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Disorders of Melanocytes Melanoma

Nevus

Histopathology:

- Main cell is nevus cell
- These are large ovoid cells with vesiculated nuclei, and pale cytoplasm
- They are derived from neural crest cells

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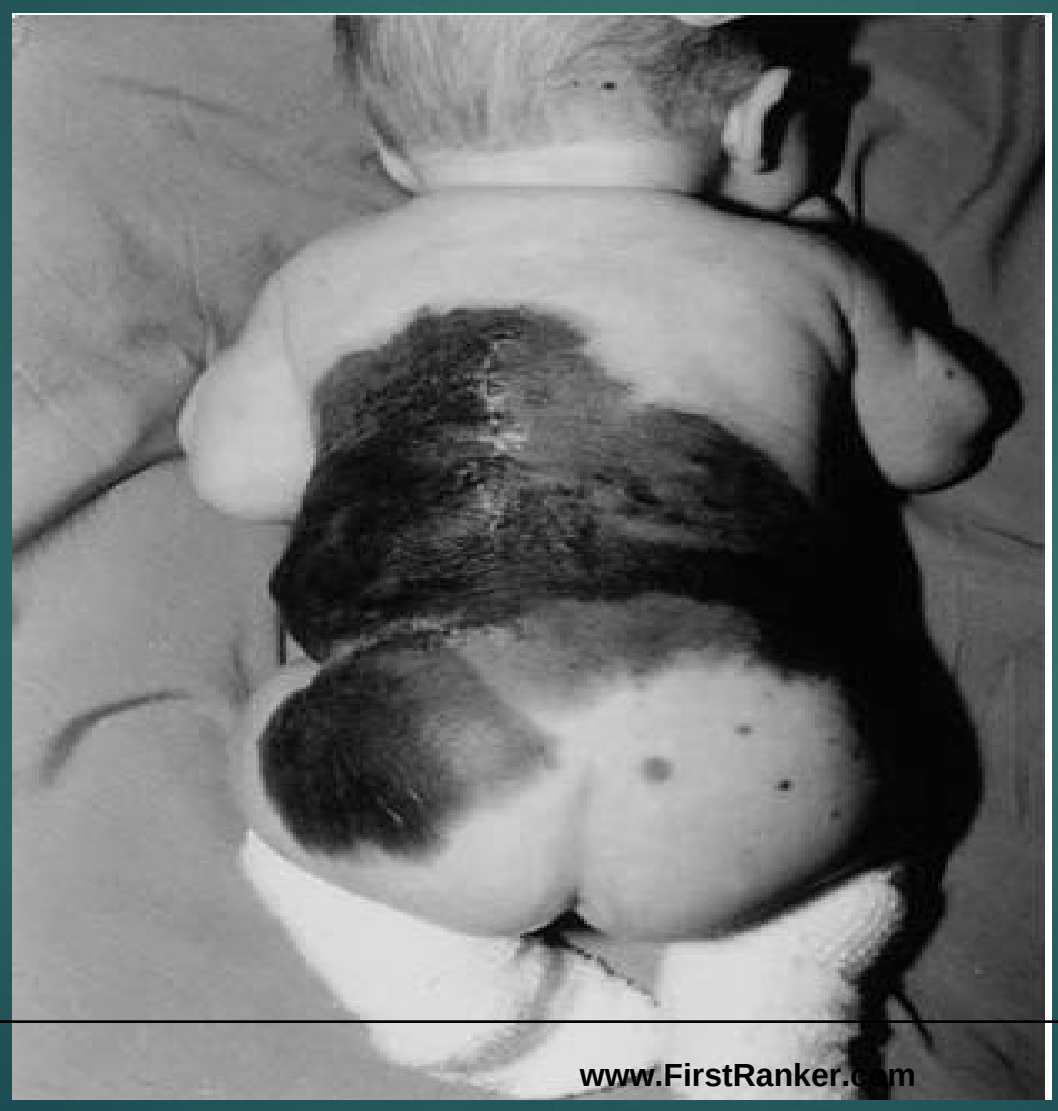
Congenital nevi

- Rarer , 1% of neonates
- larger and may contain hair
- Congenital giant lesions (giant hairy nevus) most often occur in a bathing trunk distribution or on the chest and back
- Develop malignant melanoma in 1 to 5% of the cases
- Excision of the nevus is the treatment of choice

Giant cell nevus



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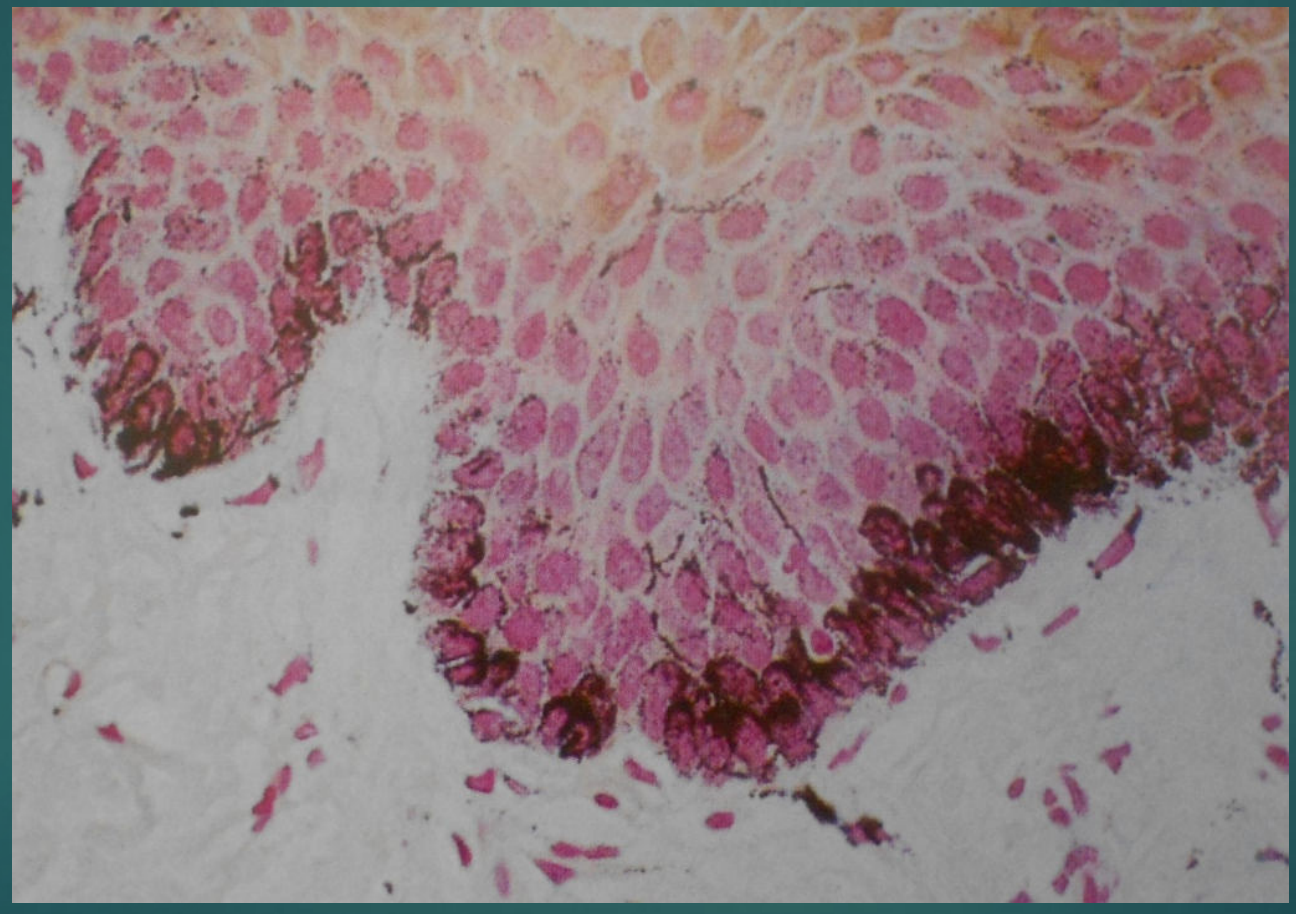
Acquired melanocytic nevi

- Classified as junctional, compound, or dermal, depending on the location of the nevus cells.
- Nevus cells accumulate in the epidermis (junctional), migrate partially into the dermis (compound), and finally rest completely in the dermis (dermal).
- Eventually most lesions undergo involution.

Melanocytes in Normal epithelium



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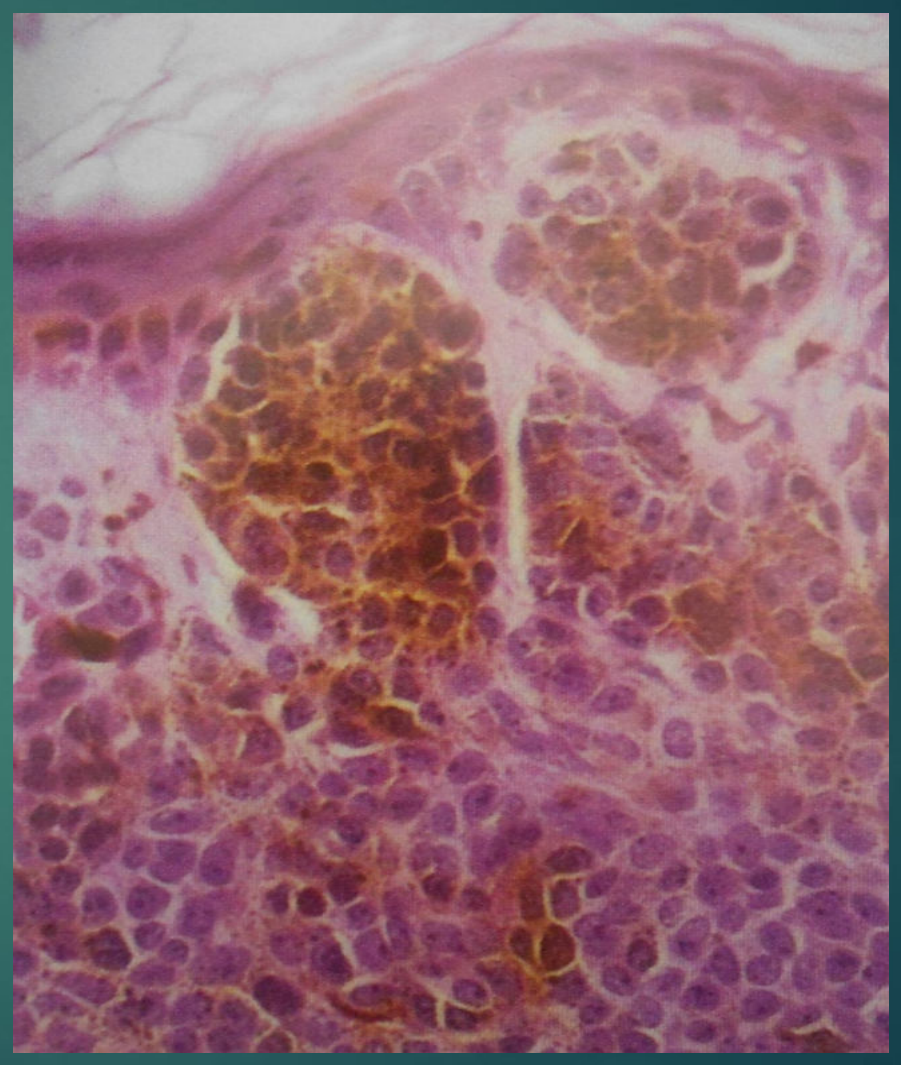
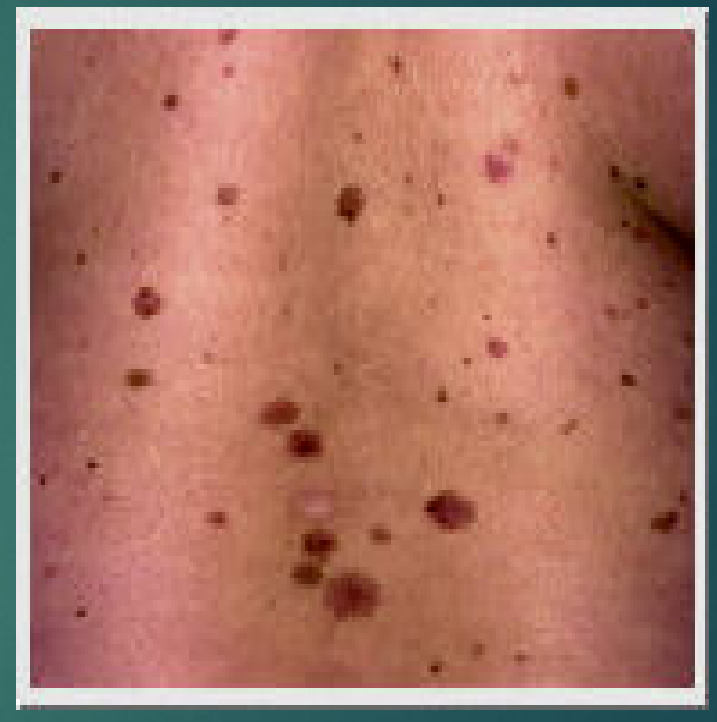
Compound Nevus

- Shows junctional activity & nests of nevus cells in connective tissue.



Dysplastic Nevus

- Multicolored
- Asymmetric pigment deposition
- Asymmetric contour-macular and papular
- Indistinct margins



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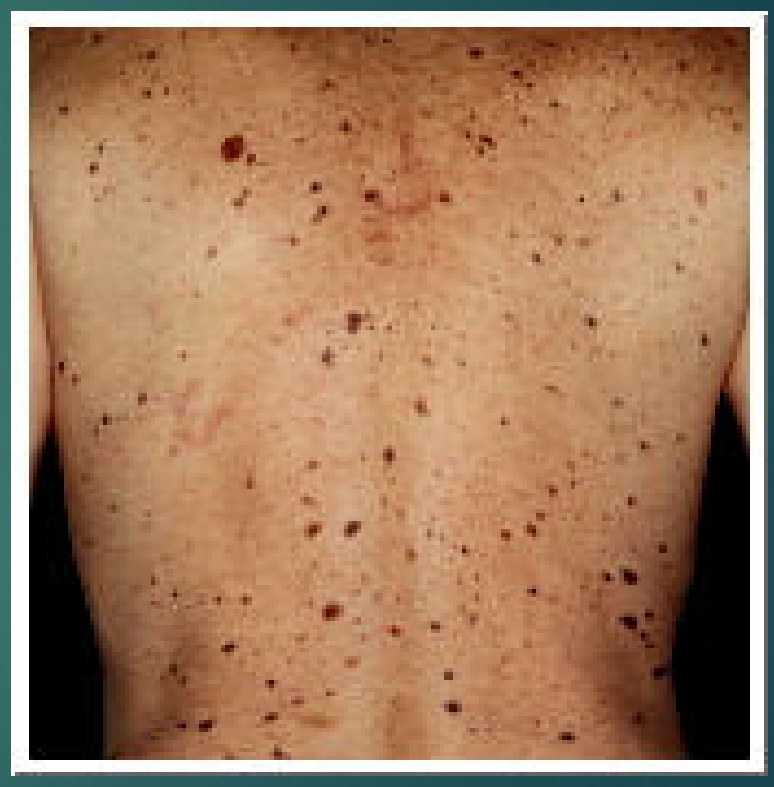
Atypical mole syndrome-(Dysplastic nevus syndrome)

- >100 melanocytic nevi
- 1 or more nevi >8mm in diameter
- 1 or more dysplastic nevi on exam



10 year risk of developing melanoma of 14%

Management

- Close monitoring- full body exams every 6 months
- Dermoscopy of all atypical appearing nevi
  - The magnified visualization of pigmented skin lesions beyond what would be visible by the physician
  - Increases diagnostic accuracy by 10-20%
- Excision of any changing or markedly atypical nevi

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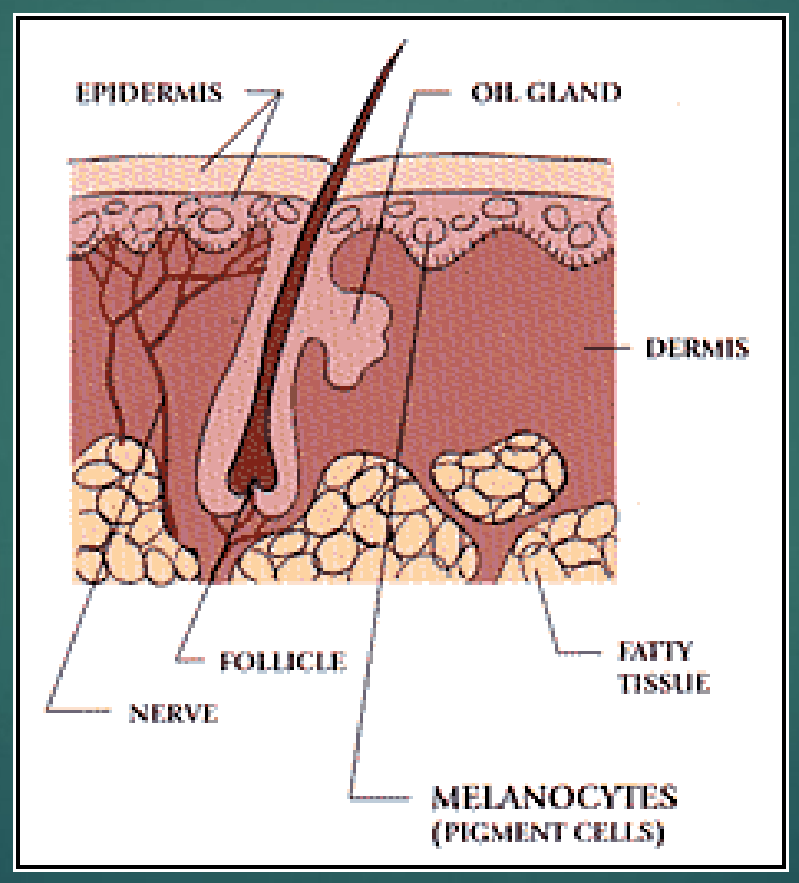
Melanoma



Melanoma: Pathogenesis

- Cell of origin: **melanocyte**
- Etiology:
  - Cumulative and prolonged **UVB and/or UVA exposure**
  - UVA exposure from tanning beds increases risk for melanoma

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Risk Factors

- **Individual risk factors** for development of melanoma
  - Increasing age
  - Fair skin; blue eyes, red or blond hair; freckling
  - Greater than 100 acquired nevi
  - Atypical nevi
  - Immunosuppression
  - Personal or family history of melanoma (two or more 1st degree relatives)
  - Ultraviolet exposure: Risk directly related to # of severe blistering sunburns before puberty; tanning booth use
  - Genetic syndromes

Heredity of Melanoma

- 10 % of melanomas are familial and have a genetic basis
- The genes CDKN2A and CDK4 together make up 50% of all inherited familial cases
- Other identified genes include p53, BRCA2
- 50% of familial melanoma patients have no identified mutation – i.e., their genes have not been identified yet

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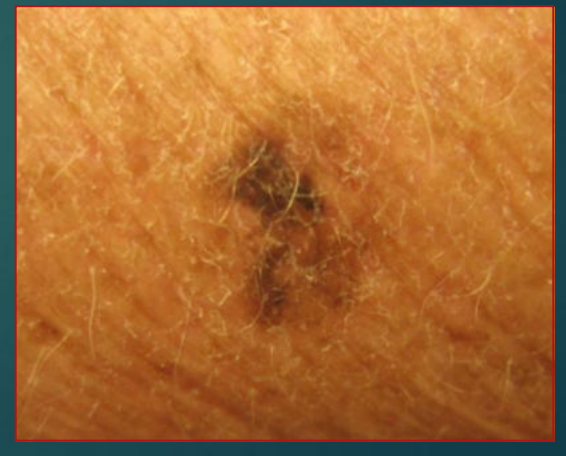
Clinical Manifestations

- May cause symptoms, but usually asymptomatic
- May develop *de novo* or arise within a pre-existing nevus
- Majority located in sun-exposed areas, but also occur in non-sun-exposed areas, such as the buttock
  - Also occur on mucous membranes (mouth, genitalia)

- Typically appears as a pigmented papule, plaque or nodule.
- Demonstrates any of the ABCDEs
  - It may bleed, be eroded or crusted
  - Patients may give history of change

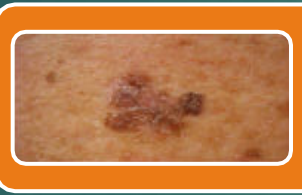


The ABCDEs of Melanoma

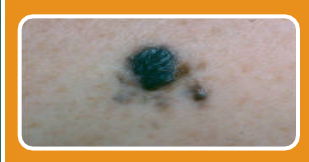
Suspicious moles may have any of the following features:

No Image

ASYMMETRY
- With regard to shape or color

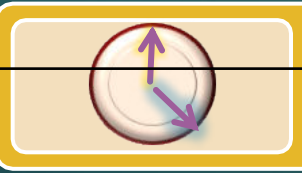


BORDER
- Irregular or notched



COLOR
- Very dark or variegated colors
- Blue, Black, Brown, Red, Pink, White

DIAMETER
- >6 mm, or “larger than a pencil eraser”
- Diameter that is rapidly changing



EVOLVING
- Evolution or change in any of the ABCD features

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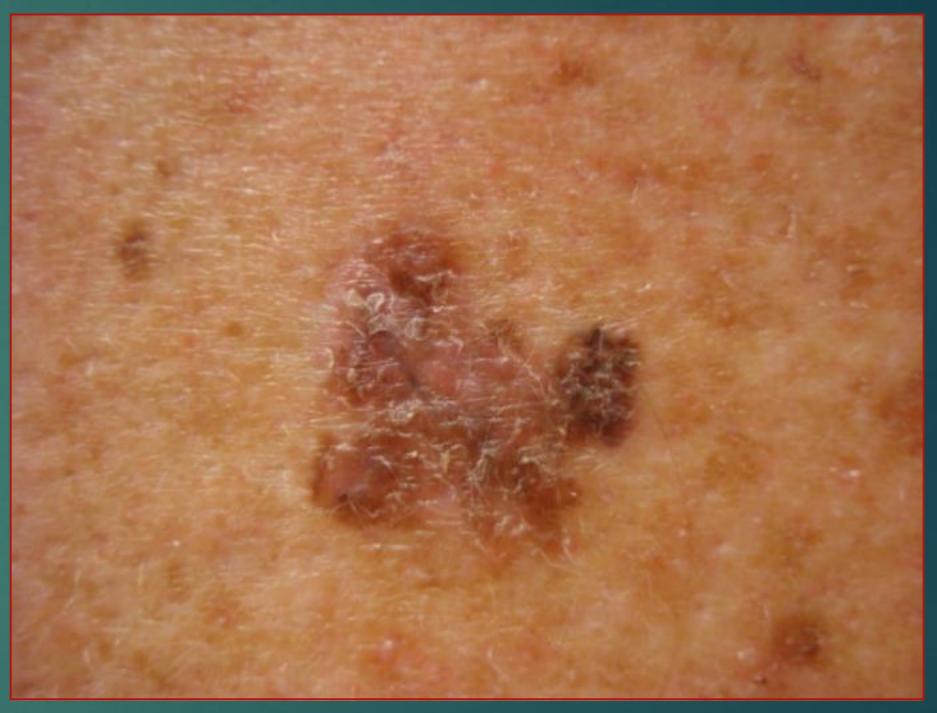
Superficial Spreading

17

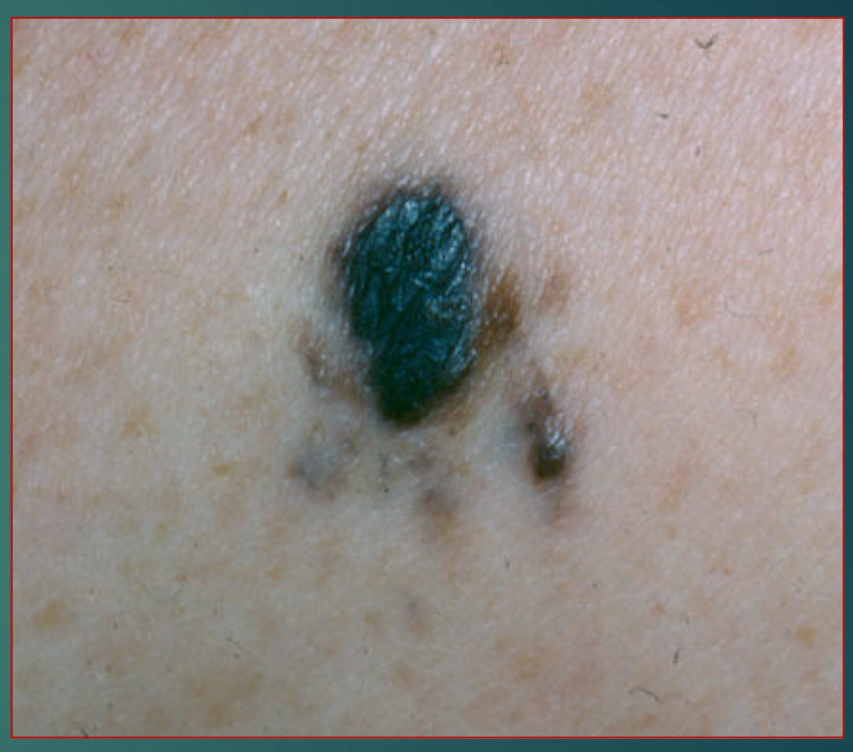
- **Superficial spreading type**
  - Most common type
  - Involves back in men; back and legs in women
  - Growth of tumor is primarily horizontal rather than down into the dermis



Nodular

18

- **Nodular type**
  - Rapid growth
  - Growth is vertical, giving tumor an increased Breslow's depth
  - **Breslow's depth** = thickness of the primary melanoma measured from the granular layer of the epidermis to the deepest part of the tumor



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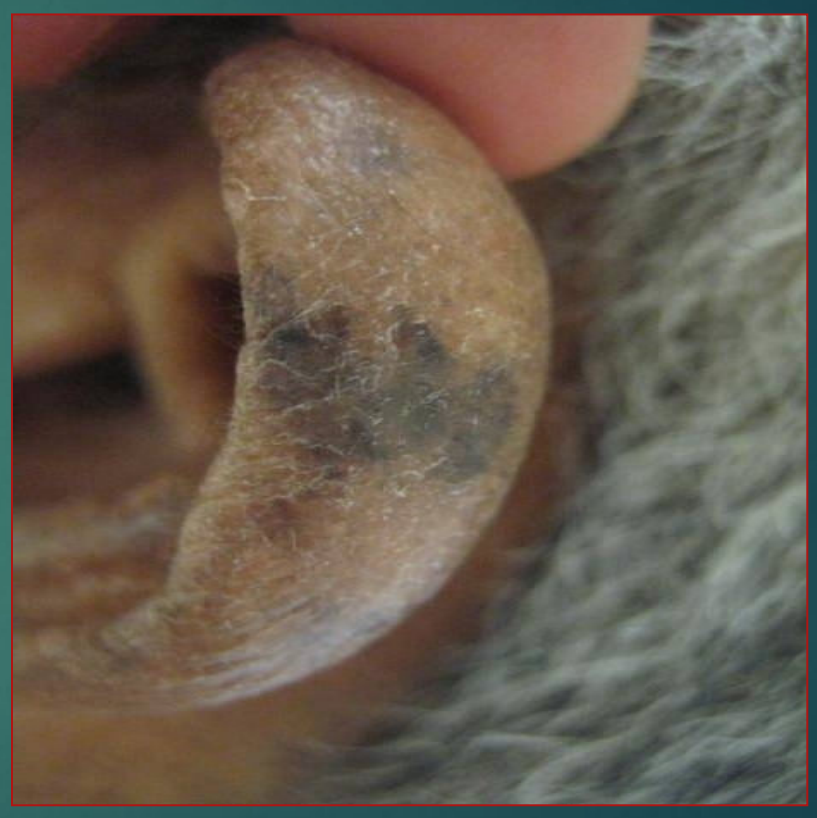
Lentigo Maligna

19

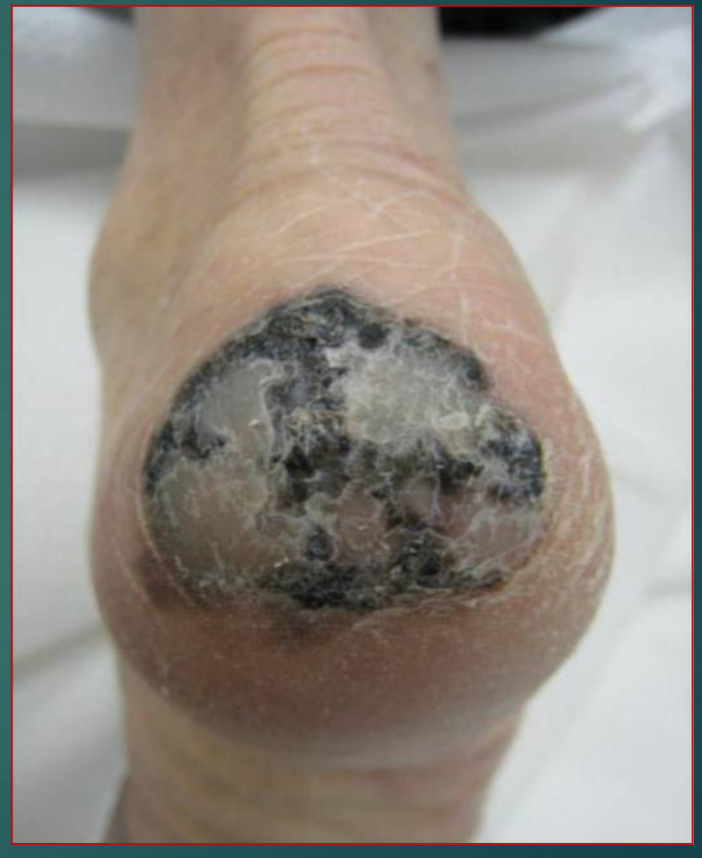
- **Lentigo maligna type**
  - Occurs on chronically sun-damaged skin, more common in elderly patients
  - Slow progression
  - Growth of tumor is primarily horizontal, and not vertical



Acral Lentiginous

20

- **Acral lentiginous type**
  - More common in people with darker skin color (Asians and persons of African ancestry)
  - Diagnosis is often delayed, so lesions tend to be many centimeters in diameter



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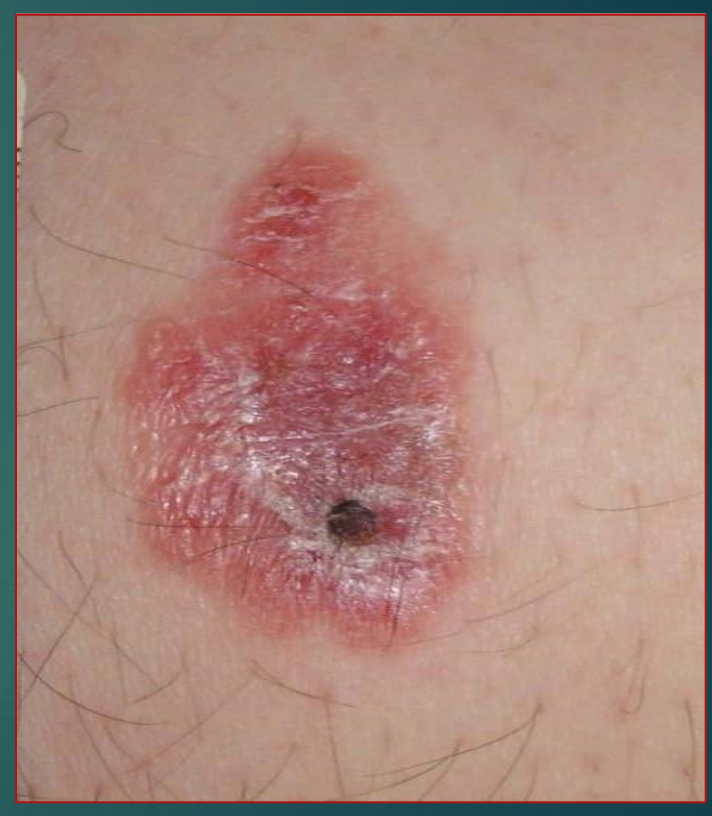
Amelanotic

- **Amelanotic type**
  - Morphologic appearance is variable, and the clinical appearance of pigment is subtle or often absent
  - As such, the lesion may be confused with a variety of benign lesions, such as psoriasis or dermatitis
  - This lesion may also be confused with a variety of malignant lesions, such as squamous cell carcinoma in situ or basal cell carcinoma
  - This is a difficult diagnosis to make, which is why it is important to biopsy when unsure of the diagnosis



Diagnosis

Biopsy

- Excision (Golden standard)
- *İncision biopsy
- *Punch biopsy
- Partial thickness or shaving biopsies are contraindicated

*All dermis layers should be removed

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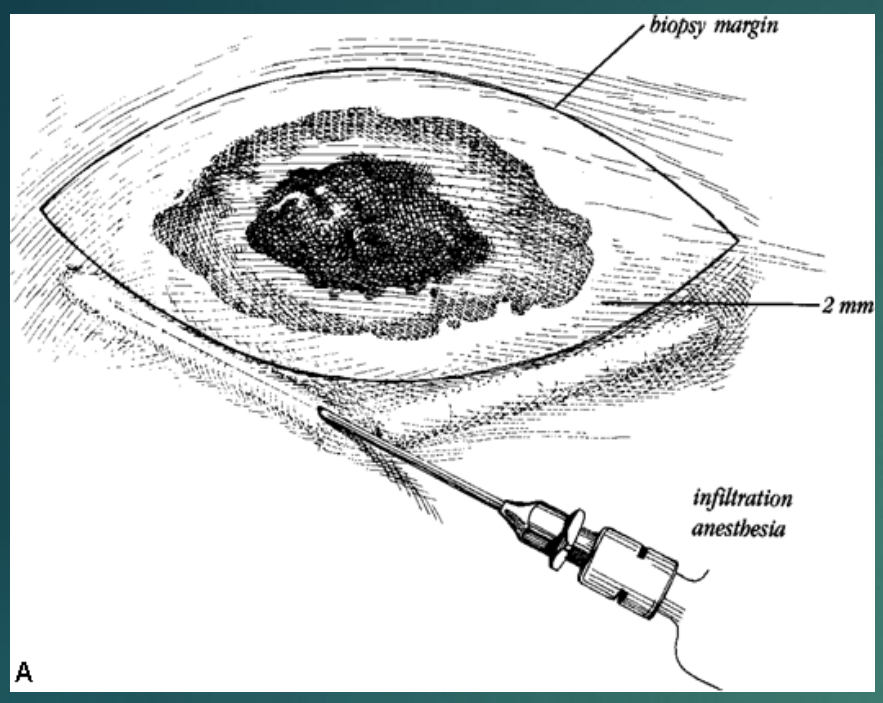

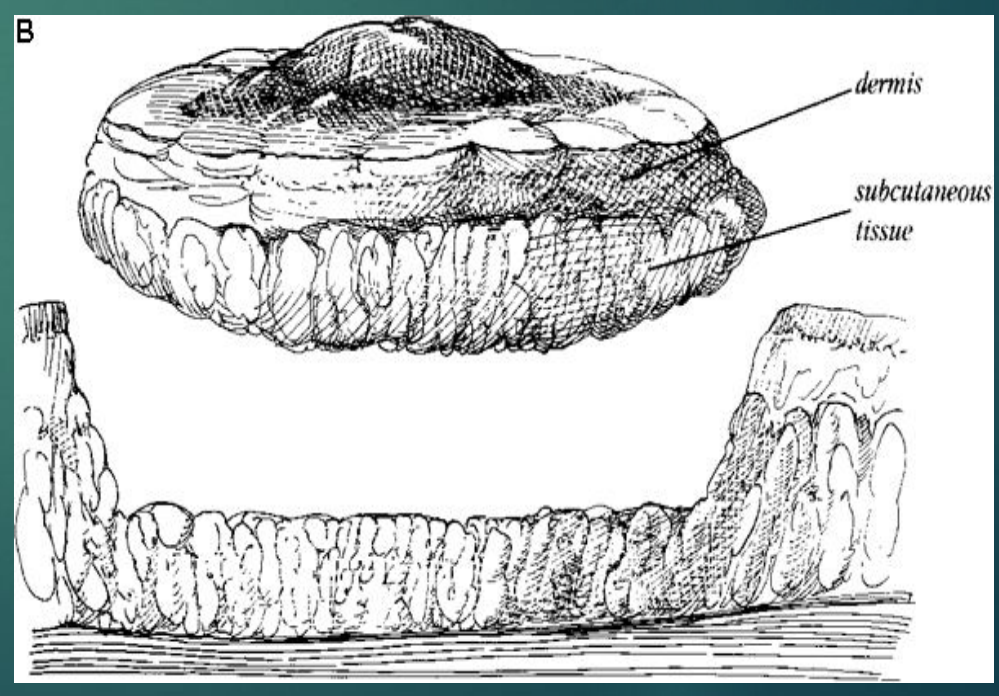

Balch CM, Houghton AN, Sober AJ, Soong S. Cutaneous Melanoma. St Louis QMP 1998

Staging (AJCC 7th Edition)

TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
T1	Melanomas 1.0 mm or less in thickness
T2	Melanomas 1.01–2.0 mm
T3	Melanomas 2.01–4.0 mm
T4	Melanomas more than 4.0 mm

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2–3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/ satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* meta-static node(s)	

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Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Clark Classification

Level I — the atypical melanocytes are confined to the epidermis (in situ melanoma);

Level II — the atypical melanocytes have extended into the papillary dermis but have not reached the reticular dermis;

Level III — the atypical melanocytes have penetrated to the interface between the papillary dermis and the reticular dermis but do not extend into the reticular dermis;

Level IV — the atypical melanocytes have extended into the reticular dermis;

Level V — the atypical melanocytes have reached into the subcutaneous fat.

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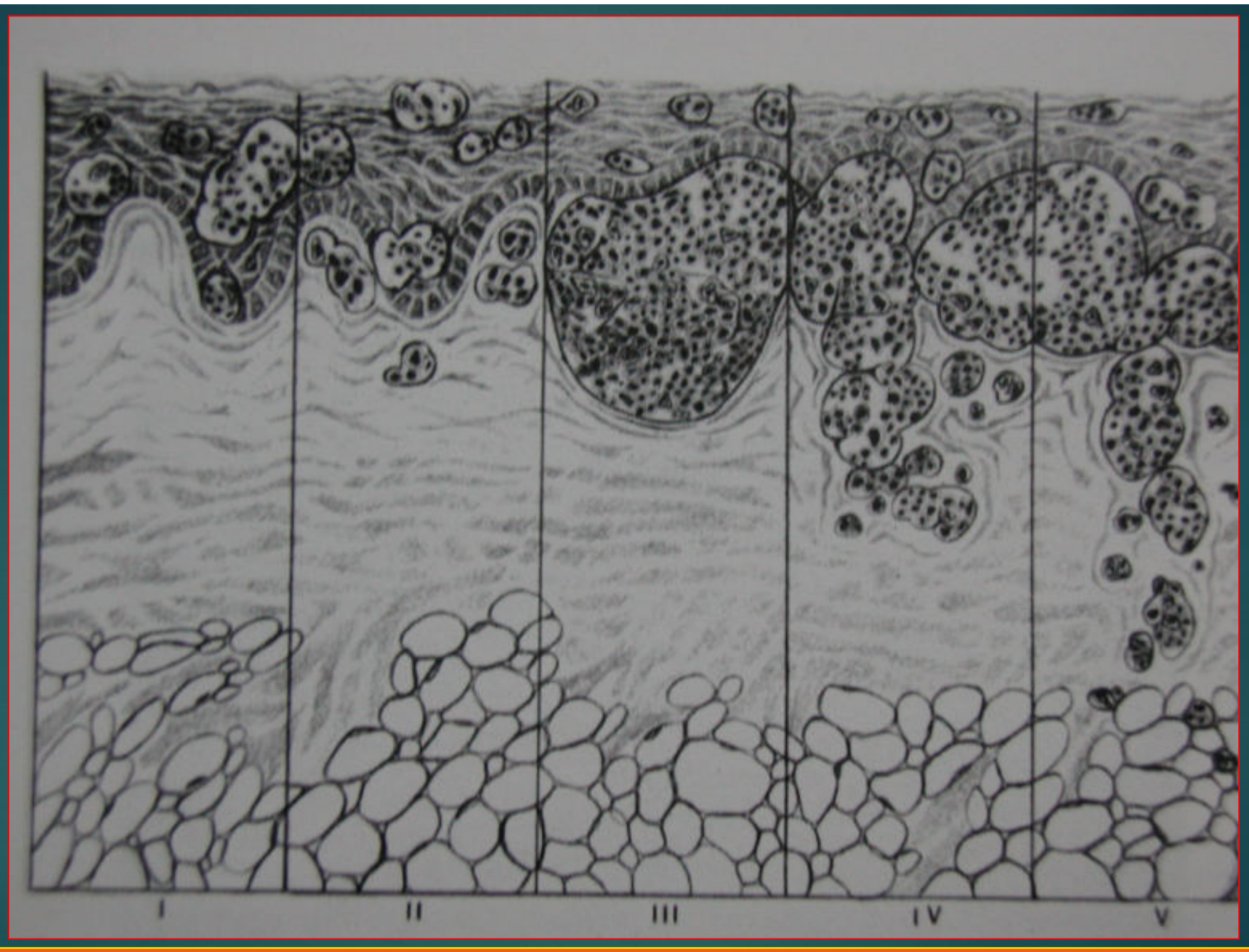

The histopathologic classification of the Melanoma by **Clark**

Breslow Classification

- Level 1: less than 0.76 mm thick
- Level 2: between 0.76– 1.50 mm
- Level 3: between 1.50 - 4.00 mm
- Level 4: exceed 4.00 mm in thickness

According to the thickness of the lesion as measured by an ocular micrometer from the top of the granular zone of the epidermis to the base of the neoplasm

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Prognostic Factors

- Breslow thickness (most important)
- Clark invasion level
- Ulceration
- Age, sex, location
- Size and surgical margins
- Others (Mitotic index, growth phase, regression...)

Surgical Treatment

- Biopsy
- Wide Local Excision
- Staging with Sentinel Lymph Node biopsy
- Therapeutic Lymph Node Dissection
- Treatment of Distant Metastasis

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Wide Surgical Excision

- Suggested surgical margins:

  (according to breslow thickness)

  - In-situ MM: 0.5-1 cm
  - Breslow thickness < 1mm : 1 cm
  - Breslow thickness 1-4 mm: 2 cm
  - Breslow thickness >4 mm: > 3 cm

Sentinel Lymphadenectomy

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Sentinel Lymphadenectomy

- Sentinel lymph node shows the regional node status
- If sentinel lymph node negative, others lymph nodes in the basin are also negative
- If sentinel lymph node contains tumor cells, It means disease spread to the regional nodal basin

Sentinel Lymphadenectomy

- Sentinel node negative
  - no additional treatment, follow the patient
- Sentinel lymph node positive
  - Therapeutic lymph node dissection

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Advantages of Sentinel Lymphadenectomy

- Provides staging
- Prevention of Elective Lymph node dissection morbidity

Sites of Distant Metastasis

- Skin
- Subcutaneous Tissue
- Distant Lymph Nodes
- Pulmonary
- Liver
- Brain
- Bone
- Intestine

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Chemotherapeutic agents

- Melphalan
- Interferon
- Interleukin-2
- Dacarbazine

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