WA Kirkbride
MELANOMA ADVISORY SERVICE

INFORMATION FOR MEDICAL PRACTITIONERS

Table of Contents

Table of Figures

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Cancer Council WA | Western Australian Clinical Oncology Group

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

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

WA Kirkbride Melanoma Advisory Service (WAKMAS)

The Western Australian Cancer and Palliative Care Network (WACPCN) has developed a model of care (MOC) for the management of cutaneous melanoma. The MOC suggests that a multidisciplinary team should review patients with clinically complex melanomas, to formulate optimum management of their disease.

The WA Kirkbride Melanoma Advisory Service (WAKMAS) was established at the Harry Perkins institute of Medical Research in January 2018. The scope of WAKMAS is to provide comprehensive advice regarding the management of complex, advanced primary and metastatic melanomas. This includes advice regarding the adequacy of margins of excision for primary melanomas, the need for further investigations and staging (including sentinel lymph node biopsy and CT/PET), information regarding prognosis and potential adjuvant therapy, including recruitment into clinical trials where available. Although WAKMAS is not a treatment centre, the service will, if asked by the referring doctor, arrange definitive medical and surgical care. WAKMAS remains the only state-wide MDT service dedicated to the

management of patients with complex or advanced melanoma, regardless of insurance status or postcode.

Patients may be referred to WAKMAS by a general practitioner or specialist. Following this, they may either be reviewed by a small group of clinicians at the HPIMR facility or reviewed externally by a WAKMAS clinician. They are then presented to the WAKMAS MDT for confirmation of the treatment plan. WAKMAS will arrange a comprehensive review of the pathology for all referred patients and will also organise investigations such as PET/CT, MRI, and molecular testing (Array CGH, FISH) of the tumour as needed.

Most patients referred to WAKMAS, will be reviewed externally by a Surgeon or Medical Oncologist either in private or through a public hospital outpatient clinic, after which, they will be offered review by a dermatologist. All external review initial appointments are provided with not out of pocket cost to the patient. Patients who are reviewed at the HPIMR are interviewed and examined by a small multidisciplinary team in a non-threatening environment, often with their immediate family present.

After review, patients are given advice regarding the management of their melanoma. The management

plan is confirmed after the patient is presented at 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.

WAKMAS clinicians are all experienced in the management of melanoma and come from a range of specialties, including Dermatology, General Surgery, Medical Oncology, Plastic & Reconstructive Surgery, Nuclear medicine, and Pathology. The nursing team consists of a Clinical Nurse and the Clinical Nurse Consultant who also serves as the coordinator for the service.

Staff of WAKMAS

Associate Professor Mark Hanikeri (Plastic and Reconstructive Surgeon) Director of WAKMAS
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Dr Suren Subramaniam

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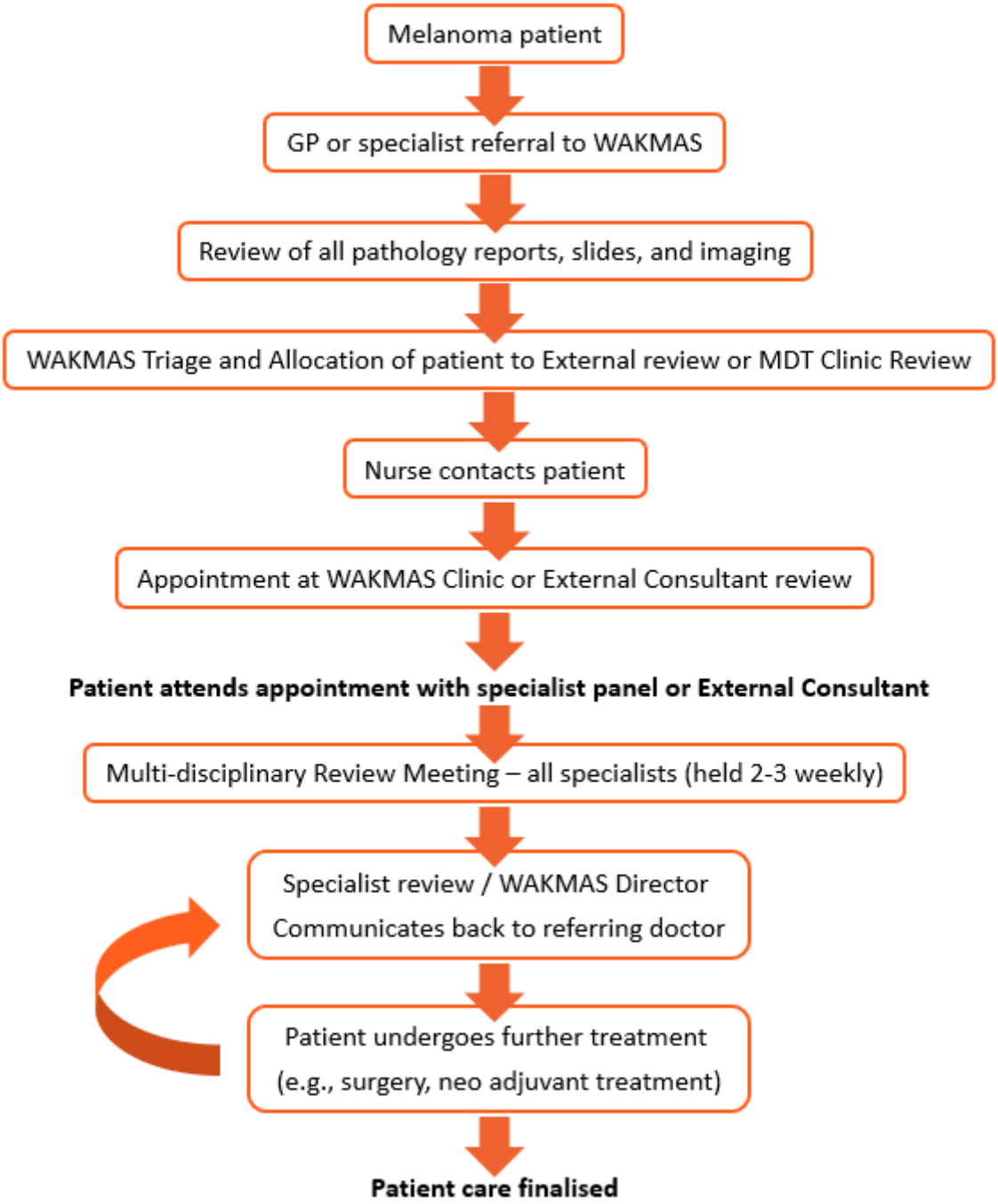
Associate Professor Elin Gray PhD – School of Medical and Health Sciences. Edith Cowan University.

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 2020 in men the rate has ranged between 54 and 73 cases per 100,000 person years. The female rate is lower, ranging between 33 and 49 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. The age-specific incidence data over this period would be useful to demonstrate whether the incidence of melanoma in young people has changed in response to education and awareness. This data is currently not available.

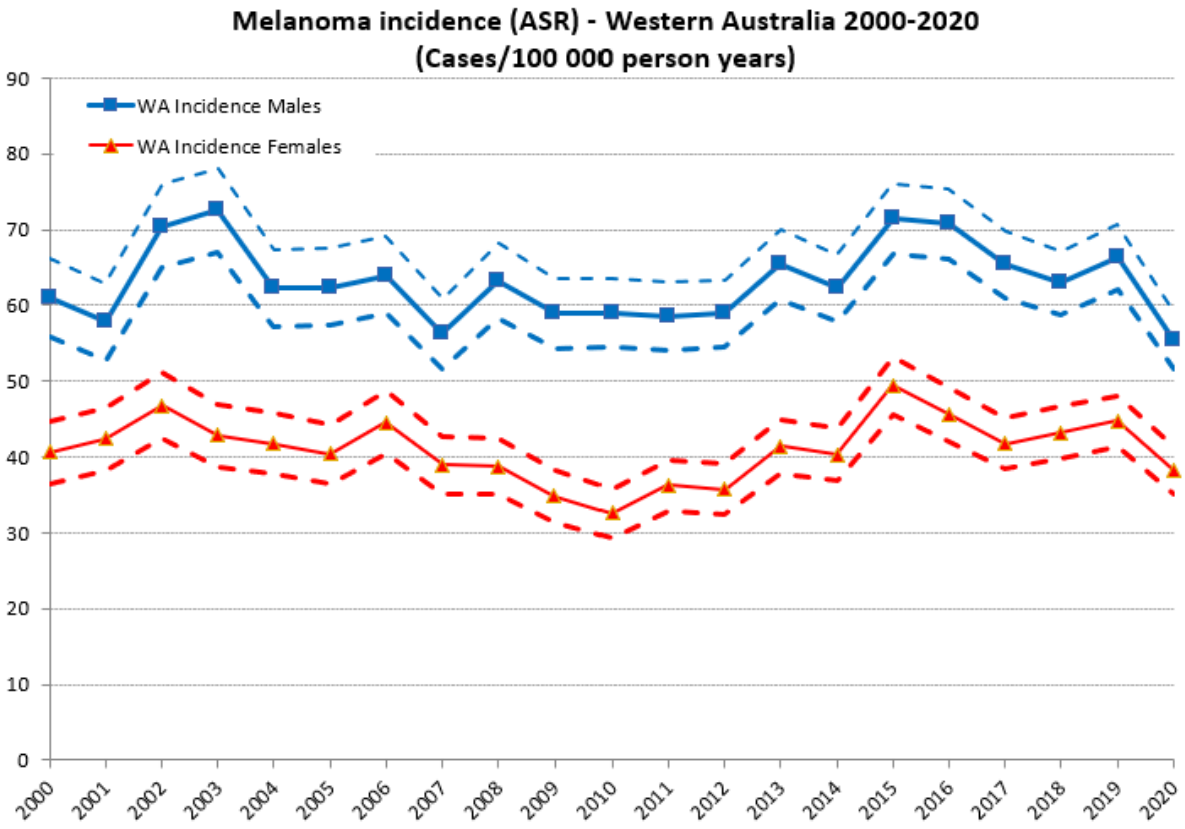


Figure 1 Melanoma Incidence (ASR) Western Australia 2000-2020*

Melanoma mortality in men has been trending downwards since 2011, which saw the rate peak over the twenty-year period (12.6 cases/100 000 person years) to its lowest rate in 2020 (5.1cases/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.

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. Randomised controlled trials have demonstrated a survival benefit from adjuvant treatment in stage III melanoma. This is now offered in most stage III cases and selected stage IIB+ cases. It is hoped that this will result in further falls in melanoma mortality in years to come.

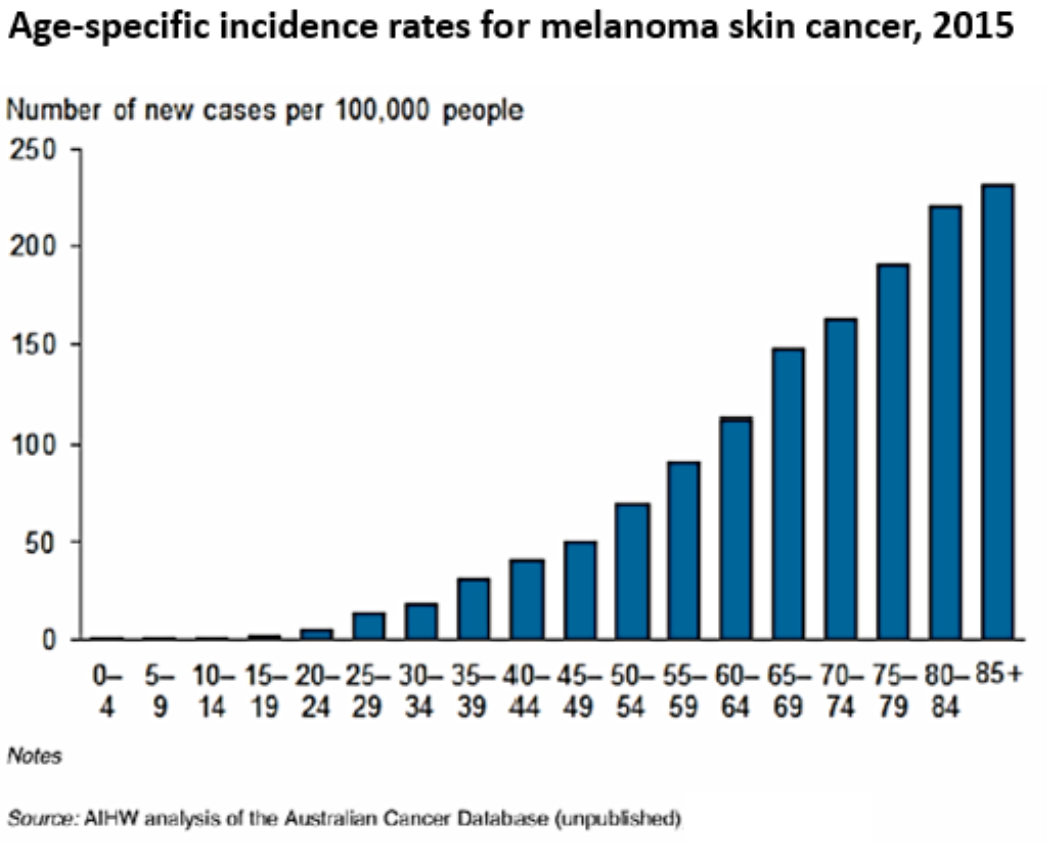


Figure 2 Age-specific incidence rates for melanoma skin cancer, 2015

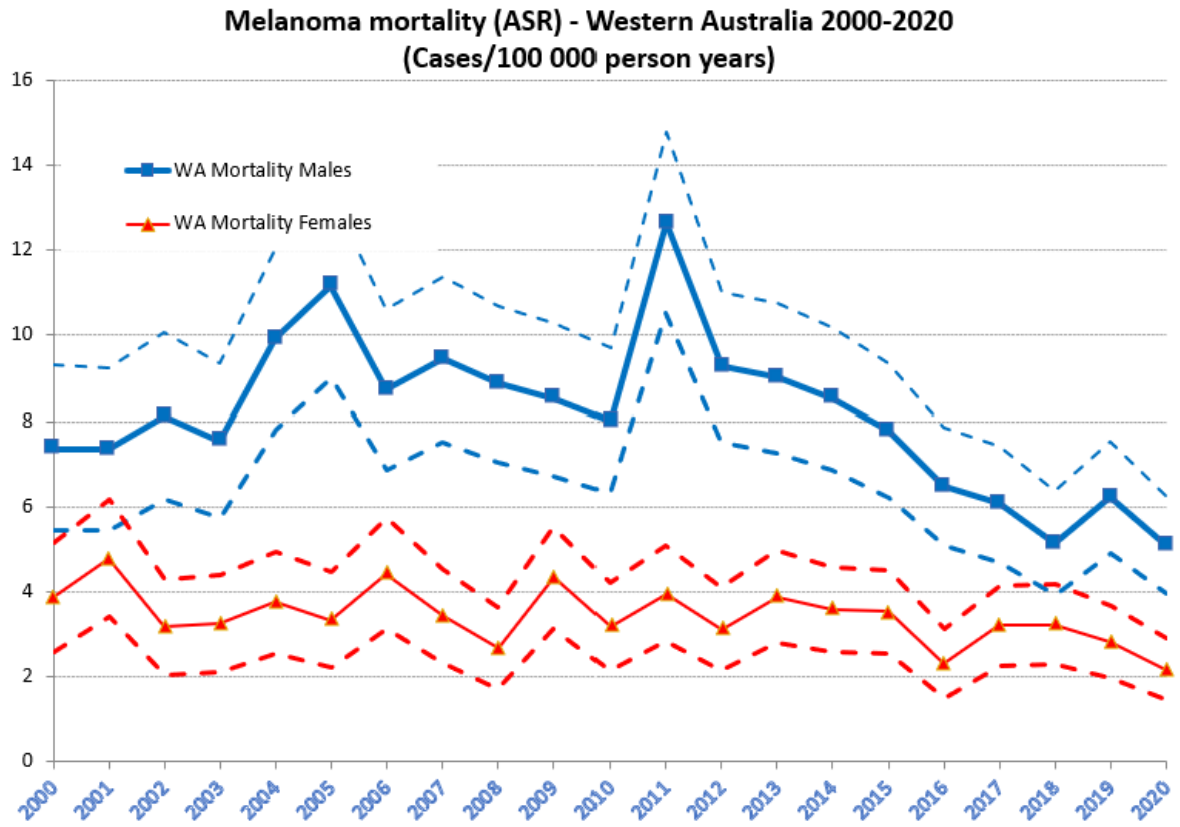


Figure 3 Melanoma Incidence - Mortality ASR WA, 2000-2020

Melanoma Detection and Screening

Melanoma that is detected early is more likely to be cured. Therefore, early diagnosis and treatment of melanoma is the goal. There has never been a benefit demonstrated 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 of these individuals 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. Early melanomas are usually asymptomatic and are often an incidental finding.

The mostly commonly used surveillance methods are:

1. Full body examination (Naked eye + magnification with good lighting – Maggie lamp if available).
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 (Artificial intelligence or dermatology review) diagnostic facility. (e.g., Molemax, Visioderm, Solarscan, Siascope, Dermogenius).

Specialised clinics use sophisticated systems like reflectance confocal microscopy and multispectral imaging. The use of telemedicine to transmit images of atypical, pigmented lesions to experts for their opinion is currently adopted by some centres.

Other techniques aimed at early detection include 3-dimensional photography, magnetic resonance imaging

(MRI), diffuse reflectance spectroscopy and ultrasound imaging. None of these at this stage have proven useful in the clinical situation.

A world-first 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.

Automated and computerised systems remain inferior to clinical and dermatoscopic examination by a clinician experienced in the technique. Whilst some are promising, claims that computerised screening offers superior detection rates are not yet supported by evidence.

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 mm2. 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 interobserver reproducibility, limiting the 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 of melanoma, none have so far 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 • RT-PCR for circulating melanoma cells.		• Vaccine therapy • Gene therapy • "Alternative" therapies

Prognostic Factors	Tumour Related	Host Related	Environment Related
	• Telomerase • MitF • ctDNA levels • Gene clusters		

** In stage IV disease*

Figure 4 Prognostic factors in cutaneous melanoma

The majority of melanomas are cutaneous in origin, however around 1% arise from mucosal sites. For the purpose of staging and prognostic information, 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 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.

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) 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.

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 A). Staging for melanoma is based on the histological report combined with clinical examination (clinical staging) and the outcome from investigations if performed, including Sentinel Lymph Node Biopsy (SLNB) (Pathological staging).

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 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 considers this risk 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 nomogram risk is over 10% in a healthy patient, SLNB would be recommended at the time of wide local excision (WLE) of the melanoma. Patients who are deemed suitable for SLNB should have a thorough discussion regarding the benefits and risks associated with the procedure

prior to proceeding. Since WLE increases the distance of residual tissue from the primary site, prior WLE increases the likelihood of a false negative result from SLNB and hence this reduces the reliability of the procedure. Consequently, SLNB is generally not performed after WLE, though it may occasionally be acceptable in this situation if flap reconstruction has not been performed. 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.

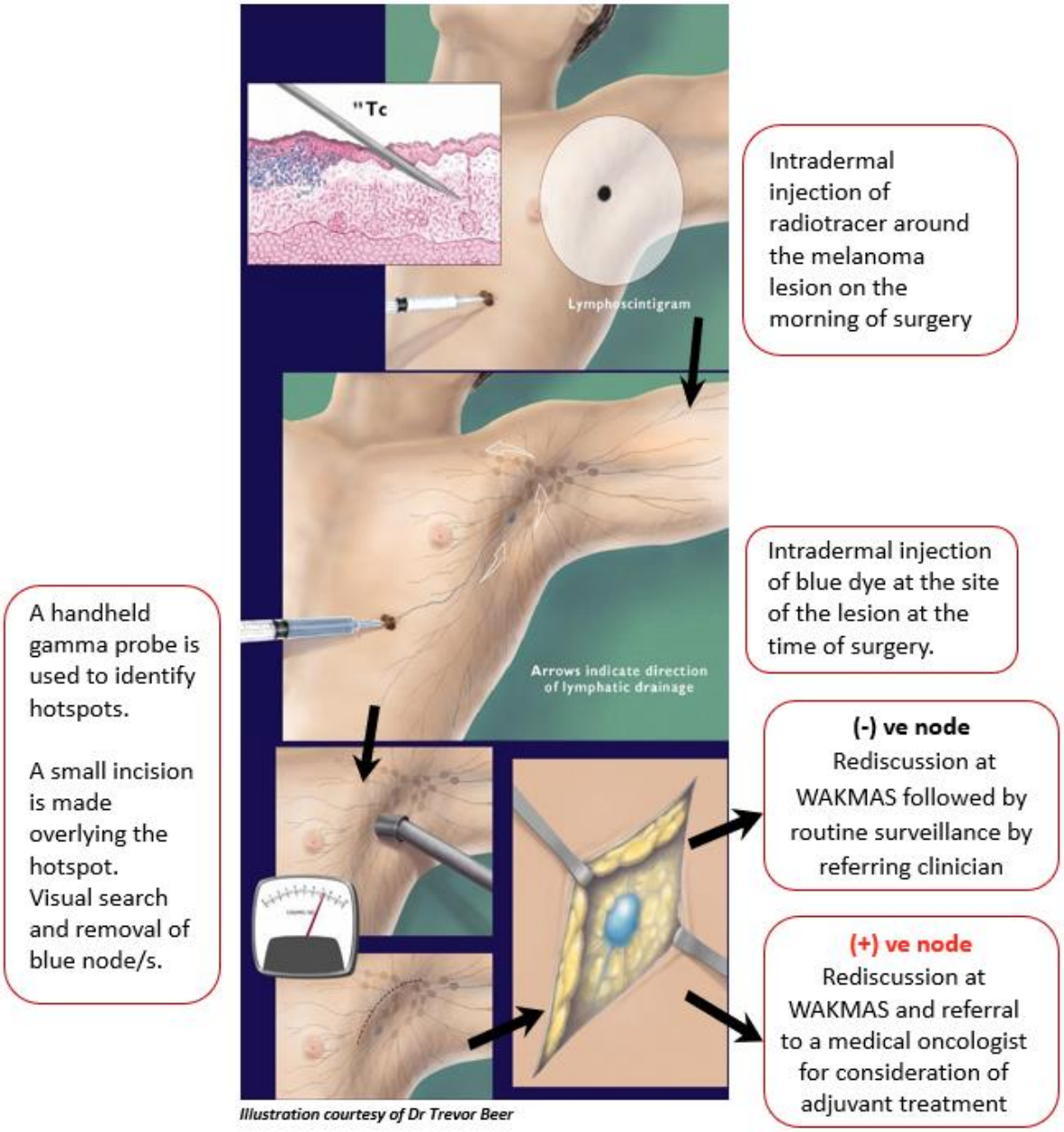


Figure 5 Sentinel Lymph Node Biopsy Procedure

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 the majority of 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. 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 primary 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	10-20 mm *clinical* margin depending on the site of the lesion, the availability of local tissues and the cosmetic outcome (After consideration of SLNB)
>4.0 mm	10-20 mm *clinical* margin depending on the site of the lesion, the availability of local tissues and the cosmetic outcome (After consideration of SLNB)

Figure 6 Summary of WAKMAS recommendations for clinical margins in primary 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 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, wider margins of 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.

Although F18-FDG PET/CT is not yet 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. Patients with confirmed macroscopic disease are advised to undergo therapeutic lymph node dissection (TLND). Most adjuvant protocols now require Stage III patients to have TLND performed unless the lymph node disease is considered “Unresectable.” The outcomes from adjuvant treatment are generally better when all known macroscopic disease has been resected.

Completion Lymph Node Dissection (CLND)

In the past WAMAS has recommended CLND after confirmation of a positive 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. Furthermore, the morbidity from this procedure outweighed any potential benefit in local control. WAKMAS no longer recommends CLND is performed for patients with micro-metastases confirmed on SLNB.

Medical Therapy for Advanced Melanoma

Systemic Therapy for Metastatic Melanoma

Treatment of unresectable stage III or metastatic (AJCC stage IV) disease

In 2010, Ipilimumab was the first systemic therapy to demonstrate an improvement in survival in metastatic melanoma in a randomised controlled trial. It marked the beginning of an era where immunotherapy has become one of the greatest breakthroughs in systemic therapy for cancer since chemotherapy was first introduced in the 1940s. Long-term results from a pooled analysis of trials of ipilimumab suggest that patients who are alive at 3 years after Ipilimumab are more likely to have extended survival, (up to 10 years in 18-20% of cases).

These results were further improved on when Pembrolizumab, an immune checkpoint inhibitor targeting PD-1 (programmed death receptor-1), was shown to result in an improved overall survival and a higher response rate compared to Ipilimumab. Updated overall survival data demonstrated a 44% survival at 4 years for treatment-naïve patients

receiving Pembrolizumab for unresectable Stage III or Stage IV melanoma. Similarly, the PD-1 inhibitor Nivolumab has a reported 5-year survival of up to 35%. All three drugs are currently approved and PBS-listed in Australia for unresectable AJCC stage III, or stage IV melanoma.

The combination of drugs targeting PD-1 (Nivolumab) and CTLA-4 (Ipilimumab) has significantly higher response rate (up to 60%) and overall survival (46-57%) than Ipilimumab alone (22-25%). In a follow-up analysis of the CheckMate 067 study at 6.5 years, the overall survival rate was 57% in patients with BRAF-mutant melanoma and 46% in BRAF wild-type patients. This combination is TGA-approved and was PBS-listed as of 1st December 2018. A number of other immune-modulatory agents are under investigation in the clinical trial setting, including single-agent novel targets and combinations with existing agents.

More recently, another dual immunotherapy regimen combining Nivolumab (anti-PD-1) and Relatlimab (LAG-3 blocking antibody) was demonstrated to have a superior progression free survival and response rate compared to nivolumab alone (2-year PFS 39% vs. 29% and response rate of 43% vs. 33%). This combination has a more favourable toxicity profile compared to the

Ipilimumab-Nivolumab regimen. Nivolumab-Relatlimab has been recently TGA approved but at this stage is not PBS listed.

Immunotherapies have a unique mechanism of action, targeting the immune system to improve the patient's own anti-tumour immune response, therefore potentially resulting in long term immunity against tumour progression. However, their side effect profile is different to conventional cancer therapies since their toxicity is immune-mediated and can affect any organ system. Most commonly affected are the skin (rash, pruritis), GI tract (diarrhoea, colitis), liver (immune hepatitis) and endocrine system (thyroid, pituitary, pancreas). While these drugs are generally more tolerable than cytotoxic chemotherapy, failure to monitor for immune toxicities can result in serious and overwhelming autoimmunity, which can be life-threatening if unrecognised. Therefore, these agents should be given under close supervision by clinicians with an understanding of the potential immune toxicities and how these can be identified and treated early.

Approximately half of advanced melanomas harbor a mutation in the BRAF gene. In parallel to the development of immunotherapy, targeted therapies

that target the mitogen-activated protein (MAP) kinase pathway have been shown to improve survival in patients with BRAF-mutant melanoma. These agents include the BRAF inhibitors Vemurafenib, Dabrafenib and Encorafenib and the MEK inhibitors Trametinib, Cobimetinib and Binimetinib. There are currently three PBS-listed combinations of BRAF/MEK inhibitors in Australia: Dabrafenib / Trametinib, Vemurafenib / Cobimetinib and Encorafenib/Binimetinib. These targeted agents also have a number of unique toxicities including skin and liver toxicity, as well as drug-induced fevers and rigors. Patients who are unable to tolerated one combination may be able to tolerate a different combination of drugs, owing to the different adverse event profiles of each regimen.

Adjuvant treatment for resected AJCC stage III disease

Patients with resected Stage III melanoma have a high risk of recurrence and mortality. Historically, high-dose interferon was the only systemic treatment associated with a survival advantage in resected Stage III disease. However, treatment is associated with significant toxicity and the survival advantage is modest. The use of high dose Interferon is declining, based on the limited benefit-risk achieved, and more importantly,

the emerging role of more effective systemic therapies that are likely to become the new standard of care in the coming years.

There are now several randomised, controlled trials that evaluated the benefit of systemic therapy following surgery for Stage III melanoma and demonstrated a significant reduction in the risk of recurrence or death, compared to placebo or observation alone. In a study of adjuvant treatment with Ipilimumab for resected Stage III melanoma (excluding metastasis <1mm or in-transit metastasis), there was a significant reduction in risk of recurrence, as well as an improvement in overall survival at 5yrs from 54% to 65%. In another recently published trial that compared Nivolumab to Ipilimumab following surgery for Stage IIIB or IIIC melanoma, the risk of recurrence at 12 months was significantly lower (35% relative risk reduction) with Nivolumab. In addition, Nivolumab was associated with less severe grade toxicities. Similar results were demonstrated for Pembrolizumab versus placebo (Keynote-054) in resected Stage III melanoma (including stage IIIA disease), with a 43% reduction in risk, recurrence, or death. For patients with Stage III melanoma whose tumours harbour a BRAF mutation, combination

treatment with Dabrafenib and Trametinib has resulted in a 4- year rate of relapse-free survival of 54%, compared to 38% for placebo, representing a statistically significant reduction in risk of recurrence or death. The 3-year overall survival was also higher at 86% for the combination-therapy group, compared to 77% in the placebo group, but this did not reach the pre-specified interim analysis boundary for significance. The BRIM 8 study also demonstrated that monotherapy with Vemurafenib substantially improved disease free survival versus placebo in patients with resected Stage IIC, IIIA, or IIIB melanoma (AJCC 7th ed.).

Adjuvant treatment for high-risk stage IIB/C 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 that can exceed that of subsets of patients with stage III disease.

In two separate randomized, placebo-controlled phase 3 trials, one year of adjuvant immunotherapy with either Pembrolizumab (KEYNOTE-716 trial) or Nivolumab (CheckMate-76K trial) were demonstrated

to reduce the risk of recurrence (2-year relapse-free survival was 81% for Pembrolizumab vs .73% for placebo). Pembrolizumab is currently TGA approved but not PBS listed for this indication.

The decision whether to consider adjuvant immunotherapy in patients with Stage IIB/C 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 in more modest than that seen in Stage IIIB/C and Stage IV melanoma.

Systemic treatment of metastatic uveal (ocular melanoma)

While uveal melanoma is a rare malignancy relative to cutaneous melanoma, certain genetic subtypes exist in some patients who have 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. 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. Internationally, there are centres conducting isolated or percutaneous hepatic perfusion with around 50% response rates (compared to 5% for investigator choice of chemotherapy or immunotherapy). Although PFS is significantly prolonged, the impact on overall survival is less pronounced.

Tebenetafusp (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.

Based on these results, Tebentafusp is now TGA approved but is not PBS listed at this time. It is available as part of a compassionate access program at one treatment site in most Australian states, including at Sir Charles Gairdner Hospital in WA. 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. Furthermore, the optimal combination or sequence of agents that are likely to give the best balance of risk and benefit in the first line setting for individual patients has yet to be determined. Which patients require combination immunotherapy versus a single agent, and whether patients with BRAF mutations should receive immunotherapy, BRAF inhibitors, or both, in the first line setting, are questions that remain unanswered. Another unanswered question is how liver-directed treatments of patients with uveal melanoma can be combined with immunotherapies. This would utilize the high response rates of perfusion with the durable responses from immunotherapy.

An evolving treatment approach in clinically detectable Stage III melanoma (IIIB/C/D) is to give pre-operative immunotherapy (also called 'neoadjuvant treatment'), followed by surgery and then further adjuvant immunotherapy. In randomized phase II trials, this approach may result in improved outcomes and reduced recurrence compared to adjuvant therapy alone. It also provides an early opportunity to assess pathological response once the lymph nodes are resected. A 'complete pathological response' is likely to correlate with better recurrence and overall survival, at least based on current preliminary data.

A different form of immunotherapy known as tumour-infiltrating lymphocyte (TIL) therapy is now being offered overseas. This therapy involves the culture and ex-vivo expansion of the patient's own tumour infiltrating lymphocytes harvested from their tumour specimens. The cultured cells are then infused back into the patient. TIL therapy is laborious and expensive but has been shown to be effective in patients with recurrence after anti-PD-1 immunotherapy. The phase III randomized control trial conducted in Denmark and Holland have resulted in the approval and PBS funding of this therapy in Denmark. While not yet available in Australia, a research project involving WAKMAS

clinicians and researchers aims to start trials with this therapy in Perth. The TIL therapy will be generated at a facility at Royal Perth Hospital.

Where available and appropriate, patients with advanced melanoma should be offered the opportunity to be considered for suitable clinical trials of novel agents, particularly those involving immunotherapy or targeted approaches. 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 another immune modulatory drug (such as inhibitors of LAG-3, TIM-3, IDO, IL2 targeted drugs, TLR9 agonists and others), or more recently in combination with patient specific personalized cancer vaccines. There is also an ongoing effort for translational studies (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. The practices of WAKMAS medical oncologists span the entire state in the public and private setting and are well placed to recruit suitable patients into

appropriate trials. Trials for stage III patient require evidence of either clinical lymph node disease or a positive sentinel lymph node. **Patients who may therefore be suitable for SLNB should be referred to a clinician who performs this procedure prior to proceeding to a wide excision of their primary disease which may render subsequent SLNB unreliable**.

Radiotherapy in Melanoma

Primary-site radiotherapy

Radiotherapy (RT) is rarely considered appropriate as a definitive modality for the treatment of cutaneous melanoma. Medical or surgical inoperability are potential examples where it may play a role recognizing 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. Factors predicting for tumour bed recurrence may include suboptimal margins (where further surgery is not possible), satellitosis, desmoplastic histology, perineural invasion, locally recurrent disease, and immunosuppression. In general, adjuvant RT can be considered to provide around a 50% relative risk reduction of local recurrence. The decision to recommend radiotherapy will depend on the

- Predicted absolute risk of local recurrence.
- Consequence of local recurrence (nearby critical structures; type of surgery required).
- Toxicity of RT (site and dose dependent).

Regional-site radiotherapy

Adjuvant radiotherapy following regional lymph node dissection may be considered if there are pathological features which predict for a high cumulative risk of regional recurrence.

These recommendations recognize a regional control benefit and no proven relapse free or overall survival benefit from the single, completed randomized control trial. Pathological features suggestive of > 25% risk of regional recurrence are:

- the presence of extranodal extension
- presence of large node(s) >/= 3cm
- a single parotid node, >2 cervical nodes, or >3 axillary or groin nodes.

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.

Other contexts where regional adjuvant radiotherapy warrants consideration include:

- Recurrent nodal disease.

- Immunosuppression (if in combination with other risk factors for residual disease)
- Unresectable regional disease- For regional control in the absence of disease elsewhere.

Distant-site radiotherapy

Radiotherapy may be considered as part of a palliative management strategy to alleviate symptoms and/or prevent imminent, severe morbidity.

Potential indications include:

- Fungating, bleeding, pain for local, in transit, recurrent or regional disease
- Bone metastases – impending fracture, pain, post-surgical fixation
- Brain metastases –RT options for brain metastases include:
  - **Stereotactic, ablative radiotherapy (SRT)** – In limited intracranial disease where surgical resection is not appropriate.
  - **Whole brain radiotherapy (WBRT)**. More extensive intracranial disease.
  - **Hippocampal-sparing intensity modulated WBRT** – Reportedly less toxic than WBRT but with a limited evidence base.

- **Post-operatively** – SRT to the tumour bed is increasingly preferred over WBRT.

In the presence of solitary or oligometastatic disease, ablative stereotactic radiotherapy (SRT) warrants consideration when surgery is not possible and an aggressive approach to limited metastatic disease is considered appropriate. However, appropriate surgery, when possible, combined with adjuvant medical management or RT remains the mainstay of treatment.

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. In asymptomatic brain metastases, systemic therapies are playing a progressively larger role which may alter the role of radiotherapy. Furthermore, the potential for toxicity with combined therapies is very real. Until trials which combine radiotherapy concurrently with immunotherapy mature, the safety of such combinations remains unknown.

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 7 Surveillance in melanoma

Clinical review should be undertaken by a combination of health professionals including the patient's primary care physician, dermatologist, surgeon, and 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 performed by radiographers and interpreted by radiologists with expertise and experience 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 major private radiology companies in WA to establish consistent guidelines for the diagnosis of lymph nodes suspicious for early involvement with metastatic disease. These are:

USS Surveillance:

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

Criteria for Abnormal Nodes

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 for this information.

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 8 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.	

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
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,	Yes

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
	and/or presence any number of matted nodes.	

Figure 9 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 10 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			

When T is….	And N is….	And M is….	The pathological stage is….
information to assign their pathological stage.			

Figure 11 AJCC Prognostic Stage Groups (pathological) – AJCC Melanoma Staging 8th edition.

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