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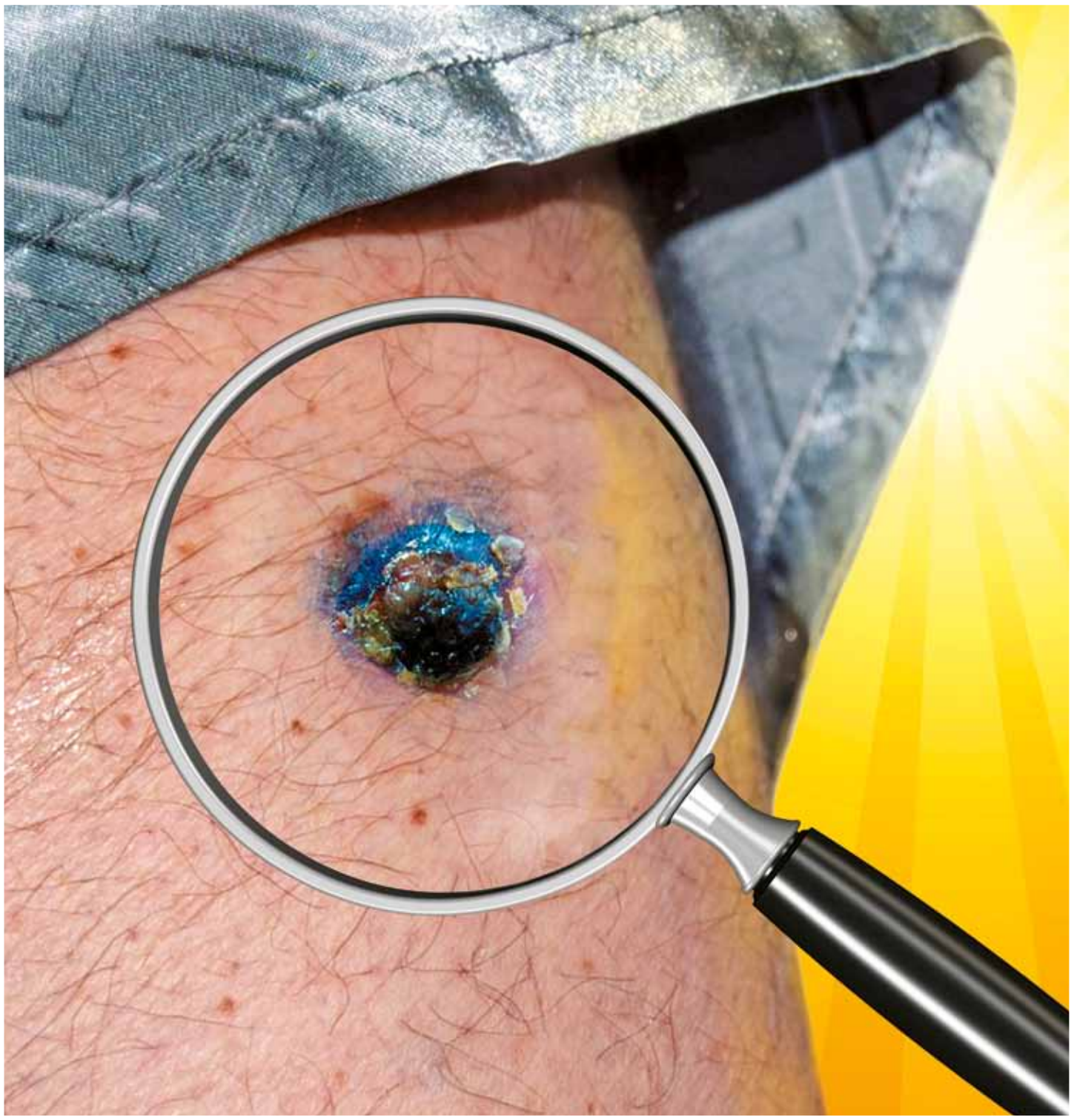

Melanoma

Background

MELANOMAS are malignant tumours derived from melanocytes. The most common site of involvement is the skin, although occasionally primary melanoma develops in other organs (eye, oral and nasal mucosa, vulval and anorectal mucosa, other gastrointestinal mucosa and CNS).

Melanomas are a major cause of premature death from cancer.

Recognised risk factors include personal or family history of melanoma, large numbers of naevi and/or dysplastic naevi, giant congenital melanocytic naevi, fair complexion, a tendency to sunburn, solar-damaged skin, a history of non-melanoma skin cancer, and immunodeficiency.

The most common sites for melanoma are the legs of women and the backs of men, despite these not being the sites of greatest sun exposure. Early detection is associated with improved survival.

Any malignancy will grow, grow irregularly, and function abnormally. A melanoma produces pigment in abnormal amounts and elicits an immune response that will be reflected in the clinical appearance. A small but significant number of melanomas are undiagnosable clinically. A history of change may be the only clue to the correct diagnosis (tables 1 and 2, see next page).

In 2008, the incidence of melanoma in Australia was 11,442 and 1224 people died from melanoma. Survival at five years following newly diagnosed invasive melanoma (Clark's level 2-5) has increased from 85% in 1986 to 90% in 2010.

In the absence of any new significant chemotherapy in that period, this improvement has been attributed to public education, early diagnosis and excision.

Scar re-excision, sentinel node biopsy, elective lymph node dissection, chemotherapy, radiotherapy and immunotherapy may improve survival at one year but have not been shown to improve five-year survival. Adjuvant therapy with interferon may improve five-year survival by 10% but is associated with significant toxicity.

Macroscopic locoregional lymph node metastasis reduces five-year survival to 50%. Distant visceral or bone metastasis (stage IV disease) has a one-year survival of about 25% and a five-year survival of less than 2.5%. Following successful surgical resection of metastasis, the median disease-free time to relapse is six weeks.

Functional mutations in genes in the mitogen-activated protein (MAP)

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kinase pathway are commonly detected in melanoma and these mutations influence growth control (figure 1). In 2009, these discoveries led to the development of the first new effective chemotherapy medication for metastatic disease in almost 40 years. Several agents based on molecular understanding of this pathway have been approved for stage IV disease and additional agents are currently being evaluated in clinical trials.

Various combinations of these agents are also being evaluated for stage IV disease and the BRAF inhibitor, dabrafenib is currently being evaluated in the US in Phase II clinical trials as adjuvant therapy for high risk primary melanoma.

The availability of adjuvant treatment, even in a trial setting, would necessitate a review of the current management of high-risk primary melanoma, and in particular the role of sentinel node biopsy.

Sentinel node biopsy is a technique performed immediately before surgical re-excision of the scar. It involves lymphatic mapping by lymphoscintigraphy and intraoperative injection of radioisotope and/or blue dye to identify the lymph node immediately downstream from the primary tumour.

Histological examination of the first ('sentinel') lymph node(s) identified with this technique has been demonstrated to identify the presence or absence of metastatic cells in the entire lymph node basin.

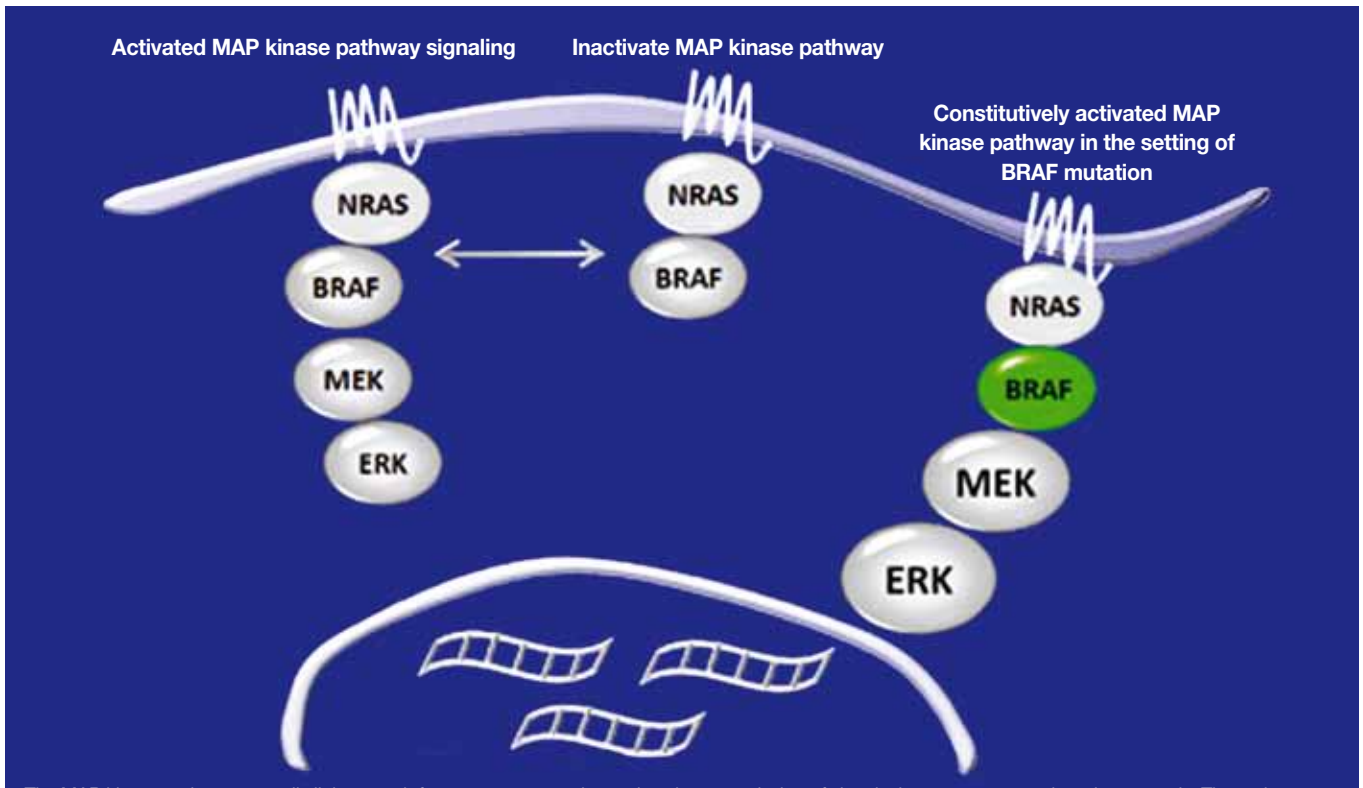
This procedure is considered the most sensitive and specific staging test for the detection of micrometastatic melanoma in regional lymph nodes. Sentinel lymph node status is the most important prognostic factor for disease-specific survival of patients with melanoma greater than 1mm in thickness. In this group, 15-20% will have micrometastasis on sentinel node biopsy.

Identification of micrometastatic disease in the sentinel lymph node is often followed by completion lymph node dissection.

While there is some evidence to suggest this procedure achieves local control, the available data do not show a survival advantage.

In view of this outcome and the significant potential morbidity associated with completion lymph node dissection, sentinel node biopsy has received only limited support in Australia.

In anticipation of adjuvant chemotherapy becoming an alternative to completion lymph node dissection for patients with a micrometastasis in the sentinel node, we suggest that patients with invasive melanoma on excision biopsy are referred to a rapid-access specialist multidisciplinary clinic for clinical staging (including sentinel node biopsy where indicated) and simultaneous re-excision of the scar.



The MAP kinase pathway normally links growth factor receptors to the nucleus by transmission of signals that promote growth and metastasis. The pathway is activated or inactivated in the presence or absence of growth factors on the cell surface. In the setting of BRAF mutation, the pathway remains constitutively activated without regard to growth factor activation of cell surface receptors. Chemotherapy that inhibits BRAF will attenuate growth in cells with a BRAF mutation (melanoma cells), but in other cells, compensatory activation of CRAF may lead to increased ERK expression. This is thought to be the mechanism of development of squamous cell carcinoma and keratoacanthoma as a side effect of BRAF inhibitors.

Figure 1: Mitogen-activated protein kinase pathway with and without BRAF mutation.

Table 1: Patient history

History	Significance
How long has the lesion been present?	Newly acquired lesions that persist for longer than one or two months may indicate neoplasm, particularly if the patient is in an older age group
Has a pigmented lesion changed in colour of shape?	Alteration in shape or colour may point towards malignancy
Has there been any bleeding?	Some benign lesions bleed (eg, pyogenic granuloma or seborrhoeic keratoses). Basal cell carcinomas may also bleed. In general, melanomas bleed only when well advanced and, in such cases, the diagnosis is usually obvious
Does the lesion itch?	Benign naevi or irritated seborrhoeic keratoses may itch when irritated by clothing, etc. While early melanomas are usually asymptomatic, some may develop an abnormal sensation that patients often find difficult to accurately describe
Is there a history of occupational sun exposure, or has the patient lived or worked in the tropics?	Skin cancers in general are related to lifetime sun exposure. Malignant melanomas may be related to a single severe episode of sunburn, particularly in childhood
Is there a family history of skin cancer?	This may indicate a genetic susceptibility, inherited skin type or condition such as dysplastic naevus syndrome

Table 2: Characteristics of benign vs potentially malignant lesions

Characteristic	Benign lesion	Potentially malignant lesion
Growth	Not growing	Growing, either slowly or more rapidly
Bleeding	Absent	Present
Number/location	Many other similar lesions	On a sun-exposed area of the body
Shape	Regular shape with smooth outline or line of symmetry	Irregular outline with no symmetry
Colour	Uniform pigmentation	Variation in colour throughout the lesion
Occurrence	Present for many years	New lesion

We suggest that patients with invasive melanoma on excision biopsy are referred to a rapid-access specialist multidisciplinary clinic for clinical staging.

Diagnosis

MELANOMA is a histological diagnosis. Pigmented or non-pigmented skin lesions clinically suspicious of melanoma require biopsy and histological examination. Complex histology and in particular, spindle-cell morphology may require immunohistochemical stains in addition to routine H&E examination. The histological interpretation of pigmented skin lesions is not always straightforward and dermatopathology has emerged as a subspecialty discipline within pathology.

Benign melanocytic naevus is usually a clinical diagnosis. Good lighting is critical. If the physician is 100% confident of the diagnosis following visual inspection, then no further action is indicated. The one caveat to this is that a history of unstable morphology (change in size, shape or colour) over several months would override the examination findings and is an indication for an excision biopsy or referral to a dermatologist.

Where a diagnosis of benign naevus cannot be made with 100% certainty on visual inspection, and ipso facto cutaneous melanoma cannot be 100% excluded on clinical grounds, the patient should be referred to a dermatologist or the lesion excised and sent for histopathology. Wherever possible, excision biopsy is preferred for diagnosis and formulation of a treatment plan. Complete excision of the suspicious lesion with a 2mm lateral margin and down to fat is recommended. Only sample a lesion by punch or shave biopsy if complete excision is difficult (eg, a large, facial pigmented lesion) because a biopsy may not be representative of the lesion as a whole, and it also alters the clinical appearance.

The initial excision of a suspicious pigmented lesion is a diagnostic procedure. It is done to exclude or confirm melanoma. Thus a benign histology does not mean that the procedure was unnecessary.

If histology proves the lesion to be a melanoma, then definitive wider surgical excision and assessment for sentinel node biopsy is needed. This should be explained to the patient before the initial excision.

Full-body photography on a single occasion can be useful in identifying new moles in patients. It is a helpful memory aid for the doctor and assists patients when performing self-mole checks. It is normal for occasional new moles to appear in adults until middle age. About one-third of melanomas appear in a pre-existing mole so it is more common for them to arise de novo than from a pre-existing mole. Thus the appearance of a new pigmented lesion or mole in an adult flags the possibility of melanoma. In general, full-body photography is most useful in patients with a high mole count (>100) who find self-examination difficult. Serial photography with or without serial dermoscopy of individual moles will identify early changes suggestive of melanoma, but is generally reserved for patients with multiple atypical naevi.

A single photograph of a benign naevus is sometimes used to document and support the clinical decision not to biopsy that benign naevus. However, serial mole photography should not be used to diagnose benign melanocytic naevi. In other words, if the physician cannot 100% exclude a diagnosis of melanoma on visual inspection the appropriate diagnostic test is a biopsy and not serial photography.

Clinical subtypes

THERE are several types of melanoma (figure 2). Superficial spreading melanoma is the most common type of melanoma, usually presenting as an irregularly pigmented macule. About 50% have functional mutations in the BRAF gene and 20% mutations in NRAS gene. About 30% of superficial spreading melanomas have no identified mutation in the ERK pathway.

Melanomas with NRAS mutations are more likely to be thicker tumours and to have a higher mitotic rate. In vitro, melanoma cells with NRAS mutations are dependent on NRAS for survival and proliferation. This would make NRAS an attractive therapeutic target in melanoma and once developed, pending an acceptable safety profile, chemotherapeutic agents that target NRAS could potentially make an important contribution to the future treatment of melanoma.

Nodular melanomas are aggressive tumours with an invasive growth pattern and can grow rapidly over weeks. They vary in colour from black through to red and amelanotic, and frequently defy the ABCD rule. The mnemonic EFG standing for 'elevated', 'firm' and 'growing for more than one month' is more appropriate. They can be pedunculated. Often they are mistaken for a haemangioma or a pyogenic granuloma. About 50% have functional mutations in BRAF and 20% mutations in NRAS.

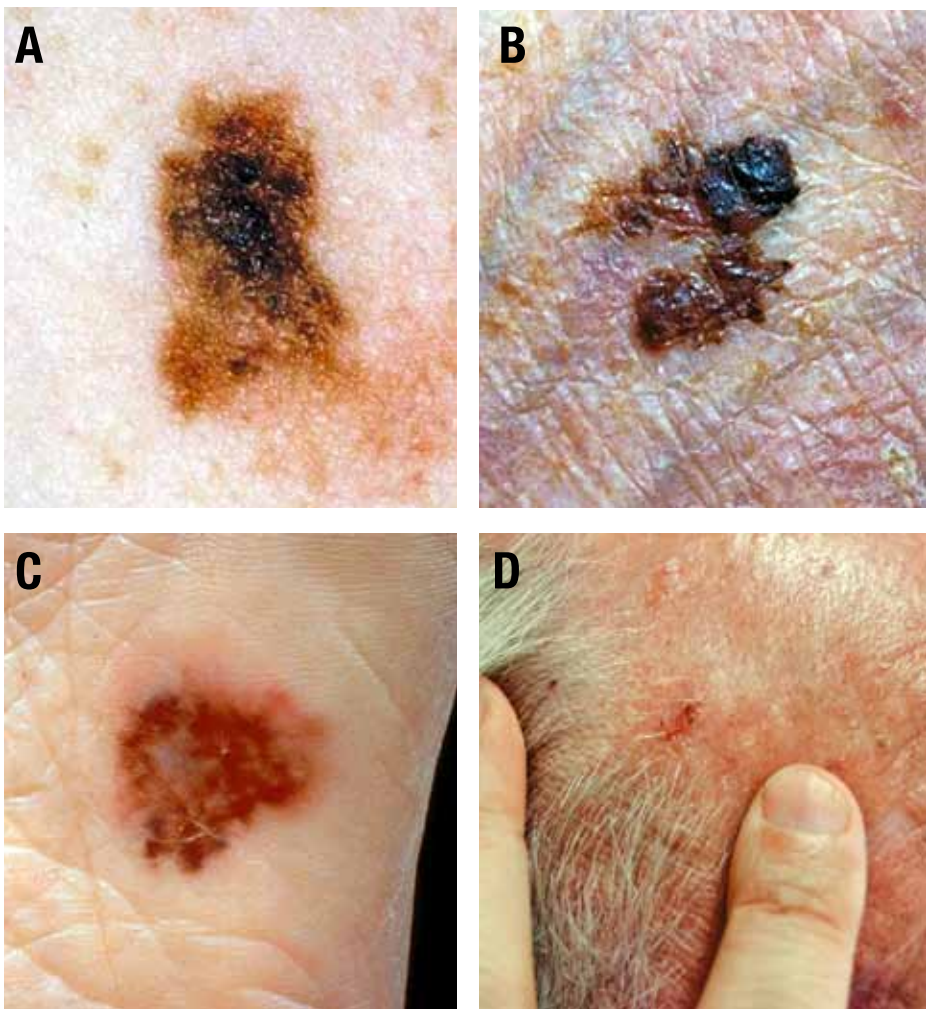


Figure 2: Clinical subtypes of melanoma.
A: Superficial spreading melanoma.
B: Nodular melanoma.
C: Acral lentiginous melanoma.
D: Amelanotic melanoma.

Acral lentiginous melanoma is the most common form of melanoma in the dark-skinned. These are seen on the palms, soles or nail bed. Not all melanomas at these sites are of acral lentiginous type. Acral lentiginous melanomas commonly have functional mutation in the c-kit gene.

Lentigo maligna (Hutchinson's melanotic freckle) is seen mostly on the face in sun-damaged elderly patients. They are a type of in situ melanoma with often a long delay before they become invasive. Patients will often be aware of these irregular, brown-to-black facial macules for many years. As such, they can be quite extensive at presentation even while still being restricted to the epidermis. Distinction from benign lentigo may be impossible without histology. Invasive melanoma or lentigo maligna melanoma (arising from a lentigo maligna) can sometimes complicate these lesions. Once this transition occurs it has the same behaviour and prognosis as de novo invasive melanoma. Invasion can develop rapidly so excision is usually advised.

Desmoplastic melanoma is a rare and aggressive subtype of melanoma that usually comprises a superficial pigmented in situ melanoma overlying a poorly differentiated non-pigmented dermal spindle cell melanoma.

Amelanotic melanoma is the most difficult to diagnose clinically. These may present as a pink nodule or patch on the skin. On dermoscopy a pigment network may be visible in some areas, but many are completely without pigment.

Ocular melanoma is rare and often diagnosed late. Uveal melanoma is associated with functional mutations in the GNAQ/GNA11 genes. These genes are not part of the ERK pathway.

Treatment

THERE are 10 steps in the management of invasive melanoma of the superficial spreading and nodular sub-types (see box, right). Subungual, mucosal, desmoplastic, ocular and acral lentiginous melanoma variants require management in a specialist centre. Further discussion of their management is beyond the scope of this article, as is the specific management of melanoma in situ.

Step 1. Excision of primary tumour

The majority of melanomas (70%) arise de novo in normal skin. A smaller percentage (30%) arises within a pre-existing acquired naevus or a congenital naevus (figure 3). Prophylactic excision of acquired naevi is not recommended. Prophylactic excision of congenital naevi is considered for large naevi where a satisfactory cosmetic outcome is achievable. For large congenital naevi (>20 cm in diameter) including bathing-trunk naevi, an alternative to prophylactic excision is lifelong serial surveillance of the patient and serial excisional biopsy of suspicious nodules that may develop within the naevus.

Excisional surgical biopsy with a lateral 2mm margin of normal surrounding skin and a deep margin that includes the subcutis is recommended for all lesions suspected clinically of being melanoma. Texts are available that describe the surgical procedure and set-up in detail. Where more than one lesion is excised, separate specimen bottles and accurate specimen labelling are essential.

The 10 steps in the treatment of invasive melanoma

1. Excision of the primary tumour. This remains the single most important step in the treatment of melanoma, and the principal determinant of patient survival
2. Tumour staging, including assessment for sentinel lymph node biopsy
3. Re-excision of surrounding skin with a margin determined principally by the Breslow thickness of the primary tumour
4. Adjuvant chemotherapy
5. Adjuvant radiotherapy
6. Adjuvant surgery
7. Surgery, chemotherapy and radiotherapy for stage IV disease
8. Follow-up surveillance for metastasis and subsequent primary melanoma
9. Lifestyle modification to reduce risk of subsequent primary melanoma
10. Counselling, taking into account the profound social, psychological and financial impact of a diagnosis of melanoma

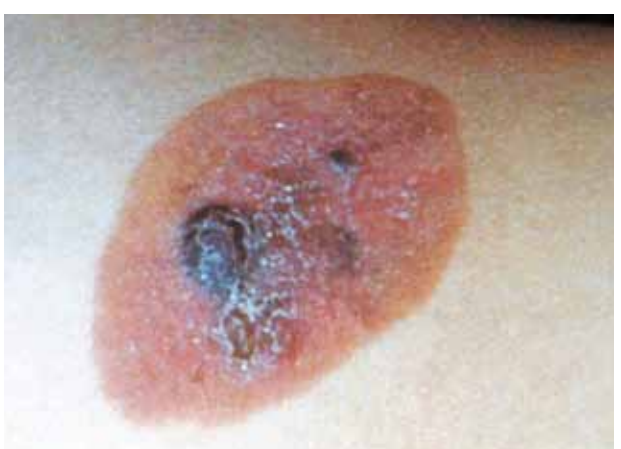


Figure 3: Melanoma arising in a giant congenital naevus.

Shave biopsy is only acceptable when excisional biopsy is not feasible. Referral for specialist assessment is appropriate if the treating doctor is not comfortable performing the biopsy of a suspected melanoma.

Punch biopsy risks sampling error when a melanoma arises within a benign naevus and is not generally recommended. However, punch biopsy does not adversely affect prognosis.

Periodic clinical observation with or without photography is not recommended for suspected melanoma as it delays diagnosis. Baseline photography is useful in some patients with multiple naevi to identify new or changing moles that are suspicious of melanoma.

Clinical suspicion is based on the history of a new or changing pigmented lesion or a new, enlarging non-pigmented nodule. Visual inspection of the lesion is the most valuable tool to identify lesions that require excisional biopsy to exclude melanoma and distinguish from benign skin lesions. Visual inspection is enhanced by illumination, magnification and polarised light or oil immersion to reduce surface reflection. Epiluminescence microscopy can help distinguish melanoma from benign naevus, seborrhoeic keratosis, haemangioma and other benign tumours. Dermoscopy requires specific training and several textbooks are recommended for those with a specific interest in dermoscopy. It is important to recognise that not all melanomas will have distinctive signs on visual inspection or dermoscopy. In addition, dermoscopy is not required for the diagnosis of most melanomas.

Population screening accelerates melanoma diagnosis and improves patient survival. While feasible, the costs and potential savings of a universal screening program in Australia are not known. In the absence of this information, screening is currently limited to patients identified to be at higher risk of primary melanoma or to people who self-select for a skin check.

High-risk patients that are usually advised to have regular screening include patients who have had one or more primary melanoma, patients with multiple non-melanoma skin cancers and some patients with multiple benign naevi. Many other at-risk patients, including those with a family history of melanoma, fair skin, red hair and freckles, also receive periodic screening. We developed informal guidelines on the appropriate frequency of skin checks for these people (table 3, see next page).

Step 2. Tumour staging

Histological staging should be provided by the pathologist in the form of a synoptic report. Clinical staging includes palpation of the regional lymph node basins and examination for hepatomegaly.

Sentinel node biopsy should be discussed with any patient with the following diagnosis: invasive melanoma greater than 1mm thick; Clark level 4 melanoma; melanoma with more than two mitoses per high-power field; ulcerated melanoma; melanoma with significant regression; or melanoma of unknown malignant potential.

Lymph node micrometastasis should be genotyped to determine whether it has acquired a BRAF (V600E) mutation. Currently, this is the key determinant of suitability for BRAF inhibition chemotherapy.

As the results of clinical trials become available and the range of chemotherapeutic agents increases, these recommendations are likely to be modified further. In remote and regional centres, where patients may not have access to clinical trials or multidisciplinary care, the recom-

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mendations regarding staging will vary.

Additional baseline staging for node-positive patients may include an FBC, and liver and renal function tests. A bone scan, CT scan, MRI or PET scan may also be required if the patient is to be enrolled in a clinical research trial. There are no guidelines available on the need for or frequency of repeat staging investigations in the absence of specific symptoms that suggest the presence of metastasis.

The recommended staging nomenclature is the AJCC system (table 4).

Step 3. Re-excise with a margin

In order to ensure complete removal of the primary melanoma, it is recommended that following excision of an in-situ melanoma (including Hutchinson's melanotic macule), the scar be re-excised with a minimum margin of 5mm. Where this is not possible, adjuvant radiotherapy can be considered. The role of imiquimod (Aldara) in this setting awaits further clarification through clinical trials, but results to date indicate a substantial failure rate. Following removal of an invasive melanoma, the scar should be re-excised with a margin of between 1 and 2cm, with the choice of excision margin determined primarily by the Breslow tumour thickness in millimetres (see box, right).

Wider excision has been demonstrated to reduce the risk of local persistence/recurrence of the tumour and local metastasis but there is no evidence that a margin greater than 1cm offers additional benefit in terms of patient survival.

Step 4. Adjuvant chemotherapy

Interferon alfa-2b

Immunotherapy with high-dose interferon alfa-2b is approved for use as an adjuvant treatment for surgically resected melanoma with regional lymph node metastasis (stage III disease). It potentially improves relapse-free survival by approximately 10% at five years and may have a small impact on overall survival. Benefit in the earlier stages of disease is less clear. These benefits must be balanced against considerable, but rapidly reversible, toxicity. In view of the toxicity associated with high-dose interferon alfa-2b, observation is presently considered an acceptable alternate strategy for patients with resected stage I or stage II melanoma.

Dacarbazine

The therapeutic armamentarium for melanoma has recently expanded. The standard therapy for advanced disease until recently has been dacarbazine. Its overall partial response rate is in the order of 10% with a minimal impact on survival. Furthermore, there is a high rate of immune-mediated side effects, some of which are potentially serious.

Ipilimumab

Ipilimumab is a fully human IgG1 monoclonal antibody that blocks the T cell surface protein CTLA-4 that has immunoregulatory functions. Ipilimumab was approved in March 2011 for metastatic melanoma and increased overall survival at three years by about 10%. Clinical trials providing ipilimumab as adjuvant chemotherapy for patients with high-risk melanoma have concluded in Australia and are currently under evaluation.

Table 3: Assessment of skin cancer risk

	High risk	Medium risk	Low risk
Skin check frequency	Annual full-body skin checks recommended	One-off full-body skin check recommended with the frequency of re-examination required determined at initial skin check	Patient self-examination recommended
Type I skin with red hair	age over 30	age 20-29	below age 20
Type I skin without red hair	age over 40	age 30-39	below age 20
Type II skin	age over 60	age 40-59	below age 40
Type III skin	—	over 60	below age 60
Type IV and V skin	—	—	all ages
Family history	melanoma in first-degree relative	NMSC in first-degree relative	—
Past history	non-melanoma skin cancer (NMSC) or more than 20 solar keratoses	solar keratoses, multiple episodes of sunburn	—

Definitions: Type 1 skin: burns, never tans. Type II skin: burns, occasionally tans. Type III skin: tans, occasionally burns. Type IV skin: tans, rarely burns. Type V skin: never burns.

Guidelines for excision margins for melanoma*

- melanoma in situ (restricted to epidermis) — margin 5mm
- melanoma <1.0mm thick — margin 1cm
- melanoma 1.0-4.0mm thick — minimum margin 1cm and maximum 2cm
- melanoma >4mm thick — minimum margin 2cm

*Recommended excision margins are under constant review.

Vemurafenib

Vemurafenib is an inhibitor of the oncogenic BRAF kinase. It received FDA approval in the US for metastatic melanoma in August 2011. It only has a role in melanomas that have a specific BRAF mutation at the V600 position. These mutations are found in about 50% of superficial spreading melanoma and nodular melanoma.

The overall response rate is 53%, though most tumours shrink to some extent, and the median duration of response is 6.7 months. In most patients the melanoma relapses as a result of the development of alternate oncogenic pathways. Research is now underway to identify ways of blocking these secondary pathways to offer real hope of longer-term survival and cure.

Vemurafenib induces a clonal T cell lymphocyte infiltration into melanoma, suggesting that the early response to this agent is due to immunological recognition of the tumour. There is a rationale that combination chemotherapy with ipilimumab or IL-2 may delay loss of response and relapse. Phase III clinical trials combining vemurafenib and ipilimumab have ceased enrolment in the US and are ongoing. Results are not yet available.

Dabrafenib

Dabrafenib is another BRAF inhibitor that, when used as monotherapy, has a similar benefit to vemurafenib. The BRAF inhibitors have significant (mainly cutaneous) toxicity including arthritis, photosensitivity, dermatitis, keratosis pilaris, hyperkeratotic palms and soles and the development of non-melanoma skin cancer. SCC and keratoacanthoma may develop in about 25% of people treated with a median time to development of eight weeks. These skin cancers show increased expression of ERK due to compensatory activation of the MEK pathway by CRAF. Many of the SCCs that develop in this setting have been found to have a KRAS G12 mutation that is thought to be co-stimulatory. Therapy can usually be continued as they are easily removed. During therapy, melanocytic naevi may also increase in number, change or disappear.

Combination chemotherapy

Combination chemotherapy using a BRAF inhibitor with the MEK inhibitor trametinib attenuates the toxicity of BRAF inhibitors and increases its efficacy. In phase II trials in metastatic melanoma there was an increase in initial tumour response, a substantial increase in duration of response and overall survival at one year was 79%. In contrast, only 25% of patients with stage IV melanoma were alive at one year without treatment. This is a rare example where combination chemotherapy does not enhance toxicity and combination BRAF/MEK chemotherapy is currently in phase II clinical trials in the US as adjuvant therapy for high-risk primary melanoma. As yet, there is no indication if or when these trials will be conducted in Australia.

However, the possible emergence of adjuvant chemotherapy as an alternative to completion lymphadenectomy for patients with a positive sentinel node has changed the landscape. We now recommend that this option should be discussed with all patients with a high-risk invasive melanoma. Where possible, patients with invasive melanoma should be given the option of early review (ideally within two weeks) in a specialist multidisciplinary clinic where assessment for sentinel node biopsy, surgical re-excision of the scar and genotyping of any lymph node melanoma can be performed.

Previous re-excision of the scar invalidates sentinel node biopsy because it interferes with the lymphatic drainage of the site. Patients with a high-risk invasive melanoma who may consider participating in an adjuvant therapy clinical trial subsequent to re-excision of the scar may require complete elective lymph node dissection for staging. There is significant morbidity associated with elective lymph node dissection and most adjuvant therapy clinical trials are not geared for this.

Step 5. Adjuvant radiotherapy

While primary radiotherapy is occasionally used for unresectable lentigo maligna or invasive melanoma, it is more commonly used as adjuvant radiotherapy for cutaneous melanoma likely to recur locally. Indications for adjuvant radiotherapy include a Breslow thickness >4mm, satellite nodules or neurotropic spread.

Adjuvant radiotherapy is also used to prevent recurrence following regional lymph node resection. Common indications include more than three nodes with metastasis, a large tumour mass in a single node or extracapsular spread.

Step 6. Adjuvant surgery

While some uncertainty remains about specific subsets of melanoma patients, therapeutic elective lymph node resection is generally not recommended as adjuvant surgical treatment. This is because there is no evidence to suggest a survival advantage and there is significant potential surgical morbidity, including postoperative lymphoedema.

Identification of suspicious lymph nodes on clinical examination should be followed by fine-needle aspiration and ultrasound imaging, MRI or PET. If nodal metastasis is confirmed histologically, immediate complete regional lymph node dissection is recommended. Cure rates in the order of 30% may be achieved with completion lymphadenectomy for palpable disease.

Completion lymph node dissection following identification of micrometastasis on sentinel lymph node biopsy is more controversial as the proportion of lymph node micrometastasis that progresses to symptomatic disease is not known. It has been suggested that early detection of occult nodal disease provides greater regional control. Patients who have completion lymph node dissection for micrometastatic disease develop fewer postoperative complications compared with patients who undergo therapeutic lymph node dissection for clinically palpable disease.

A prospective randomised multicentre selective lymphadenectomy trial (MSLT-I) comparing completion lymph node dissection with observation showed no difference in overall survival, however this is currently undergoing further investigation and patients with micrometastasis may be enrolled in the multicentre sentinel lymph node treatment trial MSLT-II.[1]

Up to 5% of patients with melanoma in lymph nodes or systemic metastasis have an occult primary melanoma. These patients should be referred for complete skin examination, including examination with a Wood's lamp to identify regressed melanoma. Referral for ophthalmological examination can also be considered. The ability to detect the primary melanoma does not influence the management of the metastatic disease.

Step 7. Surgery, chemotherapy and radiotherapy for stage IV disease

Patients with systemic metastasis require multidisciplinary specialist care. Surgical resection should be considered for isolated melanoma metastasis in the brain, lung or peritoneal cavity.

Clinical trials have identified a significant short-term survival advantage with single agent chemotherapy with ipilimumab, dabrafenib, trametinib and vemurafenib. An initial response is almost universal, but frequently short-lived. Tumour resistance to these agents is generally not reversed by substitution with a different single agent, but this may still be considered. The best response is seen in combination therapy with a BRAF inhibitor and a MEK inhibitor and in particular when dual therapy is used at the outset.

Unique in oncology, the addition of a second chemotherapeutic agent does not increase side effects and in fact reduces drug-induced toxicity.

The mechanism of this synergistic effect is that resistance to BRAF inhibitors leads to compensatory up-regulation of the AKT pathway that is prevented by the MTOR inhibitor. Up-regulation of the AKT pathway leads to both loss of efficacy and increased side effects, including skin toxicity and development of cutaneous SCC.

Conventional chemotherapy with dacarbazine or radiotherapy also has a role in the control of advanced disease.

Radiotherapy is often recommended for palliation of cerebral, bone or soft tissue metastasis. Iso-

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Table 4: Final version of 2009 AJCC melanoma staging and classification

TNM staging categories for cutaneous melanoma

Classification	Thickness (mm)	Ulceration status/mitoses
T		
Tis	NA	NA
T1	≤1.00	a: Without ulceration and mitosis <1/mm^2
		b: With ulceration or mitoses ≥1/mm^2
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	>4.00	a: Without ulceration
		b: With ulceration
	No. of metastatic nodes	**Nodal metastatic burden**
N		
N0	0	NA
N1	1	a: Micrometastasis*
		b: Macrometastasis†
N2	2-3	a: Micrometastasis*
		b: Macrometastasis†
		c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
	Site	**Serum LDH**
M		
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

NA = not applicable
LDH = lactate dehydrogenase
* Micrometastases are diagnosed after sentinel lymph node biopsy
† Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically

	Clinical stage grouping			Pathological stage grouping		
	T	**N**	**M**	**T**	**N**	**M**
O	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2b	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III	Any T	N1	M0			
	Any T	N2	M0			
	Any T	N3	M0			
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
IIIB				T1-4b	N1a	M0
				T1-4b	N2a	M0
				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0
				T1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	M1	Any T	Any N	M1

lated limb perfusion, radiotherapy or topical immunotherapy may be used to control in transit cutaneous metastasis. Palliative care health professionals play an integral role in the management of advanced melanoma.

Step 8. Follow-up examination for metastasis and subsequent primary melanoma

All patients diagnosed with invasive melanoma require periodic follow-up that includes examination and palpation for local recurrence, in transit metastasis, lymph node metastasis and hepatomegaly. Additional examination and investigation should be guided by reported symptoms.

For the 90% of Australians who survive melanoma, the risk of developing a subsequent primary melanoma is in the order of 10%. This risk is also influenced by other factors including family history, skin type, hair colour and the presence of significant solar skin damage including non-melanoma skin cancer (see table 3).

It is recommended that all melanoma patients, including those with in situ melanoma, have a complete skin check at least once a year for life following the diagnosis of melanoma.

As there is a familial tendency to melanoma, all first-degree relatives of a patient diagnosed with melanoma should be encouraged to attend for a full skin examination to identify a previously unsuspected melanoma and to assess risk of future development of melanoma. Relatives assessed to be at high risk should be offered a surveillance program.

Step 9. Lifestyle modifications to reduce risk of metastasis and subsequent primary melanoma

HRT or oral contraceptives are not contraindicated in women who have had a melanoma. It is common to advise women to avoid pregnancy for two years after apparently successful treatment of a high-risk melanoma during pregnancy, in accordance with the risk of metastatic recurrence.

Melanoma in a pregnant woman should be treated no differently to melanoma in a non-pregnant woman. Termination of a pregnancy may be considered if there is a pressing need to start radiotherapy or chemotherapy with traditional agents that will harm the fetus.

While melanoma is popularly attributed to UVB radiation, the actual UV action spectrum that causes melanoma is unknown. A number of animal models recently identified UVA as important in melanoma induction. In view of this as well as the systemic immunosuppression associated with UVA exposure, it is prudent to recommend melanoma patients avoid solaria (that predominantly emit UVA) and take precautions to minimise solar UV exposure. The 'Slip, Slop, Slap' message (ie, slip on a shirt, slop on some sunscreen and slap on a hat) should be reinforced to all melanoma patients. Some patients may require serial serum vitamin D estimation and oral vitamin D replacement if deficient. Sunscreens generally block UVB better than UVA but recent changes in sunscreen standards should result in better UVA blockage.

When first-degree relatives of the melanoma patient attend for their skin check, they should also receive advice regarding both primary and secondary prevention of melanoma. In particular, they should be advised to avoid solaria and take precautions to employ the Slip, Slop, Slap technique. Furthermore, they should be educated on the importance of early detection of melanoma and advised to seek medical assistance immediately should they suspect the development of a melanoma.

There is a growing body of evidence that patients with melanoma are also susceptible to other malignancies. While the risk of other solar-induced skin cancers is obvious, the relative risk associated with various internal malignancies is less obvious. These risks should be assessed in conjunction with any family history of internal malignancy, smoking and other cancer risk factors to determine whether any additional screening is appropriate.

Step 10. Counselling

Patients with invasive melanoma and their families will have complex social, psychological and financial issues. Life and income protection insurance may be declined even for people with thin melanomas. The nature and intensity of these issues will vary from person to person and with disease severity. Psychologists with experience in palliative care should be involved when the patients' needs and those of the family can no longer be met by the treating physician.

Author's case studies

Case study 1

LINDA was referred at 22 years of age with an atypical pigmented lesion on the back of her right shoulder that appeared clinically to be a melanoma (figure 4). She was advised of this and scheduled for surgical excision the next day.

She failed to attend for surgical excision and all attempts to contact her by phone over the next few days failed. Following advice from the medical defence organisation, a letter was sent by registered mail both to her home address and to her referring GP that outlined the provisional diagnosis, the possible implications of not having it excised, and inviting her to reschedule the surgery or seek a second opinion.

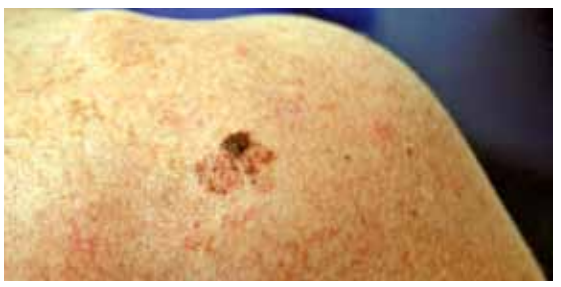

Figure 4: Stage IV superficial spreading melanoma, 0.6mm thick, on right shoulder.

Two weeks later, she phoned to say she had gone home to New Zealand to seek the advice of her GP father, who had arranged excision by a local surgeon. A copy of the histology report confirmed the lesion to be a 0.6mm thick, stage IV superficial spreading melanoma with two mitoses per high-power field. She attended for three-monthly follow-up for three years, then six-monthly follow-up for two years and then annual follow-up for a further four years.

Eleven months later and immediately post-partum, she was diagnosed with multiple systemic metastasis involving the brain and lung. The metastasis was BRAF-positive and she was commenced on vemurafenib. After an initial positive response, four brain metastases were surgically resected but the lung lesions were inoperable. Over the subsequent six months, the response to vemurafenib waned and the medication was stopped.

Following stereotactic radiotherapy, she is currently being evaluated for a combined BRAF/MEK inhibitor chemotherapy. While combined BRAF/MEK chemotherapy following the development of resistance to vemurafenib is associated with a 56% one-year survival and significant initial improvement in symptoms and disease burden, the cost to fund the therapy privately is in excess of $100,000.

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Conclusion

EXCLUDING non-melanoma skin cancer, melanoma is now the third most common cancer in Australia. Up until 2010, the gradual reduction in mortality has occurred as a direct result of improved rates of early diagnosis without concomitant improvement in the survival of advanced disease.

Chemotherapy for stage IV melanoma that is BRAF (V600E) positive is rapidly emerging and combination chemotherapy with a BRAF inhibitor and a MEK inhibitor shows particular promise. In one clinical trial, one-year survival improved from 25% to 79%, necessitating premature termination of the trial by the ethics review board. Unfortunately these agents are not suitable for BRAF-negative tumours, are not curative and most patients ultimately relapse and die. The role of these agents as adjuvant therapy to improve survival for high-risk melanoma patients is potentially of even greater significance and is currently being investigated.

These agents are expensive and not currently reimbursed through the PBS. Most patients gain access to these drugs through participation in clinical trials.

In order for melanoma patients to be eligible to participate in adjuvant therapy clinical trials, patients diagnosed with invasive melanoma should be referred to a specialist multidisciplinary clinic for staging and surgical re-excision of the scar.

Further reading

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2. Soyer HP, et al. *Color Atlas of Melanocytic Lesions of the Skin*. Springer, New York, 2007.
3. Australian Cancer Network — Melanoma Guidelines Revision Working Party. *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand*.
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5. Price C, Sinclair R: *Fast Facts — Minor Surgery*. 2nd edn. Health Press Ltd, Oxford, 2008.
6. Sinclair R. How to Treat — Skin cancer and benign lesions. *Australian Doctor*, 7 September 2012.

Online resources

Cancer Trials Australia Clinical Trials Register
www.cancertrialsaustralia.com/Clinical-Trials-Register.aspx

Reference

1. Morton DL, et al. Sentinel-node biopsy or nodal observation in melanoma. *New England Journal of Medicine* 2006; 355:1307-17.

How to Treat Quiz

Melanoma — 3 May 2013

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements are correct regarding epidemiology and aetiology of melanomas?

a) Melanoma is most commonly found in sun-exposed areas such as the lower lip, back of the ears and neck, as well as the forearms in men
b) Some melanomas may not be pigmented at all while others may be under fingernails and on the iris of the eye
c) Melanoma is a rare cancer in Australia because of the "slip slop slap" campaign
d) While some melanoma arise in congenital naevi, most new melanomas arise in normal skin

2. Which THREE statements are correct regarding the investigation, staging and surveillance of melanomas?

a) Full-body photography on a single occasion can be useful in identifying new moles in patients and assists patients when performing self-mole checks
b) Sentinel lymph node biopsy is only required in patients who have in situ melanoma where micrometastases may be presumptively missed
c) Clinical staging of identified melanoma includes palpation of the regional lymph node basins and examination for hepatomegaly
d) For staging purposes in sentinel node-positive patients, FBC, liver and renal function tests, bone scan, CT scan, MRI or PET scan may be performed

3. Which TWO statements are correct regarding the management of and survival from melanomas?

a) Survival at five years following newly diagnosed invasive melanoma has increased from 85% in 1986 to 90% in 2010 as a result of public education and early diagnosis and excision
b) In order for melanoma patients to be eligible to participate in adjuvant therapy clinical trials, patients diagnosed with invasive melanoma should be referred to a specialist multidisciplinary clinic for staging and surgical re-excision of the scar
c) Patients with multiple and large acquired naevi should be considered for prophylactic excision or treatment with imiquimod (Aldara)
d) Therapeutic elective lymph node resection in patients with invasive melanoma is recommended to improve survival

4. Mary is a 29-year-old Norwegian Australian with red hair and fair skin that burns occasionally and does not tan easily. She is 13 weeks pregnant and presents with a new 5mm diameter mole on her right leg. There are no other risk factors. Which TWO statements are correct?

a) New moles during pregnancy are normal, called melasma, and should be conservatively monitored until after delivery
b) Mary has type II skin and is younger than 40. Thus she has a low risk for melanomas and should be monitored for three months with serial photography
c) Mary's lesion should raise clinical suspicion because the legs are the most common sites for melanoma in women
d) If you cannot be 100% certain the lesion is benign, excision biopsy or referral is warranted

5. Mary tells you that the lesion has not been bleeding or sore. There is no family history of melanoma. Her father has had some BCCs removed. She recalls having been sunburnt a few times as a child. She now avoids sun exposure at the beach, but uses solaria. Which TWO statements are correct?

a) Mary should continue to tan in solaria rather than being exposed to UVB at the beach even if she uses good UVB sunblock for protection
b) Taking a family history and a history of previous episodes of sunburns can change the management of Mary's presentation
c) Mary's lesion is asymptomatic, which makes it more likely to be benign
d) While skin cancers in general are related to lifetime sun exposure, malignant melanomas may be related to a single severe episode of sunburn

6. The skin lesion looks elevated, firm and uniformly pigmented. The border is regular and symmetrical. Which TWO statements are correct?

a) All diagnoses of a melanoma requires dermoscopy. If you are not specifically trained in dermoscopy, any suspicious pigmented lesion should be urgently referred to a dermatologist
b) Epiluminescence microscopy can help distinguish whether this lesion is a melanoma or a benign naevus or some other benign tumour
c) In assessing Mary's nodular skin lesion, the ABCD rule dictates that her lesion should be followed for another three weeks for further changes
d) Visual inspection of Mary's skin lesion is the most valuable tool to determine whether an excision biopsy is needed

7. You discuss the options of referral to a dermatologist vs biopsy of the lesion. Mary chooses the latter.
Which TWO statements are correct?

a) A shave biopsy is not acceptable when the lesion can be readily excised
b) A punch biopsy should be the first step of any diagnosis in order to determine the margin required for the definitive excision biopsy if the biopsy is positive for melanoma
c) An excision biopsy with a lateral 2mm margin with a depth down to the subcutaneous fat is recommended
d) Empirical treatment with a topical antimetabolite such as imiquimod (Aldara) should be offered rather than an excision biopsy that may miss deep extensions and require re-excision

8. Mary returns three days later for the pathology result. The lesion is a nodular melanoma that is 1.22mm thick, Clark's level 4. Which TWO statements are correct?

a) The scar following removal of an invasive melanoma should be re-excised with a margin of 5mm followed by referral to a specialist clinic for annual surveillance
b) Clark's level provides the sole basis for prognosis when staging invasive melanomas
c) Before performing a re-excision of the scar you should consider referring her to a specialist multidisciplinary clinic for invasive melanomas
d) The scar will need to be re-excised with a margin up to 2cm, which will reduce the risk of local recurrence but not improve her rate of survival

9. Mary undergoes treatment at the melanoma multidisciplinary clinic. Which THREE statements are correct regarding the prognosis and follow-up?

a) Despite having undergone scar re-excision, sentinel lymph node biopsy, elective lymph node dissection, chemotherapy and radiotherapy, Mary's one-year survival has improved but her five-year survival has not
b) For the 90% of Australians who survive melanoma, the risk of developing a subsequent primary melanoma is in the order of 10%
c) Mary should have children within the two years following successful treatment of her melanoma before the melanoma recurs if it does
d) Mary will require periodic follow-up that includes examination and palpation for local recurrence, in transit metastasis, lymph node metastasis and hepatomegaly

10. Mary returns after visiting the melanoma multidisciplinary clinic for review. Which THREE statements are correct?

a) Mary's first-degree relatives now carry a higher risk of developing melanomas themselves
b) You should advise Mary that she may be at an increased risk of other internal malignancies
c) Mary should avoid taking oral contraceptives in the future because the additional oestrogen increases the risk of recurrence of her melanoma or the development of a new melanoma
d) Following complete and successful eradication of her melanoma, Mary may still have complex psychosocial and economic considerations

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Steve Liang**
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NEXT WEEK Erectile dysfunction is widely prevalent and the source of considerable morbidity, both for individuals and within relationships. The next two weeks of How to Treat will examine erectile dysfunction. Part 1 next week discusses initial evaluation and workup and gives an overview of therapy. Part 2 the following week investigates treatment options in depth. The author is **Dr Chris McMahon**, sexual health physician and director, Australian Centre for Sexual Health, St Leonards, NSW.