MELANOMA

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Epidemiology

- Melanoma accounts for 4% of all skin cancers.
- It is the greatest cause of skin-related cancer deaths.
- Median age is 53 years
- Most common cancer in women age 25 – 29 years.
- Multiple risk factors including:
    - fair complexion,
    - excessive childhood sun exposure and blistering childhood sunburns,
    - an increased number of common and dysplastic moles,
    - a family history of melanoma.
    - previous history of melanoma.
    - previous skin cancer.

Pathophysiology

- Is a malignant tumor of melanocytes.
- Melanocytes make the pigment melanin and arise from the neural crest.
- Melanocytes are located in the skin but also in the mucosal surfaces and any other sites to which neural crest cells migrate.
- Melanoma may arise in precursor melanocytic nevi, but, 60% arise de novo.
- Distinction amoung the subtypes is based on histological growth pattern.
- Controversial if the melanoma subtype affects the overall prognosis remains controversial. Molecular analysis has shown different patterns of cell death, oncogene expression, gene amplification and *BRAF* mutation frequency.
- Except for nodular melanoma most melanoma have a radial growth phase which lacks the biological potential to metastasize and may last months to years before dermal invasion occurs.

Types

- Superficial spreading
    - Most common in 30 – 50 years.
    - Common on trunk of men and women and on the legs of women.
    - Manifests as a flat or slightly elevated brown lesion with variegate pigmentation.
    - Usually > 6 mm with asymmetric borders.
- Nodular
    - Occurs in 15 – 30%.
    - Most common on the legs and trunk.
    - Growth is rapid over weeks to months.

    - Appears as a dark brown-to-black papule or dome-shaped nodule, which may ulcerate and bleed.
    - May be amelanotic.
    - Lacks the ABCDE criteria and may elude early detection.
    - Lacks a radial growth phase.
- Lentigo maligna
    - Incidence is rising.
    - Typically located on the head, neck, and arms of fair-skinned older individuals (mean age 65 years).
    - Grows slowly over 5 – 20 years.
    - In situ precursor is usually large (> 1-3 cm) and present for a minim of 10 – 15 years. May have hypopigmentation in the lesion.
- Acral lentiginous (palmar/plantar and subungual)
    - Least common in white persons
    - 29-72% of melanoma cases in dark-skinned individuals
    - Because of delays in diagnosis, may be associated with a worse prognosis
    - Occurs on the palms, soles or beneath the nail plate
    - Subungual melanoma may present as diffuse nail discoloration or a longitudinal pigmented band within the nail plate
    - Pigmented spread to the proximal or lateral nail folds is termed the Huchinson sign which is a hallmark for acral lentiginious melanoma
- Miscellaneous types (Mucosal lentiginous, desmoplastic and verrucous)

Diagnosis

- Most common presentation is a new or changing mole or blemish
- Signs are variation in colour and/or an increase in diameter, height, or asymmetry of borders of a pigments lesion
- Later symptoms are bleeding, itching, ulceration and a pain in a pigmented lesion.

- ABCDE criteria

A	Asymmetry	Half the lesion does not match the other half
B	Border irregularity	The edges are ragged, notched, or blurred.
C	Colour variegation	Pigmentation is not uniform and may display shades of tan, brown, or black: white, reddish or blue discoloration is of particular concern
D	Diameter	Diameter greater than 6 mm is characteristic; although some melanomas may have smaller diameters; any growth in a nevus warrants an evaluation
E	Evolving	Changes in the lesion over time are characteristics. This factor is critical for nodular or amelanotic (non-pigmented) melanoma, which may not exhibit the classic criteria above

- Highest accuracy when used in combination.

Staging

- Microstaging is determined on the histologic examination of the vertical thickness of the lesion in millimeters (Breslow classification) and/or the anatomic level of local invasion (Clark classification)
- Breslow thickness is more reproducible and more accurately predicts subsequent behavior of malignant melanoma for lesions > 1.5 mm in thickness.

- Clark Classification

Level	Description
I	o Involves only the epidermis o In situ melanoma (non-invasive)
II	o Invasion of the papillary dermis o Does not reach the papillary-reticular dermal interface
III	o Invasion fills and expands the papillary dermis but does not penetrate the reticular dermis
IV	o Invasion into the reticular dermis but not the subcutaneous tissue
V	o Invasion into the subcutaneous tissue

- TNM

T Primary Tumor	TX	Primary tumor cannot be assessed (e.g. shaved biopsy or regressed melanoma)
	T0	No evidence of primary tumor
	T1	Tumor 1.0 mm or less in thickness T1a: ≤ 1.0 mm, Clark level II or III, no ulceration T1b: ≤ 1.0 mm, Clark level IV or V or with ulceration
	T2	Tumor > 1.0 mm and ≤ 2.0 mm thickness T2a: > 1.0 mm and ≤ 2.0 mm, no ulceration T2b: > 1.0 mm and ≤ 2.0 mm, ulceration
	T3	Tumor > 2.0 mm and ≤ 4.0 mm thickness T3a: > 2.0 mm and ≤ 4.0 mm, no ulceration T3b: > 2.0 mm and ≤ 4.0 mm, ulceration
	T4	Tumor > 4.0 mm T4a: > 4.0 mm and no ulceration T4b: > 4.0 mm and ulceration
N Regional Lymph Nodes	NX	Regional lymph nodes cannot be assessedN0
	N0	No regional lymph nodes metastasis
	N1	Metastases to 1 lymph node N1a: Clinically occult (microscopic) metastases N1b: Clinically apparent (macroscopic) metastases

	N2	Metastases to 2 or 3 regional nodes or intralymphatic regional metastases without nodal metastases N2a: Clinically occult(microscopic) metastases N2b: Clinically apparent (macroscopic) metastases N2c: Satellite or in-transit metastases; no nodes
	N3	Metastases to > 4 nodes, or matted lymph nodes, or in-transit metastasis, or satellite(s) with metastatic regional nodes(s)
M Distant Metastasis	MX	Distant metastases cannot be assessed
	M1	Distant metastases M1a: Metatases to skin, subcutaneous tissues, or distant lymph nodes M1b: Metastasis to lung M1c: Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase

o UICC Staging

UICC Stage	TNM Groupings	5-Year Survival
0	T1s, N0, M0	100%
I	Ia: T1a, N0, M0	≥ 95%
	Ib: T1b, N0, M0 T2a, N0, M0	89 – 91%
II	IIa: T2b, N0, M0 T3a, N0, M0	77 – 79%
	IIb: T3b, N0, M0 T4a, N0, M0	63 – 67%
	IIc: T4b, N0, M0	45%
III	IIIa T1-4a, N1a, M0 T1-4a, N2a, M0	63 – 69%
	IIIb T1-4b, N1a, M0 T1-4b, N2a, M0 T1-4a, N1b, M0 T1-4a, N2b, M0 T1-4a/b N2c M0	46 – 53% 30 – 50%
	IIIc T1-4b, N2a, M0 T1-4b, N2b, M0 Any T, N3, M0	24 – 29%

IV	Any T, any N, M1	7 – 19%

Prognosis

- Better if younger, female and lesions on the extremities
- Affected by clinical and histological factors and by anatomic location of the lesion.
- Thickness and/or level of invasion of the melanoma, mitotic index, presence of tumor infiltrating lymphocytes, and ulceration or bleeding at the primary sites
- Number of regional lymph nodes involved

Initial Management

- The suspicious lesion should be biopsied by local excision.
- Suspicious lesions should never be shaved off or cauterized.
- The specimen should be examined by an experienced pathologist for microstaging.
- Regional sentinel lymph node biopsy should be done for patients with tumor $\geq$ 1 mm and when certain high-risk histologic features (eg. ulceration, extensive regression) in thinner melanomas.

Treatment by Stage

Stage 0

- Resection with minimal but microscopically free margins
- Usually the margin is 5 mm.

Stage I

- Lesions $\leq$ 2mm are resected.
- For lesions up to 1 mm, margins of 1 cm are recommended.
- Most recommend margins of 2 mc for 1 – 4 mm thickness lesions, although 1 cm margins have been shown to be effective for lesions up to 2 cm.
- Sentinel lymph node biopsy is done for lesions 1 mm or greater.

Stage II and III

- Lesions 2 – 4 mm are resected with margins of 3 cm whenever anatomically possible
- Lymphatic mapping and sentinel lymph node biopsy is used to assess the presence of occult metastasis in the regional lymph nodes potentially

identifying individuals who may be spared the morbidity of regional lymph node dissection and individuals who may benefit from adjuvant therapy

- Survival may be better amoung those patients who undergo immediate regional lymphadenectomy than it is amoung those who delay lymphadenectomy until the clinical appearance of nodal metastasis. A WHO improved 5 year survival rate (27% vs 48%).
- Adjuvant interferon is administered to patients post-operatively for patients with lesions 4 mm or greater or with positive lymph node metastases
    - Interferon-a-2b (20 mU/m2) IV daily X 5 days per week for 4 weeks followed by 10 mU/M2 sc 3 X/wk for 48 weeks.
    - Clinical trials have demonstrated
        - median survival increased from 2.8 years to 3.8 years.
        - 11% increase (26% to 37%) in 5 year relapse free survival.
        - 9 % increase (37% to 46%) in 5 year overall survival.
    - As there are substantial side effects patients must be closely monitored.

Stage IV

- Metastases to distant lymph node-bearing areas may be palliated by regional lymphadenectomy.
- Isolated metastases to the lung, gastrointestinal tract, bone, or occasionally the brain may be palliated by resection with occasional long-term survival
- Radiation therapy may provide symptomatic relief for metastases to brain, bones, and viscera
- Chemotherapy with dacarbazine (DTIC), carmustine (BCNU) and lomustine as single agents is approximately 10 to 20% with responses ranging in duration from 3 to 6 months, though long-term remissions can occur in a limited number of patients who attain a complete response
- Other agents with activity include vinca alkaloids, platinum compounds and taxanes
- Response to IL-2 regimes is in the range of 10-20%.
- Enrolment in clinical trials is strongly encouraged.
- For patients not eligible for clinical trials, the usual treatment is DTIC and carboplatinum. Taxol and Carboplatin has also been used.

Recurrent Disease

- See information for stage IV.
- For patients with recurrent melanoma in the extremities as in-transit or satellite metastases, surgical resection remains standard treatment for limited-volume disease.
- For those with regional lymph node recurrence resected, they are eligible for interferon therapy as in Stage II and III
- For multiple in-transit and/or satellite lesions hyperthermic isolated limb perfusion with melphalan has been associated with overall tumor

response rates of approximately 80 to 90% with complete response rates ranging from 7 to 82%. The addition of TNF increased response rates but was associated with increased adverse events including musculoskeletal complications of the perfused extremity.

For Further Reading

http://www.cancer.gov/cancertopics/types/melanoma

http://www.nlm.nih.gov/medlineplus/melanoma.html

http://www.emedicine.com/med/topic1386.htm

http://www.mskcc.org/mskcc/html/56598.cfmhttp://www.lhsc.on.ca/priv/library/
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