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15:00 - 15:15 Melanoma Metastasis and Treatment Resistance

Melanoma metastasis and treatment resistance – due to inadequate excision biopsy / wide local excision, or …?

What is the General Practitioner's Role?

Michael Eccles

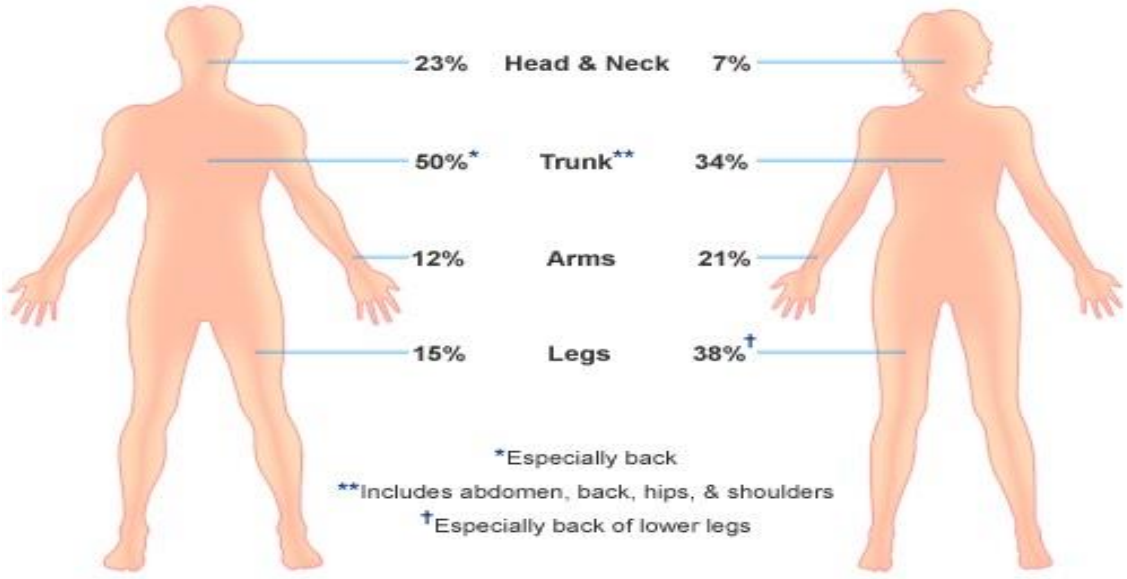
Pathology, DSM, UoO

Disclosure

- I have no conflicts of interest, or interests of a commercial nature to disclose regarding my presentation.

Early melanoma detection is vital

- NZ has the highest rate of melanoma in the world. It accounts for approximately 11% of all cancer registrations in NZ, and is the most common cancer among NZ men aged 25 to 44 years, the second most common for females in this age group, and in all people aged 45 to 64 years.
- Worldwide incidence continues to rise faster than any other form of cancer.
- GPs plays a vital role in early melanoma detection/diagnosis/prevention, if possible before it has disseminated: Vigilant surveillance is important.
- Melanoma vigilance advice to patients;
  - Awareness of personal risk & of UV exposure risk, eg use of smartphone UV level apps.
  - Awareness of use of shade; broad spectrum UVA/UVB SPF30+ sunscreens, and use of protective clothing, including hat.
  - Absolutely discourage use of, and promote banning of sunbeds.
  - Encourage regular personal, and annual specialist skin checks.

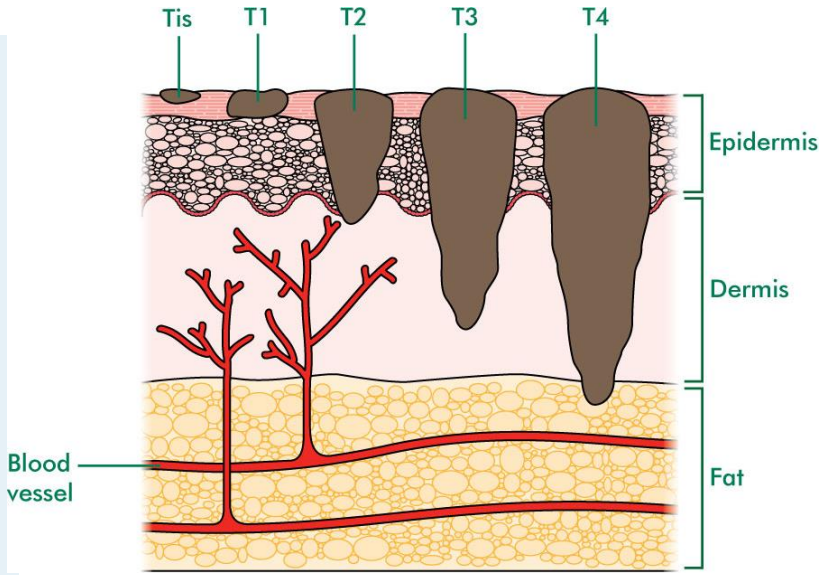


Melanoma TNM classification

TABLE 2: Anatomic stage groupings for cutaneous melanoma

Clinical staging[a]				Pathologic staging[b]			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1–4a	N1a	M0
					T1–4a	N2a	M0
				IIIB	T1–4b	N1a	M0
					T1–4b	N2a	M0
					T1–4a	N1b	M0
					T1–4a	N2b	M0
					T1–4a	N2c	M0
				IIIC	T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

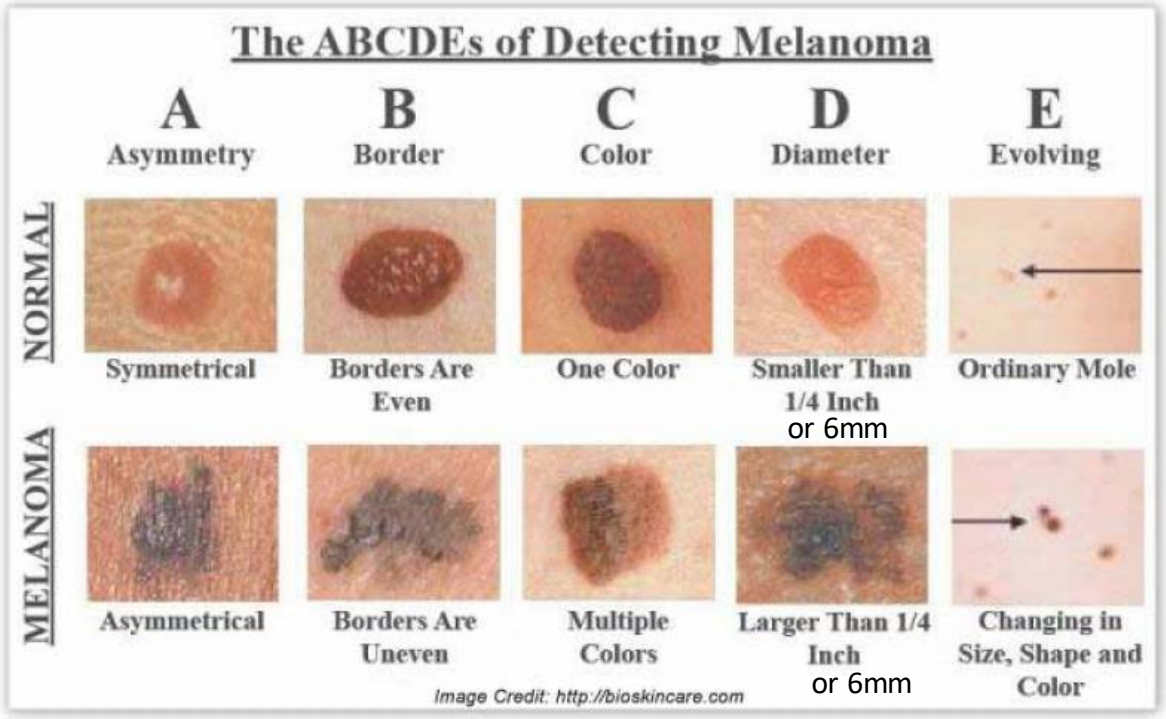
[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
[b] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
From Balch CM, Gershenwald JE, Soong SW, et al: Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27:6199–6206, 2009.



0; Tis; *in situ* melanoma
IA; up to 1mm thick, no ulceration (T1a), N0, M0.
IB; up to 1mm thick, with ulceration (T1b), or >1 up to 2mm thick, no ulceration (T2a), all N0, M0.
IIA; >1 up to 2mm thick, with ulceration (T2b), or >2 to 4mm thick, or no ulceration (T3a) all N0, M0.
IIB; >2 to 4mm thick, with ulceration (T3b) N0, M0, or > 4mm thick, no ulceration (T4a), N0, M0.
IIc; > 4mm thick, with ulceration (T4b), N0, M0.
IIIA; any depth, no ulceration, 1 node + (T1-4a) N1a, M0, or 2-3 nodes +, N2a, M0.
IIIB; any depth, no ulceration, 1 node + (T1-4a) N1b, M0, or 2-3 nodes +, N2b, M0.
IIIC; any depth, with ulceration (T1-4b), 1 node +, N1b, M0, or 2-3 nodes +, N2b, M0, or 4 or more nodes +.
IV; metastatic (M1a, M1b, M1c).

Early melanoma detection..1/

Glasgow 7-point checklist	
Major features:	**Minor features:**
Change in size	Diameter >7 mm
Irregular shape	Inflammation
Irregular colour	Oozing
	Change in sensation



- Be aware of the clinical signs of melanoma and algorithms that can assist with diagnosis, e.g. ABCDE, Glasgow checklist.
- Be familiar with which patients are at increased risk of melanoma. NCI has developed a melanoma risk assessment tool.
- Educate patients who are at increased risk of melanoma about the clinical signs to watch for and encourage them to examine their skin monthly.

- Consider periodically asking all patients if they are concerned about any moles or skin lesions, and offer full skin checks to older males.
- When examining a patient for another clinical problem take note of any skin lesions with an unusual appearance (eg an “ugly duckling”, i.e. a mole or lesion not like the others) or scars from previous excisions of suspicious lesions.

Q.: Which is more reliable, a trained GP with a dermatoscope, or a dermatologist with a smartphone skin cancer app?

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Early melanoma detection..2/

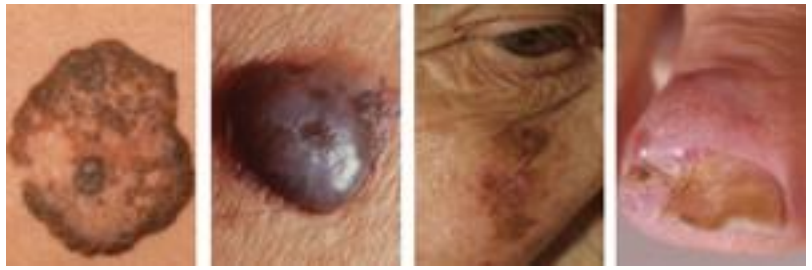
- Checking a single lesion that is of concern can be done quickly during a consultation for another clinical problem, although the entire skin surface should be examined if indicated, e.g. in high risk patients. Ensure access to good lighting when examining the skin.
- Refer, biopsy (depending on skill level and clinical situation), or carefully follow up all suspicious skin lesions.
- If a biopsy is taken, ensure that the results are followed up, e.g. place a recall or reminder in the patient notes
- Monitor clinically doubtful skin lesions for 1 to 2 months (but no more than 3 months). Consider the use of digital photography to monitor changes. Ensure the patient knows to re-present sooner if there is any concern.
- Clinical photography with macroscopic and dermoscopic views can enable a second opinion from an expert (teledermoscopy)
- Consider taking a training course in dermatoscopy

Dematoscopes and their flexibility

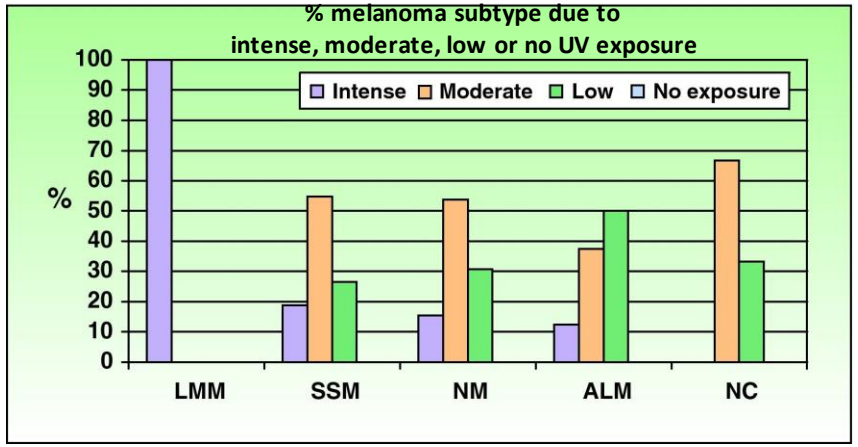
- Conventional
- Smartphone compatible
- Dual purpose
- Exercise caution about the many newly available smartphone skin cancer apps

Melanoma subtypes, and thickness

- Range of colours and uniformity, quite often with bleeding and/or ulceration. Some melanomas are amelanotic (up to 10%).
- SSM (~70%). Usually from a previous nevus. Can be anywhere on body.
- NM (10-15%). More common in males. Usually on trunk. Rapid vertical growth – tendency to be thicker. Get evaluated ASAP.
- LMM (10-15%). Typically face & neck, sun exposed areas. Typically arise from previous lesions & have hypopigmented areas.
- ALM (1-3%). On palms, soles or under nails. Extremely aggressive – refer ASAP.
- Mucosal lentiginous melanoma (MLM ~ 3%). On any mucosal surface, usually in advanced age. Aggressive – refer ASAP.
- The chance of melanoma dissemination increases with Breslow thickness (see thickness, T classification, Tis to T4) .
- Melanoma dissemination can begin when the melanoma is relatively thin – why? How?



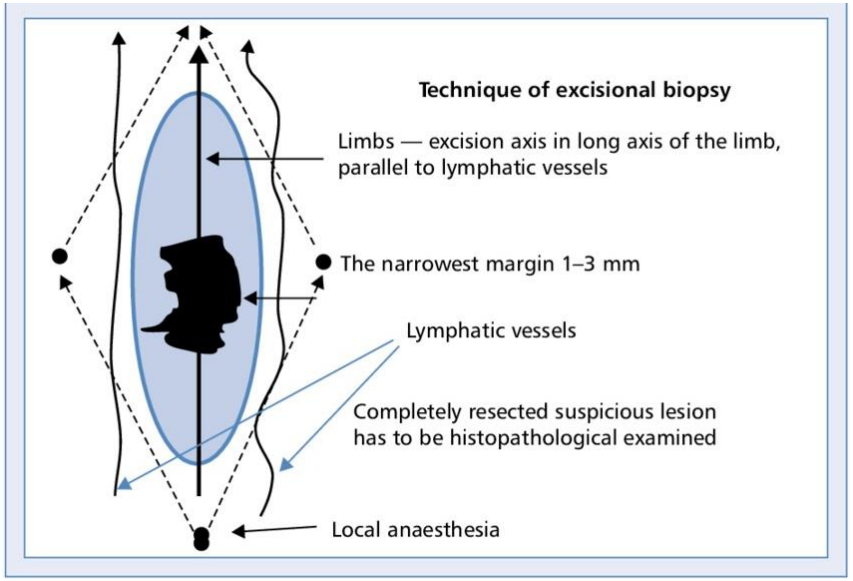
Superficial spreading or SSM | Nodular or NM | Lentigo maligna or LMM | Acral, acral-lentiginous or ALM



NC, not classified, from Fagundo et al., *Actas Dermosifiliogr* 2011;102:599-604

The role of excision biopsy…1/

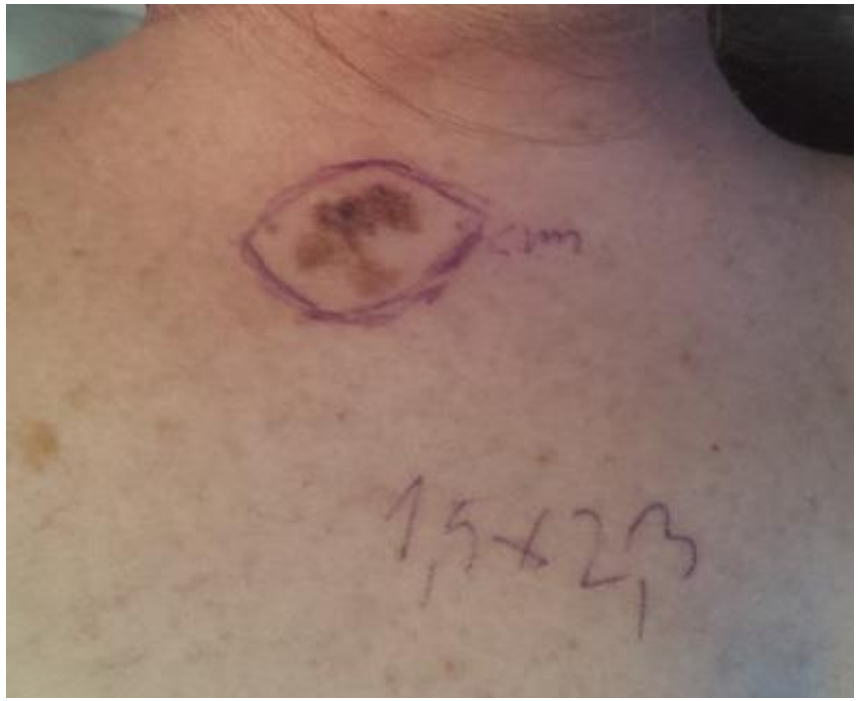
- Moh's surgery is generally inappropriate for definitive treatment of a melanoma
- **Excision biopsy is the preferred biopsy** – rather than an immediate wide local excision, even if confident of clinical diagnosis. This confirms the diagnosis and allows rational planning of definitive treatment – width and orientation of excision margins, and whether or not to recommend sentinel lymph node (SLN) biopsy.
- An immediate wide local excision with margins based on a clinical estimate of tumour thickness may result in inadequate or excessive tumour clearance. It may also compromise subsequent management by making it impossible to perform accurate lymphatic mapping to identify draining lymph node fields and SLNs within those fields.
- **Whenever possible** excision biopsy is recommended by the *Clinical practice guidelines for the management of cutaneous melanoma in Australia and New Zealand*.



The correct cut axis of excisional biopsy. A spindle-shaped excision of the suspicious melanomatous skin in parallel to the nearest lymphatic vessels (in the direction of the nearest lymphatic drainage); in the majority of cases will enable direct suture

The role of excision biopsy…2/

- If excision biopsy is indicated, biopsy of the complete lesion **with a 2 mm rim of normal skin and a cuff of fat** is recommended**. The depth of the excision** biopsy should extend to the deep fascia. This method provides sufficient material for histological examination and does not compromise a wider excision if required. Risk of seeding or dissemination of the melanoma with a partial biopsy is no longer thought to be significant.
- **Indications** for excision biopsy of a suspicious skin lesion include:
  - Lesion with typical clinical or dermoscopic features of melanoma
  - Solitary atypical naevus (e.g. > 6 mm, irregular shape, asymmetry of structure and colour) in a site that is difficult to observe
  - Atypical flat naevus that has been objectively observed to enlarge, e.g. by photographic comparison, or observation by a reliable witness
  - Enlarging pigmented or red nodule, particularly if symptomatic, or if it is not possible to confidently diagnose a benign lesion such as dermatofibroma.



The excision biopsy orientation should also take into account local lines of tension in order to decrease the necessity of skin grafting or reconstructive procedures.

Q.: Which is better to do for this patient, an excision biopsy and suturing, or an excision biopsy and a skin graft?

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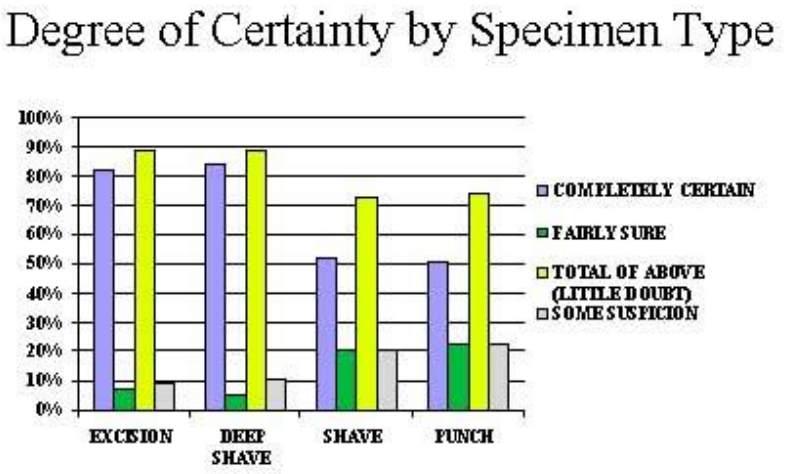
The role of excision biopsy…3/

- **Best Practice Tip**: Histological diagnosis of melanoma is often difficult. Provide the pathologist with a careful description of the lesion and explain why it is suspicious. Some pathologists find clinical photographs useful. Draw attention to areas of specific concern, e.g. eccentric pigmentation, as melanoma might be arising within an otherwise benign lesion. One way of doing this is by scoring the skin around the suspicious lesion.
- **Frequently unsatisfactory** are partial biopsies such as punch biopsies, incision biopsies and shave biopsies, as these may result in misdiagnosis due to unrepresentative sampling. The great majority of legal cases brought against doctors for alleged mismanagement of patients with melanomas are associated with incomplete biopsies. Nevertheless, an incision, punch or shave biopsy from the most suspicious area of a large pigmented lesion may be appropriate when a full excision biopsy would be difficult. A partial biopsy or multiple biopsies may be appropriate in clinical situations such as a large facial lesion or acral lesion. However, expert advice should be obtained first.
- **Flat lesions** may safely be observed if clinical concern is minimal.

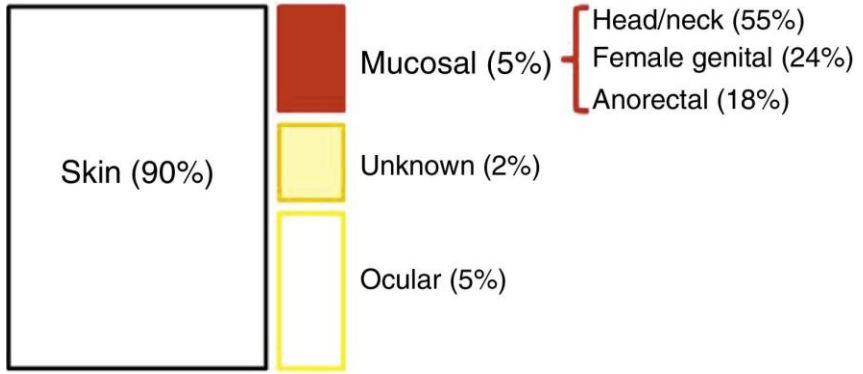


Graph shows percentages of each specimen type resulting in a histopathologic diagnosis which was completely certain or fairly sure, or in which there was some suspicion. Shown in yellow are those cases in which there was little doubt of lesion malignancy (sum of completely certain and fairly sure). 19 specimens were identified as deep shaves. 15 of them (79%) contained the entire lesion and in 16 (84%) the diagnosis was felt to be certain. 4 deep shave specimens (21%) were missing "insignificant" portions. No deep shave specimens were missing "significant" portions.
Pariser et al., *Dermatology Online Journal* 5(2):4

Locations of melanoma

- Cutaneous melanoma may arise in a pre-existing naevus (mole) or *de novo* on the skin. Sometimes a melanoma primary is never detected (melanoma of unknown primary cancer, MUP).
- Melanoma is not restricted to the cutaneous skin. Non-cutaneous melanoma may occur in primary extracutaneous sites such as the eye eg uveal melanoma, mucosa eg oral mucosa, gastrointestinal or genitourinary tracts, CNS and lymph nodes (again these may contribute to MUPs).
- Mucosal melanomas, and acral lentiginous melanomas are important types to be aware of in Māori, Pacifica and Asian patients.

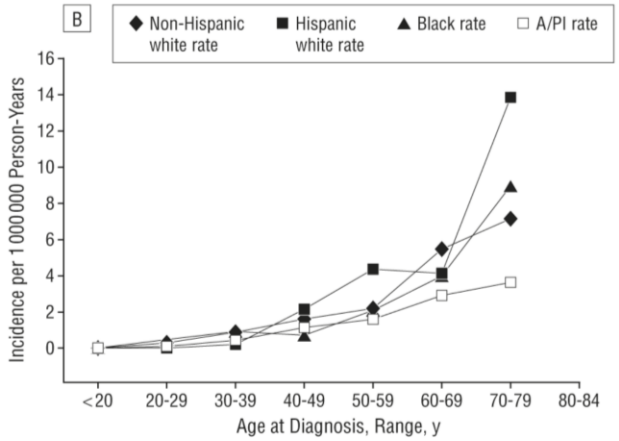
Topographical distribution of melanomas

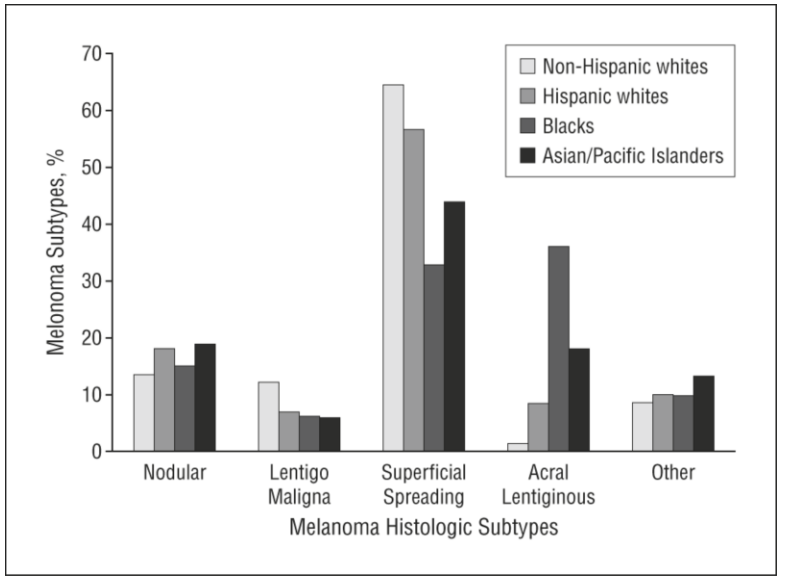


Reina et al., *Cir Esp* 2014;92:510-6

Melanoma in Maori, Pacifica, & Asians

- Melanoma is less common in Māori than non-Māori people in NZ. Evidence also indicates that melanoma is relatively uncommon in Pacific peoples, with a combined incidence rate in 2004 for Māori and Pacific peoples of 2.7 per 100,000 people, per year.
- Māori and Pacific peoples more frequently have melanomas that are thicker (eg >3 mm) than non-Māori, which affects morbidity and mortality. Their thicker melanomas may be due both to biological (genetic and tumour type) and social aspects.
- Melanoma in Māori is more common in women than men, as it is in other populations with low melanoma incidence, opposite that of non-Maori.



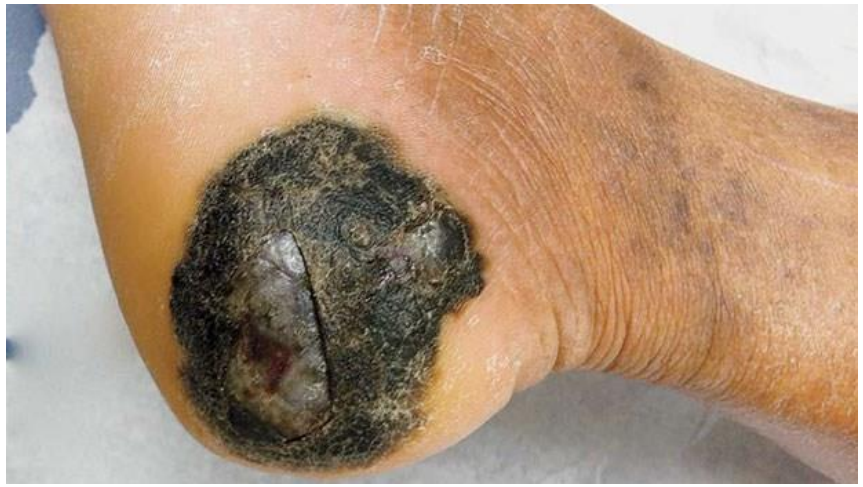


Bradford et al., *Arch Dermatol*. 2009;145(4):427-434.

Melanoma in Maori, Pacifica, & Asians

- **Investigating melanocytic lesions on the feet**
- The “CUBED” acronym can be used for investigating suspicious lesions on the feet. The presence of any two features should trigger referral or excision. The “CUBED” acronym is:
- **C**oloured lesions where any part is not skin coloured
- **U**ncertain diagnosis
- **B**leeding lesions on the foot or under the nail, including chronic granulation tissue
- **E**nlargement or deterioration of a lesion or ulcer despite treatment
- **D**elay in healing (> two months).

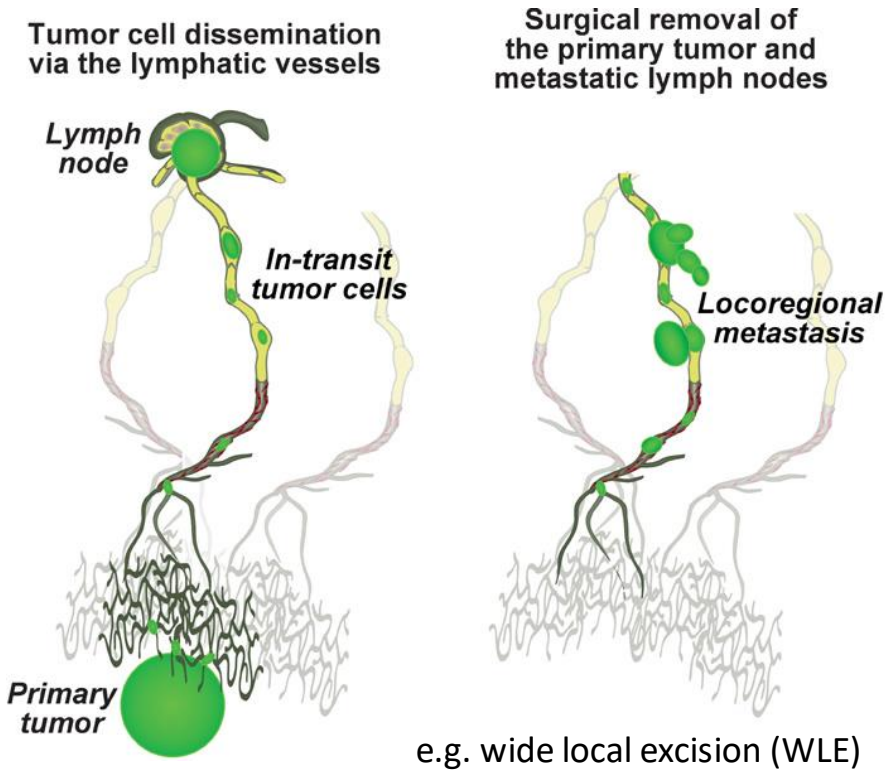
- **Best Practice Tip:** It may be difficult to determine the cause of subungual bleeding. Always ask about a history of trauma to the nail. An area of clear nail growth will develop at the base of the nail with time (weeks) if the subungual bleeding is a result of trauma (and not if the lesion is melanoma)



How, when & where does melanoma spread? (recurrence & metastasis)

- Melanoma spread occurs via superficial lymphatics giving satellite lesions, and to regional lymph nodes via deep lymphatics, and via haematogenous spread to the lungs, liver and brain.
- Melanoma begins to disseminate even when as little as <1mm thick. Circulating melanoma cells (CMCs) are detectable in the blood in ~1/3 of stage 1 SLN negative patients (CMCs are difficult to detect, and have recurrence/metastasis potential).
- Recurrence & metastasis of melanoma
  - Local recurrence rate following wide local excision with residual melanoma is 16% vs 2.7% in patients with no residual melanoma.
  - Metastasis rate following wide local excision with residual melanoma is 44% vs 22% in patients with no residual melanoma.

(Hocevar et al., 2014, *EJSO* 40, 1271–1275)



e.g. wide local excision (WLE) + Sentinel Lymph node (SLN) biopsy, vs WLE + complete lymph node dissection (CLND).

Some genetics & epigenetic changes in melanoma

Genetic changes in melanoma

BRAF mutations (Vemurafenib)

NRAS mutations (Trametinib, MEK)

NF1 mutations

EPHB6 mutations

TP53 (p53) mutations

CDKN2A (p16) mutations (also familial)

CDK4 mutations (also familial)

(none of these are consistently more frequently seen in metastatic melanoma)

Epigenetic changes in melanoma

CDKN2A promoter hypermethylation (inactivation of a tumour suppressor)

EBF3 promoter hypermethylation

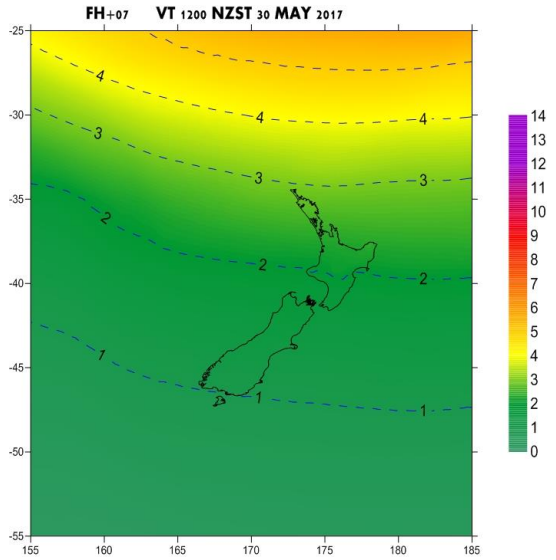
(this is an epigenetic change we saw more frequently in metastatic melanomas)

This is a relatively new field.
(see Chatterjee et al., *Oncotarget*, 2017)

DNA methylation inhibitors may also be efficacious in combination with immune checkpoint inhibitors.

Skin colour, vitamin D levels, & risk

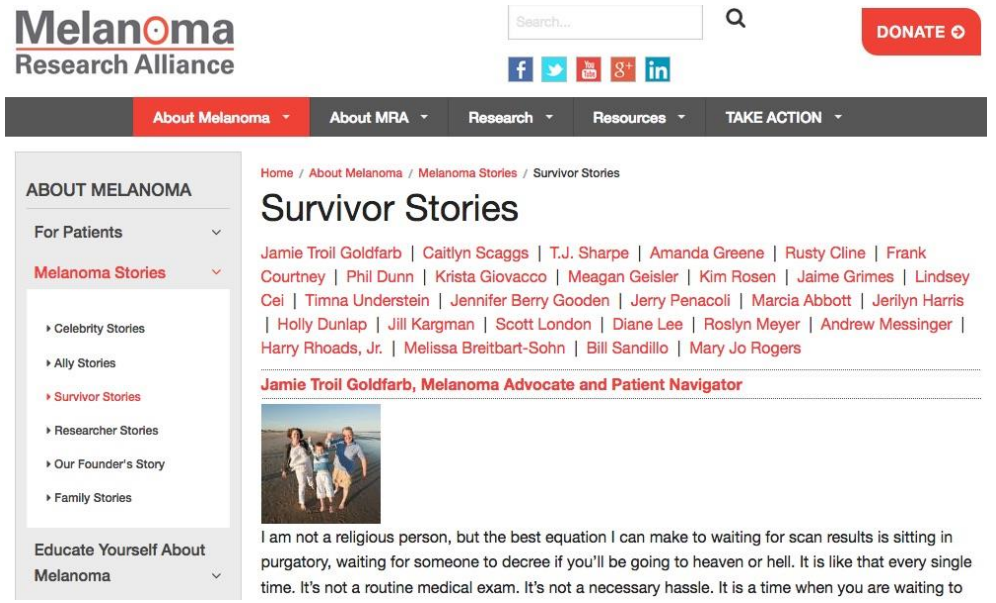
- Vitamin D levels are frequently low, or deficient.
- Perhaps all melanoma patients should consider vitamin D level testing/supplementation.
- GPs should consider advising elderly patients and patients with a dark skin about vitamin D supplementation.
- NZ has 40% higher levels of peak summer UV radiation compared to countries with a similar latitude or altitude in Northern hemisphere.
- Melanoma Incidence rates vary throughout NZ with lower rates reported in Southland (approximately 20 cases per 100,000 people per year) compared to Taranaki (approximately 70 cases per 100,000 people per year). The reason for this difference is probably related to peak UV exposure levels.
- The frequency of, and the types of gene mutations vary between North and South Islands in NZ (see Jones et al., *Oncotarget* 2016).



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Auckland	13	11	7	4	2	2	3	5	7	8	11	13
Wellington	13	9	6	3	2	1	2	4	5	8	11	12
Christchurch	12	8	5	3	1	1	2	3	4	8	10	11
Central Otago	10	8	5	2	1	1	1	3	4	7	10	11
Invercargill	8	7	4	2	1	1	1	2	3	5	9	10

“Super-survivors”

- Survivors of melanoma from successful drug treatment, or otherwise
- Follow-up for ever?
- Survival >5-10 years?
- Second malignancies?
- What to look out for?
- Treat like other patients with high-risk prediction of melanoma.



5 Take-home points

1) Evaluate patient risk, and advise patients accordingly
2) Strongly encourage self-surveillance
3) Do spot checks of suspicious lesions & consider doing a course in dermatoscopy
4) Perform excision biopsy whenever possible
5) Be aware of melanomas in Maori/Pacifica/Asian patients, esp. acral lentiginous melanoma

Acknowledgements

- MelNet (please join)
- MelanomaNZ
- Dr Amanda Oakley's DermNet website
- Colleagues in my lab; esp. A. Chatterjee, E. Rodger

- An advertisement;
  - I'm co-organising a melanoma meeting in Queenstown on 9th September, 2017

"Melanoma research and therapy in NZ – raising the bar through collaborative action"