6 Consider staging with contrast-enhanced (CE)-CT of the head, neck, chest, abdomen and pelvis for people with stage IIB melanoma. **[2022]**

1.4.7 Offer staging with CE-CT of the head, neck, chest, abdomen and pelvis to people with stage IIC to IV melanoma. **[2022]**

1.4.8 Offer whole-body and brain MRI, instead of CE-CT, for children and young adults (from birth to 24 years) with stage IIB to IV melanoma. **[2022]**

1.4.9 Offer whole-body and brain MRI, instead of CE-CT, to women with stage IIB to IV melanoma who are pregnant. **[2022]**

1.4.10 Consider brain MRI, instead of CE-CT, for people with stage IIIC to IV melanoma and one of the following risk factors:

- a mitotic index of 9 or more
- primary melanoma located on the scalp. **[2022]**

1.4.11 Consider a repeat staging scan before starting adjuvant treatment, unless imaging done within the past 8 weeks is available. **[2022]**

For a short explanation of why the committee made these recommendations see the rationale and impact section on staging with sentinel lymph node biopsy and imaging.

Full details of the evidence and the committee's discussion are in evidence review B: use of sentinel lymph node biopsy in people with melanoma.

1.5 Managing stages 0 to II melanoma

Excision for stages 0 to II melanoma

1.5.1 Consider a clinical margin of at least 0.5 cm when excising stage 0 melanoma. **[2022]**

1.5.2 If excision for stage 0 melanoma does not achieve an adequate histological margin, discuss further management with the multidisciplinary team. **[2022]**

1.5.3 Use a clinical margin of:

- at least 1 cm when excising stage I melanoma
- at least 2 cm when excising stage II melanoma. **[2022]**

For a short explanation of why the committee made these recommendations see the rationale and impact section on excision for stages 0 to II melanoma.

Full details of the evidence and the committee's discussion are in evidence review C: surgical and histopathological excision margins for people with stage 0 to II melanoma.

Imiquimod for stage 0 melanoma

1.5.4 Consider topical imiquimod to treat stage 0 melanoma in adults if surgery to remove the entire lesion with a 0.5 cm clinical margin would lead to unacceptable disfigurement or morbidity. **[2015]**

1.5.5 Consider a repeat skin biopsy for histopathological assessment after treatment with topical imiquimod for stage 0 melanoma, to check whether it has been effective. **[2015]**

In July 2022, this was an off-label use of topical imiquimod. See NICE's information on prescribing medicines.

1.6 Managing stage III melanoma

Completion lymph node dissection for stage III melanoma

1.6.1 Do not routinely offer completion lymph node dissection to people with a diagnosis of micrometastatic nodal disease detected by SLNB. **[2022]**

1.6.2 Consider completion lymph node dissection for people with stage III melanoma, after discussion with the person and the specialist skin cancer multidisciplinary team, if there are factors that might make recurrent nodal disease difficult to manage, for example:

- the person has melanoma of the head and neck
- stage III adjuvant therapies are contraindicated
- regular follow-up is not possible. **[2022]**

For a short explanation of why the committee made these recommendations see the rationale and impact section on managing stage III melanoma.

Full details of the evidence and the committee's discussion are in evidence review D: completion lymphadenectomy for micrometastatic nodal disease in stage III melanoma and evidence review E: use of sentinel lymph node biopsy for people with stage III melanoma with microsatellite lesions.

Therapeutic lymph node dissection for stage III melanoma

1.6.3 Offer therapeutic lymph node dissection to people with palpable stage IIIB to IIIC melanoma, or nodal disease detected by imaging. **[2015]**

Adjuvant treatments for resected stage III melanoma

Adjuvant systemic anticancer treatments

For guidance on specific treatments, see:

- NICE's technology appraisal guidance on dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma
- NICE's technology appraisal guidance on pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence
- NICE's technology appraisal guidance on nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease.

Adjuvant radiotherapy

1.6.4 Do not offer adjuvant radiotherapy to people with stage IIIA melanoma. **[2015]**

1.6.5 Do not offer adjuvant radiotherapy to people with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects. **[2015]**

Non-curative treatment for superficial skin metastases in stage III melanoma

1.6.6 Consider topical imiquimod to palliate superficial melanoma skin metastases. **[2015]**

In July 2022, this was an off-label use of topical imiquimod. See NICE's information on prescribing medicines.

Genomic biomarker-based treatment for stage III melanoma

The point at which to use genomic biomarker-based therapy in solid tumour treatment pathways is uncertain. See NICE's topic page on genomic biomarker-based cancer treatments for guidance on specific treatments.

1.7 Treating in-transit metastases in stages III and IV melanoma

1.7.1 Discuss management of in-transit metastases, including surgery or treatment in a regional specialist centre, with the specialist skin cancer multidisciplinary team. **[2022]**

1.7.2 Offer surgery as the first option and if surgery is not feasible, or if the person has recurrent in-transit metastases, consider one of the following options based on their suitability for the person:

- systemic anticancer therapy (see recommendations 1.8.6 to 1.8.13)
- talimogene laherparepvec in line with NICE's technology appraisal guidance on talimogene laherparepvec
- isolated limb infusion or perfusion
- radiotherapy
- electrotherapy in line with NICE's interventional procedure guidance on electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma
- a topical agent such as imiquimod. **[2022]**

In July 2022, use of the immunotherapies and targeted therapies recommended in this guideline and talimogene laherparepvec was off label for children and young people. Use of topical imiquimod for this indication was also off label. Use of dacarbazine was off label for children and young people under 15. See NICE's information on prescribing medicines.

For a short explanation of why the committee made these recommendations see the rationale and impact section on treating in-transit metastases in stages III and IV melanoma.

Full details of the evidence and the committee's discussion are in evidence review F: systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma.

1.8 Managing stage IV and unresectable stage III melanoma

Management of oligometastatic stage IV melanoma

1.8.1 Refer the care of people who appear to have oligometastatic melanoma to the specialist skin cancer multidisciplinary team for recommendations about staging and management. **[2015]**

1.8.2 Consider surgery or other ablative treatments to prevent or control symptoms of oligometastatic stage IV melanoma in consultation with other site-specific multidisciplinary teams. **[2015, amended 2022]**

Brain metastases

1.8.3 For guidance on diagnosing, monitoring and managing brain metastases in people aged 16 or over see NICE's guideline on brain tumours (primary) and brain metastases in adults. **[2022]**

1.8.4 Discuss the care of people with melanoma and brain metastases with the specialist skin cancer multidisciplinary team. **[2015]**

1.8.5 Refer people with melanoma and brain metastases that might be suitable for surgery or stereotactic radiotherapy to the neuro-oncology multidisciplinary team for a recommendation about treatment. **[2015, amended 2022]**

Systemic anticancer treatments for untreated stage IV and unresectable stage III melanoma

In July 2022, use of the immunotherapies and targeted therapies in recommendations 1.8.6 to 1.8.11 was off label in children and young people. Use of dacarbazine in recommendations 1.8.11 and 1.8.12 was off label in children and young people under 15 years. See NICE's information on prescribing medicines.

1.8.6 Offer treatment with immunotherapy to people with untreated stage IV or unresectable stage III melanoma, as set out in recommendations 1.8.7 to 1.8.9. If immunotherapy is contraindicated or unsuitable, follow recommendations 1.8.10 to 1.8.12 for alternative treatments based on BRAF type. **[2022]**

Immunotherapies

1.8.7 Offer nivolumab in combination with ipilimumab to people with untreated stage IV or unresectable stage III melanoma after a full assessment by the treating oncologist and discussion of the risks and benefits with the person. **[2022]**

See NICE's technology appraisal guidance on nivolumab in combination with ipilimumab for treating advanced melanoma.

1.8.8 If nivolumab in combination with ipilimumab is found to be unsuitable or unacceptable (for example, because of potential toxicity), after a full assessment of the risks and benefits by the treating oncologist and discussion with the person, offer pembrolizumab. **[2022]**

See NICE's technology appraisal guidance on pembrolizumab for advanced melanoma not previously treated with ipilimumab.

1.8.9 If nivolumab in combination with ipilimumab is found to be unsuitable or unacceptable (for example, because of potential toxicity), after a full

assessment of the risks and benefits by the treating oncologist and discussion with the person, consider nivolumab monotherapy. **[2022]**

See NICE's technology appraisal guidance on nivolumab for treating advanced (unresectable or metastatic) melanoma.

For other guidance on immunotherapies see NICE's webpage on technology appraisal guidance for melanoma.

Alternatives to immunotherapies for BRAF V600 mutation-positive melanoma: targeted therapies

1.8.10 Offer encorafenib in combination with binimetinib, or trametinib in combination with dabrafenib, to people with untreated BRAF-mutant stage IV or unresectable stage III melanoma if:

- nivolumab in combination with ipilimumab, pembrolizumab and nivolumab are contraindicated **or**
- there is insufficient time for an immune response due to high disease burden and/or rapid progression. **[2022]**

See NICE's technology appraisal guidance on encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma and trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma.

1.8.11 If encorafenib in combination with binimetinib, and trametinib in combination with dabrafenib, are both unsuitable or unacceptable to the person:

- offer dabrafenib or vemurafenib to people for whom binimetinib and trametinib are contraindicated **or**
- if targeted treatment is contraindicated, consider encouraging the person to enrol in a clinical trial, treatment with chemotherapy (dacarbazine) or best supportive care. **[2022]**

See NICE's technology appraisal guidance on dabrafenib for treating

unresectable or metastatic BRAF V600 mutation-positive melanoma and vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.

For other guidance on targeted therapies see NICE's webpage on technology appraisal guidance for melanoma.

Alternatives to immunotherapies for BRAF-wild type melanoma

1.8.12 For people with untreated BRAF-wild type stage IV or unresectable stage III melanoma for whom nivolumab in combination with ipilimumab, pembrolizumab and nivolumab are contraindicated, consider:

- encouraging them to enrol in a clinical trial **or**
- treatment with chemotherapy (dacarbazine) **or**
- best supportive care. **[2022]**

Cytotoxic chemotherapy in unresectable stage III or stage IV melanoma

1.8.13 Do not routinely offer further cytotoxic chemotherapy to people with stage IV or unresectable stage III melanoma who have had previous treatment with dacarbazine except in the context of a clinical trial. **[2022]**

For a short explanation of why the committee made these recommendations see the rationale and impact section on systemic anticancer treatments for stage IV and unresectable stage III melanoma.

Full details of the evidence and the committee's discussion are in evidence review F: systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma.

Genomic biomarker-based treatment

The point at which to use genomic biomarker-based therapy in solid tumour treatment pathways is uncertain. See NICE's topic page on genomic biomarker-based cancer treatments for guidance on specific treatments.

1.9 Follow-up after treatment for melanoma

Information and support for people who have had melanoma

1.9.1 Ensure that people who have completed treatment for melanoma have been given direct contact details for specialist skin cancer services that can provide advice about problems or concerns related to their melanoma. **[2022]**

1.9.2 Provide psychosocial support for the person and their family or carers at all follow-up appointments. **[2022]**

1.9.3 Ensure that local follow-up policies:

- are in line with recommendations 1.1.2 and 1.1.3 in the section on communication and support
- include:
  - reinforcing advice about self-examination
  - health promotion for people with melanoma and their families, including sun awareness and avoiding vitamin D depletion (see NICE's guideline on sunlight exposure: risks and benefits)
  - advice on stopping smoking for people who smoke (see NICE's guideline on tobacco: preventing uptake, promoting quitting and treating dependence). **[2022]**

Exceptions to routine follow-up

1.9.4 Provide advice in line with recommendation 1.9.3 to people who have had stage 0 melanoma at a clinic visit during the first year after treatment has been completed. **[2022]**

1.9.5 Offer personalised follow-up to people with unresectable stage III or IV melanoma. **[2022]**

1.9.6 Consider personalised follow-up for people who are at increased risk of further primary melanomas (for example, people with atypical mole syndrome, previous melanoma, multiple in-situ melanomas, or a history of

melanoma in first-degree relatives or other relevant familial cancer syndromes). **[2022]**

1.9.7 Offer whole-body and brain MRI, instead of CE-CT, for children and young adults (from birth to 24 years) having imaging as part of follow-up. **[2022]**

1.9.8 Offer whole-body and brain MRI, instead of CE-CT, for women who are pregnant and having imaging as part of follow-up. **[2022]**

Planning routine follow-up

1.9.9 Full examination of the skin and regional lymph nodes at clinic appointments should be done by a healthcare professional with skills and expertise in skin cancer and lymph node examination. **[2022]**

1.9.10 For people having both CE-CT and ultrasound scans, alternate between the 2 types of scan. **[2022]**

1.9.11 Do not routinely use PET-CT during follow-up of people with melanoma. **[2022]**

1.9.12 Continue to follow the recommendations on managing concurrent drug treatment. **[2022]**

1.9.13 Offer follow-up for 1 year to people who have had stage IA melanoma, and for 5 years to people who have had stages IB to IV melanoma, using the table on follow-up after stages I to IV melanoma. **[2022]**

Follow-up after stages I to IV melanoma

Stage of melanoma	Follow-up
IA	• Year 1: Consider 2 clinic appointments, with discharge at the end of year 1. Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up
IB	• Year 1: Offer 2 clinic appointments, and consider adding 2 ultrasound scans of the draining nodal basin if sentinel lymph node biopsy (SLNB) was considered but not done • Years 2 and 3: Offer 1 clinic appointment each year, and consider adding 1 ultrasound scan of the draining nodal basin each year if SLNB was considered but not done • Years 4 and 5: Offer 1 clinic appointment each year. Discharge at the end of year 5
IIA	• Years 1 and 2: Offer 2 clinic appointments each year, and consider adding 2 ultrasound scans of the draining nodal basin each year if SLNB was considered but not done. • Year 3: Offer 1 clinic appointment, and consider adding 1 ultrasound scan of the draining nodal basin if SLNB was considered but not done • Years 4 and 5: Offer 1 clinic appointment each year. Discharge at the end of year 5
IIB	• Years 1 and 2: Offer 4 clinic appointments each year, and consider 2 contrast-enhanced CT (CE-CT) scans of the head, neck, chest, abdomen and pelvis each year. Consider adding 2 ultrasound scans of the draining nodal basin each year if SLNB was considered but not done • Year 3: Offer 2 clinic appointments and consider 2 CE-CT scans of the head, neck, chest, abdomen and pelvis. Consider adding 2 ultrasound scans of the draining nodal basin if SLNB was considered but not done • Years 4 and 5: Offer 1 clinic appointment each year and consider 1 CE-CT scan of the head, neck, chest, abdomen and pelvis each year. Discharge at the end of year 5
IIC	• Years 1 and 2: Offer 4 clinic appointments and 2 CE-CT scans of the head, chest, abdomen and pelvis each year. Consider adding 2 ultrasound scans of the draining nodal basin each year if SLNB was considered but not done • Year 3: Offer 2 clinic appointments and 2 CE-CT scans of the head, chest, abdomen and pelvis. Consider adding 2 ultrasound scans of the draining nodal basin if SLNB was considered but not done • Years 4 and 5: Offer 1 clinic appointment and 1 CE-CT scan of the head, chest, abdomen and pelvis each year. Discharge at the end of year 5
IIIA to IIIC not currently having adjuvant therapy	• Years 1 to 3: Offer 4 clinic appointments and 2 CE-CT scans of the head, neck, chest, abdomen and pelvis each year. Consider adding 2 ultrasound scans of the draining nodal basin each year if the person has a positive sentinel lymph node

	• Years 4 and 5: Offer 2 clinic appointments and 1 CE-CT scan of the head, neck, chest, abdomen and pelvis each year. Discharge at the end of year 5
IIID and resected IV not currently having adjuvant therapy	• Years 1 to 3: Offer 4 clinic appointments and 4 CE-CT scans of the head, neck, chest, abdomen and pelvis each year • Years 4 and 5: Offer 2 clinic appointments and 2 CE-CT scans of the head, neck, chest, abdomen and pelvis each year. Discharge at the end of year 5
IIIA to IIIC, IIID and resected IV having adjuvant therapy	During adjuvant therapy, base follow-up on therapeutic requirements

This table sets out routine follow-up. Offer personalised follow-up to people with unresectable stage III or IV melanoma and people at increased risk of further primary melanomas, in line with recommendations 1.9.5 and 1.9.6.

For a short explanation of why the committee made these recommendations see the rationale and impact section on follow-up after treatment for melanoma.

Full details of the evidence and the committee's discussion are in evidence review G: follow-up of people with melanoma.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Monitoring and response biomarkers

Can biomarkers accurately classify recurrence, progression and response to treatment? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale section on BRAF analysis of melanoma tissue samples.

Full details of the evidence and the committee's discussion are in evidence review A: genetic testing for melanoma.

2 Safety, prognostic and predictive biomarkers

Can biomarkers be used for risk stratification and treatment planning for people with melanoma? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale section on BRAF analysis of melanoma tissue samples.

Full details of the evidence and the committee's discussion are in evidence review A: genetic testing for melanoma.

3 Effectiveness of localised treatments

What is the effectiveness of localised treatment for people with stages III and IV melanoma? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale and impact on treating in-transit metastases in stages III and IV melanoma.

Full details of the evidence and the committee's discussion are in evidence review F: systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma.

4 Histological margins

What is the optimal histological excision margin in stage 0 melanoma? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale section on excision for stages 0 to II melanoma.

Full details of the evidence and the committee's discussion are in evidence review C: surgical and histopathological excision margins for people with stage 0 to II melanoma.

5 Surveillance strategies

How frequently should surveillance imaging be conducted, and which imaging modality should be used for people with stage IIB to IIIC melanoma? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale section on follow-up after treatment for melanoma.

Full details of the evidence and the committee's discussion are in evidence review G: follow-up of people with melanoma.

Other recommendations for research

Survivorship

What are the experiences of people who are living with, through and beyond a melanoma diagnosis in terms of survivorship and their disease journey? **[2022]**

For a short explanation of why the committee made this recommendation see the rationale section on follow-up after treatment for melanoma.

Full details of the evidence and the committee's discussion are in evidence review G: follow-up of people with melanoma.

Techniques for confirming a diagnosis in people with suspected atypical spitzoid melanocytic lesions

In people with reported atypical spitzoid lesions, how effective are fluorescence in-situ hybridization (FISH), comparative genomic hybridization (CGH) and tests to detect driver mutations compared with histopathological examination alone in predicting disease-specific survival?

This should be investigated in a prospective diagnostic study. Secondary outcomes should include sensitivity, specificity, accuracy, positive predictive value, disease-specific survival and progression-free survival. **[2015]**

Why this is important

Atypical spitzoid lesions continue to be diagnostically challenging. There are no reliably reproducible histological, immunohistochemistry or molecular features that allow exact typing and prognostic assessment of these lesions. The current 'gold standard' is histological examination with expert review, but it is not always possible to distinguish spitzoid melanoma from benign spitzoid melanocytic lesions.

Current molecular technologies such as FISH and CGH provide some help, but the results are difficult to interpret and may not be conclusive. Understanding and mapping changes in molecular pathways could predict outcome and inform individual treatment planning.

Surgical excision for people with lentigo maligna

For people with lentigo maligna (stage 0 in sun-damaged skin, usually on the face) how effective is Mohs micrographic surgery, compared with excision with a 0.5 cm clinical margin, in preventing biopsy-proven local recurrence at 5 years?

This should be investigated in a randomised controlled trial. Secondary outcomes should include cosmetic and functional outcomes. **[2015]**

Why this is important

Mohs micrographic surgery is a microscopically controlled surgical technique designed to allow complete excision of the tumour with minimal tissue loss. The technique can be useful for people with lentigo maligna because their lesions can be very large and located in a cosmetically sensitive site where surgery may cause significant scarring. However, the histological detection of small numbers of melanocytes at the edge of a sample is difficult, and can lead to false negative results. In addition, lentigo maligna may occur in an area of field change with a risk of skip lesions at the edge. Therefore, although Mohs micrographic surgery may ensure complete excision of lentigo maligna, it can be accompanied by the recurrence of a similar lesion in adjacent skin.

Vitamin D supplementation

In people with stage I to III melanoma does vitamin D supplementation improve overall survival?

This should be investigated in a placebo-controlled randomised trial. Secondary outcomes should include disease-specific survival and toxicity, including the development of renal stones and hypercalcaemia. **[2015]**

Why this is important

It has been reported that suboptimal levels of vitamin D at diagnosis are common in people with melanoma from the north of England and that higher levels are associated with lower melanoma-related mortality. However, vitamin D levels are higher in leaner, fitter people and the nature of the relationship between vitamin D levels and melanoma survival is unclear.

There are 2 adjuvant trials of vitamin D supplementation listed as active currently, 1 in Italy and 1 in Australia. However, there are many uncertainties about the design of vitamin D trials, which might become clearer in the next few years. These include the dose of vitamin D, use of concurrent aspirin therapy and the baseline level at which vitamin D supplementation would be started.

The effect of drug therapy for concurrent conditions on melanoma survival

In people diagnosed with melanoma what is the effect of drug therapy to treat concurrent conditions on disease-specific survival?

This should be investigated in a national prospective cohort study. Secondary outcomes should include overall survival and quality of life. **[2015]**

Why this is important

Drugs such as immunosuppressants and those used to treat conditions such as diabetes have effects that may affect survival in people with melanoma. For example, metformin, the most frequently prescribed drug for type 2 diabetes, is thought to reduce overall cancer rates in people with diabetes but to increase mortality from melanoma in the approximately 40% of these people who have a somatic BRAF mutation.

There is a need to balance the risk of melanoma deaths with the benefits from the most effective treatment of the concurrent conditions. But there is currently no evidence to inform this decision.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

BRAF analysis of melanoma tissue samples

Recommendations 1.3.8 to 1.3.12

Why the committee made the recommendations

Immunohistochemistry

The 2015 guideline recommended genetic testing for stage IIC and above melanoma. The 2022 committee extended this by recommending that BRAF analysis be considered for stage IIA or IIB melanoma, and carried out for stage IIC to IV melanoma. The committee agreed, based on their experience and in view of advances in targeted treatments since 2015, that early determination of BRAF status has practical utility. They noted that disease relapse occurs in a significant proportion of people with stage IIA to IIC melanoma (up to 50% at 5 years in people with stage IIC melanoma). Knowing BRAF status can speed up decisions about treatment for relapsed melanoma and optimise the use of these newer treatments.

The 2015 guideline did not specify the type of genetic test. The 2022 committee looked at specific types of test. They concluded that immunohistochemistry using BRAF V600E analysis is the most rapid method and enables treatment to be started sooner than is the case with other types of genetic testing. They also noted evidence that showed BRAF V600E immunohistochemistry rarely produces false positive results. However, some false negative results do occur so the committee agreed that a different BRAF genetic test should be used to double-check a negative or inconclusive result.

The committee agreed to retain the 2015 recommendation that genetic testing should not be offered to people with stages IA to IB melanoma.

Biomarkers

Biomarkers are of increasing relevance in the diagnosis and monitoring of various cancers, but their utility in the context of melanoma is still unclear. The committee

made recommendations for research on monitoring and response biomarkers, and safety, prognostic and predictive biomarkers.

How the recommendations might affect practice

The recommendations might increase the use of genetic testing. They are expected to increase immunohistochemistry with BRAF V600E analysis as a means of genetic testing and reduce variations in genetic testing practice.

Return to recommendations

Staging with sentinel lymph node biopsy and imaging

Recommendations 1.4.1 to 1.4.11

Why the committee made the recommendations

Sentinel lymph node biopsy

Evidence showed that sentinel lymph node biopsy (SLNB) should be done (or ruled out) before imaging for most people because imaging does not accurately detect lymph node metastases during staging. The committee agreed that imaging should only be offered before SLNB if lymph node or distant metastases are suspected.

Particular risk factors were shown by the evidence to be strongly associated with a positive sentinel lymph node and the committee recommended that SLNB be considered for people with any of these risk factors. They agreed that SLNB is not cost effective if the risk of sentinel node metastases is low.

The committee noted that women who are pregnant may have concerns about having SLNB because it needs to be done under a general anaesthetic. The committee agreed that, in their experience, there is no harm associated with delaying SLNB until after pregnancy and that the decision should be made on a case-by-case basis after discussion with the woman.

Imaging

Most of the evidence concerned imaging during follow-up. There was less evidence on imaging during staging, but the committee agreed that the imaging used for staging should be consistent with the imaging that will be used during follow-up, and

made recommendations to reflect this (see the recommendations on imaging in the section on follow-up after treatment for melanoma).

The committee agreed that MRI has utility during staging, due to the increased sensitivity for detecting brain metastases compared with CE-CT. They recommended considering brain MRI instead of CE-CT when staging people with stage IIIC to IV melanoma at a higher risk of developing brain metastases.

The evidence showed a high rate of recurrence in the interim period between surgery and starting adjuvant therapy. The committee agreed that for people starting adjuvant therapy, imaging should be repeated to exclude recurrence if recent imaging is not available. They agreed to define this as imaging done within the past 8 weeks, based on their experience and noting that 1 study had used a definition of 7.4 weeks.

How the recommendations might affect practice

In current practice SLNB is commonly offered to people with melanoma and a Breslow thickness of 0.8 mm to 1.0 mm. The recommendations are expected to reduce SLNB in this group by targeting it specifically to those with risk factors for a positive SLNB. Ulceration is the most common risk factor and is therefore likely to be the main reason for offering SLNBs.

Variation in the use of imaging during staging is expected to be reduced, with an increase in the use of CE-CT.

Return to recommendations

Excision for stages 0 to II melanoma

Recommendations 1.5.1 to 1.5.3

Why the committee made the recommendations

The committee agreed to retain the 2015 recommendations on clinical margins for excision.

The 2015 committee found no evidence on the optimal clinical margin for stage 0 melanoma and made the recommendation on the basis of clinical experience

suggesting that local recurrence may be seen when margins smaller than 0.5 cm are used. The 2022 committee found no further evidence so retained the recommendation.

Evidence supported the 2015 recommendations to use minimum clinical margins of 1 cm in stage 1 melanoma and 2 cm in stage II melanoma. The evidence confirmed that larger margins of 4 cm to 5 cm are associated with more adverse events and no improvement in outcomes.

The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins.

How the recommendations might affect practice

The recommendations are unchanged and are not expected to change current practice.

Return to recommendations

Managing stage III melanoma

Recommendations 1.6.1 and 1.6.2

Why the committee made the recommendations

Completion lymph node dissection

Evidence suggested that completion lymph node dissection for people with stage III melanoma does not improve survival or melanoma-specific survival when compared with routine surveillance, and that it is associated with an increased risk of lymphoedema. The committee concluded that the overall risks of completion lymph node dissection outweigh the benefits for most people, and agreed to amend the 2015 recommendation to reflect this. However, there is some evidence of greater nodal recurrence in people who do not have completion lymph node dissection and the committee acknowledged that certain factors (see recommendation 1.7.2) can make it difficult to manage recurrent nodal disease. They therefore agreed that completion lymph node dissection can be considered for people with these factors.

SLNB

There was no evidence on SLNB for people with stage III melanoma and microsatellite lesions. The committee discussed the potential benefits and harms in the absence of evidence. They agreed that the presence of microsatellite lesions indicates that the melanoma has progressed beyond the lymph nodes and so would automatically become stage IIIC disease without the need for SLNB.

The committee agreed that SLNB may sometimes be thought useful as a way of finding out whether the melanoma has spread to the lymph nodes. However, its prognostic utility in this context is unclear. The committee also agreed that most centres in the UK do not currently offer SLNB to people with stage III disease. Therefore, they agreed not to make recommendations in this area.

How the recommendations might affect practice

Completion lymph node dissection is no longer standard practice and the recommendations will not change this.

Return to recommendations

Treating in-transit metastases in stages III and IV melanoma

Recommendations 1.7.1 to 1.7.2

Why the committee made the recommendations

Good quality evidence on localised treatments is lacking. The committee agreed that several treatment options can be considered but that in the absence of good evidence, this decision should be based on treatment suitability for the person with melanoma. They also agreed to remove the option of CO_2 laser listed in the 2015 guideline because it is no longer used in standard practice.

The committee concurred that there is uncertainty about the best option for people with different clinical characteristics and made a recommendation for research on effectiveness of localised treatments.

How the recommendations might affect practice

Treatments for in-transit metastases are rarely used. The recommendations may help to target these treatments but will not lead to substantial changes in practice.

Return to recommendations

Systemic anticancer treatments for untreated stage IV and unresectable stage III melanoma

Recommendations 1.8.6 to 1.8.13

Why the committee made the recommendations

The committee looked at evidence on immunotherapies (ipilimumab, nivolumab, pembrolizumab, and nivolumab in combination with ipilimumab) and targeted therapies (encorafenib in combination with binimetinib, trametinib in combination with dabrafenib, monotherapy with dabrafenib and monotherapy with vemurafenib). These therapies were also compared in a health economic model.

The evidence showed that, overall, the immunotherapies are more clinically effective than the targeted therapies. Within the immunotherapies, nivolumab in combination with ipilimumab was shown to be the most clinically effective. The health economic model demonstrated that it is also the most cost effective.

However, the committee noted evidence showing that the risk of toxicity with immunotherapies is higher than with targeted therapies, and that this risk increases when immunotherapies are used in combination. They therefore agreed that monotherapy should be an option if combination immunotherapy is unsuitable. The evidence showed that nivolumab and pembrolizumab have similar clinical effectiveness when used as monotherapies. The health economic model demonstrated greater cost effectiveness with pembrolizumab so the committee agreed that it should be offered for monotherapy, with nivolumab an option to be considered on a case-by-case basis.

The committee noted NICE technology appraisal guidance recommending ipilimumab monotherapy for previously treated and untreated advanced (unresectable or metastatic) melanoma, but did not include this option in their

recommendation because it is not commonly used as first-line treatment and monotherapy with either nivolumab or pembrolizumab is more cost effective in this population. The committee also acknowledged that ipilimumab is licensed for use as monotherapy in adults and young people aged 12 and over. However, based on their clinical experience, its use as a monotherapy is considered to be the same as in adults.

If immunotherapy, either in combination or as monotherapy, is unsuitable, the committee agreed that targeted therapies based on BRAF status are an option. Within the targeted therapies, evidence showed that encorafenib in combination with binimetinib, or trametinib in combination with dabrafenib, had similar clinical effectiveness. The health economic model did not demonstrate clear differences in cost effectiveness between these 2 options. Therefore, the committee agreed that either of these options for combination treatment could be recommended. If both of these options are unsuitable, the committee agreed that monotherapy with dabrafenib or vemurafenib should be offered.

If targeted treatment for BRAF-mutated melanoma is unsuitable, or if the melanoma is BRAF-wild type, the committee agreed that the options are limited to enrolment in a clinical trial, chemotherapy with dacarbazine or best supportive care.

No evidence was found for the effectiveness of systemic cancer therapies specific to children and young people. However, the committee agreed that treatment should not differ between children and adults, and that recommendations also apply to children and young people.

How the recommendations might affect practice

The recommendations are expected to increase the proportion of people who are offered nivolumab in combination with ipilimumab as systemic treatment for stage IV and unresectable stage III melanoma.

Return to recommendations

Follow-up after treatment for melanoma

Recommendations 1.9.1 to 1.9.13

Why the committee made the recommendations

Information and support for people who have had melanoma

The committee agreed, based on their experience, that the information given to people after treatment for melanoma varies, and that it is particularly important to give people details of a specialist skin cancer service that they can contact if they have questions or concerns after treatment. The committee agreed to retain the 2014 recommendation to provide psychosocial support and to include provision of advice in local follow-up policies. The committee noted the lack of evidence on the views of people who have had melanoma and made a recommendation for research on survivorship.

Exceptions to routine follow-up

Based on their experience, the committee agreed that people who have had stage 0 melanoma can be discharged when treatment has been completed. They also identified groups who should be offered personalised follow-up, including people with unresectable melanoma and those at increased risk of further primary melanomas.

The committee also identified groups for whom MRI should be considered, as a substitute for CE-CT. See the rationale section on imaging during follow-up.

Frequency of follow-up

The committee sought to find a frequency of clinic follow-up that would balance the need for prompt identification of recurrence or progression with the need to reduce the burden of follow-up appointments for people with melanoma and avoid the costs of unnecessary follow-up.

Evidence showed that for stage IB to IIC disease, a lower frequency of follow-up visits did not increase mortality or cancer recurrence, or worsen quality of life. The committee therefore agreed to reduce the frequency of follow-up visits. They agreed to retain 4 visits per year for the first 2 years after stages IIB to IIC melanoma to coincide with their recommended imaging frequency, but to reduce this to 2 visits in year 3. Recommendations for clinic visits after resected stage III to IV disease were made to allow for a clinic visit after each imaging scan.

Imaging during follow-up

The committee agreed that CT scanning during follow-up after all stages of melanoma should include the head because of the frequency of brain metastases developing during follow-up.

Evidence on stage III melanoma suggested that CE-CT is more cost effective than PET-CT. The committee agreed that frequent imaging with CE-CT, particularly in the first 2 to 3 years when rates of recurrence are highest, will ensure timely identification of recurrences. The committee therefore agreed to recommend twice-yearly imaging with CE-CT in the first 3 years, then once yearly in years 4 and 5. There was no evidence on CE-CT after stages IIB and IIC melanoma, but there was evidence suggesting a high risk of recurrence, particularly in stage IIC melanoma, that was comparable to the risk of recurrence after stage IIIA disease. Based on this, the committee agreed that CE-CT imaging should be considered after stage IIB, and offered after stage IIC, at the same frequency as stage III.

The committee agreed that MRI should be offered for children and young adults having follow-up because of the cumulative risk of radiation associated with CE-CT scanning, and for women during pregnancy when CE-CT is undesirable.

Ultrasound scanning was shown by the evidence to be more sensitive than clinical examination and alternative imaging modalities (particularly CE-CT) for detecting local lymph node metastases. The committee agreed, based on their experience, that CE-CT alone can miss or delay detection of lymph node recurrences. However, there was no good quality evidence to show that ultrasound reduces mortality or time to recurrence in people with positive sentinel lymph nodes. Moreover, in current practice people with positive sentinel lymph nodes are offered frequent cross-sectional imaging and it is unclear whether ultrasound offers practical benefit above and beyond this imaging. This guideline does not recommend routine completion lymph node dissection, based on evidence comparing it with ultrasound scanning. However, there is no evidence comparing completion lymph node dissection with surveillance alone (with no ultrasound scanning). In addition, evidence suggested that most nodal recurrences develop within the first few years of diagnosis. The committee noted that nodal status is unknown in people who have not had an SNLB, and thus their staging is incomplete. Based on this, the committee agreed to

recommend ultrasound surveillance for 3 years for people with a positive sentinel lymph node and those who were considered for but did not have an SNLB.

The committee noted the need for more evidence to inform future guidance on follow-up after melanoma and made a recommendation for research on surveillance strategies.

How the recommendations might affect practice

Current practice varies and it is expected that these recommendations will help to standardise practice across centres. Clinic visits for people with stages I to IIC melanoma may be reduced, especially for people with stage IA melanoma. It is therefore important that people are given contact details for the specialist skin cancer multidisciplinary team. The use of CE-CT and ultrasound scanning is expected to increase, with a concomitant reduction in the use of other types of imaging.

Return to recommendations

Context

Melanoma is the fifth most common skin cancer in the UK, accounting for 4% of all new cancer cases and more cancer deaths than all other skin cancers combined. During 2016 to 2018 there were 16,744 new cases of melanoma and 2,333 deaths from melanoma. Of those who develop melanoma, 87% survive for 10 years or longer.

Incidence rates for melanoma skin cancer in the UK are highest in people aged 85 to 89. Each year more than a quarter (29%) of all new melanoma skin cancer cases in the UK are diagnosed in people aged 75 and over. Since the early 1990s, melanoma skin cancer incidence rates have more than doubled (140%) in the UK. Rates in females have around doubled (106%), and rates in males have almost tripled (186%), from 2016 to 2018. Incidence rates for melanoma skin cancer are projected to rise by 7% in the UK between 2014 and 2035, to 32 cases per 100,000 people by 2035.

A person's risk of developing cancer depends on many factors, including age, genetics, and exposure to risk factors (including some potentially avoidable lifestyle

factors). Most cases of melanoma (86%) in the UK are preventable. Melanoma is most common in white people however it is often diagnosed at a more advanced stage in people with darker skin. The risk factors are skin that tends to burn in the sun, having many moles, intermittent sun exposure and sunburn.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE webpage on skin cancer.

For details of the guideline committee see the committee member list.

Update information

January 2022

This guideline is an update of NICE clinical guideline NG14 (published July 2015) and will replace it.

We have reviewed the evidence on assessment, management and follow-up for people with melanoma.

Recommendations are marked **[2022]** if the evidence has been reviewed.

Recommendations that have been changed without an evidence review

For recommendations shaded in grey and ending **[2015, amended 2022]**, we have made changes that could affect the intent without reviewing the evidence. Yellow shading is used to highlight these changes, and reasons for the changes are given in table 1.

For recommendations shaded in grey and ending **[2015]**, we have not reviewed the evidence. In some cases, minor changes have been made – for example, to update links, or bring the language and style up to date – without changing the intent of the recommendation. Minor changes are listed in table 2.

See also the previous NICE guideline and supporting documents.

Table 1 Amended recommendation wording (change to intent) without an evidence review

Recommendation in 2015 guideline	Recommendation in current guideline	Reason for change
Do not withhold or change drug treatment for other conditions, except immunosuppressants, on the basis of a diagnosis of melanoma. [1.4.1]	Do not withhold or change drug treatment for other conditions, except immunosuppressants and immunomodulators, on the basis of a diagnosis of melanoma. For people on immunosuppressive or immunomodulatory treatments, seek advice from the person's specialist team, aiming to optimise quality of life while minimising the person's risk. [1.2.3]	Immunomodulators were added to the recommendation for completeness because they also modify the body's immune response and should be taken into account as immunosuppressants are. The committee also agreed that it was useful to clarify that for such people, their specialist team should be contact to determine the best action.
Consider minimising or avoiding immunosuppressants for people with melanoma. [1.4.2]	Consider minimising or avoiding immunosuppressants for people with melanoma.	This recommendation has been deleted because it is superseded by the amendment in recommendation 1.2.3.
Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms of oligometastatic stage IV melanoma in consultation with site-specific MDTs (such as an MDT for the brain or for bones). [1.8.2]	Consider surgery or other ablative treatments to prevent or control symptoms of oligometastatic stage IV melanoma in consultation with other site-specific multidisciplinary teams. [1.8.2]	The specific examples of ablative treatments were removed to clarify that the recommendation refers to all other ablative treatments and is not limited to the 2 examples given in the 2015 recommendation.
Refer people with melanoma and brain metastases that might be suitable for surgery or stereotactic radiotherapy to the brain and other central nervous system tumours MDT for a recommendation about treatment. [1.8.4]	Refer people with melanoma and brain metastases that might be suitable for surgery or stereotactic radiotherapy to the neuro-oncology multidisciplinary team for a recommendation about treatment. [1.8.5]	The terminology was updated to specify a neuro-oncology multidisciplinary team for clarity.

Table 2 Minor changes to recommendation wording (no change to intent)

Recommendation number in current guideline	Comment
1.1.1 to 1.1.5	These recommendations have been edited to bring them into NICE's current style for recommendations. In 2021 NICE published a guideline on shared decision making that provides recommendations on helping people make decisions about their care and a link to this guideline has been added in recommendation 1.1.1.
1.8.4	The abbreviation SSMDT has been replaced by specialist skin cancer multidisciplinary team for clarity.