

Management of Cutaneous Melanoma

Clinical Guidelines



Royal College of Surgeons in Ireland
February 2006



Clinical Guidelines Committee

Royal College of Surgeons in Ireland

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Contents

Foreword	2
Grading of Evidence and Recommendations	3
Introduction	4
Risk Factors for and Prevention of Melanoma	5
Diagnosis of Melanoma	6
Definitive Surgical Management of the Primary	7
Histopathology	8
Regional Lymph Node Management	9
Clinically negative nodes	9
Regional lymphadenectomy	9
Investigations for Patients with Melanoma	10
TNM Staging System for Melanoma	11
Prognosis by Stage	12
Systemic Therapy	13
Follow-up of Patients after Treatment for Melanoma	14
References	15

Foreword

Cutaneous melanoma remains a frustrating disease for clinicians and, more especially, patients when it presents as anything other than its earliest form. Furthermore, the management of the condition, is undermined by a fractionated approach to the disease in most centres throughout the country. The development of streamlined referral systems to dedicated, specialised units is also made difficult by the tendency of this cancer to present to (and be managed by) a variety of medical practitioners at both primary and secondary levels of care. These factors combine to hinder effective audit for the development of national statistics as well as the recruitment, in meaningful numbers, of those with advanced stage disease into clinical trials. In addition to trying to provide concise, evidence-supported recommendations on the management of melanoma, it is hoped that this document may prompt its audience to consider how best this disease may be approached and targeted at both supraregional and national levels.

These guidelines aim to simplify a large body of evidence into practical and manageable recommendations. They are not intended to be construed or to serve as the standard of medical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and as patterns of care evolve. Clinicians involved in the treatment of melanoma are however encouraged to use these guidelines in the development of their patient care pathways and local protocols.

Guidelines Committee
R.C.S.I.

February 2006

Acknowledgement: The Guidelines Committee wishes to express its appreciation to Mr Karl Sweeney for his considerable endeavour in collating the literature base for these guidelines and in the composition of this document. Additionally, we are grateful to the Scottish Intercollegiate Guideline Network (SIGN) for allowing the use of their National Clinical Guidelines on Cutaneous Melanoma to act as a template for adaptation.

Grading of Evidence and Recommendations

GRADING OF EVIDENCE

The levels of evidence are taken from the US Agency for Health Care Policy and Research and are set out below.

- Ia: Evidence obtained from meta-analysis or systematic review of randomised controlled trials (RCTs)
- Ib: Evidence obtained from at least one RCT
- IIa: Evidence obtained from at least one well-designed control or cohort study
- IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study
- III: Evidence obtained from well-designed non-experimental 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

GRADING OF RECOMMENDATIONS

The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A: There is good evidence (level Ia or Ib evidence) to support the recommendation
- B: There is fair evidence (level IIa, IIb, III evidence or extrapolated evidence from level Ia or Ib studies) to support the recommendation
- C: There is poor evidence (level IV evidence or extrapolated evidence from level IIa, IIb, III studies) to support the recommendation

Letters or numerals in the text indicate the grade of recommendation depending on the level of evidence.

Introduction

The incidence of cutaneous melanoma in Ireland has risen by 3% between 1997 and 2001 (*National Cancer Registry Ireland 2005*) with an average of 401 reported cases per year. Cutaneous melanoma accounts for 2% of all new invasive cancer cases in Ireland and 1% of all cancer deaths annually (n= 64). There is a higher incidence in women (female:male ratio 249:153) and the average age of presentation is 50 years. Melanoma occurs primarily in white people and the two major aetiological risk factors are sun sensitivity and exposure to ultraviolet radiation (primarily sun exposure) (*Gandini S et al 2005*).

Level I evidence: The outcome from melanoma depends on the stage at presentation. Patients with early stage disease (i.e. <1.0mm thick) achieve long-term survival in more than 90% of cases (*Greene FL et al 2002*). For patients with melanomas greater than 1.0mm thickness, survival rates range from 90% to 50%. Long-term survival in patients with visceral metastases is less than 10%.

The importance of early detection and appropriate management of melanoma cannot be over-emphasised as this is a condition which often affects patients at a young age and one that is clinically detectable at an early stage when it is potentially curable but that is relatively resistant to current therapeutic strategies in its later stages.

Risk Factors and Prevention of Melanoma

RISK FACTORS

Level 1a evidence: Solar radiation, particularly intermittent unaccustomed exposure causing sunburn, is a principle cause of melanoma (*Gandini S et al 2005*). Sunburn is mainly due to UVB (280-320nm) radiation; however there is accumulating evidence for the role of UVA (and sun beds) in the pathogenesis of melanoma (*Wang SQ et al 2001*).

A previous history of melanoma is also a significant risk factor for developing further melanoma (in addition to recurrence) (*Goggins WB et al 2003*). The risk of melanoma also increases with the number of benign naevi (common moles) on a person (*Ferrone CR et al 2005*). Actinic lentiginos are flat, brown skin lesions associated with chronic sun exposure which have no direct malignant potential but are a risk factor for developing melanoma (*Garbe C et al 1994*). Giant congenital melanotic naevi ≥ 20 cm in diameter have a very high relative risk for extracutaneous and cutaneous melanoma.

There is a familial association with an increased risk if a first degree relative (parent, sibling or child) has developed melanoma (*Florrell Sr et al 2005*). Affluence, advancing age and female sex are further risk factors for melanoma as are red or light coloured hair, skin that does not tan easily, light coloured eyes and light coloured skin (*Gandini S et al 2005*).

PREVENTION

Individuals identified as being at higher risk should be advised about appropriate methods of sun avoidance and protection. They should also be educated about the diagnostic features of cutaneous melanoma and encouraged to perform self-examination of their skin. There is currently no appropriate genetic test for familial melanoma so this should not be recommended in a routine clinical setting. Photography may be a useful adjunct to detecting early melanoma in high-risk groups. The prophylactic excision of small congenital naevi is not recommended (*Kroon BB et al 1999*).

Grade B recommendation: Sun avoidance and the use of clothing and hats for sun-protection are recommended (*Bauer J et al 2005*). White-skinned individuals should limit their total cumulative sun exposure through life. Sun-beds, tanning booths and tanning lamps should be avoided although a recent large case control study failed to demonstrate an association with melanoma risk (*Bataille V et al 2005*). Sunscreens with a minimum sun protection factor (SP) of 15 may be used as an adjunct to other measures, provided this does not lead to increased time spent in the sun. There is no evidence that sunscreen use is itself associated with development of melanoma (*Dennis LK et al 2003*).

Diagnosis of Melanoma

DIAGNOSIS

Rapid access from primary to tertiary services for the diagnosis and management of melanoma is important. It is recommended that specialists with an interest in pigmented lesions should consult patients with suspicious lesions within 4 weeks of receipt of the referral letter. All patients who have had lesions removed by non-specialist medical practitioners that are subsequently reported as melanoma should be referred to a specialist.

Level 1b evidence: Suspicious pigmented lesions are best examined in a good light with or without magnification and should be assessed using the 7 point checklist or the ABCDE system (Table below) (*Whited JD et al 1998*). Lesions with any of the major features or three minor ones of the 7 point checklist or any of the features of the ABCDE system warrant referral to an appropriately trained specialist (some melanoma however do not demonstrate any major feature while 10% are amelanotic).

BIOPSY OF SUSPECTED MELANOMA

In concordance with the National Comprehensive Cancer Network guidelines (NCCN, 2005), excision of a lesion suspected (but not known) to be melanoma should be performed as a full-thickness excision biopsy to include the whole lesion with a 1-3 mm clinical margin of normal skin and subdermal fat. The biopsy should be planned with definitive treatment in mind (i.e. longitudinal orientation in the extremities and narrow margins to avoid interference with subsequent lymphatic mapping). Shave and punch biopsies are not recommended (because pathological staging of lesions on these biopsies is impossible). Incisional biopsy of the thickest portion of a lesion is occasionally acceptable in certain anatomic areas (e.g. palm/sole, digit, face, ear, subungal) or for very large lesions. There is little evidence that incisional biopsies of melanoma affect overall prognosis (*Lederman JS et al 1985, Lee JH et al 1991, Austin JR et al 1996*).

Clinical Diagnosis of Melanoma

Seven point checklist:	The ABCDE lesion system:
<i>Major features are:</i>	
Change in size	A Geometrical <u>A</u> symmetry in 2 axes
Irregular shape	B Irregular <u>B</u> order
Irregular colour	C At least 2 different <u>C</u> olours in lesion
<i>Minor features are:</i>	D Maximum <u>D</u> iameter >6mm
Largest diameter 7 mm or more	E <u>E</u> levation of lesion
Inflammation	
Oozing	
Itch/change in sensation	

Definitive Surgical Management of the Primary

Ideally, patients with stage II or more advanced melanoma should be managed in a cancer centre by a skin cancer multidisciplinary team. This team should include a dermatologist, surgeon, medical oncologist, pathologist, radiologist, counsellor, specialist nurse and palliative care specialist.

Level 1a evidence: Following histological confirmation of melanoma on excision biopsy, patients should undergo excision of scar with adequate margin of macroscopically normal skin. Margin diameter is based on Breslow thickness of the tumour on excision biopsy and is measured at the time of excision (*Haigh PI et al 2003*). In selected cases, margins may be modified to accommodate individual anatomic or cosmetic considerations.

In-transit Melanoma

For those with a small number of in-transit metastases, excision with histologically negative margins is acceptable for local control, however the effect on outcome is unknown (*Hayes AJ et al 2004*). If the lesions are not amenable to excision with negative margins, intradermal injection with Bacillus Calmette-Guérin (BCG), interferon alpha or CO₂ laser ablation may be appropriate, however, this is not based on published, strong scientific evidence. Other standard options for patients with irresectable in-transit disease are regional treatment with hyperthermic isolated limb perfusion (or infusion) with melphalan or localised radiotherapy.

Level 1b evidence: Prophylactic isolated limb perfusion with melphalan is not useful for those with high risk primary limb melanoma but no actual residual disease.

Margins	
Tis	Histologically confirmed excision is adequate
T1	10mm margin is recommended to achieve complete histological excision (<i>Veronesi U et al 1988</i>)
T2	10-20mm margin is recommended (<i>Cohn-Cedarmark G et al 2000</i>)
T3 & T4	20mm margin is recommended (<i>Thomas JM et al 2004</i>)
Grade A Recommendations	

Histopathology

Pathology request forms must be accurately completed and give full identification details. The biopsy type (excision, incision etc.), site and size of lesion and macroscopically normal margin size should be included in the request. The whole lesion should be adequately sampled, probably by serial transverse slicing of the biopsy at approximately 2-3mm intervals, processing all of the slices and examining sections cut at three levels.

The pathologist's report should include the following minimum data:

- Breslow thickness (mm), measured from the granular layer of the epidermis to the base of the tumour, to the nearest 0.1 mm
- Histological ulceration (measured from the base of the ulcer to the base of the tumour)
- Peripheral and deep margin status of specimen
- Satellitosis
- Mitotic rate (*Francken AB et al 2004*)

Other data which would be desirable to have stated on the report:

- Location
- Macroscopic and microscopic size of lesion
- Macroscopic appearance of lesion
- Whether the lesion is primary, recurrent or metastatic to biopsy site
- Clarke level (especially if lesion <1 mm)
- Evidence of regression
- Presence of tumour infiltrating lymphocytes (TIL)
- Vertical growth phase (VGP)
- Angiolymphatic or perineural invasion
- Histological subtype

According to the Irish National Cancer Registry report on melanoma 1997, most melanomas are described as either 'unspecified (26%), Hutchinson's freckle/Lentigo maligna melanoma (27%), superficial spreading (20%) or nodular melanoma (11%). There was a high incidence of in-situ cancers (34.6%) and this seems to be increasing with time.

Lentigo maligna 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. In the very elderly, the risk of progression of the melanoma may be unlikely within their lifespan and treatment by other methods such as radiotherapy, cryotherapy or observation only may be appropriate.

Regional Lymph Node Management

The presence of regional lymph node metastatic disease is a significant predictor of outcome in melanomas as it is associated with a 50% reduction in survival compared to that of patients without nodal involvement. In a recent large single centre study the presence of metastatic disease in a sentinel lymph node decreased melanoma specific survival from 90% to 56% (*Yee VS et al 2005*). The risk of developing lymph node metastases increases with the thickness of the primary melanoma. Melanomas <1mm rarely metastasise while at least 25% of melanomas 1.5-4.0mm and >60% of melanomas >4.0mm thick will have lymph node metastases at presentation (*Balch CM et al 2001*).

Patients with melanoma present with either a clinically normal regional lymph node basin or palpable lymphadenopathy:

Clinically Negative Lymph Nodes

Level 1a evidence: Routine elective lymph node dissection should not be recommended for patients with clinically negative drainage lymph node basins (*Veronesi U et al 1977, Cascinelli N et al 1998, Lens MB et al 2002*).

Level 1b evidence: If the sentinel lymph node technique is available this should be performed on all patients who have melanoma 1.0mm+ thick, have a positive deep margin or adverse histological features such as ulceration, vertical growth phase or extensive regression (*Morton D et al 2005*).

The sentinel node technique may be possible after wide local excision although data on its accuracy is limited (*Evans HL et al 2003*). If sentinel node biopsy is not available, in the absence of trials showing improved survival, wide excision alone may be acceptable, however, patients should be informed of the potential impact of sentinel node biopsy on their staging and this procedure should be made available to patients by appropriate referral. Sentinel nodes should be evaluated with serial sectioning and immunohistochemistry (*Abrahamsen HN et al 2004*). If the sentinel node is negative, regional lymphadenectomy is not indicated. If the sentinel node is found to contain metastatic disease (including micrometastatic deposits or isolated tumour cells), a completion lymphadenectomy should be considered (*Macripo G et al 2004*). The precise value of completion lymphadenectomy,

however, awaits the outcome of current clinical trials (*Lee JH et al 2004, Perrott RE et al 2003*).

Regional Lymphadenectomy

Level IIa evidence: Indications for therapeutic lymph node dissection are a positive sentinel lymph node biopsy or clinically palpable disease.

Fine needle aspiration cytology may be a useful means of confirming that palpable lymphadenopathy is indeed due to metastatic melanoma. A thorough dissection of the involved nodal basin is required to control locoregional disease (*Balch CM et al 1981*). In the groin, elective iliac and obturator lymph node dissection may offer a survival benefit in patients with palpable positive inguinal nodes compared with block dissection of the femoral triangle (*Sterne GD et al 1995, Karakousis CP et al 1995, Strobbe LJ et al 1999*).

Investigations for Patients with Melanoma

Initial staging: No investigations are necessary for patients with stage I or IIa disease (*National Institutes for Health 2002*). The NCCN recommend that patients at intermediate or high risk of recurrent disease (at least stage IIB) should undergo chest X-ray; liver ultrasound or contrast enhanced chest/abdomen/pelvis computed tomographic (CT) scan; liver function tests/lactate dehydrogenase (LDH); and full blood count. There is no place for a bone scan in staging except where symptoms point to possible bone disease.

TNM Staging System for Melanoma

2002 American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma

Primary Tumour (T)

- Tx** Primary tumour cannot be assessed (e.g. shave biopsy or regressed melanoma)
- T0** No evidence of primary tumour
- Tis** Melanoma *in situ*
- T1** Melanoma ≤ 1 mm in thickness
- T1a** Melanoma ≤ 1 mm in thickness, no ulceration
- T1b** Melanoma ≤ 1 mm in thickness, with ulceration
- T2** Melanoma 1.01-2 mm in thickness
- T2a** Melanoma 1.01-2 mm in thickness, no ulceration
- T2b** Melanoma 1.01-2 mm in thickness, with ulceration
- T3** Melanoma 2.01-4 mm in thickness
- T3a** Melanoma 2.01-4 mm in thickness, no ulceration
- T3b** Melanoma 2.01-4 mm in thickness, with ulceration
- T4** Melanoma >4 mm in thickness
- T4a** Melanoma >4 mm in thickness, no ulceration
- T4b** Melanoma >4 mm in thickness, with ulceration

Regional Lymph Nodes (N)

- Nx** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Metastasis in one lymph node
- N1a** Clinically occult (microscopic) metastasis
- N1b** Clinically apparent (macroscopic) metastasis
- N2** Metastases in 2 or 3 regional lymph nodes or intralymphatic regional metastases without nodal metastases
- N2a** Clinically occult (microscopic) metastases
- N2b** Clinically apparent (macroscopic) metastases
- N2c** Satellite or in-transit metastases or satellite(s) with metastases in regional lymph node(s)

Distant Metastasis (M)

- Mx** Distant metastasis cannot be assessed
- M0** No distant metastasis
- M1** Distant metastases
- M1a** Metastasis to skin, subcutaneous tissue or distant lymph nodes
- M1b** Metastasis to lung
- M1c** Metastasis to all other visceral sites or distant metastasis at any site associated with elevated serum lactate dehydrogenase (LDH)

Prognosis by Stage

Melanoma TNM Classification				
Stage	T	N	M	5 year survival rate (%)
Stage 0	Tis	N0	M0	100
Stage Ia	T1a			95.3
Stage Ib	T1b/2a			89-90.9
Stage IIa	T2b/3a			77.4-78.7
Stage IIb	T3b/4a			63-67.4
Stage IIc	T4b			45.1
Stage III	Any T			N1
		N2	63.3-59	
		N3	26.7	
Stage IV		Any N	M1	18.8-9.5

Systemic Therapy

Adjuvant Therapy in Melanoma

Melanoma is relatively resistant to non-surgical treatment. Recent trials have focussed on the use of Interferon $\alpha 2b$ and vaccines. High dose IFN $\alpha 2b$ has been shown to improve disease-free and overall survival in certain studies (*Kirkwood JM et al 2000 and 2001*) but this therapy has considerable toxic effects including acute constitutional symptoms, chronic fatigue, headache, nausea, weight loss, myelosuppression and depression. The modest benefit of high dose therapy in conjunction with its expense and significant side effects precludes consideration of its use except in high risk (stage III) patients. Low dose IFN $\alpha 2b$ has failed to show the same benefits as the high dose trials, however, trials are ongoing. There is no convincing evidence to support the routine use of vaccines in the treatment of melanoma.

Stage IV Disease

The long-term survival of stage IV has not changed significantly in the last 50 years with a median survival of between 8 and 9 months and the 5 year survival is about 2% (*Lee ML et al 2000*). Resection of an isolated visceral metastasis is appropriate in selected patients – although some authors recommend observation for a period of 3 months beforehand to ensure that further metastatic foci do not become apparent (*Barth A et al 1995, Leo F et al 2000*). If the solitary metastasis is irresectable or there are multiple visceral metastases, treatment options (for patients without brain metastases) include:

1. A clinical trial (preferred)
2. Single-agent systemic therapy (i.e. interleukin-2, dacarbazine or temozolomide) (*Middleton MR et al 2000*)
3. Dacarbazine-based combination therapy, chemotherapy, and/or immunotherapy (*Legha SS et al 1996, Eton O et al 2002*)
4. Best supportive care

Follow-up of Patients after Treatment for Melanoma

Patients with melanoma in-situ do not require follow up (Martini L *et al* 1994) whereas all patients with invasive melanoma should be followed up for a period (Poo-Hwu WJ *et al* 1999). The purpose of formal follow-up is to provide counselling, education and reassurance to the patient and to detect recurrent disease and new primary melanomas. The lifetime risk of developing a second primary melanoma is 4-6%. Between 60 and 80% of recurrences are at local and/or regional nodal sites. 80% of all recurrences occur within the first three years but 16% may occur after the first five years and recurrence after more than ten years is well recognised.

Melanoma Thickness	Annual Risk of Recurrence		
	0-5 years	5-10 years	Median recurrence
<1.5mm	<6%	<1%	25-32 months
>1.5mm	7-10%	<2%	12-16 months

However, there is little evidence for the optimum protocol for follow-up. It appears reasonable that all patients with invasive melanoma should be followed up 6-monthly for 2 years. Thereafter, those with melanomas less than 1.0 mm in depth may be discharged from routine follow-up; other patients should be followed up for a further 3 years at 6-monthly intervals. Patients with stage III or IV disease require lifelong follow up.

The following should be examined and details recorded at each follow-up: site of primary and adjacent skin, for local recurrences and local metastatic disease; the draining lymph node basins, for lymphadenopathy; the remaining skin, for any other suspicious pigmented lesion.

Regular radiological imaging is currently not a necessity but clinical photography may be helpful in follow-up, particularly in those with multiple atypical moles.

All patients should be taught self-examination because many recurrences are found by patients themselves at home rather than by clinicians in the clinic and even less frequently by tests (Weiss M *et al* 1995).

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