MALIGNANT MELANOMA
INCIDENCE, DIAGNOSIS AND TREATMENT

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The incidence of malignant melanoma (MM) is steadily increasing world-wide with figures indicating that it has doubled in incidence over a period of 10 years. Despite this, no individual general practitioner (unless working in a specialised centre) has great experience in diagnosing these lesions at earlier stages when the disease, if properly recognised and excised, has a cure rate of close to 100%. Therefore it has become imperative that all doctors should be aware of the clinical features of malignant melanoma, treatment options and prevention.

INCIDENCE, AGE AND RISKS

Cutaneous melanoma is usually visible and therefore, readily detectable and is most common in adults (average age of presentation is in the late 40’s). In some parts of the world (Northern Europe) more females develop melanoma, but in other high incidence countries such as Australia and the USA the sexual distribution is similar.

A detailed patient’s history is of importance and several factors should be investigated, such as:

1. Personal or family history of MM.
2. Personal or family history of atypical moles or dysplastic naevi syndrome.
3. Personal history of multiple episodes of sunburn during childhood and adolescence.
4. Presence of fair skin (that “burns” but does not tan), light eye and hair pigmentation.
5. Changes in colour, shape, size and other characteristics of a skin lesion.

As far as phenotypic characteristics are concerned, MM is a problem of the white skinned population, but in the black skinned population, MM appears on the soles of the feet and on the nail bed.

The aetiology of MM is closely related to ultraviolet exposure, although the exact relationship is difficult to ascertain.

CLINICAL DIAGNOSIS AND APPEARANCE

Clinical appearance

The clinical appearance of MM varies and melanomas are usually divided into 4 categories:

a. Superficial spreading melanoma
b. Lentigo maligna melanoma
c. Acral lentiginous melanoma
d. Nodular melanoma
The superficial spreading is the most common MM (60-75% of all diagnosed MM). It can occur at any site, but is most common on the trunk of men and the lower extremities of women (Fig 1).

Lentigo maligna, often called Hutchinson’s melanotic freckle, is a flat irregular pigmented lesion that usually appears on the face of middle-aged and elderly patients (Fig 2).

Acral lentiginous malignant melanoma is often found on the palm, soles and subungual surfaces, being the most common type to appear in Blacks and Asians, but only accounts for 5% of all melanomas in the White population (Fig 3).

Nodular malignant melanoma is the second most common, with an incidence of 15%. Men are more affected than women and the most common locations are the head, neck and trunk (Fig 4).

In addition, there are other variants (less common) such as the desmoplastic and neurotropic variants.

Once a MM is suspected, 2 important checklists may help in the proper diagnosis. (See Tables I and II)

Also the area around the suspected lesion should be checked for possible satelite lesions, as well as the lymphatic basins for possible enlarged lymph nodes.

**HISTOLOGIC EXAMINATION**

A biopsy is indicated for suspected lesions and only 2 techniques should be recommended.

1. Elliptical excision (saucerisation) for small lesions. (This is a modification of the shave excision technique) and
2. Full thickness incisional biopsy when the lesion is too large for complete excision (or anatomically located where a total excision is not desirable or possible).

These biopsies are the first stage of a two-stage surgical procedure if, in fact, the clinical diagnosis of MM is pathologically confirmed. The second stage will comprise a wider local excision to the fascia with margins dependent on tumour thickness and other variables.

**STAGING**

The American Joint Committee on Cancer (AJCC) staging system is based on the UICC TNM (tumour, node, metastasis) classification. (See Table III)
The Primary tumour categories in the TNM classification are based on 2 microstaging systems which are both of extreme importance.

1. Clark system – describes the level of microinvasion through the layers of the dermis. (See Fig 5 and Table IV)
2. Breslow thickness – which is considered the most important diagnostic factor for primary melanoma. (See Fig 6)

The thickness is measured in millimetres from the granular cell layer to the base of the lesion and is divided into 4 groups:
<0.75 mm; 0.75-1.50 mm; > 1.50-4 mm and > 4 mm.

The 5-year survival rate decreases steadily as tumour thickness increases.

To advise patients on the likely outcome of their primary melanoma management, the following estimates may be given for 10-year survival rates from the South Australian Cancer Registry, 1996.

- Melanoma in situ-100%
- Melanoma ≤ 0.75 mm thick – 97.9%
- Melanoma > 0.75 mm – 1.5 mm thick – 90.7%
- Melanoma > 1.5 mm – 3.0 mm thick – 75.4%
- Melanoma > 3.0 mm thick – 55.0%

A new classification will become standard in the year 2002. This classification, which took 3 years to develop, was possible after identifying and evaluating the findings of more than 17 000 patients with MM.

The results of this analysis showed that tumour thickness and ulceration are the most powerful predictors for survival, therefore ulceration was incorporated as a poorer prognostic subgroup. Also the tumour size (thickness) was simplified in the new classification to: < 1 mm, between 1 and 2 mm, 2 and 4 mm and > 4 mm.

TREATMENT OPTIONS

The therapeutic management of MM involves many disciplines and good interspecialty co-operation due to the fact that the majority of patients will require different speciality services during the natural history of their disease.

General Practitioners, Dermatologists, Plastic Surgeons, General Surgeons, Histopathologists, Medical Oncologists, Radiation Oncologists, as well as Oncology Nurses and Counsellors are all part of this multidisciplinary tumour board.
For the purpose of this manuscript, the treatment will be divided into 4 clinical areas: primary disease, locally recurrent disease, regional disease and disseminated disease.

**PRIMARY DISEASE**

**Primary surgery**

The treatment of primary MM consists of complete surgical excision of the underlying muscle fascia with a margin of normal-appearing skin.

Historically, wide excisions with margins of 5 cm were recommended but large randomised studies with long-term follow-up have shown that there is no need to perform very wide margins because the risk of local recurrence correlates more closely with tumour thickness than with excision margins.

For thickness < 1.0 mm the recommended surgical margins is 0.5-1.0 cm; for intermediate thickness 1.0-4.0 mm a 2 cm margin and for > 4.0 mm a 2-3.0 cm margin. It is correct to say that the optimal width remains unresolved but the above are general recommendations offered by the National Institute of Health Consensus Conference on Melanoma and by other organisations (such as WHO) and universities (Michigan Cancer Centre) etc.

These recommendations serve only as general guidelines and modifications may be made based on individual factors.

**Regional lymph node dissection**

This is another controversial issue in the management of MM. Patients with small melanomas (thickness < 1.0 mm) are at very low risk of developing lymph node metastasis so they do not require a lymphadenectomy. On the other hand, patients with melanomas thicker than 4.0 mm are at high risk of already having micrometastatic (distant) spread, so they also do not require an elective lymph node dissection.

But the group of patients with intermediate thickness melanomas (1-4 mm) have an increased risk of regional (occult) metastatic disease with a low risk of distant metastasis, hence elective lymphadenectomy might confer a survival benefit. No prospective randomised study has yet elucidated this controversy and at present some of these studies are still ongoing. In one study, performed by the Intergroup Melanoma Surgical Programme, a survival advantage was present in patients younger than 60 years of age and with non-ulcerated melanomas, 1.0-2.0 mm in thickness, when submitted to elective lymph node dissection.
Patients with intermediate thickness melanomas should be counselled regarding the risks and benefits of elective lymph node dissection and according to each institution's policies.

An alternative to elective lymph node dissection – the technique of lymphatic mapping and sentinel node biopsy – is undergoing intensive investigation. This technique relies on the concept that finite regions of the skin drain specifically into an initial node within the regional node basin via an organised network of specific afferent lymphatic channels. The identification of the sentinel node followed by its biopsy, may accurately determine whether melanoma cells have metastasised to that specific lymph node basin. At present, a multi-centre international research effort is accruing patients into a prospective randomised trial comparing this new technique of formal lymphadenectomy. Therefore, the value of this new surgical approach remains to be confirmed.

The preliminary consensus appears to be that this procedure is indicated for lesions greater than 1 mm in thickness (up to 4 mm).

The technique involves a combination of lymphoscintigraphy with injection of blue dye and a radioactive substance with the use of an intra-operative gamma probe. This allows the surgeon to identify the most likely sentinel node, to biopsy it and to obtain histologic confirmation. This, in turn, allows for accurate staging and to select the patients candidate for a therapeutic lymph node dissection, followed by adjuvant systemic therapy.

The pathologist receives the specimen and the lymph node is bisected and each half is sectioned at multiple levels. Representative levels are stained with immunohistochemical melanoma markers, namely S-100 and HMB45. Molecular techniques such as the polymerase chain reaction (PCR) are more sensitive than the S-100 and HMB45 stains, but are limited by the fact that the tissue is destroyed during the preparation of the specimen for PCR. In addition, false positives may be encountered as a result of inclusion of capsular naevus and Schwann cells. It must be emphasised that intraoperative frozen section analysis of the sentinel lymph node is to be avoided, as well-fixed and stained sections facilitate far more accurate nodal evaluation.

**Adjuvant therapy**

The rationale for adjuvant treatment is that early in the natural course of MM, when there is a small tumour load, there is less tendency for the tumour to undergo phenotypic changes which would render it resistant to treatment, while at the same time the individual patient is therapy naïve.

Systemic adjuvant therapy, administered following surgery, has been performed with a variety of drugs, including immunostimulants, cytostatics and more recently biologic response modifiers in an attempt to delay or stop the onset of local, regional or systemic recurrences. A variety of
immunostimulants, alone or in combination with chemotherapy have been extensively studied and administered. Of the most studied, Corynebacterium parvum and BCG have shown, in limited trials, to have a minimal impact in the delay of metastatic occurrence. When combined with chemotherapy, there was no statistical gain in survival time or relapse free interval demonstrated. The majority of these studies were performed in the late 70’s.

Over the past decade, different cytokines, including genetically engineered recombinant DNA interferons and interleukins have been studied as potential adjuvant drugs for high risk MM patients following surgery.

The therapeutic immunobiologic approach to MM has long been a goal for oncologists who have intimately observed the close interactions between the immune system and this malignancy.

Interferons, and especially the alpha 2a and 2b are the most extensively studied cytokines. Interferons are pleiotropic molecules that share a number of biologic effects such as antiviral, antiproliferative and immunomodulatory actions. The alpha interferons are produced by buffy coat leukocytes or lymphoblastoid cells. Their spectrum of toxicity is well documented with a ‘flu-like syndrome’ occurring universally in patients upon initiation of therapy but disappearing with repeated drug administration.

A number of trials performed in Europe and the USA, by different co-operative groups, have included different populations of MM patients (thin, intermediate and thick primary melanomas) and/or node positive disease and have employed a variety of doses and schedules of interferon. Based on the results of the Eastern Co-operative Oncology Group study EST 1684, the Food and Drug Administration in the USA recommended approval for the use of interferon alpha 2b in the adjuvant setup and for patients with Stage III disease.

Metanalysis of adjuvant interferon trials have shown an impact of Interferon on relapse free survival but not on overall survival, moreover no conclusive evidence for an Interferon dose effect emerges from the metanalysis.

At the recent American Society of Clinical Oncology Meeting (San Francisco, May 2001), it was stated, at the Educational Symposia that high dose interferon should not be regarded as standard adjuvant therapy nor as standard comparator arm in trials of Stage III melanoma patients.

**Vaccine therapy**

This is a promising area for the treatment of MM, particularly in the adjuvant setting. Two different approaches are currently undergoing clinical trials:

- whole cell vaccines (autologous or allogeneic) and
- peptide vaccines with defined melanoma associated antigens.
Considerable uncertainty remains regarding the benefits of vaccine treatment in melanoma patients and results of ongoing clinical trials are eagerly awaited.

**LOCALLY RECURRENT DISEASE**

The treatment of choice for solitary local recurrence is excision. For multiple local recurrences and for in transit metastases, there are a number of therapeutic approaches with limited value, such as amputation of the affected limb, radiotherapy; and/or isolated limb perfusion with a variety of chemotherapy agents such as melphalan, tumour necrosis factor, cis-platinum etc.

**REGIONAL DISEASE**

Unless there are systemic metastases or medical contraindications, radical lymphadenectomy is indicated if the metastatic disease has involved the regional lymph nodes.

Some studies have shown that the use of recombinant interferon following surgery might improve the disease-free survival of patients.

**DISSEMINATED DISEASE**

When systemic disease happens, the prognosis is poor (median survival between 6-12 months). (See table V)

The goals of treatment in patients with advanced MM are relief of symptoms and prolongation of life. This treatment depends on several factors including sites and number of metastases, their rate of growth, responses to prior therapies and the age and general condition of the patient. The most significant factor predicting for survival is the number of metastatic sites. Survival of patients with 1 metastatic site is better and prolonged when compared to patients with 2 (or more) metastatic sites. Metastatic sites with more favourable outcomes are those in soft tissues such as skin, subcutaneous and lymph nodes. Unfavourable sites are the liver and brain.

**Surgery**

Has a limited role, but allows rapid palliation of symptoms in certain circumstances (localised, single lesions). Occasionally surgical debulking is used together with other forms of therapy.

**Radiotherapy**

Although of limited benefit, there is some evidence of benefit when large doses per fraction are used for skin/subcutaneous and lymph node metastases. Irradiation of bone metastases provides excellent pain relief and whole brain irradiation reduces neurological symptoms. A recent development is radiosurgery (gamma knife) which has been reported to be useful in the treatment of solitary brain metastasis.
9.

Chemotherapy

There are only a few cytostatic agents for which consistent responses have been claimed in the treatment of advanced MM namely: dacarbazine (DTIC), the nitrosoureas and vindesine. A variety of combination chemotherapy treatments have been used to exploit possible synergism. Chemotherapy combinations such as DTIC, bleomycin, lomustine and vincristine (BOLD); cisplatin, vinblastine and DTIC (CVD); cisplatin, BCNU, DTIC and tamoxifen (Dartmouth) have induced objective responses in 30 to 50% of treated patients, with a median duration of responses ranging between 6 and 9 months. New cytostatic drugs such as taxol and fotemustine have shown similar responses to those obtained with DTIC and should be incorporated into the group of active drugs.

During the last few years and due to a wider availability of cytokines such as interferons and interleukins, an extensive investigation of the use of immunotherapy and chemo-immunotherapy has been pursued in the treatment of advanced MM. Several investigators have studied the efficacy of interleukin-2 as a single agent, or in combination with LAK (lymphocyte activated killer) cells or TIL (tumour infiltrating lymphocytes) and with other cytokines such as interferon and also with chemotherapy. Increased overall responses have not been uniform in all the studies and in some instances the toxicity experienced by the patient is considerable.

On the other hand, alpha interferons have been able to show a consistent objective response (when administered as a single agent) similar to the most active cytostatics. Interferons have been combined in a number of chemotherapeutic regimes or with single cytostatic agents, inducing a mild benefit with increase in the number and duration of responses.

Newer anti-cancer agents under investigation include the taxanes, vinorelbine and temozolomide.

At the recent Fifth World Conference on Melanoma (Venice, February 2001), reports of a randomized trial of chemotherapy versus biochemotherapy (same chemotherapy drugs plus interleukin 2 and interferon) conducted by an European Group, failed to show any major difference in survival for the 2 groups treated. The concern was that although biochemotherapy may induce more responses (while inducing more side effects and higher costs), the patient’s duration of survival is similar in both treatment arms.

In summary, over the past 15 years a dramatic increase in the number of active agents to treat malignant melanoma have become available. This has led to a cautious optimism that a substantial increase in the cure rate of patients with malignant melanoma is feasible. Further understanding of the biology of the disease as well as better identification of responsive subgroups of patients will lead to proper administration of the different cytostatics and cytokines and of their combinations.
PREVENTION

As most cases of melanoma are associated with an avoidable risk factor – excessive exposure to sunlight – it should be possible to reduce the incidence of the disease through effective education programmes. The success of an education programme depends on a number of factors.

- The aim should be to reach as wide an audience as possible, and at an early age.
- The highest priority should be education of high-risk individuals.
- The campaign message should be clear, simple and focused – avoid intense sunlight whenever possible, and if exposure is unavoidable, protect yourself with clothing and a sunscreen that has a protection factor of at least 15.
- The mass media should be used to full effect.
- Education should be carried out in schools and in the workplace by primary-care physicians and nurses.
- Elementary schools should be a major focus of any campaign – blistering sun exposure in childhood is particularly dangerous, and habits formed early in life often persist into adulthood.

A public education campaign should encourage individuals to do the following:

- Perform regular self-examination
- Recognise the ‘ABCD’ signs characteristic of early melanoma – asymmetry, border irregularity, colour variegation, and diameter > 6 mm.
- Consult a doctor of any naevus changes in shape, size or colour.

Professional education campaigns should encourage health care professionals to set up screening programmes for melanoma, either in the community at large or as part of routine primary-care. These campaigns should also aim to enhance the dermatological diagnostic skills of primary-care physicians.
References and recommended reading:


### Table I. A B C D System

<table>
<thead>
<tr>
<th>A B C D System</th>
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</thead>
<tbody>
<tr>
<td>A = Asymmetry</td>
<td></td>
</tr>
<tr>
<td>B = Boundary</td>
<td></td>
</tr>
<tr>
<td>C = Colour</td>
<td></td>
</tr>
<tr>
<td>D = Dimension</td>
<td>(diameter &gt; 6 mm)</td>
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</tbody>
</table>

### Table II. Glasgow 7 point check-list

<table>
<thead>
<tr>
<th>G L A S G O W System</th>
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<tbody>
<tr>
<td>1 = Change in size</td>
<td></td>
</tr>
<tr>
<td>2 = Change in shape</td>
<td></td>
</tr>
<tr>
<td>3 = Change in colour</td>
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<tr>
<td>4 = Inflammation</td>
<td></td>
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<tr>
<td>5 = Crusting or bleeding</td>
<td></td>
</tr>
<tr>
<td>6 = Sensory change</td>
<td></td>
</tr>
<tr>
<td>7 = Diameter &gt; 7 mm</td>
<td></td>
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</tbody>
</table>
### Table III. Present staging of malignant melanoma: modified AJCC/UICC staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Primary melanoma &lt; 0.75 mm thick and/or Clark’s level II (pT1); no nodal or systemic metastases (N0, M0)</td>
</tr>
<tr>
<td>IB</td>
<td>Primary melanoma 0.76 to 1.5 mm thick and/or Clark’s level III (pT2, N0, M0)</td>
</tr>
<tr>
<td>IIA</td>
<td>Primary melanoma 1.51 to 4 mm thick and/or Clark’s level IV (pT3, N0, M0)</td>
</tr>
<tr>
<td>IIB</td>
<td>Primary melanoma &gt; 4 mm thick and/or Clark’s level V (pT4, N0, M0)</td>
</tr>
<tr>
<td>III</td>
<td>Regional lymph node and/or in-transit metastases (any pT, N1 or N2, M0)</td>
</tr>
<tr>
<td>IV</td>
<td>Systemic metastases (any pT, any N, M1)</td>
</tr>
</tbody>
</table>

pT = primary tumour, N = regional nodal metastases, M = distant metastases
<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Melanoma in situ. All tumour cells above the basement membrane</td>
</tr>
<tr>
<td>Level 2</td>
<td>Melanoma extends through the basement membrane into the papillary dermis</td>
</tr>
<tr>
<td>Level 3</td>
<td>Tumour fills the papillary dermis but does not invade the reticular dermis</td>
</tr>
<tr>
<td>Level 4</td>
<td>Tumour extends into reticular dermis</td>
</tr>
<tr>
<td>Level 5</td>
<td>Tumour invades subcutaneous fat</td>
</tr>
<tr>
<td>Option</td>
<td>General indications</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Surgery</td>
<td>Superficial lesions, solitary brain lesions, symptomatic visceral lesions, occasional solitary lung lesion</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Palliation, superficial lesions, brain lesions, bone lesions</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Systemic disease, symptomatic lesions</td>
</tr>
<tr>
<td>Biological Therapy</td>
<td>Systemic disease, symptomatic lesions</td>
</tr>
<tr>
<td>Isolated limb perfusion</td>
<td>Local recurrences, in-transit metastases and satellites</td>
</tr>
<tr>
<td>Intralesional immuno-therapy</td>
<td>Skin and subcutaneous lesions</td>
</tr>
</tbody>
</table>

Fig. 1  Superficial Spreading Malignant Melanoma
Fig. 2  Lentigo maligna
Fig. 3  Acral lentiginous melanoma
Fig. 4  Nodular malignant melanoma
Fig. 5  Clark levels of malignant melanoma
Fig. 6 Measurement of Breslow thickness