June 2015

The scope has been amended. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (NICE technology appraisal guidance 268 [2012]) has been removed from section 5.1.2 'NICE guidance to be incorporated' and added to section 5.1.3 'Other related NICE guidance'. This is so that this guidance can be considered for review in 2017 together with Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (NICE technology appraisal guidance 319 [2014]).

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Melanoma: assessment and management of melanoma

1.1 Short title

Melanoma

2 The remit

The Department of Health has asked NICE to develop a clinical guideline on assessment and management of malignant melanoma.

3 Clinical need for the guideline

3.1 Epidemiology

a) Melanoma is the third commonest skin cancer in the UK. However, it is the cause of more cancer deaths than all other skin cancers combined. In 2010, there were 2,746 deaths from skin cancer in the UK. This includes 2,203 deaths from melanoma and 546 from other forms of skin cancer.

b) In 2010, 12,818 people in the UK were diagnosed with melanoma. Although the disease is more common in older age groups, it is often diagnosed in younger people. In the late seventies, there were around 290 cases of melanoma among 15-34 year-olds each

year. Now more than 900 young Britons are being diagnosed with the disease each year - more than two a day (CR UK statistics).

c) The incidence of melanoma is rising rapidly and is predicted to increase by 50% in the next 15 years. This is the fastest projected increase in incidence for any cancer. Most melanomas occur in white skinned people. The risk factors are skin which tends to burn in the sun, having many melanocytic naevi, intermittent sun exposure and sunburn.

d) Mortality rates for melanoma are also rising rapidly, especially in older men. In 2010, 62% of deaths from melanoma were in people aged 65 years or older, whereas 5% of deaths were in people aged 15 to 39 years.

e) There appear to be variations in survival across different cancer networks, and poorer survival may be attributable to late presentation or delays in diagnosis and initiation of treatment.

3.2 Current practice

a) The majority of melanomas are initially clinically diagnosed by dermatologists with 41% of cases being referred via the 2-week wait process.

b) Primary melanoma is treated by complete excision, pathological analysis and subsequent wide local excision. There remains some uncertainty about optimal final excision margins and this topic is the subject of current research.

c) Imaging (for example CT, MRI or positron emission tomography [PET]-CT) for staging purposes is not currently indicated for people with stage 1 or 2 disease. Sentinel node biopsy (SNB) is used to stage melanomas according to the American Joint Committee on Cancer (AJCC) staging system and is also used to identify people who might be eligible for adjuvant therapy clinic trials and to stratify during analysis of those trials. However, SNB has not been shown

to confer any survival advantage and the cost effectiveness of SNB is uncertain. There is thought to be variation in practice in the use of CT and PET-CT imaging for people with more advanced disease.

d) Adjuvant chemotherapy and immunotherapy are not currently indicated for management of melanoma and continue to be the subject of research trials. Adjuvant radiotherapy for stage IIIB and IIIC melanoma is used in some centres but with little supporting evidence.

e) Cutaneous metastases are excised if it is technically feasible. In-transit metastases are multiple skin and subcutaneous metastases (usually in a limb) which are generally treated with loco-regional therapies. Multiple in-transit metastases confined to one limb may be treated by a number of modalities including isolated limb infusion and isolated limb perfusion

f) Some people with small numbers of apparently localised metastases to other organs may also be offered surgical resection, although this is not supported by randomised trial evidence.

g) People whose metastatic melanoma carries *BRAF* mutations may be treated with specific BRAF inhibitors. These drugs have a very rapid effect on tumours but unfortunately the majority of people who take them develop resistance and the tumour relapses. Use of vemurafenib was associated with a median survival of 13.2 months in a phase 3 trial.

h) People with systemic metastases whose tumours are not found to carry *BRAF* mutations are usually treated with dacarbazine but response rates are low. Ipilimumab may be used as second-line therapy.

i) Radiotherapy may be used to treat isolated cerebral metastases and for palliation.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Children, young people and adults with suspected melanoma.

b) Children, young people and adults with newly diagnosed cutaneous melanoma, including vulval and penile melanoma.

c) Subgroups identified as needing specific consideration will be considered during development of the guideline.

4.1.2 Groups that will not be covered

a) People with primary ocular melanoma.

b) People with melanoma arising in mucosal sites. (see 4.1.1 b)

4.2 Healthcare setting

a) All settings in which NHS-funded care is provided.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) The specific information and support needs of people with melanoma and their carers at diagnosis, at treatment planning, and during and after treatment.

b) The best approach to increasing clinical diagnostic accuracy and appropriate prompt excision.

c) The best approach to resolving clinico-pathological diagnostic uncertainty for borderline or Spitzoid melanocytic lesions.

d) The best approach for mutation testing of tumours for prognostic and predictive purposes.

e) The most effective method of staging melanoma:

    i. the role of sentinel lymph node biopsy in newly diagnosed melanoma

    ii. imaging for newly diagnosed and recurrent melanoma.

f) The most effective surgical treatment for stage 0-II melanoma

g) The most effective surgical treatment for stage III melanoma (including the effectiveness of sentinel lymph node biopsy).

h) The indications for adjuvant radiotherapy for stage III melanoma after resection.

i) The most effective treatment for in-transit melanoma metastases.

j) The role of surgery, stereotactic radiotherapy and image guided ablative techniques including radioembolisation in stage IV melanoma.

k) The role of systemic anti-cancer therapy in the treatment of metastatic melanoma (for example, dacarbazine and temozolomide).

l) The optimum methods, setting and frequency of follow-up for people with melanoma.

m) The role of measuring vitamin D levels and of supplementation in people who have been diagnosed with melanoma.

n) The role of imiquimod in the treatment of melanoma.

o) Management of other intercurrent conditions with drug therapies which may increase the risk of death from melanoma (for example, immunosuppressants, levodopa, metformin)

4.3.2 Clinical issues that will not be covered

a) Referral from primary care with suspected melanoma. (This will be covered by 'Suspected cancer', the update of Referral guidelines for suspected cancer [NICE clinical guideline 27]).

b) Awareness and prevention of melanoma.

c) Ipilimumab for the treatment of stage III or IV melanoma. (This is the subject of an ongoing NICE technology appraisal. Publication expected August 2013).

d) Vemurafenib for the treatment of BRAF V600 mutation-positive, unresectable metastatic melanoma. (This is covered by NICE technology appraisal guidance 269 [2012]).

e) Dabrafenib for the treatment of BRAF V600 mutation-positive, unresectable, advanced or metastatic melanoma. (This is the subject of an ongoing NICE technology appraisal. Publication expected April 2014).

f) Ipilimumab for the treatment of previously untreated unresectable stage III or IV melanoma. (This is covered by NICE technology appraisal guidance 268 [2012]).

g) Adjuvant immunotherapy.

h) End-of-life care.

i) Complementary therapies.

4.4 Main outcomes

a) Overall survival.

b) Disease-free survival.

c) Progression-free survival.

d) Melanoma-related morbidity.

e) Melanoma-related mortality.

f) Treatment-related morbidity.

g) Treatment-related mortality.

h) Psychological wellbeing.

i) Number and length of admissions to hospital after diagnosis.

j) Number and severity of adverse events.

k) Health-related quality of life.

l) Cost effectiveness.

m) Patient-reported outcomes.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

a) What are the specific information and support needs of people with melanoma and their carers:

- at the point of first diagnosis
- at treatment planning
- during treatment
- after treatment (including follow-up and at discharge)? [4.3.1a]

b) What is the diagnostic accuracy of dermoscopy, history-taking and visual examination for the clinical identification of melanoma? [4.3.1b]

c) What is the best approach to resolving clinico-pathological diagnostic uncertainty for borderline or Spitzoid melanocytic lesions? [4.3.1c]

d) Is the accuracy of current tests for melanoma affected by reader experience (for example, comparing consultants with trainees)? [4.3.1c]

e) Is photography an effective method of monitoring progression of pigmented lesions? [4.3.1c]

f) What is the most appropriate tumour block (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies? [4.3.1d]

g) What is the best time and method to adopt in order to carry out genetic testing of the stored tumour for a person who may benefit from targeted therapies (early stage [I-IIIA] versus late stage [IIIB-IV])? [4.3.1d]

h) Should sentinel lymph node biopsy be available to all patients with newly diagnosed melanoma? [4.3.1e]

i) What is the best approach to staging disease in people diagnosed with a) new disease and b) recurrent disease (including but not limited to CT, PET, PET-CT)? [4.3.1e]

j) What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes? [4.3.1f]

k) What are the appropriate margins when surgically treating stage 0-II melanoma? [4.3.1f]

l) What is the most effective surgical treatment for stage III melanoma? [4.3.1g]

m) Who should carry out surgery for stage III melanoma? [4.3.1g]

n) What is the effectiveness of adjuvant radiotherapy for stage III melanoma in people who have undergone curative resection? [4.3.1h]

o) What is the role for different treatments for in-transit melanoma metastases (for example, surgery, isolated limb infusion, isolated limb perfusion, palliative radiotherapy, cryotherapy, electro-chemotherapy or the laser)? [4.3.1i]

p) What is the effectiveness of surgery or image guided ablative techniques (including stereotactic RT) compared with systemic drug therapy or supportive care in the management of stage IV melanoma. [4.3.1j]

q) How effective is surgery in the treatment of oligometastatic disease? [4.3.1j]

r) What are the factors which indicate the use of dacarbazine in people with stage IV melanoma? [4.3.1k]

s) What is the effectiveness of temozolomide compared with dacarbazine in the treatment of patients with stage 4 metastatic melanoma? (Temozolomide is subject to agreement with the NICE Technology Appraisal programme). [4.3.1k]

t) In asymptomatic patients who have undergone treatment with curative intent for melanoma, what is the optimal method, frequency and duration of follow-up? [4.3.1l]

u) What is the optimal setting for follow-up of asymptomatic patients who have undergone treatment with curative intent for melanoma? [4.3.1l]

v) What are the indications for imaging for brain metastasis as part of follow-up in asymptomatic patients? [4.3.1l]

w) Is CT or MRI the most appropriate method of imaging for brain metastasis as part of follow-up for asymptomatic patients? [4.3.1l]

x) Do vitamin D levels at diagnosis and during follow-up predict cancer-related or bone-related outcomes for people with melanoma? [4.3.1m]

y) How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)? [4.3.1m]

z) How effective is imiquimod in the treatment of melanoma? [4.3.1n]

aa) What is the most effective approach to the management of the risks associated with concurrent drug therapies used to treat other conditions, which may increase the risk of death from melanoma (for example, immunosuppressants, levadopa, metformin)? [4.3.1o]

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in May 2013.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

5.1.2 NICE guidance to be incorporated

- Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269 (2012).

5.1.3 Other related NICE guidance

- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 268 (2012).
- Endoscopic radical inguinal lymphadenectomy. NICE interventional procedure guidance 398 (2011).
- Skin cancer prevention: information, resources and environmental changes. NICE public health guidance 32 (2011).
- MIST therapy system for the promotion of wound healing in chronic and acute wounds. NICE medical technologies guidance 5 (2011).
- Skin tumours including melanoma. NICE cancer service guidance (2010)
- Medicines adherence. NICE clinical guideline 76 (2009).
- Surgical site infection. NICE clinical guideline 74 (2008).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Melanoma (BRAF V600, unresectable, metastatic) – dabrafenib. NICE technology appraisal guidance ID605. Publication expected April 2014
- Implementing Vitamin D guidance. NICE public health guidance. Publication expected June 2014.
- Melanoma (previously untreated unresectable stage III or IV) – ipilimumab. NICE technology appraisal guidance ID74. Publication expected June 2014.
- Suspected cancer: recognition and management of suspected cancer in children, young people and adults (update). NICE clinical guideline. Publication date to be confirmed.
- Sunlight exposure: benefits and safety. NICE public health guidance. Publication date to be confirmed.
- Melanoma (advanced and metastatic) – temozolomide. NICE technology appraisal guidance ID316 (suspended).

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.