The management of cutaneous melanoma

More than 900 adults aged under 35 are now diagnosed with melanoma annually in the UK. This article addresses areas where there is uncertainty or variation in practice. It also includes advice on managing vitamin D levels

Christian Aldridge BSc (Hons) MBChB FRCP
Email: Christian.aldridge@wales.nhs.uk

Cutaneous melanoma is a malignancy of melanocytes. It occurs mainly in white populations with fair skin. It is the fifth most common cancer in the UK with over 13,000 cases being diagnosed in 2011, but its incidence continues to rise. In Europe, the rate is approximately 20 per 100,000 per year. An increase in UV (ultraviolet) exposure with changing leisure time habits (sunbathing, use of sun beds) is thought to be the main driver for increasing incidences despite decades of public health prevention and awareness campaigns.

NICE (National Institute for Health and Care Excellence) have presented timely, updated guidance on the diagnosis and management of melanoma. NICE recommendations are based on systematic reviews of current best evidence but they also address cost-effectiveness. This work sets out to address variations in practice across the UK, especially with regards to the use of dermoscopy and photography, access to sentinel lymph node biopsy (SLNB), vitamin D measurement and the use of imaging during follow-up. Previous NICE guidance on melanoma in 2006 established the importance of the multidisciplinary team (MDT) in managing melanoma. The current recommendations apply to secondary and tertiary settings where patients are managed by MDTs.

Key priorities for implementation

Communication and support

Nationally standardised written information should be made available to all patients. The information given must be specific to the histopathological type of lesion. Each MDT should have a skin cancer clinical nurse specialist (CNS) who plays a leading role in supporting patients and carers. MDTs should have access to psychological support services for skin cancer patients.

Assessing melanoma: dermoscopy

Dermoscopy is a non-invasive imaging technique that permits the visualisation of colours, structures and patterns in skin lesions that are not visible to the naked eye. Dermoscopy should be carried out, by trained health professionals, on all pigmented skin lesions referred in for assessment. NICE do not recommend the routine use of confocal microscopy or computer-assisted diagnostic tools.

Assessing melanoma: photography

For a clinically atypical melanocytic lesion that does not need excision at first presentation in secondary or tertiary care, baseline photography (ideally with dermatoscopic imagery) should be undertaken and the lesion should then be reviewed at three months and compared with baseline images to identify early signs of melanoma.

| Table 1: Possible advantages and disadvantages of sentinel lymph node biopsy (SLNB) |
|---------------------------------|---------------------------------|
| **Advantages**                  | **Disadvantages**               |
| SLNB helps to find out whether the cancer has spread to the lymph nodes | 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 |
| In people with a 1–4mm thick primary melanoma, about one in 10 dies within 10 years if SLNB is negative; about three in 10 die if SLNB is positive | For every 100 people with a negative SLNB result, about three will develop a recurrence in the same group of lymph nodes |
| People who have had SLNB may be able to take part in clinical trials of new treatments for melanoma | 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 |
Vitamin D
The recommendation is that vitamin D levels should be measured in all individuals with a diagnosis of melanoma and in those patients whose vitamin D levels are suboptimal, they should be provided with advice on supplementation and monitoring in line with local policies. The rationale for this advice stems from the fact that 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 melanoma, thus compounding the problem. Vitamin D is important for bone health and possibly for other aspects of health.

Staging investigations
The stages of melanoma referred to in the NICE guidance are from the American Joint Committee on Cancer’s (AJCC) Melanoma of the Skin staging (7th edition). The staging of melanoma is detailed and complex and reference should be made to the AJCC publication when discussing staging.

Sentinel lymph node biopsy (SLNB)
The role of SLNB remains controversial. Its use in the UK is variable. It can clearly upstage a patient from stage IIC to stage III and thus make them eligible for ongoing clinical trials entry. The technique of SLNB requires collaboration across nuclear medicine, surgical and pathology teams. Preoperative lymphoscintigraphy is performed to identify at-risk regional nodal basins and to localise the sentinel nodes. Histological analysis is performed with a combination of step-sectioning and immunohistochemical analysis.

Below are the recommendations with regards to its use:
(a) Do not offer imaging or SLNB to people who have stage I melanoma with a Breslow thickness of 1mm or less.
(b) Consider SLNB as a staging rather than a therapeutic procedure for people with stages IB–IIC melanoma with a Breslow thickness of more than 1mm. Discuss the advantages and disadvantages of SLNB with the patient. (Table 1).
(c) Offer computed tomography (CT) 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).
(d) Consider whole body magnetic resonance imaging (MRI) for children and young people (from birth to 24 years) with stage III or suspected stage IV melanoma.

Managing melanoma by stage
As treatments are becoming more targeted, genetic testing of tumour samples for mutations (such as BRAF), which can determine the likelihood of clinical response to therapy, is becoming more important. For those patients with stage IIC or higher, genetic testing should be undertaken. Those patients with stage IA–IIB primary melanoma (<4mm thick with ulceration or >4mm thick with no ulceration, no spread) at presentation require no genetic testing, except as part of a clinical trial. There are specific recommendations per stage of melanoma:

Stage 0–II melanoma
- Consider a clinical margin of 0.5cm when excising stage 0 (in situ) melanoma.
- For stage I melanoma (<2mm thick) excise with at least 1cm margins.6
- For stage II melanoma (1.01–2mm thick if ulcerated or >2mm thick) excise with at least 2cm margins.7

Stage III melanoma (lymph nodes or in-transit spread)
Although completion lymphadenectomy (CLND), the removal of residual local lymph nodes, has been the standard of care for patients with a positive SLNB for over 20 years, its role in these patients continues to evolve. The current NICE recommendations outline a therapeutic strategy:

| Table 2: Possible advantages and disadvantages of complete lymphadenectomy |
|-------------------------|-----------------|
| Advantages               | Disadvantages               |
| Removing the rest of the lymph nodes before cancer develops in them reduces the chance of cancer returning in the same part of the body. | Lymphoedema (long-term swelling) may develop. |
| The operation is less complicated and safer than waiting until the cancer develops in the remaining lymph nodes and then removing them. | In four out of five people, cancer will not develop in the remaining lymph nodes. |
| People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. | There is no evidence that people who have this operation live longer than those who do not have it. |

Stage IV melanoma (distant metastases)
It is obvious that many patients with metastatic disease (stage III and stage IV disease) will be treated with targeted therapies such as dabrafenib and vemurafenib or immunotherapies such as ipilimumab and pembrolizumab. NICE guidance already exists for these agents and their use, however, some specific situations require separate advice:
- Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms in consultation with the MDT. The MDT will also be the place to discuss those with brain metastases that may be suitable for surgery.10
- Consider dacarbazine for patients with stage IV metastatic melanoma if immunotherapy or targeted therapy is not suitable but do not offer further cytotoxic chemotherapy in those previously treated with dacarbazine except in the context of a clinical trial.11

Follow-up after treatment for melanoma
Follow-up regimes can vary. What should be consistent is the message to patients...
Table 3: Possible advantages and disadvantages of follow-up imaging

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>There is currently no evidence that treating recurrent melanoma earlier increases the probability of a better outcome</td>
</tr>
<tr>
<td>Some patients find it reassuring to have regular scans</td>
<td>Regular scans increase the body's exposure to radiation, which itself increases the risk of second cancers in later life</td>
</tr>
<tr>
<td></td>
<td>Imaging of the brain and neck results in a small increase in the risk of developing cataracts</td>
</tr>
<tr>
<td></td>
<td>Incidental abnormalities of no clinical significance that require further investigations might be identified, and this may cause anxiety until the situation is resolved</td>
</tr>
</tbody>
</table>

Advantages

• To regularly self-examine and to take heed of sun protection. NICE have put together recommendations for follow-up which are stage specific:
  • Patients with stage 0 melanoma (melanoma-in-situ) can be discharged after treatment.
  • For stage IA melanoma, the recommendation is for 12 months follow-up and to discharge after that. No imaging should be undertaken.
  • For stage IB-IIIB or stage IIC with a negative SLNB, consider three-monthly follow-ups for the first three years and then six-monthly for the final two years. No imaging should be routinely undertaken as part of follow-up.
  • For stage IIC melanoma but no SLNB or stage III (involved lymph nodes) melanoma consider three-monthly follow-up for the first three years and then six-monthly for the final two years.
  • Obviously, for stage IV melanoma patients, individualised follow-up is recommended here.

The question of regular imaging of patients with stage IIC and stage III melanoma arises often. These policies can vary depending on local MDT preferences but there are advantages and disadvantages to this type of screening (Table 3).

Conclusions

With the ever-increasing field of targeted and immune therapies widening the potential for significant advances in melanoma treatment, in particular through clinical trial work, it remains a challenge in many centres to set up a SLNB service. Upgrading from stage IIC to stage III (micrometastases), with the use of SLNB, allows an access route for patients into those therapeutic clinical trials, which are recruiting stage III disease and above. There are economic and manpower issues which are stage specific:

References