Established Malignant Melanoma Pathway

This pathway is for adults who have recently been diagnosed with melanoma and those being actively treated by a specialist or specialist unit. See also the Melanoma Follow-up Pathway and Melanoma referral Pathways

Disclaimer

Contents

About malignant melanoma[1]

- The prognosis of melanoma is highly variable, ranging from > 95% five-year survival for a thin lesion to 10% five-year survival for stage IV disease.
- There are various histological types. Superficial spreading melanoma predominates, especially in white skinned individuals. In darker skinned persons, acral lentiginous melanoma (uncommon in Caucasians) is commonly seen.
- 15 to 20% of patients with melanoma develop lymph node metastases (Stage III disease) over time. Staging by appropriate modality imaging is followed by resection of the nodal basin involved.

Red flags

Red flags signal the most serious clinical risks that are easily missed. The list is not comprehensive. Each one meets all these criteria:

- *It indicates a serious differential diagnosis, or high risk of deterioration without intervention, or severe treatment risk.*
- *It is commonly missed, or not widely known.*
- *If missed, it can significantly threaten the patient's health or have legal consequences for the clinician.*

The red flags for established malignant melanoma are:

- ❖ Inadequate excision
- ❖ Signs of local, regional nodal, or distant recurrence
- ❖ Immunosuppression with infection

Assessment

1. If new diagnosis of melanoma is confirmed by excision biopsy:
   - Assess the healing wound and arrange suture removal.
   - Assess whether adequate histological clearance margins have been achieved.

Clearance margins[1]

Initial excision	
Suspected melanoma	2 mm
Benign lesions, dysplastic naevi	2 mm
BCC nodular	2 to 3 mm
BCC other	4 to 5 mm
SCC in situ (Bowen's disease)	2 mm
SCC	3 to 5 mm
Re-excision	
Melanoma in situ	5 mm
Lentigo maligna	5 to 10 mm (occasionally more)
Thin < 1 mm Breslow thickness[1]	10 mm with sentinel node biopsy if thickness > 0.75 mm
Intermediate 1 to 4 mm Breslow thickness[1]	10 to 20 mm with sentinel node biopsy
Thick > 4 mm Breslow thickness[1]	20 mm (occasionally more) with sentinel node biopsy
Histological margin for SCC or BCC < 1 mm	Discuss with specialist taking into account clinical and histological features of high risk BCC or SCC.

This table is a guide only. Recommended excision margins depend on many variables and involve weighing risks of wider excision with those of recurrence. Definitive evidence based recommendations remain elusive. Best practice relies on thorough deliberative evidence based consensus guidelines (still in review 2019). Updated guidelines will be made available as links in this table when released. Seek specialist advice if in doubt.

- Examine the regional lymph nodes and consider re-examining the skin for other suspicious lesions. See Suspected Melanoma Pathway.
- If adequate excision has been achieved and there are no signs of metastases, assess for factors that predispose to further melanomas

Factors that predispose to melanomas

Patient factors:

- High past sun exposure (especially in childhood), including sunburn and sun damaged skin
- Past melanomas especially at an early age, or multiple primary melanomas (melanoma is uncommon under the age of 12 years but can occur)
- Personal history of non-melanoma skin cancers
- Immunosuppression – especially organ transplant recipients, lymphoproliferative disease, radiation exposed patients, and HIV/AIDS
- Multiple benign (> 100) and/or > 5 atypical naevi

Atypical naevi

An atypical naevus is a mole with ≥ 3 of:

- Size > 5 mm diameter
- Ill-defined or blurred borders
- Irregular margin resulting in unusual shape
- Varying shades of colour – mostly pink, tan, brown, black
- Flat and bumpy components
- Erythema

See DermNet NZ – Atypical Melanocytic Naevus

- Congenital naevi confer a slightly increased risk
- Any large dysplastic naevus (> 20 cm, which are rare) warrants referral

Family history:

- Melanoma – melanoma risk approximately doubles with each first-degree relative. Family history of 3 or more family members may warrant genetic testing
- Familial- atypical naevi[2]
- Certain associated cancers. See also Cancer Council Victoria – Familial Melanoma.

2. If patients are under specialist treatment for metastatic melanoma:

- Take a history including a limited systems review

History

In particular, ask about:

- signs of infection, especially for immunosuppressed patients and those on immunotherapy, targeted therapy, or both.
- other intercurrent illness or recently developed co-morbidities which require notifying the treating team.
- local symptoms, skin or subcutaneous changes, and new lesions whether pigmented or not.
- symptoms of lymphoedema if lymph node clearance (or even biopsy) has been performed.

- current smoking status, social support, and lifestyle, including diet, exercise, sleep, home environment
- factors which increase the probability of melanomas

Factors that predispose to melanomas

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- side effects to all treatment:
  - Common side-effects to all treatment modalities

These symptoms are common to all treatment modalities:

- Lethargy
- Gastrointestinal symptoms
- Fever, which occurs in up to 50% of patients on targeted therapy and does necessarily mean infection[1]
- Sweats
- Infections, e.g. respiratory, mouth

  - Side effects-of targeted therapy

Side-effects of targeted therapy

About half of melanomas have a mutated BRAF oncogene which encodes an oncogenic protein, B-Raf. BRAF and MEK inhibitors target different proteins in this oncogenic pathway. BRAF inhibitors include vemurafenib, encorafenib, and dabrafenib. MEK inhibitors include trametinib, binimetinib, and cobimetinib. These are oral and generally well tolerated.

BRAF inhibitors:

- Common side-effects:
  - Rash, skin irritation and photosensitivity, nausea, modest increase in squamous cell carcinoma and keratoacanthoma
  - Headache, fever, joint pain, fatigue, hair loss

- Rare but serious side-effects:
  - Heart arrhythmias or failure, severe eye problems or vision loss, skin infections
  - Excess bleeding and lung problems

MEK inhibitors:

- Common side-effects:
  - Rash, skin irritation and photosensitivity, nausea, modest increase in squamous cell carcinoma and keratoacanthoma
  - Diarrhoea, rash, nausea, organ inflammation
- Rare but serious side-effects:
  - Hepatic, cardiorespiratory or renal failure, severe allergic reactions
  - Hyperglycaemia, bleeding disorders, vision problems, muscle damage, and skin infections

See also:

- American Cancer Society – Targeted Therapy for Melanoma Skin Cancer
- Immunotherapy Related Adverse Events

- Chemotherapy – now rarely used except in terminal palliation.

Chemotherapy side-effects

- Fever, sweats, local infections
- Mouth sores
- Fatigue
- Loss of appetite, weight loss
- Nausea, vomiting
- Diarrhoea or constipation
- Easy bruising or bleeding
- Hair loss

- Radiation therapy – ask about skin problems and dysfunction of the organs in the radiated field.

Radiation therapy side-effects

- Hair loss if scalp melanoma is treated
- Skin effects, including recurrent cellulitis as a sequel of lymphoedema, especially if immunocompromised
- Field-specific mucosal effects, e.g. dry mouth, dysphagia
- Bone flare pain following radiation therapy
- Lymphoedema peripheral to node fields irradiated

See also Cancer.Net – Side Effects of Radiation Therapy

- Perform an examination assessing weight, skin, lymph nodes, and potential metastasis sites.

Examination

- Measure and record weight
- Assess for signs of regional lymph node involvement

- Assess for signs of distant recurrence, e.g. unexpected weight loss or signs of hepatic, brain, or bone involvement
- Examine the skin for synchronous primaries or further melanomas, looking carefully for new squamous cell carcinoma and keratoacanthoma if the patient is on immunotherapy
- Assess for physical sequelae of surgical treatment, particularly field of excision, local lymph fields, and for lymphoedema.

- Review:
  - Intention of treatment detailed in the cancer treatment summary letter

Cancer treatment summary letter

Most importantly should include:

- risk of recurrence and intentions of treatment.
- goals and quantitative benefit of proposed treatment.
- risks of treatment.
- what the patient has been told

Usually includes:

- diagnostic tests performed and results.
- tumour characteristics and other factors determining prognosis.
- type and date of treatments and a treatment summary.
- expectations of disease course, including expected discharge from oncology services.
- interventions and treatment plans from other health professionals.
- a process for rapid re-entry to specialist medical services for suspected recurrence.
- a list of symptoms that might need prompt investigation.
- a list of supportive care services provided and a plan for community care services, including what each service is to provide.
- contact information for key care providers.

Intention of treatment

This is modified by indicators of poorer prognosis:

- Older patients
- Melanoma sited on upper arm, back, neck, or scalp
- Males, Aboriginal and/or Torres Strait Islander, Maori or Pacific Islanders, other diverse background.
- Histological melanoma type
- Poorer survival rates by stage (improvements in prognosis from current advances are not yet reflected in these figures) which include:
  - extent of local invasion
  - greater involvement of regional nodes on sentinel node biopsy, lymphadenectomy or imaging (optimally PET scan). See PET scan Medicare eligibility

Curative intent:

- Applies to stage 1 or 2 disease, and excision is usually extremely effective.

- Other options include immunotherapy (including agents undergoing clinical trials) and radiation.

Non-curative intent:

- Anti-cancer therapy to improve quality of life or longevity without expectation of cure.
- Symptom palliation which may include other modalities to reduce tumour mass, including cytotoxic treatment.
- patient centredness, especially understanding, hopes, and expectation
- investigations and imaging used in staging

Investigations and imaging used in staging

- Common investigations:
  - FBE
  - Urea, electrolytes and creatinine, serum magnesium
  - Liver function tests
  - Calcium and phosphate levels
  - BRAF mutational status

BRAF mutational status

- Ensure familiarity with the BRAF mutational status
- BRAF status is critical in determining the management of advanced disease.
- 50% of melanomas have mutations of the BRAF gene, which may be susceptible to drugs targeting BRAF pathways, e.g., BRAF and some MEK inhibitors[1]

- Optimal staging imaging modality is PET scan, but appropriate modalities include PET/CT and MRI brain. See Medicare eligibility.

- Enquire about family, including supports and effects of the diagnosis on family members. Ask about a family history in three first-degree relatives, of melanoma or other cancers especially pancreatic cancer.

Management

Manage fever carefully

Manage fever in patients on targeted therapy or immunotherapy in consultation with the treating team as a certain degree of fever in the absence of infection is common with these agents.

Patients with new diagnosis of melanoma confirmed by excision biopsy

1. Manage preventative health

Preventive health

- Avoid or defer minor procedures e.g., routine cervical screening during chemotherapy treatment.
- Maintain immunisation recommendations, noting guidelines for immunocompromisation if relevant.
- If significant family risk, consider genetic testing. This may require tertiary centre attendance, is not routinely performed, and may be costly if Medicare criteria are not met.
- Encourage physical activity and a healthy diet high in vegetables and fibre. A safe recommendation is a diet consisting of foods rich in vitamin D and carotenoids, and low in alcohol and refined sugar[1] If the patient is taking nutritional supplements, enquire whether the caloric and protein component can be obtained from natural food, minimising supplementary sugars. Advise sun protection and provide patient education.

Patient education

It is important that the patient:

- avoids excessive sun exposure.
- understands skin surveillance and the value of photography by themselves and specialist services.
- has regular inspections to detect recurrence or new primary melanoma.
- understands the role of blood tests and imaging in melanoma, and the importance of regular follow-up.
- understands the importance of catching nodal metastases early to improve survival.

2. Ensure adequate understanding of the condition and outlook.
3. For histologically confirmed melanoma with adequate clearance margins[3] and no evidence of regional or distant metastases, arrange Melanoma Follow-up**.**
4. For biopsies with incomplete excision including partial biopsies, arrange for re-excision. If referral is required to ensure adequate re-excision, arrange as per Skin Lesion Excision pathway.
5. If enlarged lymph nodes in drainage fields or hepatomegaly, refer to a surgeon who treats complex melanoma for staging e.g., sentinel node biopsy, CT or PET imaging.

Patients with metastatic melanoma undergoing specialist management

General practitioners perform a shared care role. Management as per points below is always in consultation with the treating team.

1. Manage preventive health
2. Ensure adequate understanding of the condition and outlook.
3. If there is sepsis or serious side effects of therapy, request acute oncology assessment.
4. To avoid missing fever in biologic agents, seek acute oncology advice. While a certain degree of fever in the absence of infection is common with these agents, do not manage without consultation.
5. Make sure the patient knows the intention of treatment. General practitioners generally avoid discussion about poor prognosis despite patients desire for it.[1] Discuss sensitively and advise early referral for palliative care services which can improve quality of life, and in some cases, survival. Offer enrolment in clinical trials if they offer feasible options more aligned with patient hopes and expectations.

6. If patient has lymphoedema or high risk of lymphoedema, manage and refer early to the appropriate service.
7. If signs of unexpected recurrence or spread during active treatment, arrange referral within 1 week for one of:
    - non-acute oncology assessment
    - review by the treating general surgeon with experience in complex melanoma
    - plastic surgeon if appropriate.
8. Manage in primary care:
    - mental health concerns or emotional distress:

      Emotional distress

      Emotional distress may be experienced due to a variety of factors:

        - Anxiety and/or depression due to the trauma of the diagnosis and treatment
        - Fear of disease recurrence
        - Changes in body image
        - Returning to work
        - Interpersonal problems and sexuality concerns.

      - Consider referral for cancer supportive care services for counselling, or if familial cancer and family distress, referral for familial genetic counselling service. Alternatively, provide Cancer Victoria support line **13-11-20**.

      Familial genetic counselling service

      If significant family risk, consider genetic testing. This may require tertiary centre attendance, is not routinely performed, and may be costly if Medicare criteria are not met.

      - Manage depression and anxiety.
      - Advise about free relaxation and meditation CDs provided by the Cancer Council Victoria.
      - Refer to Look Good, Feel Better programs.
    - side-effects of treatment in consultation with the treating team – remain highly vigilant and assume new symptoms to be caused by immunotherapy:
        - Common side-effects to all treatment modalities
        - Side-effects of targeted therapy
        - Chemotherapy – now rarely used except in terminal palliation

    - Radiation therapy – ask about skin problems and dysfunction of the organs in the radiated field
- co-morbidities, intercurrent illnesses, notifying the treating team.

Referral

You can find the Melanoma Referral Pathways here

- If there is sepsis or serious side-effects of therapy, request acute oncology assessment
- If non-serious immunological side-effects e.g. fever without acute illness, seek acute oncology advice.
- If signs of unexpected recurrence or spread during active treatment, arrange referral within 1 week for one of:
    - non-acute oncology assessment
    - review by the treating general surgeon with experience in complex melanoma
    - plastic surgeon if appropriate
- If patient with newly diagnosed melanoma and:
    - completely excised, request non-acute dermatology assessment.
    - enlarged lymph nodes in drainage fields, or hepatomegaly, refer to a surgeon who treats complex melanoma for staging e.g. sentinel node biopsy, CT or PET imaging.
- If mental health concerns or emotional distress, consider referral for cancer supportive care services and Look Good, Feel Better programs.
- Refer as early as appropriate to palliative care, based on need, not prognosis. Early referral can improve quality of life and in some cases, survival. Consider enrolment for research and clinical trials, where available and appropriate.
- If a significant familial cancer is identified, refer for familial genetic counselling service. Alternatively, provide Cancer Victoria support line **13-11-20**.

Information

For **health professionals**

- American Cancer Society:
    - Survival Rates for Melanoma Skin Cancer, by Stage
    - Targeted Therapy for Melanoma Skin Cancer
- Cancer Council Victoria – Optimal Cancer Care Pathway for People with Melanoma
- Cancer Research Institute – Immunotherapy for Melanoma

For **patients**

- Cancer Council – What to Expect: Melanoma
- Cancer.net – Side Effects of Radiation Therapy
- Melanoma Research Foundation – Just Diagnosed with Melanoma... Now What?

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