Melanoma crash course

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Cutaneous melanoma represents about 4% of skin cancers but is responsible for more than 75% of deaths from skin cancer. The incidence of cutaneous melanoma is reported as 25 per 100,000 people in North America and 60 per 100,000 people in Australia and New Zealand.[1] Melanoma diagnoses are increasing worldwide, possibly owing to improved detection; in Canada the largest increase in age-standardized incidence of melanoma has occurred in males, with an increase of 2.2% per year between 1984 and 2019.[2] Mortality rates for melanoma have declined since 2013 due to the use of immunotherapy[2]; however, there has been no noted reduction in mortality among non-White patients or among populations with lower socioeconomic status, with a study demonstrating that these populations have higher incidences of thick melanoma with poorer prognoses.[3,4]

There is insufficient evidence to support the effectiveness of skin cancer screening in reducing melanoma mortality, with an Australian study published in 2022 finding that skin screening increases the risks of biopsy and melanoma in situ without increasing the detection rate of invasive melanoma, compared with unscreened individuals.[5] The United States Preventive Services Task Force also does not recommend regular skin checks in the average individual as part of age-appropriate screening guidelines.[6] A guideline published by the Canadian Task Force on Preventive Health Care, based on reports from Australia and New Zealand, recommends regular skin examinations for those at high risk of melanoma (**Table 1**).[7]

Ultraviolet (UV) radiation is a key causative factor of cutaneous melanoma and primary prevention education aimed at reducing exposure to UV radiation is imperative. Consistent sunscreen use reduces dyspigmentation, fine-line formation, and the risk of all skin cancers (including melanoma).[8] Sunscreen use, avoidance of the sun at peak hours, use of UV-blocking clothing, and shade-seeking are all encouraged. Physicians should ask patients about tanning bed use and quantify their exposure. Use of tanning beds before age 25 and repeated sessions (>10) are most strongly associated with development of melanoma and nonmelanoma skin cancers, especially in female patients younger than 45.[9,10] Consistent sunscreen use does not meaningfully compromise vitamin D levels.[11]

Evaluation of a melanocytic lesion

Family physicians most commonly assess skin lesions of concern, and can use the ABCDE (asymmetry, border, colour, diameter, evolution) criteria to determine which skin lesions should be considered for further workup.[12] Lesions satisfying 1 or more of the criteria should be considered for biopsy (**Box 1**).[12] An example of melanoma in situ is shown in **Figures 1A** and **1B**.

Dermoscopy is a technique that uses a magnifier and polarized light to examine the surface of the skin. It increases the accuracy of melanoma diagnosis by a dermatologist by 10% to 27%.[13] Primary care physicians who used dermoscopy after a 1-day training course were able to increase their sensitivity for detecting melanoma by approximately 25%.[14] Technologies such as reflectance confocal microscopy and optical coherence tomography, as well as artificial intelligence pattern recognition, are emerging but are not the standard of care at this time.[15,16]

Table 1. Risk factors for melanoma

RISK FACTOR	DESCRIPTION
Phenotype	• Fair skin, light eyes • High nevus count and presence of clinically atypical moles are the most important phenotypic risk factors, especially when combined with family history
Environment	• High latitude environment • History of living near the equator
Habits	• Tanning bed use • People from northern latitudes who take annual short, intensely sunny holidays • Blistering sunburns <18 y
Genetic conditions	• Xeroderma pigmentosum • History of retinoblastoma • Familial atypical melanocytic mole syndrome
History	• Previous melanoma • Solid-organ transplant recipients • Hematopoietic cell transplant recipients • High cumulative dose of PUVA* therapy

*PUVA therapy uses both psoralen (P) and ultraviolet (UV) A radiation.
Data from the Canadian Task Force on Preventive Health Care.[7]

Box 1. ABCDE criteria for skin lesion evaluation

- Asymmetry
- Border
  - -Irregular, blurred
- Colour
  - -Multicolour or uneven
- Diameter
  - -Greater than 6 mm
- Evolution
  - -Recent change in size, shape, colour, or presence of crusting or ulceration

Data from Abbasi et al.[12]

When a patient presents with a concerning pigmented macule or plaque, the biopsy should include a full thickness sample with adequate depth, as melanoma thickness on pathologic analysis is a key prognostic factor and dictates recommended treatment. Biopsy techniques such as punch biopsy and excision with narrow margins are acceptable, and deep shave can be considered if the clinician can ensure adequate depth of the sample. The entire lesion should be excised, but if removing the entire specimen is not possible clinicians should comment on the size of the original lesion, note where the biopsy was taken, and consider multiple specimens if the lesion is large. If the lesion is on an extremity, orientation of the biopsy specimen should be longitudinal so as not to interfere with lymphatic drainage for potential future lymph node biopsy.[13]

Pathology

Classically, 4 histologic subtypes of melanoma have been described: superficial spreading, nodular, lentigo maligna melanoma, and acral lentiginous. All subtypes expand along the basement membrane of the epidermis in a radial growth phase, creating nests of mutated melanocytes before moving into the vertical growth phase, during which the melanoma extends deeper into the dermis. Nodular melanoma, the most aggressive subtype with the poorest prognosis, moves quickly into the vertical growth phase, allowing less time for detection. Dysplastic nevi, where pathology reports cytologic atypia and not architectural disorder, are usually treated as melanoma in situ.

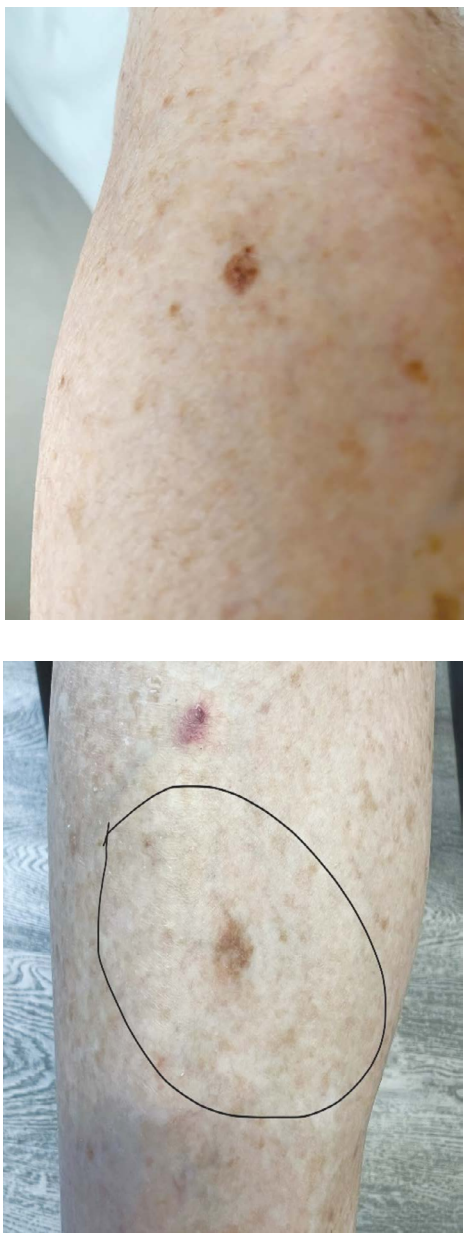
In addition to histologic subtype, pathology reports will comment on the depth of the tumour (Breslow thickness), mitotic rate, ulceration, presence of perineural or perivascular disease, and margin status.[17] Pathologic features that indicate a poor prognosis for melanomas are shown in **Box 2**.[17] Pathology may also report mutations in *BRAF*, *MEK*, and *KIT* genes. Mutations in *BRAF* occur in 50% to 80% of superficial spreading and nodular melanomas. The presence of these mutations has implications for the ability to use targeted therapies.

More recently, melanomas arising on chronically sun-damaged skin have been differentiated from those that develop on skin exposed to intermittent sunlight. Melanomas on sun-damaged skin, such as lentigo maligna melanoma and desmoplastic melanoma, are genetically different, with *BRAF* mutations present only in 10% to 21% of cases.[18]

Staging of and surgery for melanoma

Once the diagnosis of melanoma is confirmed with biopsy, definitive management of the melanoma is required, usually requiring referral to a plastic or general surgeon. Nodal basins should be examined clinically for nodal metastases and ultrasound can be employed if examination is equivocal. Broadly, melanomas can be considered localized when there is no nodal involvement (stages I and II), regional when there is nodal involvement (stage III), or metastatic (stage IV). Staging investigations should be performed for regional disease.

Figure 1. Example of a melanoma in situ: ***A) patient with a background of substantial sun damage had a mole with unusual features upon first presentation (black dots, asymmetry): The patient declined biopsy at the first appointment, so the dermatologist elected for surveillance. B)*** **At a reassessment 12 months later, regression of pigment in the centre was noted:** ***The macule was biopsied and the patient was later diagnosed with melanoma in situ.***



Photograph courtesy of Dr Michael Robern of the Dermatology Ottawa Research Centre in Ontario.

Box 2. Poor prognostic features of melanoma on histopathologic examination

- Breslow thickness >2 mm
- Ulceration
- Mitotic rate >1/mm^2
- Lymphovascular invasion
- Regression

Data from Swetter et al.[17]

A wide local excision is employed to remove the primary tumour, with surgical margins dictated by the thickness of the lesion (**Table 2**).[17] If there is no clinically evident nodal disease but the Breslow thickness is greater than 0.8 mm with ulceration or 0.8 mm to 1.0 mm without ulceration (T1a and T1b, respectively), sentinel lymph node biopsy (SLNB) should be considered at the time of wide excision. In SLNB, a radioactive tracer and dye are injected into the primary melanoma site and a probe is used to detect the target node to which the lymphatic systems drain. The target node is then excised and sent for pathologic examination. Completion nodal dissection is no longer routinely recommended for patients with nodal disease identified on SLNB; rather, these patients may be followed with close ultrasound surveillance of the nodal basin. Patients with clinically evident nodal disease are typically still recommended to have completion lymph node dissection. Patients with any confirmed nodal disease should be considered for adjuvant therapy.[19]

Immunotherapy and targeted therapy

Immune checkpoint proteins such as programmed cell death 1 ligand 1 and cytotoxic T lymphocyte–associated protein 4 are expressed by tumours to prevent autoimmune attack by T cells. This allows the cancer to "immune escape" checkpoint proteins and proliferate. Immune checkpoint inhibitors, also called immunotherapy, can be used to restore immunosurveillance by the body's T cells to recognize and destroy cancer cells.

Immunotherapy has proven very effective in patients with melanoma: a landmark trial found that patients with metastatic melanoma treated with doublet immunotherapy (cytotoxic T lymphocyte–associated protein 4 and programmed cell death 1 ligand 1) had a median overall survival of 72.1 months.[20] Immunotherapy is now the standard of care for patients with stage IV melanoma and as adjuvant therapy for patients with high-risk or unresectable stage II or III melanomas. Family physicians should be aware that immunotherapy may result in immune-related adverse events, where an overactivation of the immune system causes an autoimmune attack on any tissue or organ in the body. These can develop months after the last treatment and were described in a previous Oncology Briefs article in *Canadian Family Physician*.[21-23]

Table 2. Recommended margins for wide local excision of melanoma: *Removal of all tissue to the level of, and not into, the fascia is recommended.*

TUMOUR THICKNESS	MARGIN
In situ (does not penetrate the basement membrane of the epidermis)	0.5 cm
≤1.0 mm	1.0 cm
>1.0-2.0 mm	1.0-2.0 cm
>2.0-4.0 mm	2.0 cm
>4.0 mm	2.0 cm

Data from Swetter et al.[17]

Tumours with *BRAF* mutations can be treated with targeted *BRAF* inhibitors such as dabrafenib, encorafenib, and vemurafenib. Due to resistance, *MEK* inhibitors such as trametinib are used in conjunction with these agents.[24]

Follow-up

Patients who have a history of melanoma have a 4% to 8% risk of developing subsequent primary melanomas.[25,26] Most metastases occur in the first 3 to 5 years after treatment of the primary tumour. The most common site of recurrence or metastasis is the skin or subcutaneous tissue, but in 18% to 27% of people, distant organs such as the lungs, brain, liver, and bones are involved.[26]

Recommendations for clinical follow-up are highly variable in the literature, but a recent review of multiple guidelines indicates that survivorship care should consist of self-examinations and lifelong annual skin and lymph node examinations by a clinician, especially in patients with more advanced stages of disease.[27] Obtaining serial serum lactate dehydrogenase levels is not recommended. British guidelines recommend that patients with melanoma in situ may be discharged after postsurgical follow-up and do not require ongoing surveillance.[28]

Conclusion

Family physicians are involved in all aspects of melanoma care, especially in diagnosis and follow-up. This brief provides an up-to-date review of melanoma treatment and highlights notable improved mortality rates in patients with later-stage disease as well as the need for family physicians to be aware of immune-related adverse events as they follow patients with a diagnosis of melanoma.

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Competing interests
None declared

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