WA Kirkbride
MELANOMA ADVISORY SERVICE

INFORMATION FOR MEDICAL PRACTITIONERS

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Government of **Western Australia**
Department of **Health**
WA Cancer and Palliative Care Network

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WA Kirkbride Melanoma Advisory Service (WAKMAS)

The Optimal Care Pathway (melanoma-optimal-cancer-care-pathway) for people with melanoma provides a national standard for high quality care for Australian patients. The pathway recommends patients with advanced stage primary melanoma, lymph node involvement or melanoma in unusual sites (e.g. mucosal and disseminated melanoma) are best managed by multidisciplinary teams in a specialist or melanoma facility.

The WA Kirkbride Melanoma Advisory Service (WAKMAS-https://wakmas.org.au) was established at the Harry Perkins institute of Medical Research (HPIMR-http://perkins.org.au) in January 2018. The service conducts an MDT consisting of nurses and clinicians who come from a range of specialties, including Dermatology, General Surgery, Medical Oncology, Plastic & Reconstructive Surgery, Nuclear medicine and Pathology. All are all experienced in the management of melanoma. The WAKMAS nursing team consists of Clinical Nurses who also serves as the coordinators for the service.

The scope of WAKMAS is to provide advice regarding the management of advanced primary and metastatic melanoma including advice on the adequacy of excision margins, the need for further investigations and information regarding prognosis. WAKMAS also provides information on and facilitates, adjuvant or neo-adjuvant therapy including recruitment into clinical trials where available.

Patients may be referred to WAKMAS by a general practitioner or specialist. Only referred patients, who may benefit from MDT discussion, are reviewed by WAKMAS. This may occur in one of two ways. The majority are seen externally by a Surgeon or Medical Oncologist in private or through a public hospital outpatient clinic, after which, they will be offered review by a dermatologist. Those who are not seen externally are reviewed at the HPIMR where they are interviewed and examined by a small multidisciplinary team in a non-threatening environment, with their own support members present if needed. All review patients are presented at the WAKMAS MDT for confirmation of the treatment plan. WAKMAS will organise investigations such as PET/CT, MRI, and molecular testing (BRAF mutation status, Array CGH, FISH) of the tumour as needed. WAKMAS does not arrange the biopsy (FNA/Core biopsy or excision biopsy) of undiagnosed lesions.

Indications for WAKMAS review are a primary melanoma that warrants sentinel lymph node biopsy (SLNB) or known metastatic disease. WAKMAS uses the Melanoma Institute of Australia (MIA), risk assessment nomogram (See later in the SLNB section) to determine the need for SLNB. The threshold risk for MDT discussion is currently 10%. The pathology for patients who require MDT discussion is reviewed by a WAKMAS cutaneous histopathologist. The pathology for patients referred to the service who do not need MDT discussion, is reviewed only if required on a case-by-case basis to facilitate appropriate advice to the referring or treating clinicians. Although WAKMAS is not a treatment centre, the service will, if asked by the referring doctor, arrange definitive medical and surgical care. After review, patients are given advice regarding the management of their melanoma. The management plan is confirmed

the WAKMAS MDT where the results of pathology review and all investigations are discussed. The recommendations from the MDT are communicated to the referring doctor and treating team.

Staff of WAKMAS

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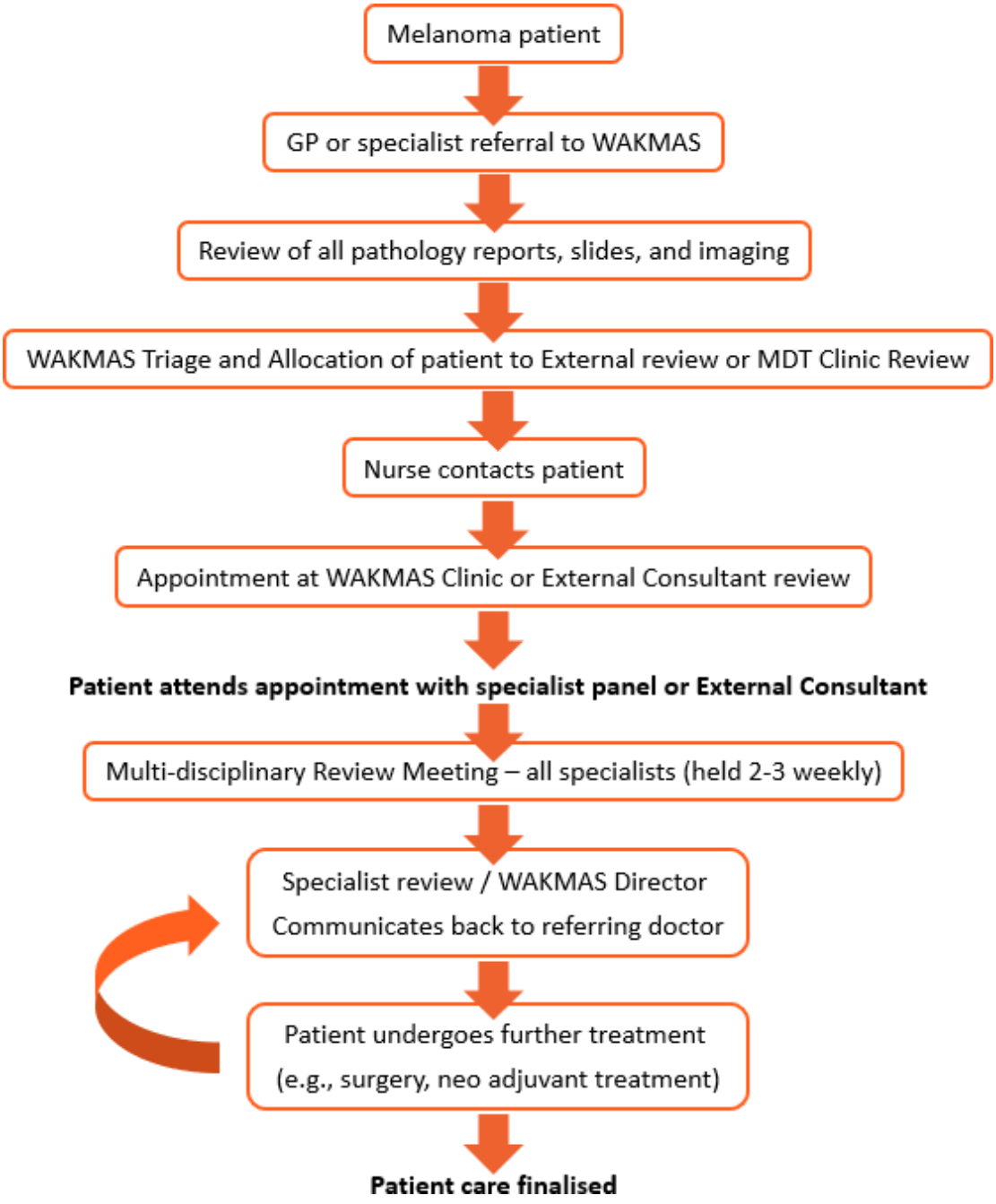
Flow path for patients referred to WAKMAS.



Melanoma Incidence and Mortality in WA

The age-standardised rate of Melanoma incidence and mortality in Western Australia is presented in the figures below. These demonstrates that between 2000 and 2022 in men the rate has ranged between 54 and 74 cases per 100,000 person years. The female rate is lower, ranging between 33 and 50 cases per 100,000 person years. Strategies to reduce the incidence of melanoma in the Western Australian population through education and awareness campaigns appear to have had little effect, however since melanoma is predominantly a disease of the elderly, it is possible that the effect of these campaigns on melanoma incidence may not be seen for some time. (Fig 1, 2)

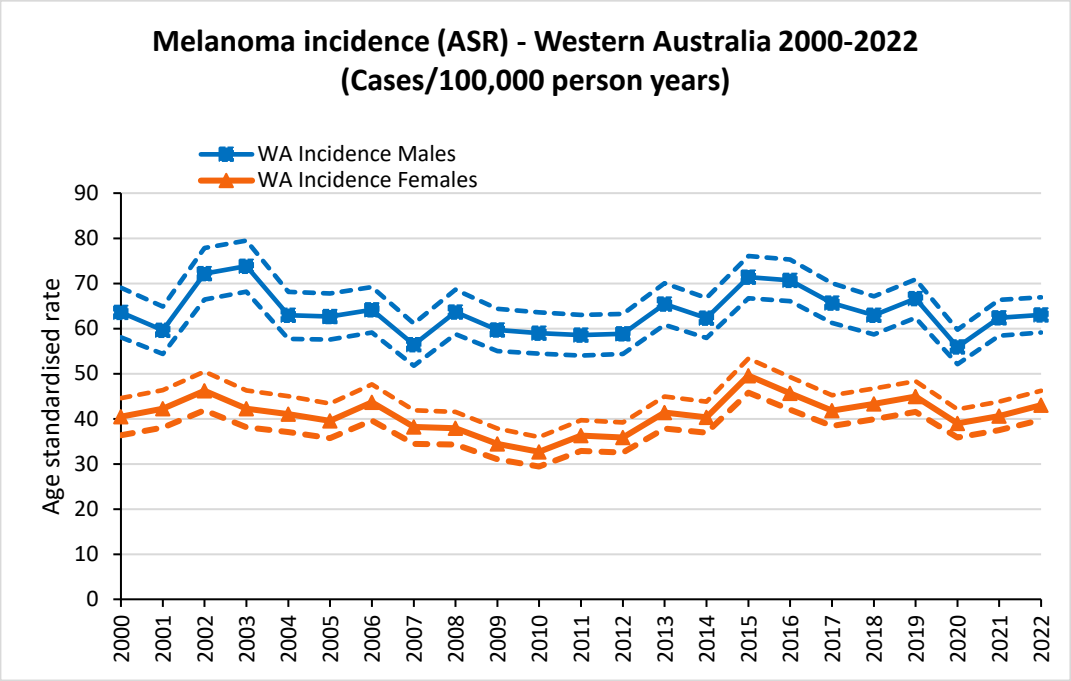


Figure 1 Melanoma Incidence (ASR)* Western Australia 2000-2022

(Data and graphs from the WA cancer registry and Epidemiology Directorate, Public and Aboriginal Health Division, WA DoH)

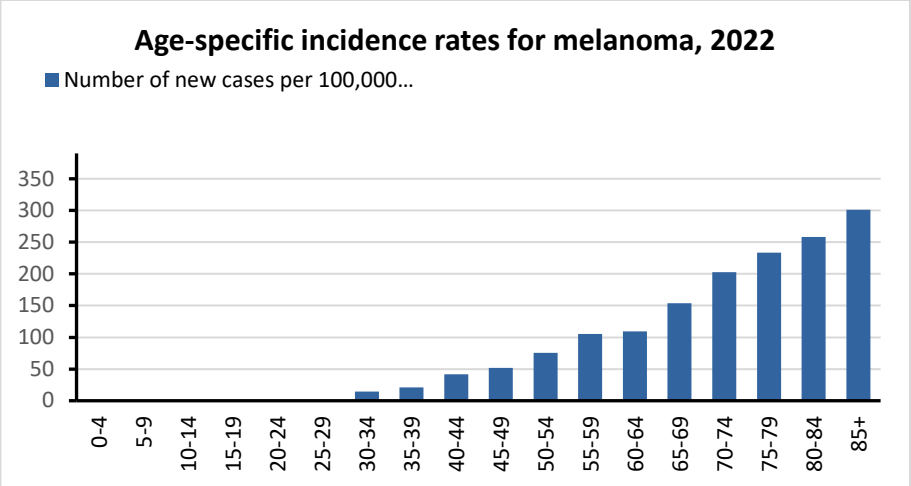


Figure 2 Age-specific incidence rates for melanoma skin cancer, 2022

(Data and graphs from the WA cancer registry and Epidemiology Directorate, Public and Aboriginal Health Division, WA DoH)

Melanoma mortality in men has been trending downwards since 2011, which saw the rate peak over the period (13 cases/100 000 person years) to its lowest rate in 2020 (5.6 cases/100 000 person years). In 2022, the rate was 5.8 cases/100 000 person years. This fall in the male melanoma mortality rate is statistically significant since the confidence intervals (CI) have not overlapped that of 2011 since 2014. In women this trend has not been observed, however mortality from melanoma in women across all age groups is significantly lower than in men (Fig 3).

Immunotherapy for stage IV melanoma (the checkpoint inhibitor Ipilimumab) was introduced in 2010. Since that time there has been a steady introduction of new medical therapies for advanced disease, including targeted therapies and immune modulating drugs in isolation or in combination. (See later in systemic treatment section)

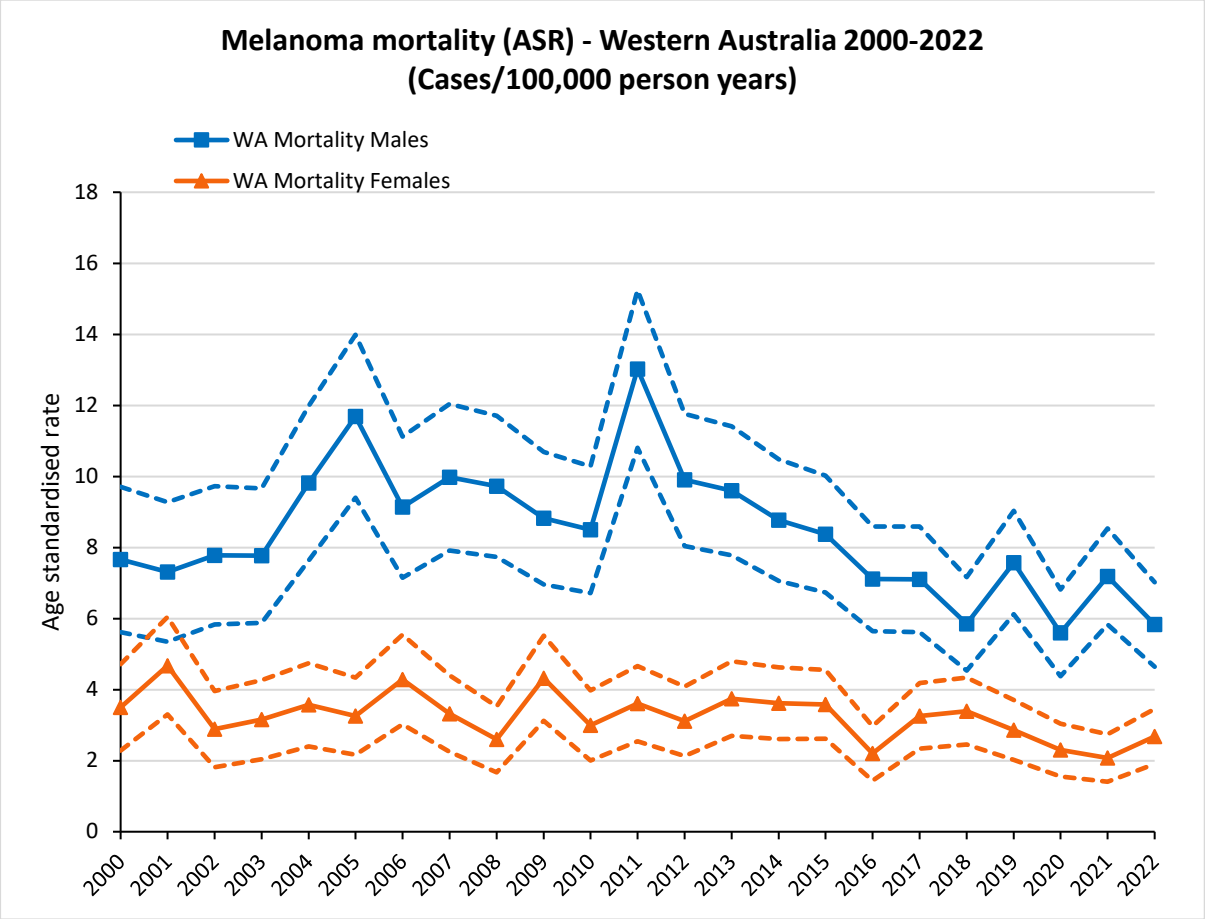


Figure 3 Melanoma Incidence - Mortality ASR WA, 2000-2022

(Data and graphs from the WA cancer registry and Epidemiology Directorate, Public and Aboriginal Health Division, WA DoH)

Survival data suggests that most patients with melanoma survive the disease with 5-year survival data in Western Australia from 2017 to 2021 indicating that 95.5% of patients diagnosed with melanoma are still alive at that time (Fig 4).

Number of years following diagnosis	5-year Relative Survival 2017-2021 (%)	LCI	UCI
1	98.4%	98.0%	98.9%
2	97.7%	97.1%	98.3%
3	97.0%	96.3%	97.7%
4	96.4%	95.5%	97.1%
5	95.5%	94.6%	96.4%

LCI=95% lower confidence limit for Relative Survival; UCI=95% upper confidence limit for Relative Survival

Figure 4: Relative Survival for Melanoma from 2017-2021, WA

(Data from the WA cancer registry and Epidemiology Directorate, Public and Aboriginal Health Division, WA DoH)

Melanoma Detection and Screening

Melanoma, when detected early is more likely to be cured. Therefore, early diagnosis and treatment of melanoma is the goal. There is no demonstrable benefit in the morbidity and mortality from melanoma from population screening programmes. Population screening for melanoma is therefore not recommended. There may be subgroups in the population, such as those with known risk factors, where targeted screening is beneficial.

The most important risk factors for melanoma are a personal or family history of melanoma, a personal history of non-melanoma skin cancer, the presence of numerous naevi (over 50), the presence of large, irregular naevi or dysplastic naevi. One or more of these risk factors may occur in as much of 5% of the population. Many different groups of health professionals currently perform skin-screening examinations. This includes patients who are not at high risk for developing melanoma, where this type of examination has an unproven role.

When examining at-risk patients for melanoma, the skin is examined thoroughly. The whole skin surface from the top of the scalp to the soles of the feet should be visualised systematically. Checking individual skin lesions, such as the lesions concerning patients only, is inadequate since early melanomas are usually asymptomatic.

The most commonly used surveillance methods are:

1. Full body examination with the naked eye and magnification
2. Examination of individual lesions with the dermatoscope
3. Full body photography with comparison of lesions over time
4. Examination with a digital photography system with or without an automated diagnostic facility (such as using artificial intelligence)

The use of telemedicine to transmit images of atypical, pigmented lesions to experts for their opinion is adopted by some centres.

Other techniques aimed at early detection include 3-dimensional photography, magnetic resonance imaging (MRI), confocal microscopy, multispectral imaging, diffuse reflectance spectroscopy and ultrasound imaging. None of these have proven useful in the clinical situation.

A pilot study, led by Edith Cowan University, using a blood test to detect melanoma antibodies demonstrated potential future clinical benefit. Circulating tumour DNA (ctDNA) is also a blood test being investigated to assess subclinical disease and to monitor early relapse after therapy. These are still experimental and not in routine clinical use.

Prognostic factors in cutaneous melanoma

Tumour stage is the key determinant of melanoma prognosis. The prognosis for localised disease (stages I or II), is principally determined by Breslow thickness. In patients with thin, invasive melanoma (<1mm), the prognosis is generally very good, though even in this group, death from melanoma may still occur. The Clark level (1-5) describes the histological degree of penetration of the skin by melanoma and is of limited independent prognostic value. It is less useful than the Breslow thickness and is a source of confusion since it is commonly mistaken for the melanoma stage (I-IV) by patients and doctors alike. As a result, there is mounting support to eliminate the Clark level from histological reports on melanoma.

Tumour ulceration is established as an adverse prognostic factor. It is uncommon in thin melanomas. Mitotic rate has established prognostic value with the most critical influence being between tumours with no mitoses and those with at least one mitosis per mm^2. Increasing mitotic rate correlates with an increasingly adverse prognosis.

Identification of lymphovascular invasion, though rare, is an adverse finding and may infer a higher likelihood of lymphatic and vascular spread, irrespective of Breslow thickness.

Regression, in which a tumour undergoes immunologically mediated involution, has been associated with a worse prognosis in many studies. The reasons for this are unclear, but it may be related to underestimation of Breslow thickness or the development of an immunological reaction representing a marker of antigen exposure. This phenomenon may account for metastases arising from in-situ tumours with dermal regression or metastatic melanoma without a detectable primary lesion. Unfortunately, identification of regression is subject to poor inter-observer reproducibility, limiting practical application of this feature.

Most other histological findings are of limited prognostic value. These include lymphocytic infiltrate, cell type and growth phase. Histological subtype plays little role in prognosis, except in the case of pure desmoplastic melanomas, (>95% desmoplastic), which appear to have a lower risk of metastasizing than other histological subtypes.

The Nodal status is a powerful prognostic indicator for melanoma. Macroscopic nodes are associated with a worse prognosis than microscopic nodes detected through sentinel lymph node biopsy. However, involvement of nodes with microscopic melanoma has been identified as a marker of risk for systemic disease and will upstage the primary lesion. The sentinel node status is routinely employed to determine the need for further investigations such as PET/CT scans and it also directs subsequent management including the recommendation for adjuvant systemic therapy.

When systemic metastases are present, the prognosis declines with the number of sites involved, especially with visceral or brain involvement. Poor performance status and increased serum lactate dehydrogenase are also predictors of reduced survival. Patients who present with metastatic disease without a known primary have a similar outlook to that of

patients with the same disease distribution with a known primary tumour. Pregnancy or previous biopsy of the melanoma does not appear to affect prognosis.

Other potential histological, immunohistochemical and genetic markers are being evaluated for assessing melanoma prognosis. These include the detection of circulating tumour DNA (ctDNA) and the presence of certain, identifiable gene clusters within melanomas. Whilst these have promising application for future detection, staging, monitoring and prognosis assessment, none have been convincingly validated for incorporation into routine care.

Prognostic Factors	Tumour Related	Host Related	Environment Related
Essential	Stage: AJCC (TNM)		Completeness of excision
Additional	• Ulceration • Mitotic rate • Lymphovascular invasion • Regression • Desmoplastic type	• Age • Gender • Site • Sentinel node status • Raised serum LDH* • Poor performance status*	• Lymph-node dissection • Excision of metastases • Immunotherapy • Targeted therapy • Radiotherapy
Limited or Unestablished Role	• Clark's level • Tumour infiltrating lymphocytes Growth phase. • Serum S100 protein • Tumour suppressor genes Proliferation markers Angiogenesis • Adhesion molecules • Growth factors • Circulating melanoma cells (RT-PCR or cell quantity) • Telomerase • MitF • ctDNA levels • Gene clusters		• Vaccine therapy • Gene therapy • "Alternative" therapies

** In stage IV disease*

Figure 5 Prognostic factors in cutaneous melanoma

Most melanomas are cutaneous in origin, however around 1% arise from mucosal sites. Mucosal melanomas are defined as three major types.

1. Head and neck
2. Vulvar and vaginal
3. Anorectal

Like cutaneous melanoma, staging of mucosal melanoma of the head and neck as well as vulval melanomas uses the AJCC-TNM (The American Joint Committee on Cancer — Tumour, Node, and Metastasis) classification. There are no specific staging systems for vaginal and anorectal mucosal melanomas, therefore clinical-stage classification systems are used for these lesions.

Since most mucosal melanomas are diagnosed in an advanced stage of disease, they commonly require multimodality treatment, combining surgery with postoperative radiotherapy. Due to their rarity, treatment is individualised in consultation with WAKMAS.

Management of Suspicious Pigmented Skin Lesions

Excisional biopsies

Lesions suspicious for melanoma should be excised with a 2mm margin to the level of subcutaneous tissue. This allows optimal assessment of tumour depth and characteristics if melanoma is confirmed.

The orientation of the excision should be performed such that any subsequent wider excision is not compromised by the scar orientation. Specialist referral is advised if the clinician is unable to confidently achieve an adequate sample or a good cosmetic result.

Flap reconstruction prior to definitive resection is contra-indicated. The incisions from flap reconstruction will alter lymphatic drainage and impair subsequent sentinel lymph node biopsy. **Halo grafts, which are used by some practitioners, will eliminate normal cutaneous lymphatic drainage and are contra-indicated after excision of lesions suspicious for melanoma or after excision of confirmed melanoma.**

If direct closure is not possible after excision with a 2mm margin is undertaken, it is reasonable to dress the defect until the definitive histology has been received.

Partial biopsies

Inadequate or inappropriate biopsies may confound subsequent histological assessment and evaluation of prognostic data such as tumour thickness. Therefore, all types of partial biopsy should be avoided if complete excision is feasible. If complete excision of suspicious lesions is not feasible, partial biopsy may be considered. This may occur for example, if there is a low index of suspicion, if the defect from excision will be too large to close or if complete excision may cause cosmetic or functional problems. The biopsy should include the most suspicious area and include the full thickness of the skin. ***Incisional biopsy provides good representation of a lesion. It should include as much of the atypical component of the lesion as is practical and as much of the lesion as can be excised whilst facilitating direct closure or wound dressings of the defect***. If complete excision is not practical, then a large incisional biopsy is the WAKMAS preferred method for assessment.

- **Curettage of suspicious pigmented lesions should NOT be performed**.
- Punch biopsies of large lesions may result in a sampling error. Multiple punch biopsies spanning the most suspicious areas may be employed if the practitioner is unable to perform a surgical excision with a narrow margin or incision biopsy.
- Broad, superficial shave biopsies yield a wide area of epidermis for examination, **but dermal sampling may be minimal**. ***Deep*** shave biopsies (saucerisation) include reticular dermis and subcutis but may still transect the base of deeper melanomas. **Transection of the base of a melanoma on partial biopsy impairs assessment of tumour depth preventing accurate prognostic information, surgical planning, and**

staging. **For this reason, shave biopsies are not recommended by WAKMAS, and a large punch biopsy (over 5mm) with dressing of the defect, may be preferable**.

Frozen section and cytology should not be used for primary assessment of suspicious pigmented lesions. Clinical observation supported by dermoscopy, photographs and precise measurement may be appropriate if clinical suspicion is low.

When the pathology report does not correlate with the clinical impression, the case should be discussed with the pathologist. A repeat biopsy or excision is indicated if suspicion is high. Specialist referral may be appropriate in these cases.

Where the Breslow thickness from a partial biopsy is under 0.8mm, excision of the lesion, with a **2mm margin**, should be performed to confirm the Breslow thickness.

If the partial biopsy confirms that the Breslow thickness of the lesion is over 0.8mm or demonstrates other features such as ulceration or lymphovascular invasion, then definitive wider excision and SLNB may be offered without the need for prior complete excision, after consideration by WAKMAS. This will depend on the need to exclude advanced or metastatic disease where further investigation with PET/CT or MRI may be indicated or excision biopsy confirming a dermal metastasis will render sentinel lymph node biopsy unnecessary.

Management of Primary Melanoma- Staging of Primary Disease

WAKMAS uses the AJCC staging system for melanoma. The AJCC 8th edition was implemented in 2018 (See appendix). Staging for melanoma is based on the histological report combined with clinical examination and the outcome from investigations if performed, including Sentinel Lymph Node Biopsy (SLNB).

There is no evidence to support any routine blood tests or radiological investigations for patients without evidence of metastases, however for patients with thicker primary lesions, (T3b, T4), a PET/CT scan is generally requested.

Sentinel Lymph Node Biopsy (SLNB)

SLNB is a two-stage process. The lymph node basin containing the sentinel node is identified through lymphoscintigraphy by injecting a radioactive tracer into the site of the melanoma. The dye travels to the node which receives lymphatic fluid from the site of injection. Surgery is performed immediately utilizing a gamma probe to detect the radioactive node with the help of a blue-coloured dye injected into the same site, turning the sentinel node blue. Current evidence suggests a survival benefit to patients with positive sentinel nodes who receive adjuvant medical treatment (discussed later). This has shifted the role of SLNB from one of gaining local control to that of staging so that adjuvant treatment may be offered.

WAKMAS does not yet recommend SLNB for pathological staging of T1a patients (Breslow thickness <0.8mm without ulceration). Accurate pathological staging of all other patients with invasive primary lesions requires the results from SLNB.

The Melanoma institute of Australia (MIA https://melanoma.org.au) has produced a web-based tool for assessing the risk of sentinel lymph node positivity, expressed as a percentage, based on patient and histological factors (https://www.melanomarisk.org.au/SNLLand). WAKMAS only recommends applying this Prediction Tool for Sentinel Node Metastasis Risk (PTSNMR), **for lesions with a Breslow thickness of 0.8mm or more**, unless other poor prognostic indicators are demonstrated (such as a mitotic rate$\geq$1/mm^2, ulceration or lympho-vascular invasion) or in patients who are very young and healthy, where the desire for accurate staging, in the context of a thin lesion, may be greater. The role for application of the risk calculator for melanomas thinner than 0.8mm outside this group of patients is still being established.

WAKMAS considers this risk, determined by the PTSNMR, in the context of the patient preference, their age, comorbidities, and social factors before making recommendations as to whether SLNB should be offered. Generally, if the risk is over 10% in a healthy patient, SLNB would be recommended at the time of wider local excision (WLE) of the melanoma. Where the assessed risk falls between 5% and 10%, in patients whose co-morbidities do not preclude SLNB, WAKMAS recommends they discuss this with a surgeon who is experienced in the technique of SLNB for melanoma and can consider it in the context of the patient and

their lesion. All patients who are deemed suitable for SLNB should have a comprehensive discussion regarding the benefits and risks associated with the procedure prior to proceeding.

Prior WLE increases the distance of residual tissue from the primary site, which increases the likelihood of a false negative result from SLNB and hence this reduces the reliability of the procedure. Consequently, SLNB is not usually offered after WLE, though it may occasionally be acceptable in this situation if flap reconstruction or halo grafting has not been performed, since these techniques will alter local lymphatic flow. SLNB is unnecessary when a patient presents with systemic disease or an FNA positive node. WAKMAS do not consider prior SLNB a contraindication for SLNB.

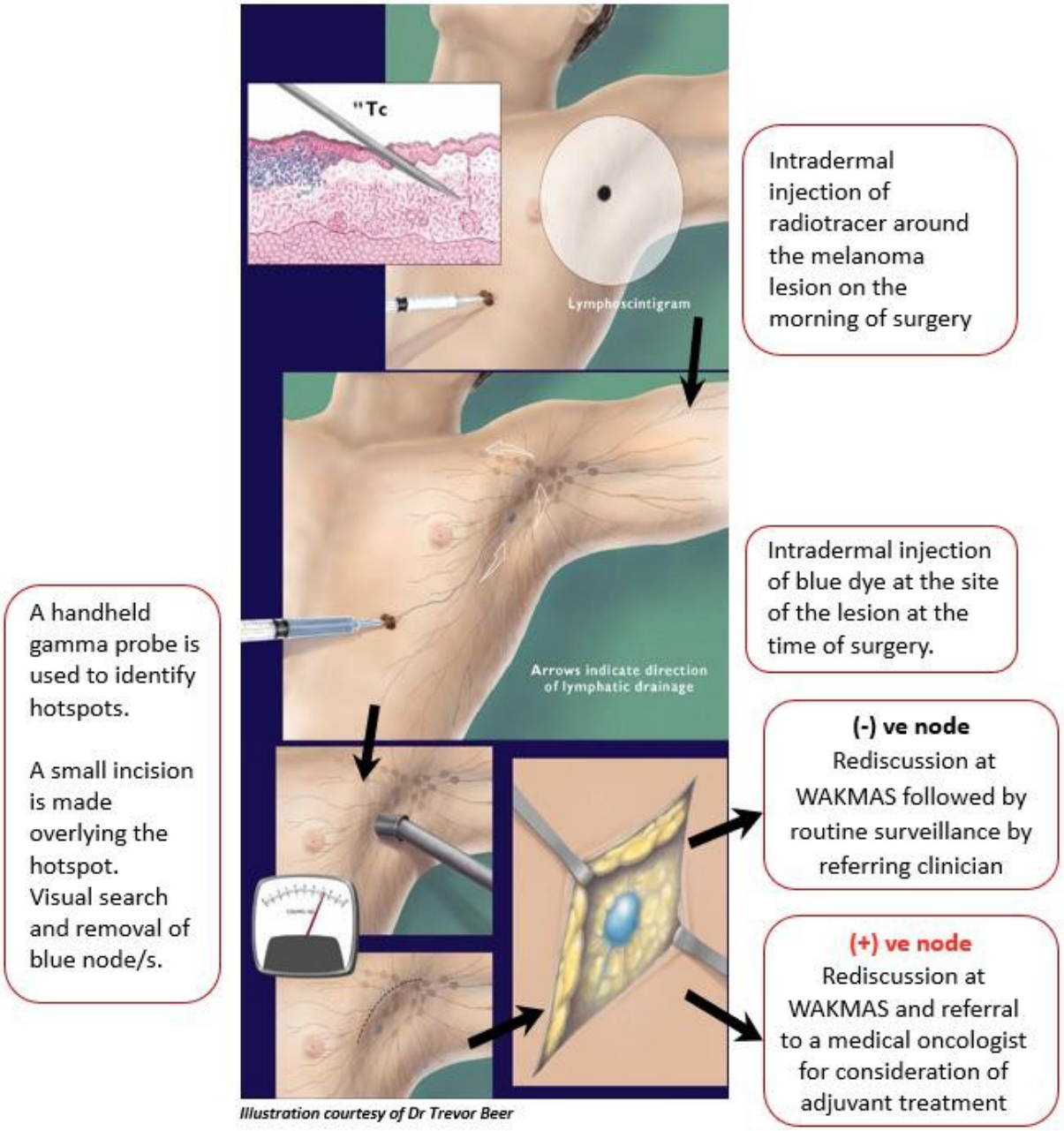


Figure 6 Sentinel Lymph Node Biopsy Procedure

Surgical Treatment of Primary Cutaneous Melanoma

Once the diagnosis of invasive melanoma has been made, excision of the lesion or biopsy scar with an appropriate clinical margin remains the mainstay for management of the lesion.

Margins of Excision for Primary Melanoma

Appropriate excision margins for invasive melanoma have been debated extensively. There is no evidence that an excision margin over 1cm has any influence on overall survival or disease-free survival, regardless of the thickness of the primary lesion. Definitions of local recurrence, (LR) have been inconsistent and ambiguous in many studies that have not been based on the correct definition of LR. Local recurrence should be defined accurately as recurrence of the melanoma within or adjacent to the scar or graft from a previous excision of primary melanoma.

If adequate histological clearance of the melanoma has been confirmed, LR represents a local metastasis. Local metastases have the same microscopic morphology and prognostic implications as other cutaneous metastases (satellites, in-transit and distant). The concept that a wider margin reduces the likelihood of LR by "Capturing" more local metastases relies on chance alone and remains unproven. In this context, any margin over that required to achieve adequate histological clearance is arbitrary, regardless of the Breslow thickness of the primary lesion.

Local recurrence that occurs in the context of inadequate histological margins at the time of WLE should be considered as persistence of primary disease. These two types of LR have distinct histologic features with entirely different implications for prognosis.

For most melanomas, WAKMAS considers a **clinical margin** of 1cm to be adequate to confirm histological clearance for invasive lesions and a **clinical margin** of 5mm, adequate for **in-situ** lesions. Rarely, a margin of 2cm may be considered for lesions over 2mm thick, depending on the histopathology subtype, the site of the lesion, the availability of local tissues and the likely cosmetic outcome (After consideration of SLNB).

There is currently an international, multicentre trial (Mel-Mar T2) which aims to compare clinical outcomes in patients with invasive melanoma who have had either a 1.0 cm or a 2.0 cm margin at the time of WLE. The protocol for the Mel-Mar T2 trial, however, does not include a valid definition of local recurrence but will stratify cases according to the site and the distance of the LR from the primary lesion.

Summary of WAKMAS recommendations for clinical margins in 1º melanoma

WAKMAS recommends clinical margins consistent with the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand.

Breslow thickness	Recommended Clinical Margin around lesion or scar
In situ	5mm
< 1.0 mm	10 mm (After consideration of SLNB)
>1.0mm to ≤4.0 mm	At least 10 mm *clinical* margin (After consideration of SLNB)
>4.0 mm	10-20 mm *clinical* margin (After consideration of SLNB)

Figure 7 Summary of WAKMAS recommendations for clinical margins in 1º melanoma

Histological margins

It is recommended by WAKMAS that the complete histological clearance of all atypical melanocytes should be achieved at the time of WLE. There is no agreed histological clearance appropriate for in situ or invasive lesions. Acceptable histological clearance should be considered in the context of the histological features of the tumour, the patient, the site and size of the primary lesion and the ability to monitor the patient for local recurrence.

Histological margins under 3.0 mm may be considered an indication for a conservative wider excision for in situ lesions and for invasive lesions with histological margins under 8.0 mm. Where the histological margins are less than these, wider excision may be recommended after discussion with WAKMAS if it is considered necessary in the context of the patient, the site, the histopathology, and the tumour growth pattern.

Some melanoma sub-types, such as desmoplastic and spindle cell melanomas may extend in the dermis for a considerable distance beyond the main tumour mass. The histological margin for these more “infiltrative” lesions may also be difficult to accurately define. It is reasonable when these lesions have been identified to aim for a wider histological margin and, if diagnosed before WLE has been performed, a wider clinical margin after discussion at WAKMAS.

Positron Emission Tomography-Combined with CT scan (PET/CT)

Positron Emission Tomography (PET) is an imaging technique that provides valuable information about tissue metabolism. It involves intravenous injection of a radioactively labelled glucose analogue, known as fluoro-deoxyglucose (FDG) into the patient. Malignant tumours, having a higher glucose metabolism, tend to take up more FDG compared to the surrounding normal tissue. This increased FDG uptake is visualized as increased activity on the PET scan.

Currently, hybrid PET/CT machines are considered the gold standard. PET images can be fused with either a non-diagnostic CT scan, which is used for PET signal attenuation correction and anatomic localisation, or a diagnostic CT scan, which offers detailed morphologic information. The radiation dose associated with PET/CT is slightly higher than that of a standard whole-body CT scan.

The combination of F18-FDG PET and CT has shown improved performance in the detection of metastatic disease. It is particularly effective in high-risk cases such as stage III and IV melanoma, primary melanoma with Breslow thickness over 4mm (all T4 patients), and T3b lesions (2.0-4.0mm with ulceration). The sensitivity and specificity of F18-FDG PET/CT can reach up to 83% and 85%, respectively.

F18-FDG PET/CT is not considered the standard of care for early stages of malignant melanoma (stage I and II), some studies have demonstrated its high diagnostic accuracy in detecting metastasis in patients with high-risk melanoma at these stages.
Sensitivities of 91% and 98% have been reported. It may be recommended to perform PET/CT in selected patients with early-stage melanoma after consultation with WAKMAS, especially when there is a suspicion of metastatic disease based on history or examination findings. Additionally, PET/CT can be useful for surveillance purposes, tailored to the individual patients and their specific disease context and treatment.

Patients considered at risk of brain metastases should also be staged with brain MRI, which is more sensitive in detecting small brain metastases.

All services accept Specialist only referrals for funded indications.

For the request to be eligible for the Medicare rebate it must fit the following criteria: Whole body PET/CT study, following initial therapy, performed for the evaluation of suspected metastatic or recurrent melanoma in patients considered suitable for active therapy (MBS February 2009) and requested by a specialist.

Most private facilities and all public hospital facilities accept Medicare or DVA payment alone for funded indications. Appointment waiting times are usually 1 week or less in private facilities.

Waiting times are based on clinical urgency in public facilities.

Referral forms are available from:

1. Perth Radiological Clinic (Nedlands) Ph: (08) 9386 7800; Fax: (08) 9386 7888
2. Perth Radiological Clinic (Joondalup) Ph: (08) 9400 0600; Fax: (08) 9400 0690
3. SKG Radiology (Subiaco) Ph: (08) 9286 6400; Fax: (08) 9286 6481
4. Envision Medical Imaging (Wembley) Ph: (08) 6382 3888; Fax: (08) 6382 3800
5. Qscan Radiology Clinic (Rockingham) Ph: (08) 9500 8950; Fax: (08) 6444 7480
6. Qscan Radiology Clinic (Midland) Ph: (08) 6155 5500; Fax: (08) 6266 3719
7. Apex Radiology (Bunbury) Ph: 1300 209 975
8. Sir Charles Gairdner Hospital (Nedlands) Ph: (08) 6457 3333
9. Fiona Stanley Hospital (Murdoch) Ph: (08) 6152 2222

Management of Metastatic Melanoma

Advances in the development of adjuvant agents has meant that the treatment of metastatic melanoma is rapidly evolving. However, surgical excision remains the mainstay of treatment of isolated metastasis which can be excised with acceptable morbidity.

Investigations for Stage III and IV disease

Patients who have confirmed metastatic disease on clinical or pathological grounds (from SLNB) should be fully investigated for the presence of occult metastases. This may include serum LDH, PET/CT scan and Brain MRI as indicated by history and clinical examination.

Therapeutic Lymph Node Dissection (TLND)

There is no role for prophylactic lymph node dissection (In the absence of known macroscopic lymph node metastases). The role of lymph node dissection in the management of patients with known lymph node melanoma metastases is still evolving. Previous studies have failed to demonstrate overall survival (OS) or a Melanoma specific survival (MSS) benefit for patients with stage III disease (LN metastases) following block lymph node dissection, in the absence of adjuvant treatment. Block dissection of draining lymph nodes has therefore been performed primarily for local control of disease and removal of all known and potential lymphatic melanoma metastases. Recent evidence has confirmed that patients with macroscopic lymph node metastases have better survival outcomes when neo-adjuvant systemic therapy is employed.

For patients with resectable macroscopic stage III melanoma, the integration of immunotherapy ***prior*** to surgery—known as **neoadjuvant therapy**—has emerged as a highly effective strategy and is now considered the standard of care (See next section on Systemic Therapy for advanced melanoma)

Completion Lymph Node Dissection (CLND)

In the past WAMAS has recommended CLND, which involves removing the remaining lymph nodes in the lymph node basin which contained a positive lymph node, after SLNB. However, the Multi-centre Selective Lymphadenectomy Trial II (MSLT II) confirmed no benefit from CLND in overall survival or disease specific survival from melanoma, compared with TLND performed once a lymph node metastasis has been confirmed. WAKMAS no longer recommends CLND for patients with micro-metastases confirmed on SLNB.

Systemic Therapy for advanced melanoma

Over the past two decades several therapies have been approved by the United States Food and Drug Administration (US FDA) which have resulted in significant improvements in overall survival (OS) for advanced stage melanoma patients. Treatments for melanoma are divided into targeted therapy and immunotherapy.

Immunotherapy

Immune checkpoints are regulators of the immune system and control the extent of immune response through maintaining homeostasis and preventing autoimmunity (1).
Ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), was the first immune checkpoint inhibitor to demonstrate a survival advantage in advanced melanoma for over three decades. The most notable outcome from this trial was the duration of response seen with ipilimumab (up to 10 years in 18-22% of cases) (2).

Stemming from the success of ipilimumab, further immune checkpoint inhibitors have been evaluated and translated into meaningful survival benefit for advanced melanoma patients. These include agents targeting PD-1. Current PD-1 checkpoint inhibitors used in the management of melanoma include pembrolizumab and nivolumab. There have been three randomised phase III trials of anti PD-1 therapy (nivolumab and pembrolizumab) in patients with advanced melanoma demonstrating improved response rates, progression free survival (PFS) and OS over both chemotherapy and ipilimumab (3-5).

Attempts to synergise the effectiveness of anti-PD-1 and anti-CTLA-4 was tested in CheckMate 067 clinical trial. This landmark trial evaluated combination ipilimumab and nivolumab, ipilimumab alone or nivolumab alone (6). The results were impressive. Treatment naïve advanced melanoma patients (n=945) were randomised to one of the three immunotherapy groups. The combination arm had significantly higher response rate (up to 60%). At 10-year follow-up of the CheckMate 067 trial, the median overall survival (OS) was reached at 71.9 months for the nivolumab plus ipilimumab (NIVO + IPI) group (7).

More recently, another dual immunotherapy regimen combining nivolumab and relatlimab (LAG-3 blocking antibody) was demonstrated to have a superior PFS (and response rate compared to nivolumab alone. This combination has a more favourable toxicity profile compared to the ipilimumab + nivolumab regimen (8).

All these drugs are currently approved and PBS-listed in Australia for unresectable stage III and stage IV melanoma. Several other immune-modulatory agents are under investigation in the clinical trial setting, including novel targets and combinations with existing agents.

Immunotherapy toxicity profile

Immune checkpoint inhibitors are commonly used in the management of melanoma and several other solid organ tumours. Unlike chemotherapy, these agents work by enhancing the immune system's ability to target cancer, but this can also result in inflammation of healthy tissues—known as immune-related adverse events (irAEs).

Immune mediated toxicity can affect any organ system. IrAEs can occur at any time but often emerge within the first 12 weeks of treatment, especially with combination immunotherapy. Endocrine toxicities may appear later and are often permanent. Most commonly affected are the skin (rash, pruritis), gastrointestinal tract (diarrhoea, colitis), liver (immune hepatitis) and endocrine system (thyroid, pituitary, pancreas). Skin rash and fatigue are common early side effects. While most irAEs are mild, some can be life-threatening and require prompt recognition and treatment. Management generally involves withholding immunotherapy and initiating corticosteroids for moderate to severe toxicity. It is strongly recommended that the patient's oncology team is contacted promptly in case of suspected immune related adverse event.

General practitioners play a key role in the early detection and long-term monitoring of these adverse effects, especially as some patients may remain on treatment for months or years. Any new symptom—such as fatigue, diarrhoea, cough or joint pain—should prompt consideration of an immune-related cause. We recommend liaising with the patient's medical oncology team if an irAE is suspected or in case of unexplained symptoms in patients on ICIs. Routine monitoring of thyroid function, liver enzymes, glucose, and cortisol is recommended during and after treatment and is co-ordinated by the treating oncologist. Timely communication with the treating oncology team is essential for coordinated management. These agents are given under close supervision by oncology clinicians, with significant education of patients, with an understanding of the potential immune toxicities and how these can be identified and treated early.

Targeted therapy

The introduction of targeted therapy marked a major advance in the treatment of patients with *BRAF*-mutated melanoma. Approximately 40% of advanced melanomas harbour a mutation in the *BRAF* gene. Four major phase III trials (COMBI-d, COMBI-v, coBRIM, and COLUMBUS) demonstrated superior clinical outcomes with dual BRAF/MEK inhibition compared to BRAF monotherapy (9-11). These combinations—dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib (all available on the PBS in Australia)—significantly improved response rates, PFS, and OS, and are now standard options for patients with BRAF-mutant metastatic melanoma.

These targeted agents also have a number of unique toxicities including skin and liver toxicity, as well as drug- induced fevers. Patients who are unable to tolerate one combination may be able to tolerate a different combination of targeted therapy drugs, owing to the different adverse event profiles of each regimen.

Recent studies have explored the optimal sequencing of therapies in patients with BRAF-mutant melanoma. The SECOMBIT and DREAMseq trials evaluated the impact of starting treatment with immunotherapy versus targeted therapy (12, 13). Both studies demonstrated a survival advantage when first-line treatment was with combination immunotherapy (anti-CTLA-4 and anti-PD-1) rather than BRAF/MEK inhibitors, suggesting that immunotherapy should be considered the preferred initial approach for most patients with good performance status. Targeted therapy remains an important option, particularly in patients with contraindications to immunotherapy or symptomatic and rapidly progressive disease.

Neoadjuvant treatment for macroscopic stage III melanoma

Traditionally, adjuvant therapy was given after surgery to eliminate residual disease. However, neoadjuvant immunotherapy, particularly with immune checkpoint inhibitors, is believed to enhance the immune response by exposing the immune system to the intact tumour, thereby promoting a broader and more durable anti-tumour effect (Figure 8).

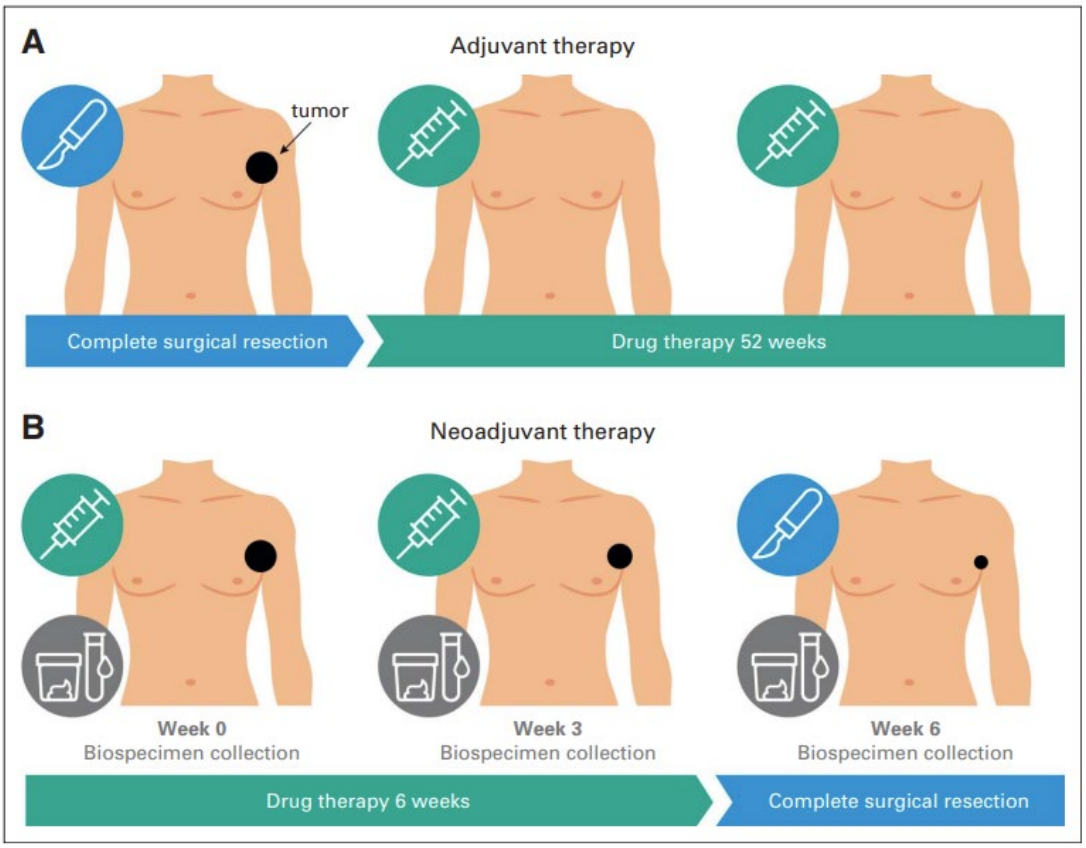


Figure 8 Adjuvant treatment vs Neoadjuvant therapy for resectable stage III melanoma.

Neoadjuvant therapy offers several clinical advantages. Pathological response in resected tissue—especially major pathological response (MPR, ≤10% viable tumour)—strongly predicts long-term outcomes. Importantly, neoadjuvant therapy allows response-adapted strategies: patients with excellent responses may require less intensive follow-up treatment, while those with incomplete responses can be considered for escalation of additional systemic therapy post-surgery through clinical trials.

Multiple studies, including the pooled International Neoadjuvant Melanoma Consortium (INMC) analysis and recent randomised trials (NADINA, SWOG S1801), have shown that neoadjuvant immunotherapy significantly improves event-free survival (EFS) compared with adjuvant treatment (14, 15). In both trials, most adverse events were mild to moderate; rates of treatment-related discontinuation or surgery delay were low.

Neoadjuvant pembrolizumab is available on the PBS and neoadjuvant ipilimumab plus nivolumab is PBAC approved and is now available on the PBS for this indication.

Adjuvant treatment for resected AJCC stage III/IV disease

Patients with **resected** Stage III and Stage IV melanoma have a high risk of recurrence and mortality. Even after complete surgical removal, patients with stage II or III melanoma remain at risk of local or distant recurrence. The likelihood of relapse and melanoma-specific mortality is influenced by several tumour-related factors, including Breslow thickness, ulceration, lymph node involvement, and in-transit metastases. The goal of adjuvant systemic therapy is to eliminate residual microscopic disease and reduce the risk of recurrence, thereby improving long-term outcomes. Adjuvant therapy for resected stage III/stage IV melanoma is now a standard of care.

Three different therapeutic strategies are available for resected stage III melanoma based on randomised controlled trials (pembrolizumab- based on Keynote 054, nivolumab- based on Checkmate 238 and dabrafenib/trametinib for those with a BRAF mutation based on COMBI-AD) (16-18). All three treatments options have shown a benefit in sustained recurrence free survival (RFS). These treatments however, come with the risk of toxicity. In the case of immunotherapy, this can be in the form of long term irreversible endocrine immune related adverse events.

Adjuvant treatment for high-risk stage IIB and IIC disease

Patients' primary melanoma with no nodal involvement but with high-risk features, defined as having a Breslow thickness >4mm with or without ulceration, or a thickness of 2-4mm with ulceration, are at an increased risk of recurrence and metastatic disease, despite having no lymph node involvement. Recent clinical trials have demonstrated that adjuvant

immunotherapy can reduce the risk of recurrence and distant metastases in this group, marking a significant shift in treatment options for earlier-stage melanoma. This indication is TGA approved but not yet available on the PBS. Patients should be referred to a medical oncologist to discuss their treatment options including clinical trials. Overall survival benefit for both of these trials has not been demonstrated to date.

The decision whether to consider adjuvant immunotherapy in patients with Stage IIB and IIC disease, whether as part of a clinical trial, an access program or once the drugs become routinely available in Australia, is typically made after a discussion with the patient about the potential benefits but also the risks of short- and long-term toxicities from treatment. This is especially relevant in Stage II disease as the absolute reduction in risk is more modest than that seen in Stage IIIB, IIIC and Stage IV melanoma.

Systemic treatment of metastatic uveal

Ocular melanomas include conjunctival and uveal melanoma. The biology and molecular presentation of these lesions is different with conjunctival melanoma more closely resembling cutaneous melanoma. The management of both is different also. Uveal melanoma is a rare malignancy relative to cutaneous melanoma. Certain genetic subtypes of uveal melanoma result in an increased risk of metastatic disease of around 50%.

The systemic treatment of metastatic uveal melanoma has been historically very challenging. These patients can potentially respond to combined immune checkpoint inhibitors, but with a significantly lower response rate relative to cutaneous melanoma (this is not available on PBS). Some patients may be suitable for surgical resection of metastases (the liver is the most common site of systemic recurrence), or alternatively local targeted approaches such as radiofrequency ablation or radiosurgery.

Tebentafusp (IMCgp100) is a novel monoclonal antibody that is immune stimulating in patients who have a specific HLA haplotype (HLA-A*02:01). It recently became the first systemic therapy to demonstrate an overall survival benefit in uveal melanoma (one-year overall survival 73% vs. 59% for investigator choice of chemotherapy or immunotherapy). At a minimum follow-up of 36 months, median overall survival was 21.6 months in the Tebentafusp group and 16.9 months in the control group. The estimated percentage of patients surviving at 3 years was 27% in the Tebentafusp group and 18% in the control group (19).

Based on these results, Tebentafusp is now both TGA approved and PBS listed. However, prior to deciding on the initial therapy for metastatic disease, patients undergo HLA typing, as only those with the HLA-A*02:01 genotype are eligible for Tebentafusp (as the genotype forms part of the target of the antibody).

Clinical Trials in Melanoma

Despite the advances in systemic treatment for metastatic melanoma, many patients do not respond to current therapies. Patients who progress following targeted therapies and/or immunotherapy have limited treatment options. Ongoing clinical trials are evaluating approaches to combine two or more immunotherapy agents, combining targeted therapies and immunotherapy, and other strategies to improve response and prevent the emergence of resistance and treatment failure.

Where available and appropriate, patients with advanced melanoma should be offered the opportunity to be considered for suitable clinical trials of novel agents. Some trials are suitable for first-line therapy, while others include patients who have failed prior therapies. A large number of trials are underway, many including combinations of immunotherapy with a backbone of a PD-1 inhibitor, combined with other immune modulatory drugs.

Tumour-infiltrating lymphocytes (TILs) represents one such strategy. TIL therapy involves extracting a patient's own immune cells from tumour samples, expanding and activating them in the lab, and reinfusing them to target melanoma cells. Studies have shown meaningful response rates, even in patients who have progressed on prior immunotherapy, offering hope in refractory cases. Currently this is not available in Australia outside of clinical trial.

Personalised cancer vaccines are another exciting area of research. These vaccines are tailored to individual tumour neoantigens, training the immune system to specifically recognise and attack the patient's melanoma cells. Early-phase trials have demonstrated immune activation and, in some cases, durable responses. When used alongside checkpoint inhibitors, these vaccines may help prevent recurrence or deepen responses in advanced-stage disease, a particularly relevant development for patients with resected stage III or IV melanoma.

An emerging area of interest is the role of neoadjuvant immunotherapy, which may allow for surgical de-escalation in select patients with stage III melanoma. Early trials suggest that robust pathological responses to preoperative treatment could potentially spare patients from extensive lymph node dissections, reducing surgical morbidity without compromising outcomes. Ongoing studies are exploring how best to integrate this approach into standard care.

There is also an ongoing effort in translational studies in WA (e.g., research into circulating tumour cells or DNA as well as biobanking of tissue for cell therapy) that aim at identifying predictors of response and resistance, and/or monitoring for relapse and design of trials of new therapies such as TIL therapy.

Radiotherapy in Melanoma

Primary-site radiotherapy

In the era of effective systemic therapies, radiotherapy (RT) is rarely required as a definitive modality for the treatment of cutaneous melanoma. Medical or surgical inoperability and unsuitability of systemic treatment are potential examples where it may have a role whilst recognising that disease outcomes are likely to be compromised.

Adjuvant RT following primary or secondary resection may be recommended if there is a perceived high risk of local recurrence whereby further resection or systemic treatment are not feasible. The decision to recommend radiotherapy should be discussed in a multi-disciplinary team meeting considering disease and patient related factors.

Regional-site radiotherapy

Adjuvant radiotherapy following regional lymph node dissection is not usually required. It may be considered in carefully selected patients if there are pathological features which predict for a high cumulative risk of regional recurrence and there is any contraindication to adjuvant systemic therapy.

These recommendations recognise a regional control benefit and no proven relapse free or overall survival benefit.

Adjuvant, regional radiotherapy is associated with morbidity which includes a risk of lymphoedema. A higher threshold for adjuvant RT to the groin is typically employed due to the increased risk of developing lymphoedema relative to other regional sites.

Regional adjuvant radiotherapy may also warrant consideration when for recurrent nodal disease despite adequate systemic treatment where further surgery is not feasible.

Distant-site radiotherapy

Radiotherapy is infrequently used in the treatment of advanced melanoma. It may be considered as part of a palliative management strategy to alleviate symptoms or prevent imminent, severe morbidity where systemic treatment is not feasible or may be inadequate to achieve timely disease control.

Potential indications include:

- Fungating, bleeding, pain for local, in transit, recurrent or regional disease
- Bone metastases – impending fracture, pain, post-surgical fixation
- Selected cases for brain metastases (See below)

The decision to offer radiotherapy should be discussed in a multidisciplinary team meeting.

In the presence of oligometastatic or oligoprogressive disease, ablative stereotactic radiotherapy (SRT) may be considered when surgery is not possible, and a systemic treatment approach is limited.

The role of radiotherapy in the environment of immunotherapy and new systemic therapies is uncertain. Synergism between immunotherapy and RT is the subject of multiple trials worldwide.

Brain metastases

Melanoma presenting with brain metastases remains an area of unmet need. In patients with asymptomatic disease, systemic treatment is typically the first line treatment approach. The role of adding stereotactic radiotherapy to combination immunotherapy in asymptomatic brain metastases is currently under investigation (ABC-X trial)

Radiotherapy may also have a role in initial treatment to control symptomatic brain metastases and enable the incorporation of immunotherapy by reducing the need of corticosteroids.

Whole brain radiotherapy is typically reserved for disease that is not amenable to stereotactic radiotherapy or systemic therapy.

Surveillance in melanoma

WAKMAS recommends the following routine surveillance:

AJCC staging	Frequency of review
Stage I - in situ disease	6 monthly for 5 years then annually thereafter.
Stage II and III disease	3-4 monthly for 2-3 years then 6 monthly for 2-3 years and annually thereafter.
Stage IV disease	3-4 monthly for 5 years then 6 monthly thereafter or as directed by their medical oncologist.

Figure 9 Surveillance in melanoma

Clinical review should be undertaken by a combination of health professionals including the patient's primary care physician, and a dermatologist, surgeon or medical oncologist, depending on the needs of the individual patient and the nature of their disease.

The current recommendations for surveillance in those patients with a positive SLNB who do not proceed to adjuvant medical therapy, or who do not tolerate adjuvant therapy is for ultrasound assessment of the affected lymph node basin at the time of each clinical review. The ultrasound scan should be interpreted by radiologists with expertise in the assessment of early malignant lymph nodes. These patients should also have had a baseline PET/CT scan to confirm the absence of distant metastases prior to USS surveillance.

WAKMAS has worked with the various radiology service providers in WA to establish consistent guidelines for the frequency of ultrasound surveillance in these cases.

1. Every four months for the first two years
2. Every six months from year three through five
3. Annually thereafter

Furthermore, they have identified the following features to establish the diagnosis of lymph nodes suspicious for early involvement with metastatic disease:-

1. Length: depth ratio of less than two.
2. A hypoechoic centre.
3. Absence of hilar vessels.
4. Focal nodularity with increased vascularity.

The area for surveillance should be clearly noted on the request form after confirmation of the site of the positive sentinel lymph node. GP's who require information on appropriate centres to refer their patients to for USS surveillance should contact WAKMAS.

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APPENDIX

AJCC MELANOMA STAGING

[From AJCC Cancer Staging Manual, 8th Edition (pages 577 & 578)]

Definition of Primary Tumour (T)

T Category	Thickness	Ulceration status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Figure 10 Definition of Primary Tumour (T) – AJCC Melanoma Staging 8th edition.

Definition of Regional Lymph Node (N)

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason). **Exception:** pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected.	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes.	
N1a	One clinically occult (i.e., detected by SLN biopsy).	No
N1b	One clinically detected.	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node.	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy).	No
N2b	Two or three, at least one of which was clinically detected.	No
N2c	One clinically occult or clinically detected.	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes with or without in-transit, satellite, and/or microsatellite metastases.	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy).	No
N3b	Four or more, at least one of which was clinically detected, or presence any number of matted nodes.	No
N3c	Two or more clinically occult or clinically detected, and/or presence any number of matted nodes.	Yes

Figure 11 Definition of Regional Lymph Node (N) – AJCC Melanoma Staging 8th edition.

Definition of Distant Metastasis (M)

M Category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or non- regional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
Suffixes for M category: (0) LDH not elevated; (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

Figure 12 Definition of Distant Metastasis (M) – AJCC Melanoma Staging 8th edition.

AJCC Prognostic Stage Groups (pathological)

When T is….	And N is….	And M is….	The pathological stage is….
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a-N2b	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV
Pathological stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

Figure 13 AJCC Prognostic Stage Groups (pathological) – AJCC Melanoma Staging 8th edition.

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