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PRACTICE

GUIDELINES

Melanoma: summary of NICE guidance

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This is one of a series of BMJ summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Melanoma is the fifth most common cancer in the United Kingdom, with more than 13 000 cases diagnosed in 2011 and its incidence is rising rapidly.[1] Clinical practice seems to vary in the UK, especially with regard to the use of dermoscopy and photography, access to sentinel lymph node biopsy, vitamin D measurement and advice, follow-up policies, and the use of routine follow-up imaging. Patient groups have reported inadequate information on management options.

This article summarises the most important recent recommendations from the National Institute for Health and Care Excellence (NICE) on the diagnosis and care of people with melanoma.[2]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline development group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets. The recommendations specifically apply to secondary and tertiary care locations, where these patients should all be managed by specialist multidisciplinary teams (MDTs), but they will also affect the management of patients with melanoma in primary care.

The staging of melanoma is detailed and complex and the full staging system is available online.[3] The brief explanations of stage given may not be precise and are there to help make the context of the recommendation clearer.

Communication and support

- To help people make decisions about their care, follow the recommendations on communication, information provision, and support in the NICE guideline on improving outcomes for people with skin tumours including melanoma.[4] [*Based on low to high quality evidence from observational studies and on the experience and opinion of the guideline development group (GDG).*]

Assessing melanoma

- Assess all pigmented skin lesions that are referred for assessment or identified during follow-up using dermoscopy carried out by healthcare professionals trained in this technique. Do not routinely use confocal microscopy or computer assisted diagnostic tools. [*Based on moderate quality evidence from diagnostic studies.*]

Photography

- For a clinically atypical melanocytic lesion that does not need excision at first presentation use baseline photography (preferably dermoscopic). Also use this technique to review the clinical appearance of the lesion three months after first presentation to identify early signs of melanoma [*Based on low to moderate quality evidence from diagnostic studies.*]

Taking tumour samples for genetic testing

With the advent of effective treatments for people with metastatic disease, genetic testing of tumour samples for driver mutations (such as *BRAF*), which determine the likelihood of response to therapy, is becoming more important. For those who are being considered for systemic therapy:

- Offer genetic testing using a secondary (metastatic) melanoma tissue sample or a primary melanoma tissue sample if a secondary sample is not available or is of inadequate cellularity. [*Based on moderate to high quality evidence from diagnostic studies.*]

However:

- Do not offer genetic testing of stages IA-IIB primary melanoma (≤4 mm thick with ulceration or >4 mm thick

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The bottom line

- Use dermoscopy to examine all pigmented lesions referred for assessment and ensure that all staff are adequately trained in its use
- Consider sentinel node biopsy as a staging tool for patients with stage II melanoma and stage 1B melanoma thicker than 1 mm. Use box 1 or the options grid being developed to discuss the potential advantages and disadvantages of the procedure with patients
- If a sentinel node biopsy is positive for melanoma, discuss the potential advantages and disadvantages of completion lymphadenectomy with the patient using box 2 or the options grid being developed
- Consider regular imaging in patients at greater risk of progression to stage IV (metastatic) melanoma. Use box 3 or the options grid being developed to discuss potential advantages and disadvantages of this with the patient

How patients were involved in the creation of this article

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here. Patient and carer organisations were among the stakeholders who commented on the draft guideline.

with no ulceration, no spread) at presentation except as part of a clinical trial. [*Based on the experience and opinion of the GDG.*]

- For stage IIC primary melanoma (>4 mm thick, no spread, ulcerated), consider genetic testing. [*Based on the experience and opinion of the GDG.*]
- For stage III melanoma (spread to lymph nodes or the cutaneous or subcutaneous lymphatics proximal to those nodes—"in transit" metastases), consider testing metastatic tissue; if insufficient material is available, genetic testing of the primary tumour may be necessary. [*Based on the experience and opinion of the GDG.*]

Managing suboptimal vitamin D levels

Many people with melanoma have suboptimal levels of vitamin D at diagnosis but are usually advised to avoid sun exposure to reduce the risk of further melanomas. Vitamin D is important for bone health and possibly for other aspects of health, so further reduction in levels should be avoided. The guideline also suggests avoiding high levels as a result of unnecessary supplementation.

- Measure vitamin D levels at diagnosis in all people with melanoma.
- For people whose vitamin D levels are thought to be suboptimal, provide advice on supplementation and monitoring in line with local policies and the NICE guideline on vitamin D.[5] [*Based on moderate to very low quality evidence from observational studies.*]

Staging investigations

The role of sentinel lymph node biopsy (SLNB) is controversial, with its routine use varying greatly across England and Wales. Not all people routinely need imaging at diagnosis:

- Do not offer imaging or SLNB to people who have stage I melanoma with a Breslow thickness of 1 mm or less. [*Based on very low to high quality evidence from observational studies and on the experience and opinion of the GDG.*]
- Consider SLNB as a staging rather than a therapeutic procedure for people with stages IB-IIC melanoma with a Breslow thickness of more than 1 mm, and give these people detailed verbal and written information about the possible advantages and disadvantages (see box 1). [*Based on very low to high quality evidence from observational studies and cost effectiveness analysis.*]
- Offer computed tomography staging to people with stage IIC melanoma who have not had SLNB and to people with stage III (lymph nodes or in transit spread) or suspected stage IV melanoma (distant metastases). Include imaging of the brain for people with suspected stage IV melanoma. [*Based on very low to high quality evidence from observational studies and on the experience and opinion of the GDG.*]
- Consider whole body magnetic resonance imaging for children and young people (from birth to 24 years) with stage III or suspected stage IV melanoma. [*Based on very low to high quality evidence from observational studies and on the experience and opinion of the GDG.*]

Managing stages 0-II melanoma

With regard to excision margins:

- Consider a clinical margin of at least 0.5 cm when excising stage 0 melanoma (in situ), but if excision does not achieve an adequate histological margin, discuss further management with the MDT. [*Based on low quality evidence from randomised trials.*]
- Offer excision with a clinical margin of at least 1 cm to people with stage I (≤2 mm thick) and of at least 2 cm to people with stage II melanoma (1.01-2 mm thick if ulcerated or >2 mm thick). [*Based on low quality evidence from randomised trials.*]

Managing stage III melanoma (lymph nodes or in transit spread)

There is controversy and practice variation about the management of involved lymph nodes found at SLNB, by imaging, or at clinical examination.

- Consider completion lymphadenectomy (removing residual local lymph nodes) for people whose SLNB shows micrometastases and give them detailed verbal and written information about the possible advantages and disadvantages (see box 2). [*Based on very low quality evidence from observational studies.*]
- Offer therapeutic lymph node dissection to people with palpable stages IIIB-IIIC nodal melanoma or nodal disease detected by imaging. [*Based on very low quality evidence from observational studies.*]
- Do not offer adjuvant radiotherapy to people with stage IIIA disease or to those with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of serious adverse effects. [*Based on very low quality evidence from observational studies.*]

Box 1: Possible advantages and disadvantages of sentinel lymph node biopsy (SLNB)

Advantages

- SLNB helps to find out whether the cancer has spread to the lymph nodes and is better than ultrasound scans at finding very small cancers in the lymph nodes
- It can help predict what might happen in the future. For example, in people with a 1-4 mm thick primary melanoma, about one in 10 dies within 10 years if SLNB is negative; about three in 10 die if SLNB is positive
- People who have had SLNB 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

Disadvantages

- The purpose of SLNB is not to cure the cancer. There is no good evidence that people who have the operation live longer than those who do not have it
- The result needs to be interpreted with caution. For every 100 people with a negative SLNB result, about three will develop a recurrence in the same group of lymph nodes
- The operation requires a general anaesthetic
- The procedure results in complications such as deep venous thrombosis, seromas, or wound infections in 4-10 of every 100 people

Box 2: Possible advantages and disadvantages of completion lymphadenectomy

Advantages

- 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
- The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them
- 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

Disadvantages

- Lymphoedema (long term swelling) may develop; it is more likely if the operation is in the groin and least likely in the head and neck
- In four out of five people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily
- There is no evidence that people who have this operation live longer than those who do not have it
- Having any operation can cause complications

Managing stage IV melanoma (distant metastases)

Many patients with metastases will be treated with targeted therapy in line with NICE guidance on dabrafenib, ipilimumab and vemurafenib.[6-9] However, some situations require separate advice:

- Refer the care of people with oligometastases (metastases of limited extent, for which ablation or surgery may be feasible) to the specialist skin cancer MDT for recommendations about staging and management. [*Based on very low quality evidence from observational studies.*]
- Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms in consultation with site specific MDTs (such as MDTs for the brain or bones). [*Based on very low quality evidence from observational studies.*]
- Discuss the care of people with melanoma and brain metastases with the specialist skin cancer MDT. [*Based on the experience and opinion of the GDG.*]
- 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. [*Based on the experience and opinion of the GDG.*]

Cytotoxic chemotherapy may be indicated for patients who are unsuitable for targeted systemic therapies:

- Consider dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy is not suitable. [*Based on high quality evidence from randomised trials and cost effectiveness evidence.*]
- Do not routinely offer further cytotoxic chemotherapy for stage IV metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial. [*Based on high quality evidence from randomised trials.*]

Follow-up after treatment for melanoma

- All local follow-up policies should include reinforcing advice about self examination as well as health promotion for people with melanoma and their families, including sun awareness while avoiding vitamin D depletion (in line with local policies and the NICE guideline on vitamin D),[5] and smoking cessation. [*Based on very low quality evidence from observational studies and on the experience and opinion of the GDG.*]
- Discharge people who have had stage 0 melanoma after completing treatment. [*Based on very low quality evidence from observational studies and on the experience and opinion of the GDG.*]
- For those with stage IA melanoma (≤1 mm thick, no spread, no ulceration, no mitoses), consider follow-up two to four times during the first year after completing treatment and discharge at the end of that year. Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up. [*Based on very low quality evidence from observational studies and on the experience and opinion of the GDG.*]
- For those with stages IB-IIB melanoma (any thickness if not ulcerated, up to 4 mm thick if ulcerated, no spread) or stage IIC melanoma (>4 mm thick, ulcerated, no spread) with a negative SLNB, consider follow-up every three months for the first three years after completing treatment,

then every six months for the next two years and discharge at the end of five years. Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up. [*Based on very low quality evidence from observational studies and on the experience and opinion of the GDG.*]

- For people who have had stage IIC melanoma but no SLNB or stage III (involved lymph nodes) melanoma, consider follow-up every three months for the first three years after completion of treatment, then every six months for the next two years, and discharge at the end of five years. [*Based on very low quality evidence from observational studies, cost effectiveness analysis, and the experience and opinion of the GDG.*]
- For people who have had stage IIC melanoma, but no SLNB, or stage III melanoma, and who would become eligible for systemic therapy as a result of early detection of metastatic disease, consider surveillance imaging as part of follow-up if there is a clinical trial of the value of regular imaging or if the specialist skin cancer MDT agrees to a local policy and specific funding for imaging six monthly for three years is identified. Discuss the possible advantages and disadvantages of surveillance imaging (box 3) with the person. [*Based on very low quality evidence from observational studies, a cost effectiveness analysis, and the experience and opinion of the GDG.*]
- For people who have had stage IV (distant metastases) melanoma, offer personalised follow-up. [*Based on very low quality evidence from observational studies and on the experience and opinion of the GDG.*]

Overcoming barriers

Dermoscopy is not routinely used in all clinics where pigmented lesions are assessed, so equipment will need to be purchased and staff trained. Vitamin D is rarely measured and there is uncertainty about how best to manage suboptimal levels. New guidance from the Scientific Advisory Committee on Nutrition (SACN) expected in 2015 will be helpful. Not all MDTs offer SLNB and some that do reportedly do not always offer the choice of not having it. Change is needed both in how this is discussed with patients and in its provision where it is currently unavailable.

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1 National Cancer Intelligence Network. Mortality, incidence and gender—malignant melanoma. www.ncin.org.uk/publications/data_briefings/mortality_incidence_and_gender_malignant_melanoma.
2 National Institute for Health and Care Excellence. Melanoma—assessment and management of melanoma. (NG14.) 2015. www.nice.org.uk/guidance/ng14.
3 American Joint Committee on Cancer. Melanoma of the skin staging. 7th ed. 2009. https://cancerstaging.org/references-tools/quickreferences/Documents/MelanomaSmall.pdf.
4 National Institute for Health and Care Excellence. Improving outcomes for people with skin tumours including melanoma. (NICE guidelines [CSGSTIM].) 2010. www.nice.org.uk/guidance/csgstim.
5 National Institute for Health and Care Excellence. Vitamin D: increasing supplement use among at-risk groups. (Public health guidance 56.) 2014. www.nice.org.uk/guidance/ph56.
6 National Institute for Health and Care Excellence. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. (Technology appraisal guidance 321.) 2014. www.nice.org.uk/guidance/ta321.
7 National Institute for Health and Care Excellence. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. (Technology appraisal guidance 268.) 2012. www.nice.org.uk/guidance/ta268.
8 National Institute for Health and Care Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. (Technology appraisal guidance 319.) 2014. www.nice.org.uk/guidance/ta319.
9 National Institute for Health and Care Excellence. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. (Technology appraisal guidance 269.) 2012. www.nice.org.uk/guidance/ta269.

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Box 3: Possible advantages and disadvantages of follow-up imaging

Advantages

Early detection of recurrence may allow people to receive treatment with drugs such as immunotherapeutic agents earlier than they would otherwise, which might lead to better outcomes

Some patients find it reassuring to have regular scans

Disadvantages

There is currently no evidence that treating recurrent melanoma earlier increases the probability of a better outcome

Having regular scans may increase some people's anxiety, even though for many, no recurrence will ever occur

Regular scans increase the body's exposure to radiation, which itself increases the risk of second cancers later in life. For example, imaging of the chest results in a very small increase in the risk of thyroid cancer

Imaging of the brain and neck results in a small increase in the risk of developing cataracts

Incidental abnormalities of no clinical significance that require further investigations might be identified, and this may cause anxiety until the situation is resolved

Further information on the guidance

Methods

This guidance was developed by the National Collaborating Centre for Cancer using current NICE guideline methodology (www.nice.org.uk/guidelinesmanual). The guidance review process involved literature searches to identify relevant evidence, with critical appraisal of the quality of the identified evidence. A multidisciplinary team of service users, carers, and healthcare professionals (including dermatologists, surgeons, clinical and medical oncologists, a general practitioner, a histopathologist, a radiologist, clinical nurse specialists, and patient and carer representatives)—the guideline development group (GDG)—was established to review the evidence and develop the subsequent recommendations. The guidance then went through an external consultation with stakeholders. The GDG considered the stakeholders' comments, reanalysed the data where necessary, and modified the guidance as appropriate.

NICE has produced three different versions of the guidance: a full version; a summary version known as the "NICE guidance"; and a version for people using NHS services, their families, and carers (www.nice.org.uk/guidance/ng14/informationforpublic), and the public. All these versions are available from the NICE website (www.nice.org.uk/guidance/ng14). Further updates of the guidance will be produced as part of NICE's guideline development programme. Implementation tools are available at www.nice.org.uk/guidance/ng14/resources.

Future research

Based on its review of evidence, the GDG has made the following recommendations for research to improve NICE guidance and patient care in the future:

- In people with reported atypical spitzoid lesions, how effective are fluorescence in situ hybridization, comparative genomic hybridisation, and tests to detect driver mutations compared with histopathological examination alone in predicting disease specific survival?
- 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 confirmed local recurrence at five years?
- In people treated for high risk stages II and III melanoma, does regular surveillance imaging improve melanoma specific survival compared with routine clinical follow-up alone?
- In people with stages I-III melanoma, does vitamin D supplementation improve overall survival?
- In people diagnosed as having melanoma, what is the effect of drug therapy to treat concurrent conditions on disease specific survival?