Melanoma and keratinocyte cancers

A guide for medical practitioners

SunSmart®

Australia has one of the highest rates of skin cancer in the world. At least 2 in 3 people in Australia will develop skin cancer in their lifetime.

Skin cancer is divided into two main types:

Melanoma

Melanoma develops in the melanocytic (pigment-producing) cells in the epidermis. Untreated, melanoma has a high risk for metastasis. The most common clinical subtype is superficial spreading melanoma (SSM) and is most commonly found on the trunk in males and lower limbs in females.

Melanomas can develop on any part of the body, including parts not heavily exposed to ultraviolet (UV) radiation.

In Victoria:

- Melanoma is the fifth most common cancer diagnosed.
- Every year, more than 2500 new cases of invasive melanoma are diagnosed and there are over 250 deaths from the disease.
- The risk of melanoma increases with age. However, melanoma is the third most common cancer in males and females aged 25–59.
- In Australia, the lifetime risk of developing melanoma by age 85 years is estimated to be 1 in 13 for males and 1 in 21 for females.

Keratinocyte cancers (non-melanoma skin cancers – NMSC)

- **Squamous cell carcinoma (SCC)** develops from the keratinocytes in the epidermis and is associated with risk of metastasis. SCC is most commonly found on the face, particularly the lip region, ears, nose, cheek and eyelid, and then on the neck, dorsa of hands and forearms in both sexes. In males, SCC is commonly found on the head and neck. In females, it is commonly found on the upper limbs, followed by the head and neck. It is believed that many SCCs arise from premalignant actinic keratoses.
- **Basal cell carcinoma (BCC)** also develops from keratinocytes in the epidermis and is the most frequently diagnosed cancer in Australians. BCC is most commonly found on the face: the eyelid, lip and nasolabial fold, followed by ears, nose and cheek in both sexes. In males, BCC is common on the neck, back and shoulders, and in females, on the neck, shoulders and outer arms.

Causes of melanoma and keratinocyte cancers

- Unprotected exposure to UV radiation remains the single most important lifestyle risk factor for melanoma and other skin cancers.
- UVA and UVB radiation contribute to skin damage, premature ageing of the skin and skin cancer.
- Melanoma and BCC are associated with both amount and pattern of sun exposure, with an intermittent pattern carrying the highest risk.
- Premalignant actinic keratosis and SCC are associated with the total amount of sun exposure accumulated over a lifetime.
- Other significant risk factors include immunosuppression, exposure to arsenic or ionising radiation, sunbeds or psoralen-UVA treatment, HPV infection and rare genetic conditions.

Risk factors for melanoma

- Personal history of melanoma
- Multiple atypical naevi (>5)
- Multiple naevi (>100 or >11 on arm)
- Family history of melanoma/Personal history of keratinocyte cancer
- Having fair or red hair and blue or green eyes
- Fair skin that burns easily, freckles and does not tan
- High levels of intermittent sun exposure (e.g. during outdoor recreation or sunny holidays)
- Immune suppression and/or transplant recipients
- Increasing age

See www.alfredhealth.org.au/melanoma-risk-calculator/public

Gender

In Victoria, males are 1.3 times more likely to be diagnosed with melanoma and over 2 times more likely to die from it than females. Mortality from melanoma increases with age and rises steeply for males from 65 years.

Prevention

Cancer Council Victoria recommends five steps to protect against sun damage during daily sun protection times:

Slip on sun-protective clothing – that covers as much skin as possible.

Slop on SPF50+ sunscreen – make sure it is broad-spectrum and water-resistant.

Slap on a hat – that protects the face, head, neck and ears.

Seek shade.

Slide on sunglasses – that meet Australian Standards.

Check the daily sun protection times on the free SunSmart Global UV app.

Dermatology Australasia

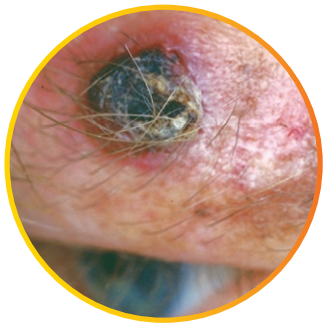
Cancer Council Victoria

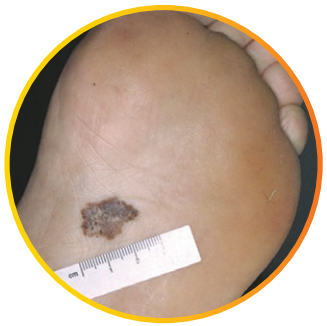
VICTORIA State Government

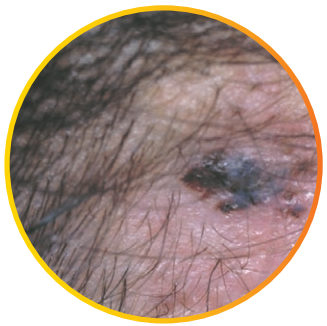
Superficial spreading melanoma (SSM)

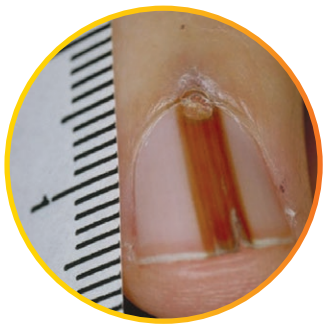
Melanoma can develop in pre-existing moles in the skin, or more commonly *de novo* from melanocytes found in the epidermis of previously normal-appearing skin.

- SSM is the most common form of melanoma.
- SSM can appear as a new spot or an existing spot, freckle or mole that changes size, colour or shape.
- A patient diagnosed with melanoma is at increased risk of new primary melanomas (relative risks ranging above 10).









The ABCDE acronym can help distinguish a superficial spreading melanoma from a normal mole:

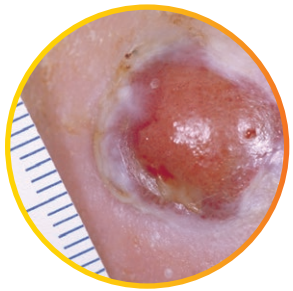
- **A** **Asymmetry:** the lesion is asymmetric in colour, shape or pattern.
- **B** **Border:** the border or outline of a melanoma is usually irregular.
- **C** **Colour:** there is variation in colour within the lesion.
- **D** **Diameter:** the lesion is greater than 6mm across. However, suspect lesions of smaller diameter should also be investigated.
- **E** **Evolving:** the lesion changes over time (size, shape, surface, colour, symptoms e.g. itch, bleeding).

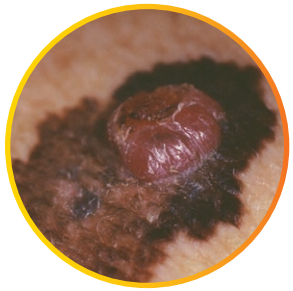
The use of dermoscopy by experienced clinicians has been found to increase diagnostic accuracy.

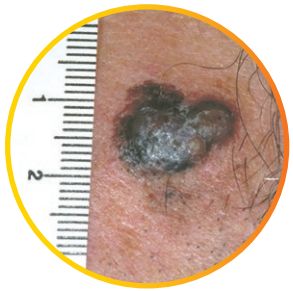
Nodular melanoma (NM)

This is an aggressive form of melanoma that grows quickly. NM differs from SSM in appearance and is easily misdiagnosed. NM has little radial growth within the epidermis but penetrates vertically into the dermis early. It is more likely to be symmetrical and uniform in colour (red, pink, brown or black), is more frequently less pigmented than SSM, and feels firm to touch. Over time, it may develop a crusty surface that bleeds easily.

- NM may grow rapidly and can be life threatening in 6-8 weeks.
- Approximately 15% of total melanomas diagnosed are NM.
- NM does not necessarily arise from a pre-existing mole and is commonly found on the head and neck.
- NM develops most commonly in older people, particularly men.







The ABCDE acronym cannot be used to aid diagnosis of nodular melanoma; however, the following features can be of help:

- **E** **Elevated:** the lesion can appear as a small, round and raised lump on the skin. Colour may be uniform throughout the lesion and may be black, brown, pink or red.
- **F** **Firm:** the lesion feels firm to touch.
- **G** **Growing:** a nodule that has been growing progressively for more than a month should be assessed as a matter of urgency.

If nodular melanoma is suspected, urgent diagnostic excision is recommended. Diagnosis should not be delayed, and urgent referral to a non-GP specialist or immediate excision is recommended.

Biopsy and excision for melanoma or suspicious naevi

- Complete excisional biopsy with a 2mm margin and upper subcutis (underlying fat) is recommended.
- Partial biopsies (e.g. punch biopsies and shave excisions) can be less accurate than excisional biopsy and should be performed by trained practitioners.

Unless suitably experienced, suggest referring the following lesions to Tertiary level of care:

- high-risk melanoma (deeply invasive >1mm)
- metastatic melanoma
- lesions at sites that are difficult to biopsy e.g. nails
- lesions with histological uncertainty
- incompletely excised lesions, that cannot be treated definitively in primary care.

Where appropriate, referral to a non-GP specialist should occur within two weeks. There will be selected patients where management in primary care is appropriate.

Treatment for melanoma

Selecting appropriate primary treatment will depend on the Breslow thickness (vertical depth) of the tumour. Breslow thickness is measured using the following system:

- (pTis) Melanoma *in situ*. The abnormal cells are found only in the non-vascular epidermis and have not penetrated into deeper tissue that contains blood vessels.
- (pT1) Melanoma cells reach the upper part of the dermis. The melanoma is up to 1mm thick.
- (pT2) Melanoma cells reach the upper part of the dermis. The melanoma is between 1.01mm and 2mm thick.
- (pT3) Melanoma cells reach deeper into the dermis. The melanoma is between 2.01mm and 4mm thick.
- (pT4) Melanoma is more than 4mm thick or it has invaded through the dermis and into the underlying fat.

Treatment is based on the T1–T4 classification. Wide excision of the primary tumour is recommended with the following safety margins for each of the T-classification groups:

- (pTis) Melanoma *in situ*: 5–10mm clearance
- (pT1) Melanoma <1.0mm: 1cm clearance
- (pT2) Melanoma 1.01–2.0mm: 1–2cm clearance
- (pT3) Melanoma 2.01–4.0mm: 1–2cm clearance
- (pT4) Melanoma >4.0mm: 2cm clearance.

Note: Evidence for optimal excision clearance for melanoma 2–4mm thick is unclear.

The *Clinical Practice Guidelines* recommend it may be desirable to take a wider margin for these tumours, depending on tumour site and surgeon/patient preference.

In some cases of melanoma in situ 5mm margins are inadequate and may lead to significant rates of disease recurrence.

Other treatment options

Patients with melanomas >1mm thick should be referred to a specialised melanoma unit for multidisciplinary team input.

Surgery

Sentinel lymph node biopsy (SLNB) should be discussed with patients with pT2 and thicker lesions, and performed by trained practitioners. SLNB may also be offered to patients with melanomas >0.75mm thick with other high risk pathological features.

Surgical resection of isolated metastases can be performed in both definitive and palliative treatment settings.

Immunotherapy

- For unresectable or as neoadjuvant treatment for stages III and IV melanoma (melanoma.org.au/news/major-advance-for-neoadjuvant-treatment-of-melanoma/)
- PD-1 inhibitors (Nivolumab, Pembrolizumab): given as IV infusion
- CTLA-4 inhibitor (Ipilimumab): given as IV infusion

Note: Immunotherapy can cause a unique set of side effects, referred to as immune-related adverse events. Patients with pre-existing auto-immune conditions are at risk of exacerbation of their auto-immune disease. Practitioners involved in managing these patients should seek expert advice from the patient's treating unit if toxicity is suspected.

Targeted therapy

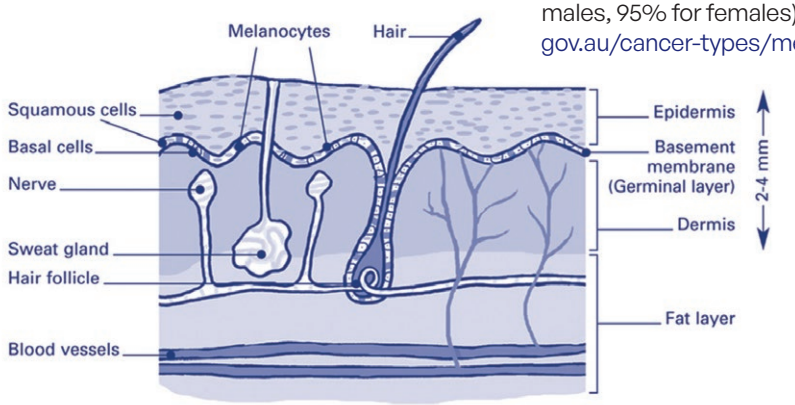
- BRAF inhibitors (Dabrafenib and Vemurafenib): for treatment of BRAF V600 +ve unresectable stage III or stage IV metastatic melanoma, oral tablets
- ~50% of all melanomas have mutation in BRAF gene
- Used in combination with MEK inhibitor (Trametinib)

Radiation

Radiation treatment can be used to treat lentigo maligna when surgical approaches are considered less suitable. Post-operative radiotherapy can be performed for melanomas likely to recur locally or regionally. Radiotherapy can be used for palliative management of cerebral and bone metastases, and for other metastases where temporary local control is needed.

Follow-up for melanoma

After the removal of a primary melanoma, in most circumstances follow-up care can safely and effectively be provided in the primary care setting. For patients who have had treatment for metastatic melanoma, the short-term follow-up should be shared between the specialist and the primary care practitioners until specialist assessment is no longer considered necessary.



Surveillance after curative treatment for melanoma can be as follows:

- Patients should be seen 6 monthly for 2 years, then at least annually for an indefinite period.
- Tumours more than 1mm thick: follow-up 3–4-monthly for the first two years, 6-monthly review to five years, and lifelong yearly review thereafter.
- Stage III disease: follow-up 3–4-monthly for the first two years, 6-monthly for the next two to three years, and then as deemed clinically necessary.

Imaging/total body photography may be required according to clinical indication and stage of disease. Patients with asymptomatic stage I–II disease do not require routine scans. Once the intense follow-up has finished there should be a minimum of annual skin surveillance. Follow-up assessment should include a comprehensive history and examination including examination of the primary site and lymph nodes and potential sites of metastases and full skin assessment.

Patients should be made aware that self-examination is essential. Preventative information about sun protection should be provided to patients to prevent future skin cancers. Supportive care needs should be assessed and recorded.

Survival

In Australia for the period 2015-2019, the 5 year survival rate for melanoma was 94% (92% for males, 95% for females). www.canceraustralia.gov.au/cancer-types/melanoma/statistics

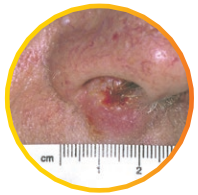
Clinical practice guidelines for the diagnosis and management of melanoma. www.cancer.org.au

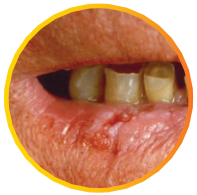
Keratinocyte cancer

Diagnosis

Squamous cell carcinoma (SCC)

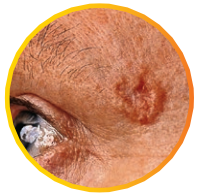
- It appears as a thickened, red, scaly nodule that may bleed, is usually tender when pressed and ulcerates over time.
- May arise from solar keratoses.
- It grows over a period of some months. Rapid growth is associated with increased risk of mortality.
- SCC can spread to other parts of the body if not treated. Lesions on the ears and lips have a higher risk of metastasis. Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology if possible. Open surgical biopsy should be avoided.
- SCC in situ (Bowen's disease) occurs when abnormal cells are confined to the epidermis. SCC in situ appears as a red scaly plaque and if left untreated, carries a small risk of progressing to invasive SCC.

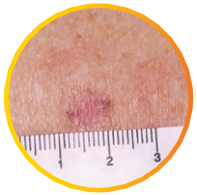




Basal cell carcinoma (BCC)

- BCC is the most common and least dangerous form of skin cancer.
- It appears as a well-defined lump or scaly area that is red or pearly in colour.
- It may bleed or become ulcerated early on, then heal and break down again.
- It usually grows relatively slowly.





Treatment

Treatment options for keratinocyte cancer include:

Surgical:

- Wide local excision
- Curettage and cautery
- Mohs micrographic surgery

Non-surgical:

- Topical agents (5-fluouracil for multiple solar keratosis or localised Bowen's disease, Imiquimod cream for biopsy proven superficial BCCs less than 2cm diameter)
- Cryotherapy, to be used in appropriate cases only. Double freeze thaw technique
- Radiotherapy
- Photodynamic therapy for superficial BCC and SCC in situ
- Rarely chemotherapy or immunotherapy

The choice of treatment will depend on:

- Histological features
- Tumour size
- Thickness and grade
- Anatomical site
- Patient factors

Follow-up

Frequency of follow-up of patients treated for keratinocyte cancer for evidence of recurrence, metastasis and/or any new primary skin cancers will depend on histological clearance and risk level of tumour. Patients should be educated on recognising changes in their skin (including examination of draining lymph nodes for patients with SCC), have a professional full skin examination as deemed appropriate, and have further investigations as required.

Clinical practice guidelines for keratinocyte cancer: basal cell carcinoma, squamous cell carcinoma and related lesions
www.cancer.org.au

Screening for melanoma and keratinocyte cancer

There is no evidence demonstrating that population-based screening for melanoma and keratinocyte cancer is effective in reducing morbidity or mortality, and it is not recommended.

Skin surveillance is recommended for patients identified to be at high risk of melanoma and keratinocyte cancer, including patients with a previous diagnosis of melanoma.

Skin self-examination

Approximately 50% of melanomas are detected by the patient. There is no specific technique or recommended frequency of self-examination that has shown to reduce morbidity; however, regular skin examination may increase the probability of detecting skin cancer at an early and treatable stage.

Patients at high risk for melanoma should:

- Be taught to self-screen (including examination of draining lymph nodes) and recognise suspicious lesions
- Have a full body examination with a clinician every 6 to 12 months.

Patients treated for keratinocyte cancer should:

- Be taught to self-screen and recognise changes to their skin
- Have a full body examination with a clinician every 12 months.

For the general population, the Australasian College of Dermatologists recommends that people examine their skin 4 times a year or as often as recommended by their medical practitioner.

Adapted and revised with kind permission from Cancer Council New South Wales, 2016. Images are supplied courtesy of the Sydney Melanoma Diagnostic Centre and the Victorian Melanoma Service

Victorian skin cancer clinics

Skin cancer clinics provide specialised diagnostic services and treatment services. Melanoma management and treatment is guided by a multidisciplinary panel including pathology services, medical specialists, treatment options and clinical trials. Patients may be referred to these units by their GP or specialist.

Victorian Melanoma Service
Alfred Hospital, Commercial Road,
Melbourne VIC 3004
T 9076 0365 **F** 9076 5799

Melanoma and Skin Service
Peter MacCallum Cancer Centre,
Victorian Comprehensive Cancer Centre building, 305 Grattan Street, Melbourne VIC 3000
T 8559 5000 **F** 8559 7371
E referrals@petermac.org

Royal Melbourne Hospital Melanoma Service
300 Grattan Street, Parkville VIC 3052
T 9342 8187

Austin Hospital Melanoma Clinic
Medical Oncology Unit
Level 6, Harold Stokes Building
145-163 Studley Road,
Heidelberg VIC 3084
T 9496 5763 **F** 9457 6698

St Vincent's Dermatology Clinic
41 Victoria Parade, Fitzroy VIC 3065
T 9231 2898 **F** 9231 3489

Skin Health Institute
Level 1, 80 Drummond Street,
Carlton VIC 3053
T 9623 9400

Bendigo Health Dermatology Clinic
100 Barnard Street, Bendigo VIC 3550
T 5454 8896

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