Therapeutic trends in cutaneous melanoma

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Many advances in the management of melanoma have occurred in the last few years. These make this an exciting time for clinicians and allows them to offer glimmers of hope for patients with this disease. This article looks at the therapeutic aspects of the treatment of cutaneous melanoma.

This article is the continuation of our previous article on cutaneous melanoma (Hall and Javaid, 1998). The first article looked at issues of identification of at-risk patients, public education, and making clinical and differential diagnosis of cutaneous melanoma. This article will consider the different therapeutic aspects including challenges met in the management of the primary lesions, regional lymph nodes and advanced systemic disease.

CONFIRMATION OF CLINICAL DIAGNOSIS

Biopsy

Suspicious lesions should be excised for histological examination. Shave biopsy is to be deplored in suspicious lesions and incision biopsy should only be performed by specialists in certain circumstances (such as in the differential diagnosis of lentigo maligna or in confirming an acral melanoma before excision which is usually radical and may involve amputation). Excision should include the whole lesion with a 2 mm margin laterally and a cuff of fat deeply (*Figure 1*). Those unable to effectively perform such a biopsy and achieve primary closure should ask themselves if they should be doing the procedure at all.

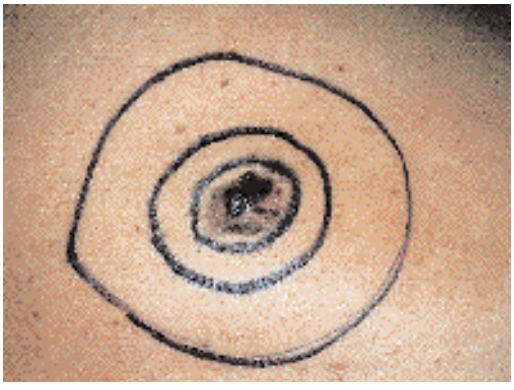

Figure 1. Excision biopsy and definitive excision margins. Histological diagnosis should be performed, where possible on an excision biopsy to include the whole lesion plus a 2 mm margin. The definitive margins depend upon the Breslow thickness.

Histological diagnosis

Specimens of suspicious pigmented lesions must be examined histologically, ideally by a histopathologist with an interest in skin lesions. With increasing pick up of borderline and early lesions, some specialization is needed. Many histopathologists exchange slides and discuss results. A standardized method of reporting has been suggested by the Association of Directors of Anatomic and Surgical Pathology (1997) to help with classification and prognostic information (*Table 1*).

The Breslow thickness (Breslow, 1970) is still the most useful single prognostic indicator and guides clinicians on wider excision margins. It is a measure of the thickness of the invasive component of the tumour in millimetres from the top of the granular layer to the deepest point of invasion (*Figure 2*). There is a recent tendency to refer to radial and vertical growth phase of lesions. Radial growth phase is lateral growth of atypical melanocytes in a basal or suprabasal position. Elder and Murphy (1991) have produced an algorithm based on histological features which appears predict outcome more accurately when features, especially vertical growth phase which is more sinister, are taken into account. These include level of invasion, tumour thickness, tumour cell type, mitotic rate, location of the lesion, ulceration, sex of the patient and infiltrative lymphocyte response at the base of vertical growth phase.

Staging

One of the most important factors influencing treatment of melanoma is the stage of disease at

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the initial presentation (McCarthy and Shaw, 1994). Different staging systems proposed include clinical staging, American Joint Committee on Cancer (AJCC) staging and TNM staging system. Most people now use the AJCC system (*Table 2*).

TABLE 1.
Minimum features for histopathological reporting of malignant melanoma

Is the lesion a primary or secondary?	
Presence or absence of ulceration	
Histogenic type	Nodular
	Superficial spreading
	Lentigo maligna melanoma
	Acral lentiginous melanoma
	Desmoplastic
	Spitz like
	Other unclassifiable
Clark level	
Breslow thickness	
Mitotic rate	
Presence of regressive fibrosis	
Completeness of excision	
Presence of vascular invasion (blood and or lymphatic)	
Presence of microsatellites	
Presence of neurotropism	

From Association of Directors of Anatomic and Surgical Pathology (1997)

TABLE 2.
American Joint Committee on Cancer staging system of malignant melanoma

Stage	Primary tumour (pt)*	Lymph node (N) #	Distant metastasis (M)
IA	pT	N0	M0
IB	pT2	N0	M0
IIA	pT3	N0	M0
IIB	pT4	N0	M0
IIIA	Any pT	N1	M0
IIIB	Any pT	N2	M0
IV	Any pT	Any N	M1
*Primary	Breslow thickness		Clark's level
PTis	Melanoma in situ		I
PT1	Melanoma <0.75 mm		II
PT2	Melanoma 0.76–1.5 mm		III
PT3	Melanoma 1.51–4.0 mm		and/or IV
PT4	Melanoma 4.0 mm and/or satellites within 2 cm of primary		and/or V
# Nodes			
N0	No nodes involved		
N1	No node 3 cm		
N2	Any node 3 cm or in transit metastases		

Stage I and stage II disease is localized to the primary lesion site, stage III disease is affecting the lymphatics and stage IV is distant spread. From Ketcham and Balch (1985)

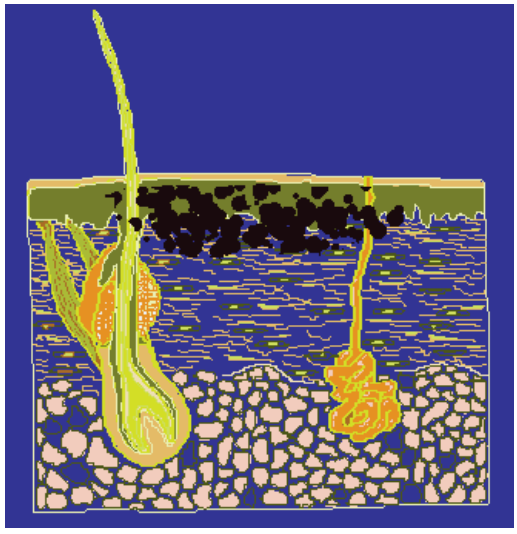

Figure 2. Invasive melanoma. The Breslow thickness is that of the invasive component of the tumour in millimetres form the top of the granular layer to the deepest point of invasion. Tumours which have only just begun to invade the dermis have a good prognosis compared with those invading through the fat.

Management of the primary

Primary melanoma is treated by excision biopsy confirmed histologically. All invasive melanomas should have, where anatomically possible, a minimum excision margin of 1 cm (*Figure 1*). This is supported by the randomized clinical trial of 1 cm *vs* 3 cm excision margins performed by the World Health Organization and reported by Veronesi and Cascinelli (1991) for tumours less than 2 mm in Breslow thickness, and the trial reported by Balch et al (1993) of 2 cm *vs* 4 cm for tumours up to 4 mm Breslow thickness.

It is not known whether excision margins of more than 1 cm for tumours thicker than 2 mm affects prognosis or local recurrence and this question forms the basis of a trial conducted by the Melanoma Study Group and the British Association of Plastic Surgeons. Once this trial is concluded it may be possible to simplify the guidelines for excision recommended in *Table 3*. Generally there is a trend towards narrower margins, often enabling procedures to be performed under local anaesthetic as day cases and avoiding the need for skin grafts. There is no place for excision margins greater than 3 cm now.

A follow-up regimen based on tumour thickness should be arranged for all patients with invasive melanoma. Follow-up should include examination of the scar, draining lymph node basins and a periodic total skin examination to check for further primary lesions (*Figures 3a* and *b*).

Lymph nodes and soft tissue metastases

Removal of the draining lymph nodes at the time of excision of the primary (elective lymph node dissection) is generally not practiced in the UK. The morbidity is great and two prospective randomized trials (Veronesi et al, 1982; Sim et al, 1986) have failed to show a definite advantage. Drepper et al (1993) suggested that elective lymph node dissection for trunk lesions between 1.5 and 4 mm in males may have a survival advantage.

For the majority, therefore, close clinical observation and dissection when clinically palpable nodes are found will be the norm. Fine needle aspiration (FNA) of clinically suspicious nodes is recommended (Rompel et al, 1995). A negative FNA result in a clinically suspicious node should be repeated after a short observation period, e.g. 1 month. Open biopsy is not recommended but if it has to be performed (e.g. after a second negative FNA in a clinically suspicious node) then the incision should be in such a way as to enable en block resection of the scar with the formal block dissection.

Radical lymph node dissections should be performed by those with expertise in the surgery, since Calabro et al (1989) have shown there is a substantial risk of recurrence in the dissected node fields. If secondary deposits are detected clinically, a staging investigation with computed tomography is recommended, and when investigating the iliac nodes, contrast is helpful. When only one or two inguinal nodes are present below the inguinal ligament, a subinguinal node dissection of the femoral triangle is indicated. If there is gross involvement of the subinguinal nodes or the node of Cloquet is involved then some would recommend extended dissection to include the iliac and obturator nodes (Australian Cancer Network, 1997). This is particularly so when considering entering patients into trials of adjuvant treatment since macroscopic disease should first be cleared.

Metastases affecting the soft tissues such as skin or a further lymph node basin should be treated surgically in the first instance to achieve local control. Radiotherapy is not recommended in the first instance.

Sentinel node biopsy

Rivers and Ross (1997) have summarized the position of sentinel node sampling in the management of melanoma. This is the identification of the first draining node (or nodes) in a lymphatic basin initially described by Morton et al (1992a, b) using a patent blue dye and now refined to include radioactive lymphoscintigraphy. Its role in the UK is currently uncertain but is of interest since it may identify the subgroup of patients for whom immediate lymph node dissection (termed selective lymphadenectomy) is worthwhile. Possibly the mere removal of the sentinel node, which seems to be the only affected node in a significant proportion, will have a beneficial effect. Sentinel node biopsy, and methods to detect micro-metastasis in nodes using a polymerase chain reaction for tyrosinase, can be used to accurately stage (or even 'up stage') patients before stratification in adjuvant trials (Wang et al, 1994).

Adjuvant therapy

Patients at high risk of relapse should be considered for adjuvant therapy. High-risk patients are

TABLE 3
Excision margins for primary melanoma

Breslow thickness (mm)	Minimum margin recommended	Maximum margin recommended
Melanoma in situ	0.5 cm	1.0 cm
<1 mm	1.0 cm	1.0 cm
>1 mm<2 mm	1.0 cm	2.0 cm
>2 mm<4 mm	1.0 cm*	2.0 cm*
>4 mm	2.0 cm*	3.0 cm*

*Lesions >2 mm can be entered into the Melanoma Study Group/British Association of Plastic Surgeons trial comparing 1 cm *vs* 3 cm margins (randomization telephone no: 0181 643 7150)

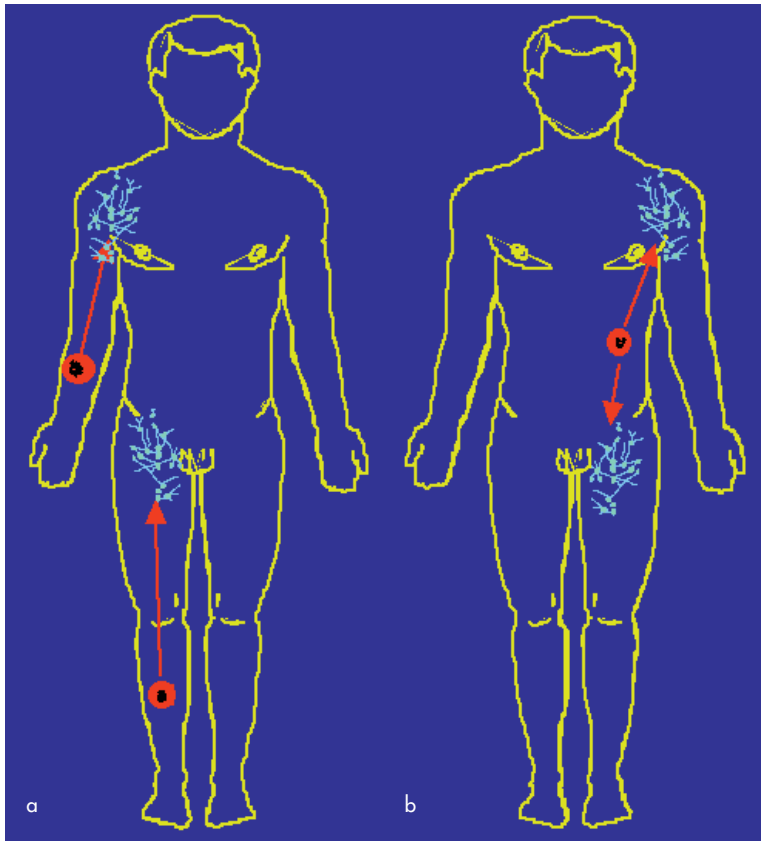

Figure 3. Patterns of lymph node drainage. a. Limb lesions. Drainage of these is usually a fairly ordered event. b. Trunk lesions. Drainage can be more variable, so care must be taken to examine all possible nodal basins when reviewing these patients.

those with a primary tumours >4 mm thick or those with resectable positive locoregional lymph nodes. These patients have around a 50% chance of developing recurrent disease within 2 years of surgery.

There is no standard adjuvant systemic therapy today. In the USA, following publication of the Eastern Cooperative Oncology group trial EST 1684 by Kirkwood et al (1996), the 'Kirkwood' regimen of interferon alpha-2b is regarded as standard adjuvant therapy. This study showed a significant prolongation of disease free survival (1.7 years *vs* 1.0 years) and overall survival (3.8 years *vs* 2.8 years). Five-year survival was 47% in those treated with interferon compared with 31% in controls. The data are mature, with follow-up of 6.9 years.

de Takats et al (1998) explain that, should a further study from the Eastern Cooperative Oncology Group (EST 1690) be confirmatory, then it is expected that in the UK the Kirkwood regimen will also be regarded as standard adjuvant therapy for high-risk patients. However, in view of the cost and toxicity of this schedule, some caution is required before recommending this treatment to all-comers. Currently in the UK, although interferon is licensed for adjuvant use, it is not funded routinely. Specialist oncologists would advise that, where possible, patients should be entered into ongoing randomized trials of adjuvant therapy (*Table 4*).

Immunotherapy

There has been considerable interest in immune modulations of melanoma for several decades. To date in controlled trials, the response rates for patients with advanced disease treated with immunotherapeutic modalities do not exceed those of chemotherapy. However, occasional prolonged remissions occur. Morton (1997) has claimed prolongation of median survival (by 36 months) and 5-year survival (by 42%) in those who responded to his polyvalent melanoma cell vaccine by a demonstrable cellular immune response. Multicentre, randomized trials of such relatively non-toxic tumour vaccines are currently getting underway in patients with both high and intermediate risk of disease recurrence.

METASTATIC DISEASE

The outlook of patients with advanced melanoma is extremely poor (*Figures 4* and *5*), with an average life expectancy of around 6 months. Single agent dacarbazine is used as standard chemotherapy, but response rates are at

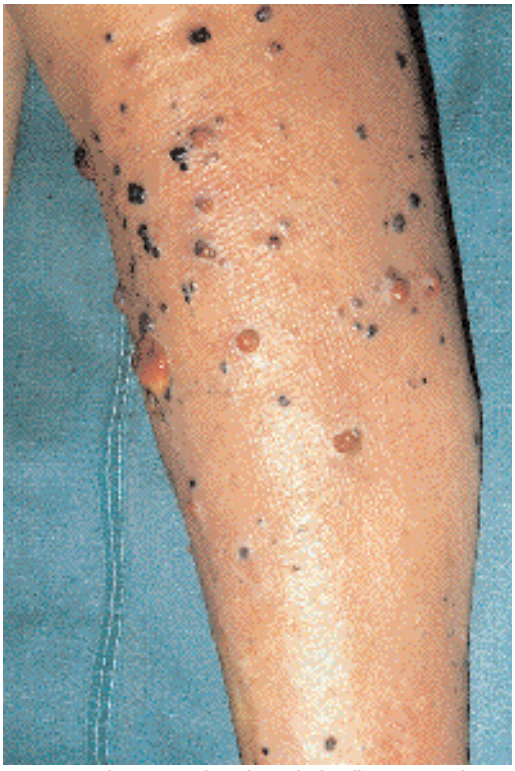

Figure 4. Melanoma involving lower limb. All conventional treatment modalities including chemotherapy, radiotherapy, laser therapy and isolated limb perfusion failed. Limb amputation for palliation was required.

TABLE 4.
Trials of adjuvant interferon currently available to UK patients

Trial	Coordinated by	Randomization/regimen	Type of interferon
AIM HIGH	UKCCCR	2-way randomization (50% chance of receiving interferon)	IFN α2a
		3MU three times per week subcutaneously for 2 years *vs* observation	
EORTC #18952	EORTC Melanoma Cooperative Group Enquiries EORTC Data Centre +32-2-7741600	3-way randomization (80% chance of receiving interferon)	IFN α2b
		Arm A — Induction 10MU subcutaneously days 1–5 for 4/52 then 10MU subcutaneously three times per week for 1 year	
		Arm B — Induction 10MU subcutaneously days 1–5 for 4/52 then 5MU subcutaneously three times per week for 2 years	
		Arm C — Observation	

AIM HIGH = Adjuvant Interferon in Melanoma HIGH risk; EORTC = European Organisation for Research and Treatment of Cancer; UKCCCR = UK Coordinating Committee on Cancer Research

best around 20%. Fit, motivated patients should therefore be considered for clinical trials of novel treatment if available. Metastatic disease is best managed by a multidisciplinary team to include surgeon, oncologist, radiotherapist, counsellor and palliative care specialists and quality of life is the highest priority. Surgical removal of amenable deposits may be appropriate (e.g. local recurrence, single brain metastases and possibly resectable single liver metastases).

Radiotherapy to bone, brain and skin metastases can provide symptomatic control but should be used with caution. Isolated limb perfusion should be considered in uncontrolled local disease but should only be undertaken in specialist centres. Carbon dioxide laser ablation can be very effective at providing local disease control (Waters et al, 1991).

CONCLUSIONS

Surgical management of the primary lesion is becoming less radical. On the horizon are exciting developments in selecting those lymph nodes which may contain disease (sentinel node mapping) and new adjuvant treatments of biological and vaccine therapies. Suddenly things are beginning to happen to improve the outcome for patients with this disease which has previously been considered extremely dismal. In the UK we should be entering our patients into national and local trials to properly evaluate the efficacy (and cost) of such novel therapeutic interventions. HM

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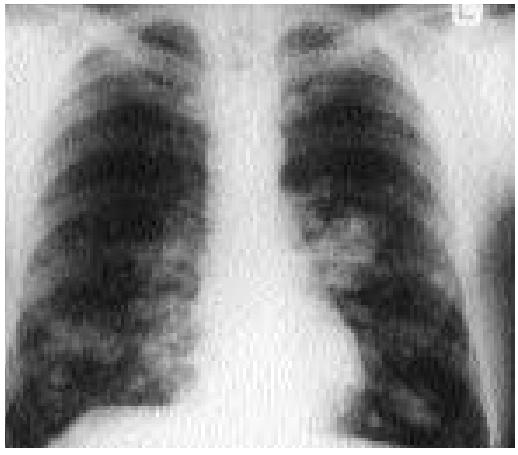

Figure 5. Chest X-ray of extensive lung metastasis from malignant melanoma. A 52-year-old gentleman with a history of primary melanoma removed 3 years previously from his anterior chest wall (Breslow thickness 4.5 mm) presented to his GP with a 3-month history of loss of appetite, weight loss and persistent dry cough.

KEY POINTS

- Suspicious lesions should be excised and submitted for histological evaluation.
- Surgical margins should be based on evidence and be clearly recorded.
- Histological reports should include a minimum data set.
- Adjuvant therapy should be considered for those at high risk of relapse
- Follow-up should include examination of the scar, draining lymph node basins and a periodic total skin examination to check for further primary lesions.
- Metastatic disease should be managed by a multidisciplinary team.