Most melanomas that are detected and treated early are cured. However, advanced disease carries a dismal diagnosis, and timely intervention from members of the multidisciplinary skin cancer team at all stages of the disease is essential to maximise cure rates. The management of patients with incurable disease is highly specialised and requires the input of surgeons, medical and clinical oncologists, palliative care teams, and clinical nurse specialists. In the second of this two part series on melanoma we review its management from primary lesion through to metastatic disease.

How is melanoma managed in primary care?

In the past, suspicious lesions were often removed in primary care. However, recent national guidance recommends that patients with suspicious pigmented lesions are referred to a specialist member of the hospital based skin cancer team using the two week cancer wait procedure. This has been the subject of much debate and if fully implemented will result in a change in practice for many general practitioners. Primary melanoma is often difficult to diagnose, even for those with a specialist training. A prospective study showed that dermatologists were better than general practitioners at recognising melanoma. However, a systematic review failed to identify a statistically significant advantage in favour of specialists, but the amount of available evidence for review was limited. Several studies have shown that the incomplete excision rate is higher in patients treated by general practitioners than by specialists and that general practitioners send fewer lesions for histopathological review. Training programmes using internet based tutorials have improved diagnostic accuracy in the United States. Dermatoscopy improves diagnostic accuracy for experienced users but not for inexperienced users.

Primary care doctors who wish to treat skin cancer and be part of the multidisciplinary team can train as general practitioners with a special interest in dermatology. The Department of Health has recently defined the training needed.

The seven point check list (box) may help identify melanoma. Worrying signs are a new mole growing quickly in patients over the age of puberty; change in shape, colour, or size of a long standing mole; a mole with three or more colours or which has lost its symmetry; a mole that has changed and is also itching or bleeding; any new skin lesion or nodule persisting for more than eight weeks, especially if it is growing and pigmented or vascular in appearance; a new pigmented line in a nail, especially where there is nail damage; a lesion growing under a nail. Any of these signs warrants a prompt referral for a specialist opinion.

How should a suspicious lesion be managed?

Primary excision

Guidance from the United Kingdom states that lesions suspected to be melanoma should be excised completely, with a clinical margin of 2 mm of normal skin and a cuff of fat. This allows confirmation of the diagnosis by examination of the entire lesion, so that definitive treatment can be based upon histological features. Shave biopsies are discouraged because they may lead to incorrect diagnosis as a result of sampling error and make accurate pathological staging of the lesion impossible. Incisional or punch biopsies are sometimes acceptable—for example, in the differential diagnosis of lentigo maligna on the face or of acral melanoma—but incisional biopsy of a suspicious pigmented lesion has no place outside the skin cancer multidisciplinary team.

Staging

Staging of primary melanoma is based on the histological features of the lesion. Accurate staging is vital to determine appropriate treatment, follow-up, and calculation of risk of recurrence. The current American Joint Committee on Cancer (AJCC) staging is based on measurement of the invasive component of the tumour (the Breslow thickness) and the presence or absence of microscopic ulceration. The staging system is in the process of being revised and an update is expected in 2009. Additional histological features...
such as number of mitoses per mm², which have independent prognostic value, are likely to be included. Melanocytic lesions can be notoriously difficult to diagnose, and expert dermatopathological assessment is needed. The National Institute for Health and Clinical Excellence has recommended double reporting of all melanomas if the report can be produced within 14 days. The Royal College of Pathologists has produced a minimum dataset, which defines the histological features of a melanoma that should be included in the histopathology report.

The risk of death from a primary melanoma increases dramatically with increasing stage (table 1), reinforcing the importance of early diagnosis and treatment.

**What are the benefits of wide local excision and sentinel lymph node biopsy?**

Wide local excision of a cuff of normal tissue after excision biopsy reduces local recurrence rates. Up until the 1980s, disfiguring radical wide local excision margins of 4-5 cm were used on the basis of anecdotal evidence from 1907. Prospective studies carried out in the US and Europe under the World Health Organization melanoma programme determined that a 1 cm excision margin could be safely used for melanomas less than 2 mm thick. Further prospective studies in the US and the UK showed that 2 cm and 3 cm excision margins were safe for lesions greater than 2 mm and 4 mm thick, respectively. Table 2 outlines the current guidelines for wide local excision margins. Wide local excision reduces local recurrence rates but has no statistically significant effect on survival. Decisions on the size of the margin are therefore usually taken by members of the multidisciplinary team, who balance the morbidity of the procedure with the potential benefit to the patient.

Sentinel lymph node biopsy, a procedure that identifies and removes the lymph node(s) immediately draining the area of the primary tumour for histological analysis, has been the subject of much debate. The procedure provides powerful prognostic information. Microscopic lymph node involvement is an integral part of the AJCC staging system, and sentinel node status is therefore used to stratify patients who enrol into current clinical trials of adjuvant treatment. However, completion lymphadenectomy, in which the locoregional lymph nodes are removed when a sentinel node biopsy is positive, has not been shown to improve overall survival. Whether sentinel lymph node biopsy can identify a group of patients who are particularly likely to benefit from adjuvant treatment needs to be examined prospectively.

**What adjuvant treatments are available?**

Adjuvant treatments increase the chance of cure in patients at risk of recurrence after potentially curative surgery. Despite much effort, no treatment has yet been shown to be efficacious enough to become routine.

**Interferon alfa**

The value of adjuvant interferon alfa, which is given intravenously or subcutaneously depending on the dose and regimen used, has been widely discussed. After initial reports of a highly significant overall survival benefit, later reports and further studies have found this drug to be less active.

A recent meta-analysis of individual patient data from randomised controlled trials of adjuvant interferon alfa found no dose-response relation but did show a proportional benefit in overall survival of 3% at five years (95% confidence interval 1% to 5%). Results indicated that patients whose primary lesion was ulcerated were more likely to benefit from adjuvant interferon, but this observation requires prospective assessment.

Preliminary results from the EORTC (European Organisation for Research and Treatment of Cancer) 18991 study randomising weekly pegylated interferon alfa versus observation were recently reported. They showed a significant improvement in relapse-free survival (hazard ratio 0.82, 0.71 to 0.96) but not in distant metastasis-free survival or overall survival.

**Melanoma seven point checklist**

**Major features**
Change in size
Irregular shape
Irregular colour

**Minor features**
Largest diameter 7 mm or more
Inflammation
Oozing
Change in sensation
Lesions with any of the major features or three of the minor ones are suspicious of melanoma

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**Table 1** Staging and survival for primary melanoma

<table>
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<th>Pathological stage</th>
<th>Breslow thickness (mm)</th>
<th>Microscopic ulceration</th>
<th>5 year survival (%)</th>
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<tr>
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**Table 2** Recommended wide local excision margins

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Subgroup analysis of patients with N1 disease (microscopic nodal disease—those with a positive sentinel lymph node biopsy) suggested that these patients may benefit most, and a planned EORTC study will look at this question.

There is currently no accepted adjuvant standard of care in the UK, so patients should be referred for entry into clinical trials. The current UK National Cancer Research Network adjuvant phase III study is examining whether bevacizumab (Avastin), a humanised anti-vascular endothelial growth factor antibody, reduces the risk of relapse in high risk primary and resected locoregional disease.

How do I treat metastatic disease?

Metastases can occur virtually anywhere and at any time after a diagnosis of melanoma. Common sites are nodal basins, liver, lung, bone, and brain.

NICE guidance is that all patients diagnosed with distant metastases should be referred to a specialist oncologist and have access to a clinical nurse specialist and palliative care team. All new diagnoses of metastatic disease should be discussed by the specialist multidisciplinary team.2

In advanced disease, no intervention has been shown to have a significant effect on overall survival. Management of various clinical scenarios is outlined below.

Metastasectomy in oligometastatic relapse may be considered in highly selected patients who have been disease free for a long time.26,27

Cutaneous metastases, in-transit metastases (deposits from a focus of cells moving along regional lymphatic channels), or nodal metastases are generally treated surgically with palliative intent. A carbon dioxide laser and radiotherapy can also help provide an element of local control.

Multiple cutaneous deposits in a single limb (with no distant metastases) can be treated by isolated limb perfusion or infusion using melphalan as a single agent or combined with other cytotoxic and biological agents.29,30 This can have excellent results in appropriately selected patients but can cause considerable morbidity.

Metastases to the central nervous system carry a poor prognosis. Surgery may be indicated for isolated lesions if amenable.31,32 Stereotactic radiotherapy including newer techniques such as gamma knife treatment can also be used.33 No survival benefit has been proved for whole brain radiotherapy or chemotherapy, although both are commonly used as standard of care.

Systemic treatment in melanoma is unsatisfactory—few drugs are available and response rates are limited. Patients with metastatic disease have a median survival of six to nine months.34

Despite many studies over the past 20 years investigating various chemotherapy regimens, dacarbazine remains the standard of care. It has a response rate of 5-15% and improves progression-free survival by a few months at best. There is no randomised evidence for an improvement in overall survival. Patients with raised lactate dehydrogenase are less likely to benefit from systemic treatment.34

Adding interferon alfa and interleukin-2 to chemotherapy increases response rates and toxicity, but does not significantly improve overall survival; it is therefore not recommended. High dose interleukin-2 did not extend overall survival in a randomised clinical trial, although a small number of patients experience durable complete responses.36

What therapeutic agents are being investigated?

Significant advances have been made in understanding the pathways that drive the growth and survival of melanoma cells.37 Activating mutations in two cell signalling pathways have been identified, and targeted treatments are in early phase clinical development. Current opinion is that inhibition of signalling through both pathways may be required. Single agent sorafenib, a multitarget kinase inhibitor with modest activity against b-raf, was not significantly active.38 Combination studies with chemotherapy are currently under way after phase II studies showed some promise.39 Agents that induce

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apoptosis and potentiate the activity of chemotherapy are also being investigated in large clinical trials. New activators of the immune system have shown promise in a subset of patients with advanced disease, and studies are planned in the adjuvant setting. Because current therapeutic options are so limited, patients should be offered entry into clinical trials.

Conclusions and future directions
Treatments for melanoma are limited. The main emphasis must be in primary prevention, prompt identification, and referral of suspicious lesions. Surgery has a central role in the management of melanoma. Advances in understanding the molecular pathology of melanoma and in immunotherapeutics provide some hope for future improvements in the treatment of advanced disease and in the adjuvant setting for patients at high risk of relapse. Thanks to Veronique Bataille for helpful comments in the preparation of the manuscript.

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