



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

The Western Australian Melanoma Advisory Service (WAMAS), funded by the Department of Health, was established as a state-wide service in 2000. The scope of the WAMAS 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. The service was run in collaboration with St John of God Hospital in Subiaco until the end of 2017. However, in January 2018, WAMAS was relocated to the Harry Perkins Institute of Medical Research, in collaboration with the Kirkbride Melanoma Centre, and is now known as WA Kirkbride Melanoma Advisory Service (WAKMAS).

Patients may be referred to WAKMAS by their general practitioner or specialist. Following this, they are personally interviewed and examined by a small multidisciplinary team in a non-threatening environment, often with their immediate family present. This includes a comprehensive review of the pathology and other investigations. They are then given advice regarding management of their melanoma and where requested, subsequent management is organised by the reviewing team.

WAKMAS clinicians are all experienced in the management of melanoma and come from a range of medical and surgical specialties, including dermatology, general surgery, medical and radiation oncology, plastic & reconstructive surgery and pathology. The nursing team consists of a clinical nurse and the clinical nurse consultant who also serves as the coordinator for the service. Patients benefit from many specialist opinions at one consultation, followed by discussion in the multidisciplinary setting, after which the recommendations of the team are communicated to the referring doctor. Patients are not charged for this service that is independent, objective and unaffected by insurance status or postcode.

Although WAKMAS is not primarily a treatment centre for patients with melanoma, the service will, if asked by the referring doctor, arrange definitive medical and surgical care through the public and private hospital systems. 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 in order to formulate optimum management of their disease. At present, WAKMAS is the only multidisciplinary unit to offer patients with cutaneous melanoma the opportunity for this review.

Staff of WAKMAS

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Dr Minh Lam

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ENT SURGEON

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Melanoma Incidence and Mortality in WA

The age-adjusted incidence of Melanoma in Western Australia is presented in the table below. It demonstrates that in men the rate has ranged between 30 and 51 cases per 100,000 person years, whilst the female rate is lower, ranging between 23 and 33 cases per 100,000 person years. Strategies to reduce the incidence of melanoma in the Western Australian population through education and awareness campaigns have therefore had little effect during this period. Melanoma is predominantly a disease of the elderly and it is possible that the effect of these campaigns on melanoma incidence may not be seen for some time, as the population exposed to them reaches the most at-risk period. 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. However, this data is not available at the time of publication but may be added in future editions of this book.

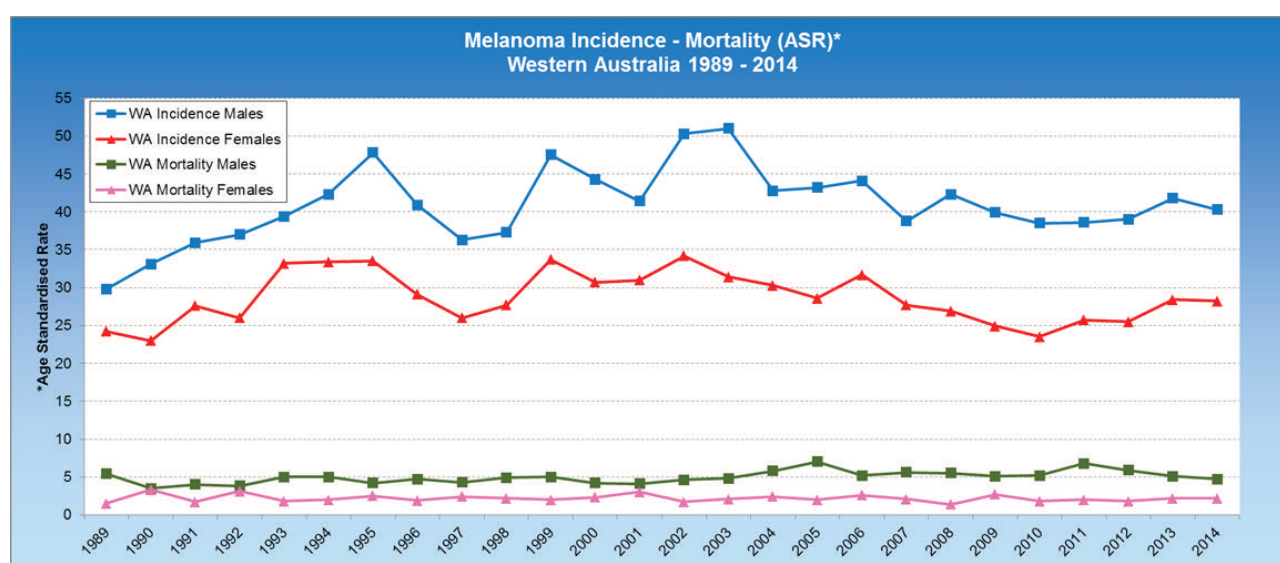


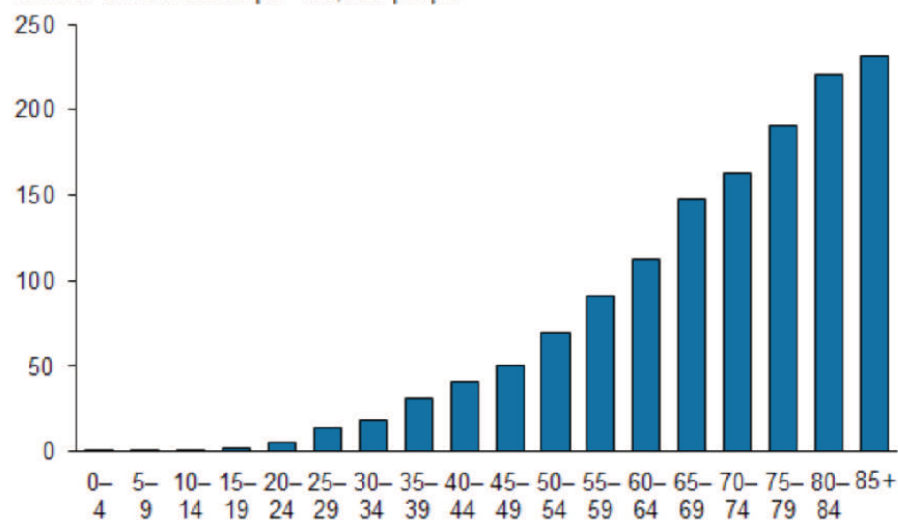
Figure 1 Melanoma Incidence-Mortality (ASR)* Western Australia 1989- 2014

* The Age-standardised rate is a measure of adjusting the crude rate to remove differences in the population age structures when comparing for different periods of time, different regions, or different population subgroups.

Melanoma mortality has been stable for the past 25 years. There appears to be a downward trend in mortality from melanoma in men since 2011, which corresponds to the time of introduction of new modalities for medical management of advanced disease. This is encouraging though there is not yet a statistically significant decline since the confidence intervals for 2011 and 2014 overlap as can be seen in the table on the following page. It is hoped that when the 2015 data is released in 2018, a further fall will be seen in the age standardized rate for male melanoma-associated mortality such that there is no overlap in confidence intervals over the 5 year period and meaningful conclusions may then be made.

Age-specific incidence rates for melanoma skin cancer, 2015

Number of new cases per 100,000 people



Notes

Source: AIHW analysis of the Australian Cancer Database (unpublished), (see [source data](#)).

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

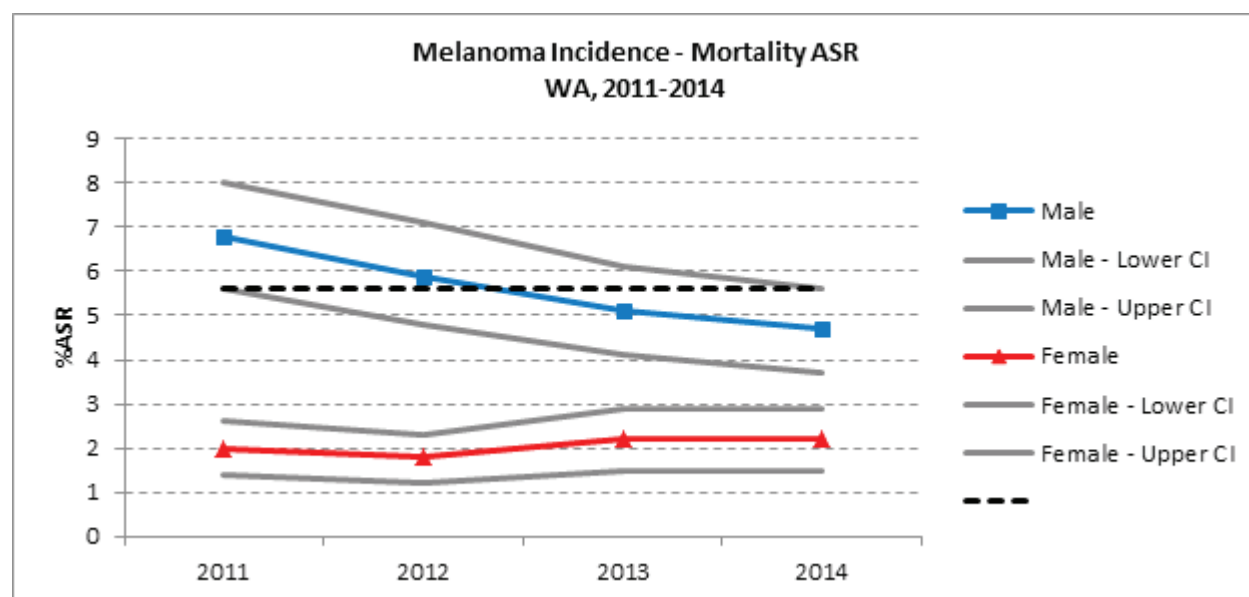
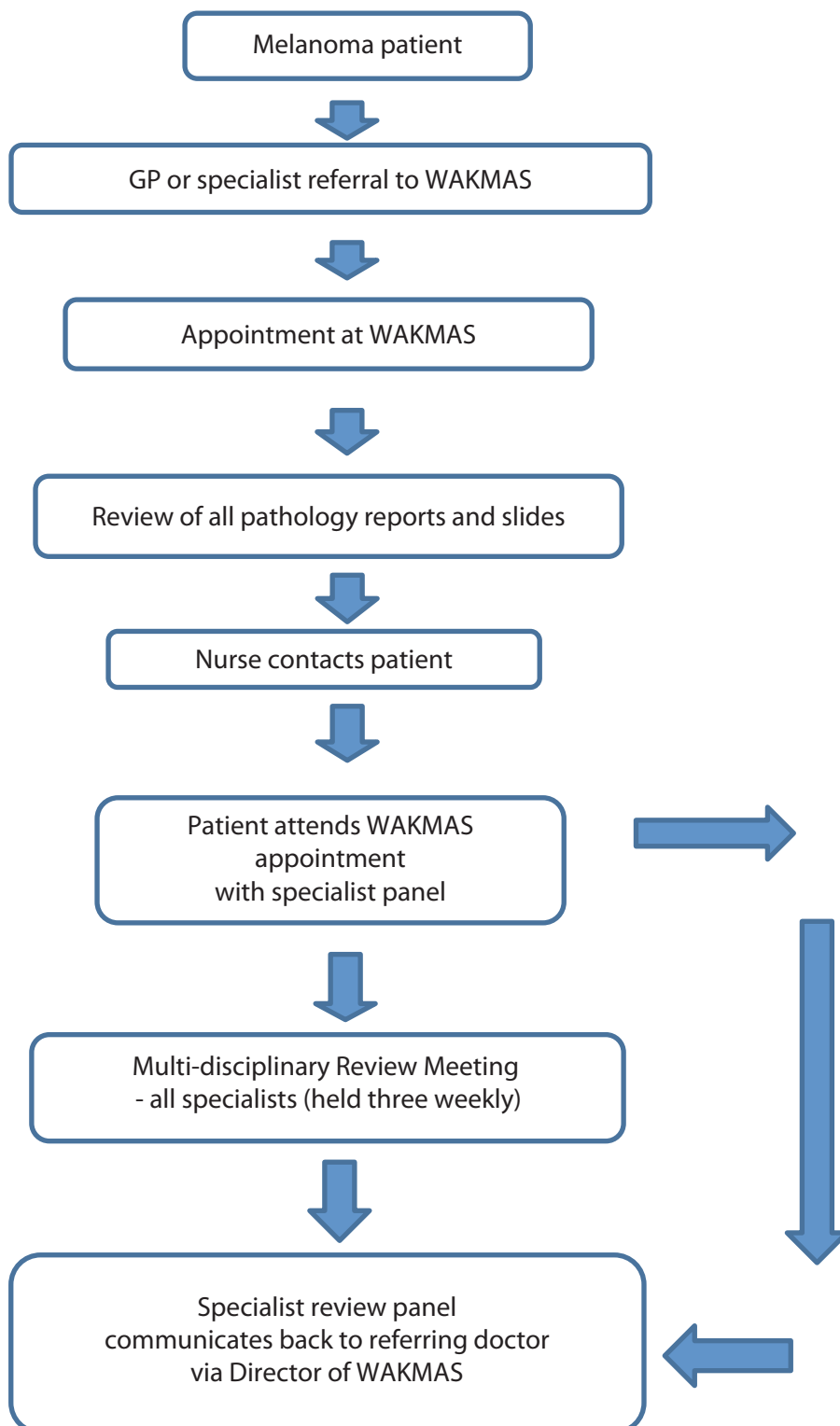


Figure 3 Melanoma Incidence - Mortality ASR WA, 2011-2014

Flow path for patients referred to WAKMAS



Melanoma Detection and Screening

Melanoma that is detected early is more likely to be cured. Therefore, early diagnosis and treatment of melanoma is the aim. Screening of the general population for melanoma has never been shown to decrease morbidity or mortality from this disease. Without a proven cost-benefit ratio for population-based screening, this method of screening cannot be recommended.

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

When examining at-risk patients for melanoma, it is paramount that the skin is examined thoroughly. The whole skin surface from the top of the scalp to the soles of the feet should be visualised in a systematic way. Checking individual skin lesions, such as the lesions concerning patients only, is inadequate. Melanomas in early development are usually asymptomatic and are very often identified as an incidental finding.

Surveillance methods include practices in widespread use, those used in specialised clinics and experimental techniques.

The mostly commonly used are:

1. Full body examination with the naked eye with good lighting and magnification.
2. Examination of individual lesions with the dermatoscope.
3. Full body photography and comparison of lesions over time.
4. Examination with a digital photography system with or without an automated diagnostic facility. (eg. 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 pigmented lesions to experts for their opinion is currently being explored (Molemap).

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. An experimental method currently under investigation is tape sampling of the surface of suspect pigmented lesions to detect differing forms of ribonucleic acid.

Automated and computerised systems are inferior to clinical and dermatoscopic examination by a clinician experienced in the technique. Some have performed very poorly in trials. Claims in media advertisements that computerised screening offers superior detection rates are not 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 tumour (Breslow) thickness. In patients with thin invasive melanoma (≤ 1 mm), the prognosis is generally very good, though even in this group there is no guarantee of cure and death from melanoma still may occur. Clark level is related to Breslow thickness and is of limited independent prognostic value.

Tumour ulceration is established as an adverse prognostic factor, although it is rarely present 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 1/mm². Increasing mitotic rate also correlates with an increasingly adverse prognosis.

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 apparently in situ tumours or metastatic melanoma without a detectable primary lesion. Unfortunately, the data is conflicting and identification of regression is subject to poor interobserver reproducibility. This limits the practical utility of this pathological feature.

Recognition of lymphovascular invasion should be considered as an adverse finding, but it is only rarely seen, so that this factor does not generally appear as a statistically significant factor in most studies.

Most other histological features are of limited or controversial prognostic value. These include lymphocytic infiltrate, cell type, growth phase and lymphatic/vascular space invasion. Histological type has traditionally been stressed in melanoma reports. However it plays little role in prognosis, except in the case of pure desmoplastic melanomas which appear to have lower rates of nodal metastasis.

When regional metastases are present (stage III) the number of nodes affected and their size is of prognostic significance. Patients with clinically identifiable nodes have a worse prognosis than those whose nodal involvement is only identifiable microscopically on sentinel lymph node biopsy (SLNB).

When distant metastases are found (stage IV) the prognosis is worse with increasing number of sites affected and when there is visceral involvement. Poor performance status and increased serum lactate dehydrogenase are also predictors of reduced survival.

Pregnancy or previous biopsy of the melanoma does not appear to affect prognosis.

Patients who present with metastatic disease without a known primary have an outlook similar to that of patients with the same disease distribution but with a known primary tumour.

Many other potential histological, immunohistochemical and genetic markers have been evaluated in melanoma prognosis, but as yet, none have been convincingly validated for incorporation into routine care.

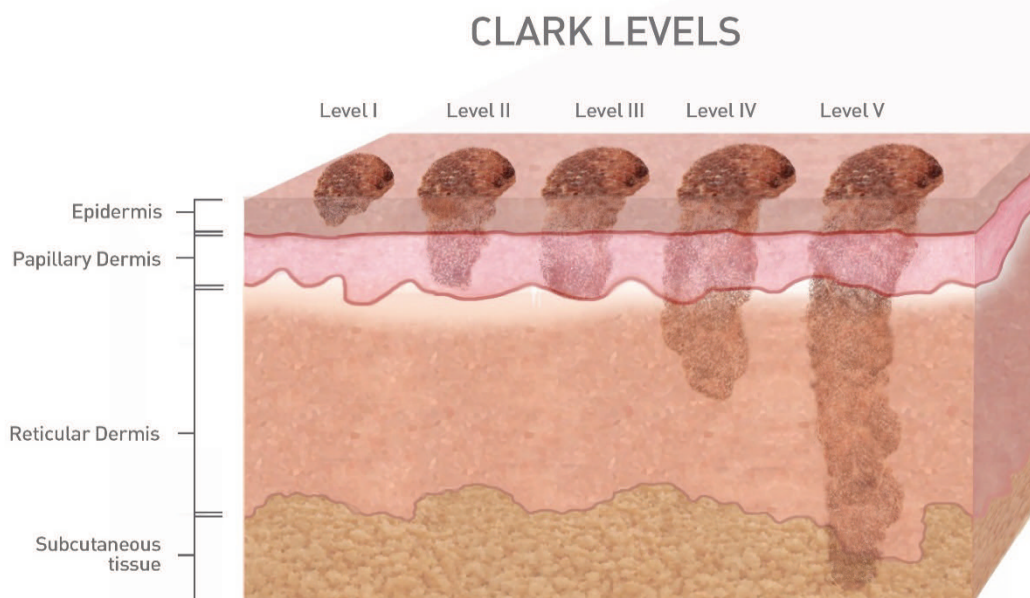


Figure 4 Clark Levels

Clark level measures depth of invasion by anatomic structure. Level 1 is synonymous with in situ melanoma. Although prognosis is worse with increasing level of invasion, it should be noted that Breslow thickness generally provides superior prognostic information.

Prognostic Factors	Tumour Related	Host Related	Environment Related
Essential	Stage: TNM		Completeness of excision
Additional	Ulceration Mitotic rate Regression Clark's level ^a Tumour infiltrating lymphocytes Growth phase Desmoplastic type Vascular invasion Serum S100 protein	Poor performance status ^b	Lymph-node dissection Excision of metastases Chemotherapy Radiotherapy Immunotherapy
Unestablished or Potential Role	Tumour suppressor genes Proliferation markers Angiogenesis Adhesion molecules Growth factors RT-PCR for circulating melanoma cells Telomerase MitF		Gene therapy

Figure 5 Prognostic factors in cutaneous melanoma

(a) Principally applies to thin melanomas, (b) In stage IV disease

Whilst the majority of melanomas are cutaneous in origin, around 1% arise as mucosal melanoma. For the purpose of staging and prognostic information, they are broken down into 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 melanoma and anorectal mucosal melanoma, therefore clinical stage classification systems are used for these lesions.

Since most of these lesions are diagnosed in an advanced stage of disease, mucosal melanoma commonly requires multimodality treatment, combining surgery with postoperative radiotherapy. Due to their rarity their treatment is individualized on a case by case basis in consultation with WAKMAS.

Management of Suspicious Pigmented Lesions

Excisional biopsies

Lesions in which melanoma is suspected should be excised with a 2mm margin to the level of subcutaneous tissue. This allows optimal assessment of the lesion and tumour depth in the event of a diagnosis of melanoma.

The direction of the excision should be performed such that any subsequent wide local 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.

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 appropriate. This may occur for example, if there is a low index of suspicion, if the lesion is too large to excise and close the defect or if it is in an area where excision may cause cosmetic or functional problems. The biopsy should include the most suspicious area and include the full thickness of the skin. Incisional biopsies can provide good representation of a lesion. If performed, 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 of the defect.

- **Curettage of any suspicious pigmented lesion is contraindicated and should NOT be performed.**
- Punch biopsies demonstrate a limited amount of larger lesions leading to potential for sampling error. If used at all, multiple punch biopsies spanning the most suspicious areas should be taken.
- 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 or subcutis and can also transect the base of a deeper melanoma. Transection of the base of a melanoma on partial biopsy impairs assessment of tumour depth preventing accurate prognostic information and staging. For this reason, shave biopsies are not recommended by WAKMAS, although, they may be appropriate in certain instances, when performed by clinicians with appropriate knowledge and expertise.

Frozen section and cytology should not be used for the primary assessment of suspicious pigmented lesions. Observation supported by dermatoscopy, clinical photographs and precise description and 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 may be indicated. Specialist referral may be appropriate in these cases.

Management of Primary Melanoma

Investigations for Stage I and II disease

There is no evidence to support any routine investigations for Stage I and II disease. However, for Stage IIb and IIc disease, (T3b, T4), a PET/CT scan is generally requested.

Staging of Primary Melanoma

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).

WAKMAS uses the AJCC staging system for melanoma. The AJCC has recently published their 8th edition which will be implemented in 2018 (See appendix A). Accurate pathological staging requires the results from SLNB in appropriate cases. Changes in the AJCC 8th edition compared with previous versions has resulted in up-staging of primary lesions over T2b (over 1.0mm with ulceration) to pathological stage IIIb in the presence of a SINGLE positive sentinel lymph node. Recent evidence suggests a significant benefit to stage IIIb patients (From the AJCC 7th ed.) with adjuvant medical treatments after completion lymph node dissection (CLND). It is felt likely that in time, this benefit will extend to pathological stage IIIb (AJCC 8th ed.) patients even without CLND. With this in mind, patients who are T2b or over may be offered adjuvant treatment if they have a confirmed positive sentinel lymph node. This may direct lymph node dissection to be more selective in melanoma patients. The primary role of lymph node dissection in these cases may shift from one of local control to one of pathological staging and reduction of the tumour burden so that adjuvant treatments can be applied.

Sentinel Lymph Node Biopsy (SLNB)

Sentinel node biopsy assists in providing prognostic information to the patient, as well as accurate staging for the purpose of offering adjuvant treatments or entering clinical trials. Furthermore, there is some evidence that patients with intermediate thickness primary melanoma in whom the lymph node metastases are removed whilst microscopic have better survival outcomes than those in whom the lymph nodes are allowed to become clinically apparent before removal, even in the absence of adjuvant treatment. In the past, the advice from Melanoma specialists has been that patients in whom a sentinel node has confirmed the presence of micrometastases has been to undergo CLND.

This is no longer the routine advice but may be applied in special circumstances. These circumstances are discussed later in this booklet.

SLNB should be discussed with patients who have a clinically negative nodal basin and a primary melanoma where the Breslow thickness is 0.8mm in depth or more. In addition, WAKMAS will consider recommending SLNB for melanoma under 0.8mm in thickness with ulceration.

Where the Breslow thickness from a partial biopsy is under 0.8mm with malignant melanoma in the biopsy extending to the base of the specimen, definitive excision of the lesion should be performed wherever possible, to confirm the true Breslow thickness prior to recommending SLNB. If complete excision of the lesion is not practical, then a full thickness incisional biopsy of the most atypical area in the lesion should be performed.

All patients deemed suitable for SLNB should have a thorough discussion regarding the potential benefits and risks of harm associated with the procedure prior to proceeding.

For patients with thick melanomas (>4 mm) without evidence of metastatic disease, referral to WAKMAS for consultation regarding SLNB is appropriate. This may include discussion of access for the patient to clinical trials and adjuvant therapy.

SLNB is unnecessary when a patient presents with systemic disease or an FNA positive node.

Whilst SLNB is generally not performed after a wide local excision it may be acceptable in this situation provided that flap reconstruction has not been performed. The distance away from the primary site increases the likelihood of a false negative result and hence the reliability of the test is reduced in these circumstances.

No definitive recommendations exist in the melanoma literature as to whether a repeat SLNB may be performed after a prior SLNB. WAKMAS do not consider prior SLNB a contraindication for SLNB.

SLNB involves a two stage process. The initial stage is to identify the lymph node basin in which the sentinel node is located through the use of lymphoscintigraphy where a radioactive tracer is injected into the site of the melanoma. This dye then travels to the sentinel node which is the node that receives lymphatic fluid from the site of the melanoma. Whilst the radioactive tracer is in the lymph node, surgery is performed 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.

Sentinel Lymph Node Biopsy

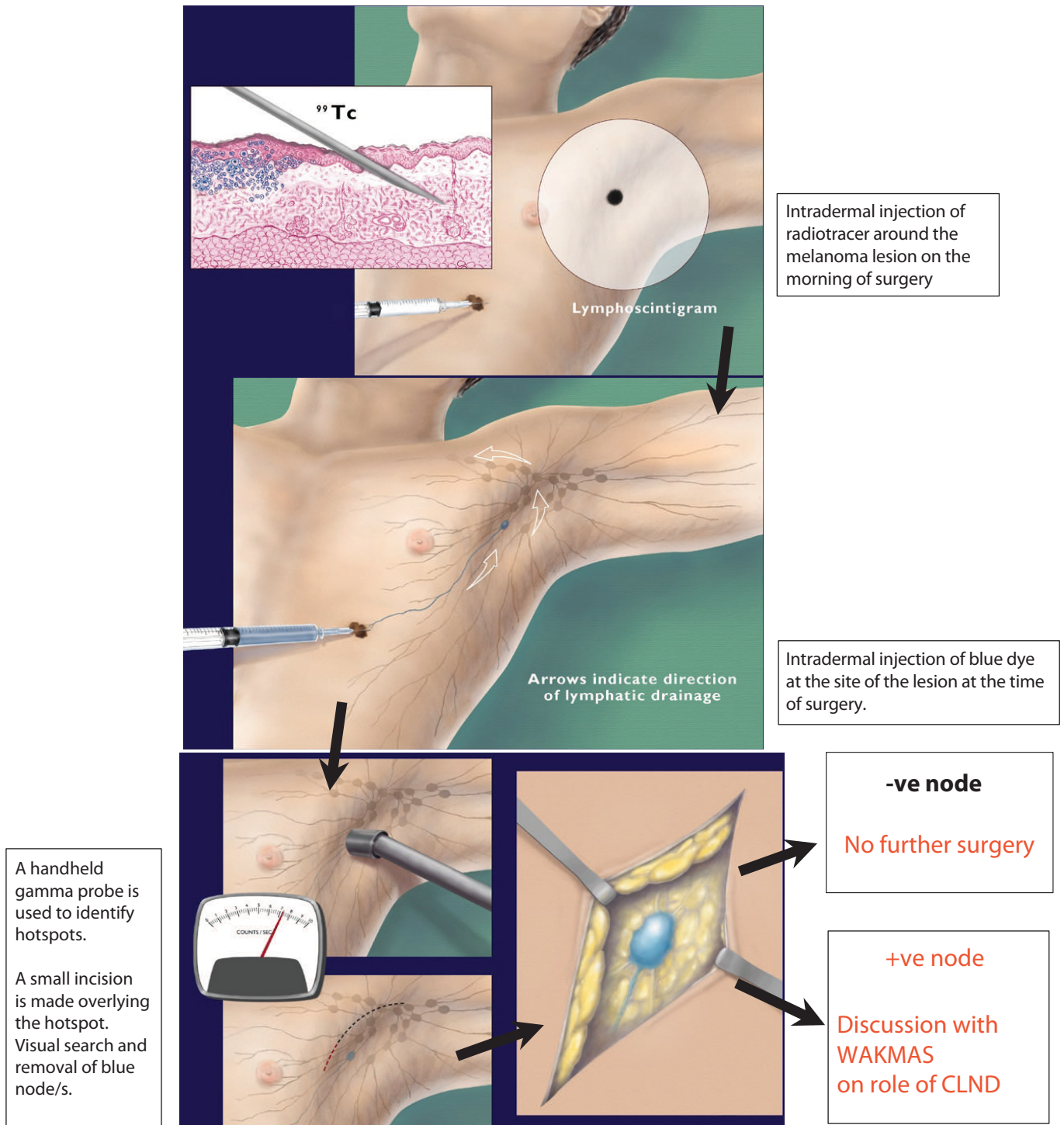


Illustration courtesy of Dr Trevor Beer

Figure 6 Sentinel Lymph Node Biopsy Procedure

Surgical Treatment of Primary Cutaneous Melanoma

Once a 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 primary melanoma. If the lesion has a Breslow thickness under 1mm with no ulceration, mitoses, lymphovascular invasion or in a patient under 40 years of age, referral to WAKMAS is not necessary. However, lesions with a Breslow thickness over 1mm should be discussed with WAKMAS for consideration of sentinel lymph node biopsy (SLNB). This test, if appropriate, should be performed at the same time as the subsequent wider excision of the lesion and not afterwards.

Margins of Excision for Primary Melanoma

Appropriate excision margins for invasive melanoma have stimulated considerable debate over the years. There is no convincing evidence that an excision margin over 1cm has any influence on survival from melanoma or the risk of local recurrence, 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. Local recurrence after incomplete excision usually represents persistent growth of the primary tumour at that site, either in-situ or invasive ('Persistent melanoma'). Recurrence at that site after histologically confirmed complete excision, however, is usually due to metastasis (Local metastasis). The two types of LR each have distinct histologic features with entirely different implications for prognosis. Although local metastasis has the same microscopic morphology and prognostic implications as other cutaneous metastases (satellites, in-transit and distant), in the context of wide excision with the aim of preventing local recurrence, it should be considered separately from those other forms because it involves the primary site. In this context, prescriptive clinical margins may be considered arbitrary. The current international MelMar trial aims to determine whether margins of more than 1.0 cm influence clinical outcomes in patients with invasive melanoma. The protocol for the MelMar trial, however, does not include a valid definition of local recurrence.

Summary of WAKMAS recommendations for clinical margins in primary melanoma

WAKMAS recommends surgical 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 (After consideration of SLNB) with consideration of the site, the availability of local tissues and the cosmetic outcome
>4.0 mm	<i>Consideration</i> should be given to a 20 mm <i>clinical</i> margin depending on the site of the lesion, the availability of local tissues and the cosmetic outcome (After consideration of SLNB)

Figure 7 Summary of WAKMAS recommendations for clinical margins in primary melanoma

Histological margins

It is recommended by WAKMAS that the clinician excising the primary melanoma should achieve complete histological clearance of all atypical melanocytes. 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 3mm may be considered an indication for a conservative wider excision for in situ lesions and for invasive lesions with histological margins under 10 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.

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

Positron Emission Tomography (PET) is an imaging technique, which provides information about cellular function. A glucose analogue (deoxyglucose) is labelled with positron emitting fluorine (F-18) to make an imaging agent known as fluoro-deoxyglucose (FDG). This is injected into the patient and because malignant tumours have a higher glucose metabolism, the tumour cells take up more FDG than the surrounding normal tissue thus show up as increased activity on the scan.

Combined PET/CT machines are now the gold standard. In addition to the PET scan a low dose CT is performed on the same machine and the PET and CT data fused. This results in increased accuracy in detection of disease and shortens the duration of the scan. The radiation dose for PET/CT is equivalent to approximately one standard whole body CT scan.

The main role of FDG PET in melanoma is in the assessment of patients with known metastatic disease. This was specifically assessed in the Australian Prospective Multi-Centre PET Data Collection Project (2003-2005). In this study PET identified at least 189 additional sites of disease (in 134 patients) not identified on conventional imaging (usually CT). PET affected management in 61.9% of patients. The PET scan also identified patients whose disease was likely to progress within 12 months. This data has been replicated worldwide and FDG PET/CT imaging is now part of the standard staging algorithm for recurrent melanoma.

In high-risk patients, primary staging with FDG PET/CT has been shown to upstage or change management. FDG PET/CT appears to have limited utility in intermediate thickness lesions

FDG PET/CT has also been shown to be of benefit in follow up of melanoma patients particularly those diagnosed with Stage III or IV disease to assess early recurrence and treatment response. The optimal frequency of follow-up has not been determined. Some studies have also shown the benefit of early FDG PET/CT in assessing immunotherapy response with early "flare" possibly related to successful immune activation.

There are 4 private and 2 public PET CT service providers in Perth (Oceanic Molecular at Hollywood Medical Centre, Nedlands; Perth Radiological Clinic at Shenton House, Joondalup; SKG Radiology at St John of God, Subiaco; Envision Medical Imaging, Wembley; Sir Charles Gairdner Hospital, Nedlands and Fiona Stanley Hospital, Murdoch) and there is also 1 country private provider of PET CT (Global Diagnostics – St John of God Bunbury). A new PET/CT facility will open in Perth at Theranostics Australia at St John of God, Murdoch in early 2018.

WAKMAS recommends that PET/CT is performed for any newly diagnosed stage III or IV patients or in all T4 patients (primary melanoma over 4mm). PET/CT can also be considered in T2b lesions after consultation with WAKMAS in selected patients or where clinically indicated such as where there is suspicion of metastatic disease on history or examination. PET/CT may also be appropriate for surveillance of all these patients, as indicated by their disease in the context of the individual and the treatment received in consultation with WAKMAS or their treating clinician.

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 FDG PET 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. Oceanic Molecular (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. Sir Charles Gairdner Hospital (Nedlands) Ph: (08) 9346 3333
6. Fiona Stanley Hospital (Murdoch) Ph: (08) 6152 2222
7. Global Diagnostics (Bunbury) Ph: (08) 9780 7999

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, Thoracic CT scan and Brain MRI as indicated by history and clinical examination.

Management of Draining Lymph Nodes

There is no role for prophylactic lymph node dissection without evidence of either microscopic or macroscopic lymph node disease. The role of lymph node dissection in the management of patients with known lymph node melanoma metastases is currently 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. It has been associated with significant morbidity in this group of patients.

Completion Lymph Node Dissection (CLND)

In the past WAMAS *has* recommended block dissection after confirmation of a positive SLNB. However, the recently published Multicentre Selective Lymphadenectomy Trial II (MSLT II) has called into question the benefit of CLND *in the absence of adjuvant medical treatment*. The morbidity from this procedure is thought to outweigh any potential benefit in local control, with no proven OS or MSS benefit over SLNB alone.

However, there is now evidence for a benefit in some stage III patients from adjuvant medical treatment, following CLND. Furthermore, there are a number of current and planned clinical trials in this group of patients with single and combination therapies. Therefore, WAKMAS now recommends that patients with a positive SLNB be discussed before proceeding to CLND. The role of CLND in these patients will be determined in the context of the primary lesion, the patient and the SLN status. Patients who do not proceed to CLND should have the affected LN basins assessed periodically using targeted ultrasound scans. This is discussed later in the section on melanoma surveillance.

Adjuvant Medical Therapy Metastatic Melanoma

Systemic Therapy for Metastatic Melanoma

Treatment of 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 used 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 some cases).

More recently, 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. 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 2-year survival (up to 58%) than ipilimumab alone (34%). This combination is now TGA-approved but not PBS-listed at this time. 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.

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 and dabrafenib, and the MEK inhibitors trametinib and cobimetinib. The combinations of dabrafenib and trametinib (which is superior to dabrafenib alone), and of vemurafenib and cobimetinib, are PBS listed for the first-line treatment of advanced BRAF-mutant melanoma. These targeted agents also have unique toxicities including skin and liver toxicity, as well as drug-induced fevers and rigors.

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 randomized, 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. For patients with stage III melanoma whose tumours harbour a BRAF mutation, combination treatment with dabrafenib and trametinib has resulted in a 3-year rate of relapse-free survival of 58%, compared to 39% for placebo, representing a statistically significant, 53% 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).

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.

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. There is also an ongoing effort for translational studies (e.g. research into circulating tumour cells or DNA) that aim at identifying predictors of response and resistance, and/or monitoring for relapse. 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 and 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) ≥ 3 cm
- 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:-

- Fungation, 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:
 1. **Stereotactic, ablative radiotherapy (SRT)**- In limited intracranial disease where surgical resection is not appropriate.
 2. **Whole brain radiotherapy**- (WBRT). More extensive intracranial disease.
 3. **Hippocampal-sparing intensity modulated WBRT** – Reportedly less toxic than WBRT but with a limited evidence base.
 4. **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 remains undefined. 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 uncertain and extreme caution is warranted.

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 8 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 CLND is for ultrasound assessment of the affected lymph node basin at the time of each clinical review. The experience in the assessment of early malignant lymph nodes.

Patients seeking USS surveillance should have firstly opted for observation rather than completion lymph node dissection after discussion of the various merits with their treating surgeon and/or GP. 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 three - four months for the first three 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 centers to refer their patients to for USS surveillance should contact WAKMAS for this information.

Appendix A

AJCC MELANOMA STAGING

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

Definition of Primary Tumor (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

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

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.

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 9 AJCC Melanoma Staging 8th edition



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