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## **INTRODUCTION**

Cutaneous melanocytes originate in the neural crest and migrate to their position in the basal layer of the epidermis during embryological life. Their function is to produce melanin for the surrounding epithelial cells to protect them from ultraviolet light. Abnormalities of melanocytes may give rise to a series of benign and malignant conditions.

The benign lesions have a characteristic natural history. Firstly, there is a proliferation of melanocytes at the dermal epidermal junction to form junctional activity. Melanocytes then descend from the epidermis into the dermis where they become naevus cells. At this stage there is both a junctional component and a dermal component and the lesion is termed a compound naevus (Fig 1). Next, the junctional activity ceases, leaving only a dermal component - the intradermal naevus. Finally, the naevus cells disappear and become incorporated into the fibrous tissue of the dermis. Distinct varieties of benign naevi, arising from epidermal melanocytes, are the spindle-cell (Spitz) naevus and the halo naevus.

During embryological migration, some melanocytes do not reach the epidermis and remain within the dermis. These melanocytes give rise to the Mongolian spot.

## **PIGMENTED LESIONS**

The appearance of a new pigmented nevus should arouse suspicion of melanoma. About one-third of all melanomas arise from pigmented nevi.

Since the average white adult has 15-20 nevi, it is imperative that clinicians be able to recognize the various benign pigmented skin lesions and have a clear idea of the indications for biopsy or excision. Recognition and early excision of atypical pigmented lesions are potentially lifesaving, since surgery is the only effective treatment.

### ***Junctional naevus***

These are the common moles in pre-pubertal children, appearing as flat, hairless, well-defined brown patches. On close inspection the normal skin markings are present and this distinguishes them from melanomas.

Histologically, the lesion is characterized by a focal proliferation of melanocytes which still remain in contact with the epidermis, known as junctional activity. These lesions usually evolve into compound and then intradermal naevi and very few ever become malignant.

### ***Compound naevus***

These are commonly found in adolescents as dark brown or black, elevated or nodular lesions. They may be hair-bearing and the nodularity may lead to confusion with a malignant melanoma. Histologically, as well as junctional activity, nests of naevus cells are seen in the dermis. The cells become smaller as they progress more deeply into the dermis. This is known as 'maturation' and when seen in a naevus it is strong evidence that it is benign. Most of these develop into intradermal naevi and very few undergo malignant change.

### ***Intradermal naevus***

This is the mature mole of adults. Grossly, the appearance is variable. It

can be flat, raised, nodular or pedunculated. It may be pigmented or non-pigmented and hairs may be present. Histologically, there is no junctional activity and naevus cells are seen only in the dermis. Intra-dermal naevi virtually never undergo malignant change.

### ***Spindle cell (Spitz) naevus***

This lesion is also known as a juvenile melanoma which is an unsatisfactory term as it can occur in adults and is benign. Grossly, it appears as a raised lesion, often occurring on the face with a characteristic reddish-brown colour. The importance of this variety of naevus is that it can easily be confused histologically with malignant melanoma.

### ***Congenital naevus***

These vary widely in size from a small spot to a large area (giant congenital naevus) which may be in the bathing trunk distribution. They may be melanotic or amelanotic and in the later stages they become hairy (giant hairy naevus). Congenital naevi are more prone to undergo malignant change than other naevi.

### ***Dysplastic naevus***

Certain patients have naevi which are atypical both clinically and histologically. These dysplastic naevi may occur familiarly or non-familiarly and their importance is that affected patients have an increased risk of developing malignant melanomas. Dysplastic naevi differ clinically from normal naevi in that they are larger, more irregular in shape, indistinctly bordered and variably pigmented. They are commonest on the trunk but tend also to occur in unusual sites such as the scalp, buttocks and breast. Patients with familial form have a family history of atypical moles and malignant melanomas. They have a cumulative lifetime incidence of melanoma approaching 100% and it is estimated that 5-10% of all malignant melanomas occur in patients who have a family history of the disease. Patients with atypical moles should be

carefully followed up and any moles which change in appearance should be excised.

## **MALIGNANT MELANOMA**

Melanoma is a malignant tumour of melanocytes, accounting for 3% of all malignant tumours. During the last 2 decades, the incidence of melanoma has steadily increased, but 5-year survival rates have also increased from 40% to 70% during this period, reflecting improved methods of early diagnosis and treatment.

The incidence increases with advancing age and melanomas are multiple in 1-4% of patients. They tend to occur on the trunk in males and on the legs in females. Several factors have been implicated in the aetiology and pathogenesis.

### ***Aetiology***

Malignant melanoma is one of the sun cancers. Sunlight is regarded as a major aetiological factor, because of melanomas association with sun-damaged skin, correlation with intensity of ultraviolet exposure and predominance on exposed anatomical areas. Melanoma are commoner in fair skinned individuals with blonde or red hair, who have reduced tolerance to solar radiation and burn rather than tan. The highest incidence in the world is in Queensland, Australia, due to the combination of increased ultraviolet exposure and a high proportion of Celtic descendants who are unusually susceptible to skin cancers. Melanoma occurs more commonly on sun-exposed skin and is unusual on the doubly covered bathing trunk areas. It is rare in the dark-skinned races, occurring in less pigmented areas such as palms, soles and mucosal surfaces. Melanoma is exceedingly rare before puberty, and the incidence increases with age. There is no overall relation between the use of oral contraceptives and the subsequent development of melanoma. Pregnancy does not

increase the risk of melanoma nor affect the prognosis.

### ***Clinical Diagnosis***

The majority of melanoma can be recognised by careful history and examination without sophisticated investigation. The development of malignancy within a naevus should be suspected if any of the following changes occur:

- **Change in size** - a pigmented lesion spreads to cover a larger surface area.
- **Change in outline** - the edge of the lesion becomes indented, notched or irregular.
- **Change in colour** - usually darker or black, either uniformly or in part. Irregularity of colour within the lesion itself is very characteristic producing all shades of brown, blue, red, black and pink. The development of depressed pale areas of depigmentation in the pigmented tumour is almost pathognomonic of malignant melanoma and microscopically represents areas of local tumour regression.
- **Change in elevation** - a previously flat lesion becoming thickened and readily palpable with the fingertip. Alternatively, one or more nodules, pigmented or otherwise, develop within the tumour.
- **Change in the surface characteristics** - the earliest change may be loss of normal skin markings and a smooth mole may become rough, scaly or ulcerated.
- **Change in the surrounding tissues** - pigmented or non-pigmented lumps in the immediate vicinity of a naevus may indicate satellite tumours.
- **Intermittent itching** or tingling within the mole
- **Recurrent minor bleeding** after trivial trauma or a serous discharge is highly suspicious.

### ***Clinicopathological Types of Melanoma***

Cutaneous melanoma occurs in four clinically different forms, each with a distinct pathological appearance and a characteristic behaviour pattern.

1. Superficial spreading melanoma
2. Lentigo maligna melanoma
3. Nodular melanoma
4. Acral lentiginous melanoma

With the exception of nodular melanoma, each type progresses through a biological period during which metastases are unlikely to occur. This pre-metastatic phase is described as the radial growth phase and can be diagnosed clinically. During this period, the tumour grows radially without vertical penetration. With the onset of the vertical growth phase, the metastatic capability of the lesion increases. Nodular melanoma does not have a perceptible radial phase and starts the vertical growth phase early.

Despite the fact that four clinicopathological types are described, it is now generally accepted that the biological behaviour of melanoma is determined largely by its depth of penetration. In other words, no matter what clinicopathological type the melanoma is, the course and prognosis of the disease depends mainly on the depth of penetration of the tumour which can be measured histologically.

#### ***Superficial Spreading Melanoma***

This is the commonest variety accounting for 65% of cutaneous melanoma. The lesion is seen most often in early middle age on any part of the body, but especially on the lower legs of women. The lesion is brown-black and the outline may become irregular with deep notches. After a radial growth phase lasting months or years, the surface becomes irregular and raised with a variety of colours. The colour production is due to the increase in either cellular activity

or melanin production, or due to areas of regression and inflammatory response.

### ***Lentigo Maligna Melanoma***

This lesion constitutes 10% of cutaneous melanomas and occurs in sun-damaged skin, especially on the face of elderly people. It starts as a Hutchinson's melanotic freckle which appears as a brown or black macular lesion looking like a smudge of boot polish. It may enlarge and recede producing an irregular outline with paler areas due to regression. Initially it is impalpable, but with invasion, palpable nodules develop.

### ***Nodular Melanoma***

This type constitutes 12% of melanomas and presents as a dark, palpable nodule in the skin.

The surface is taut and shiny due to intense cellular activity, often with overlying desquamation. While it is characteristically dark blue in colour, occasionally it may be amelanotic and confused with a pyogenic granuloma. Careful examination will however, reveal pigmentation in the skin at the base of the lesion. The history of a nodular melanoma is short since it lacks a clinically recognisable radial growth phase.

### ***Acral Lentiginous Melanoma***

This type has recently been included as a separate clinical entity and is responsible for 5% of cases in Caucasians. This is the most common melanoma in Africans, occurring in areas where there is less pigmentation, such as palms, soles, nail beds and mucous membranes. In its early stages the lesion may appear misleadingly harmless, due to the thick overlying skin, and may not be diagnosed until late. The subungual variety may be confused with a subungual haematoma, but careful inspection will reveal pigment in the overlying nail fold or cuticle.

### ***Classification by depth of invasion***

Clark has classified melanomas by level of cutaneous invasion, and Breslow has correlated total tumor thickness with biologic behaviour of melanoma. Survival rates vary inversely with either of these criteria, while the incidence of lymph node metastasis varies directly with depth of invasion. Regardless of the type of melanoma, nodal and distant metastases are rare with level I and II lesions or lesions less than 0.75 mm thick. Lesions reaching levels III, IV, and V or lesions more than 1.5mm thick have an increased incidence of metastatic spread. There is also a correlation between aggressiveness of the tumor type and level of invasion. Lentigo maligna rarely extends deeply, but large numbers of superficial spreading melanomas reach levels II and III, and nodular melanomas often involve level IV or level V. On the basis of the microstage classification, low-risk and high-risk primary lesions can be defined.

### ***Anatomic Subsites and risk of recurrence***

Recent studies have correlated poor survival rates and high risk of recurrence with specific locations of primary melanoma. High-risk areas include the upper back, posterolateral arm, posterior neck and posterior scalp (BANS region). Location and thickness are the most accurate predictors of prognosis.

### ***Management***

The diagnosis of melanoma must be confirmed histologically before definitive treatment is undertaken. Lesions should be excised for histology and in most cases this is possible under local anaesthesia. The elliptical excision biopsy should include the full thickness of skin, a 3mm margin, and some subcutaneous tissue. If this is technically difficult, it is recommended that the patient be referred for specialist management. All pigmented lesions which are excised must be submitted for

histology. In exceptionally large lesions, incision biopsy is justified provided that the site of biopsy is carefully selected. Histology is done by paraffin section. Frozen section is not justified since the pathologist must establish both that the lesion is a melanoma and comment on the level of penetration, with measurement of the depth of invasion. Histological micro-staging of the excised specimen examining both the levels of invasion (Clark levels) and depth of penetration (Breslow's) provide essential information which will determine extent of further surgery and prognosis. (Fig 2) Once the diagnosis is confirmed, further excision of the skin surrounding the tumour may be indicated. Lesions with a depth of penetration less than 0.76mm need a margin of 1cm. Lesions deeper than 0.76mm have a greater metastatic potential and require wider excision. For lesions deeper than 2mm, a margin of excision should be 3cms, except where there are anatomical constraints such as on the face and hands. Excision usually extends to deep fascia and closure is by skin grafting although on the back local flaps may be preferable.

Table I: Clarks levels in malignant melanoma	
<b>Level I</b>	Intra epidermal melanoma above the basement membrane
<b>Level II</b>	Invasion into the papillary dermis
<b>Level III</b>	Filling the papillary layer and extending to the junction of the papillary and reticular layers but not entering the reticular layer.
<b>Level IV</b>	Into the reticular layer of the dermis.
<b>Level V</b>	Subcutaneous tissue involvement.

### **Adjuvant Chemotherapy**

Hyperthermic regional limb perfusion is used for prophylactic treatment of lesions in the lower limb deeper than 1.5mm, to prevent local or in transit recurrence, or may be used therapeutically for patients who

present with local recurrence. This procedure requires general anaesthesia and vascular isolation of the leg using a tourniquet around the upper thigh, supported by a Steinman pin placed in the iliac crest. The femoral vessels are cannulated and blood from the limb is circulated through a heart lung bypass machine. The temperature of the limb is raised to 40°C, at which stage Melphalan is added to the perfusate, and circulated for one hour. The tourniquet is then removed and the femoral vessels extubated and repaired. This technique enables a high dose of cytotoxic to be used in the limb without causing serious systemic effects.

### **Lymphadenectomy**

Elective or prophylactic lymphadenectomy (ELND) is the removal of clinically normal regional lymph nodes following excision of a primary melanoma. Prospective clinical data indicates that ELND has no beneficial effect on the ultimate outcome of the disease. The one indication for prophylactic node dissection is during a mono-block resection, when excision of the tumour and surrounding skin with lymph nodes is performed in continuity, occurring with a deeply penetrating primary tumour, which is situated over or close to its draining lymph nodes.

Therapeutic lymphadenectomy (TLND) is the removal of lymph nodes which are clinically involved or suspicious. At GSH we practice TLND, removing the complete group of nodes when one or more is clinically involved.

### **Patient Follow-up**

Since melanoma may recur regionally or systemically, careful follow-up of patients with tumours deeper than 0.76mm is essential. Most local or regional lymph node metastases occur within two years. Early surgical removal of involved lymph nodes improves survival. Patients are examined clinically every two months with routine chest x-rays and liver

function tests at 6 monthly intervals for the first two years. In patients who are disease-free after two years, the period between follow-up visits is generally lengthened to a maximum of 6 months. Earlier recognition and treatment of metastases is important, and patients are advised on the necessity for lifelong follow-up.

**Management of Disseminated Disease**

Malignant melanoma is the anecdotal tumour par excellence and although the overall response rate of metastases to cytotoxics, immunotherapy and radiotherapy, is discouragingly low, remarkable instances of remission have been encountered.

**Cytotoxics**

Single agent and combination chemotherapy are used for palliation and prolongation of life. DTIC is the most effective single agent currently in use, producing remission with worthwhile palliation in 25% of cases. The major side-effects are nausea and vomiting, although bone marrow suppression occasionally occurs. In patients who do not respond to DTIC, Procarbazine (Natulan) and cyclophosphamide (Endoxan) may be tried. Combination therapy offers no advantage over single agent therapy.

**Radiotherapy**

Although melanoma has in the past been regarded as resistant to radiotherapy in conventional fractionation, larger doses and the addition of hyperbaric oxygen may provide satisfactory responses. Radiotherapy is useful for palliation of bone and brain secondaries and in the management of irresectable lymph node disease.

**Immunotherapy**

Initial enthusiasm for BCG as immunotherapy, both as an adjuvant to surgery, and in advanced disease, has waned in the light of recent large studies which have shown no benefit.

**Surgery**

Palliative surgery for symptomatic subcutaneous secondaries and removal of isolated metastases in the brain, lungs or bowel often affords worthwhile relief or remission.

The single most important prognostic factor in malignant melanoma is the depth of penetration which is measured histologically. The key to successful management is early diagnosis. Public awareness, early recognition by the clinician and adequate initial surgical therapy are

**Table II: Level of invasion, tumour thickness, and incidence of recurrence or metastasis**

Clark's Levels	Recurrence or Metastasis at 5 years	Breslow's Thickness (mm)	Recurrence or Metastasis at 5 years
I	0%	<0.76	2%
II	4%	0.76-1.5	5%
III	15%	1.5-2.5	15%
IV	30%	2.5-4	30%
V	50%	>4	50%

essential for continued improved survival in the future



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