

MALIGNANT MELANOMA

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BACKGROUND

- MM. of the skin is a malignant neoplasm of the epidermal melanocytes
- The incidence rates show considerable variation between the countries:
 - Australia/New Zealand → high incidence (50 cases /100,000inhabit.)
 - Sweden/ UK/ USA / Netherlands → medium incidence (10-20 cases/ per 100.000 inhabitants)
 - Most Western-Eastern European countries → 4-10 cases / 100.000
- No. of deaths due to MM. has increased for the past decades and continue to rise in most fair skinned populations throughout the world
- Mortality rates have not risen as quickly as the incidence of melanoma
- (↑ mortality rates in older males ; ↓ mortality in middle-aged women & young individuals)

Why is early detection of Melanoma worthwhile ?

- The stage of initial Dx. determines the patient`s chance of survival
- There is a direct relationship between the depth of tumor (Breslow thickness) and the chances of survival
- Increased knowledge about the early signs and symptoms of MM in the public and in primary health care workers → important
- 20% melanoma patients have recurrence of their disease (Pts. with thicker melanomas)
- Rationale for screening of melanoma → identification of high risk population
- “ Melanoma writes its message in the skin with its own ink and is there for all to see it”

RISK FACTORS

- There is no single cause of melanoma (multifactorial)
- The development of MM occurs as a result of interaction between the environmental factors and individual (host) factors :
- Environmental factors : sun exposure in childhood
 - - No. of sunburns in childhood / adolescence
 - - Intermittent high exposure during holidays
- Host factors : Genetic factors (mutations in CDKNA2 gene ; many variants of MC1R gene detected)→ Family History
 - - Genetic diseases : XP, OCA (Albinism)
 - - Skin type / phenotype (Fitzpatrick scale – 6)
 - - Many banal melanocytic naevi (> 50)
 - - Congenital naevi > 5 ; AMN > 5 / DNS

Skin types/phototypes

Definition of 6 phototypes



Risk Factors – Ctd.

- Handy mnemonic is MM RISK :
 - M : Moles (multiple atypical moles)
 - M : Moles (numerous common moles + moles present at birth)
 - R : Red hair, fair skin , blue eyes, ↑ freckling
 - I : Inability to tan : skin phenotype I—II
 - S : Sunburn → severe sunburn < age of 15 years
 - K : Kindred → family Hx. of MM in first degree relatives
- Melanoma in children → very rare (Spitz nevus or Juvenile Melanoma)
- Melanoma diagnosed in Pregnancy → poor prognosis ?

Melanoma Growth Pattern

- Majority of MM have a radial growth phase (in situ / microinvasive) before the development of vertical growth phase
- Body sites involved (primaries): Skin (90%)
 - Ocular (2%) → conjunctiva, sclera
 - Other mucosal membranes(1%): anus,oral
 - Visceral < 0.1% (adrenals, lung, esophagus
 - Nail (subungual) < 1%
 - Unknown primary (5%)
- BANS areas : back, arms, neck, scalp → poor prognosis
- Amelanotic Melanoma (absence of pigment) → poorly differentiated state
- Depigmented haloes → Not a diagnostic feature of melanoma

CLINICO-PATHOLOGICAL VARIANTS OF MELANOMA

- There are 5 classic clinical subtypes of MM each having typical features
 1. Superficial spreading MM (70%) → develops slowly, from a pre-existing AMN, in people aged 40-60 years
 2. Nodular MM (20%) → fast growing (within a few months) often de novo, in people aged 50-60 yr.
 3. Lentigo Maligna Melanoma (5%) → develop very slowly from a lentigo maligna on sun damaged skin , in people > 65yr. (elderly)
 4. Acrolentiginous Melanoma (5%) → most common type in Blacks ; located on hands, feet, nails
 5. Mucosal MM (1%) → more often seen in Blacks (ocular, anal, vagina, oral mucosa) ; late Dx. ; younger / middle age group

UNUSUAL TYPES OF MELANOMA

- 1. Amelanotic Melanoma → nodular or polypoid, late Dx , poor prognosis
ulceration is common
- 2. Desmoplastic Melanoma → sun exposed skin, more often in white men, flat-pigmented patch or an amelanotic papule ; late Dx, poor prognosis ; tendency to local recurrence
- 3. Malignant Blue Naevus → white men > 45yr , scalp, nodule/plaque >2cm
- 4. Naevus of Ota –associated Melanoma (ophthalmo-maxilaris)+ mucosal involvement (ocular, palate, nasal/tympanic mucosa)
- 5. Subungual Melanoma → Blacks : 20-31% over age of 60yr, brown longitudinal nail band, mainly on thumb

CLINICAL ASSESSMENT OF MALIGNANT MELANOMA

- Assess the skin phenotype and the extend of sun damage
- Estimate the total No. of moles and presence/absence of AMN
- Measure the diameter of a changing mole + monitor the colour, borders, presence/absence of Ulceration
- Check whether a mole is different from other moles (ugly duckling sign)
- Apply ABCDE rule or 7 point-checklist for early detection of melanoma
 - A → asymmetry
 - B → borders (irregular)
 - C → colour variation
 - D → diameter >7 mm
 - E → elevation of formerly flat lesion or evolution (change)

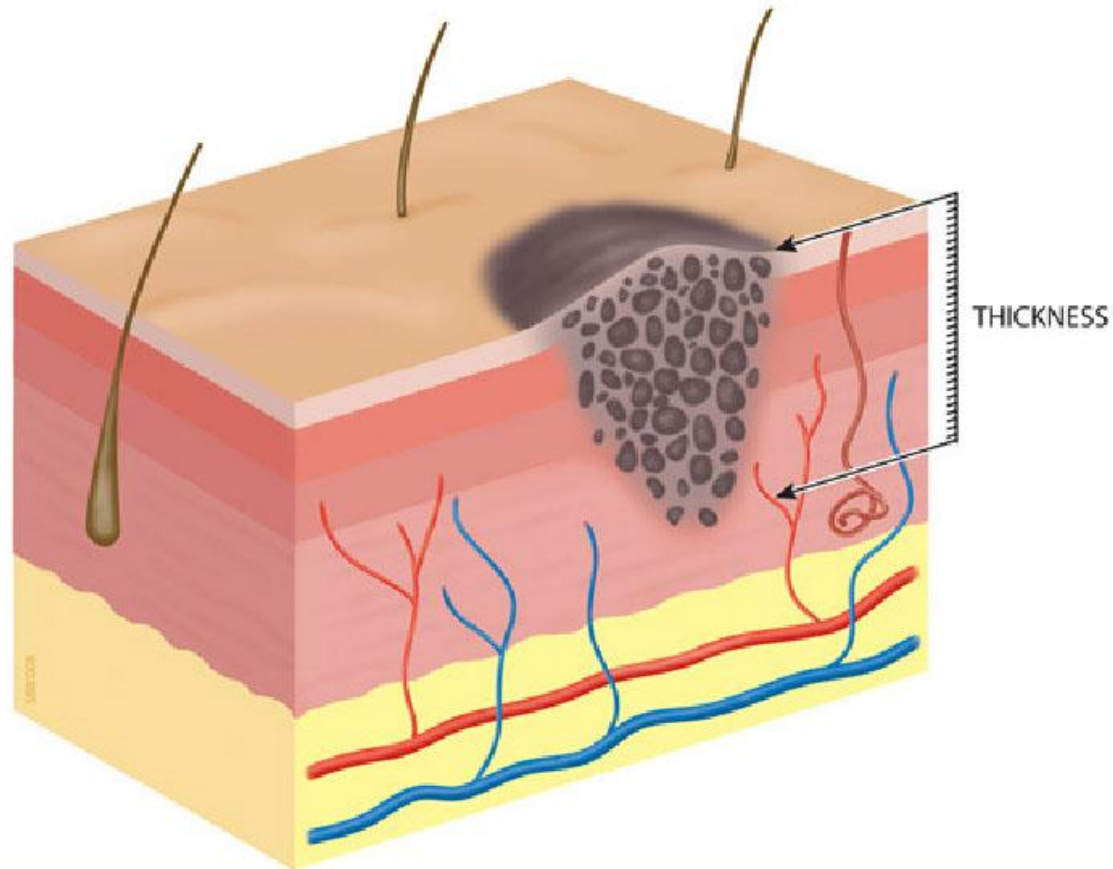
CLINICAL ASSESSMENT OF MALIGNANT MELANOMA—Ctd.

- Recently → F was added standing for : Feeling (itching, stinging, burning or for Funny Mole (ugly Duckling `sign)
- 7 point-checklist → emphasis on changing mole in adulthood :
 - Major features : change in size (1), shape (2), colour (3)
 - Minor features : diameter > 7mm (1), inflammation (2), oozing/crusting bleeding (3), changing in sensation (4)
- 1 Major Criterion or 3 Minor Criteria are fulfilled → Melanoma (see Dr. within a few weeks)
- What determines how long a melanoma will remain in situ is not clear ? (combination of factors)

STAGING OF MELANOMA

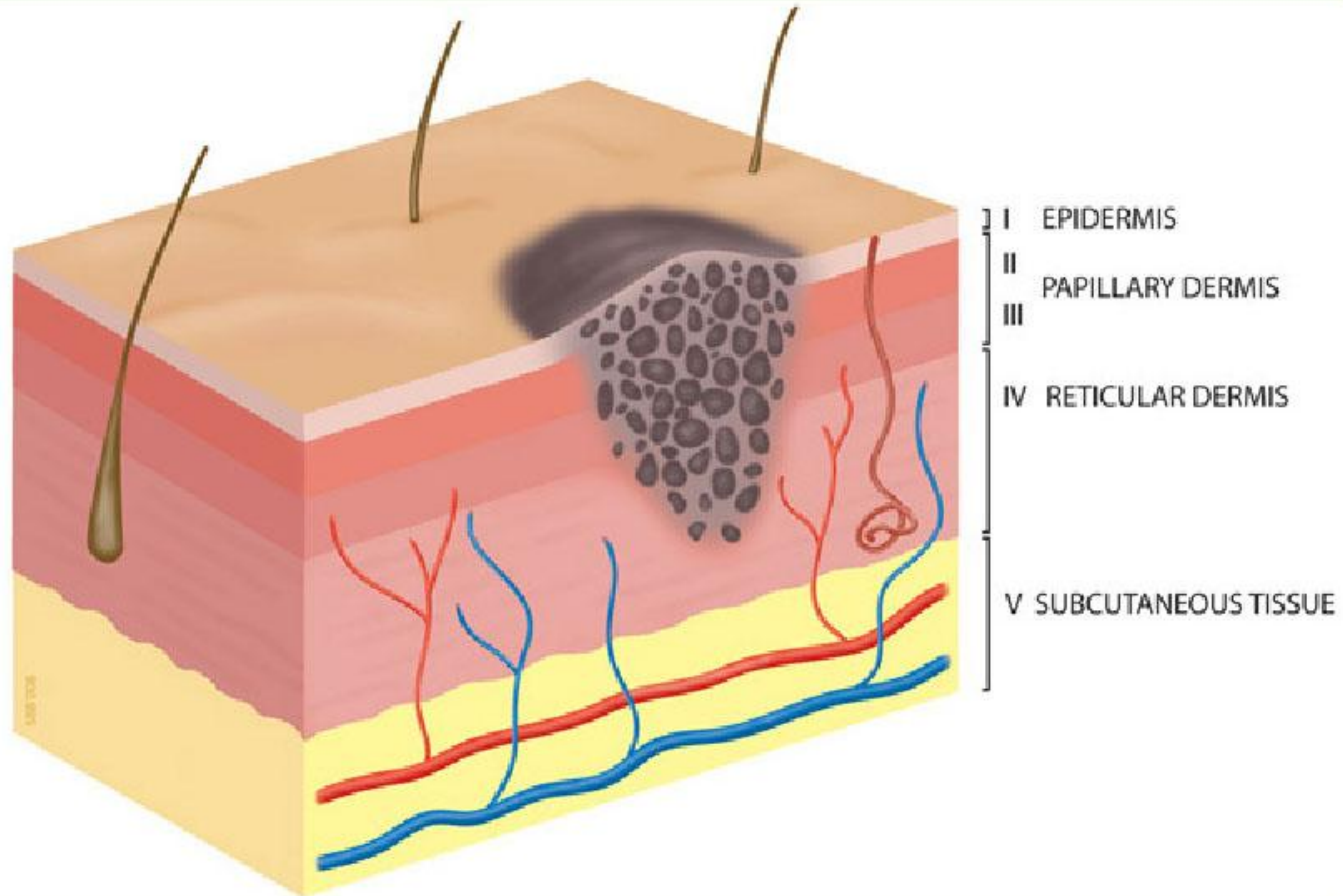
- Breslow depth is the most important prognostic factor in Melanoma, with stratification cutoffs of <1mm, 1.01-2mm, 2.01-4mm, >4mm in the revised 2002 AJCC melanoma staging
- Ulceration is the next most important adverse prognostic feature (its presence upstages the patient into the next worst prognostic level)
- The number of LN involved is a powerful predictor of survival
- Sentinel LN status is the most important prognostic factor for recurrence and predictor of survival
- Clark's pathological level of invasion in the skin is useful in staging very thin melanomas

Measuring the Breslow thickness



Determining the Clark's level

This diagram shows a Clark's level IV melanoma (invasion into the reticular dermis).



STAGING OF MELANOMA – Ctd.

- The stage of Melanoma in an individual patient results from Clinical Examination + Histopathology of Tumor specimen + Sentinel LN investig.
- No further investigations (X-Rays, CT-scans, MRI scans)→ Stages I & II
- There is no consensus of further investigations in advanced stages
- Serum LDH levels may indicate metastases (low specificity / sensitivity) → is useful in TX of stage IV (disseminated) disease
- Total body CTscans + liver/brain/bone imaging → Not useful in detecting occult melanoma metastasis in asymptomatic patients

American Joint Committee on Cancer staging system for melanoma

Stage	Primary tumour (Breslow thickness)	Lymph node	Metasasis
0	In-situ tumours	Nil	Nil
IA	≤ 1.0 mm, no ulceration	Nil	Nil
IB	≤ 1.0 mm + ulceration 1.01-2.0 mm, no ulceration	Nil	Nil
IIA	1.01-2.0 mm + ulceration 2.01-4.0 mm, no ulceration	Nil	Nil
IIB	2.01-4.0 mm + ulceration > 4.0 mm, no ulceration	Nil	Nil
IIC	> 4.0 mm + ulceration	Nil	Nil

continued on the next page ...

American Joint Committee on Cancer staging system for melanoma

Stage	Primary tumour (Breslow thickness)	Lymph node	Metastasis
IIIA	Any thickness, no ulceration	Nodal micrometastases	Nil
IIIB	Any thickness + ulceration	Nodal micrometastases	Nil
	Any thickness, no ulceration	≤ 3 palpable nodes	Nil
	Any thickness ± ulceration	No nodes but in-transit metastases or satellites	Nil
IIIC	Any thickness + ulceration	≤ 3 palpable nodes	Nil
	Any thickness ± ulceration	≥ 4 palpable nodes, matted nodes or nodes and in-transit metastases	Nil
IV:M1		Distant nodes	Skin or subcutaneous metastases
IV:M2			Lung metastasis
IV:M3			Other sites or metastasis at any site and raised LDH

Adapted from Balch et al, 2003

APPROACH TO THE EARLY DETECTION OF MELANOMA

- Educating people about early warning signs and self-examination
- Screening of selected high-risk individuals (family Hx. of melanoma)
- Training of Primary Health Care Workers
- Using ABCDEF rule / 7-point-checklist
- Setting up dedicated Pigmented Lesion Clinics (PLC)
- Primary prevention by educating people about risks of UV radiation is essential to reduce the chances of developing Melanoma
- When should you refer a patient ?
 1. When there is a high index of suspicion of MM
 2. When the lesion is large & complete excision would be disfiguring
 3. Patients with multiple AMN/ changing mole/ Family Hx. of MM

Characteristics of Familial Melanomas

- FAMMM Syndrome = Familial Atypical Multiple Mole Melanoma
- (many individuals with atypical moles and melanomas within a family)
- MM tend to occur at a younger age
- People are more likely to have multiple melanomas
- MM usually develop from precursor lesions (AMN)
- Other cancer types may be associated (pancreatic cancer)
- Familial Melanoma is the most important indicator of melanoma risk for an individual
- A positive family history of one MM increases the patient`s risk 10X

MANAGEMENT

- Use of Sunscreens → controversial (protective role vs. ↑ risk of MM)
- Use of Sunbeds + Sunlamps → same adverse effect on skin as solar UV rad.
- Avoid sun exposure between 11 AM → 15 hr. PM (children + adolescents)
- Planning out-door activities in the mornings/ evenings
- No prospective data exist regarding appropriate margins for melanomas thicker than 4mm (margins > 2cm have no effect on recurrence/survival)
- Surgical margins of 5mm → melanoma in situ
- Surgical margins of 1 cm for MM up to 2mm depth
- Intermediate –thickness tumors (1-4mm) → 2cm margins
- Wider margins may be necessary to achieve local control (head/neck, hands/feet melanomas)

MANAGEMENT—Ctd.

- Stage II B, IIC, III melanomas → surgical excision with 2cm margins + block dissection of the draining LN and IFN-alfa for 1yr. Post-surgery
- Stage III and Stage IV are suitable for Chemotherapy combined with Immunotherapy: Dacarbazine , Cisplatin or Texanes(Docetaxel)+ IFN
- Combination → Chemotherapy (CVD) + IFN + IL-2→ 40-69% response
- Intra arterial Chemotherapy (Melphalan)→ in transit metastases
- Vaccines are currently being investigated for therapeutic use in patients with Extracutaneous Melanoma(survival advantage with vaccines ?)

CUTANEOUS T-CELL LYMPHOMA (Mycosis Fungoides)

- Misnomer (coined by Alibert)
- Peripheral non-Hodgkin T-cell lymphoma
- Indolent course (develops slowly over many years)
- Unknown aetiology (controversies about HTLV-1, HIV, HHV-8, occupational exposure)
- Urban areas > rural areas
- Males > Females
- Age : Mid /late adulthood
- Blacks > Caucasians
- Gradual progression from patches – plaques - tumours

Mycosis Fungoides – Ctd.

- Clinical presentation : unusual forms of eczema / psoriasis (failure to Tx.)
- Predilection : photoprotected areas (trunk , thighs , buttocks)
- Very pruritic lesions
- Prognosis of early stage MF – variable
- Progression means skin involvement + extracutaneous involvement (LN , hepato-splenomegaly, bone marrow infiltration , peripheral blood atypical Lf. > 5%)
- Diagnosis : Skin biopsy + immunohist. stains
- Treatment : PUVA, Re-PUVA , topical steroids ,Bexaroten (patch stage)
Localised Radiotherapy / Electron beam radiation (plaque stage)
Chemotherapy (CHOP) – tumour stage

TNMB classification for CTCL

T—T₀ Nondiagnostic (eg. Parapsoriasis)

T₁ Limited patch/plaque (< 10% total skin surface)

T₂ Generalized patch/plaque (> 10% total skin surface)

T₃ Tumors

T₄ Erythroderma

N—N₀ Lymph nodes clinically uninvolved

N₁ Lymph nodes enlarged, histologically uninvolved

N₂ Lymph nodes clinically uninvolved, histologically involved

N₃ Lymph nodes enlarged and histologically involved

TNMB classification –Ctd.

M—M₀ No visceral involvement

M₁ Visceral involvement

B— B₀ Circulating atypical / Sezary cells < 5% of lymphocytes

B₁ Circulating atypical / Sezary cells > 5% of lymphocytes

Adverse prognostic factors:

- Age > 60 years
- Type and extension of skin involvement (tumor > plaque > patch)
- >5% Sezary cells or atypical lymphocytes in the peripheral blood
- Increased serum-LDH levels
- Palpable lymphadenopathy (poor prognostic sign : LN3 and LN4)
- Bone marrow involvement (occurs in the advanced stage of disease)
- Transformation into a large cell lymphoma

CUTANEOUS METASTASES

- Neoplastic lesion arising from another neoplasm with which is no longer in continuity
- Skin metastases are uncommon (1-2%)
- Portend a grave prognosis (survival 3-6 months)
- Mode of spread :
 - direct invasion , local metastases (contiguous extension) , distant metastases , accidental implantation during surgery
- Tend to occur near the site of the primary tumour
- Metastases may occur at radiation site , in surgical scars

METASTASES- Ctd.

- Differences in localisation + different patterns of cutaneous metas.
- Age : elderly people (50-70 years)
- Sex differences
- Growth pattern of skin metastases is unpredictable and may not reflect that of primary tumour
- May occur concurrently with metas. to the other organs or skin involvement may be the presenting finding
- Cutaneous metastases may simulate other cutaneous disorders
- High index of suspicion maintained :
 - non-healing ulcers
 - persistent indurated erythema
 - unexplained skin nodules