Ministry of Defence

Synopsis of Causation

Melanoma (of Skin)

Author: Dr Arthur Morris, Ninewells Hospital and Medical School, Dundee
Validator: Professor Colin Munro, Southern General Hospital, Glasgow

September 2008

Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

The Ministry of Defence accepts full responsibility for the contents of this synopsis, and for any claims for loss, damage or injury arising from the use of this synopsis by the Ministry of Defence.

1. Definition

1.1. Cutaneous melanoma is a malignant tumour arising from melanocytes, which are the pigment producing cells of the skin.

1.2. Melanoma can also affect mucosal surfaces and the choroid of the eye.

2. Clinical Features

2.1. Cutaneous melanoma most commonly presents as an expanding, variably pigmented, irregular, changing patch on the skin. Most of these lesions are multicoloured and may be black, brown, tan, blue or pink, and are painless. A common symptom is itch.

2.2. This patch occurs in 80% of melanomas and represents the superficial "radial" growth phase. Eventually, the tumour will usually progress to form a nodule and begin to invade deeper tissue – the "vertical" growth phase.

2.3. One third of melanomas develop in a pre-existing benign naevus (mole). Two thirds develop *de novo* on pre-existing normal skin.

2.4. There are 4 main types of cutaneous melanoma[1] which differ greatly in their presentation. This increases the difficulty of diagnosis. Although each type is very different in character the overall survival of each is similar – see 4.1.

2.4.1. **Superficial spreading melanoma**. This is the most common type in people with lightly pigmented skin. It starts with a flat (radial) growth patch, which within a period of up to 2 years, can develop a nodule of invasive (vertical) growth. Eventual progression to invasive nodular melanoma is common but may be delayed for many years.

2.4.2. **Lentigo maligna melanoma.** This occurs on the habitually exposed areas of pale skinned, elderly patients. It starts with an irregularly pigmented patch of non-invasive lentigo maligna, which, after a prolonged period of up to 15 years, can develop into invasive melanoma.

2.4.3. **Nodular melanoma.** This starts as a pigmented nodule of vertical invasive tumour with no preceding patch. It is the most rapidly growing, aggressive type.

2.4.4. **Acro-lentiginous melanoma.** This develops on the soles of the feet, palms of the hands or nail beds of the digits. It starts as a pigmented superficial patch of radial growth which changes to an invasive nodular phase.

2.5. Melanoma is said to be amelanotic where pigment is not produced. This variety is more difficult to diagnose and presents as a non-pigmented lesion.

2.6. The tumour initially spreads locally in the skin by radial or vertical growth. It can then spread by lymphatic invasion, causing in transit nodules which are deposits of tumour in the surrounding skin, or lymph node metastases. It can also produce distant metastases throughout the body. Current management is based on the assumption that all locally invasive lesions have the potential to progress to metastatic disease.

2.7. Most recurrences of melanoma occur within 2 years of the first definitive excision treatment but can occur up to 30 or more years later. Definitive

treatment involves full excision of the tumour with a margin of normal surrounding skin.

2.7.1. There has been a well-documented rise in the incidence of melanoma in pale skinned populations, with the rate doubling each decade for the past 50 years.

2.7.2. Long-term follow-up is recommended but there is little consensus about the frequency and the length of follow-up needed, varying from 5 years up to 8 years, or life.

2.8. **Incidence**

2.8.1. The Scottish figures are the most complete and accurate that are available for a defined population. It should be understood that these figures vary with time and region of the UK.

- Although melanoma carries the reputation of being a disease of young people, it rarely occurs before puberty and half of the tumours occur over the age of 53 in Scotland[2]
- Melanoma is the third most common cancer in the 15-34 age group over the period 1986-95 in Scotland[3]
- The incidence of new melanomas in Scotland was 10 per 100,000 population per year in 1991-95
- The incidence in females is higher; for example, it was 25% greater in Scotland in 1988-92
- In younger females a larger proportion of melanomas occur on the lower limb while in younger males a larger proportion occur on the back[4]
- The high leg rate seen in women is probably lower in males as the latter tend to cover their legs. Females tend to cover their back area and have less melanoma there. Modern dress trends may have an effect on this in future

2.9. Melanoma can occur anywhere on the body, even in the perineum and on the soles and palms. There is a background rate of melanoma incidence of about 10-20 % which is not related to sun exposure.

3. Aetiology

3.1. Ultraviolet radiation is a cause of melanoma.[5] The role of sunlight is explored further in the Synopsis *Ultraviolet Radiation and the Skin*.

3.1.1. Intermittent, unaccustomed exposure to the sun is more important than the age at sunburn.[6] Exposure to high levels of sunlight in childhood is a strong determinant of risk but exposure in adult life also plays a part.[7]

3.1.2. There is evidence that UVA and sun beds have a role in causing melanoma.[8]

3.2. Cutaneous melanoma is most common in fair skinned people, with red or light-coloured hair and who have skin which tans poorly. It is more common where there is a family history of melanoma.[9] To date, inherited genetic defects predisposing to melanoma have been identified in only a minority of familial cases.[10] The contribution of identifiable genetic susceptibility to melanoma risk in sporadic cases remains to be established.

3.3. The risk of melanoma rises with the number of common moles on a patient. For example, more than 100 moles gives a sevenfold increase of incidence.[9]

3.4. The presence of atypical moles, which in some cases is familial, increases the risk.[9]

3.5. A person with a previous history of melanoma has a greatly increased chance of developing a further primary melanoma.[9]

3.6. The acral lentiginous melanoma is equally common in people of all skin types and race. It develops in areas not exposed to sun, suggesting a different aetiology from other types of melanoma.

3.7. **Evaluation**

3.7.1. To evaluate an individual who develops melanoma, basic principles apply. The person must be assessed for basic risk factors including life history of sun exposure, family history, number of moles and presence of atypical moles.[9] The exposure while on duty and at leisure must be taken into account. Personnel should have access to suitable protection advice, clothing and sunscreen.

3.7.2. The link between sun exposure and melanoma is not direct. However, although melanoma is a multifactorial problem, ultraviolet radiation is one of the main known risk factors.

3.7.3. The fact that a service person gets melanoma after 6 months service in a sunny climate is unlikely to be enough to accept a causal link. There is no minimum time of exposure, but the likelihood of service in a sunny climate contributing to the occurrence of melanoma will increase with the duration and intensity of exposure.

4. Prognosis

4.1. Prognostic factors for melanoma survival are mostly determined at the time of diagnosis. The chief indicator of prognosis is the histological thickness of the primary tumour - the "Breslow thickness". This is the thickness, measured in millimetres, of the thickest part of a melanoma on a paraffin section of the first excision biopsy when viewed under the microscope.[11] This applies equally to all tumour types.

4.1.1. ≤ 0.75mm thick	98% 5 year survival.
4.1.2. > 0.75mm – 1.5mm thick	90% 5 year survival.
4.1.3. >1.5mm – 3.0mm thick	75% 5 year survival.
4.1.4. > 3.0mm thick	50% 5 year survival.

4.2. **Gender** Females have a 10% better prognosis than males 5 years after diagnosis in Scotland over the period 1989 – 95.[3]

4.3. **Site**. Prognosis is worse when the primary tumour is on the back, upper arm, neck and scalp.

4.4. **Ulceration** Ulcerated primary tumours have a worse prognosis.

4.5. **Clinical stage.** Once the tumour has spread, the prognosis is much worse. After spreading to local lymph nodes (stage 2), the prognosis is reduced to 25% 5 year survival. After it has spread elsewhere in the body, fewer than 5% of patients survive 5 years.

4.6. Recent developments in the management of melanoma have centred on early diagnosis as the chief means of improving survival. Surgical excision biopsy to establish the diagnosis is the crucial diagnostic step.

4.7. The recommended width of margin of surgical excision for treatment is now reduced as a result of trials of width of excision.[12] The margin may be reduced in the future as the results of further trials emerge.

4.8. Primary treatment strategies in addition to surgery are the subject of ongoing research but as yet none is sufficiently effective to be used except as part of ongoing clinical trials.

4.9. Sentinel node biopsy at the time of primary surgery is being investigated to see if it will have a therapeutic benefit by allowing selective lymph node removal.

4.10. Treatment of recurrent disease is under vigorous investigation and there is a variety of possible further methods which can be applied but these have to be tailored to the individual patient. They include surgery to remove lymph node and other recurrences, chemotherapy and radiotherapy.

5. Summary

5.1. Cutaneous melanoma carries a very gloomy reputation. However, if diagnosed early, before the tumour has become thick or has spread, the prognosis is comparable to, or better than other cancers, for example breast or colon cancer.

5.2. Early diagnosis and complete excision of the primary tumour is the mainstay of treatment. Any change in a mole should be investigated thoroughly and the patient should be referred to an appropriate practitioner.

5.3. It is more common in younger people; for example, 50% of tumours first develop between puberty and the age of 53 years. Therefore, although melanoma is a rarely occurring tumour, it will be likely to occur in a small proportion of service personnel.

5.4. Sun exposure is strongly associated with the development of melanoma. Sun exposure in childhood is a main factor but sun exposure in adults is also involved.

5.5. Preventative measures should aim to limit sun exposure and are relevant to service personnel. Limiting exposure can be obtained by reducing outdoor activity in the sun at peak times of solar radiation, particularly for 2 hours on either side of the solar noon. The nearer the latitude of exposure is to the equator the greater the risk.

5.6. Physical solar protection measures should also be used when outdoor activity is planned and include wearing sun protection clothing, such as hats and long trousers or skirts and sleeves, particularly during summer months.[9] Light coloured clothing may be translucent and offer only limited protection against strong sunlight.

5.7. Sunscreen should be used as an adjunct to other protection. A minimum of 15 sun protection factor (SPF) should be used.[9] Regular re-application of sunscreen is important to maximise benefit.

5.8. The incidence of melanoma is very variable depending on the ethnic origin, natural sun susceptibility of the individual's skin and the geographical latitude.

5.9. The incidence of melanoma has doubled each decade for the last 50 years and is still continuing to do so.

6. Related Synopses

Ultraviolet Radiation and the Skin

7. Glossary

amelanotic	Without melanin. A skin lesion that is amelanotic lacks the pigment melanin and, therefore, is essentially colourless.
biopsy	The process of removing tissue from living patients for diagnostic evaluation.
choroid	The thin, blood-rich membrane that covers the white of the eyeball; responsible for supplying blood to the retina.
cutaneous	Relating to or existing on or affecting the skin.
malignant	Having the properties of cancer that can invade and destroy nearby tissue and that may metastasise to other parts of the body.
melanocytes	Cells in the skin that produce and contain the pigment melanin.
metastasis	The process where cancer cells break away from their original site and spread to other parts of the body.
sentinel node	The first lymph node or nodes to which cancer is likely to spread from the primary tumour. Cancer cells may appear first in the sentinel node(s) before spreading to other lymph nodes.
ulcerated	An ulcer (from Latin ulcus) is an area of erosion of the skin, eyes or mucous membrane, often caused by an initial abrasion and generally maintained by an inflammation and/or infection.

8. References

1. Hunter JA. Malignant melanoma. In: Clinical dermatology. Malden Mass: Blackwell Science; 1995. p. 268-74.

2. MacKie RM, Bray CA, Hole DJ, Morris A, Nicolson M, Evans A, et al. Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. Lancet 2002;360:587-91.

3. Harris V, Sandridge A, Black RJ, Brewster DH, Gould A. Cancer Registration Statistics Scotland, 1986-1995. Edinburgh: National Health Service in Scotland, Information and Statistics Division; 1998.

4. Mackie RM, Hole D, Hunter JA, Rankin R, Evans A, McLaren K et al. Cutaneous malignant melanoma in Scotland: incidence, survival and mortality 1979-94. Br Med J 1997;315:1117-21.

5. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 55: solar and ultraviolet radiation. Lyon: International Agency for Research on Cancer; 1992.

6. Elmwood JM, Jopson J. Melanoma and sun exposure; an overview of published studies. Int J Cancer 1997;73:198-203.

7. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69-82.

8. Wang SQ, Setlow R, Berwick M, Polsky D, Marghoob AA, Kopf AW et al. Ultraviolet A and melanoma: a review. J Am Acad Dermatol 2001;44:837-46.

9. Cutaneous melanoma: a National clinical guideline 72. Edinburgh: Scottish Intercollegiate Guideline Network; 2003.

10. Begg et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. J Natl Cancer Inst 2005;97:1507-15.

11. Breslow A. Thickness, cross-sectional area and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970;172:902-8.

12. Veronesi U, Cascinelli N, Adamus J, Balch C, Bandiera D, Barchuk A, et al. Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 centimetres. N Eng J Med 1988;318:1159-62.