MODULE 2

MELANOMA STAGING, PROGNOSIS AND INVESTIGATIONS

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In partnership with Novartis

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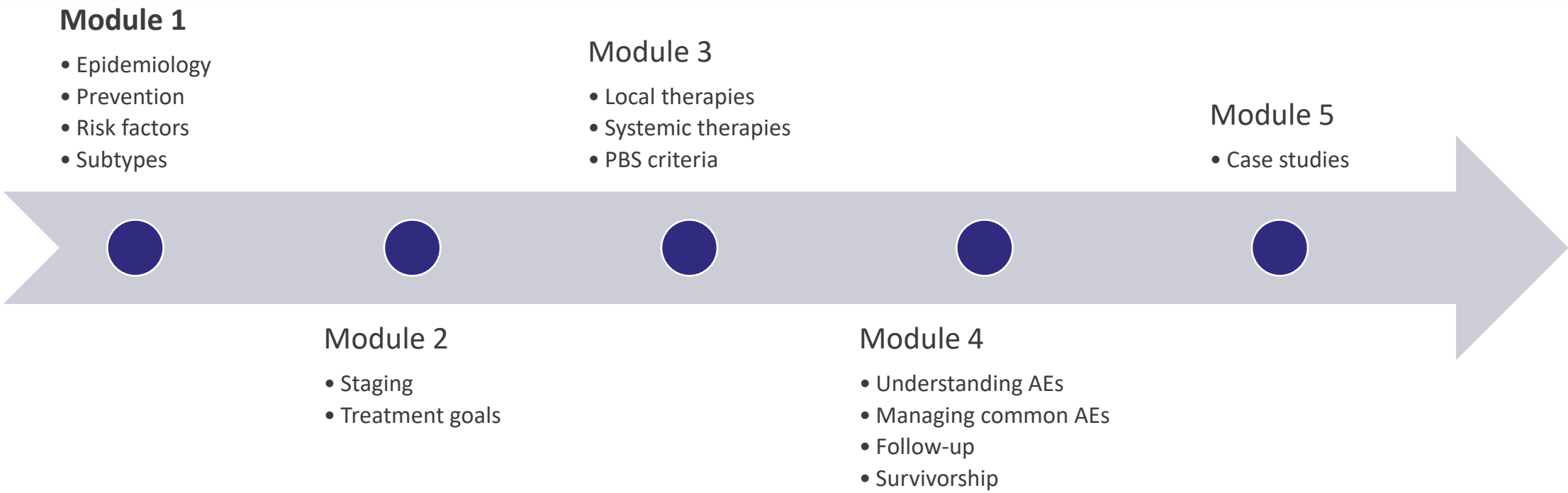
*We would like to acknowledge the contributions of **Ms Sarah Lane** and **Ms Megan Trewhella** who contributed to the module development, but no longer work in their previous capacity as a melanoma nurse consultant*

COURSE OVERVIEW



- To help you understand more about the varying severity of the disease **Module 2** will look at staging in melanoma and how this impacts treatment

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LEARNING OBJECTIVES

- To accurately identify melanoma stage using the AJCC v8 guidelines
- To understand patient prognosis and predictors of outcome using staging guidelines and relevant baseline characteristics
- To understand the role of specific investigations across the stages of melanoma (PET/CT, FNA, MRI, biopsy, ultrasound)
- To be aware of goals of treatment and available treatment options in specific settings and patient populations

AJCC, American Joint Committee on Cancer; CT, computed tomography; FNA, fine needle aspiration; MRI, magnetic resonance imaging; PET, positron emission tomography.

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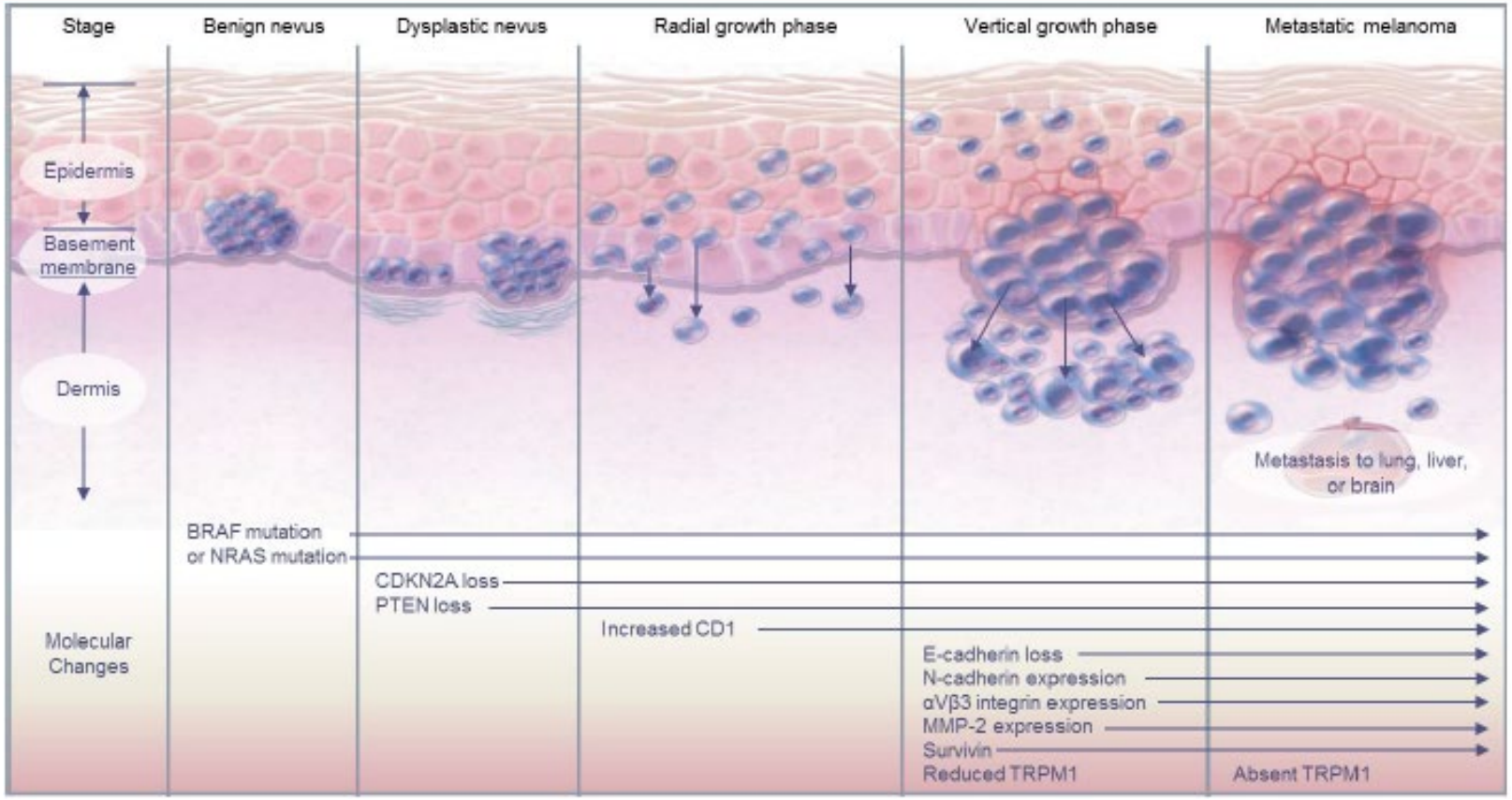
KNOWING THE PATHOLOGY DETAILS HELPS DETERMINE A PATIENT'S RISK AND NEXT BEST STEPS[1]

- Melanoma is thought to advance in a series of steps
- A pathology report will show how advanced a patient's disease is, and may give an indication of how likely it is to spread
- Understanding a patient's pathology report is an important early step to determining their prognosis and treatment options



Proposed steps of malignant transformation of normal melanocytes into metastatic melanoma, highlighting many of the biological and molecular events that are thought to be involved during this process:

Adapted from: **1.** Miller AJ, Mihm MC Jr. *N Engl J Med* 2006;355:51–65.

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DECISION MAKING STARTS WITH PATHOLOGY

Bloggs, Jo E 12/3/45 MRN 1234567

Pathologist Diagnostic Opinion
Left lateral buttock-superficial spreading melanoma, Clark level IV, depth of invasion 1.9 mm, in situ 4 mm to the closest lateral margin.

Synoptic
Diagnosis of primary melanoma: Superficial spreading melanoma
Breslow thickness: 1.9 mm
Clark level: 4
Surgical margins involved?: no
Surgical margins:
Nearest peripheral margin to in-situ: 4mm
Nearest peripheral margin to invasive component: 5mm
Ulceration: no
Mitotic rate of the dermal invasive melanoma: 2per mm^2
Microsatellites: no
Lymphovascular invasion: yes
Tumour-infiltrating lymphocytes (T!Ls): none
Intermediate/late regression: no
Desmoplasia: no
Neurotropism: no
Evidence of an associated benign melanocytic lesion?: no
Clinical Information Provided Clinical Notes: 6 o'c enlarging pigmented lesion with central amelanotic vascular area L lateral buttock. SSM invasive, ? >2cm

Macroscopic Description
Labelled "Left lateral buttock". An unorientated elliptical excision of skin, 20 x 8 x 4 mm (L x W x D). There is a central dark nodule, 5 x 5 x 1, 1 mm from the nearest margin. Margins are inked blue.

MIcroscopIc Description
Of skin, show surface para keratin deep to which atypical melanocytes are seen infiltrating the epidermis with vertical migration and also infiltrating the dermis with no evidence of maturation, to a depth of 1.9 mm. The cells are epithelioid in appearance and there is minimal lymphocytic reaction. Two mitoses are seen per millimetre squared. Laterally, atypical melanocytes extend within the epidermis. The in situ melanoma is 4 mm to the lateral margin, the invasive melanoma is 5 mm lateral margin. Lymphovascular invasion is identified.

- Pathology reports contain many of the pieces of the puzzle to determine a patients prognosis
- Type of melanoma (superficial spreading) is important, as sometimes this may change treatment options
- Breslow thickness (how deep the melanoma is) and presence of ulceration dictates the stage of disease
  - Clark level (measures how invasive the tumour is) and mitotic rate (how quickly the tumour is growing) are useful indicators, but **do not contribute to the staging** of the patient
- Much of this information is predictive of lymph node involvement and metastatic spread and ultimately a patients outcome e.g. ulceration, thickness
- Like many other cancers, a patients prognosis is summarised in the disease “stage”.

How this is determined from a pathology report like this and what other investigations are required will be explained later in this module

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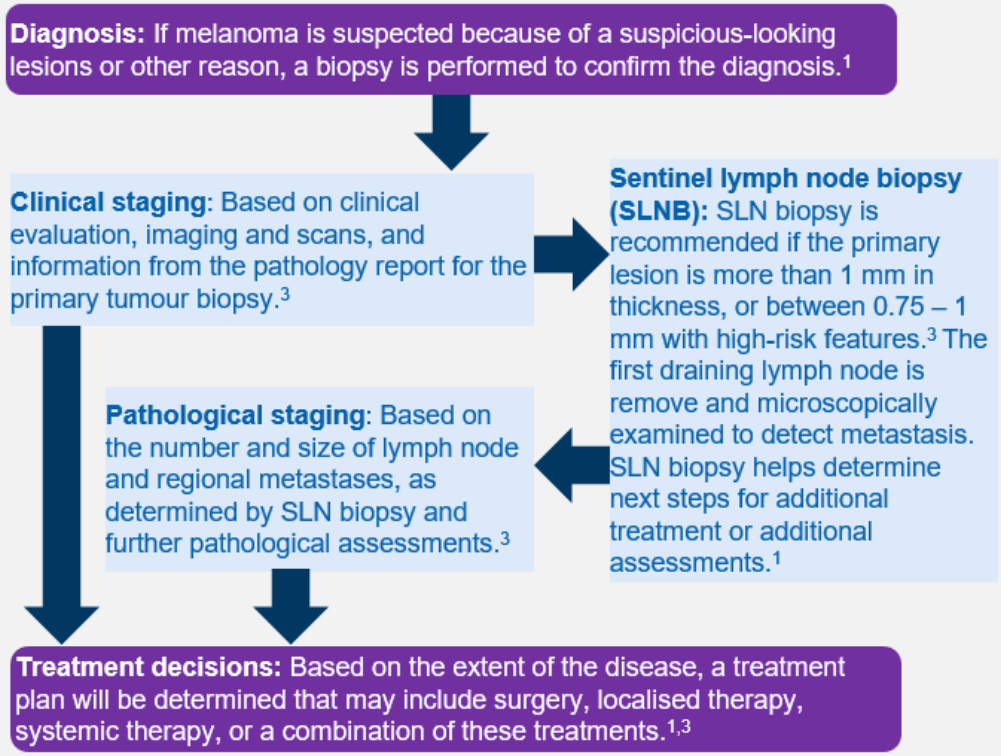
OVERVIEW: MELANOMA DIAGNOSIS AND STAGING

- Some of the prognostic factors are sufficiently predictive of outcome that they are involved in disease staging and in turn guide treatment decisions
- Disease stage characterises the extent of disease in the body, including the size of the tumour, whether lymph nodes contain cancer, and whether the cancer has spread to other parts of the body[1]
- AJCC staging guidelines are the internationally preferred classification system for melanoma[2]

AJCC stage is determined based on clinical and pathological staging



1. American Cancer Society. Melanoma skin cancer early detection, diagnosis, and staging. https://www.cancer.org/content/dam/CRC/PDF/Public/8825.00.pdf. Accessed June 23, 2020. **2.** Michielin O *et al. Ann Oncol* 2019;30:1884-–901. **3.** Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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AJCC STAGING GUIDELINES: TNM CLASSIFICATION SYSTEM[1,2]

- The current melanoma staging system is the **American Joint Committee on Cancer (AJCC) 8th edition** that went into effect in 2018. It considers the disease in the primary lesion (T), lymph nodes (N) and if further metastatic spread has occurred (M)[1]

Clinical Staging

Pathological Staging

Tumour size (T)

Based on thickness of the melanoma and key factors seen in skin biopsy e.g. ulceration

Lymph node involvement (N)

Based on the number of tumour-involved lymph nodes as well as the presence of in-transit, satellite and/or microsatellite metastases

Metastasis (M)

Based on whether the melanoma has metastasised to distant organ/s and which organ/s it has reached as well as blood levels of LDH

Subdivisions of these three categories are available for cases which need greater specificity.

1. Gershenwald JE, Scolyer RA. *Ann Surg Oncol* 2018;25:2105–10. **2.** Gershenwald JE *et al. CA Cancer J Clin* 2017;67:472–92.

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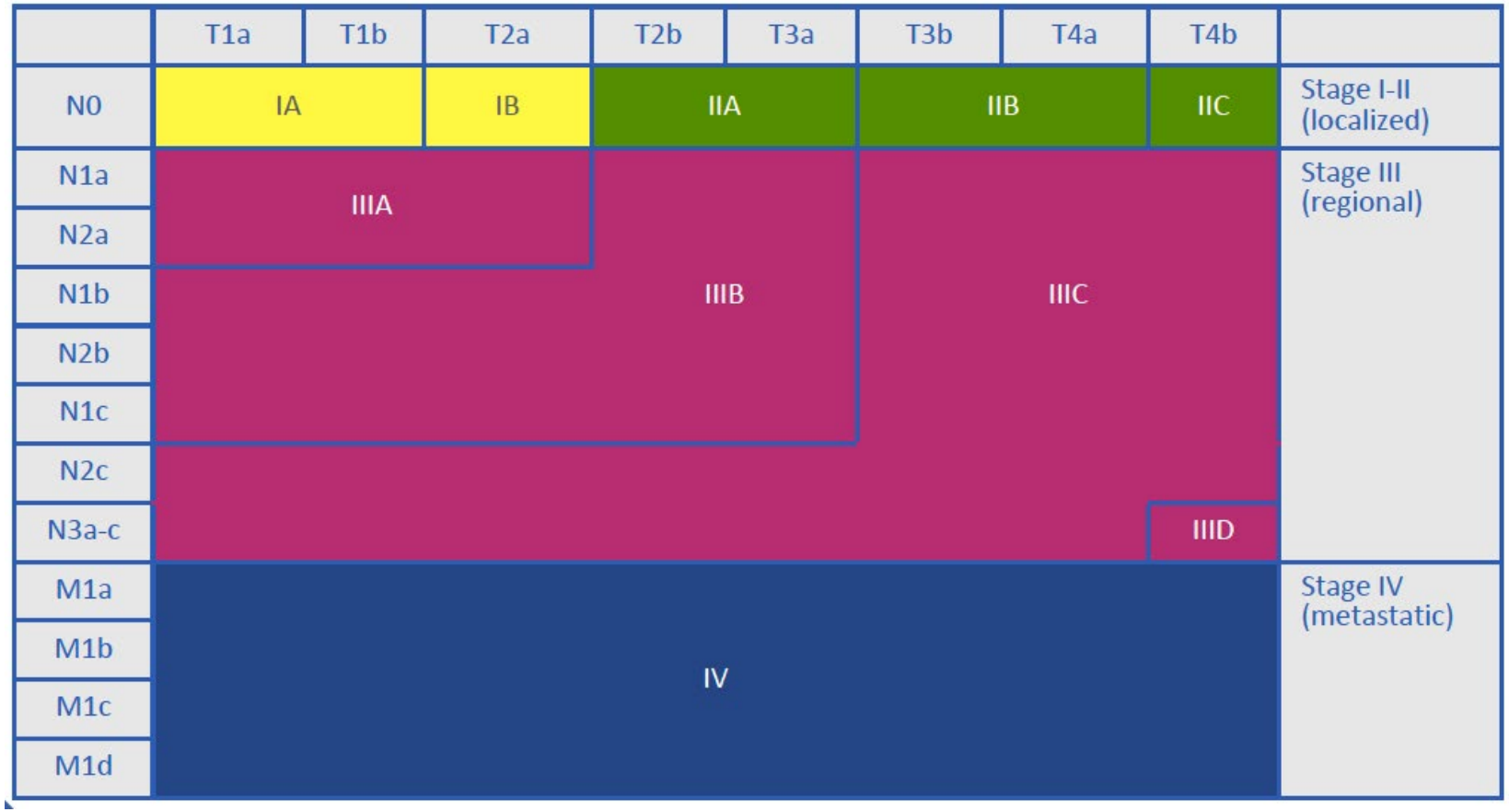
AJCC STAGING GIVES THE RELATIONSHIP BETWEEN TUMOUR (T), NODE (N) AND METASTASIS (M) STATUS AND DISEASE STAGE[1]



- T, N, and M categories are combined to give an overall AJCC stage from I to IV
  - Stage I and II correspond to local disease
  - Stage III corresponds to disease that has spread regionally
  - Stage IV corresponds with disease that has metastasised to other areas of the body
- These stages predict prognosis and guide treatment plans

How we determine TNM scores will now be described. Further information on the investigations involved then follows

Adapted from Gershenwald *et al,* 2017.[1]

1. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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PATHOLOGY INFORMATION WILL HELP IDENTIFY A T SCORE[1,2]

Report feature in AJCC 8	Description
Thickness	Routinely referred to as Breslow thickness. The depth of the lesion helps determine T category in staging, with thresholds of 1.0, 2.0 and 4.0 mm. Staging will be explained further in the next module
Ulceration	Broken skin on the surface of a lesion. May indicate a more aggressively growing melanoma and is associated with worse survival outcomes.
Other factors pathology report	
Anatomical location	Location of the tumour on the body. Whether the tumour is located on sun-exposed or covered areas of the body is important. Tumours in the eye or mucous membranes indicate a distinct type of melanoma.
Sun damage	Degree of damage to surrounding skin.
Melanoma subtype	Superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral-lentiginous melanoma.
Regression	Presence and extent of tumour shrinkage or cell death. May be prognostic because it indicates that the tumour may have been larger previously.
Surgical margins	0.5–2 cm margin of healthy skin surgically removed with the tumour. Presence or absence of tumour cells in this margin is noted.
Mitotic rate	Rate of cell division in the lesion. Higher rate may indicate faster growing melanoma.

1. Michielin O *et al. Ann Oncol* 2019;30:1884–901. **2.** Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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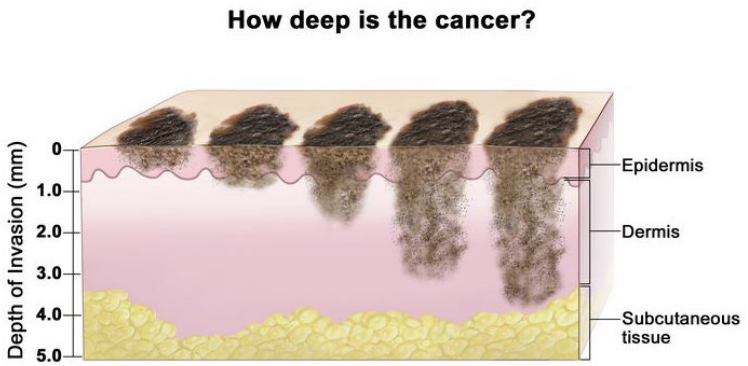
DETERMINING TUMOUR SCORE (T)[1,2]

- Tumour size refers to the thickness of the primary (original) tumour (measured from the surface of the skin to the deepest part of the tumour)



- Tumours are further categorised based on whether they are ulcerated (i.e. have broken through the skin)

Category	Thickness (mm)	Ulceration Status
T0	No evidence of primary tumour	
Tis	Melanoma *in situ*	
T1	≤1.0	a. < 0.8 mm without ulceration b. < 0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2	> 1.0-2.0	a. Without ulceration b. With ulceration
T3	> 2.0-4.0	a. Without ulceration b. With ulceration
T4	> 4.0	a. Without ulceration b. With ulceration

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
2. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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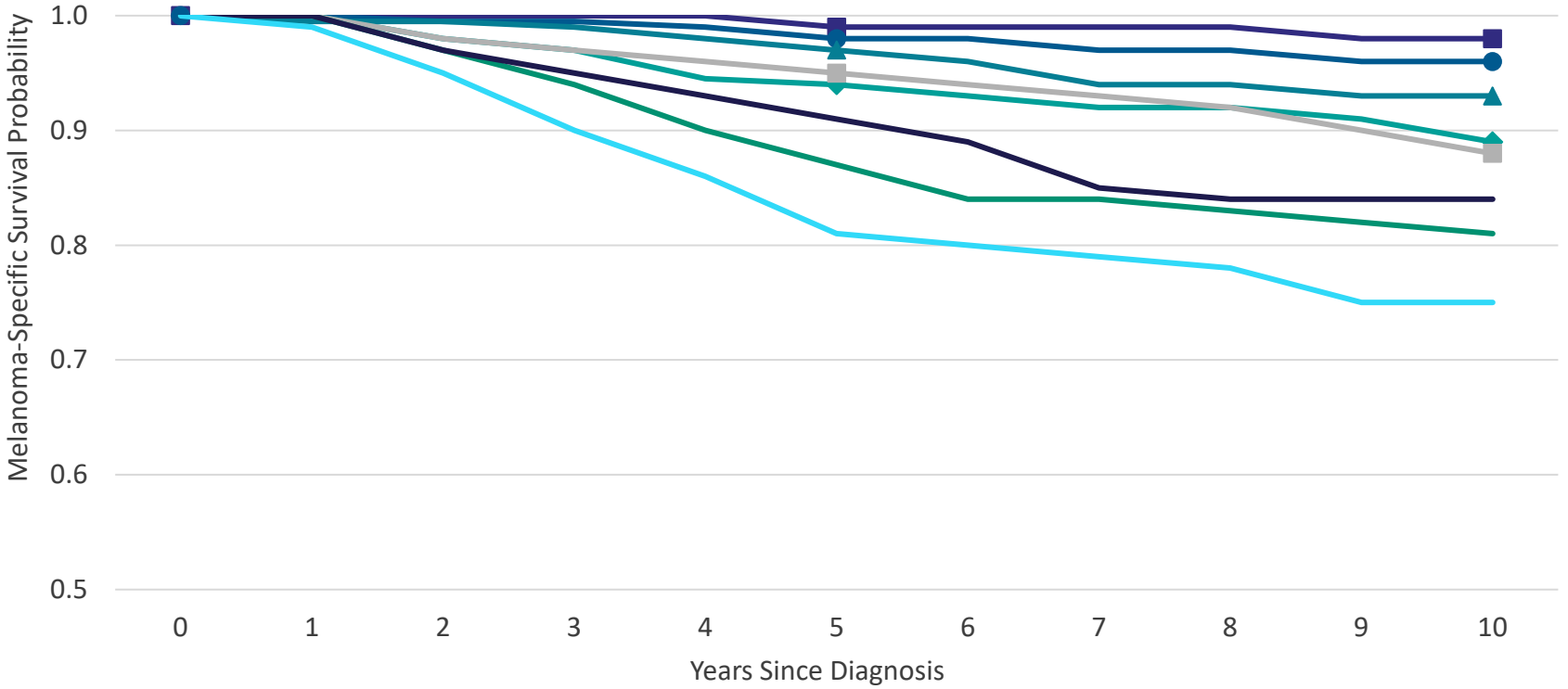
SURVIVAL PROBABILITY WORSENS WITH INCREASING T STAGE

Survival probability for stage I and II melanoma*



	N	5-YR	10-YR
T1a	5225	99%	98%
T1b	2495	99%	96%
T2a	3254	96%	92%
T2b	748	93%	88%
T3a	1590	94%	88%
T3b	1150	86%	81%
T4a	538	90%	83%
T4b	691	82%	75%

AJCC 8th edition. Adapted from Gershenwald *et al* 2017.

*Patients with N0 melanoma have been filtered, so that patients with T2 to T4 melanoma were included only if they had negative sentinel lymph nodes, whereas those with T1N0 melanoma were included regardless of whether they underwent sentinel lymph node biopsy.

Gershenwald JE, *et al. CA Cancer J Clin.* 2017; 67(6): 472–492

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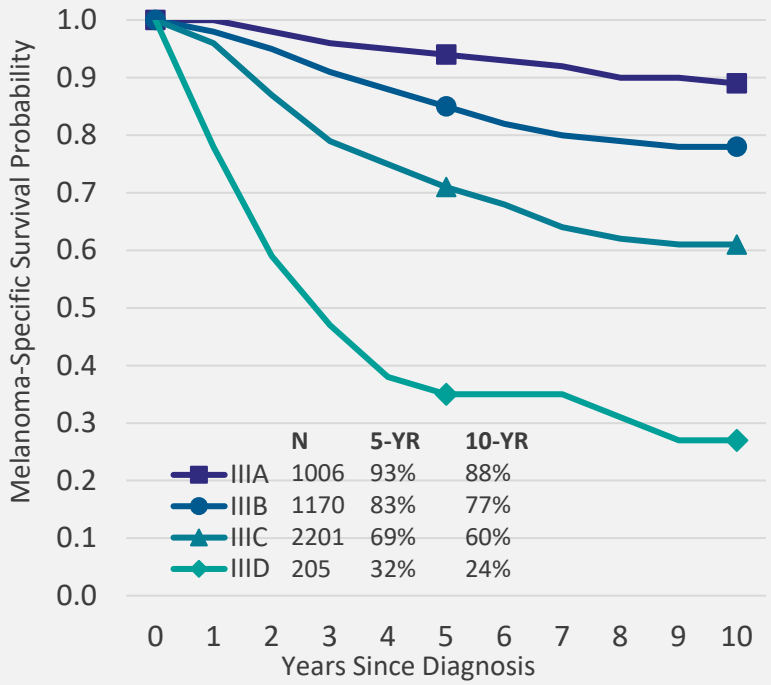
WHY CHECK THE LYMPH NODES?

- Knowing if your patient has melanoma in the lymph nodes is important prognostic information
- The most common site of metastatic disease in melanoma is the regional lymph nodes, indicating that metastatic spread usually occurs via the lymphatic system[2]
- Regional lymph node metastasis is associated with a poor prognosis, with 10-year survival rates of 35% (stage IIID only)[2]
- Understand your patient's risk is an important piece of information in determining the best treatment for your patient

Survival probability AJCC 8th edition stage III[1]



Adapted from Gershenwald & Scolyer 2018.

1. Gershenwald JE, Scolyer RA. Ann Surg Oncol. 2018;25(8):2105-2110. 2. White RR, et al. Ann Surg. 2002;235(6):879-87.

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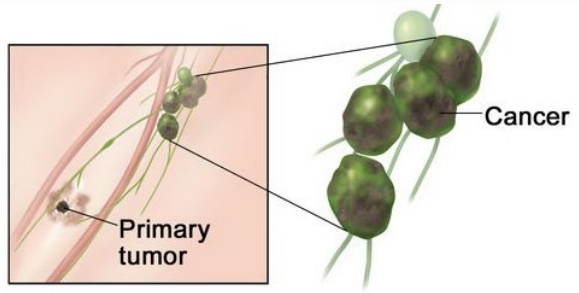
DETERMINING NODAL (N) STATUS [1,2]

Lymph node involvement describes whether:

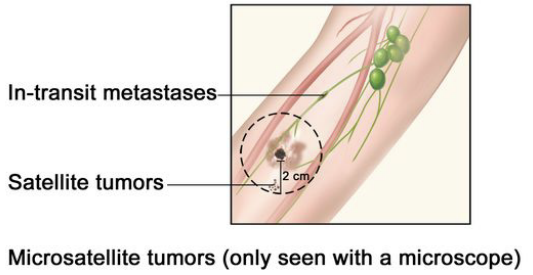
1. Cancer is found in the lymph nodes only following investigations i.e. imaging tests, fine needle aspiration or a sentinel lymph node biopsy **(clinically occult)**
2. Cancer is found in lymph nodes by a physical exam **(clinically detected)**
3. The lymph nodes are matted (i.e. joined together)
4. There is evidence of spread near the primary tumour:
   - Satellite tumours: small groups of tumour cells have spread within 2 cm of the primary tumour
   - Microsatellite tumours i.e. small groups of tumour cells have spread to an area right beside or below the primary tumour
   - In-transit metastases i.e. tumours that have spread to lymph vessels in the skin >2 cm away from the primary tumour, but not to the lymph nodes

Cancer in the lymph nodes?



Are lymph nodes matted?

Have cancer cells spread near the primary tumour?



1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
2. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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NODAL STATUS (N) SCORE SUMMARISES EXTENT OF EARLY SPREAD[1]

Category	No. of Tumour-Involved Regional Lymph Nodes	Presence of In-Transit, Satellite, and/or Microsatellite Metastases
N0	No regional metastases detected	No
N1	a. 1 clinically occult	a. No
	b. 1 clinically detected	b. No
	c. No regional lymph node disease	c. Yes
N2	a. 2-3 clinically occult	a. No
	b. 2-3 with ≥ 1 clinically detected	b. No
	c. One clinically occult or detected	c. Yes
N3	a. ≥4 clinically occult	a. No
	b. ≥ 4 with ≥1 clinically detected, or any matted	b. No
	c. ≥2 clinically occult or detected, and/or any matted	c. Yes

1. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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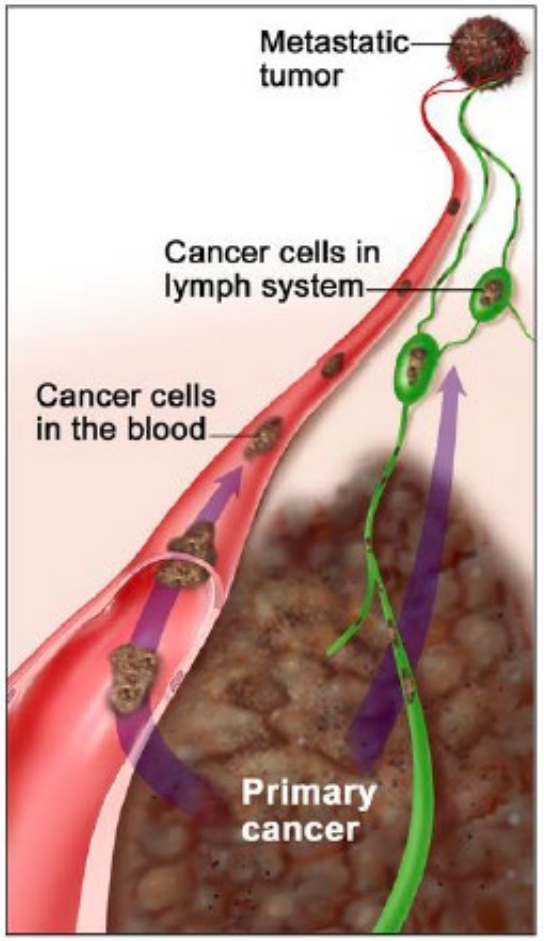
DETERMINING METASTASIS (M) SCORE[1,2]

- Metastasis describes the spread of melanoma throughout the body
- The site(s) of metastases are used to delineate the M categories into three groups: M1a, M1b, M1c and M1d
- A suffix is added to each M1 substage to denote whether levels of serum lactate dehydrogenase (LDH) are normal (0) or elevated (1)
  - Elevated LDH levels are associated with a worse prognosis in metastatic disease



M Category	Anatomic Site	Serum LDH Level
M0	No evidence of distant metastases	Not applicable
M1a	Distant skin, soft tissue including muscle, and/or non-regional lymph node	(0) Normal (1) Elevated
M1b	Lung metastases with or without M1a sites of disease	(0) Normal (1) Elevated
M1c	Non-CNS visceral metastases with or without M1a or M1b sites of disease	(0) Normal (1) Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	(0) Normal (1) Elevated

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
2. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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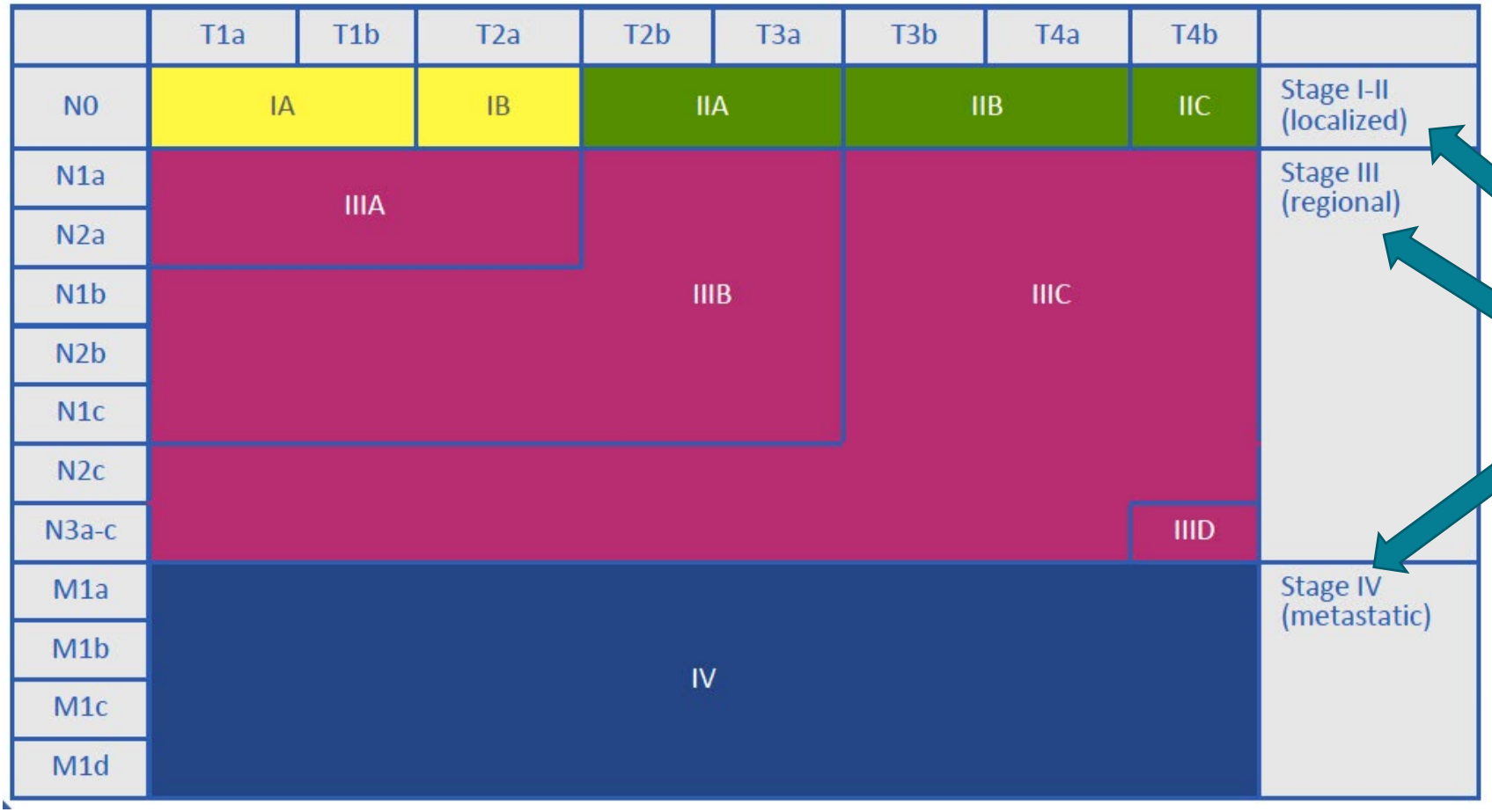
DISEASE STAGE IS DETERMINED BY COMBINING T, N AND M SCORES. THIS INFORMS TREATMENT DECISIONS[1]



- Once T, N, M categories are known, they are combined to give an overall AJCC stage from I to IV
  - Stage I and II correspond to local disease
  - Stage III corresponds to disease that has spread regionally
  - Stage IV corresponds with disease that has metastasised to other areas of the body
- These stages predict prognosis and guide treatment plans

Each stage will now be described

Adapted from Gershenwald *et al,* 2017.[1]

1. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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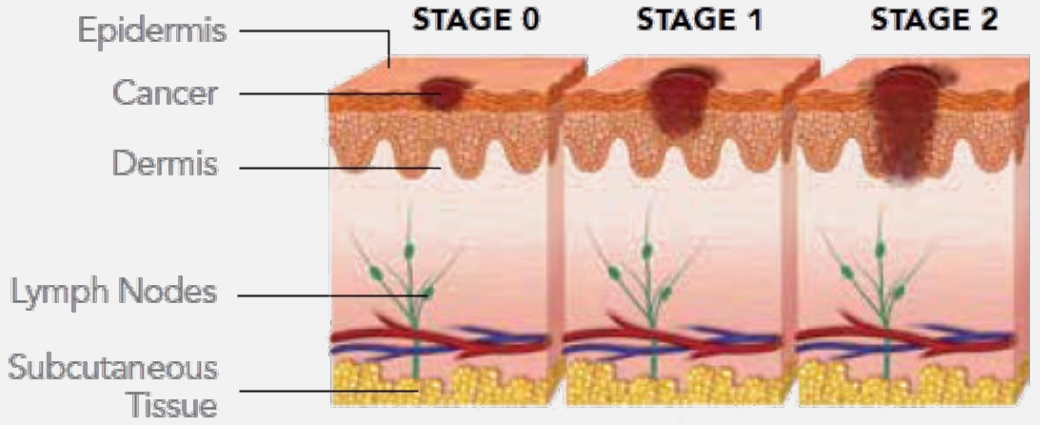
STAGES OF MELANOMA: 0, 1 AND 2[1,2]

Melanoma is categorised into stages based on the thickness of the tumour and how far it has spread:

- **Stage 0:** (melanoma *in situ*): The tumour has not grown deeper than the outer layer of the skin (epidermis). There is no evidence that the cancer has spread
- **Stage 1:** The tumour has grown thicker past the epidermis, and there may or may not be ulceration (when the skin above the tumour breaks down). There is no evidence that the cancer has spread
- **Stage 2:** The tumour has grown even thicker (Breslow depth, thickness measured in mm), generally >1 mm thick with ulceration or >2 mm thick without ulceration. There is no evidence that the cancer has spread



The microstage of malignant melanoma is determined on histologic examination by the vertical thickness of the lesion in millimetres (known as Breslow classification)[2]

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
2. National Cancer Institute. Melanoma treatment (PDQ®)- health professional version. Available at: https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq. Accessed December 2021.

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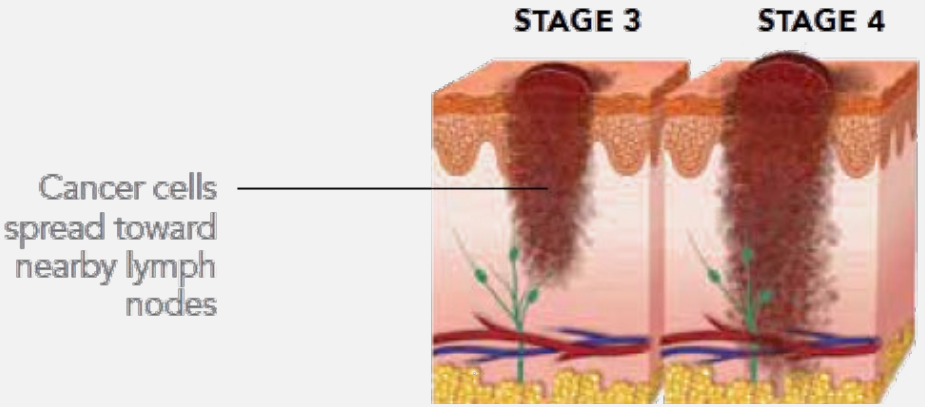
STAGES OF MELANOMA: 3 AND 4[1,2]

Melanoma is categorised into stages based on the thickness of the tumour and how far it has spread:

- **Stage 3:** The cancer has spread towards one major lymph node, but has not spread to other parts of the body or has developed a deposit of melanoma called an in-transit or satellite
- **Stage 4:** The cancer has spread to distant lymph nodes and/or other places in the skin or parts of the body, like the lungs, liver, brain, and bones. Serum lactate dehydrogenase (LDH) may or may not be elevated



1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
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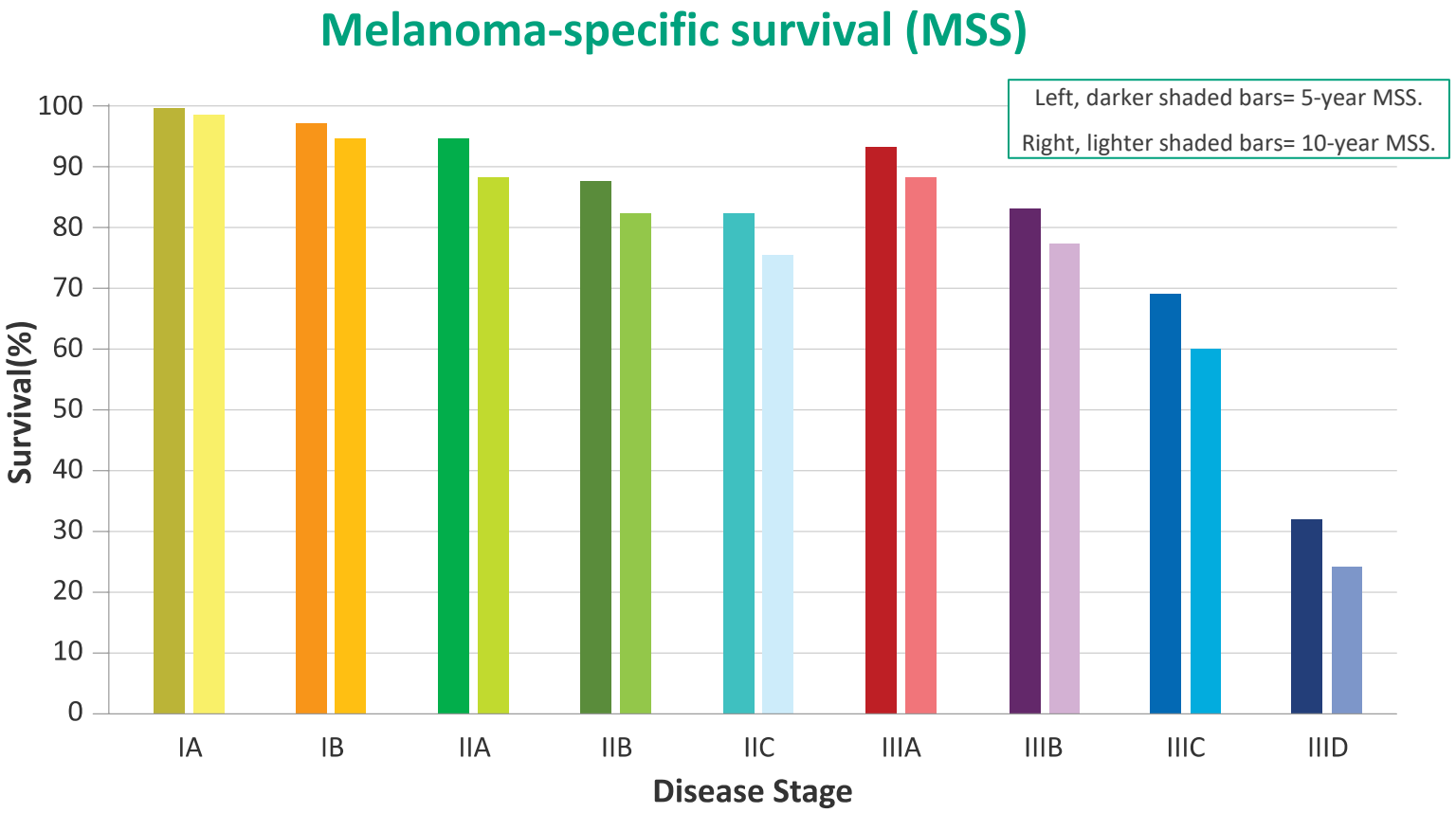
HIGHER DISEASE STAGE PREDICTS WORSE SURVIVAL[1]



- Five and ten year survival tends to reduce with advancing stage
- Stage IV disease outcome is highly variable, dependent disease and patient factors are not shown

?

Survival outcomes for Stage IIC disease are worse than Stage IIIA

- Why do you think this is?

Adapted from Gershenwald *et al,* 2017.[1]

1. Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92.

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INVESTIGATIONS REQUIRED TO DIAGNOSE AND STAGE MELANOMA START IN PRIMARY CARE[1,2]

Primary Care: Diagnosing the primary lesion (T score)		Secondary Care: Identifying distal spread (N and M score)
Clinical examination	Patients with clinically detected spread or high risk features should be referred	Fine needle aspiration (FNA) or core biopsy or sentinel lymph node (SLN) biopsy; will require a core biopsy if FNA is not diagnostic
Dermoscopy		CT scan
Histopathology of biopsied specimen via excisional (preferable), punch or shave biopsy		PET-CT scan
		MRI
		Ultrasound
		Blood tests e.g. for LDH

A **dermoscope** is a small lighted tool used to shine light on and magnify suspicious lesions. Examining a patient with this tool helps improve the accuracy of melanoma diagnoses[3]

CT, computed tomography; FNA, fine needle aspiration; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography.

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021. **2.** Cancer Council Australia. Understanding Melanoma. A guide for people with cancer, their families and friends. January 2021. **3.** European Society for Medical Oncology. Melanoma: a guide for patients. https://www.esmo.org/content/download/6618/115129/file/ESMO-ACF-Melanoma-Guide-For-Patients.pdf. Accessed December 2021.

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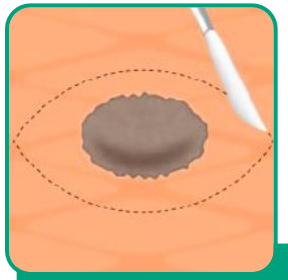
INVESTIGATIONS START WITH THE BIOPSY OF PRIMARY LESION[1,2]

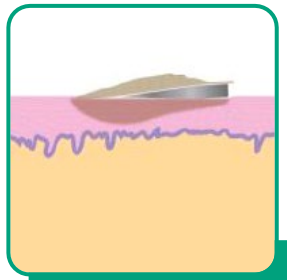
Suspicious lesions require biopsy for confirmation and disease staging by pathology

There are four common types of skin biopsies:



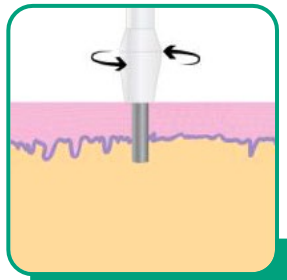
Excisional biopsy

A scalpel is used to remove the entire growth with a ~2mm margin (**most common**)



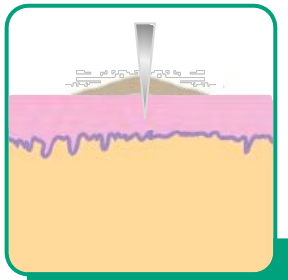
Shave biopsy

A thin, sharp blade is used to shave off the abnormal growth



Punch biopsy

A sharp, hollow tool is used to remove a circle of tissue from the abnormal area



Incisional biopsy

A scalpel to remove part of the growth

If possible, the entire tumour can be removed at biopsy stage

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
2. Mayo Clinic. Skin biopsy. Available at: https://www.mayoclinic.org/tests-procedures/skin-biopsy/about/pac-20384634. Accessed December 2021.

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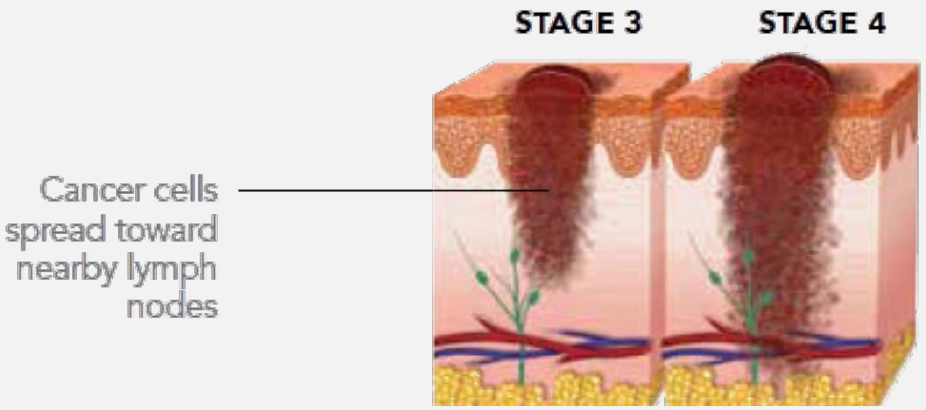
NODES ARE CHECKED FOR HIGH-RISK PATIENTS

- Nodal status (N score) should be determined for patients with elevated risk of disease spread

MIA have produced a risk calculator to help identify patients most at risk of node positivity https://www.melanomarisk.org.au/SNLForm

- For clinically detected nodes a fine needle aspiration (FNA) or core biopsy can be used
- For patients with elevated risk but without clinically detectable disease, a sentinel lymph node biopsy (SLNB) may be indicated

Each of these interventions will now be discussed in more detail



1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.

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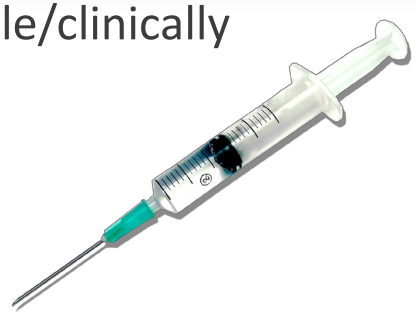
FINE NEEDLE ASPIRATION (FNA)/CORE BIOPSY OF CLINICALLY DETECTED LYMPH NODES[1]

- FNA or core biopsy may be used to diagnose melanoma in a lymph nodes that is palpable/clinically detected
  - Though it may be associated with the primary melanoma, the nodes involved may not be near the primary



- For FNA a thin, hollow needle is used to remove a few cells from the node
- For core biopsies a special device with a large hollow needle is used to remove a cylinder of tissue under local anaesthetic
- Under some circumstances an ultrasound or a CT scan is used to help guide the needle into place
- FNA biopsies are not as invasive as core biopsies, but they may not always collect enough of a sample. In these cases, a more invasive type of biopsy may be needed
- If the sample is positive for melanoma, meaning lymph nodes were clinically detected, patients are generally considered for a lymph node dissection (LND) (removal of all **affected** lymph nodes)
- For nodes that **are not clinically detectable** (i.e clinically occult), a sentinel lymph node biopsy may be conducted

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.
LND, lymph node dissection

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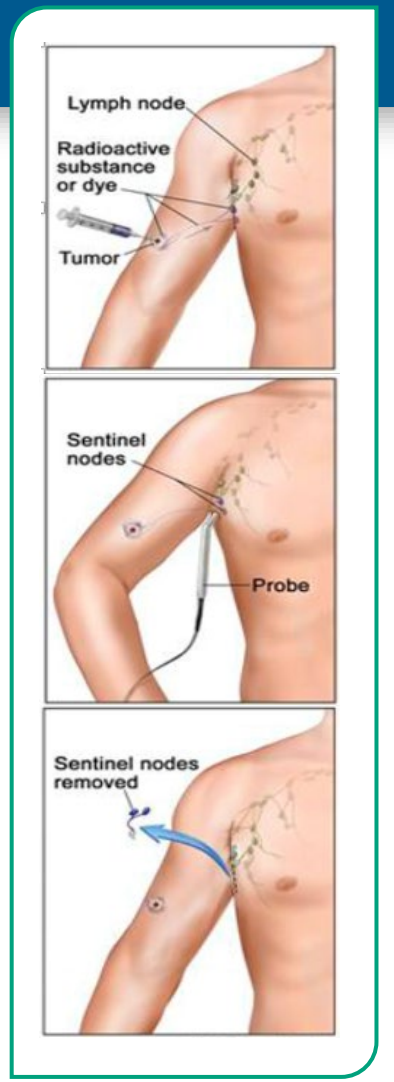
SENTINEL LYMPH NODE BIOPSY (SLNB) TO DETECT CLINICALLY OCCULT LYMPH NODES

- Based on findings from the initial assessment and clinical staging (T category), a SLNB may be recommended to determine if melanoma cells are in the lymph nodes when they can't be detected clinically[1,2]
- SLNB involves removal and examination of the sentinel node(s)
- The sentinel node is the first lymph node(s) to which cancer cells are likely to spread to from a primary tumour[3]
  - To identify the sentinel lymph node(s), the surgeon injects a radioactive substance, blue dye, or both near the tumour[3]
  - The surgeon then uses a probe to find the sentinel lymph node(s) containing the radioactive substance or looks for the lymph node(s) stained with dye[3]
  - The surgeon then removes the sentinel node(s) to check for the presence of cancer cells[3]
- If the first lymph node is negative, the entire lymph node basin should be negative[3,4]



1. Michielin O *et al. Ann Oncol* 2019;30:1884–901. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)for Cutaneous Melanoma. V.1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed December 2021. **3.** National Cancer Institute. Sentinel lymph node biopsy. Available at: http://www.cancer.gov/about-cancer/diagnosis-staging/staging/sentinel-node-biopsy-fact-sheet. Accessed December 2021. **4.** Sondak VK *et al. Am Soc Clin Oncol Educ Book* 2013.

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SENTINEL NODE STATUS DETERMINES ELIGIBILITY FOR ADJUVANT TREATMENT

- Cancer Council Australia and Melanoma Institute Australia guidelines recommend that SLN biopsy should be considered for all patients with melanoma >1 mm in thickness and for those with melanoma >0.75 mm with other high-risk pathological features[1]
- The aim of this recommendation is to provide optimal staging and prognostic information and to maximise management options for patients who are node positive[1]
- For patients who have undergone a complete resection of a Stage III/IV melanoma, the decision to recommend adjuvant therapy depends upon the risk of disease recurrence[1,2]
- This is based on stage at diagnosis, specific tumour characteristics that impact drug selection (e.g., BRAF V600E or V600K mutation) and risks associated with treatment, along with patient-related factors that affect ability to tolerate therapy such as the patient's age, comorbidities and personal preferences[1,2]

Adjuvant treatment will be covered in more detail in Module 3

1. Cancer Council Australia. Cancer Guidelines Wiki. When is a sentinel node biopsy indicated? Available from: https://wiki.cancer.org.au/australia/Clinical_question:When_is_a_sentinel_node_biopsy_indicated%3F. Accessed December 2021. **2.** Kwak M *et al. J Surg Oncol* 2019;119:222–31.

POSSIBLE SIDE EFFECT OF SENTINEL LYMPH NODE BIOPSY (SLNB)[1]

While SLNB is generally straightforward, it can come with some risks. It is important your patient understands what they are. Some of the more common procedure specific risks include:

- Perioperatively:
  - Skin or allergic reactions to the blue dye used in SNLB
- Postoperatively:
  - Lymphoedema or tissue swelling
  - Seroma or a mass or lump caused by the build-up of lymph fluid at the site of the surgery
  - Numbness, tingling, swelling, bruising, or pain at the site of the surgery, and an increased risk of infection
  - Difficulty moving the affected body part

1. National Cancer Institute. Sentinel lymph node biopsy. Available at: http://www.cancer.gov/about-cancer/diagnosis-staging/staging/sentinel-node-biopsy-fact-sheet. Accessed December 2021.

LYMPHOEDEMA – A RISK AFTER LYMPH NODE PROCEDURES[1]

- Any procedure involving the lymph nodes, especially LND, increases the chance of lymphoedema
- Symptoms may include ache or tension, feeling of heaviness or tightness in the area
- Exercises and other self management strategies play an important role in the postoperative course to minimise lymphoedema and shoulder pain
- There are a lot of resources available for patients who have had this procedure:

For patient education information on lymphoedema, visit the **Australasian Lymphology Society**

For information on Accredited Lymphoedema Practitioners in Australia and New Zealand, visit the **National Lymphoedema Practitioners Register**

1. Melanoma NZ Organisation. Lymphoedema. Available at: https://www.melanoma.org.nz/lymphoedema. Accessed September 2022

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QUESTIONS AROUND SLNB?

- It is important for patients to understand that an SLNB is a diagnostic procedure, not a treatment
- Understanding the nodal status is an important step to determining stage of disease and the best treatment course
- If the SLNB is found to be positive for melanoma cells, patients are generally required to come back to discuss eligibility for systemic treatment

?

Ask a colleague involved in consenting patients for SLNB what common questions patients and caregivers ask

Check what information is available within your institution- have a read through these

Alternatively, or if none are available, MIA has resources available at https://melanoma.org.au/for-patients/patient-information/

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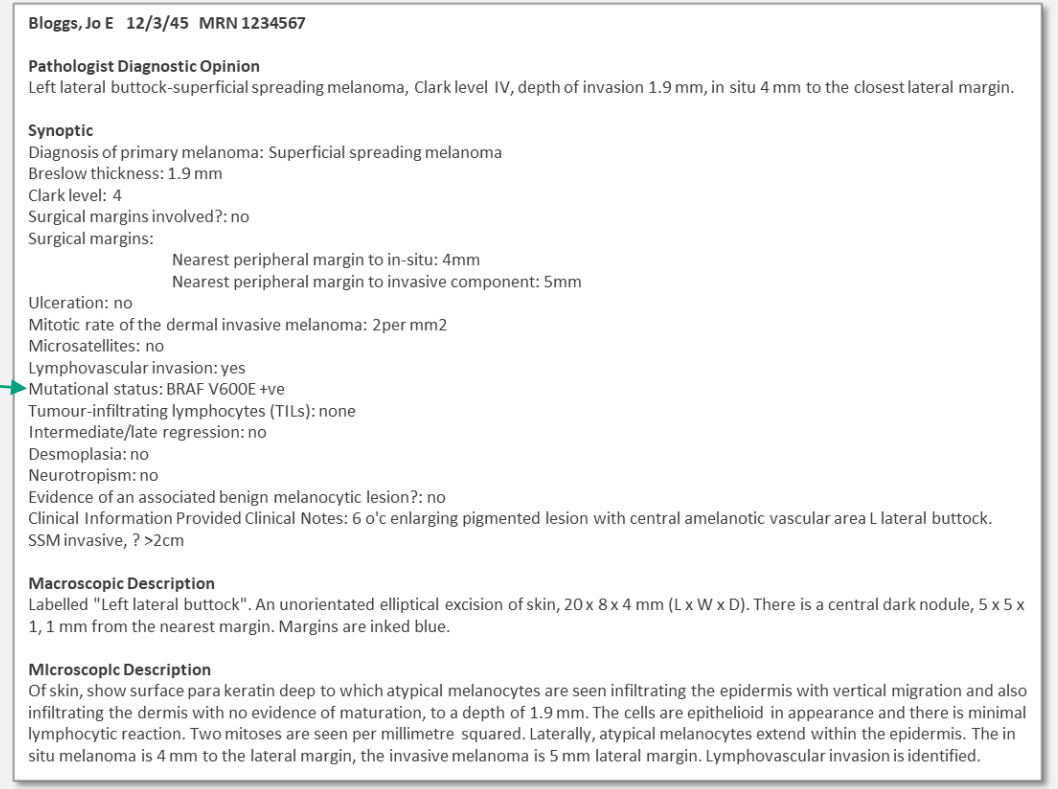
SPECIMENS ARE ANALYSED FOR MUTATIONAL STATUS[1,2]

- Core biopsy retrieved material can be used for assessment of mutation status and may be more successful than FNA retrieved material due to the increased volume of tissue available for testing
- All patients with Stage III or IV melanoma should have BRAF status prior to commencing systemic treatment. This determines eligibility for targeted treatments
- In addition to BRAF, other mutations may be identified which may be used to determine a patients eligibility for investigational treatments such as in a clinical trial (e.g. NRAS, cKIT mutations)



Bloggs, Jo E 12/3/45 MRN 1234567

Pathologist Diagnostic Opinion
Left lateral buttock-superficial spreading melanoma, Clark level IV, depth of invasion 1.9 mm, in situ 4 mm to the closest lateral margin.

Synoptic
Diagnosis of primary melanoma: Superficial spreading melanoma
Breslow thickness: 1.9 mm
Clark level: 4
Surgical margins involved?: no
Surgical margins:
Nearest peripheral margin to in-situ: 4mm
Nearest peripheral margin to invasive component: 5mm
Ulceration: no
Mitotic rate of the dermal invasive melanoma: 2per mm2
Microsatellites: no
Lymphovascular invasion: yes
Mutational status: BRAF V600E +ve
Tumour-infiltrating lymphocytes (TILs): none
Intermediate/late regression: no
Desmoplasia: no
Neurotropism: no
Evidence of an associated benign melanocytic lesion?: no
Clinical Information Provided Clinical Notes: 6 o'c enlarging pigmented lesion with central amelanotic vascular area L lateral buttock. SSM invasive, ? >2cm

Macroscopic Description
Labelled "Left lateral buttock". An unorientated elliptical excision of skin, 20 x 8 x 4 mm (L x W x D). There is a central dark nodule, 5 x 5 x 1, 1 mm from the nearest margin. Margins are inked blue.

Microscopic Description
Of skin, show surface para keratin deep to which atypical melanocytes are seen infiltrating the epidermis with vertical migration and also infiltrating the dermis with no evidence of maturation, to a depth of 1.9 mm. The cells are epithelioid in appearance and there is minimal lymphocytic reaction. Two mitoses are seen per millimetre squared. Laterally, atypical melanocytes extend within the epidermis. The in situ melanoma is 4 mm to the lateral margin, the invasive melanoma is 5 mm lateral margin. Lymphovascular invasion is identified.

1. Cancer Council Australia. Cancer Guidelines Wiki. What investigations should be performed when in-transit and/or regional node disease (stage III melanoma) is diagnosed? Available from: https://wiki.cancer.org.au/australia/Clinical_question:What_investigations_should_be_performed_when_in_transit_and/or_regional_node_disease_(Stage_III_melanoma)_is_diagnosed%3F. Accessed March 2022.
2. Cancer Council Australia. Cancer Guidelines Wiki. What investigations should be performed when stage IV melanoma is diagnosed? Available from: https://wiki.cancer.org.au/australia/Clinical_question:What_investigations_should_be_performed_when_Stage_IV_melanoma_is_diagno sed%3F. Accessed March 2022.

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IDENTIFYING METASTATIC DISEASE

- Effective public health interventions have meant that the vast majority of patients with melanoma are detected early with Stage I or II disease
- As discussed above, patients with high risk features of their primary lesion (T score) should also have their sentinel lymph nodes checked to determine if they have advanced to Stage III
- A minority of patients may present with de novo metastatic (Stage IV) disease
- For those patients, following confirmation of the melanoma, imaging (e.g. PET/CT, MRI or ultrasound imaging) may be more appropriate to determine the extent of the spread than conducting any investigation to ascertain presence of melanoma in the nodes

THE EVOLVING MELANOMA TREATMENT LANDSCAPE

- Fortunately, most patients are diagnosed with Stage I/II melanoma (78%/14.1%) and this may be cured by having the primary melanoma surgically removed in the majority of cases[1,2]
- For the remaining patients diagnosed with Stage III/IV disease, treatment options were historically limited and the 5-year survival rate for patients with Stage IV disease was 26% in 2011[1]
- Over the past ~8 years, treatment options for patients with advanced Stage III/IV melanoma have greatly expanded to include targeted therapies and immunotherapy, significantly extending survival in this patient population[3]
  - For example, for people with completely resected Stage III/IV melanoma, the standard of care has now changed from observation to active adjuvant treatment with the approval of both targeted therapies and immunotherapies[2]

1. Australian Institute of Health and Welfare 2019. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW. **2.** Melanoma Institute Australia. Melanoma Facts and Statistics [Internet]. Available from: https://www.melanoma.org.au/understanding-melanoma/melanoma-facts-and-statistics/. Accessed December 2021. **3.** Kwak M *et al. J Surg Oncol* 2019;119:222–31.

FOLLOWING STAGING, IDENTIFY THE INTENT OF TREATMENT WITH THE PATIENT[1]

- It is important to work with the patient and their caregivers to understand what their treatment goals are once the diagnosis is made:
  - Curative
  - Loco-regional control
  - Palliative intent to improve symptoms/quality of life +/- longevity of life
  - Symptom palliation

- This is a very personal decision; however it should be ensured the patient is aware of the likely outcome of all options available to them
- Advances in systemic therapies over the last decade have made significant improvements beyond traditional “chemo”, however the patient or their caregiver may not be aware of these

1. Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with melanoma, 2nd edn, Cancer Council Victoria, Melbourne.

INTRODUCTION TO TYPES OF TREATMENT FOR MELANOMA[1]

Melanoma treatment options will be discussed in more detail in Module 3

Type of treatment	Description
Surgery	• Surgery to remove the tumour is the primary treatment of all stages of melanoma • Surgery to remove cancer that has spread to the lymph nodes, lung, GI tract, bone, or brain may also be performed to improve QOL by controlling symptoms
Radiation therapy	• Radiation therapy uses high-energy x-rays or other types of radiation to kill cancer cells or stop them from growing • External radiation therapy is used to treat melanoma in instances of extra-capsular extension or oligometastis. It may also be used as palliative therapy to relieve symptoms and improve QOL e.g. SRS for brain metastases

CSF, cerebrospinal fluid; GI, gastrointestinal; QOL, quality of life; SRS, stereotactic radiosurgery

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.

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TYPES OF TREATMENT FOR MELANOMA (CONTINUED)[1]

Type of treatment	Description

Targeted therapy	• Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells. As a result, they usually cause less harm to normal cells than chemotherapy or radiation therapy
	• Types of targeted therapy include BRAF inhibitors (dabrafenib, vemurafenib, encorafenib) that block the activity of proteins made by mutant *BRAF* genes; and MEK inhibitors (trametinib, cobimetinib, binimetinib) that block proteins called MEK1 and MEK2 which affect the growth and survival of cancer cells
	• Combinations of BRAF inhibitors and MEK inhibitors used to treat melanoma include:
	  • Dabrafenib plus trametinib
	  • Vemurafenib plus cobimetinib
	  • Encorafenib plus binimetinib

Immunotherapy	• Immunotherapy uses the patient's own immune system to fight cancer • Types of immunotherapy used to treat melanoma include checkpoint inhibitors (e.g. CTLA-4 inhibitors and PD-1/PD-L1 inhibitors)
Chemotherapy	• Chemotherapy is rarely used as standard of care, and is an option if patients have progressed through all other treatment options

1. National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021.

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MODULE 2: SUMMARY

- Disease stage characterises the extent of disease in the body, including the size of the tumour, whether lymph nodes contain cancer, and whether the cancer has spread to other parts of the body[1]
- AJCC staging guidelines are the internationally preferred classification system for melanoma based on Tumour size (T), Node involvement (N) and Metastasis (M)[2]
- Patient prognosis varies due to staging at diagnosis and other factors such as age and sex of the patient and tumour location[3]

- The following investigations can aid in the diagnosis and staging of melanoma:[4,5]
  - Biopsy (excisional, shave, punch or incisional)
  - Fine needle aspiration and sentinel lymph node biopsy
  - PET/, CT, MRI and ultrasound imaging
  - Blood tests
- Types of treatment available for melanoma include:[4]
  - Surgery – generally the primary form of treatment
  - Radiotherapy – mainly utilised in the palliative setting, to improve QoL
  - Targeted therapy – standard of care, specifically for patients with a BRAFV600E/K mutation
  - Immunotherapy – standard of care
  - Chemotherapy – rarely used, only for patients who have progressed all other treatment options

1. American Cancer Society. Melanoma skin cancer early detection, diagnosis, and staging. https://www.cancer.org/content/dam/CRC/PDF/Public/8825.00.pdf. Accessed June 23, 2020. **2.** Michielin O *et al. Ann Oncol* 2019;30:1884-–901. **3.** Gershenwald J *et al. CA Cancer J Clin* 2017;67:472–92. **4.** National Institutes of Health. Melanoma Treatment (PDQ®)-Patient Version. Available at: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq. Accessed December 2021. **5.** Cancer Council Australia. Understanding Melanoma. A guide for people with cancer, their families and friends. January 2021

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PRACTICE YOUR PRACTICE

- Discuss with surgical colleagues involved in the process of sentinel node biopsy
- Read the information given to the patients in your institution prior to this procedure
- Discuss with colleagues involved in consenting patients what questions patients typically ask
- If possible, observe the procedure
- If this procedure is performed in your institution try and meet with a patient who has had this procedure done and is willing to chat about it
  - How are they feeling now?
  - What concerns did they have before the procedure?
  - How are they feeling about the future?

FOR **PRESCRIBING INFORMATION**, PLEASE CLICK:

Dabrafenib | Trametinib | Vemurafenib | Cobimetinib | Encorafenib
Binimetinib | Nivolumab | Ipilimumab | Pembrolizumab

FOR **PBS INFORMATION,** PLEASE CLICK:

Dabrafenib | Trametinib | Vemurafenib | Cobimetinib | Encorafenib
Binimetinib | Nivolumab | Ipilimumab | Pembrolizumab

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The curriculum and learning objectives were set by MSCNO and Novartis has provided medical writing and digital support to develop the modules. The modules include some content reused from Novartis in house training material, used with permission.