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GUIDELINE ON THE MANAGEMENT OF MELANOMA

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Guideline on the Management of Melanoma

Melanoma Advisory Board

Objective.

- 1. The Guideline for the Management of Melanoma has been developed in an attempt to improve management through the process of locating the best available evidence on which to base decisions. It is expected to help to improve the quality of care.
- 2. Melanoma remains a common cancer in South Africa. Despite the achievement of earlier diagnosis, it would appear from current statistics that at least 850 people continue to die of melanoma each year. Many of these deaths occur at a younger age than for other solid tumours, so the number of years of life lost due to melanoma exceeds that of many other cancers. It is seen as imperative to maximise effective management of melanoma.
- 3. Prevention of melanoma has not yet been achieved, and there are no conclusive data to show that current promotion of sun avoidance has substantially altered its incidence.
- 4. Early detection is an important factor in melanoma management, with diagnosis based mainly on changes in colour, diameter, elevation and border (irregularity of outline) of a skin lesion, asymmetry of a lesion, or a lesion different from other naevi. People at high risk of melanoma should be offered a surveillance programme.

1. Introduction

Invasive primary malignant melanoma in whites shows the greatest and most rapid increase of all cancer worldwide. The incidence in South Africa is unknown but what is known is that the incidence in the Cape Town area is similar to that in Australia (24.4 per 100 000), and epidemiological studies to determine the exact incidence are in progress. In Australia it is one of the most common cancers¹⁻³ with the estimated risk of developing a melanoma before the age of 75 (in 1993) being 1 in 27 for males and 1 in 36 for females.³

Melanoma is therefore an important clinical and health problem and it is essential that the management of the disease

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Recommendations.

- 1. All clinicians should be trained in the recognition of *early* melanoma.
- 2. If there is doubt about a lesion, the patient should be referred for specialist opinion (if readily available) or a biopsy should be undertaken. Biopsy of a pigmented lesion should be done only on the basis of suspicion of melanoma. Excision with a 2 mm margin is adequate.
- 3. Prophylactic excision of benign naevi is not recommended. In general, elective lymph node dissection is not indicated.
- 4. People with high-risk primary melanoma, lymph node involvement and melanoma in unusual sites (e.g. mucosal and disseminated melanoma) should be managed with support from a melanoma centre.

Validation. Melanoma management involves many medical specialties. Guidelines should therefore be developed through a multidisciplinary consensus. The Melanoma Advisory Board consists of a forum of dermatologists, oncologists, plastic surgeons and pathologists.

Guideline sponsor. The meetings of the Melanoma Advisory Board are sponsored by Schering-Plough.

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is as effective as possible. This clinical practice guideline is designed to assist those involved in the management of this common cancer to provide optimal management for their patients. It is based on the guideline developed and published by the Australian Cancer Network⁴ and has been summarised and adapted as follows.

2. Prevention

Exposure to sunlight is strongly associated with the development of melanoma.⁵

The pattern of exposure is important, with intermittent exposure being more closely linked to the development of melanoma than the regular patterns of exposure of the outdoor worker.⁵ The action spectrum that is causative for melanoma, in particular the relative roles of UVB and UVA, is as yet unknown. However, in animal models UVA has been found to be a highly significant component in melanoma induction.⁶⁷

In addition, the use of sunbeds, which deliver mainly UVA radiation, may be a risk factor for melanoma.⁸



Other members of the Melanoma Advisory Board: Daniel Vorobiof, David Presbury, Peter Scott, Helen Stubbings, Charles Thatcher, A Giraud, Brian Ritchie, Constant Nel, Gary Levy

The following protection measures are recommended:

- Physical protection should be the primary preventive measure. Avoid direct exposure to sunlight during the 2 hours either side of solar noon.
- Use sun-protective clothing when exposed to direct sunlight for periods greater than 15 minutes.
- People should be advised to choose dark clothing of closely woven fabrics, which is more protective than light loosely woven garments. Fabrics with an inbuilt protection factor are available in sports/diving/climbing shops.
- Use broad-spectrum sunscreens as an adjunct to sun avoidance and other sun protective measures. New sunscreens should contain a UVA as well as UVB screen and in contrast to previous recommendations that a factor 15 sunscreen is adequate the advice is the higher the factor the better (> SP30).
- Provide and use sun-protective structures (e.g. shade structures) whenever possible.
- Provide children with appropriate sun protection for outdoor activities. Emphasis should be placed on the protection of children and adolescents from excessive sunlight exposure.⁹ Sunlight exposure at this age is closely related to the development of naevi. The presence of multiple naevi is a strong risk factor for melanoma.¹⁰¹⁴
- Advise against the use of sunbeds, tanning booths and tanning lamps. These deliver mainly UVA radiation, and UVA radiation causes DNA mutation which is a predisposing factor for subsequent carcinogenic UVB damage.

3. Clinical diagnosis of melanoma

The dignosis of melanoma should be considered in all cases of pigmented or changing lesions on the skin.

The key to the clinical diagnosis of a pigmented melanoma is irregularity of the lesion. Irregularity of colour is most important and the presence of a variety of colours in any one lesion is a key feature. While a black or blue/black colour is the most common, many other shades of brown, blue, red, grey or white are often seen. Irregularity of outline is the second most common feature with indentations and outgrowths around the lesion often apparent. Irregularity of the surface is another important sign.

Amelanotic melanoma is clinically difficult to diagnose, usually appearing as an enlarging smooth reddish nodule or patch. Sometimes an area of brown pigment can be discerned in these lesions. Surface microscopy may be helpful.

The ABCDE system of diagnosis of melanoma has gained general support.^{15,16}

A = ASYMMETRY

A lesion is **asymmetrical** if opposite segments of the lesion are appreciably different.

B = BORDER

The **border** of a melanoma is usually irregular, resembling a coastline with bays and promontories around the edge. All or part of the border is often well defined, in contrast with the dysplastic naevus, whose border is often ill-defined and fades into the background of the surrounding tissues.

C = COLOUR

Variation in **colour** is an important feature. A narrow red halo is sometimes seen around the edge of a melanoma. It is important to remember that amelanotic melanoma will have little or no distinguishing colour.

D = DIAMETER

Superficial spreading melanomas are often greater than 6 mm in **diameter** when first diagnosed, but it is possible to diagnose smaller melanomas, particularly nodular lesions, which appear not only as small shiny dark nodules but can also be reddish in amelanotic forms.

E = ELEVATION

While E designates **elevation**, it is important to diagnose melanoma while it is flat or with marginal elevation. At that stage the lesion is more likely to be curable. Thus E should remind the clinician to **examine** the patient's other pigmented lesions.

A feature which may be helpful in diagnosing melanomas is a 'ground glass' amorphous appearance to part of the lesion. Where the skin lines have been destroyed by the tumours, a shiny, glassy appearance is noted. Many melanomas will also have small flakes of keratin on the surface, but it is extremely rare for the lesion to be extensively keratinised. The presence of hairs does not exclude a diagnosis of melanoma, but most pigmented lesions with hairs are benign. However, more advanced melanomas will not have hair in the deeply invasive parts of the tumour because the melanoma will destroy the hair follicles as it invades. Thick melanomas are firm to touch and not compressible, unlike haemangiomas, and are rarely waxy to feel, unlike a seborrhoeic keratosis.

The differential diagnosis of pigmented melanoma includes dysplastic naevus, Spitz naevus, pigmented basal cell carcinoma, blue naevus, haemangioma, pigmented seborrhoeic keratosis and some rare adnexal tumours. In children, pigmented Spitz naevus is a likely diagnosis.

The amelanotic or hypomelanotic tumour differential diagnosis includes dermatofibroma, desmoplastic melanoma, basal cell carcinoma and other spindle cell tumours.

- Good lighting and magnification is recommended when lesions are being examined.
- All clinicians should become trained in the recognition of early melanoma.





- A good clinical history of change in the lesion, if any, a
 past history of skin lesions, and a family history of
 melanoma should be obtained. A family history is defined
 as melanoma in a direct line family member —
 grandparent, parent, sibling or child of the patient.
- Refer for a specialist opinion or biopsy lesions which are suspicious.
- High-risk individuals should be advised on the specific changes which suggest melanoma and encouraged to undertake self examination.
- Take note of any recent change or sensation reported by the patient.

4. Surface microscopy

- Skin surface microscopy should be carried out by specialists who have had specific training and are experienced, owing to the highly specialised nature of this examination (dermatoscope).¹⁷⁻²¹
- Digital epiluminescence microscopy (Molemax[®]) can be used to monitor high-risk patients because it allows viewing of morphological features (colours, pigmentation pattern) not seen with traditional surface microscopy and is an effective documentation system.

5. Screening and surveillance

Risk factors for development of melanoma include a family history of melanoma, a fair complexion, a tendency to burn rather than tan, the presence of freckles, the presence of solar lentigines, light eye colour, light or red hair colour and a past history of non-melanoma skin cancer.²²⁻²⁴

All individuals who are at high risk for the development of melanoma should be advised about the changes that might suggest the development of an early melanoma, encouraged to undertake regular self-examination and advised regarding appropriate methods of sun protection.

The presence of large numbers of melanocytic naevi and the presence of clinically determined atypical or dysplastic naevi are very strong risk factors for melanoma.^{13, 22-25} Dysplastic naevi are generally larger than normal moles with ill-defined edges and irregular pigmentation, mostly shades of brown.²⁶ They tend to have a poorly defined edge.²⁶ Melanoma risk increases with increasing numbers of total naevi and dysplastic naevi.^{13,22-25} The risk associated with clinical dysplastic naevi has been shown to be independent of that associated with the total numbers of naevi.²⁵ Clinically dysplastic naevi are not always dysplastic on histopathological examination.

Prophylactic excision of dysplastic naevi and other benign naevi is not useful in minimising melanoma risk. A significant proportion of melanomas begin as new lesions rather than developing from pre-exsiting naevi.27-29

Consider referral of these high-risk individuals to a specialist with an interest in melanoma management.

6. Familial risk and family surveillance

Recent Australian data indicate that 10% of patients with melanoma will have at least one confirmed melanoma-affected first-degree relative,³⁰ potentially resulting from inheritance of uncommon, major melanoma susceptibility gene(s).³¹

Consider referral of family members with a strong history of melanoma among close relatives, particularly those with large numbers of naevi, to a specialist with interest in melanoma management and refer for genetic studies if available.

7. Biopsy of pigmented lesions

- Biopsy of pigmented lesions should be done only on the basis of suspicious clinical features. Prophylactic excision of clinically benign lesions is not recommended. Primary biopsy should always be performed by complete excision.
- Shave and punch biopsies of pigmented lesions should be avoided.
- Lesions suspected to be melanoma should be excised with a 2 mm lateral margin and to the depth of the upper layer of the fat.
- Where doubt exists, a period of observation based on the history and clinical features of the lesion is acceptable. The period of observation will be short if a high level of suspicion of melanoma is present. However, if the clinician considers that the lesion is unlikely to be melanoma and it does not change, it is appropriate to continue observation until evidence of change appears.
- If melanoma is suspected, referral for a specialist opinion, where available should be considered before biopsy is undertaken.

8. Congenital melanocytic naevi

Congenital naevi are present at birth and are diagnosed with specific histological features.^{32,34} The lesions are arbitrarily divided into three groups based on diameter: < 1.5 cm, 1.5 - 20 cm and ≥ 20 cm.

Small (< 1.5 cm) lesions occur in 1% of births. They are not thought to have an increased malignant potential.²⁹⁻³⁴

Medium (1.5 - 20 cm) lesions have not been subject to adequate research so the malignant potential of this group is unclear.^{35,36} If excision is undertaken, it should be during the teenage years, since a study of 31 patients with melanomas arising from small congenital naevi (1.5 - 10 cm) found none of these melanomas presenting before puberty. However, at this





stage the body of evidence suggests that observation only is required.

Large (> 20 cm) lesions. There are only two prospective studies addressing these lesions. These show a crude risk of 3%.^{37.39} A literature review⁸ has shown that 70% of melanomas in this group develop before puberty.

Superficial removal of the naevus by dermabrasion or tangential excision is not recommended as two-thirds of melanomas develop in non-epidermal sites.^{40,41}

Patients with large congenital naevi of the head and neck are also at risk from neurocutaneous melanosis. 42

Magnetic resonance imaging (MRI) scan should be considered for screening these patients.⁴³ Lifelong surveillance for large and possibly for medium congenital naevi is recommended.

- Excisional biopsy of suspicious areas in large congenital naevi is recommended but should be carried out at a specialist centre.
- Surgical excision of congenital naevi is appropriate where patient concern is high and where an acceptable cosmetic outcome can be achieved. The removal of large naevi for cosmetic reasons only has no contraindications provided the patient is made fully aware of the likely appearance of the end result.

9. Lentigo maligna

Lentigo maligna (Hutchinson's melanotic freckle) is a common pigmented lesion on the exposed skin of the older patient. These lesions are regarded as *in situ* melanoma and may progress to invasive melanoma (lentigo maligna melanoma) in many people, and so must be managed carefully. These lesions occur predominantly on the face.

- Biopsy is indicated for changing pigmented lesions on the face.
- Where lentigo maligna is histologically confirmed, complete excision is the preferred management.
- For some patients, treatment by observation for change, with measurement, is an acceptable alternative to immediate excision.
- A Wood light is helpful to determine the extent of the lentigo maligna.
- Cryotherapy and shave biopsies should be left to the discretion of a specialist.

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10. Histopathological report

An accurate histopathology report is an essential prerequisite for optimal therapy for melanoma.

Request forms for pathology should include adequate

patient identification, and clinical details of all lesions removed.

- Where more than one lesion is excised, separate specimen bottles are essential.
- The pathologist's report should include all important features of the lesions (histopathological type, tumour thickness and ulceration).
- Tumour thickness, ulceration and clearance margins are essential. A standardised format of histological reporting on melonoma is advocated.
- Where clinical and pathological diagnoses do not concur, a second opinion should be sought from a pathologist with expertise in the diagnosis of pigmented tumours.

11. Classification of melanoma

Use of the American Joint Committee on Cancer (AJCC) and Union against Cancer Committee (UICC) classification system (2002) is recommended.⁴⁴

The primary tumour categories in the TNM classification are based on two microstaging systems. The **Clark system** describes the level of micro-invasion through the layers of the dermis. This is now mainly of historic value and relevant only for very thin melanomas. It has been replaced by the **Breslow thickness**, which is considered the most important diagnostic factor for primary melanoma. The thickness is measured in millimetres from the granular cell layer to the base of the lesion and is divided into four groups:

- < 0.75 mm
- 0.75 1.50 mm
- > 1.50 4 mm
- > 4 mm.

11.1 Primary tumor (T)⁴⁵

- TX Primary tumour cannot be assessed (e.g. shave biopsy or regressed melanoma)
- T0 No evidence of primary tumor
- Tis Melanoma in situ
- T1 Melanoma \leq 1.0 mm in thickness, with or without ulceration
- T1a Melanoma \leq 1.0 mm in thickness and level II or III, no ulceration
- T1b Melanoma \leq 1.0 mm in thickness and level IV or V, with ulceration
- T2 Melanoma 1.01 2 mm in thickness, with or without ulceration
- T2a Melanoma 1.01 2.0 mm in thickness, no ulceration
- T2b Melanoma 1.01 2.0 mm in thickness, with ulceration
- T3 Melanoma 2.01 4 mm in thickness, with or without ulceration



- T3a Melanoma 2.01 4.0 mm in thickness, no ulceration
- T3b Melanoma 2.01 4.0 mm in thickness, with ulceration
- T4 Melanoma > 4.0 mm in thickness, with or without ulceration
- T4a Melanoma > 4.0 mm in thickness, no ulceration
- T4b Melanoma > 4.0 mm in thickness, with ulceration.

N.B. Note that Clark level is only important for thin melanomas (T1).

11.2 Regional lymph nodes (N)45

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in one lymph node
- N1a Clinically occult (microscopic) metastasis
- N1b Clinically apparent (macroscopic) metastasis
- N2 Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
- N2a Clinically occult (microscopic) metastasis
- N2b Clinically apparent (macroscopic) metastasis
- N2c Satellite or in-transit metastasis without nodal metastasis
- N3 Metastasis in four or more regional nodes, or mated metastatic nodes, or in-transit metastasis or satellite(s) *with* metastasis in regional node(s).

11.3 Distant metastasis (M)45

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis to skin, subcutaneous tissues or distant lymph nodes
- M1b Metastasis to lung
- M1c Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH).

12. Treatment of primary melanoma

- The AJCC/UICC system (2002) is recommended as the basis for melanoma therapy.⁴⁵
- Complete excision with margins determined by tumour thickness measurement should be the basis for management of primary melanomas.
- A minimum margin of 1 cm and a maximum margin of 3 cm should be used for invasive melanoma, with a choice of excision margin determined by tumour thickness. A depth of excision equal to the margin is advised but it is not necessary to excise further than the deep fascia.

 Other pathological features should be used to make an assessment of prognosis and modify management decisions. In very thin lesions, thickness alone does not accurately predict the prognosis.

The following is recommended:46-49

1.	pTis	Melanoma in situ	margin 5 mm
2.	pT1, pT2	Melanoma 0 - 1.5 mm	margin 1 cm
3.	pT3	Melanoma 1.5 - 4.0 mm	minumum margin 1 cm
			and maximum margin 2 cm
4.	pT4	Melanoma > 4.0 mm	minimum margin 2 cm
			and maximum margin 3 cm

It should be noted that there is no evidence that a margin greater than 1 cm offers additional benefit to the patient in terms of survival, but it may decrease local recurrence.^{47:50}

Primary lesions in special sites should be referred to a specialist centre.

13. Survival outcomes of primary melanoma management

• Survival after diagnosis of melanoma falls with increasing tumour thickness.⁵¹⁻⁵² To advise patients on the likely outcome of their primary melanoma management, the estimates in Table I may be given for 5-year survival rates from the AJCC 2002:

Table I. Five-year survival rates (%) of pathologically stagedpatients (adapted from Balch *et al.*47)

	IA	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC
Ta: Non- ulcerated	T1a	T2a	ТЗа	T4a		N1a, N2a	N1b, N2b	N3
melanoma	95	89	79	67		67	54	28
Tb: Ulcerated melanoma		T1b	T2b	T3b	T4b		N1a, N2a	N1b, N2b, N3
		91	77	63	45		52	24

• Other prognostic variables influence outcome. Such factors as a thin melanoma which reaches Clark level 4, ulceration, the presence of lymphatic invasion, satellites and high mitotic rate may *adversely affect* the prognosis for the individual patient with melanoma.^{53,54}

14. Treatment of lymph nodes

All patients with invasive melanoma are at risk for metastases to the lymph nodes. Metastases to lymph nodes are uncommon for melanomas < 1.0 mm in tumour thickness. For primary melanomas 1.0 mm and greater in thickness, an increasing proportion of patients will develop regional lymph node





involvement. At least 25% of patients with melanomas between 1.5 mm and 4.0 mm thick will have microscopic lymph node involvement at the time of primary diagnosis. Sixty per cent of melanomas thicker than 4.0 mm will have nodal involvement,⁵⁵⁻⁵⁷ but these involved nodes are usually not clinically apparent at the time of primary diagnosis.

- Needle aspiration is preferable to excision biopsy of lymph nodes suspicious of metastatic melanoma.⁵¹ This should only be performed by doctors who are thoroughly familiar with the technique. If the local radiologist has expertise in ultrasound of nodes then it may be appropriate to do ultrasound and proceed directly to a block dissection if nodes are suspicious.
- Excision biopsy of suspicious nodes should be followed by immediate node dissection if nodal metastases are detected.⁵¹
- Elective lymph node dissection is generally not recommended.⁵⁸⁻⁶⁶
- Therapeutic node dissection should be undertaken only by surgeons trained in these procedures.⁶⁷⁻⁷⁴
- The recent surgical technique of lymphatic mapping and selective sentinel node biopsy provides an alternative approach to the treatment of melanoma > 1 mm thick.⁶⁹⁻⁷¹

Sentinel node biopsy means identification of the first lymph nodes (the sentinel nodes) to take up radioactive tracer injected around a primary site. These nodes are then marked on the skin and identified at surgery by injection of patent blue dye. The blue-stained nodes are selectively biopsied and examined by histology and immune histochemistry. Should they be positive the lymph nodes are dissected. This ensures that patients with nodal involvement are subjected to full regional lymph node dissection.

Sentinel node biopsy should only be performed by surgeons trained in this procedure.

Adequate node dissection is associated with a reasonably good prognosis, with a 10-year survival of up to 50% where only one node is involved. Even when two or three nodes are involved, 10-year survival rates of up to 30% can be achieved.⁵¹ However, extranodal spread is associated with a high fatality rate, and radiotherapy could be considered if this is detected, if the nodes are extensively involved or if tumour spillage occurs during the surgery.

• CT scans could be used to assess the iliac nodes where *inguinal* lymph node dissection is contemplated.

15. Occult primary melanoma

• Melanoma in lymph nodes or systemic metastases should be treated in accordance with guidelines regardless of inability to detect the primary lesion.⁷⁵⁻⁷⁸

16. Locoregional recurrent melanoma

- Excision of a single local or regional metastasis is the treatment of choice.
- Limb perfusion in a specialised centre should be considered if satellite lesions are present.⁷⁹⁻⁸²

17. Adjuvant therapy

• Patients with melanomas > 4 mm thick or with lymph node metastases should be referred to a specialised centre for consideration for adjuvant therapy.

18. Disseminated melanoma

- Patients with systemic metastases should be referred to a specialised centre for consideration for systemic therapies.
- All clinicians dealing with patients with systemic melanoma should be appropriately skilled in psychological management and palliative care.^{83,85}
- Surgical resection should be considered for isolated melanoma metastases in lung, brain and peritoneal cavity.⁸⁶ Multiple subcutaneous metastases may be well controlled with surgery in some cases if the patient is followed up carefully.

19. Radiotherapy for melanoma

- Postoperative radiotherapy could be considered for cutaneous melanomas likely to recur, e.g. where wide resection of the primary tumour is not feasible, as sometimes happens on the face⁸⁷ or regionally (multiple node involvement or extra-capsular spread) and following resection of mucosal melanomas.
- Primary radiotherapy should be considered for unresectable lentigo maligna melanomas or large unresectable primary lesions in the elderly and frail.⁸⁷
- Radiotherapy may be recommended for treatment of extensive cutaneous metastases where surgery is not feasible and for palliative management of cerebral and bone metastases and for other metastases where temporary local control is needed, e.g. large nodal or soft-tissue masses.⁸⁸⁻⁹¹

20. Palliative care

- Educating patients and carers as to the behaviour of metastatic melanoma with its unique features (i.e. subcutaneous spread and acute episodes of pain due to bleeding) and the appropriate intervention will assist them in coping with the disease.
- Clinicians should be aware of the palliative care services available within the patient's community, so that referral

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can be made if the patient so wishes.

21. Follow-up

- A follow-up regimen based on tumour thickness should be arranged for all patients with melanoma.^{92,93}
- The follow-up examination should include palpation for local recurrence, in-transit and lymph node metastases and signs of systemic relapse. A general examination of the skin for new primary melanomas and other skin cancers should be performed.

22. Appropriate investigations

- Extensive investigation for systemic metastases in patients with primary melanoma is not recommended.⁹⁴⁻⁹⁶ Baseline investigations such as a full blood count, chest radiograph and liver functions, including LDH, may be undertaken. Patients with deep lesions should have a computed tomography (CT) scan of the chest and upper abdomen. The latter may serve as a baseline for future comparison.
- Generally investigations such as MRI and PET (positron emission tomography) should be utilised only where specific symptoms suggest the presence of metastases.

23. Specific sites and types of melanoma

23.1 Mucosal melanoma

Mucosal melanoma is rare, comprising < 1% of all melanomas. It occurs in the mouth, nose, oesophagus, gallbladder, urethra, anus, vulva and vagina, and is usually asymptomatic.^{97,98} For this reason mucosal melanoma is generally detected late and thus has a very poor prognosis..⁹⁹

Patients with mucosal melanoma should be referred to a suitable specialised clinic or clinician.

23.2 Acral lentiginous melanoma (ALM)

ALM is defined as melanoma of the acral skin, i.e. the thickened skin of the soles and palms. The main interest of the ALM classification is that it is the predominant melanoma of non-white individuals. Its prognosis may be marginally worse than other melanomas but this is yet to be conclusively proven.¹⁰⁰⁻¹⁰²

ALM on the sole of the foot should be referred for specialist excision and appropriate reconstructive procedures and therapies.

23.3 Subungual melanoma

Subungual melanoma should be considered as a possible cause of any pigmentary changes under the nail.¹⁰³ In cases of doubt,

removal of the nail and biopsy is recommended.¹⁰⁴⁻¹⁰⁶ Subungual melanoma should be treated with excision margins that accord to the lesion thickness. This usually involves amputation of the terminal phalanx.¹⁰⁴

Because most subungual melanomas are advanced at the time of presentation, elective node dissection may be appropriate for these patients.^{107,108}

Naevi on the soles of the feet or on the genitals should not be removed routinely, because the incidence of malignant transformation of the these lesions is not higher than that of other lesions.

23.4 Desmoplastic melanoma

Desmoplastic and neurotropic melanomas are associated with a high risk of local recurrence related to their poorly defined clinical borders, frequent amelanosis and infiltration along nerve sheaths, predisposing to incomplete excision and persistence of the primary tumour.^{109,110}

Wider excision than is normal for other histological types of melanoma is recommended for desmoplastic melanoma.

Postoperative radiotherapy in consultation with a specialist should be considered after surgical excision of a recurrent desmoplastic or neurotropic melanoma.

23.5 Multiple primary melanoma

Multiple new primary melanomas may occur in at least 5% of patients with melanoma.¹¹¹⁻¹¹³ They are more common in patients with multiple atypical naevi, especially in a familial melanoma setting, but can occur in any patient who has had a melanoma.^{114,115}

Multiple primary melanoma should be treated according to the tumour thickness of each lesion. $^{\rm 116}$

23.6 Melanoma in childhood

Melanoma is rare in children below the age of 12, but clinical features are identical to those in the adult.¹¹⁶

Melanoma in children should be treated as appropriate for the same tumour thickness as melanoma in the adult.^{117,118}

23.7 Melanoma during pregnancy

Melanoma in a pregnant woman should be treated according to the tumour thickness.¹¹⁹⁻¹²¹ It has not been conclusively demonstrated that pregnancy alters the prognosis in a patient who has a melanoma diagnosed either before or during pregnancy.¹²⁰ Pregnant women with thicker melanomas and nodal metastases should be treated in consultation with specialised centres and psychological support may need to be obtained.

Because of the possibility of metastatic recurrence, pregnancy is not advisable for 2 years after removal of high-risk primary





melanoma or melanoma in nodes.122

Termination of pregnancy should be considered in women with high-risk primary or recurrent melanoma only after detailed discussion with the patient and her partner.

23.8 Hormone replacement therapy and oral contraceptives

Hormone replacement therapy and oral contraceptives are not contraindicated for women who have or have had melanoma.^{123,124}

24. Disclaimer

This document is a general guide to appropriate practice, to be followed only subject to the clinician's judgement in each individual case. It was compiled by members of the Melanoma Advisory Board, a multidisciplinary forum consisting of Dermatologists, Oncologists, Plastic Surgeons and Pathologists.

The guideline is designed to provide information to assist decision making and was based on the best information available at the date of compilation (November 2003).

25. References

- Coates M, McCredie M, Armstrong B. Cancer in New South Wales: Incidence and Mortality 1993. Sydney: New South Wales Cancer Council, 1996.
- Jelfs PL, Giles G, Shugg D, et al. Cutaneous malignant melanoma in Australia, 1989. Med J Aust 1994; 161: 182-187.
- Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. Cancer Series Number 10. Canberra: AIHW, 1998.
- Australian Cancer Network et al. Clinical Practice Guidelines: The Management of Cutaneous Melanoma. Sydney: ACN, 1999.
 IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Solar and Ultraviol.
- IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. *Solar and Ultraviolet Radiation* 1992; **55**: 95-122.
 Setlow RB, Woodhead AD. Temporal changes in the incidence of malignant melanoma:
- Setow KD, Woounead AD. reinport and ranges in the inductive of manipular metanoma. explanation from action spectra. *Mutal Res* 1994; 307: 365-374.
 Hussain Z, Pathak MA, Flotter *J*, *et al.* Role of ultraviolet radiation in the induction of
- Prussan Z, Patnak MA, Piotte F, et al. Nole of ultraviolet radiation in the induction of melanocytic tumors in hairless mice following 7,12 dimethylbenz(a)anthracene application and ultraviolet radiation. *Cancer Res* 1991; **51**: 4964-4970.
- Westerdahl J, Olsson H, Masback A, et al. Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol 1994; 140: 691-699.
- Holman CD, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. J Natl Cancer Inst 1984; 73: 75-82.
- Elwood JM. Melanoma and sun exposure: contrasts between intermittent and chronic exposure. World J Surg 1992; 16: 157-165.
- Swerdlow AJ, English J, MacKie RM, et al. Benign melanocytic naevi as a risk factor for malignant melanoma. BMJ Clin Res Ed 1986; 292: 1555-1559.
- Tucker MA, Fraser MC, Goldstein AM. Risk of melanoma and other cancers in melanoma-prone families. J Invest Dermatol 1993; 100: 350S-355S.
- Masri GD, Clark WH, Guerry D, et al. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. J Am Acad Dermatol 1990; 22: 1042-1048.
- English DR, Armstrong BK (1988). Identifying people at high risk of cutaneous malignant melanoma: results from a case-control study in Western Australia. BMJ Clin Res Ed 1988; 296: 1285-1288.
- Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. CA Cancer J Clin 1985; 35: 130-151
- First patrick TB, Rhodes AR, Sober AJ, *et al.* Primary malignant melanoma of the skin: the call for action to identify persons at risk: to discover precursor lesions: to detect early melanomas. *Pigment Cell* 1988; 9: 110-117.
- Menzies SW, Crotty KA, Ingvar C, et al. eds. An Atlas of Surface Microscopy of Pigmented Skin Lesions. Sydney: McGraw-Hill, 1996.
- Binder M, Swcharz M, Winkler A, et al. Epiluminescence microscopy. A useful test for the diagnosis of pigmented skin lesions for formally trained dermatologists. Arch Dermatol 1985; 131: 286-291.
- Steiner A, Pehamberger H, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. II Diagnosis of small pigmented skin lesions and early detection of

malignant melanoma. J Am Acad Dermatol 1987; 17: 584-591.

- Pehamberger H, Binder M, Steiner A, et al. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. J Invest Dermatol 1993; 100: 356S-362S.
- Mayer J. Systematic review of the diagnostic accuracy of dermatoscopy in detecting malignant melanoma. *Med J Aust* 1997; 167: 206-210.
- Holly EA, Kelly JW, Shpall SN, et al. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987; 17: 459-468.
- Augustsson A, Stierner U, Rosdahl I, et al. Common and dysplastic naevi as risk factors for cutaneous melanoma in a Swedish population. Acta Derm Venereol 1991; 71: 518-524.
 Halnem AC, Guerry D, Elder DE, et al. Dysplastic nevi as risk markers of sporadic
- Halpern AC, Guerry D, Elder DE, et al. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. Arch Dermatol 1991; 127: 995-999.
 Roush GC. Nordlund II. Forget B. et al. Independence of dusplastic newi from total
- Roush GC, Nordlund JJ, Forget B, *et al.* Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. *Prev Med* 1988, **17**: 273-279
 Kellv IW, Crutcher WA, Sagebiel RW, Clinical diagnosis of dysplastic melanocytic nevi.⁻A
- Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi. A clinicopathologic correlation. J Am Acad Dermatol 1986; 14: 1044-1052.
- Marks R, Dorovitch AP, Mason G. Do all melanomas come from 'moles'? A study of the histological association between melanocytic naevi and melanoma. *Australas J Dermatol* 1990; 31: 77–80.
- Sagebiel RW. Melanocytic nevi in histologic association with primary cutaneous melanoma of superficial spreading and nodular types: effect of tumor thickness. J Invest Dermatol 1993; 100: 322S-325S.
- Skender-Kalnenas TM, English DR, Heenan PJ. Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? J Am Acad Dermatol 1995; 33: 1000-1007.
- Aitken JF, Duffy DL, Green A, et al. Heterogeneity of melanoma risk in families of melanoma patients. Am J Epidemiol 1994; 140: 961-973.
- Easton DF, Cox GM, Macdonald AM, et al. Genetic susceptibility to naevi a twin study. Br J Cancer 1991; 64: 1164-1167.
- Walton RG, Jacobs AH, Cox AJ. Pigmented lesions in newborn infants. Br J Dermatol 1976; 95: 389-396.
- Kroon S, Clemmensen OJ, Hastrup N. Incidence of congenital melanocytic nevi in newborn babies in Denmark. J Am Acad Dermatol 1987; 17: 422-426.
- Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. J Am Acad Dermatol 1987; 16: 788-792.
- Illig L, Weidner F, Hundeiker M, et al. Congenital nevi less than or equal to 10 cm as precursors to melanoma. Arch Dermatol 1985; 121: 1274-1281.
- Rhodes AR, Sober AJ, Day CL, *et al*. The malignant potential of small congenital nevocellular nevi. *J Am Acad Dermatol* 1982; 6: 230-241.
 Marehoob AA. Schoenbach SP. Kopf AW. *et al*. Large congenital melanocytic nevi and the risk
- Marghoob AA, Schoenbach SP, Kopf AW, et al. Large congenital melanocytic nevi and the risk for the development of malignant melanoma. A prospective study. Arch Dermatol 1996; 132: 170-175.
- Ruiz-Maldonado R, Tamayo L, Laterza AM, et al. Giant pigmented nevi: clinical, histopathologic, and therapeutic considerations. J Pediatr 1992; 120: 906-911.
- Lorentzen M, Pers M, Bretteville-Jensen G. The incidence of malignant transformation in giant pigmented nevi. *Scand J Plast Reconstr Surg* 1977; 11: 163-167.
- Rhodes AR. Congenital nevonelanocytic nevi. Histologic patterns in the first year of life and evolution during childhood. *Arch Dermatol* 1986; **122**: 1257-1262.
- Rhodes AR, Wood WC, Sober AJ, et al. Nonepidermal origin of malignant melanoma associated with giant congenital nevocellular nevus. Plast Reconstr Surg 1981; 67: 782-790
- Kadonaga JN, Frieden JJ. Neurocutaneous melanosis: definition and review of the literature. J Am Acad Dermatol 1991; 24: 747-755.
- Frieden IJ, Williams ML, Barkovich AJ. Giant congenital melanocytic nevi: brain magnetic resonance findings in neurologically asymptomatic children. J Am Acad Dermatol 1994; 31: 423-429.
- Vorobiof DA. Malignant melanoma: the new revised staging system. Dermatology Review 2001; Winter: 43.
- American Joint Committee on Cancer (AJCC). Cancer Staging Manual. 6th ed. Philadelphia: Lippincott-Raven, 2002: 211-213.
- Anonymous. NIH Consensus Conference. Diagnosis and Treatment of Early Melanoma. JAMA 1992; 268: 1314-1319.
- Balch CM, Urist MM, Karakousis CP, et al. Efficacy of 2-cm surgical margins for intermediate thickness melanomas 1 to 4mm. Results of a multi-institutional randomized surgical trial. Ann Surg 1993; 218: 262-269.
- Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. Arch Surg 1991; 126: 438-441.
- Ringborg U, Andersson R, Eldh J, et al. Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm. Cancer 1996; 77: 1809-1814.
- O'Rourke MG, Altmann CR. Melanoma recurrence after excision. Is a wide margin justified? Ann Surg 1993; 217: 2-5.
- Balch CM, Soong SJ, Shaw HM. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott 1992.
- McCarthy WH, Shaw HM. The influence of prognostic factors on melanoma management. In: Lejeune FJ, Chaudhuri PK, Das Gupta TK, eds. *Malignant Melanoma*. New York: McGraw Hill, 1994.
- Kelly JW, Sagebiel RW, Clyman S, et al. Thin level IV malignant melanoma. A subset in which level is the major prognostic indicator. Ann Surg 1985; 202: 98-103.
- Shaw HM, McCarthy WH, McCarthy SW, et al. Thin malignant melanoma and recurrence potential. Arch Surg 1987; 122: 1147-1150.
- Veronesi U, Adamus J, Bandiera DC, et al. Stage I melanoma of the limbs. Immediate versus delayed node dissection. *Tumori* 1980; 66: 373-396.
- Coit D, Sauven P, Brennan M. Prognosis of thick cutaneous melanoma of the trunk and extremity. Arch Surg 1990; 125: 322–326.

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- McCarthy WH, Shaw HM, Cascinelli N, et al. Elective lymph node dissection: two perspectives. World J Surg 1992; 16: 203-213.
- Crowley NJ. Lymph node dissection in malignant melanoma. The case against elective lymphadenectomy. Surg Oncol Clin North Am 1992; 1: 223-246.
- 59 Lyons JH, Cockerell CJ. Elective lymph node dissection for melanoma. J Am Acad Dermatol 1994; 30: 467-480.
- Slingluff CL, Stidham KR, Ricci WM, et al. Surgical management of regional lymph nodes in patients with melanoma. Experience with 4682 patients. Ann Surg 1994; 219: 120-130.
- Harris MN, Shapiro RL, Roses DF. Malignant melanoma. Primary surgical management (excision and node dissection) based on pathology and staging. *Cancer* 1995; 75: 715-725.
- Coates AS, Ingvar CI, Petersen-Schaefer K, et al. Elective lymph node dissection in patients with primary melanoma of the trunk and limbs treated at the Sydney Melanoma Unit from 1960 to 1991. J Am Coll Surg 1995; 180: 402-409.
- Reintgen DS, Cox EB, McCarty KS, et al. Efficacy of elective lymph node dissection in patients with intermediate thickness melanoma. Ann Surg 1983; 198: 379-385.
- Drepper H, Kohler CO, Bastian B, *et al.* Benefit of elective lymph node dissection in subgroups of melanoma patients. Results of a multicenter study of 3616 patients. *Cancer* 1993; 72: 741-749.
- Rompel R, Garbe C, Buttner P, et al. Elective lymph node dissection in primary malignant melanoma: a matched-pair analysis. *Melanoma Res* 1995; 5: 189-194.
- Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. Ann Surg 1996; 224: 255-266.
- Calabro A, Singletary SE, Balch CM. Patterns of relapse in 1001 consecutive patients with melanoma nodal metastases. Arch Surg 1989; 124: 1051-1055.
- O'Brien CJ, Gianoutsos MP, Morgan MJ. Neck dissection for cutaneous malignant melanoma. World J Surg 1992; 16: 222-226.
- Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative mapping for early stage melanoma. Arch Surg 1992; 127: 392-399.
- Morton DL, Wen DR, Cochran AJ. Management of early-stage melanoma by intra-operative lymphatic mapping and selective lymphadenectomy. Surg Oncol Clin North Am 1992; 1: 247-259.
- Morton DL, Wen DR, Foshag LJ, et al. Intraoperative lymphatic mapping and selective cervical lymphadenectomy for early-stage melanomas of the head and neck. J Clin Oncol 1993; 11: 1751-1756.
- Thompson JF, McCarthy WH, Bosch CM, et al. Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. Melanoma Res 1995; 5: 255-260.
- Uren RF, Howman-Giles RB, Shaw HM, et al. Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node. J Nucl Med 1993; 34: 1435-1440.
- Uren RF, Howman-Giles R, Thompson JF, et al. Lymphoscintigraphy to identify sentinel nodes in patients with melanoma. *Melanoma Res* 1994; 4: 395-399.
- Balch CM, Houghton AN. Diagnosis of metastatic melanoma at distant sites. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott, 1992;
- Velez A, Walsh D, Karakousis CP. Treatment of unknown primary melanoma. *Cancer* 1991; 68: 2579-2581.
- Milton GW, Shaw HM, McCarthy WH. Occult primary malignant melanoma: factors influencing survival. Br J Surg 1977; 64: 805-808.
- Norman J, Cruse CW, Wells KE, et al. Metastatic melanoma with an unknown primary. Ann Plast Surg 1992; 28: 81-84.
- Krementz ET, Ryan RF, Muchmore JH, et al. Hyperthermic regional perfusion for melanoma of the limbs. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott, 1992:
- Thompson JF. Management strategies for locally advanced primary and secondary malignancies. *Cancer Forum* 1993; **17**: 224-226.
 Thompson JF, Waugh RC, Saw RPM, et al. Isolated limb infusion with melphalan for
- Thompson JF, Waugh RC, Saw RPM, et al. Isolated limb infusion with melphalan for recurrent limb melanoma: a simple alternative to isolated limb perfusion. *Reg Cancer Treat* 1994; 7: 188-192.
- Koops HS, Kroon BBR, Lejeune FJ. Management of local recurrence, satellites, and in transit metastases of the limbs with isolation perfusion. In: Lejeune FJ, Chaudhuri PK, Das Gupta TK, eds. *Malignant Melanoma*. New York: McGraw Hill, 1994:
- Coates A, Gebski V, Bishop JF, et al. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. N Engl J Med 1987; 317: 1490-1495.
- Coates A, Gebski V, Signorini D et al. Prognostic quality-of-life scores during chemotherapy for advanced breast cancer. Australian & New Zealand Breast Cancer Trials Group. J Clin Oncol 1992; 10: 1833-1838.
- Coates A, Thomson D, McLeod GR, et al. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. Eur J Cancer 1993; 29A: 1731-1734.
- Houghton AN, Balch CM. Treatment for advanced melanoma. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott, 1992:
- Peters LJ, Byers RM, Ang KK. Radiotherapy for melanoma. In: Balch CM, Houghton AN, Milton GW et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott
- Rosenthal MA, Bull CA, Coates A, et al. Synchronous cisplatin infusion during radiotherapy for the treatment of metastatic melanoma. Eur J Cancer 1991; 27: 1564-1566.
- 89. Stevens G, Firth I, Coates AS. Cerebral metastases from malignant melanoma. Radiother Oncol

1992; **23:** 185-191.

- Singletary SE, Balch CM. Recurrent regional metastases and their management. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott, 1992:
 Burmeister H, Smithers BM, Poulsen M, et al. Radiation therapy for nodal disease in malignant melanoma. World J Surg 1995; 19: 369-371.
- McCarthy WH, Shaw HM, Thompson JF, et al. Time and frequency of recurrence of cutaneous stage I malignant melanoma with guidelines for follow up study. Surg Gynecol Obstet 1988; 166: 497-502.
- Kelly JW, Blois MS, Sagebiel RW. Frequency and duration of patient follow-up after treatment of a primary malignant melanoma. J Am Acad Dermatol 1985; 13: 756-760.
- Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines for the care of malignant melanoma. J Am Acad Dermatol 1993; 28: 638-641.
- Browman GP, Levine MN, Mohide EA, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13: 502-512.
- Weiss M, Loprinzi CL, Creagan ET, et al. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanoma. JAMA 1995; 274: 1703-1705.
- Ross MI, Stern SJ, Wanebo HJ. Mucosal melanomas. In: Balch CM, Houghton AN, Milton GW, et al., eds. Cutaneous Melanoma. Philadelphia: Lippincott, 1992:
- Wong JH, Morton DL. Management of primary mucosal melanoma. In: Lejeune FJ, Chaudhuri PK, Das Gupta TK, eds. *Malignant Melanoma*. New York: McGraw Hill, 1994; 337-342.
- Sutherland CM, Chmiel JS, Henson DE, et al. Patient characteristics and methods of treatment of mucous membrane melanoma in the United States of America. J Am Coll Surg 1994; 179: 561-566.
- Sutherland CM, Mather FJ, Muchmore JH, et al. Acral lentiginous melanoma. Am J Surg 1993; 166: 64-67.
- Ridgeway CA, Hieken TJ, Ronan SG, et al. Acral lentiginous melanoma. Arch Surg 1995; 130: 88-92.
- Cascinelli N, Zurrida S, Galimberti V, et al. Acral lentiginous melanoma. A histological type without prognostic significance. J Dermatol Surg Oncol 1994; 20: 817-822.
- Fleegler EJ. A surgical approach to melanonychia striata. J Dermatol Surg Oncol 1992; 18: 708-714.
- 104. Finley RK, Driscoll DL, Blumenson LE, et al. Subungual melanoma: an eighteen-year review. Surgery 1994; 116: 96-100.
- Hayes IM, Thompson JF, Quinn MJ. Malignant melanoma of the toenail apparatus. J Am Coll Surg 1995; 180: 583-588.
 O'Toole FA, Stephens R, Young MM, et al. Subungual melanoma: a relation to direct injury? J
- Tobe Try September 2018, Stark and September 2018, Stark
- Interforms of cutaneous melanoma. Australas J Dermatol 1985; 26: 61-64.
 Heaton KM, El-Naggar A, Ensign LG, et al. Surgical management and prognostic factors in
- ob. Freaton Kwi, Er-Vaggar A, Ensigh Ca, et al. Surgical management and prognostic factors in patients with subungual melanoma. Ann Surg 1994; 219: 197-204.
- Smithers BM, McLeod GR, Little JH. Desmoplastic melanoma: patterns of recurrence. World J Surg 1992; 16: 186-190.
- Baer SJ, Schultz D, Synnestvedt M, et al. Desmoplasia and neurotropism. Cancer 1995; 76: 2242-2247.
- Kang S, Barnhill RL, Mihm MC, et al. Multiple primary cutaneous melanomas. Cancer 1992; 70: 1911-1916.
- Slingluff CL, Vollmer RT, Seigler HF. Multiple primary melanoma: incidence and risk factors in 283 patients. Surgery 1993; 113: 330-339.
 Arier G, Da W. B. Denzi, L. de Multiple primary and an additional primary strategy of the second strategy of the
- Ariyan S, Poo WJ, Bolognia J, *et al.* Multiple primary melanomas: data and significance. *Plast Reconstr Surg* 1995; 96: 1384-1389.
 Tucker MA, Crutcher WA, Hartge P, *et al.* Familial and cutaneous features of dysplastic nevi:
- a case-control study. J Am Acad Dermatol 1993; **28**: 558-564.
- Lucchina LC, Barnhill RL, Duke DM, et al. Familial cutaneous melanoma. Melanoma Res 1995; 5: 413-418.
- Gupta BK, Piedmonte MR, Karakousis CP. Attributes and survival patterns of multiple primary cutaneous malignant melanoma. *Cancer* 1991; 67: 1984-1989.
- 117. Ceballos PI, Ruiz-Maldonado R, Mihm MC. Melanoma in children. N Engl J Med 1995; 332: 656-662.
- Piepkorn M. On the nature of histologic observations: the case of the Spitz nevus. J Am Acad Dermatol 1995; 32: 248-254.
- Driscoll MS, Grin-Jorgensen CM, Grant-Kels JM. Does pregnancy influence the prognosis of malignant melanoma? J Am Acad Dermatol 1993; 29: 619-630.
- Holly EA, Cress RD. Melanoma and pregnancy. In: Gallagher RP, Elwood JM, eds. Epidemiological Aspects of Cutaneous Malignant Melanoma. Boston: Kluwer, 1994:
- Travers RL, Sober AJ, Berwick M, et al. Increased thickness of pregnancy associated melanoma. Br J Dermatol 1995; 132: 876-883.
 Mansfield PF, Lee JE, Balch CM. Cutaneous melanoma: current practice and surgical
- Johnsteid FF, Lee JE, Balch CM. Outlaneous metanoma: current practice and surgical controversies. *Curr Probl Surg* 199; **31**: 253-374.
 Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause.
- Itali Poly EA, Cress RD, Ahn DK. Cutaneous melanoma in women. III Reproductly actions and oral contraceptive use. *Am J Epidemiol Biomarkers Prev* 1994; 3: 661-668.
 Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women. III Reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; 141: 943-950.



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