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Revised U.K. guidelines for the management of cutaneous melanoma 2010

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None declared.

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Guidelines produced in 2002 by the British Association of Dermatologists; reviewed and updated 2009.

Guidelines review process
These guidelines were initially reviewed at a multidisciplinary meeting on 8 November 2007. Those attending were the authors plus:
Dermatology: V. Doherty, D. Roberts, F. Wojnarowska, H. Bell, D. de Berker, C. Harwood, S. Bailey, R. Barlow, V. Bataille, L. Rhodes
Surgery: A. Hayes, J. Kenealy, G. Perks, M. Timmins
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Histopathology: N. Kirkham, H. Rigby, J. Theaker
Imaging: J. Smith, P. Guest, A. Dancey
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NHS Evidence has accredited the process used by the British Association of Dermatologists to produce guidelines. Accreditation is valid for three years from May 2010 and is applicable to guidance produced using the processes described in the British Association of Dermatologists' guidelines development manual (Bell & Ormerod, 2009). More information on accreditation can be viewed at www.evidence.nhs.uk.

Disclaimer

These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

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These guidelines for the management of cutaneous melanoma present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiology, diagnosis, investigation and follow up.

Contribution to these guidelines has been made by a large number of clinicians. They have also been endorsed by, or have had input from, representatives of the following groups or organizations: the U.K. Melanoma Study Group, the British Association of Dermatologists, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, the Royal College of Physicians, London, the Association of Cancer Physicians, the Royal College of Radiologists, London, the Royal College of Surgeons of England, the Royal College of Pathologists (pathology section only), the Royal College of General Practitioners, London, and the Department of Health.

These consensus guidelines have been drawn up by a multidisciplinary working party with membership drawn from a variety of groups and coordinated by the U.K. Melanoma Study Group and the British Association of Dermatologists.

The guidelines deal with aspects of the management of melanoma from its prevention, through the stages of diagnosis and initial treatment to palliation of advanced disease.

PubMed literature searches for this guidelines revision were carried out to identify publications from 2000 to April 2010, with search terms including: melanoma genetics, epidemiology, early diagnosis, risk factors, clinical features, pathology, surgery, chemotherapy and clinical trials. Relevant materials were also isolated from reviews and other publications identified from the PubMed searches, independent searches carried out by the authors, as well as materials collected by the authors as part of their ongoing professional interest in the latest developments in this clinical area. Levels of evidence to support the guidelines are quoted according to the criteria stated in Appendix 1. The consultation process for British Association of Dermatologists guidelines and their compliance with guideline recommendations have been published elsewhere.[1,2] There are arguments in favour of newer guideline grading methods, such as those of GRADE,[3] but the authors believe that the system used here allows greater potential for consensus in areas of conflicting evidence or where evidence sources are not directly comparable. In some instances, this is not due to an absence of high quality (Level Ib) trials but because different entry criteria or endpoints preclude direct comparison of results; in other cases interpretation of the clinical significance of results has been challenged. To assist production of unified guidelines taking account of these issues, the 'quality of evidence' grading used in these guidelines differs slightly from that used in other British Association of Dermatologists current guidelines; the 'strength of recommendations' grading is the same as used in many other publications. Where no level is quoted the evidence is to be regarded as representing Level IV (i.e. a consensus statement).

The intention of the working party was to agree best practice for the management of melanoma in the belief that this will promote good standards of care across the whole country. However, they are guidelines only. Care should be individualized wherever appropriate. These guidelines will be revised as necessary to reflect changes in practice in light of new evidence.

Integration with national cancer guidance

Multidisciplinary care of the patient is held to be the most desirable model, as recommended in the Calman/Hine report.[4] This has been defined by the National Institute for Health and Clinical Excellence (NICE) *Improving Outcomes for People with Skin Tumours including Melanoma*.[5] Core services will be provided within each Cancer Network by Local Skin Cancer Multidisciplinary Teams (LSMDTs). Specialist services will be provided by Specialist Skin Cancer Multidisciplinary Teams (SSMDTs). For melanoma there is a clear demarcation of care such that more advanced primary melanoma, rare subtypes of melanoma, melanoma in children, and patients eligible for trial entry or sentinel lymph node biopsy (SLNB) should be promptly referred for investigation and treatment from an LSMDT to an SSMDT (Table 1).

Prevention of melanoma

Individuals, and particularly children, should not get sunburnt (Level I).[6–9] Meta-analysis of case–control studies provides good evidence that melanoma is caused predominantly by intermittent intense sun exposure; fair-skinned individuals should therefore limit their recreational exposure through life (Level I).[10] People with freckles, red or blond hair, skin which burns in the sun, increased numbers of naevi, and those with a family history of melanoma are at increased risk and should heed this advice.

Adequate sun exposure to allow vitamin D synthesis, or sufficient dietary intake of vitamin D_3, is essential to human health; insufficiency of vitamin D is now recognized to be common.[11] It would therefore be inappropriate to greatly limit sun exposure in people without the risk factors listed above. Recent studies have shown that in the U.K. vitamin D levels are often suboptimal in melanoma patients, and are lower in fair-skinned people.[12,13] Fair-skinned people who avoid the sun rigorously to reduce the risk of melanoma should consider supplementing their intake of vitamin D_3 in the absence of medical contraindications.

There is evidence from a recent meta-analysis that sunbed usage does increase the risk of melanoma, particularly under the age of 35 years, and therefore it is recommended that this should be avoided (Level Ia).[14]

Referral and clinical diagnosis

Melanoma remains relatively uncommon and therefore the opportunity to develop diagnostic skills is limited in primary

Table 1 Melanoma patients who must be referred from a Local Skin Cancer Multidisciplinary Team to a Specialist Skin Cancer Multidisciplinary Team (SSMDT) (National Institute for Health and Clinical Excellence *Improving Outcomes for People with Skin Tumours including Melanoma*, 2006[5])

- Patients with melanoma managed by other site specialist teams, e.g. gynaecological, mucosal and head and neck (excluding ocular)
- Patients with stage IB or higher primary melanoma when sentinel lymph node biopsy (SLNB) is available within their Network. In the absence of SLNB then patients with stage IIB or higher should be referred to the SSMDT (American Joint Committee on Cancer staging system)
- Patients with melanoma at any stage who are eligible for clinical trials that have been approved at Cancer Network level
- Patients with multiple primary melanomas
- Children and young adults under 19 years with melanoma
- Any patient with metastatic melanoma diagnosed at presentation or on follow up
- Patients with giant congenital naevi where there is suspicion of malignant transformation
- Patients with skin lesions of uncertain malignant potential

care. All lesions suspicious of melanoma should be referred urgently under the 2-week rule to local screening services usually run by dermatologists. In England and Wales, this would be to an LSMDT. In Scotland, referral should be made to a local Rapid Access Cancer Clinic according to Scottish Cancer Referral Guidelines. The seven-point checklist or the ABCD rule may be helpful in the identification of melanomas although they are more sensitive than specific.[15–18] Urgent referral to the LSMDT is indicated where there is:

- A new mole appearing after the onset of puberty which is changing in shape, colour or size
- A long-standing mole which is changing in shape, colour or size
- Any mole which has three or more colours or has lost its symmetry
- A mole which is itching or bleeding
- Any new persistent skin lesion especially if growing, if pigmented or vascular in appearance, and if the diagnosis is not clear
- A new pigmented line in a nail especially where there is associated damage to the nail
- A lesion growing under a nail

Lesions which are suspicious for melanoma should not be removed in primary care. This is because clinicopathological correlation is vital for diagnostic accuracy, which in turn determines prognosis and defines adjuvant treatment options, and because diagnostic surgery requires specialist training. Early recognition of melanoma presents the best opportunity for cure[15,19–22] (Level III, Grade A).

All patients presenting with an atypical melanocytic lesion or a large number of moles should have a complete skin examination and assessment of risk factors. The dermoscope is a useful tool for the trained clinician screening pigmented lesions, as it can increase diagnostic accuracy.[23] It is also useful for monitoring multiple pigmented lesions where photography of dermoscopic images provides a record of change (Level Ia, Grade A). Recommendations for LSMDT record keeping of clinical features are provided in Table 2.

Table 2 Recommendations for Local Skin Cancer Multidisciplinary Team record keeping of clinical features

As a minimum the following should be included:
History (the presence or absence of these changes should be recorded)
- Duration of the lesion
- Change in size
- Change in colour
- Change in shape
- Symptoms (itching, bleeding etc.)

Examination
- Site
- Size (maximum diameter)
- Elevation (flat, palpable, nodular)
- Description (irregular margins, irregular pigmentation and if ulceration is present)

(Level III, Grade B)

Screening and surveillance of high-risk individuals

There are some individuals at higher risk of melanoma who should be considered for referral to specialist clinics. These individuals can be divided broadly into two groups based upon the degree of risk:

1 Individuals at moderately increased risk (approximately 8–10 times that of the general population) should be counselled about this risk and taught how to self-examine for changing naevi, but long-term follow up is not usual. Such patients are those with either a previous primary melanoma or large numbers of moles, some of which may be clinically atypical (Level Ia, Grade B).[24–28] Organ transplant recipients are also at this level of increased risk (Level III, Grade B).[29,30]

2 Those at greatly increased risk of melanoma (more than 10 times that of the general population). Patients with a giant congenital pigmented hairy naevus (definitions include '20 cm or more in diameter' and '5% of body surface area') should be monitored by an expert for their life time because of the risk of malignant change, which is significant but poorly quantified (Level III, Grade B).[31,32] Excision biopsy of suspicious areas in large congenital naevi may be necessary but requires expert histopathological review. Patients with a strong family history of melanoma are also at greatly increased risk. In some families, most clearly in mainland Europe and North America, families at risk of melanoma are also at increased risk of pancreatic cancer.[33] Those with three or more cases of melanoma or pancreatic cancer in the family should be referred to appropriate clinics managing inherited predisposition to cancer (involving dermatologists and/or clinical geneticists) for counselling. It is the consensus of the Melanoma Genetics Consortium (http://www.genomel.org) that it is premature to suggest gene testing routinely but this may change as more is known of the genes predisposing to melanoma.[34] The risk to families associated with the presence of two family members affected with melanoma is lower. In these families, if affected individuals also have the atypical mole syndrome, or if there is a history of multiple primary melanomas in an individual or pancreatic cancer, then referral should also be made for counselling; otherwise family members should probably be considered at moderately increased risk.

All of the above individuals at increased risk of melanoma should be advised on the specific changes that suggest melanoma and encouraged to undertake monthly skin self-examination (Level III, Grade B). Close-up and distant photography may be a useful adjunct to detecting early melanoma in either of these high-risk groups (Level III). They should be given written information and access to images of moles and melanomas. Such images are available at: http://www.genomel.org or http://www.rcplondon.ac.uk/pubs/contents/f36b1656-cc74-4867-8498-cc94b378312a.pdf. Recommendations for screening and surveillance of high-risk individuals are summarized in Table 3.

Table 3 Recommendations for screening and surveillance of high-risk individuals

- Patients who are at moderately increased risk of melanoma should be advised of this and taught how to self-examine. This includes patients with atypical mole phenotype, those with a previous melanoma, and organ transplant recipients (Level Ia, Grade B)
- Patients with giant congenital pigmented naevi are at increased risk of melanoma and require long-term follow up (Level IIIa, Grade B)
- Individuals with a family history of three or more cases of melanoma, or of pancreatic cancer, should be referred to a clinical geneticist or specialized dermatology services for counselling. Those with two cases in the family may also benefit, especially if one of the cases had multiple primary melanomas or the atypical mole phenotype (Level IIa, Grade B)

Biopsy of suspected melanoma

A lesion suspected to be melanoma, or where melanoma needs to be excluded, should be photographed, and then excised completely. The axis of excision should be orientated to facilitate possible subsequent wide local excision; generally on the limb this will be along the long axis. If uncertain, direct referral to the multidisciplinary team (MDT) will allow appropriate planning for future surgery. The excision biopsy should include the whole tumour 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, such that subsequent definitive treatment can be based on Breslow thickness.[35–37]

Diagnostic shave biopsies should not be performed as they may lead to incorrect diagnosis due to sampling error, and make accurate pathological staging of the lesion impossible (Level III). For the same reasons partial removal of naevi for diagnosis must be avoided and partial removal of a melanocytic naevus may result in a clinical and pathological picture very like melanoma (pseudomelanoma). This gives rise to needless anxiety and is avoidable. Incisional or punch biopsy is occasionally acceptable, for example in the differential diagnosis of lentigo maligna (LM) on the face or of acral melanoma, but there is no place for either incisional or punch biopsy outside the skin cancer MDT (Level III). It is acceptable in certain circumstances to excise the lesion entirely but without repair, and to dress the wound while awaiting definitive pathology.

Biopsies of possible subungual melanomas should be carried out by surgeons regularly doing so. The nail should be removed sufficiently for the nail matrix to be adequately sampled: clinically obvious tumour should be biopsied if present.

Prophylactic excision of naevi, or of small (< 5 cm diameter) congenital naevi in the absence of suspicious features is not recommended (Level III, Grade D).

Full clinical details should be supplied on the histopathology form, including history of the lesion, relevant previous history, site and differential diagnosis. All melanocytic lesions excised for whatever reason must be sent for histopathological review to the pathologist associated with the LSMDT or SSMDT.

The diagnosis of melanoma, both *in situ* and invasive, should be given or supervised by doctors who have received advanced communication skills training, following local policies for breaking bad news. A skin cancer trained nurse should be present to provide continuing support.

Histopathology

General comments

The Royal College of Pathologists has produced a minimum dataset which should be included in the histopathology report.[38] Double reporting is recommended for all melanomas and all naevi showing severe dysplasia if resources allow this to be achieved within 14 days.[5]

The histopathology report

The report should include the following:

Clinical information

- Site of the tumour
- Type of surgical procedure: excision or re-excision, incision biopsy, punch biopsy
- Any other relevant clinical information

Macroscopic description

Contour, colour and size of the tumour and the excised skin specimen in millimetres.

Microscopy

Presence or absence of ulceration Ulceration has prognostic value, and its presence should be confirmed microscopically as full-thickness loss of epidermis with reactive changes which include a fibrinous exudate and attenuation or acanthosis of the adjacent epidermis. These distinguish true ulceration from artefact.[39]

Thickness The tumour should be measured from the granular layer of the overlying epidermis to the deepest cells in the dermis judged to be malignant, to the nearest 0·1 mm. Ulcerated tumours should be measured from the base of the ulcer. Tumour forming a sheath around appendages should be excluded when measuring thickness except when the melanoma extends out into the adjacent reticular dermis when it should be measured in the conventional manner. In the presence of histological regression thickness measurements should be of the residual melanoma. Microsatellites should not be included in thickness measurements (Level III, Grade B).

Mitotic count The number of mitoses has prognostic value and is now included in the American Joint Committee on Cancer (AJCC) staging system for melanomas ≤ 1·0 mm.[40,41] It should be recorded as number of mitoses mm^{-2} in the area of greatest number of mitoses in the vertical growth phase (VGP). It has prognostic value at all thicknesses.

Histological subtypes Desmoplastic melanoma with or without neurotropism should be recorded because of its different biological behaviour and clinical outcome.[42] The subtypes superficial spreading, nodular, LM and acral lentiginous melanomas have good clinicopathological correlation, but their prognostic value has not been established.

Margins of excision This indicates whether excision is complete and the minimum margin of excision to peripheral and deep aspects measured in millimetres. If the excision or re-excision is not complete, whether the tumour is *in situ* or invasive at the resection margin should be indicated. When possible a statement should be made of whether the lesion is primary or secondary melanoma.

Pathological staging Staging using TNM and AJCC (Table 4), and coding, e.g. SNOMED, should be given.[41]

Growth phase Invasive melanoma without a VGP is termed microinvasion.[43] The assessment of microstaging criteria should be applied to the VGP only.

Regression The presence or absence of tumour regression has not been shown consistently to affect long-term outcome. Until its relevance is clear it should be reported as segmental replacement of melanoma by fibrosis, as this is subject to less observer variation.[44]

Tumour-infiltrating lymphocytes It remains unclear whether tumour-infiltrating lymphocytes have prognostic value.[40] The categories absent, non-brisk and brisk are subject to wide observer variation. 'Absent' indicates no lymphocytes infiltrating among

Table 4 The 2009 American Joint Committee on Cancer (AJCC) staging system

Stage	Primary tumour (pT)	Lymph nodes (N)	Metastases (M)
IA	< 1 mm, no ulceration, mitoses < 1 mm^{-2}		
IB	< 1 mm, with ulceration or mitoses ≥ 1 mm^{-2} [a]		
	1·01–2 mm, no ulceration		
IIA	1·01–2 mm, with ulceration		
	2·01–4 mm, no ulceration		
IIB	2·01–4 mm, with ulceration		
	> 4 mm, no ulceration		
IIC	> 4 mm, with ulceration		
IIIA	Any Breslow thickness, no ulceration	Micrometastases 1–3 nodes	
IIIB	Any Breslow thickness, with ulceration	Micrometastases 1–3 nodes	
	Any Breslow thickness, no ulceration	1–3 palpable metastatic nodes	
	Any Breslow thickness, no ulceration	No nodes, but in-transit or satellite metastasis/es	
IIIC	Any Breslow thickness, with ulceration	Up to three palpable lymph nodes	
	Any Breslow thickness, with or without ulceration	Four or more nodes or matted nodes or in-transit disease + lymph nodes	
	Any Breslow thickness, with ulceration	No nodes, but in-transit or satellite metastasis/es	
IV, M1a			Skin, subcutaneous or distant nodal disease
IV, M1b			Lung metastases
IV, M1c			All other sites or any other sites of metastases with raised lactate dehydrogenase

[a]In the rare circumstances where mitotic count cannot be accurately determined, a Clark level of invasion of either IV or V can be used to define T1b melanoma. Every patient with melanoma should be accurately staged using the AJCC system; this may include performing a sentinel lymph node biopsy when this is recommended by the Specialist Skin Cancer Multidisciplinary Team. Staging should be updated following relapse.

the tumour cells, but does not exclude lymphocytes in the surrounding dermis. 'Non-brisk' is a patchy or discontinuous infiltrate either among the peripheral cells or in the centre of the tumour, whereas 'brisk' is a continuous infiltrate but may be confined to peripheral cells. These are qualified as mild, moderate or severe in intensity.

Lymphatic or vascular invasion Vascular or lymphatic infiltration has prognostic value, and its presence should be recorded even though it is infrequently observed.[45]

Perineural infiltration Perineural infiltration occurring beyond the main bulk of the tumour correlates with increased local recurrence. It is most commonly associated with desmoplastic melanoma.[46]

Microsatellites These are defined as islands of tumour > 0·05 mm in the tissue beneath the main invasive mass of melanoma, but separated from it by 0·3 mm of normal collagen (i.e. not tumour stroma or sclerosis of regression).[47] Current AJCC staging also requires that satellites must be intralymphatic, which has not previously been required; this may be subject to revision. Microsatellites are predictive of regional lymph node metastases; this is reflected by stage N2c.

Precursor naevus The presence of contiguous melanocytic naevus should be recorded.

Clark level of dermal invasion This is a less reliable indicator of prognosis than thickness and is subject to poor observer agreement. It is not used to define T1 melanomas in the 2009 AJCC staging system, except that Clark levels IV or V may be used for defining T1b melanoma in rare instances when mitotic count cannot be determined in a nonulcerated T1 melanoma.

Requirements for microscopy of melanoma

These are given in Table 5.

Table 5 Requirements for microscopy of melanoma

• Ulceration	• Growth phase
• Thickness	• Regression
• Mitotic count[a]	• Tumour-infiltrating lymphocytes
• Histological subtype	• Lymphatic or vascular invasion
• Margins of excision	• Perineural invasion
• Pathological staging	• Microsatellites[b]

[a]Mitotic count is included in the 2009 American Joint Committee on Cancer staging system. [b]Microsatellites are not included in thickness measurement.
[Correction to Table 5 – removal of column headings and 'Clark level' under column previously headed 'Desirable features'-made after online publication on 15th July 2010]

Equivocal lesions

It may not be possible to distinguish pathologically between a melanoma and a benign melanocytic lesion. Such patients must be referred to the SSMDT for clinical and pathological review. A decision to treat as a melanoma should be made by the SSMDT in discussion with the patient. Thickness should be measured as for melanoma.

Sentinel lymph node pathology

Pathological assessment

This needs to be done in a standardized way so that findings between centres are comparable (Level III, Grade B).

Dissection

The dissection should be either by bivalving or multiple slicing, although the former is recommended.[48–50] A minimum of six serial sections should be taken, but a higher incidence of metastases is detected by extended step sectioning with immunohistochemistry at each level. The clinical relevance of the smaller metastases detected by these extended procedures is still unclear.

Staining

Use of haematoxylin and eosin and immunohistochemistry is essential. S100 and Melan A are most favoured immunohistochemical stains but a composite method such as PanMel is also appropriate.

Assessment of tumour burden

This gives additional prognostic information. The following are recommended:

Assessing the depth of the metastasis from the inner aspect of the sentinel lymph node capsule; categorizing the metastasis according to its site, either subcapsular or parenchymal; measuring the maximum dimension of the largest confluent group of melanoma cells.[50–52]

Completion lymphadenectomy specimens

The pathological examination of regional nodes dissected following positive SLNB should include an attempt to examine all lymph nodes at least at one level, and count the number involved. The presence of extracapsular spread and involvement of perinodal fat should be recorded together with the size of the tumour-free margin. The use of immunohistochemistry such as S100 or Melan A facilitates this.

Investigations and imaging

Stage I and II melanoma

Routine investigations are not required for asymptomatic patients with primary melanoma. Blood tests are unhelpful.

Routine computed tomography (CT) is not recommended for patients with stage I and II melanoma as this has a very low incidence of true-positive and high incidence of false-positive findings. Patients with particularly high-risk primary melanoma may undergo staging investigations if deemed appropriate by the SSMDT and/or as a prerequisite to trial entry. There is no indication for routine imaging with any other modality including plain X-ray, positron emission tomography (PET)/CT and magnetic resonance imaging (MRI). PET/CT is not effective in detecting positive sentinel lymph nodes and/or distant metastases in patients with primary melanoma[53–58] (Level IIa, Grade E).

Sentinel lymph node biopsy and ultrasound/fine needle aspiration cytology

SLNB, as discussed later, has high sensitivity and specificity for diagnosing subclinical regional lymph node involvement.

Ultrasound and fine needle aspiration cytology (FNAC) is the next best method but quoted sensitivities range from 4·7% to 80%, with the higher sensitivities being achieved only by sentinel node mapping and FNAC of the sentinel node in all cases regardless of morphological appearance.[59–62] Further staging by CT imaging following a positive sentinel lymph node, and prior to completion lymphadenectomy, has a very low yield.[63–65] Consequently this should be done only after discussion with an informed patient and the SSMDT (Level IIa, Grade D).

Stage III and IV melanoma

In stage III and IV melanoma, imaging strategies will be planned by the SSMDT.

CT scanning of the head, chest, abdomen and pelvis will normally adequately exclude metastases, and is most relevant in stage III melanoma before planning regional lymph node dissection (LND) and regional chemotherapy. If patients are considering entry to an adjuvant study following lymphadenectomy, the timing of scans should be determined by the SSMDT to avoid duplication.

When stage IV disease is suspected clinically, CT scanning of the head and whole body should be considered. Further imaging will be determined by symptoms, clinical trial protocols, and for clarification or reassessment of previous imaging findings. Generally, the added yield of PET/CT is unlikely to be clinically relevant in established stage IV melanoma (Level III, Grade D). Where metastasectomy is planned, PET/CT may be useful in excluding disease that might make surgery inappropriate. Serum lactate dehydrogenase (LDH) should be measured in all patients with suspected stage IV melanoma.

There is no indication for a bone scan in staging except where symptoms point to possible bone disease. Staging investigations are summarized in Table 6.

Table 6 Staging investigations for melanoma

- Patients with stage I, II and IIIA melanoma should not routinely be staged by imaging or other methods as the true-positive pick-up rate is low and the false-positive rate is high (Level IIa, Grade E)
- Patients with stage IIIB or IIIC melanoma should be imaged by computed tomography of head, chest, abdomen and pelvis prior to surgery after SSMDT review (Level IIa, Grade A)
- Patients with stage IV melanoma should be imaged according to clinical need and SSMDT review. Lactate dehydrogenase should also be measured (Level III, Grade A)

SSMDT, Specialist Skin Cancer Multidisciplinary Team.

Treatment of the primary lesion

Surgery is the only curative treatment for melanoma. Following excision for diagnosis and for measurement of microscopic Breslow thickness, a wider and deeper margin is taken to ensure complete removal of the primary lesion, and to remove any micrometastases. The depth of the therapeutic excision has conventionally been to the muscle fascia or deeper, and there is no evidence to support altering this approach.

Lateral surgical excision margins for invasive melanoma depend on Breslow thickness and are based on five randomized controlled trials (RCTs) including about 3300 patients, and a National Institutes of Health Consensus Panel.[66–73] However, only one of these studies is adequately powered, and two provide little scope for detecting reduced disease-free or overall survival due to narrow margins.[68,69,71] Most exclude melanoma on the head and neck and/or extremities.[74] A recent systematic review estimated overall survival in favour of wide excision (hazard ratio 1·04; 95% confidence interval 0·95–1·15; P = 0·40), although the difference was not significant. Therefore a small, but potentially important, difference in overall survival between wide and narrow excision margins cannot be confidently ruled out. Current randomized trial evidence is insufficient to address optimal excision margins for primary cutaneous melanoma.[75]

The recommended surgical margins are those measured clinically at the time of surgery, but adequacy of excision should be subsequently confirmed by review of re-excision histology, making an adjustment for average shrinkage of 20%.[76] The final decision about the size of the margin should be made by the MDT, after discussion with the patient. The recommendation should be made with consideration of functional and cosmetic implications of the margin chosen. All patients with primary melanoma stage IB and higher should be referred before treatment to an SSMDT when this provides an SLNB service. When the SSMDT does not provide this, all primary melanomas stage IIB or IIC should be referred. There are no RCT data for margin size for LM or other *in situ* melanoma.

Lentigo maligna and *in situ* superficial spreading melanoma

LM and other *in situ* melanomas have no potential for metastatic spread and the aim should be to excise the lesion

completely with a clear histological margin, although margin size remains undefined. No further treatment is then required.

LM is best treated by complete excision because of the risk of subclinical microinvasion. This may be missed on incisional biopsy due to sampling error.[73] The risk of progression to invasive melanoma is poorly quantified, and in the very elderly may be unlikely within their lifespan. Therefore, for some particular clinical situations, treatment by other methods such as radiotherapy, or observation only may be appropriate.[77–81] There is little evidence to support the use of cryotherapy, and this treatment may make subsequent progression difficult to detect. Topical treatment with imiquimod is as yet of unproven value so should be used only in the context of a clinical trial.[82] If the patient with LM is treated by nonsurgical means then the reason for this choice should be discussed and clearly documented by the MDT.

Local recurrence of LM occurs in about 5% of patients by 2 years.[77] Excision with micrographic control of surgical margins should be considered, although histological clearance is often difficult to define.[83] *In situ* melanoma on acral and genital skin is also associated with a higher risk of local recurrence, but this is less common in other types of *in situ* melanoma. In theory, *in situ* melanoma should not metastasize, but occasional cases do recur. This may be due to histological regression obscuring a more advanced tumour, missed microinvasion, or progression after incomplete removal of *in situ* disease.

Melanoma up to 1·0 mm Breslow thickness

There have been three RCTs of patients with melanomas in this thickness band.[66,68,69,73] The recommended surgical margins are based on the World Health Organization (WHO) Melanoma Co-operative Group Trial 10.[66,73] This randomized trial compared 1 and 3 cm margins for melanomas up to 2 mm thick. No local metastases, and similar overall survival, were seen in patients with melanomas < 1 mm in depth with either excision margin. However, this was based on analysis of data from only 359 patients. The French and Swedish studies compared 2 cm with 5 cm margins, and the latter included only patients with melanomas 0·8 mm or more in thickness in this group.[68,69] A 1 cm margin is deemed safe for this group (Level Ib, Grade A).

Melanoma 1·01–2·0 mm Breslow thickness

There have been four randomized studies that have included patients in this category. The WHO study showed a small excess of local metastasis as first site of relapse in the 1 cm margins group.[66,73] There was no difference in overall survival between 1 and 3 cm margins but the study was inadequately powered to detect this. The Intergroup Melanoma Trial compared 2 vs. 4 cm margins of excision for lesions of 1–4 mm in thickness.[67,70] No difference was seen between the two groups in either local recurrence or survival. Two other studies have included patients with melanomas up to 2 mm, also treated with either 2 or 5 cm margins.[68,69] There was no difference in outcome between the groups. The 1 vs. 3 cm, 2 vs. 4 cm and 2 vs. 5 cm studies cannot be compared directly, but no study using 2 cm margins as one comparator has shown any advantage of wider margins than this. However, trials of narrower margins have either not been performed (e.g. 1 vs. 2 cm margins) or have been underpowered, and do not permit a definite conclusion that a 1 cm margin is adequate. Evidence to date shows that a minimum margin of 1 cm is required, although 2 cm margins are equally appropriate. The final decision will be determined by anatomical site, MDT review, and after discussion with an informed patient (Level Ib, Grade A).

Melanoma 2·01–4·0 mm Breslow thickness

The Intergroup Melanoma Trial showed no difference in rates of local metastasis between patients treated with 2 cm, and those treated with 4 cm margins.[67] However, longer follow up showed reduced overall survival in the 2 cm margins group, although this fell just short of reaching statistical significance.[70] The results of a randomized trial with 3 cm margins showed significantly increased rates of locoregional recurrence in patients treated with 1 cm margins, and a reduction in melanoma-specific survival, again just short of significance, although no difference in overall survival.[71] The significance of this is unclear, and the 2 vs. 4 cm and 1 vs. 3 cm trials cannot be directly compared. Until the resulting uncertainty is resolved, which may not happen as the number of patients required to detect a difference between 2 and 3 cm margins is considerable, the default position should be to minimize locoregional and distant metastatic risk. Therefore a minimum 2 cm margin is required in this group, although 3 cm margins are equally appropriate. The final decision will be determined by anatomical site, need for skin grafting, MDT review, and after discussion with an informed patient (Level Ib, Grade A).

Melanoma greater than 4 mm in thickness

The risk of locoregional and distant metastasis is 50% or more in this group. None the less, the same surgical objectives apply to minimize locoregional and distant metastatic risk. There is only one randomized study which includes melanomas thicker than 4 mm.[71] This trial compared 1 cm with 3 cm margins. The results show a significant increase in locoregional recurrence when 1 cm margins are used, and a reduction in melanoma-specific survival just short of significance, although no difference in overall survival. As there are no data that margins smaller than 3 cm are as effective, the evidence suggests 3 cm margins for this group. There is no evidence that margins > 3 cm are required. The final decision will be determined by anatomical site, need for skin grafting, MDT review, and after discussion with an informed patient (Level Ib, Grade B).

Recommended surgical excision margins are summarized in Table 7.

Table 7 Recommended surgical excision margins

Breslow thickness	Excision margins	Level of evidence	Grading of evidence
In situ	5-mm margins to achieve complete histological excision	III	B
< 1 mm	1 cm	Ib	A
1·01–2 mm	1–2 cm	Ib	A
2·1–4 mm	2–3 cm	Ib	A
> 4 mm	3 cm	Ib	B

Table 8 Recommendations for the management of clinically node-negative patients

- There is no role for elective lymph node dissection (Level I, Grade E)
- SLNB can be considered in stage IB melanoma and upwards in Specialist Skin Cancer Multidisciplinary Teams (Level Ia, Grade A)
- Patients should be introduced to the concept of SLNB as a staging procedure but should also understand that it has no proven therapeutic value
- Surgical risks of SLNB, the possibility of failure to find a sentinel lymph node, and of a false-negative result, should also be explained

SLNB, sentinel lymph node biopsy.

Management of lymph node basins

Investigation and management of lymph node basins in melanoma patients should be carried out by SSMDTs so that surgical treatment planning and investigations can run in parallel. There is no place for elective LND in the management of primary melanoma unless this is unavoidable because the primary melanoma lies over the lymph node basin (Level Ib, Grade A). Patients should have access to a skin cancer specialist nurse when relapse is suspected.

Clinically node-negative patients

SLNB was developed as a means of identifying the first lymph node draining the skin in which the melanoma arises.[84] The procedure is carried out at the same time as definitive wider excision of the primary melanoma.[85] SLNB gives information about prognosis, and is increasingly used in conjunction with adjuvant therapy clinical trials. Patients with melanoma of Breslow thickness 1·2–3·5 mm and a positive SLNB have a 75% 5-year survival compared with 90% if the SLNB is negative.[86] SLNB is normally considered for patients with melanoma ≥ 1 mm, when about 20% are positive; however, the risk of a positive SLNB in a melanoma < 1·0 mm is still 5%.[86,87] The procedure is associated with a 5% morbidity, which is less than that seen with complete nodal dissection. In patients with a positive SLNB, 20% have pathological evidence of metastases in additional regional nodes.[84] Patients with a positive SLNB usually choose to proceed to completion lymphadenectomy. In about 5% it is not possible to identify the sentinel node either on lymphoscintigraphy, at surgery, or both. Patients should be aware of this limitation. The relevance of increasingly detailed evaluation of the sentinel node and its correlation with prognosis remains to be defined.[88] MSLT-1 showed no overall 5-year survival benefit following SLNB and completion lymphadenectomy, and it is unclear whether SLNB improves local control of lymph node basins.[85,86] A final report with longer follow up is awaited.

Recommendations for the management of clinically node-negative patients are summarized in Table 8.

Management of patients with clinically or radiologically suspicious lymph nodes

FNAC of nodes is recommended when there is clinical doubt about the significance of the nodes. If there is a negative FNAC result but ongoing suspicion, then the fine needle aspiration should be repeated or an image-guided core biopsy arranged.

Open biopsy is recommended when there is clinical suspicion even in the presence of negative FNACs in which lymphocytes have been successfully aspirated. If open biopsy is performed, the incision must be such as to allow subsequent complete formal block dissection of the regional nodes without compromise. It should be done only by SSMDT members.[5]

Exploration or removal of a mass within a nodal basin which drains a known primary melanoma site, and prior to definitive surgical treatment, may increase the risk of melanoma recurrence in that basin.[89] Any melanoma patient who develops a mass in a nodal basin should be referred urgently to the SSMDT, and without prior investigation, for investigation and treatment planning (Level III, Grade B).

Management of patients with confirmed positive lymph node metastasis

Radical LND should be performed only by SSMDT members who do a combined minimum of 15 axillary and groin block dissections for skin cancer each year.[5,90]

Preoperative staging investigations should be carried out as already discussed for stage III melanoma. If such staging is not feasible prior to surgery, and surgery is considered necessary even if distant metastatic disease were to be detected, then a chest X-ray and LDH measurement is recommended.

The block dissection specimen should be marked and orientated for the pathologist. Axillary LND for melanoma should include all nodes in levels I–III, and this may require either resection or division of pectoralis minor. The management of

inguinal lymph node metastases is controversial. Between 30% and 44% of patients with clinically involved superficial inguinal nodes will have involved pelvic nodes, and the risk increases with the number of involved superficial nodes.[91–97] If Cloquet's node is positive the risk of pelvic node involvement ranges from 44% to 90%.[93,96,97] There is no reported increased morbidity associated with combined pelvic and superficial node dissection.[94] Following ilioinguinal dissection for palpable inguinal disease 5-year survival varies with extent of pelvic involvement: 49% with one pelvic node, 28% with two to three nodes, and 7% with more than three nodes.[97–100]

A superficial inguinal LND should be considered in the presence of:

- A single clinically involved inguinal node or femoral triangle node
- A single positive superficial inguinal sentinel node (Level Ib, Grade A).

A pelvic lymph node dissection should be considered in the presence of:

- More than one clinically palpable inguinal and/or femoral triangle node/s
- CT or ultrasound evidence of more than one inguinal and/or femoral triangle node/s, or of pelvic node involvement
- More than one microscopically involved node at SLNB
- A conglomerate of inguinal or femoral triangle lymph nodes
- Microscopic or macroscopic involvement of Cloquet's node (Level III, Grade B).

Cervical nodal recurrence should be treated either by surgeons in the SSMDT specializing in head and neck skin cancer including melanoma or by a head and neck MDT with a special interest in melanoma.[5] A comprehensive, and not a selective, neck dissection should be performed (Level III, Grade A). The term 'comprehensive' allows either:

- A radical dissection of levels 1–5
- Modified radical – the above, sparing spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle
- Extended radical – radical dissection including parotid and/or posterior occipital chain.

The risk of further locoregional recurrence is 16–32% despite comprehensive surgery.[101,102]

Locoregional recurrent melanoma: skin and soft tissues

Surgery is the treatment of choice for single local or regional metastases. Excision should be clinically and histologically complete, but a wide margin is not required. Multiple small (< 1 cm) dermal lesions respond well to treatment with the CO_2 laser.[103] Dermal disease which is progressing despite surgery or laser, and subcutaneous or deeper limb metastases, should be considered for regional chemotherapy with isolated limb infusion (ILI) with melphalan and actinomycin D, or with isolated limb perfusion (ILP)[104,105] (Level IIb, Grade B). ILI is less invasive than ILP, and can be more easily repeated, but may be less effective.[105] ILI is suitable for patients with low volume (< 5 cm) disease and those with comorbidities which prevent ILP. Patients with bulky disease (> 5 cm) may be more likely to benefit from ILP using melphalan with tumour necrosis factor (TNF), but a recent trial comparing this combination with melphalan alone did not confirm additional benefit from adding TNF.[106] Radiotherapy may be considered for disease which cannot otherwise be controlled. Selected patients suitable for ILI/ILP should be referred to specialized centres. The role of electrochemotherapy using intralesional or systemic bleomycin is still being evaluated. Recommendations for locoregional recurrent melanoma are given in Table 9.

Table 9 Recommendations for locoregional recurrent melanoma

- Nodes clinically suspicious for melanoma should be sampled using fine needle aspiration cytology (FNAC) prior to carrying out formal block dissection. If FNAC is negative although lymphocytes were seen, a core or open biopsy should be performed if suspicion remains (Level III, Grade B)
- Prior to lymph node dissection, performed by an expert,[5] staging by computed tomographic scan should be carried out other than where this would mean undue delay (Level III, Grade B)
- The treatment of locoregional recurrence in a limb is palliative. Surgical excision, CO_2 laser, or isolated limb infusion or perfusion may be considered (Level IIb, Grade B)

Adjuvant therapy

There is no evidence of a survival benefit for adjuvant chemotherapy in patients with melanoma.[107] This includes adjuvant regional chemotherapy using ILP, and therefore ILI.[108]

Interferon has been evaluated in low-, intermediate- and high-risk patients using various doses and schedules. A recent individual patient data meta-analysis concluded that interferon was associated with a significant impact on relapse-free survival and a small effect on overall survival (5-year survival benefit 3%, $P < 0{\cdot}05$).[109] However, the benefit was seen across all interferon regimens, and was greatest in those with ulcerated melanomas. There was no clear indication as to optimum dose or duration. The results are awaited of further analysis including more recent data. Interferon is not recommended as standard of care for adjuvant therapy of primary or stage III melanoma (Level Ia, Grade A). This is because its effect on disease-free survival is of uncertain clinical relevance, and although overall survival is improved in meta-analysis, the effect is small and is associated with significant drug toxicity. Prospective studies are required to establish whether a subset of patients who derive most benefit can be identified.

Clinical trials of adjuvant melanoma vaccines have not so far been successful.

Patients should be offered entry into adjuvant clinical trials approved by the local Cancer Network. They should have access to a melanoma specialist who is conversant with current

melanoma adjuvant trials, and who is able to ensure their access to such studies. Details may be found on the websites of the National Cancer Research Network and the European Organization for Research and Treatment of Cancer.

Adjuvant radiotherapy

The Tasmanian Radiation Oncology Group has completed a randomized study of adjuvant radiotherapy to dissected nodal basins, 48 Gy in 20 fractions, in 250 patients with a high (> 25%) risk of local recurrence following lymphadenectomy.[110] Eligible patients had ≥ 1 parotid, ≥ 2 cervical or axillary or ≥ 3 groin nodes, or extranodal spread of tumour, or node diameter ≥ 3 cm in neck or axilla or ≥ 4 cm in the groin. Interim results show a 15% improvement in local control following radiotherapy, but there was no effect on overall survival. There are no data yet on morbidity following this treatment, and so at present the risk:benefit of adjuvant radiotherapy is unclear. If there is clinical or histological doubt about the adequacy of surgery following recurrence, or about the feasibility of salvage surgery, adjuvant radiotherapy may be considered by the SSMDT (Level Ib, Grade B).

Occult primary melanoma

Patients with occult primary melanoma may present with a solitary metastasis, lymph node disease, or systemic disease. Such patients should be referred promptly to the SSMDT for investigation and treatment planning. All patients should have a thorough examination of the skin. Occult primary uveal tract melanoma nearly always causes liver metastases before these are apparent at other sites; searching for a uveal tract primary in a patient with occult nodal disease is not appropriate. For patients presenting with inguinal lymphadenopathy, examination of the genital and urinary tracts and anorectum is especially relevant. All patients should be staged with CT scans of head, chest, abdomen and pelvis. Various reports from institution-based series suggest that patients presenting with stage III disease from an unknown primary have a better prognosis than patients with a similar stage and a known primary.[111,112] One published series suggested a survival advantage in patients with stage IV disease from an unknown primary compared with those with a declared primary.[113]

Patients presenting with lymph node disease from an occult primary involving a single lymph node basin should be presumed to have regional rather than distant metastasis, and treated as for stage III disease with lymph node block dissection.

Metastatic disease

All patients should have access to a skin cancer clinical nurse specialist and a palliative care team providing expertise in symptom control and psychosocial support. Links should be made with community cancer support networks as soon as possible. All patients with metastatic disease should have access to an oncologist specializing in melanoma for management advice.

Selected patients who relapse with oligometastatic disease may benefit from metastatectomy. Although this has not been evaluated in a prospective randomized trial, median survival of 21 months for selected surgically treated patients has been reported[114–119] (Level IIb, Grade B).

No systemic therapy has been shown to extend survival significantly. Dacarbazine is standard chemotherapy outside a clinical trial, although its benefits are limited, and it is ineffective in brain metastases (Level IIa, Grade C). The oral dacarbazine derivative temozolomide has greater central nervous system (CNS) penetration but has not shown significant clinical advantages over dacarbazine in two multicentre clinical trials.[120,121] Biochemotherapy (the addition of biologically active agents such as interferon-α and interleukin-2 to chemotherapy) increases response rates and toxicity but does not significantly increase overall survival.[122] The same is true for combination chemotherapy, and so this is not recommended other than in highly selected patients in whom palliation is dependent upon maximizing response in symptomatic deposits. High-dose interleukin-2 has not been evaluated in a randomized phase III trial although a small minority of patients may experience durable complete responses.[123]

Patients with elevated LDH have a reduced likelihood of benefiting from currently available systemic treatment. Given the limited benefits with standard systemic therapy, all patients with metastatic melanoma should be considered for entry into clinical trials of novel therapies.

Patients with CNS metastases have a poor prognosis. Surgery or stereotactic radiotherapy should be considered for selected patients with limited disease.[114,115,124–126] The benefits of treating patients with cerebral metastases with whole-brain radiotherapy are limited, but this may sometimes have palliative value. Supportive care is therefore the most appropriate strategy for many patients (Level IIb, Grade B).

Spinal cord compression should be treated surgically if feasible, but multiple sites of disease, poor prognosis and poor performance status may make this inappropriate. Radiotherapy may be useful for palliation of rapidly enlarging or painful metastases involving soft tissues and bones (Level IIb, Grade B).

Recommendations for metastatic disease are shown in Table 10.

Table 10 Recommendations for metastatic disease

- All patients should be managed by Specialist Skin Cancer Multidisciplinary Teams[5]
- Surgery should be considered for oligometastatic disease at sites such as the skin, brain or bowel (Level IIb, Grade B), or to prevent pain or ulceration
- Radiotherapy may have a palliative role in the treatment of metastases (Level II, Grade B)
- Standard chemotherapy is dacarbazine although its role is palliative (Level II, Grade C)
- Patients with stage IV melanoma should be considered for entry to clinical trials

Melanoma, hormone replacement therapy and pregnancy

There is no evidence that melanoma at or near the time of pregnancy adversely affects prognosis.[127] Breslow thickness, site and presence of ulceration are still the key determinants of outcome, and are not different from a control population.[128] The outcomes of pregnancy for both mother and baby are not worsened (Level IIa).[128,129]

Surgical treatment should be determined in the normal way, but the risks of exposure to ionizing radiation and blue dye during sentinel node biopsy will need special consideration.

There is no medical reason to justify delaying conception after a diagnosis of melanoma (Level IIa) but the social and family effects of developing recurrent melanoma during pregnancy or after birth are great.[127,130] It is proper therefore to counsel a woman in the reproductive age range about her risk of recurrence over time so that she and her partner can make their decision about conception with adequate information. These social or family considerations may also be relevant to a male patient whose partner is pregnant or if he and his partner are considering a pregnancy.

There is no evidence that the use of the oral contraceptive pill plays any role in the natural history of melanoma (Level Ia).[130–133] Decisions about use of the contraceptive pill should be made on the basis of health issues other than melanoma.

There is no evidence that hormone replacement therapy plays any role in the natural history of melanoma,[130,132] neither does it worsen prognosis in stage I and II melanoma (Level IIa).[133] Decisions about use of hormone replacement therapy should be made on the basis of health issues other than melanoma.

In pregnancy, staging using X-rays should be avoided where possible especially in the first trimester. MRI should be used in preference to CT scan, where feasible.

Because chemotherapy does not have a survival benefit in stage IV disease its use in pregnancy requires careful discussion. Use of chemotherapy agents in the first trimester should be avoided. There are case reports of the successful birth of normal babies who were exposed to dacarbazine *in utero* later in pregnancy, but this does not exclude later toxicity. Melanoma can metastasize to the placenta and to the fetus more frequently than any other solid tumour. This has a poor prognosis for both mother and baby. At delivery in patients with stage IV melanoma the placenta should be examined for melanoma.

Recommendations regarding pregnancy and hormone replacement therapy are summarized in Table 11.

Table 11 Recommendations regarding pregnancy and hormone replacement therapy

Pregnancy with primary melanoma
• No worsening of prognosis
• No increase in adverse outcomes for mother or baby
Pregnancy in advanced melanoma
• Placental and fetal metastases possible in stage IV disease
Oral contraceptives and melanoma
• No increased risk of melanoma
Hormone replacement therapy
• No increased risk of melanoma
• No worsening of prognosis

Use of drugs in melanoma patients

There are theoretical reasons to suggest that L-DOPA may have an adverse effect on patients with melanoma. There are no data to support this idea, however, and such an association seems unlikely.[134] The use of immunosuppressants after melanoma is a cause for concern. The results of a recent cohort study of patients with rheumatoid arthritis treated with biologic agents showed an increased risk of melanoma (odds ratio 2·3, 95% confidence interval 0·9–5·4).[135] However, there is usually little that can be done to avoid these drugs without an unacceptable loss of quality of life. Their use after treatment of primary or secondary melanoma should be discussed between the prescribing doctors and patients, and the decision to continue their use and their dosage should be subject to ongoing review following a diagnosis of melanoma (Level III, Grade C).

Organ and blood donation

The decision about whether organs or tissue are suitable for transplant is made on an individualized basis, taking into account the patient's medical history.[136] A melanoma patient would not normally be considered as a donor.

Follow up

There are three main reasons for follow up after treatment of primary cutaneous melanoma. The first is to detect recurrence when further treatment can improve the prognosis, the second is to detect further primary melanomas and the third is to provide support, information and education. The proportion of patients with melanoma who have impaired health-related quality of life is comparable with other cancers, and their needs for psychosocial support are likely to be similar.[137] Provision of this is an important part of MDT management.[138] There are no RCTs which have formally evaluated follow up. Numerous follow-up regimens have been reviewed but few are evidence based.[139–141] Sixty-two per cent of all recurrences were detected by patients themselves in one review, but definition of patient or doctor detection is unclear and other series emphasize the importance of physician-detected recurrence.[134] Patient opinion was equally divided as to whether follow-up visits were reassuring or provoked further anxiety. There is little evidence of survival advantage following self-detection of metastases.[139–141] Most first relapses occur in the 5 years following diagnosis, but there is a significant risk of later first relapse; both patients and their doctors should be aware of this.

A primary melanoma follow-up clinic should be provided by an MDT of dermatologists and surgeons with clinical nurse specialist support, and there should be continuity of care. Patients should be taught to self-examine to detect locoregional recurrence and new primary melanoma. Photography can be useful for follow up of patients who also have atypical moles. Patients should routinely be examined for locoregional and distant metastases, and the whole skin should be checked for new primary melanomas. A defined rapid-access pathway must be provided to all patients and general practitioners for suspected recurrence. Suspected new primary melanoma should be referred as normal through the 2-week wait system. For Scotland this needs to be compliant with the 62-day rule. Follow up of patients with AJCC stage III and IV disease should be led by melanoma SSMDTs.

Follow-up intervals and duration should be tailored to the stage group of the primary melanoma and therefore to the risk of recurrence. The follow-up plan should be agreed between the patient and the responsible doctors.

Care can be shared with primary care, but only if the secondary care team have defined and explained to the primary care team what is required, and only if the primary care team are prepared to accept responsibility for this. In the event of suspected recurrence, even after discharge from follow up, it is recommended that the patient contact the secondary care team directly to avoid possible delay in diagnosis.

Screening asymptomatic clinically normal patients with lymph node ultrasound is sensitive and can detect nodal disease, but this has not been shown to be useful in primary melanoma follow up.[142] The same applies to CT and PET imaging. These investigations should not be used outside a clinical trial.

In situ melanoma

Patients with a surgically treated single *in situ* melanoma do not require follow up, as there is no risk of metastasis. They require a return visit after complete excision to explain the diagnosis, check the whole skin for further primary melanoma/s, and to teach self-examination for a new primary melanoma. Clinical nurse specialist support may be required despite the absence of metastatic risk.

Stage IA melanoma

Patients with invasive primary cutaneous melanoma < 1·0 mm have a 5-year disease-free survival of over 90% or better. A recent review of 430 patients with melanomas < 0·5 mm showed no recurrences at 5–15 years follow up but 4% of patients developed a second primary melanoma over this period.[143] Patients with invasive, nonulcerated primary tumours 0·5–1·0 mm thick have only slightly worse 5-year disease-free survival, and are in the same stage group. Therefore, for stage IA patients a series of two to four visits over up to 12 months is suggested to teach self-examination, and then they may be discharged from regular follow up (Level III, Grade B).

Stage IB and IIA melanoma

This group are at 15–35% risk of recurrence, but most of this risk is in years 2–4. Once they have learnt how to self-examine for locoregional metastasis and new primaries, and understand how to access the follow-up team promptly for suspected recurrence, they should be seen every 3 months for 3 years, then 6-monthly to 5 years. No routine investigations are required (Level III, Grade B).

Stage IIB and IIC melanoma

This group are at 40–70% risk of recurrence. Most of this risk is in years 2–4. They should be taught self-examination and be seen 3-monthly for 3 years, and 6-monthly to 5 years. No routine investigations are required (Level III, Grade B).

Sentinel lymph node biopsy

Patients who have had a negative SLNB should be followed up on the basis of Breslow thickness.

Most patients who have had a positive SLNB will have had a completion lymphadenectomy. As these patients now have at least stage IIIA disease, their follow up should be supervised by the SSMDT, and entry into appropriate trials considered. Risk of recurrence depends on extent of sentinel lymph node involvement, and may be less than for some with stage II melanoma. They should be followed up as for stage IB–IIC melanoma (Level III, Grade B).

Stage IIIB, IIIC, and resected stage IV melanoma

The risk of further metastasis in this group is high. Many will be eligible for adjuvant trials. Those outside trials should be seen 3-monthly for 3 years from the date of staging, 6-monthly to 5 years, then annually to 10 years by an SSMDT. Investigations should be carried out on the basis of clinical need, and may include CT surveillance if considered appropriate by the SSMDT. This might be used to monitor a site considered at high risk of relapse. The SSMDT will need to balance the use of follow-up investigations for this group against the need for early detection of further stage III and IV disease. Early detection facilitates both effective treatment and trial entry (Level III, Grade B).

Unresectable stage IV melanoma

These patients should be followed up and investigated by the SSMDT according to clinical need. They may be eligible for clinical trials.

Clinical trials

Many patients will be in clinical trials. These will have defined follow-up intervals which should be adhered to.

Follow up for melanoma is detailed in Table 12.

Table 12 Follow up for melanoma

- Patients with *in situ* melanomas do not require follow up
- Patients with invasive melanomas have differing risk of relapse according to their stage group
- Patients with stage IA melanoma should be seen two to four times over up to 12 months, then discharged
- Patients with stage IB–IIIA melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years
- Patients with stage IIIB and IIIC and resected stage IV melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years, then annually to 10 years
- Patients with unresectable stage IV melanoma are seen according to need

(Level III, Grade B)

Audit points

The following are suggested points for audit:

1 Timeliness and appropriateness of referral from LSMDT to SSMDT (referenced to the standard described in the NICE *Improving Outcomes for People with Skin Tumours including Melanoma*, February 2006, available at: http://www.nice.org.uk/nicemedia/live/10901/28906/28906.pdf).

2 Comparison and appropriateness of stated clinical, and measured histological, surgical margins (referenced to the standards described in these guidelines).

3 Use of investigations at diagnosis in primary melanoma by stage grouping (referenced to the standards described in these guidelines).

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References

1 Griffiths CEM. The British Association of Dermatologists' guidelines for the management of skin disease. *Br J Dermatol* 1999; **141**:396–7.
2 Cox NH, Williams HC. The British Association of Dermatologists therapeutic guidelines: can we AGREE? *Br J Dermatol* 2003; **148**:621–5.
3 Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**:924–6.
4 Calman K, Hine D. *Report by the Advisory Group on Cancer Services to the Chief Medical Officers of England and Wales*. Cardiff: Department of Health/Welsh Office, 1995.
5 National Institute for Health and Clinical Excellence. *Improving Outcomes for People with Skin Tumours including Melanoma*, 2006. Available at: http://www.nice.org.uk/nicemedia/live/10901/28906/28906.pdf (last accessed 25 May 2010).
6 Marks R, Whiteman D. Sunburn and melanoma: how strong is the evidence? *BMJ* 1994; **308**:75–6.
7 Whiteman D, Green A. Melanoma and sunburn. *Cancer Causes Control* 1994; **5**:564–72.
8 Armstrong BK. Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J Dermatol Surg Oncol* 1988; **14**:835–49.
9 Armstrong BK, Kricker A. Sun exposure causes both nonmelanocytic skin cancer and malignant melanoma. In: *Proceedings on Environmental UV Radiation and Health Effects. Health Rep* 1993; **5**:106–13.
10 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**:2040–59.
11 Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81**:353–73.
12 Newton-Bishop J, Beswick S, Randerson-Moor J *et al.* Serum 25-hydroxyvitamin D3 levels are associated with Breslow thickness at presentation, and survival from melanoma. *J Clin Oncol* 2009; **27**:5439–44.
13 Randerson-Moor JA, Taylor JC, Elliott F *et al.* Vitamin D receptor gene polymorphisms, serum 25-hydroxyvitamin D levels and melanoma: UK case–control comparisons and a meta-analysis of published VDR data. *Eur J Cancer* 2009; **45**:3271–81.
14 International Agency for Research on Cancer Working Group on Artificial Ultraviolet Light and Skin Cancer. The association of use of sunbeds with cutaneous melanoma and other skin cancers: a systematic review. *Int J Cancer* 2007; **120**:1116–22.
15 McGovern TW, Litaker MS. Clinical predictors of malignant pigmented lesions. A comparison of the Glasgow seven-point checklist and the American Cancer Society's ABCDs of pigmented lesions. *J Dermatol Surg Oncol* 1992; **18**:22–6.
16 Abbasi NR, Shaw HM, Rigel DS *et al.* Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA* 2004; **292**:2771–6.
17 MacKie RM. *Clinical Dermatology*, 5th edn. Oxford: Oxford University Press, 2003; 345–6.
18 Du Vivier AWP, Williams HC, Brett JV *et al.* How do malignant melanomas present and does this correlate with the seven-point check-list? *Clin Exp Dermatol* 1991; **16**:344–7.
19 Cox NH, Madan V, Sanders T. The U.K. skin cancer 'two-week rule' proforma: assessment of potential modifications to improve referral accuracy. *Br J Dermatol* 2008; **158**:1293–8.
20 Melia J, Cooper EJ, Frost T *et al.* Cancer Research Campaign health education programme to promote the early detection of cutaneous malignant melanoma I. Work-load and referral patterns. *Br J Dermatol* 1995; **132**:405–13.
21 Melia J. Early detection of cutaneous malignant melanoma in Britain. *Int J Epidemiol* 1995; **24** (Suppl. 1):S39–44.
22 MacKie RM, Hole D, Hunter JAA *et al.* Cutaneous malignant melanoma in Scotland: incidence, survival, and mortality, 1979–94. The Scottish Melanoma Group. *BMJ* 1997; **315**:1117–21.
23 Braun RP, Oliviero M, Kolm I. Dermoscopy: what's new? *Clin Dermatol* 2009; **27**:26–34.
24 Melia J. Changing incidence and mortality from cutaneous malignant melanoma. *BMJ* 1997; **315**:1106–7.
25 Parkin DM, Muir CS. Cancer incidence in five continents: comparability and quality of data. *IARC Sci Publ* 1992; **120**:45–173.
26 Rhodes AR, Weinstock MA, Fitzpatrick TB *et al.* Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. *JAMA* 1987; **258**:3146–54.
27 Newton JA, Bataille V, Griffiths K *et al.* How common is the atypical mole syndrome phenotype in apparently sporadic melanoma? *J Am Acad Dermatol* 1993; **29**:989–96.

28 Bataille V, Newton Bishop JA, Sasieni P *et al.* Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case–control study. *Br J Cancer* 1996; **73**:1605–11.
29 Le Mire L, Hollowood K, Gray D *et al.* Melanomas in renal transplant recipients. *Br J Dermatol* 2006; **154**:472–7.
30 Brown VL, Matin RN, Cerio R *et al.* Melanomas in renal transplant recipients: the London experience and invitation to participate in a European study. *Br J Dermatol* 2007; **156**:165–7.
31 Marghoob AA, Schoenbach SP, Kopf AW *et al.* Large congenital melanocytic nevi and the risk for the development of malignant melanoma. A prospective study. *Arch Dermatol* 1996; **132**:170–5.
32 Illig L, Weidner F, Hundeiker M *et al.* Congenital nevi less than or equal to 10 cm as precursors to melanoma: 52 cases, a review, and a new conception. *Arch Dermatol* 1985; **121**:1274–81.
33 Goldstein AM, Chan M, Harland M *et al.* High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res* 2006; **66**:9818–28.
34 Leachman SA, Carucci J, Kohlmann W *et al.* Selection criteria for genetic assessment of patients with familial melanoma. *J Am Acad Dermatol* 2009; **61**:677.e1–14.
35 Lederman JS, Sober AJ. Does biopsy type influence survival in clinical stage I cutaneous melanoma? *J Am Acad Dermatol* 1985; **13**:983–7.
36 Lees VC, Briggs JC. Effect of initial biopsy procedure on prognosis in stage I invasive cutaneous malignant melanoma: review of 1086 patients. *Br J Surg* 1991; **78**:1108–10.
37 Austin JR, Byers RM, Brown WD, Wolf P. Influence of biopsy on the prognosis of cutaneous melanoma of the head and neck. *Head Neck* 1996; **18**:107–17.
38 Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of tissues removed as part of the surgical treatment of cutaneous melanoma. *Pathol Int* 1998; **48**:168–70.
39 Spatz A, Cook M, Elder D *et al.* Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. *Eur J Cancer* 2003; **39**:1861–5.
40 Gimotty PA, Guerry D, Ming ME *et al.* Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol* 2004; **22**:3668–76.
41 Edge SE, Byrd DR, Compton CC *et al.* (eds). *Melanoma of the Skin. AJCC Cancer Staging Manual*, 7th edn. New York, NY: Springer, 2009.
42 Hawkins WG, Busam KJ, Ben-Porat L *et al.* Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. *Ann Surg Oncol* 2005; **12**:207–13.
43 Elder DE, Murphy GF. Malignant tumors (melanoma and related lesions). In: *Melanocytic Tumors of the Skin. Atlas of Tumor Pathology* (Elder DE, Murphy GF, eds). Washington, DC: Armed Forces Institute of Pathology, 1990; 103–205.
44 Kaur C, Thomas RJ, Desai N *et al.* The correlation of regression in primary melanoma with sentinel lymph node status. *J Clin Pathol* 2008; **61**:297–300.
45 Straume O, Akslan LA. Independent prognostic importance of vascular invasion in nodular melanoma. *Cancer* 1996; **78**:1211–19.
46 Quinn MJ, Crotty KA, Thompson JF *et al.* Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. *Cancer* 1998; **83**:1128–35.
47 Harrist TJ, Rigel DS, Day CL Jr *et al.* Microscopic satellites are more highly associated with regional lymph node metastases than is primary melanoma thickness. *Cancer* 1984; **53**:2183–7.
48 Cook MG, Di Palma S. Pathology of sentinel lymph nodes for melanoma. *J Clin Pathol* 2008; **61**:897–902.
49 Cochran AJ. Surgical pathology remains pivotal in the evaluation of 'sentinel' lymph nodes. *Am J Surg Pathol* 1999; **23**:1169–72.
50 Starz H, Balda BR, Kramer KU *et al.* A micromorphometry-based concept for routine classification of sentinel lymph node metastases and its clinical relevance for patients with melanoma. *Cancer* 2001; **91**:2110–21.
51 Dewar DJ, Newell B, Green MA *et al.* The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. *J Clin Oncol* 2004; **22**:3345–9.
52 van Akkooi AC, de Wilt JH, Verhoef C, Eggermont AM. The Rotterdam criteria for sentinel node tumor load: the simplest prognostic factor? *J Clin Oncol* 2008; **26**:6011.
53 Basseres N, Grob JJ, Richard MA *et al.* Cost-effectiveness of surveillance of stage I melanoma. A retrospective appraisal based on a 10-year experience in a dermatology department in France. *Dermatology* 1995; **191**:199–203.
54 Khansur T, Sanders J, Das SK. Evaluation of staging workup in malignant melanoma. *Arch Surg* 1989; **124**:847–9.
55 Yancovitz M, Finelt N, Warycha MA *et al.* Role of radiologic imaging at the time of initial diagnosis of stage T1b–T3b melanoma. *Cancer* 2007; **110**:1107–14.
56 Maubec E, Lumbroso J, Masson F *et al.* F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. *Melanoma Res* 2007; **17**:147–54.
57 Clark PB, Soo V, Krass J *et al.* Futility of fluorodeoxyglucose F 18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. *Arch Surg* 2006; **141**:284–8.
58 Wagner JD, Schauwecker D, Davidson D *et al.* Prospective study of fluorodeoxyglucose positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel lymph node biopsy. *J Clin Oncol* 1999; **17**:1508–15.
59 van Rijk MC, Teertstra HJ, Peterse JL *et al.* Ultrasonography and fine-needle aspiration cytology in the preoperative assessment of melanoma patients eligible for sentinel node biopsy. *Ann Surg Oncol* 2006; **13**:1511–16.
60 Sibon C, Chagnon S, Tchakérian A *et al.* The contribution of high-resolution ultrasonography in preoperatively detecting sentinel-node metastases in melanoma patients. *Melanoma Res* 2007; **17**:233–7.
61 Starritt EC, Uren RF, Scolyer RA *et al.* Ultrasound examination of sentinel nodes in the initial assessment of patients with primary cutaneous melanoma. *Ann Surg Oncol* 2005; **12**:18–23.
62 Voit C, Kron M, Schäfer G *et al.* Ultrasound-guided fine needle aspiration cytology prior to sentinel node biopsy in melanoma patients. *Ann Surg Oncol* 2006; **13**:1682–9.
63 Aloia TA, Gershenwald JE, Andtbacka RH *et al.* Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. *J Clin Oncol* 2006; **24**:2858–65.
64 Horn J, Lock-Anderson J, Sjøstrand H, Loft A. Routine use of FDG-PET scans in melanoma patients with positive sentinel node biopsy. *Eur J Nucl Mol Imaging* 2006; **33**:887–92.
65 Constantinidou A, Hofman M, O'Doherty M *et al.* Routine positron emission tomography and emission tomography/computed tomography in melanoma staging with positive sentinel node biopsy is of limited benefit. *Melanoma Res* 2008; **18**:56–60.
66 Veronesi U, Cascinelli N, Adamus J *et al.* Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. *N Engl J Med* 1988; **318**:1159–62.

67 Balch CM, Urist MM, Karakousis CP *et al.* Efficacy of 2 cm surgical margins for intermediate-thickness melanomas (1–4 mm): results of a multi-institutional randomized surgical trial. *Ann Surg* 1993; **218**:262–7.

68 Cohn-Cedermark G, Rutqvist LE, Andersson R *et al.* Long term results of a randomized study by the Swedish Melanoma Study Group on 2 cm versus 5 cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0·8–2·0 mm. *Cancer* 2000; **89**:1495–501.

69 Khayat D, Rixe O, Martin G *et al.* Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2·1-mm thick). Long-term results of a large European multicentric phase III study. *Cancer* 2003; **97**:1941–6.

70 Balch C, Soong SJ, Smith T *et al.* Long term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. *Ann Surg Oncol* 2001; **8**:101–8.

71 Thomas J, Newton-Bishop J, A'Hern R *et al.* Excision margins in high-risk malignant melanoma. *N Engl J Med* 2004; **350**:757–66.

72 NIH Consensus Conference. Diagnosis and treatment of early melanoma. *JAMA* 1992; **268**:1314–19.

73 Veronesi U, Cascinelli N. Narrow excision (1 cm margin) – a safe procedure for thin cutaneous melanoma. *Arch Surg* 1991; **126**:438–41.

74 Lens M, Nathan P, Bataille V. Excision margins for primary cutaneous melanoma: updated pooled analysis of randomized controlled trials. *Arch Surg* 2007; **142**:885–91.

75 Sladden MJ, Balch C, Barzilai DA *et al.* Surgical excision margins for primary cutaneous melanoma. *Cochrane Database Syst Rev* 2009; **4**:CD004835.

76 Silverman MK, Golomb FM, Kopf AW *et al.* Verification of a formula for determination of pre-excision surgical margins from fixed-tissue melanoma specimens. *J Am Acad Dermatol* 1992; **27**:214–19.

77 Preston P, Matey P, Marsden JR *et al.* Surgical treatment of lentigo maligna using 2 mm excision margins. *Br J Dermatol* 2003; **149** (Suppl. 64):109–10.

78 Mahendran RM, Newton-Bishop JA. Survey of U.K. current practice in the treatment of lentigo maligna. *Br J Dermatol* 2001; **144**:71–6.

79 Schmid-Wendtner MH, Brunner B, Konz B *et al.* Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. *J Am Acad Dermatol* 2000; **43**:477–82.

80 Tsang RW, Liu FF, Wells W *et al.* Lentigo maligna of the head and neck. Results of treatment by radiotherapy. *Arch Dermatol* 1994; **130**:1008–12.

81 Pitman GH, Kopf AW, Bart RS *et al.* Treatment of lentigo maligna and lentigo maligna melanoma. *J Dermatol Surg Oncol* 1979; **5**:727–37.

82 Rajpar S, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155**:653–6.

83 Walling HW, Scupham RK, Bean AK, Ceilley RI. Staged excision versus Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol* 2007; **57**:659–64.

84 Morton DL, Wen DR, Wong JH *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**:392–9.

85 Morton DL, Thompson JF, Cochran AJ *et al.* Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; **355**:1307–17.

86 Morton DL, Cochran AJ, Thompson JF *et al.* Sentinel node biopsy for early stage melanoma – accuracy and morbidity in MSLT-1, an international multicentre trial. *Ann Surg* 2005; **242**:302–13.

87 Wright BE, Scheri RP, Ye X *et al.* Importance of sentinel lymph node biopsy in patients with thin melanoma. *Arch Surg* 2008; **143**:892–9.

88 Li W, Stall A, Shivers SC *et al.* Clinical relevance of molecular staging for melanoma: comparison of RT-PCR and immunohistochemistry staining in sentinel lymph nodes of patients with melanoma. *Ann Surg* 2000; **231**:795–803.

89 Nathansohn N, Schachter J, Gutman H. Patterns of recurrence in patients with melanoma after radical lymph node dissection. *Arch Surg* 2005; **140**:1172–7.

90 National Cancer Peer Review Programme. *Manual for Cancer Services 2008: Skin Measures*. Available at: http://www.library.nhs.uk/integratedSearch/viewResource.aspx?resID=299673 (last accessed 25 May 2010).

91 Karakousis CP, Emrich LJ, Rao U *et al.* Groin dissection in malignant melanoma. *Am J Surg* 1986; **152**:491–5.

92 Badgwell B, Xing Y, Gershenwald JE *et al.* Pelvic lymph node dissection is beneficial in subsets of patients with node-positive melanoma. *Ann Surg Oncol* 2007; **14**:2867–75.

93 Finck SJ, Giuliano AE, Mann BD, Morton DL. Result of ilioinguinal dissection for stage II melanoma. *Ann Surg* 1982; **196**:180–6.

94 Sterne GD, Murray DS, Grimley RP. Ilioinguinal block dissection for malignant melanoma. *Br J Surg* 1995; **82**:1057–9.

95 Essner R, Scheri R, Kavanagh M *et al.* Surgical management of the groin lymph nodes in melanoma in the era of sentinel lymph node dissection. *Arch Surg* 2006; **141**:877–82.

96 Shen P, Conforti A, Essner R *et al.* Is the node of Cloquet the sentinel node for the iliac/obturator node group? *Cancer J* 2000; **6**:93–7.

97 Hughes TMD, A'Hern R, Thomas J *et al.* Prognosis and surgical management of patients with palpable inguinal lymph node metastases from melanoma. *Br J Surg* 2000; **87**:892–901.

98 Karakousis CP, Driscoll DL. Positive deep nodes in the groin and survival in malignant melanoma. *Am J Surg* 1996; **171**:421–2.

99 Balch CM, Ross MI. Melanoma patients with iliac nodal metastases can be cured. *Ann Surg Oncol* 1999; **6**:230–1.

100 Strobbe LJA, Jonk A, Hart AA *et al.* Positive iliac and obturator nodes in melanoma: survival and prognostic factors. *Ann Surg Oncol* 1999; **6**:255–62.

101 O'Brien CJ, Coates AS, Petersen-Schaefer K *et al.* Experience with 998 cutaneous melanomas of the head and neck over 30 years. *Am J Surg* 1991; **162**:310–14.

102 Turkula LD, Woods J. Limited or selective nodal dissection for malignant melanoma of the head and neck. *Am J Surg* 1984; **148**:446–8.

103 Hill S, Thomas JM. Use of the carbon dioxide laser to manage cutaneous metastases from malignant melanoma. *Br J Surg* 1996; **83**:509–12.

104 Thompson JF, Kam PC. Current status of isolated limb infusion with mild hyperthermia for melanoma. *Int J Hyperthermia* 2008; **24**:219–25.

105 Beasley GM, Petersen RP, Yoo J *et al.* Isolated limb infusion of intransit malignant melanoma of the extremity: a well-tolerated but less effective alternative to hyperthermic isolated limb perfusion. *Ann Surg Oncol* 2008; **15**:2195–205.

106 Cornett WR, McCall LM, Petersen RP *et al.* Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. *J Clin Oncol* 2006; **24**:4196–201.

107 Veronesi U, Adamus J, Aubert C *et al.* A randomised trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982; **307**:913–16.
108 Koops HS, Vaglini M, Suciu S *et al.* Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. *J Clin Oncol* 1998; **16**:2906–12.
109 Wheatley K, Ives N, Eggermont A *et al.* Adjuvant therapy for melanoma: an individual patient meta-analysis of randomised trials. *J Clin Oncol* 2007; **25**:8526.
110 Henderson MA, Burmeister B, Thompson JF *et al.* Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: results of an intergroup randomized trial. *J Clin Oncol* 2009; **27** (Suppl.): 18 (Abstract LBA9084).
111 Chang P, Knapper WH. Metastatic melanoma of unknown primary. *Cancer* 1982; **49**:1106–11.
112 Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. *J Clin Oncol* 2008; **26**:535–41.
113 Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival for stage IV melanoma from an unknown primary site. *J Clin Oncol* 2009; **27**:3489–95.
114 Patchell RA, Tibbs PA, Walsh JW *et al.* A randomised trial of surgery in the treatment of single metastases of the brain. *N Engl J Med* 1990; **322**:494–500.
115 Miller JD. Surgical excision for single cerebral metastasis? *Lancet* 1993; **341**:1566.
116 Sondak V, Liu P, Warneke J *et al.* Surgical resection for stage IV melanoma: a Southwest Oncology Group Trial (S9430). *J Clin Oncol* 2006; **24** (Suppl.): 8019 (Abstract).
117 Overett TK, Shiu MH. Surgical treatment of distant metastatic melanoma. Indications and results. *Cancer* 1985; **56**: 1222–30.
118 Meyer T, Merkel S, Goehl J, Hohenberger W. Surgical therapy for distant metastases of malignant melanoma. *Cancer* 2000; **89**:1983–91.
119 Essner R, Lee JH, Wanek LA *et al.* Contemporary surgical treatment of advanced-stage melanoma. *Arch Surg* 2004; **139**:961–7.
120 Middleton MR, Grob JJ, Aaronson N *et al.* Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; **18**:158–66.
121 Patel P, Suciu S, Mortier L *et al.* Extended schedule escalated dose temozolomide versus dacarbazine in stage IV malignant melanoma; final results of the randomised phase 3 study (EORTC 18032). *Ann Oncol* 2009; **19** (Suppl. 8):viii3.
122 Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. *J Clin Oncol* 2007; **25**:5426–34.
123 Tarhini AA, Kirkwood JM, Gooding WE *et al.* Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. *J Clin Oncol* 2007; **25**:3802–7.
124 Zacest AC, Besser M, Stevens G *et al.* Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. *J Neurosurg* 2002; **96**:552–8.
125 Mori Y, Kondziolka D, Flickinger JC *et al.* Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys* 1998; **42**:581–9.
126 Selek U, Chang E, Hassenbusch SJ III *et al.* Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys* 2004; **59**:1097–106.
127 Lens MB, Rosdahl I, Ahlbom A *et al.* Effect of pregnancy on survival in women with cutaneous malignant melanoma. *J Clin Oncol* 2004; **22**:4369–75.
128 O'Meara AT, Cress R, Xing G *et al.* Malignant melanoma in pregnancy. A population-based evaluation. *Cancer* 2005; **103**: 1217–26.
129 Daryanani D, Plukker JT, De Hullu JA *et al.* Pregnancy and early-stage melanoma. *Cancer* 2003; **97**:2248–53.
130 Naldi L, Altieri A, Imberti GL *et al.* Oncology study group of the Italian Group for Epidemiologic Research in Dermatology (GISED). Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case–control study from Italy. *Ann Epidemiol* 2005; **15**:545–50.
131 Karagas MR, Stukel TA, Dykes J *et al.* A pooled analysis of 10 case–control studies of melanoma and oral contraceptive use. *Br J Cancer* 2002; **86**:1085–92.
132 Lea CS, Holly EA, Hartge P *et al.* Reproductive risk factors for cutaneous melanoma in women: a case–control study. *Am J Epidemiol* 2007; **165**:505–13.
133 MacKie RM, Bray CA. Hormone replacement therapy after surgery for stage I or II cutaneous melanoma. *Br J Cancer* 2004; **90**:770–2.
134 Siple J, Schneider D, Wanlass W *et al.* Levodopa therapy and risk of malignant melanoma. *Ann Pharmacother* 2000; **34**:382–5.
135 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum* 2007; **56**:2886–95.
136 NHS Blood and Transplant. *Organ Donation: How to Become a Donor*. Available at: http://www.organdonation.nhs.uk/ukt/how_to_become_a_donor/how_to_become_a_donor.jsp (last accessed 25 May 2010).
137 Cornish D, Holterhues C, van der Poll-Franse L *et al.* A systematic review of health-related quality of life in cutaneous melanoma. *Ann Oncol* 2009; **20** (Suppl. 6):51–8.
138 Sollner W, Zschocke I, Augustin M. Melanoma patients: psychosocial stress, coping with illness and social support. A systematic review. *Psychother Psychosom Med Psychol* 1998; **48**:338–48.
139 Francken AB, Bastiannet E, Hoekstra HJ. Follow up in patients with localized primary melanoma. *Lancet Oncol* 2005; **6**:608–21.
140 Hofmann U, Szedlak M, Ritgen W *et al.* Primary staging and follow up in melanoma patients – monocenter evaluation of methods, costs and patient survival. *Br J Cancer* 2002; **87**: 151–7.
141 Garbe C, Hauschild A, Volkenandt M *et al.* Evidence and interdisciplinary consensus-based German guidelines: diagnosis and surveillance of melanoma. *Melanoma Res* 2007; **17**:393–9.
142 Balfounta ML, Beauchet A, Chagnon S *et al.* Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. *Lancet Oncol* 2004; **5**:673–80.
143 Einwachter-Thompson J, MacKie RM. An evidence base for reconsidering current follow-up guidelines for patients with cutaneous melanoma less than 0.5 mm thick at diagnosis. *Br J Dermatol* 2008; **159**:337–41.

Summary of 2010 guidelines for management of melanoma

(See full manuscript for details of evidence and recommendation gradings)

Melanoma patients who must be referred from the Local Skin Cancer Multidisciplinary Team to the Specialist Skin Cancer Multidisciplinary Team

- Patients with stage IB or higher primary melanoma when sentinel lymph node biopsy (SLNB) is available within their Network. In the absence of SLNB then patients with stage IIB or higher should be referred to the Specialist Skin Cancer Multidisciplinary Team
- Patients with melanoma stage I or above who are eligible for clinical trials that have been approved at Cancer Network level
- Patients with melanoma managed by other site specialist teams, e.g. gynaecological, mucosal and head and neck (excluding ocular)
- Patients with multiple primary melanomas
- Children younger than 19 years with melanoma
- Any patient with metastatic melanoma diagnosed at presentation or on follow up
- Patients with giant congenital naevi where there is suspicion of malignant transformation
- Patients with skin lesions of uncertain malignant potential

Recommendations for Local Skin Cancer Multidisciplinary Team record keeping of clinical features

See National Institute for Health and Clinical Excellence *Improving Outcomes for People with Skin Tumours including Melanoma*, February 2006. Available at: http://www.nice.org.uk/nicemedia/live/10901/28906/28906.pdf

Recommendations for screening and surveillance of high-risk individuals

- Patients who are at moderately increased risk of melanoma should be advised of this and taught how to self-examine. This includes patients with atypical mole phenotype, those with a previous melanoma, and organ transplant recipients
- Patients with giant congenital pigmented naevi are at increased risk of melanoma and require long-term follow up
- The prophylactic excision of small congenital naevi is not recommended
- Individuals with a family history of three or more cases of melanoma should be referred to a clinical geneticist or specialized dermatology services for counselling. Those with two cases in the family may also benefit, especially if one of the cases had multiple primary melanomas or the atypical mole syndrome

Requirements for microscopy of melanoma

Essential

- Ulceration
- Histological subtype
- Thickness
- Margins of excision
- Mitotic count
- Pathological staging

Desirable

- Level of dermal invasion
- Tumour-infiltrating lymphocytes
- Perineural invasion
- Growth phase
- Lymphatic or vascular invasion
- Microsatellites
- Regression

Surgical wider excision margins for primary melanoma

Breslow thickness	Lateral excision margins to muscle or muscle fascia
In situ	5-mm margins to achieve complete histological excision
< 1 mm	1 cm
1·01–2 mm	1–2 cm
2·1–4 mm	2–3 cm
> 4 mm	3 cm

Staging investigations for melanoma

- Patients with stage I, II and IIIA melanoma should not routinely be staged by imaging or other methods as the true-positive pick-up rate is low and the false-positive rate is high
- Patients with stage IIIB or IIIC melanoma should be imaged by computed tomography prior to surgery and with Specialist Skin Cancer Multidisciplinary Team (SSMDT) review
- Patients with stage IV melanoma should be imaged according to clinical need and SSMDT review; lactate dehydrogenase should also be measured

Recommendations for the management of clinically node-negative patients

- There is no role for elective lymph node dissection
- Sentinel lymph node biopsy (SLNB) can be considered in stage IB melanoma and upwards in Specialist Skin Cancer Multidisciplinary Teams
- SLNB is a staging procedure with no proven therapeutic value
- Surgical risks of SLNB, and of a false-negative result, should also be explained

Recommendations for locoregional recurrent melanoma

- All patients should be managed by Specialist Skin Cancer Multidisciplinary Teams
- Nodes clinically suspicious for melanoma should be sampled using fine needle aspiration cytology (FNAC) prior to carrying out formal block dissection. If FNAC is negative although lymphocytes were seen, a core or open biopsy should be performed if suspicion remains
- Prior to formal dissection, performed by an expert, staging by computed tomographic scan should be carried out other than where this would mean undue delay
- The treatment of locoregional limb recurrence is palliative and, depending on extent and response, includes excision or CO_2 laser, isolated limb infusion or perfusion

Recommendations for metastatic disease

- All patients should be managed by Specialist Skin Cancer Multidisciplinary Teams
- Surgery should be considered for oligometastatic disease at sites such as the skin, brain or gut, or to prevent pain or ulceration
- Radiotherapy may have a palliative role in the treatment of metastases
- Standard chemotherapy is dacarbazine although its role is palliative
- Patients with stage IV melanoma should be considered for entry to clinical trials

Pregnancy, oral contraceptives and hormone replacement therapy

Pregnancy in melanoma	Oral contraceptives	Hormone replacement therapy
• No worsening of prognosis • No increase in adverse outcomes for mother or baby • Placental metastases possible in stage IV disease	• No increased risk of melanoma	• No increased risk of melanoma • No worsening of prognosis

Follow up of melanoma patients

- Patients with *in situ* melanomas do not require follow up
- Patients with stage IA melanoma should be seen two to four times over up to 12 months, then discharged
- Patients with stage IB–IIIA melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years
- Patients with stage IIIB and IIIC and resected stage IV melanoma should be seen 3-monthly for 3 years, 6-monthly to 5 years, then annually to 10 years
- Patients with unresectable stage IV melanoma are seen according to need

Appendix 1

Definition of the levels of evidence used in preparation of these guidelines

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials, or meta-analysis of epidemiological studies
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
Grade of recommendation	
A	There is good evidence to support the use of the procedure
B	There is fair evidence to support the use of the procedure
C	There is poor evidence to support the use of the procedure
D	There is fair evidence to support the rejection of the use of the procedure
E	There is good evidence to support the rejection of the use of the procedure