



# Fact File

The Royal College of Pathologists of Australasia

## Malignant Melanoma

Medicine is Pathology 



## Contents

1. Incidence .....	1
2. Risk factors.....	1
2.1. Risk Factors for the Development of Melanoma .....	1
3. Genetic factors .....	2
4. Classification of melanoma .....	2
4.1. Lentigo maligna melanoma; .....	3
4.2. The superficial spreading melanoma; .....	3
4.3. Nodular melanomas; .....	3
4.4. Acral lentiginous melanomas; .....	3
4.5. Desmoplastic melanoma; .....	3
4.6. Precursor of Melanomas; .....	4
5. The Pathology .....	4
5.1. Lentigo maligna melanoma; .....	4
5.2. Superficial spreading melanoma; .....	4
5.3. Verrucous melanoma; .....	4
5.4. Nodular melanoma; .....	5
5.5. Acral lentiginous melanomas; .....	5
5.6. Desmoplastic/spindle-cell melanomas; .....	5
5.7. Neurotropic melanoma .....	5
5.8. Special variants of malignant melanoma.....	5
6. Level and thickness.....	6
7. Metastases .....	6
8. Multiple primary lesions.....	7
9. Prognostic factors in melanoma .....	7
10. Management of malignant melanoma .....	8
11. Survival data.....	8

## Fact File on Malignant Melanoma

### 1. Incidence

The incidence of malignant melanoma has increased significantly over the last two decades, in the white populations of various industrialized countries, although there is some evidence to suggest that incidence rates have now begun to stabilize or even decline. The incidence of melanoma is highest in Queensland with 42.89 new cases in women and 55.8 in men, annually, per 100,000 of the population. Melanoma in the elderly appears to be the new public health problem for this decade.

### 2. Risk factors

The incidence data suggest a role for sun in the etiology of malignant melanoma. Many studies have examined the sun-exposure habits of patients with melanoma, and have found increased sun sensitivity which is associated with pale skin, blond or red hair, the presence of numerous freckles and a tendency to burn and to tan poorly. Sometimes there is a history of painful or blistering sunburns during childhood or adolescence. Two or more such episodes before the age of 15 appear to be important as a risk factor. Recent studies suggest that childhood, per se, may not be a critical period for sunburn and that melanoma risk is increased regardless of the timing in life of the sunburns.

□□The presence of certain types of nevi is also a risk factor. Large congenital nevi and dysplastic (atypical) nevi have been recognized as precursor lesions for some time. The dysplastic (atypical) nevus syndrome phenotype is present in 15% or more of patients with melanoma. It is only comparatively recently that the etiological significance of large numbers of common (banal, typical), acquired nevi has been appreciated. This risk appears to be significant when the number of nevi exceeds 50. The presence of nevi >6mm in diameter appears to be an independent risk factor. Proneness to develop nevi correlates not only with sun exposure, including blistering episodes, but also with skin complexion, hair color and tanning ability. □□Various other associations have been reported. These various risk factors are listed in the table:

#### 2.1. Risk Factors for the Development of Melanoma

- Skin and hair colour
- Numerous freckles
- Tendency to burn and tan poorly
- Blistering sunburns (? Any age)
- PUVA therapy
- Tanning salons
- Presence of nevi (numerous, large, atypical)
- Genetic factors (CDKN2A and CDK4 mutations)
- Xeroderma pigmentosum
- Immunosuppression
- Exposure to chemicals
- Miscellaneous rare associations

### 3. Genetic factors

Because 8–12% of melanomas occur in a familial setting, attempts have been made to find a candidate gene or genes for this familial basis. It is now known that mutations of the gene CDKN2A (cyclin-dependent kinase inhibitor 2A), encoding the tumor-suppressor protein p16INK4a (p16) and linked to chromosome 9p21, confer susceptibility to familial melanoma. Nearly half of the families predisposed to melanoma are linked to this abnormality. Recently germline mutations within the exon 2 of the CDK4 gene on chromosome 12q15 have been reported in families with familial melanoma.

Partial or complete loss of p16 expression is also prevalent in sporadic melanomas. In one study, loss of chromosome 9 was found in 81% of melanomas studied by comparative genomic hybridization. Other chromosomal losses (and gains) have also been demonstrated.

A gene for mole density, another risk factor for melanoma, is linked to the familial melanoma gene CDKN2A.

### 4. Classification of melanoma

The clinicopathological classification of malignant melanoma has evolved into six groups, based on proposals by Clark and McGovern over 20 years ago. The relative incidence of each type of melanoma varies considerably in different areas – for example, there is a higher proportion of lentigo maligna melanomas in Caucasians living in subtropical and tropical areas and of acral lentiginous melanomas in Japanese. The figures quoted in parentheses are therefore only a guide to the relative incidence of each type.

- Lentigo maligna melanoma (5–15%)
- Superficial spreading melanoma (50–75%)
- Nodular melanoma (15–35%)
- Acral lentiginous melanoma (5–10%)
- Desmoplastic (and neurotropic) melanoma (rare)
- Miscellaneous group (rare).

Attempts have been made to characterize the clinical features of melanoma in an easily remembered mnemonic. The ABCD rule highlights the clinical characteristics: asymmetry, border irregularity, color variegation and diameter more than 6mm. Many exceptions to this rule occur, leading to clinical misdiagnoses.



#### **4.1. Lentigo maligna melanoma;**

occurs most frequently on the face and sun-exposed upper extremities of elderly people. Its precursor lesion, the lentigo maligna (Hutchinson's melanotic freckle), is an irregularly pigmented macule which expands slowly. There is great variation in color, with tan-brown, black and even pink areas present. An amelanotic variant has been reported; rarely, this takes the form of an inflammatory plaque or follows cryosurgery for lentigo maligna. Invasive malignancy (vertical growth phase) is characterized by thickening of the lesion with the development of elevated plaques or discrete nodules. The proportion of lentigo malignas which progress to lentigo maligna melanoma is said to be quite small, with a lifetime risk of only about 5%. Rapid progression to a deeply invasive tumor has been reported. Cryotherapy, superficial radiotherapy, surgical excision with mapping or peripheral vertical sections for margin control, and a modified Mohs' micrographic technique, using immunoperoxidase staining with HMB-45, have all been proposed as suitable methods of treatment for lentigo maligna. Unfortunately, cryotherapy may be followed by lentiginous hyperpigmentation in the scar, which requires differentiation from a recurrence.

#### **4.2. The superficial spreading melanoma;**

may develop on any part of the body, and at any age. It is particularly common on the trunk in males and the lower extremities in females. It has a shorter radial growth phase than lentigo maligna melanoma and is usually at least superficially invasive at the time of presentation. It also has a variegated color with an irregular expanding margin. An amelanotic variant has also been reported; rarely, it may clinically simulate a patch of vitiligo. Areas of regression are not uncommon in both this type of melanoma and the lentigo maligna form.

#### **4.3. Nodular melanomas;**

have no antecedent radial growth phase. They are therefore nodular, polypoid or occasionally pedunculated, dark brown or blue-black lesions occurring anywhere on the body. Occasionally flesh-colored amelanotic variants are found. Ulceration may be present.

#### **4.4. Acral lentiginous melanomas;**

develop on palmar, plantar and subungual skin. They are particularly common in black people and the Japanese and Taiwanese, and are found predominantly in elderly patients, with a male preponderance. They present as pigmented plaques or nodules which are often ulcerated. Melanomas of the oral cavity and other mucous surfaces, such as the vagina, have been included in this group by some, but excluded by others. In a large Swedish series of 219 cases of melanoma of the vulva, the vast majority were of the mucosal (acral) lentiginous type. The prognosis of vulvar melanomas (37 – 47% 5-year survival) is poorer than for other cutaneous melanomas. They tend to be thicker lesions and to occur in older women.

#### **4.5. Desmoplastic melanoma;**

is usually found on the head and neck region as a spreading indurated plaque or bulky firm tumefaction. Atypical presentations occur. The lesions are often non-pigmented, although areas of lentigo maligna may overlie part of the lesion or be found at the periphery. Sometimes the desmoplastic pattern is found only in the recurrence, or in the metastases of a more usual type of melanoma. Desmoplastic melanomas are often stubbornly recurrent; in many instances this is a reflection of inadequate surgical excision of a lesion which is often, locally, quite advanced in its growth. In one series



the 5-year disease-free survival rate was 68%, better than is seen for other categories of melanoma of comparable thickness. In another, desmoplastic melanomas with neurotropism had a significant decrease in survival. In a large series reported from the Sydney Melanoma Unit, the 5-year survival was 75% which was similar to that for patients with other cutaneous melanomas of similar thickness.

#### **4.6. Precursor of Melanomas;**

there is considerable controversy regarding the nomenclature to be used for presumed precursor lesions of malignant melanoma. Terms such as 'atypical melanocytic hyperplasia', 'pagetoid melanocytic proliferation', 'pagetoid melanocytosis', 'precancerous melanosis', 'severe melanocytic dysplasia' and, more recently, 'dysplastic (atypical) nevus' have been used for these precursor lesions, and not always consistently. Some have used the term 'melanoma in situ' for evolving melanocytic atypias, whereas others have avoided the term because of the connotation for insurance purposes of the word 'melanoma' in this title. This latter practice has been criticized. The Consensus Conference on the early diagnosis and treatment of melanomas, convened by the National Institutes of Health (USA), agreed that 'melanoma in situ' was a distinct entity.

## **5. The Pathology**

There is a disappointing degree of disagreement between experts in the diagnosis of melanocytic neoplasms. Errors in diagnosis, leading to litigation, are not uncommon. Nevertheless, it is generally agreed that in a very small number of cases the diagnosis is elusive and that expressing diagnostic uncertainty is acceptable.

#### **5.1. Lentigo maligna melanoma;**

is characterized by an epidermal component of atypical melanocytes, singly and in nests, and usually confined to the basal layer and with little pagetoid invasion of the epidermis. The invasive component may be composed of spindle or epithelioid melanocytes. Solar elastosis is not a prerequisite for the diagnosis. □ It is a well recognized phenomenon that a subsequent excision may show more pronounced (atypical) features than a previous biopsy specimen. This is particularly so for lesions on actinically damaged skin in which up to 40% of excisions may show more pronounced changes.

#### **5.2. Superficial spreading melanoma;**

is characterized by a proliferation of atypical melanocytes, singly and in nests, at all levels within the epidermis. This pagetoid spread within the epidermis is sometimes known as 'buckshot scatter'. Superficial adnexal epithelium may also be involved. The cells may be epithelioid, nevus cell-like, or even spindle-shaped without evidence of maturation during their descent into the dermis.

#### **5.3. Verrucous melanoma;**

A rare variant of melanoma, usually of the superficial spreading type, is the verrucous melanoma. This occurs most often on the back and limbs of middle-aged to older males. It is characterized by marked epidermal hyperplasia, elongation of the rete ridges and overlying hyperkeratosis. This variant is often misdiagnosed clinically as a seborrheic keratosis.



#### **5.4. Nodular melanoma;**

has no adjacent intraepidermal component of atypical melanocytes, although there is usually epidermal invasion by malignant cells directly overlying the dermal mass. The dermal component is usually composed of oval to round epithelioid cells but, as in other types of melanoma, this can be quite variable.

#### **5.5. Acral lentiginous melanomas;**

have a radial growth phase which is characterized by a lentiginous pattern of atypical melanocytes, with some nesting. There may be some 'buckshot scatter' of melanocytes, but this is never as marked as in superficial spreading melanoma (see above). The epidermal component may look misleadingly benign. The invasive component may consist of epithelioid cells or spindle cells, or resemble nevus cells.

#### **5.6. Desmoplastic/spindle-cell melanomas;**

are composed of strands of elongated spindle-shaped cells surrounded by mature collagen bundles. The stromal component varies considerably in different tumors. Sometimes there are scattered spindle cells and abundant collagen, whereas in others there is little stroma. This latter group is usually referred to as spindle-cell melanomas, although it should be noted that desmoplastic melanoma and spindle-cell melanoma form a continuum without a discrete separation. The desmoplastic features are usually more prominent in the local recurrences, in contrast to lymph node and visceral metastases, which often resemble conventional melanomas. The tumor infiltrates deeply. The full extent of the tumor is sometimes difficult to discern with accuracy. The use of S100 staining is a valuable adjunct in determining the extent of some lesions. There may be scattered collections of lymphocytes and plasma cells within the tumor. In paucicellular tumors these small foci of inflammatory cells can provide a clue to the diagnosis on scanning magnification. This paucicellular variant is easy to misdiagnose on a small punch biopsy or superficial shave.

#### **5.7. Neurotropic melanoma**

In the neurotropic variant there are spindle-shaped cells with neuroma-like patterns (neural transformation) and a tendency to adopt a circumferential arrangement around small nerves in the deep dermis and subcutaneous tissue (neurotropism). Interlacing bundles of cells are seen.

#### **5.8. Special variants of malignant melanoma**

Rare variants of malignant melanoma include myxoid, balloon cell, signet-ring cell, rhabdoid, osteogenic, small cell, nevoid, small-diameter, ganglioneuroblastic, angiomatoid, animal (equine) and bullous types.



## 6. Level and thickness

In any report on a malignant melanoma the anatomical level of invasion (Clark's level) and the thickness of the tumor (Breslow thickness) should be stated. Five anatomical levels are recognized:

- 1 – Confined to the epidermis (in-situ melanoma)
- 2 – Invasion of the papillary dermis
- 3 – Invasion to the papillary/reticular dermal interface
- 4 – Invasion into the reticular dermis
- 5 – Invasion into subcutaneous fat.

The thickness of a melanoma is measured from the top of the granular layer (undersurface of the stratum corneum) to the deepest tumor cell. The Breslow thickness is a reproducible measurement, although some interobserver variation occurs. Melanomas less than 0.76 mm in thickness are regarded as being 'thin melanomas' and generally have an excellent prognosis. It has been suggested that either 0.85mm or 1mm is a better breakpoint than 0.76mm for defining a prognostically favorable group of melanomas. 1 mm is about to be adopted internationally as the cut off point for thin melanomas.

## 7. Metastases

Metastases in cases of malignant melanoma are usually to regional lymph nodes in the first instance. The probability of nodal metastases is related to the Clark level and the Breslow tumor thickness (see above). Nodal metastases are quite uncommon in lesions less than 1mm in thickness; their frequency exceeds 50% among lesions greater than 4mm in thickness. It has been suggested that the propensity for spindle-cell melanomas to metastasize to lymph nodes is relatively low, despite their thickness. Metastases also take place to the skin and subcutaneous tissue, skin graft donor sites, lungs, brain and dura, gastrointestinal tract, heart, liver and adrenal glands. Lymphatic

permeation in primary cutaneous melanoma is rarely seen. However, it is the likely cause of in-transit metastases. Such metastases are clonal in type.

When cutaneous metastases of malignant melanoma extend into the epidermis (epidermotropic metastases), differentiating them from a primary melanoma can be particularly difficult.

## 8. Multiple primary lesions

Additional primary lesions may develop in approximately 2% of patients with malignant melanoma. Up to a third are diagnosed concurrently with the initial melanoma.

Patients with multiple primary lesions will show the CDKN2A and CDK4 mutations more often than in patients with solitary lesions, a reflection of the familial setting of an underlying risk factor for multiple lesions, the dysplastic nevus syndrome.

## 9. Prognostic factors in melanoma

Survival rates for malignant melanoma continue to improve because patients are now presenting earlier with thinner (and therefore low-risk) melanomas. However, this trend for presentation with thinner lesions appears to be declining. 5-year survival rates of 85% or better for females and 75% for males are being reported. Survival rates approaching 100% are seen with superficial melanomas in the invasive radial growth phase. The various prognostic features, with their significance, are listed as follows:

### **Morphological**

- Increasing Breslow thickness (A)
- Ulceration (A)
- Mitotic rate/mitotic index (A)
- Increased nuclear volume (A)
- Satellite deposits (A)
- Hemangiolymphatic invasion (A)
- Advanced clinical stage (A)
- 'Occult' metastasis (A)
- Local recurrence (A)
- Clark level (C)
- Site (C)
- Histological subtype (C)
- Coexisting nevus (C)
- Lymphocytic infiltrate (C/F)
- Absence of regression (C/F)

### **Clinical**

- Female (F)
- Vitiligo (F)
- Increasing Age (A)
- Pregnancy (C)

### **Immunohistochemical**

- Metallothionein (A)
- Osteonectin (A)
- Integrins (A)
- Serum S100 (A)

(A) = Adverse    (F) = Favourable    (C) = Conflicting reports or limited value



## 10. Management of malignant melanoma

The treatment of malignant melanoma is beyond the scope of this fact sheet. However, two related aspects impinge upon the dermatopathologist:

resection margins

sentinel lymph node biopsy.

They will be discussed in turn.

Resection margins

Controlled studies suggest that arbitrary wide margins of excision are not justified. Local recurrence rates for thick melanomas are increased when the surgical margin is less than 3cm, although the overall survival rates do not appear to be affected. In the light of available information from these various studies, the current recommendations for the excision margins for melanomas of various Breslow thicknesses are as follows:

melanoma in situ 0.5 cm margins

<1 mm – 1 cm margins

1–2 mm – 1–2 cm margins (2 cm if primary closure can be achieved)

2–4 mm – 2 cm margins (1.5-2.5 cm also suggested)

>4 mm – 3 cm margins.

Despite these recommendations, Piepkorn and Barnhill have stated that ‘the choice of a resection margin materially more than 1 cm has no basis in scientifically observable fact’. These margins are usually reduced for facial lesions for cosmetic reasons.

Sentinel lymph node biopsy

Lymphatic mapping and sentinel lymph node (SLN) biopsy have had a significant impact on the management and prognostication of patients with melanoma. The status of the regional lymph node is a powerful predictor of recurrence rates and survival for most solid tumors, including melanoma. The SLN is defined as the first node in the lymphatic basin that drains the lesion in question. It is at the greatest risk for the development of a metastasis. The histology of the SLN has been shown to be representative of the entire lymph node basin, although the use of a tyrosinase PCR has shown that micrometastasis may occur in nonsentinel lymph nodes and be undetectable using standard techniques. This technique enhances the yield of positive SLNs and has prognostic importance.

## 11. Survival data

Hazard-rate analyses suggest that the peak hazard rate for death in clinical stage I cutaneous melanoma is the 48th month of follow-up, and that after 120 months’ survival the risk of dying from melanoma is virtually zero. With respect to recurrences, patients with thick melanomas have a marked reduction in future risk (of recurrence) with time. Put another way, their greatest risk is in the first few years after removal of their thick lesion. With melanomas 0.76–1.5mm thick there is a relatively constant risk of recurrent disease and death. Overall, 80% of recurrences occur within the first three years. Although rare, late recurrences (beyond 10 years) are recorded. Low tumor vascularity and low but comparable rates of proliferation and apoptosis may account for the long period of dormancy of micrometastases, the ultimate source of macrometastases.