Skin Cancer

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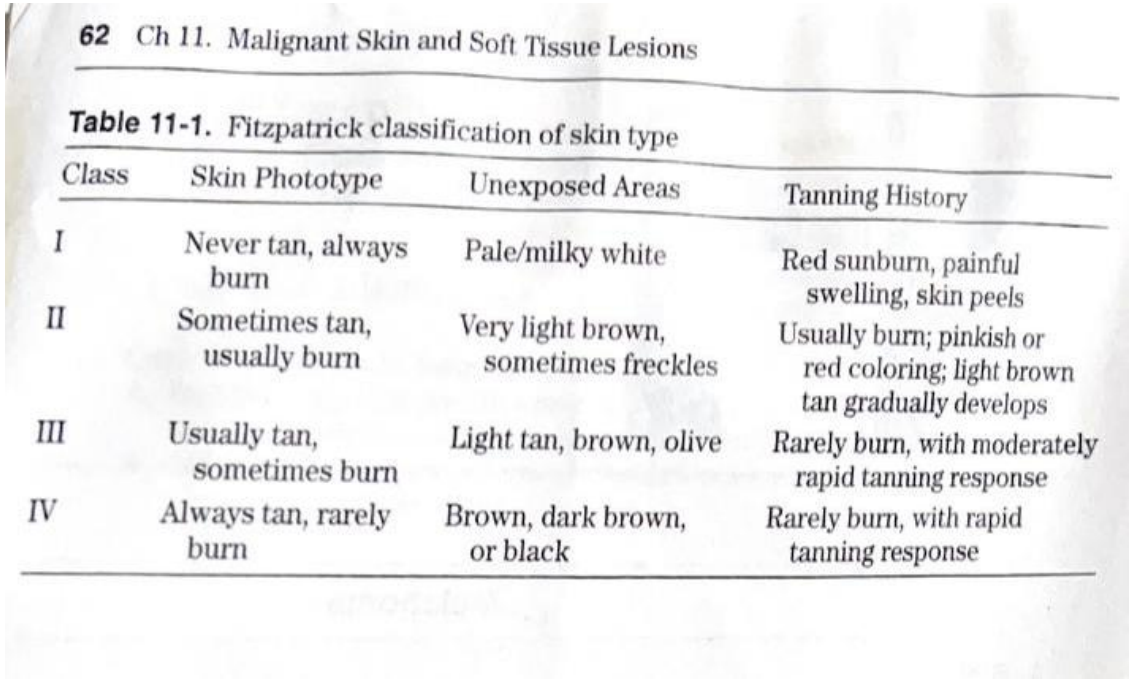
Table of content

Melanoma

Biology

A. Epidemiology

1. Eighth most common cancer diagnosis in the United States
2. Incidence is increasing faster than any other cancer.
3. 40,000 new cases are diagnosed per year in the United States.
4. Lifetime risk in general population is 0.5%.



62 Ch 11. Malignant Skin and Soft Tissue Lesions

Table 11-1. Fitzpatrick classification of skin type

Class	Skin Phototype	Unexposed Areas	Tanning History
I	Never tan, always burn	Pale/milky white	Red sunburn, painful swelling, skin peels
II	Sometimes tan, usually burn	Very light brown, sometimes freckles	Usually burn; pinkish or red coloring; light brown tan gradually develops
III	Usually tan, sometimes burn	Light tan, brown, olive	Rarely burn, with moderately rapid tanning response
IV	Always tan, rarely burn	Brown, dark brown, or black	Rarely burn, with rapid tanning response

Melanoma

B. Demographic risk factors

1. Phenotypic risk factors include fair skin (Fitzpatrick I and I) (Table 11-1),freckling, light eye color, and light hair color (stronger risk factor than eye color). Darker skin is protective against melanoma
2. Geographic risk factors: High altitude and higher latitude. Extreme southern latitudes (Australia, New Zealand) experience additional ultraviolet (UV) exposure from ozone depletion

Table 11-2. Distribution of melanomas with respect to gender

Location	Men (%)	Women (%)
Scalp	7	3
Face	12	9
Neck	5	3
Arm	13	19
Front of trunk	16	8
Back of trunk	**36**	23
Leg	9	**31**
Sole of foot	2	4

Melanoma

B. Demographic risk factors

3.Gender: Females have lower risk and better prognosis; the lower extremity is the most common site in females (Table 11-2). Males more commonly have lesions on the head and trunk.

Melanoma

B. Demographic risk factors

4. Prognosis is worse for African Americans (acral lentiginous type leads to delayed diagnosis)

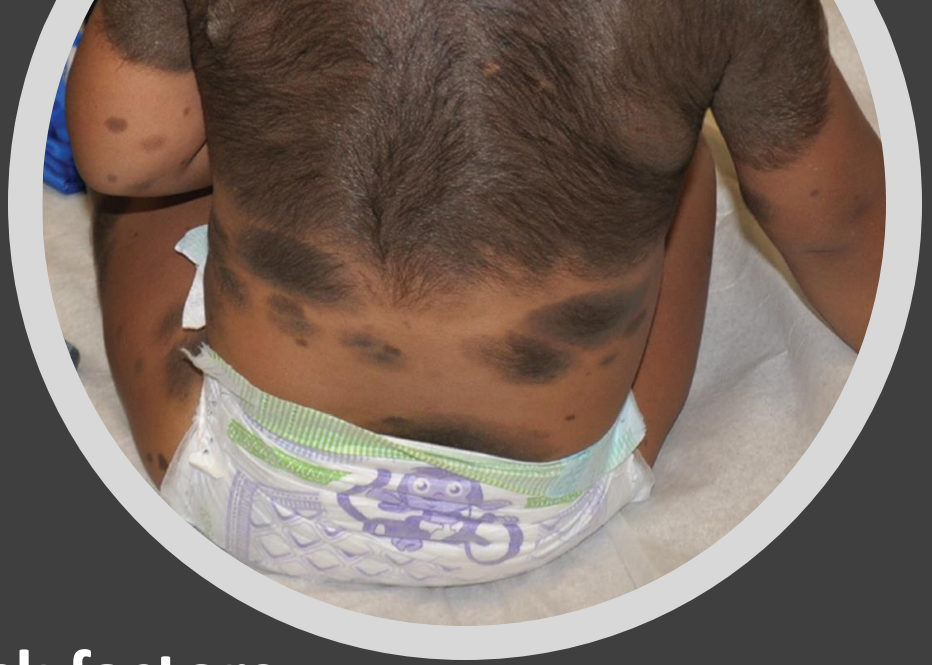
5. Higher socioeconomic status is associated with higher risk

6. History of ultraviolet radiation exposure (both UVA and UVB), especially a history of blistering sunburns, sunburns in early life, and intermittent exposure to UV light.

Melanoma

C. Precursor lesion risk factors

1. **Melanoma is caused by multiple processes** leading to malignant trans-formation of melanocytes.
2. **A previous melanoma confers a 3% to 5% chance** of developing a second melanoma



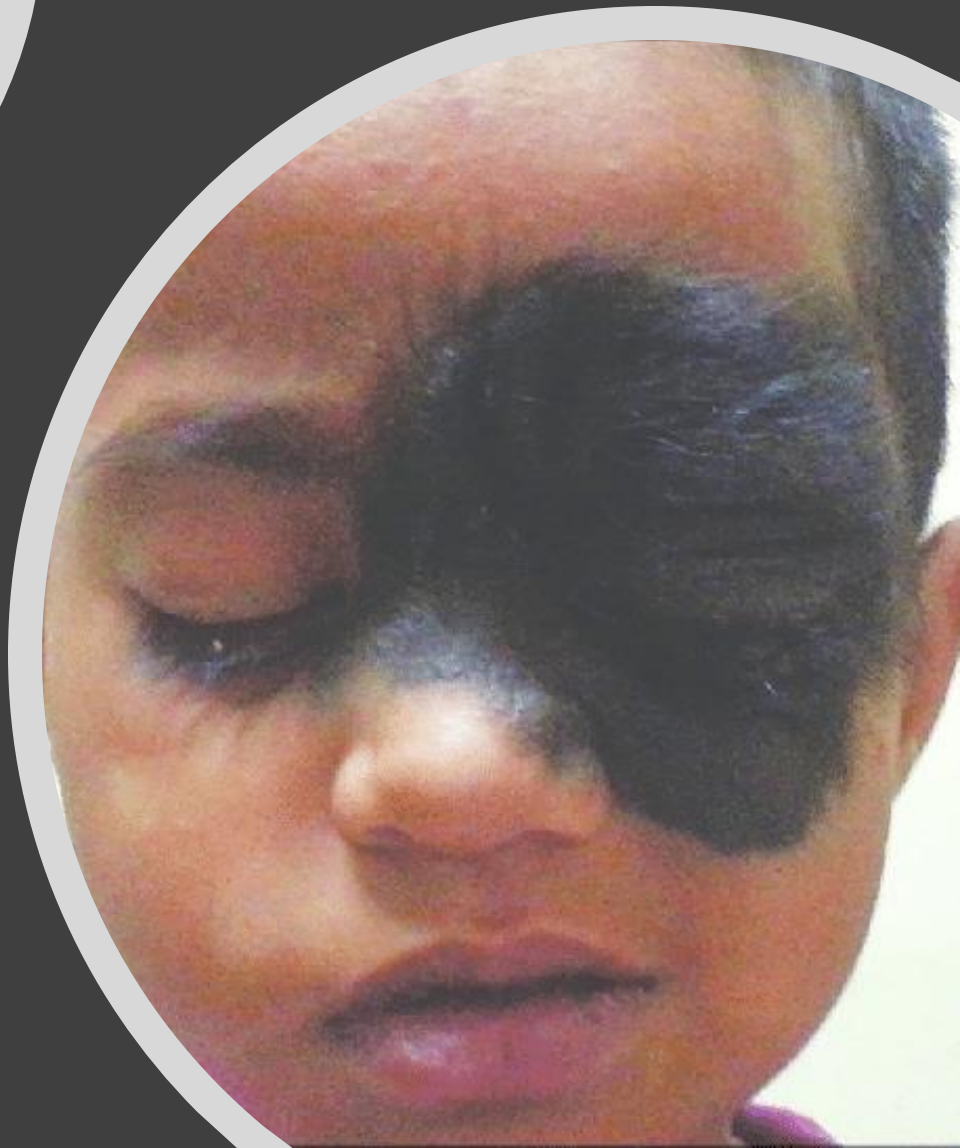
Melanoma

C. Precursor lesion risk factors

3. Congenital nevia.

a. Malignant potential is more dependent on histology than size.

b. Giant hairy nevi confer a 5% to 20% lifetime risk of melanoma; most commonly occur on head or pelvic region; prophylactic excision is recommended.



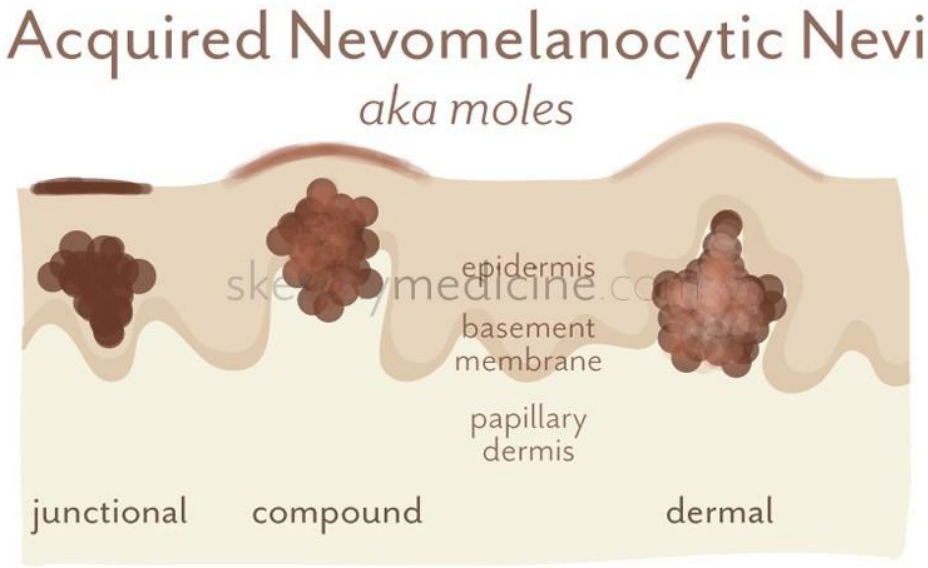
Melanoma

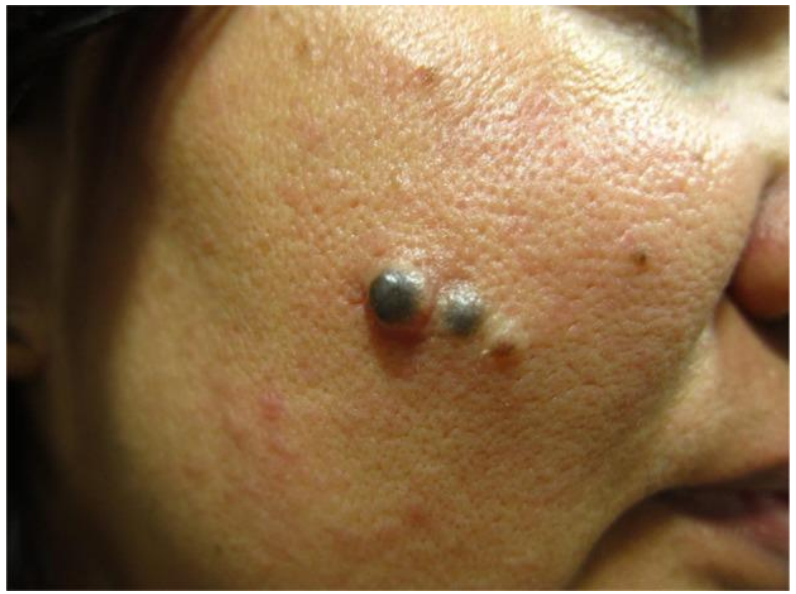
4. Acquired melanocytic nevia.

a. Typically appear at 6 to 12 months of age; usually smaller than 5 mm.

b. Increase in number through the fourth decade then slowly regress.

c. The greater the number of nevi (>50), the greater the chance of melanoma.





Melanoma

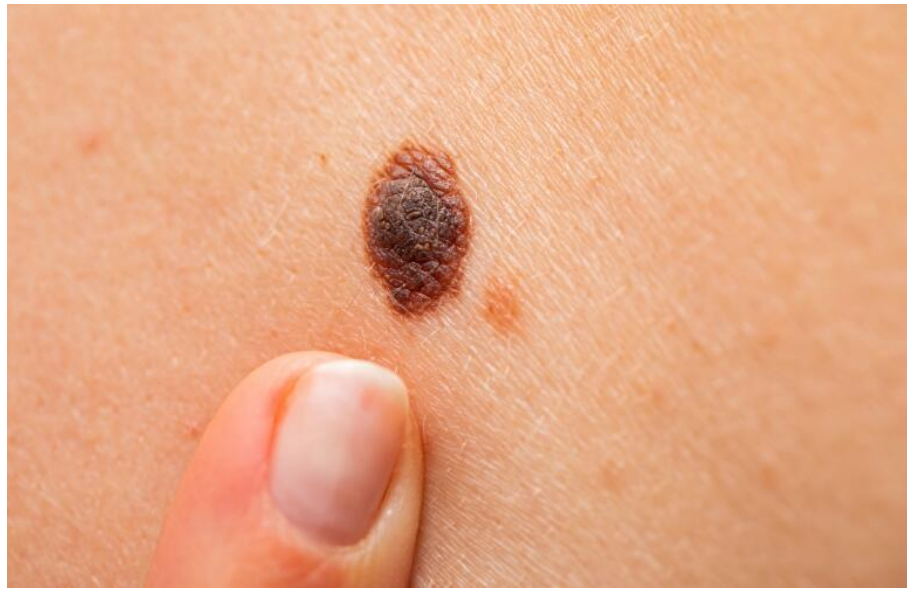
5. Dysplastic or atypical nevia.

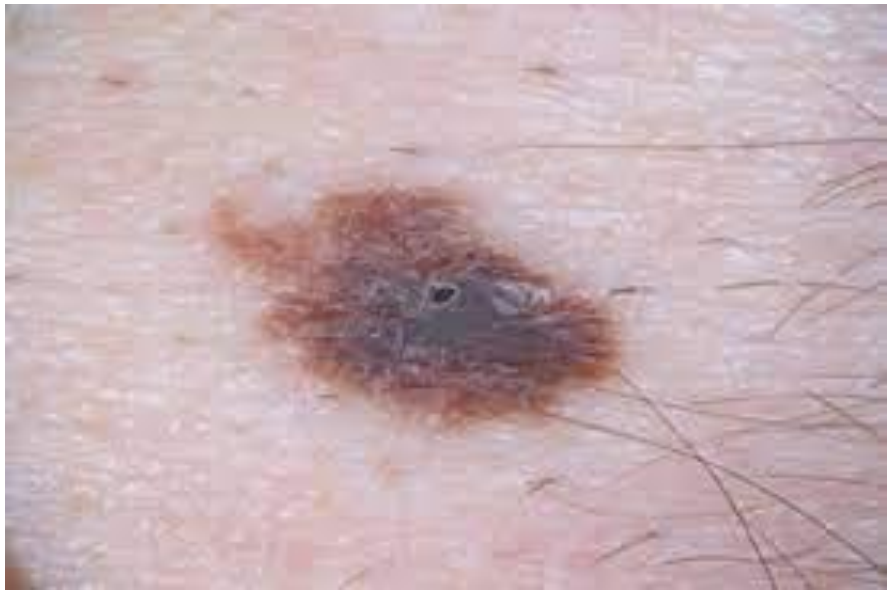
a. Appear near puberty.

b. Larger than common nevi (5-12 mm).

c. Commonly found in covered areas.

d. Most likely represent both a precursor lesion and a marker for patients with increased risk for development of melanoma.





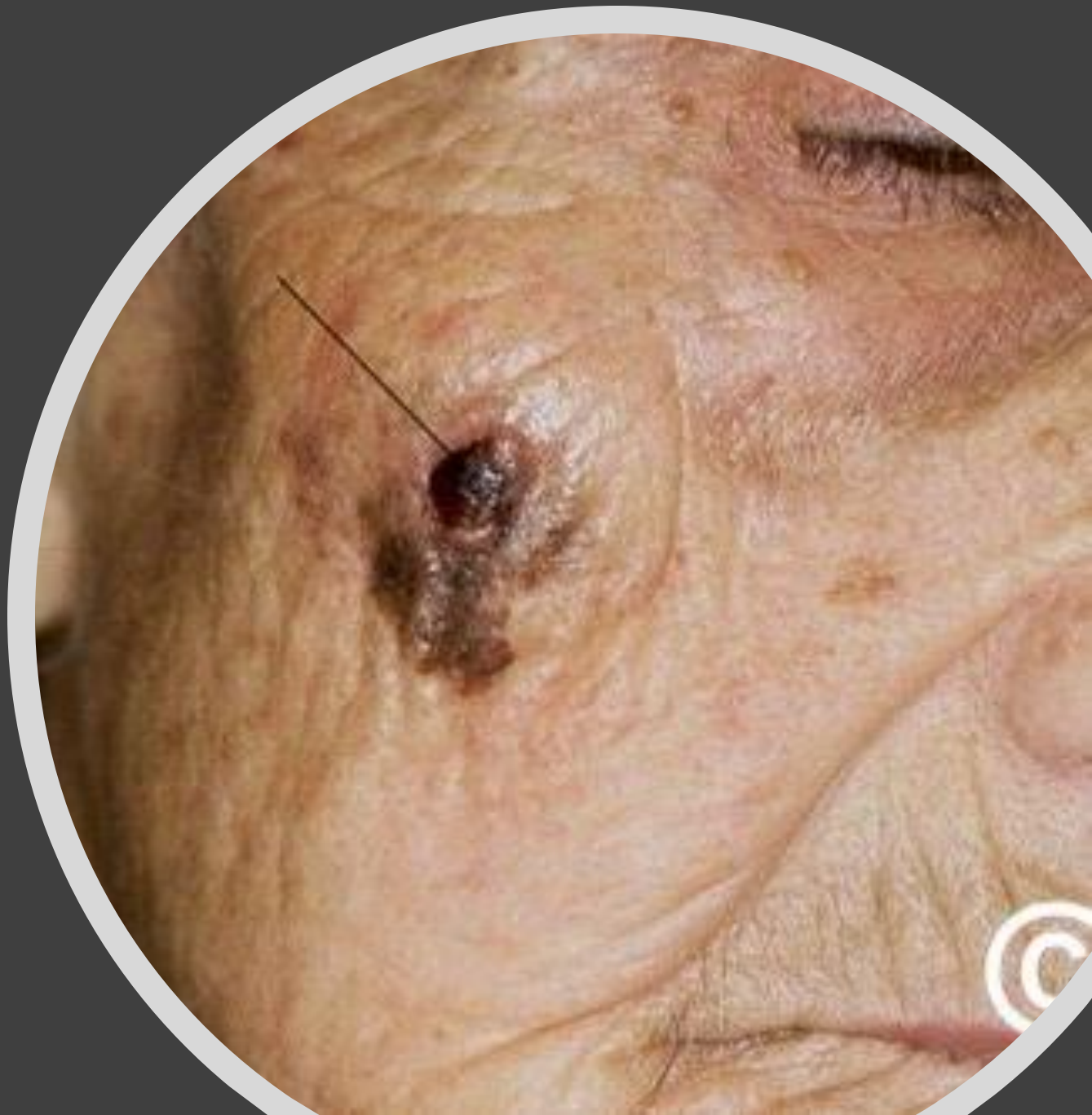
Melanoma

6. **A typical junctional melanocytic hyperplasia (AJMHi)** (also known as lentigo maligna, or Hutchinson freckle)

a. Thought to represent a melanoma precursor lesion.

b. Can be present in dysplastic nevi that tend to be more irregular and lighter in color.

c. Needs to be fully excised; 5-mm margins are recommended, but are typically inadequate.



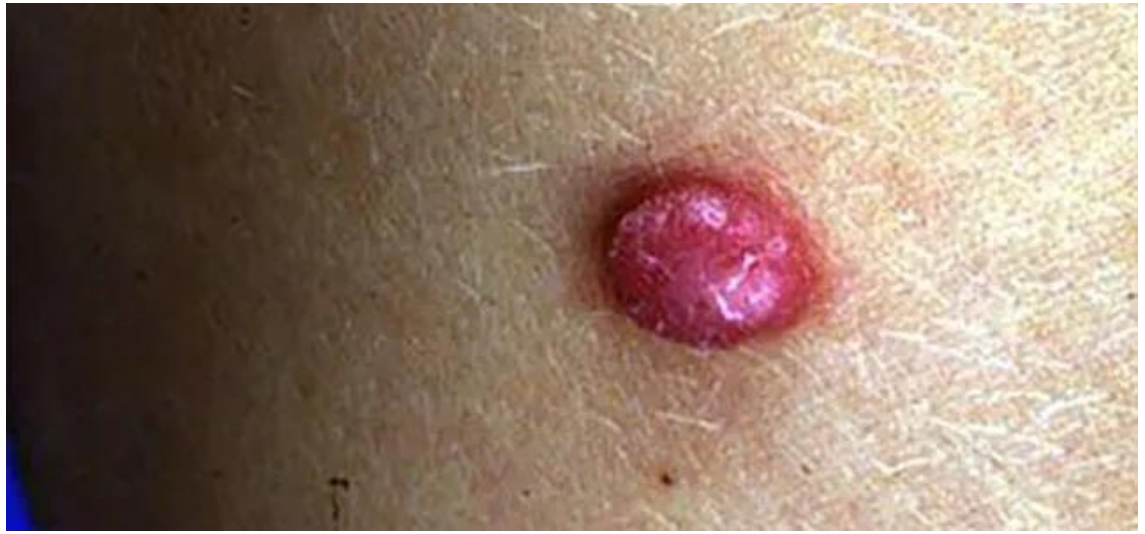
Melanoma

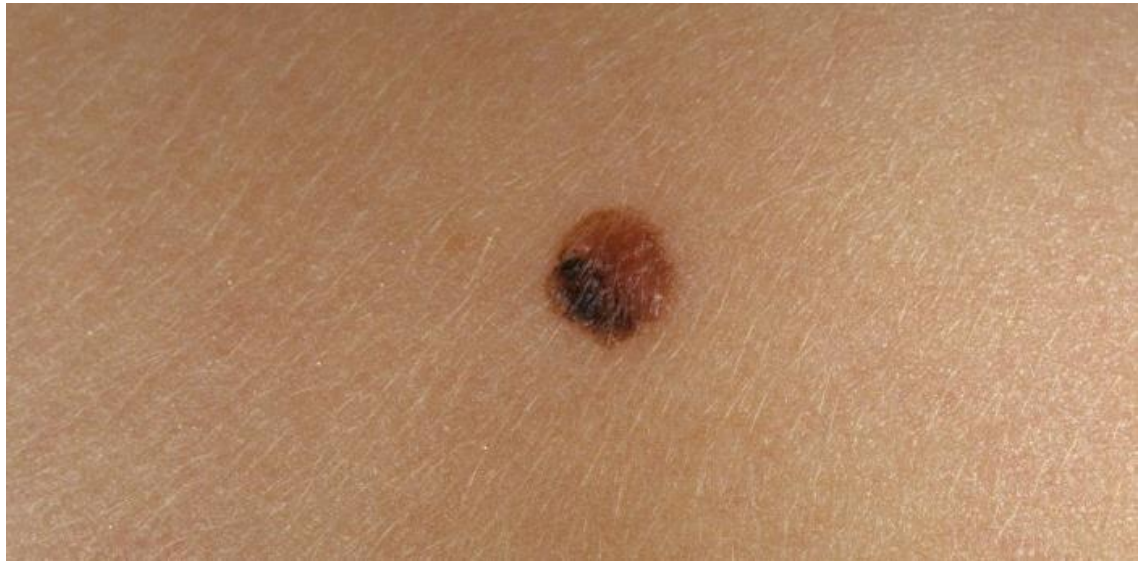
7. **Spitz nevusa.**

a. Most commonly found in children and young adults (formerly called juvenile melanoma).

b. Easily confused with melanoma, and almost always benign.

c. Well circumscribed and raised, with variable pigmentation.





Melanoma

D. Genetic risk factors

1. Family history: Two or more cases of melanoma in first-degree relatives. Hereditary melanoma shows autosomal dominant transference with variable penetrance.
2. Suppressor genes and oncogenes.

a. p16/CDKN2A: Tumor suppressor gene that is mutated or deleted in the majority of melanoma cell lines.

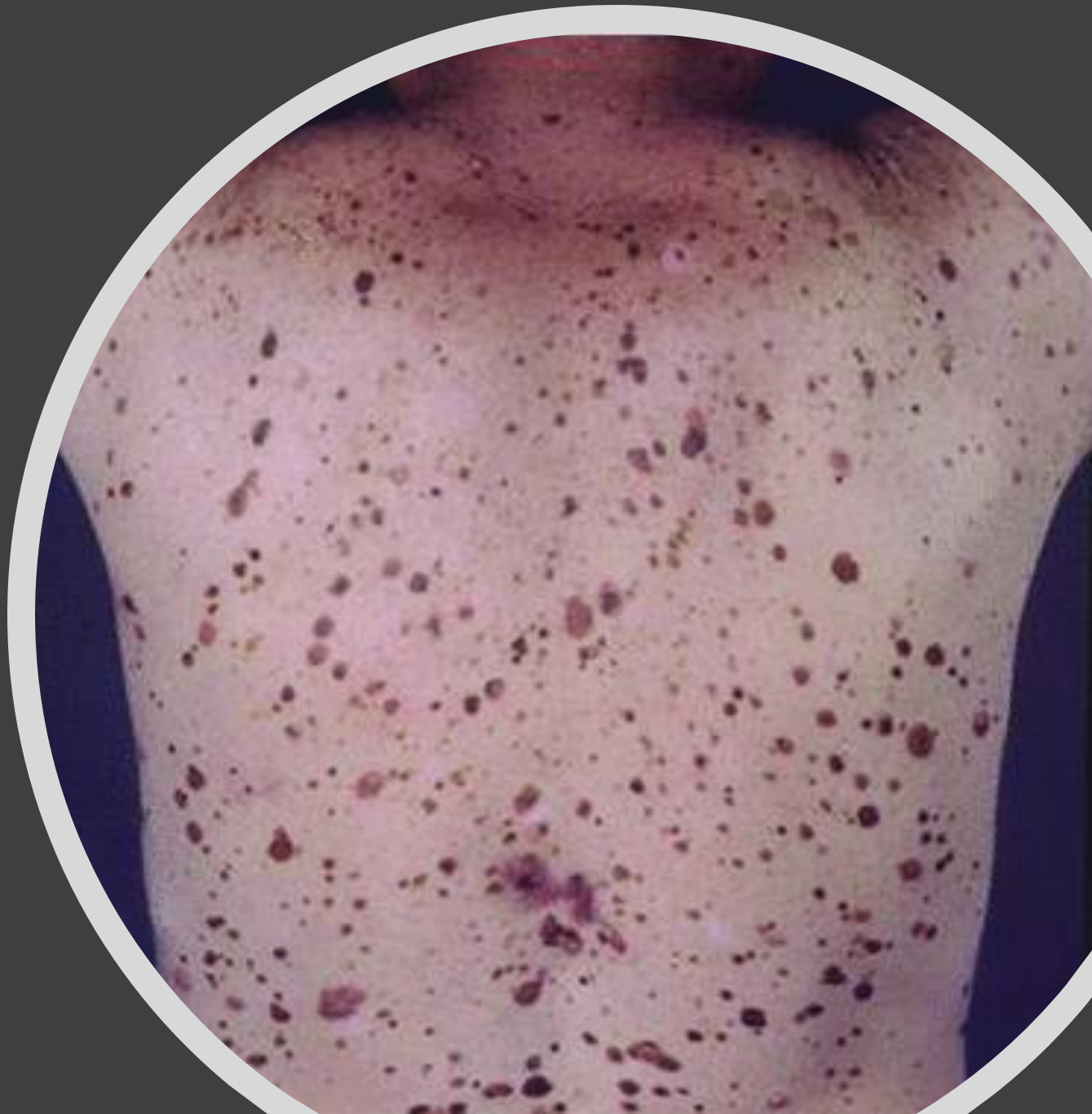
b. RB1: Tumor suppressor gene expressed in higher levels in certain melanomas. Uncommon mechanism in melanoma development.

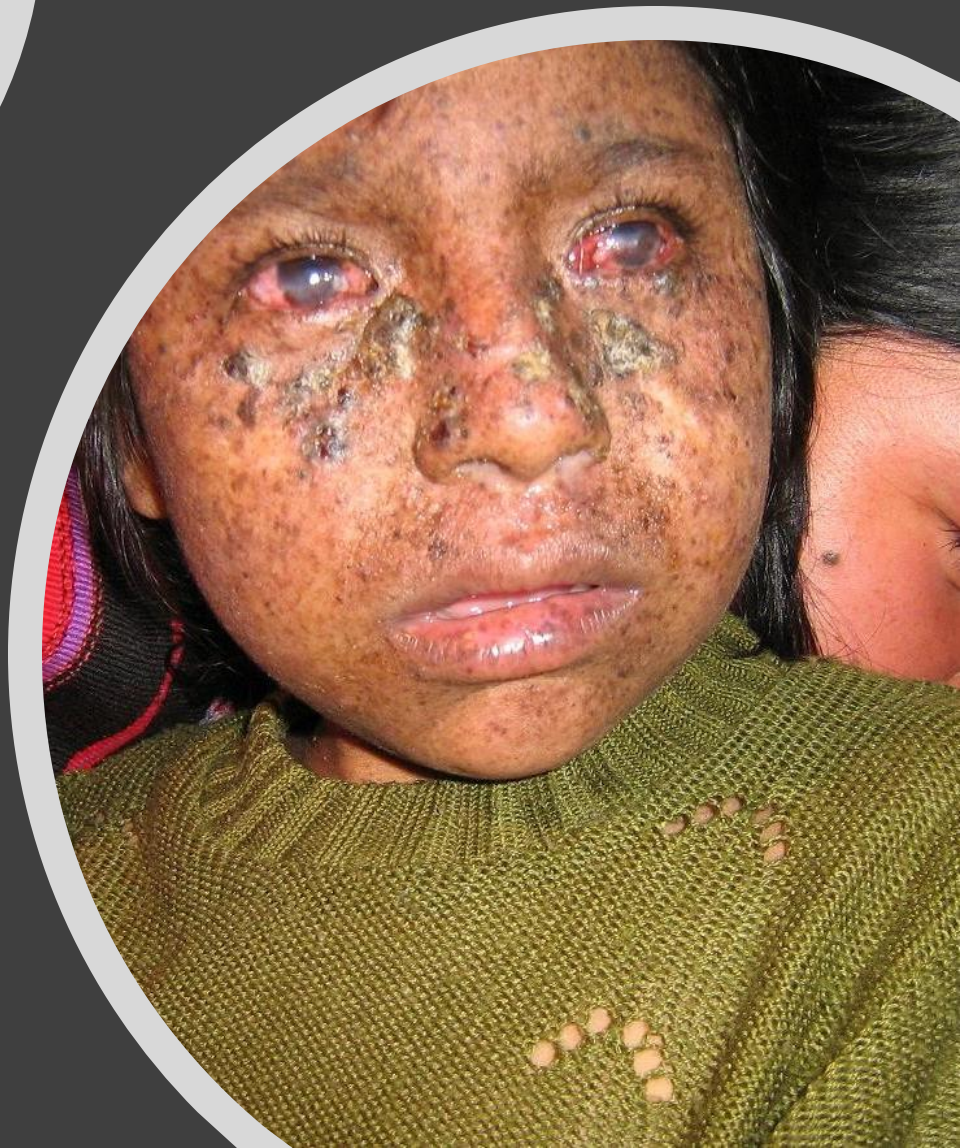
c. c. CDK4: Oncogene thought to play a role in melanoma progression in a small proportion of familial and sporadic melanomas.

Melanoma

D. Genetic risk factors

3. **Dysplastic nevus syndrome** (also known as familial atypical mole and melanoma syndrome): Patients have a first- or second-degree relative with malignant melanoma, and typically have at least 50 melanocytic nevi.





Melanoma

D. Genetic risk factors

4. Xeroderma pigmentosum (XP): Typically presents in childhood with early death secondary to metastatic spread of skin tumors. DNA damaged

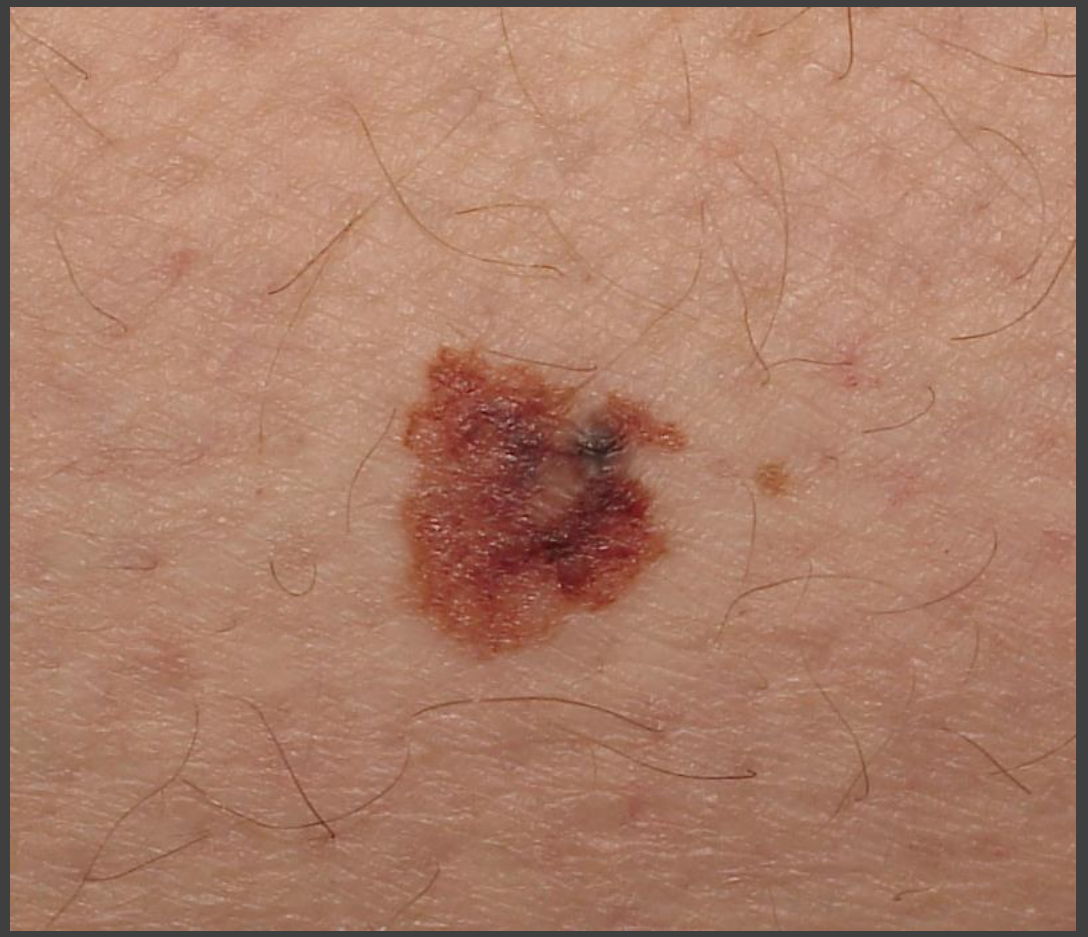
Common clinical features of melanoma (ABCDE mnemonic)

1. Asymmetry
2. Border irregularity
3. Color variation (shades of blue are the most ominous)’
4. Diameter more than 6 mm.

Major types of melanoma

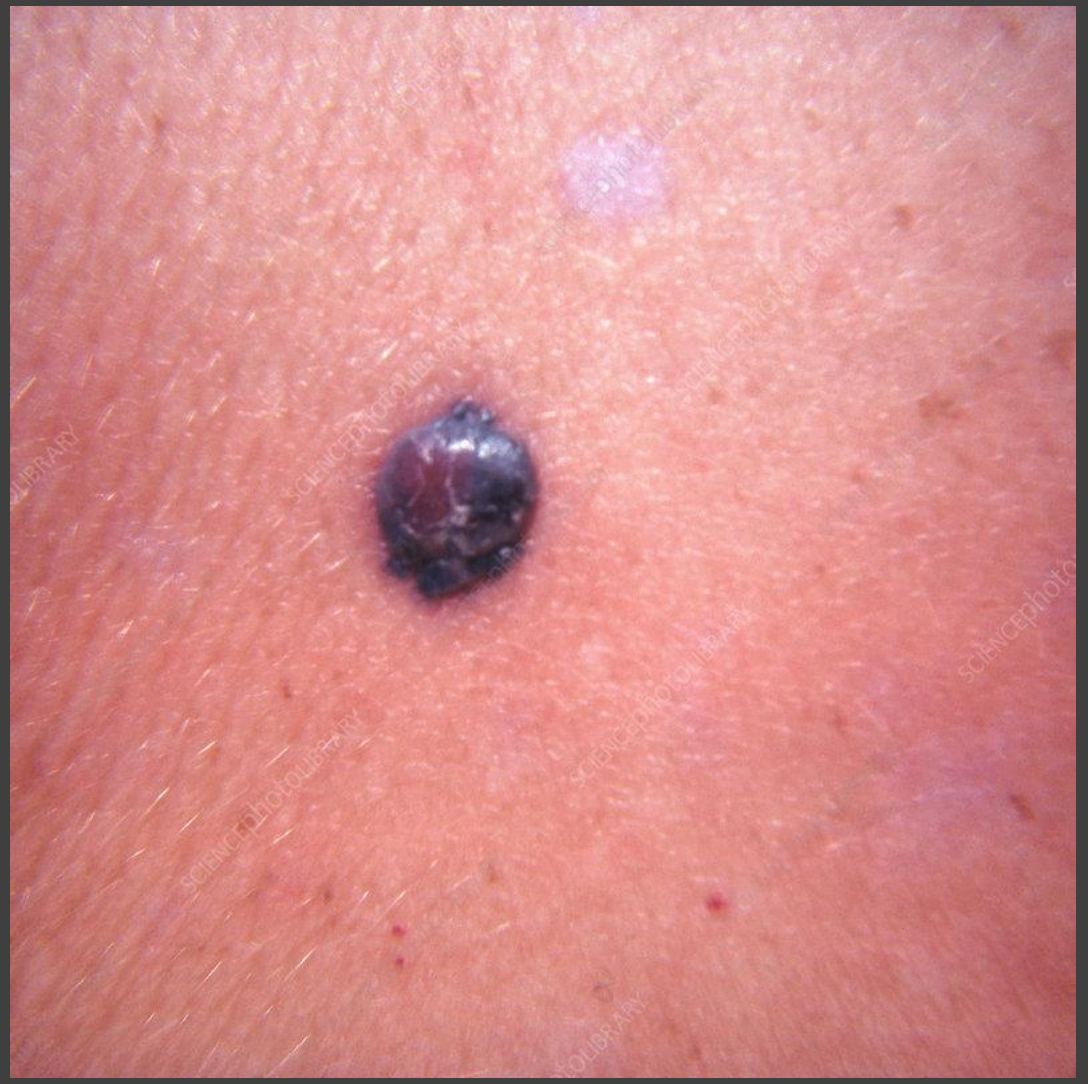
1. **Superficial spreading melanomaa.**

- Most common type: 70% of cases
- Intermediate in malignancy
- Usually arises from preexisting nevus
- Affects both genders equally
- Median age at diagnosis: fifth decade
- Most common sites: Upper back in men and lower legs in women
- Irregular, asymmetric borders with color variegation
- Radial growth phase early; vertical growth phase late.



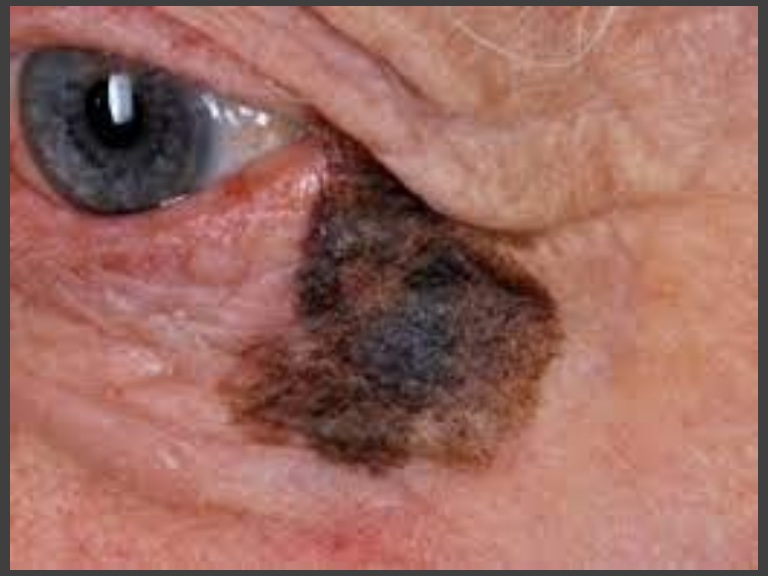
2. Nodular melanomaa.

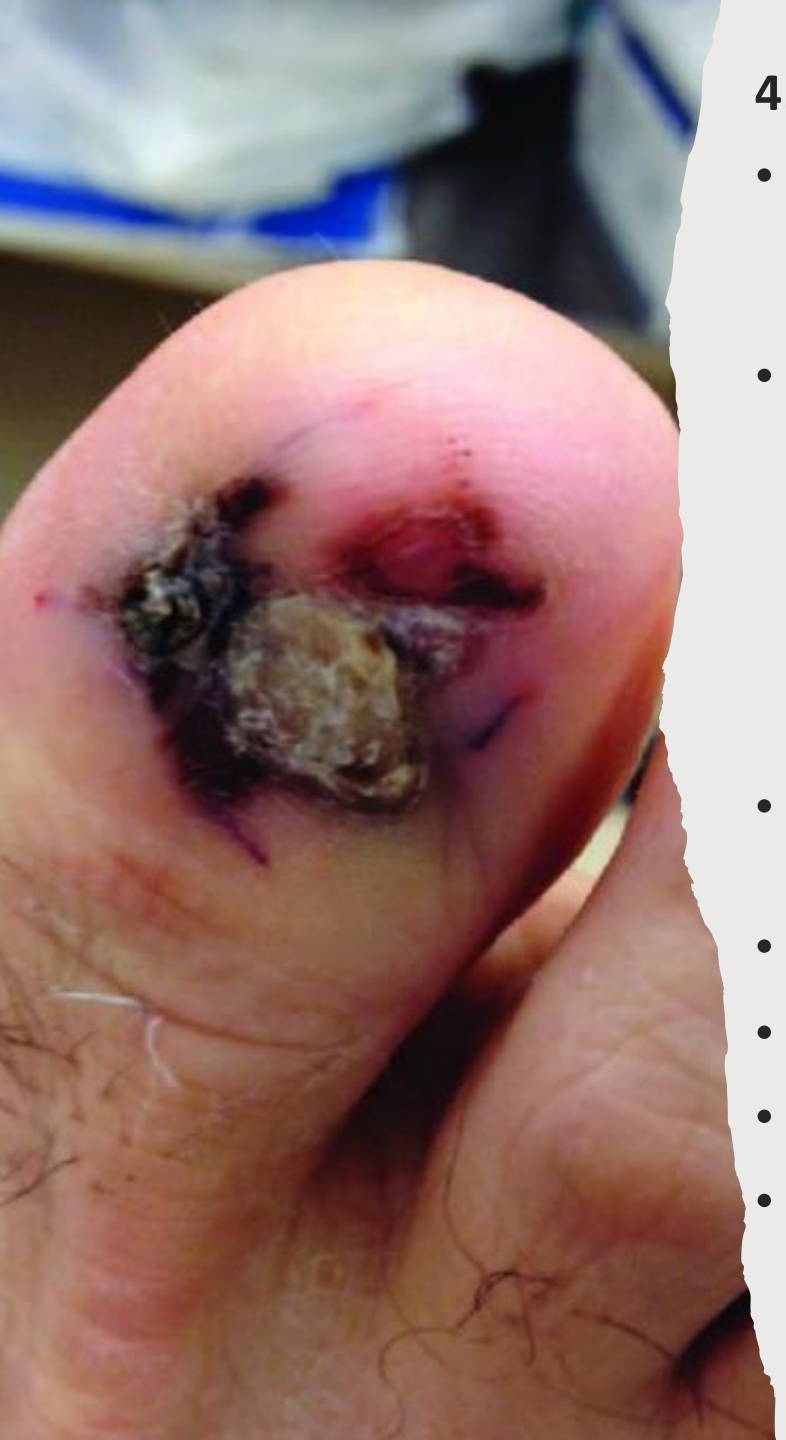
- Second most common: 15% to 30% of cases
- Most aggressive type
- Typically does not arise from preexisting nevi
- Men are affected twice as frequently as women
- Median age at diagnosis is 50 years
- Bluish-black, with uniform, smooth borders
- Vertical growth phase is a hallmark feature
- Not directly associated with sunlight exposure
- 5% are amelanotic-associated with a poorer prognosis because of delayed diagnosis



3.Lentigo maligna melanoma (LMM)

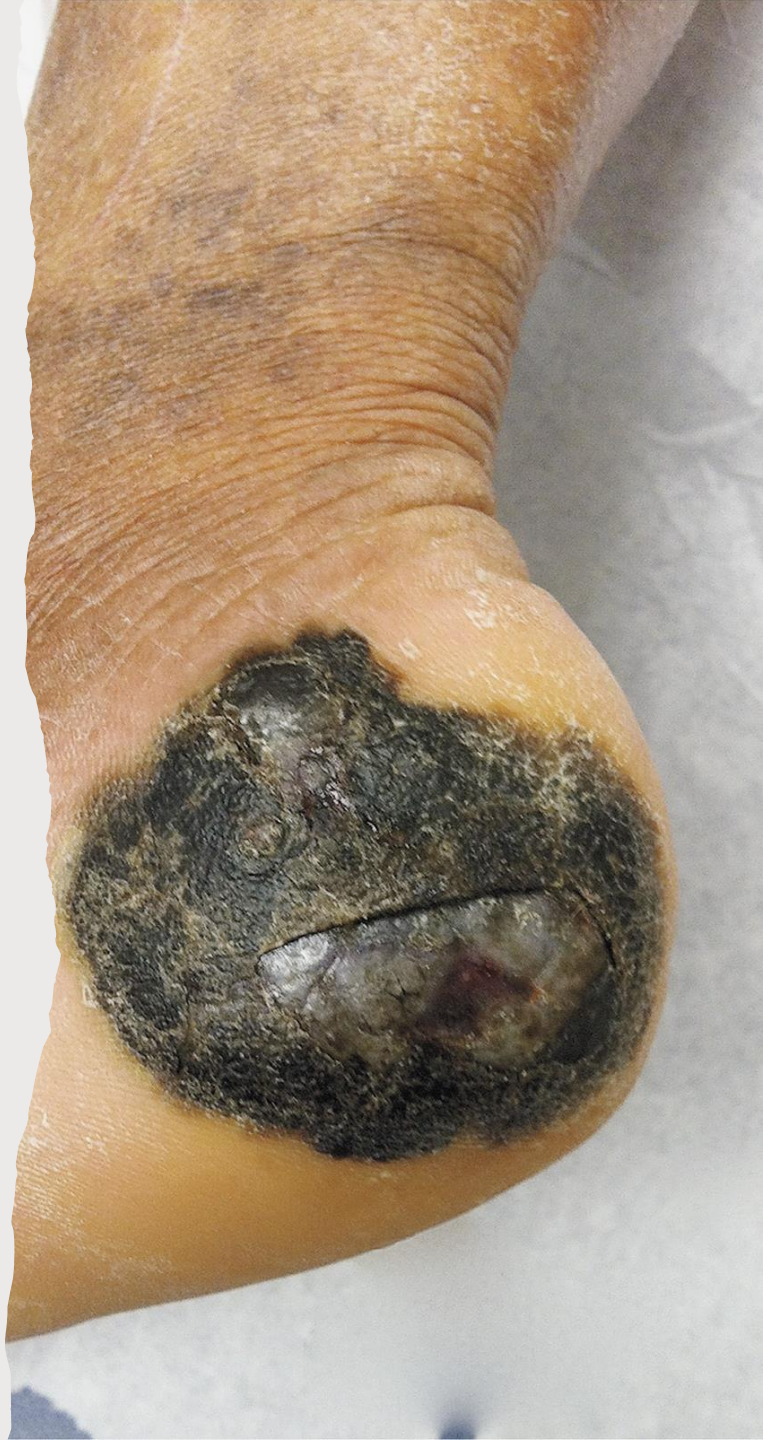
- 10% to 15% of cutaneous melanomas
- LMM is the least aggressive type and the only one clearly associated with sunlight exposure
- Head, neck, and arms of elderly (sun-exposed areas)
- Women are affected more frequently than men
- The median age at diagnosis is 70 years
- Usually greater than 3 cm in diameter; irregular, asymmetric with color variegation; areas of regression may appear hypopigmented
- Precursor lesion is lentigo maligna or Hutchinson freckle (histologically equivalent to melanoma in situ, or AJMH): radial growth phase only. Transition to vertical growth phase marks development of lentigomaligna melanoma
- Malignant degeneration is characterized by nodular development.





4.Acral lentiginous melanomaa.

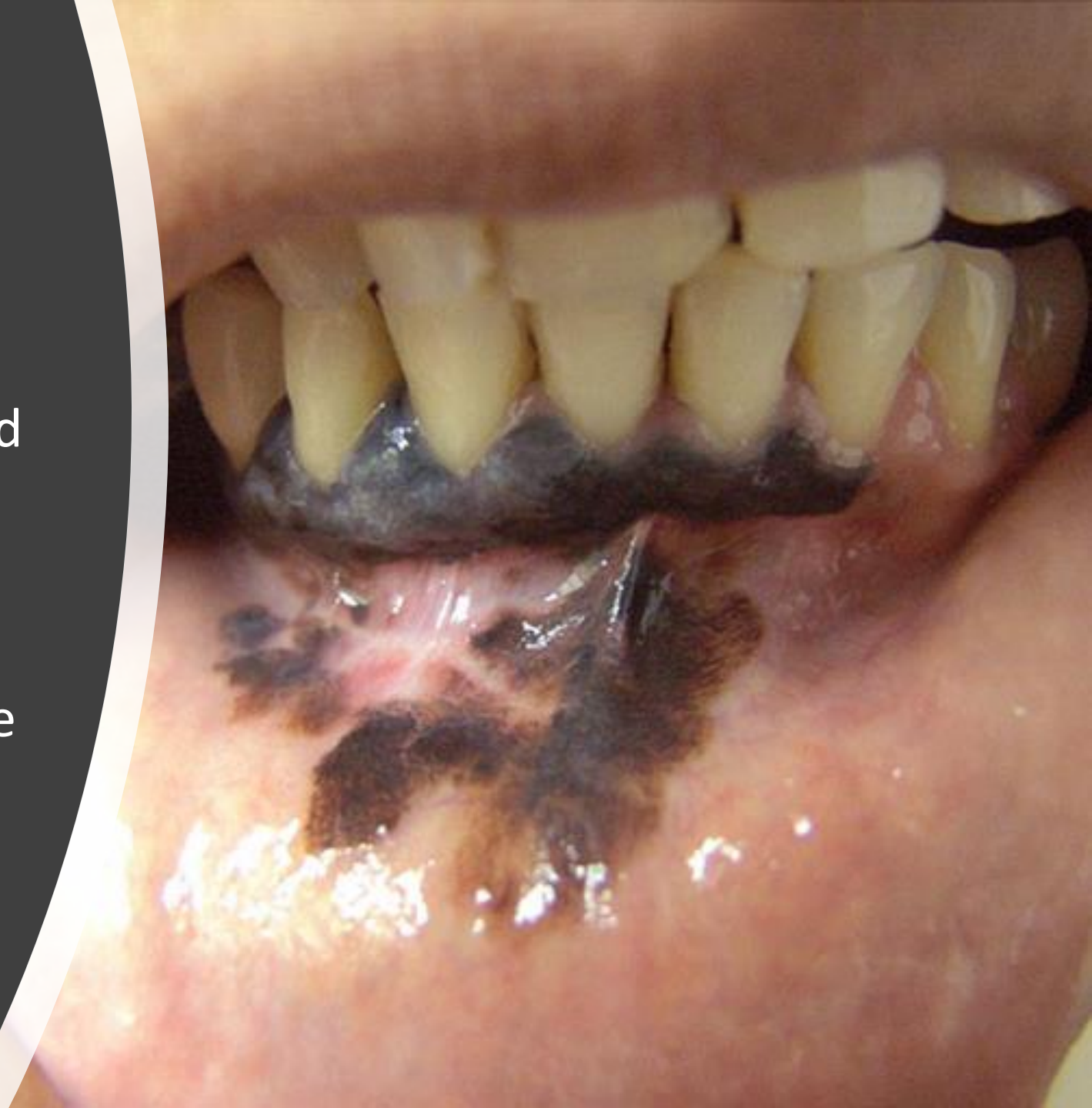
- 2% to 8% of melanomas in whites and 35% to 60% of melanomas in blacks, Hispanics, and Asians
- Presents in palms, soles, and beneath nail plate (subungual). Note: Melanonychia is a linear pigmented streak in the nail, which is often benign and is more common in black and Asian populations. Due to the risk of melanoma, biopsy of suspect lesions should be performed
- Median age at diagnosis is approximately 60 years.
- Irregular pigmentation is common
- Large size (>3 cm)
- Majority involve great toe or thumb
- Long radial growth phase; transition to vertical growth phase occurs with high risk of metastasis.



Noncutaneous melanoma

1. Mucosal melanomaa.

- Mucosal melanomas represent fewer than 2%6 of melanomas, Usuallypresenting within the genital tract, anorectal region, and head andneck mucosal surfaces
- They are usually large at diagnosis, with poor prognosis
- Radical excision is of questionable benefit



2. Ocular melanomaa

- Represent 2% to 5% of melanomas (most common noncutaneous mela-noma
- Interference with vision leads to earlier diagnosis.
- The eye has no lymphatic drainage; therefore, no nodal metastases areseen
- The liver is the main site of metastatic disease
- Treatment is by enucleation

Melanoma with an unknown primary

- Represents 3% of melanomas
- Diagnosis is by exclusion
- Nodal metastases are the most common presentation
- Prognosis is similar to melanomas with a known primary.

Melanoma staging and prognostic factors

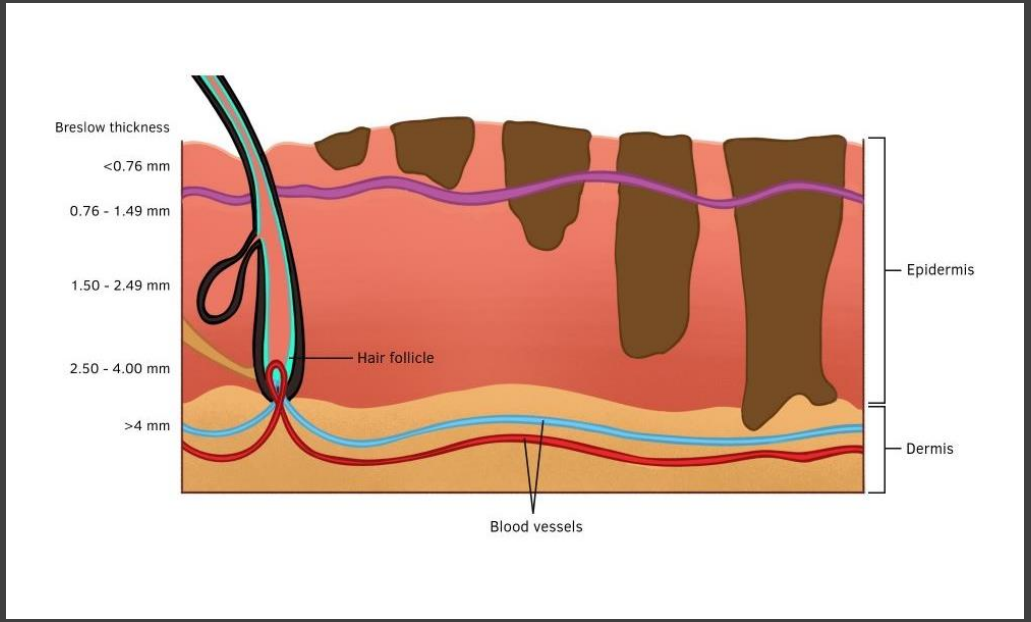
- Major prognostic factors: Tumor thickness, Nodal status, and Metastases-TNM (Table 11-3)

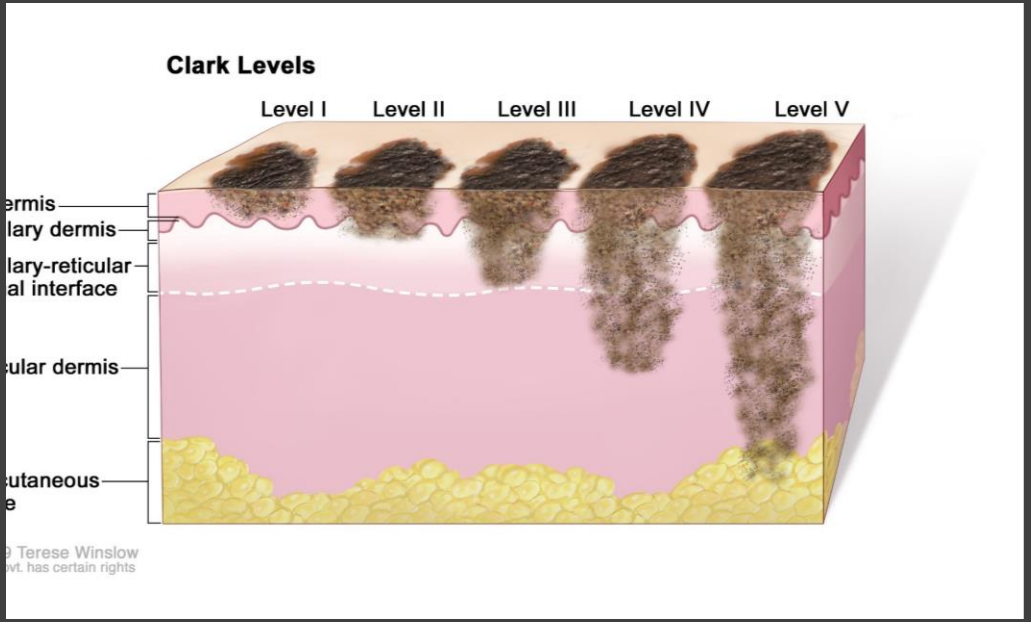
Table 11-3. Melanoma thickness grading

Skin	5-Year Survival (%)
Clark Level	
I–In situ	100
II–Papillary dermis	88
III–Papillar-reticular dermis	66
IV–Reticular dermis	55
V–Subcutaneous	22
Breslow Depth (mm)	
<1.00	89–95
1.01–2.00	77–89
2.01–4.00	63–79
>4.00	7–67

1. **Breslow thickness** is reported in millimeters; it is more accurate than Clark's level and is a better prognostic indicator.

2. **Clark's level** is based on invasion through the histologic layers of the skin





Other significant prognostic factors

- Anatomic location: Trunk lesions generally carry a worse prognosis than those on the extremities.
- Sex: For a given melanoma, women tend to have a better prognosis women are also more likely to have extremity melanomas, which have a better prognosis
- Ulceration is a poor prognostic sign
- Lymph node involvement or in-transit metastases are more significant than any other prognostic factors

- **The American Joint Committee on Cancer**
- has developed a staging system based on TNM classification (Table 11-4)

Table 11-4. AJCC Melanoma Staging System (2002)

TNM Definitions

Primary Tumor		*Ulceration status*
Tis	Melanoma in situ	
T1	≤1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01–2.0 mm	a: without ulceration b: with ulceration
T3	2.01–4 mm	a: without ulceration b: with ulceration
T4	>4.0 mm	a: without ulceration b: with ulceration
Regional Lymph Node Involvement		*Nodal Metastatic Mass*
N0	Negative	
N1	1 node	a: micrometastasis* b: macrometastasis°
N2	2–3 nodes	a: micrometastasis* b: macrometastasis° c: in-transit met(s)/satellites(s) without metastatic nodes
N3	4 or > metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic node(s)	

* Micrometastases are diagnosed after sentinel or elective lymphadenectomy
° Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal matastasis exhibits gross extracapsular extension

Distant Metastasis		*Serum Lactate Dehydrogenase*
M0	No distinct metastasis	Normal
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastasis	Elevated
	Any distant metastasis	

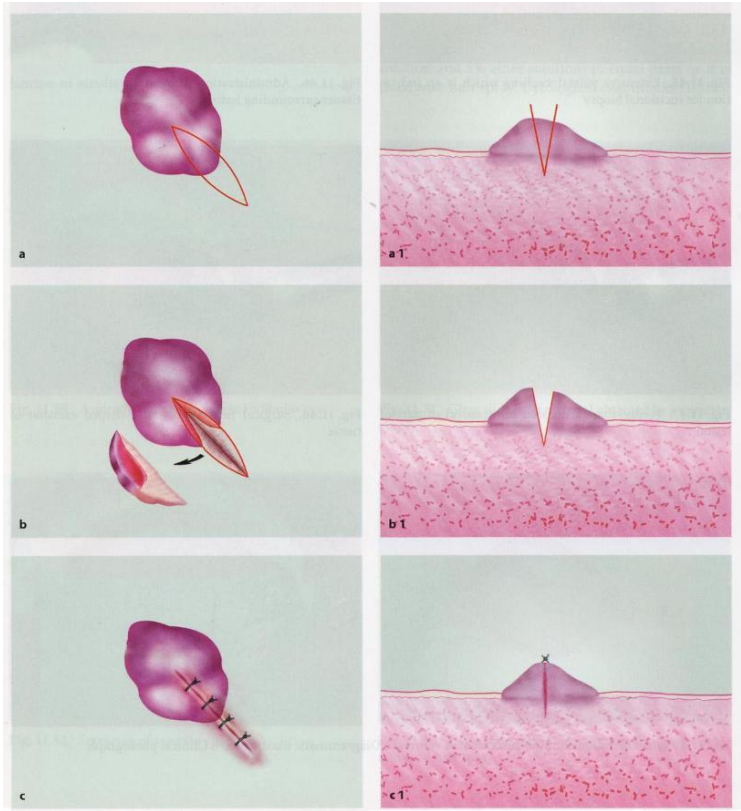
Staging

Stge 0	Tis N0 M0
Stage IA	T1a N0 M0
IB	T1b N0 M0, T2a N0 M0
Stage IIA	T2b N0 M0, T3a N0 M0
IIB	T3b N0 M0, T4a N0 M0
IIC	T4b N0 M0
Stage IIIA	T1-4a N1a M0, T1-4a N2a M0
IIIB	T1-4b N1 M0, T1-4b N2a M0, T1-4a N1bM0, T1-4a N2b M0, T1-4a/b N2c M0
IIIC	T1-4b N1b M0, T1-4b N2b M0, any T N3 M0
Stage IV	any T any N M1a, any T any N M1b, any T any N M1c

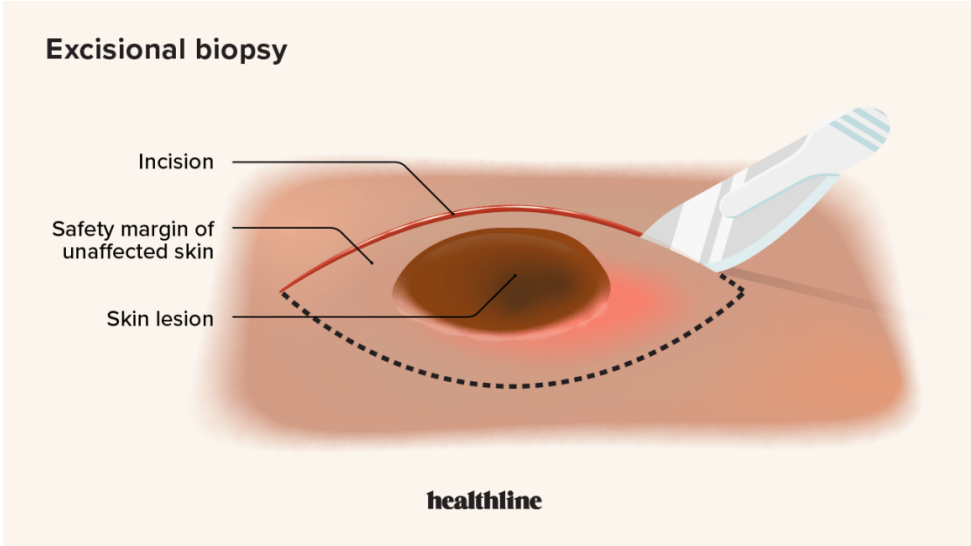
Diagnosis and treatment

A. Diagnosis of primary melanoma is made by histologic analysis of full-thickness biopsy specimens.

- **Excisional biopsy** is preferred for lesions less than 1.5 cm in diameter. If possible, excise lesion with 1- to 2-mm margins
- **incisional biopsy** is appropriate when suspicion is low, the lesion is large (>1.5 cm) or is located in a potentially disfiguring area (face, hands,and feet), or when it is impractical to perform complete excision. Incisional biopsy does not increase risk of metastasis or affect patient survival
- **Permanent sectioning** is used to determine tumor thickness.
- **Avoid shave biopsies**, because they forfeit the ability to stage the lesion based on thickness
- **Do not cauterize or freeze** the specimen: Tissue destruction makes impossible to evaluate thickness and margins.



Diagrammatic representation of incisional biopsy technique
a Demarcation of incision. b Surgical field after removal of specimen.
c Operation site after suturing. a_1, b_1, c_1 Steps correspond to a, b, c, in vertical cross-sectional view



- **Wide local excision** for tissue diagnosis can decrease the efficacy of future Lymphatics mapping because of disruption of local lymphatics. Biopsy incisions should result in scars parallel to lymphatic drainage
- **Orientation of biopsy** incisions should also take definitive surgical therapy into consideration.

a) Extremity biopsies should use longitudinal incisions.

b) Transverse incisions are sometimes preferable for preventing contractures over joints.

c) Head and neck incisions should be placed within relaxed skin tension lines, keeping facial aesthetic units in mind.

B. Definitive management of melanoma

1. **Wide local excision** is the treatment of choice.

2.**Recommended surgical margins** depend on tumor thickness (Table 11-5)

3. **subungual melanoma** requires amputation the distal to the distal metalingual joint for fingers, and proximal to the interphalangeal joint of the thumb

Table 11-5. Recommended surgical margins for melanoma excision

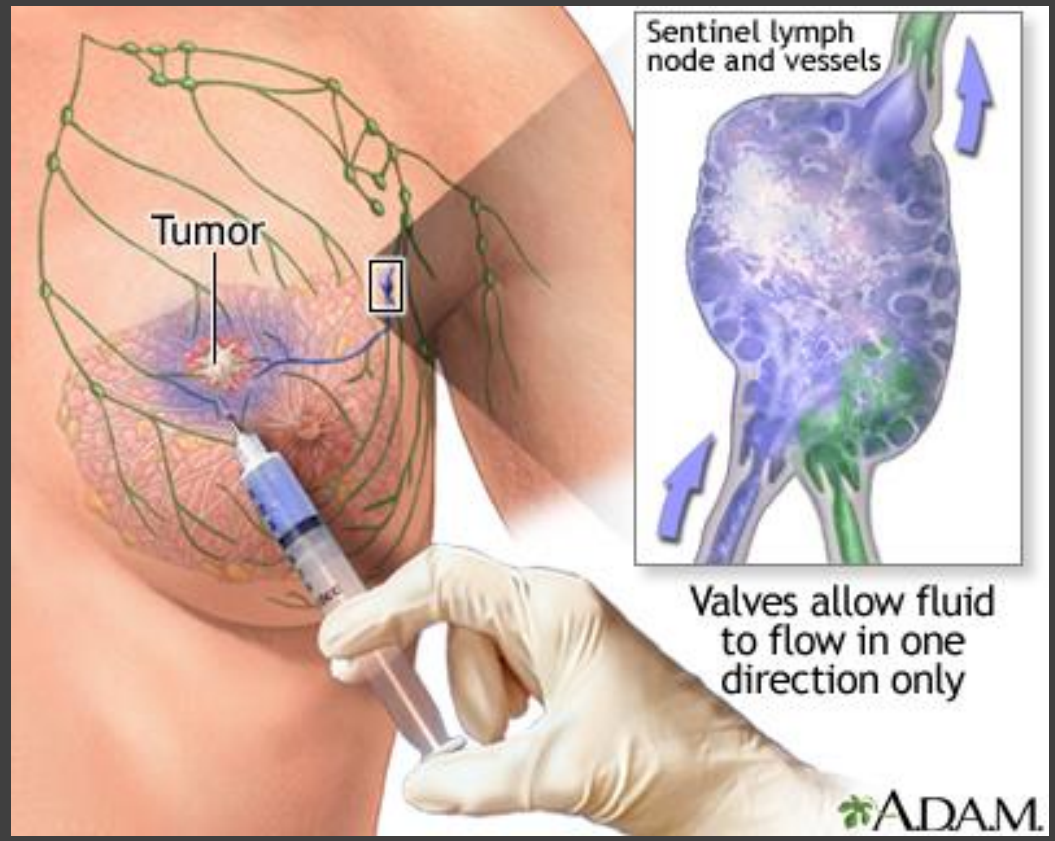
Melanoma Thickness (mm)	Margin (cm)
In situ	0.5
<1	1
1–4	2
>4	2–3 (controversial)

C. Management of regional lymph nodes

1- **Elective lymph node dissection (ELND)** involves removal of clinical, negative lymph nodes from the nodal basin. A survival benefit was demon. Stated in retrospective reviews; however, no survival benefit has been seen with prospective trials except for a subgroup with I- to 2-mm (intermediate thickness) melanomas

2. **Sentinel lymph node biopsy (SLNB)**

a. In the sentinel node theory, a sentinel node will be the first lymph node seeded by tumor cells; therefore, excision of sentinel node(s) alone is adequate to determine nodal status. The morbidity of SLNB is considerably less than END. Sentinel node(s) can be detected in more than 20%to 95% of patients. SLNB is now widely considered the standard of care

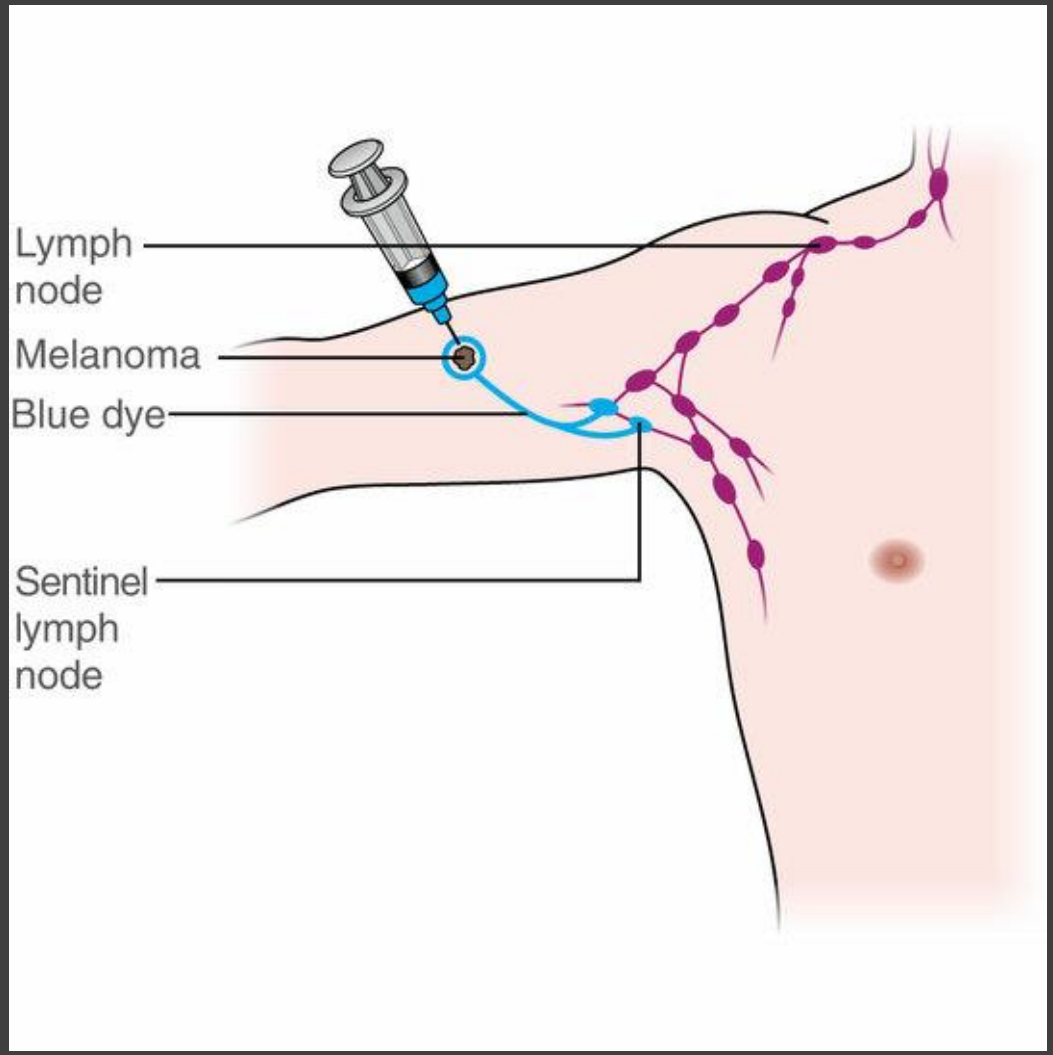


b. SLNB is performed in conjunction with wide local excision of the primary tumor. Lymphatic mapping is performed to determine the first lymph node that drains the primary tumor site (sentinel node)

2. **Sentinel lymph node biopsy (SLNB)**

c. SLNB-positive patients undergo staged regional lymphadenectomy and may be candidates for adjuvant therapy

d. Preoperative nuclear imaging: Radiolabeled colloid solution (technetium99) is injected intradermally at the primary tumor. Lymphoscintigraphic imaging localizes the sentinel node basin(s) (some tumor sites can drain to multiple basins).



2. Sentinel lymph node biopsy (SLNB)

E. In the operating room, blue lymphangiography dye (Lymphazurin) Is injected intradermally at the periphery of the primary tumor site prior to excision of the primary tumor.

(1) Mark edges of the lesion before injection to avoid obscuring them with the dye.

(2) Potential sentinel nodes will appear blue when exploring the nodal basin, giving secondary confirmation to localization with Geiger counter detection of 99Tc.

(3) Dye injection may briefly interfere with pulse-oximeter readings; alert anesthesiologist at time of injection

(4) Caution: Risk of allergy or anaphylaxis with dye injection

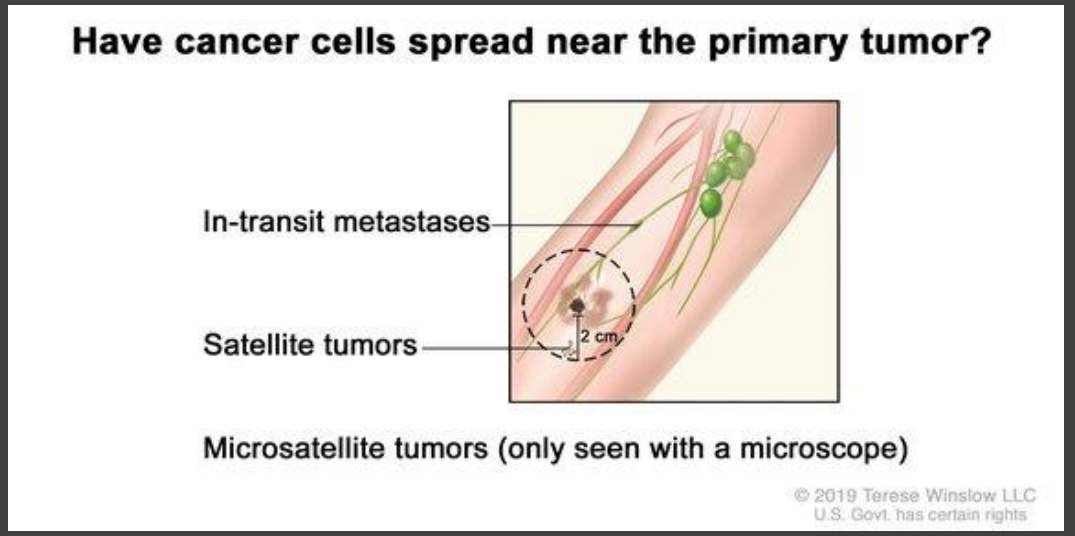
- **2. Sentinel lymph node biopsy (SLNB)**

F.Following excision of the primary tumor, drapes, instruments, gowns, and gloves are changed and the regional lymph node basin(s) identified by lymphoscintigraphy are explored. All radioactive ("hot") and/or blue nodes are excised

G.Histologic analysis of sentinel node(s) with immunohistochemical staining identifies micro metastases. Permanent sections are required; frozen sections cannot reliably differentiate normal from neoplastic melanocytes.

D. Surveillance and treatment of melanoma recurrence

1. Guidelines vary depending on stage of melanoma
2. **Asymptomatic patients** should be seen every 3 to 4 months for 2 years then every 6 months for 3 years, then annually. The most accurate way to detect metastatic disease is to take a thorough history
3. **Chest x-ray and liver function tests** (LDH and alkaline phosphatase)are usually sufficient; more extensive workups including computed tomo-graphic (CT) scans have not altered outcomes.
4. **Local recurrence** typically occurs within 5 cm of the original lesion, usually within 3 to 5 years after primary excision; most often this represents incomplete excision of the primary tumor.



D. Surveillance and treatment of melanoma recurrence

5. **The most common sites** of recurrence are the skin, subcutaneous tissues, distant lymph nodes, and then other sites (lung, liver, brain, bone, gastrointestinal tract).

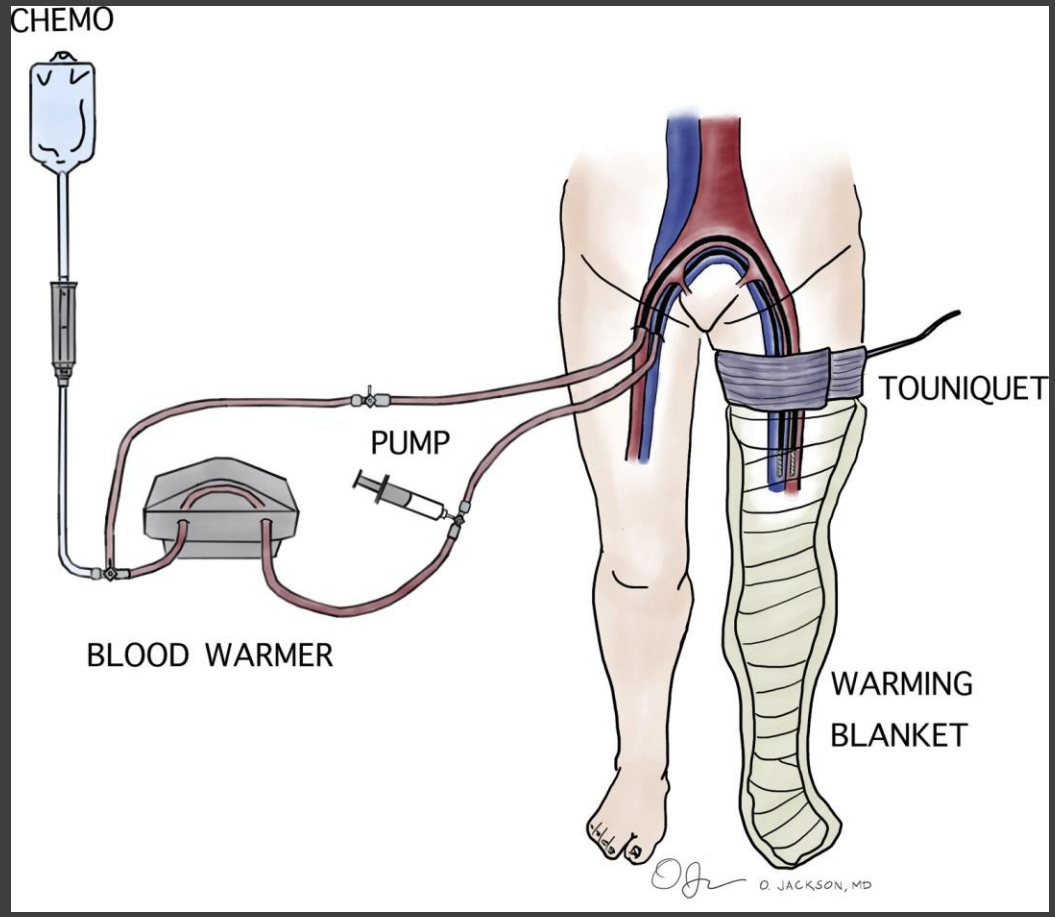
6. **Excision** is the primary treatment for local, small, isolated lesions.

7. Surgery is effective for palliation in patients with isolated recurrences in skin, central nervous system, lung, or gastrointestinal tract

8. **Chemotherapy**: Complete remission is rare.

a. Dacarbazine (DTIC), carmustine, cisplatin, and tamoxifen in combination are most frequently used.

b. b. Isolated hyperthermic limb perfusion for extensive cutaneous disease(melphalan and tumor necrosis factor) is used at some centers



D. Surveillance and treatment of melanoma recurrence

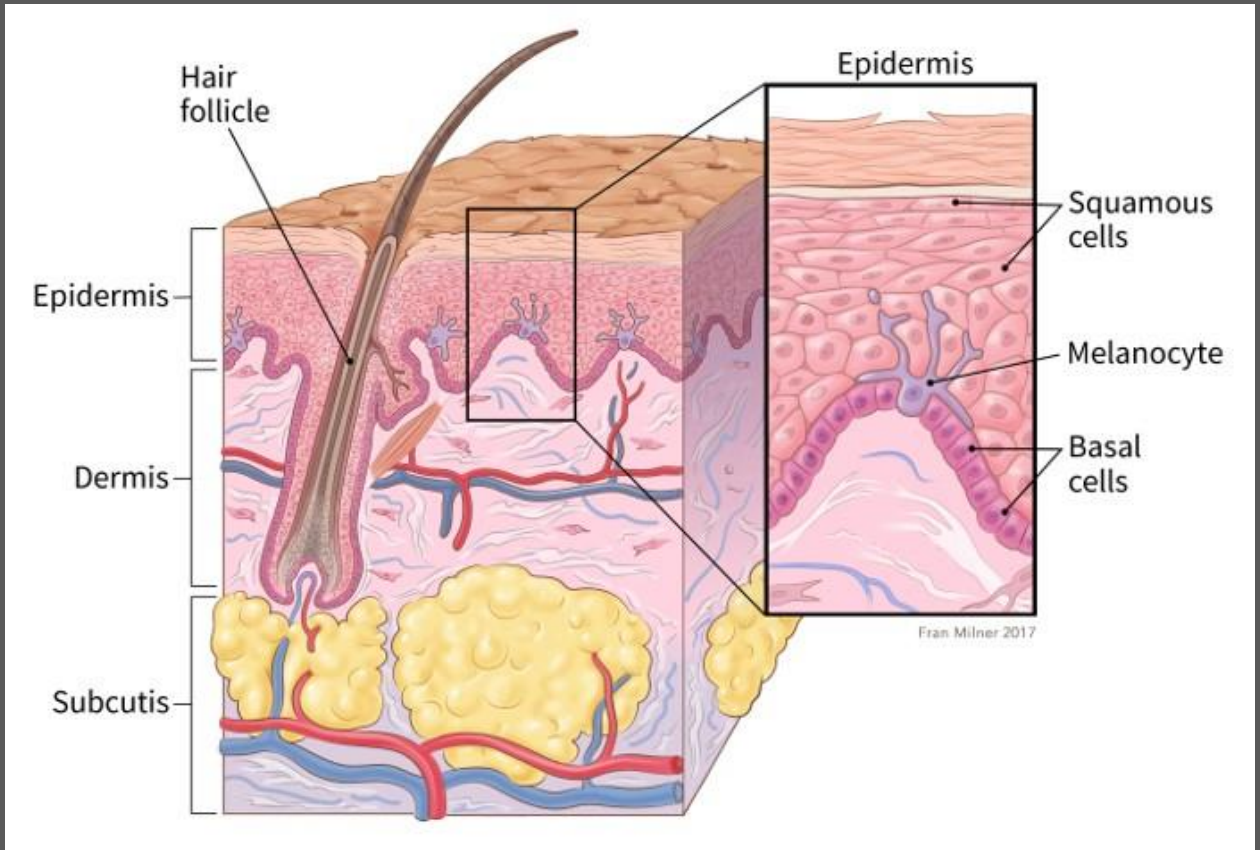
9. **Immunotherapy** with vaccines and cytokines is the subject of ongoing clinical trials. FDA-approved regimens include interferon- α (IFN-α) for stage III disease and interleukin 2 (IL-2) for stage IV disease.

10. **The mean survival with disseminated disease** is 6 months. Respiratory failure and central nervous system complications are the most common causes of death.

11. Radiotherapy

Table of content

- **Non Melanoma skin Cancer**



- **Non Melanoma skin Cancer**

•**Squamous cells:** These are flat cells in the upper (outer) part of the epidermis, which are constantly shed as new ones form. When these cells grow out of control, they can develop into squamous cell skin cancer (also called *squamous cell carcinoma*).

•**Basal cells:** These cells are in the lower part of the epidermis, called the *basal cell layer*. These cells constantly divide to form new cells to replace the squamous cells that wear off the skin's surface. As these cells move up in the epidermis, they get flatter, eventually becoming squamous cells. Skin cancers that start in the basal cell layer are called basal cell skin cancers or *basal cell carcinomas*.

- # Non Melanoma skin Cancer
- ## Basal and Squamous Cell Skin Cancer Risk Factors
  - Ultraviolet (UV) light exposure
  - Having light-colored skin
  - Being older
  - Being male
  - Exposure to certain chemicals
  - Radiation exposure
  - Previous skin cancer
  - Long-term or severe skin inflammation or injury
  - Psoriasis treatment
  - Xeroderma pigmentosum (XP)
  - Basal cell nevus syndrome (also known as nevoid basal cell carcinoma syndrome or Gorlin syndrome)
  - Weakened immune system
  - Human papillomavirus (HPV) infection
  - Smoking

- **Non Melanoma skin Cancer**
  - There are four main clinical variants of basal cell carcinoma. These are nodular, superficial spreading, sclerosing and pigmented basal cell carcinomas.

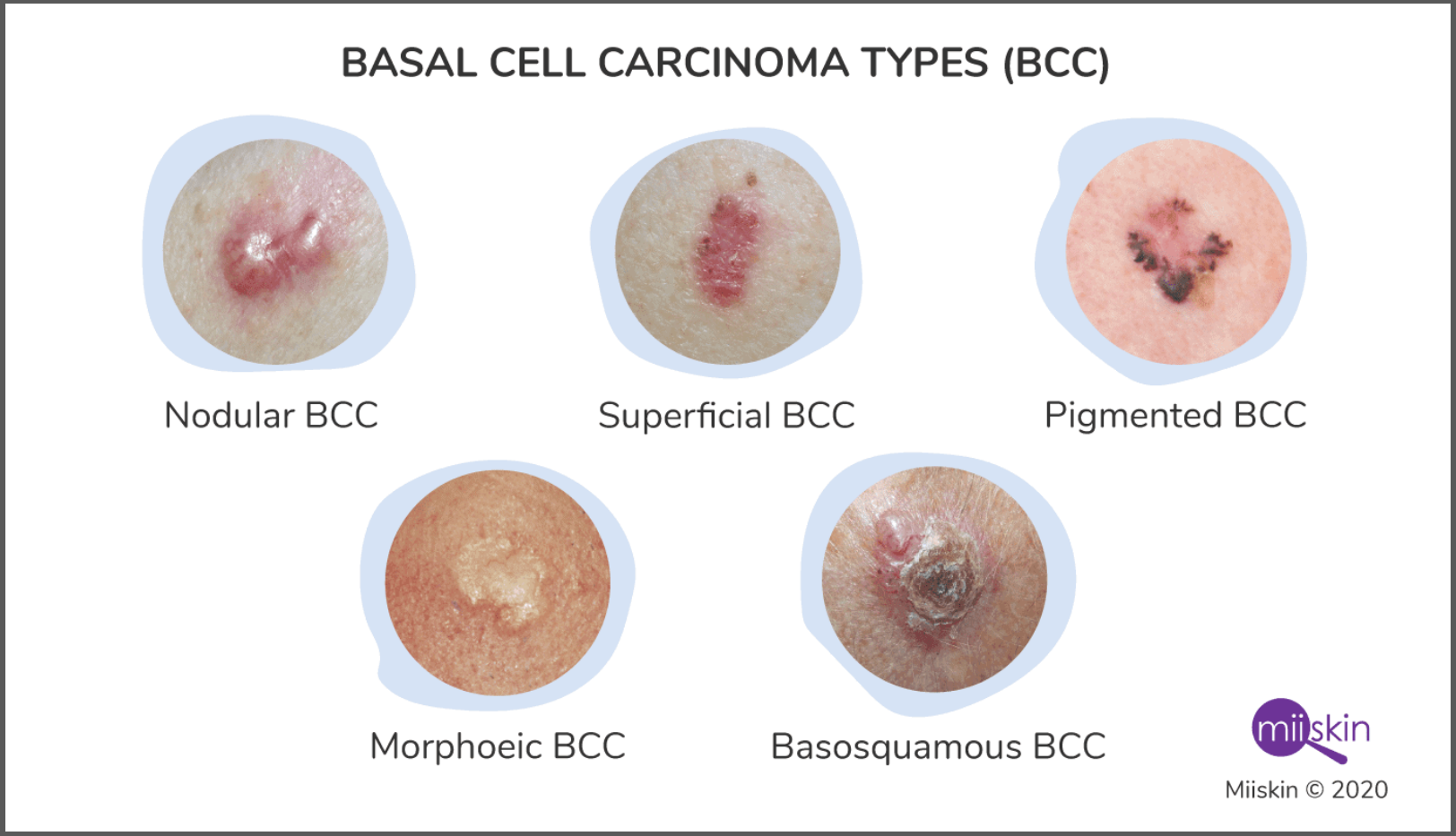
- **a) Nodular Basal Cell Carcinoma**
- Nodular basal cell carcinoma is clinically manifested as a translucent nodule, often with telangiectatic vessels being very evident. As the nodule expands beyond 1 cm the center can begin to break down causing an ulcer surrounded by a rolled edge. The alternative name for this is "rodent ulcer".
- Nodular basal cell carcinomas are common on the face, particularly along embryonal fusion planes such as the inner canthus, peri-nasal skin and peri-auricular skin. They can occur anywhere on the body that has been subject to intermittent severe sun exposure.
- Childhood exposure appears to be of considerable significance, as it is for melanoma, in the development of basal cell carcinoma.

- **Non Melanoma skin Cancer types**
- **b) Superficial Spreading Basal Cell Carcinoma**
- Superficial spreading basal cell carcinoma is most common on the upper back. It consists of shallow plaques, pink to almost skin coloured, that slowly expand over many years. The shallowness of the lesion prevents ulceration until quite late. Typically, these lesions are very friable, and minor trauma such as dragging a fingernail across the lesion while often result in multiple pinpoint bleeding areas.
- Superficial spreading basal cell carcinomas are almost all secondary to sun damage.

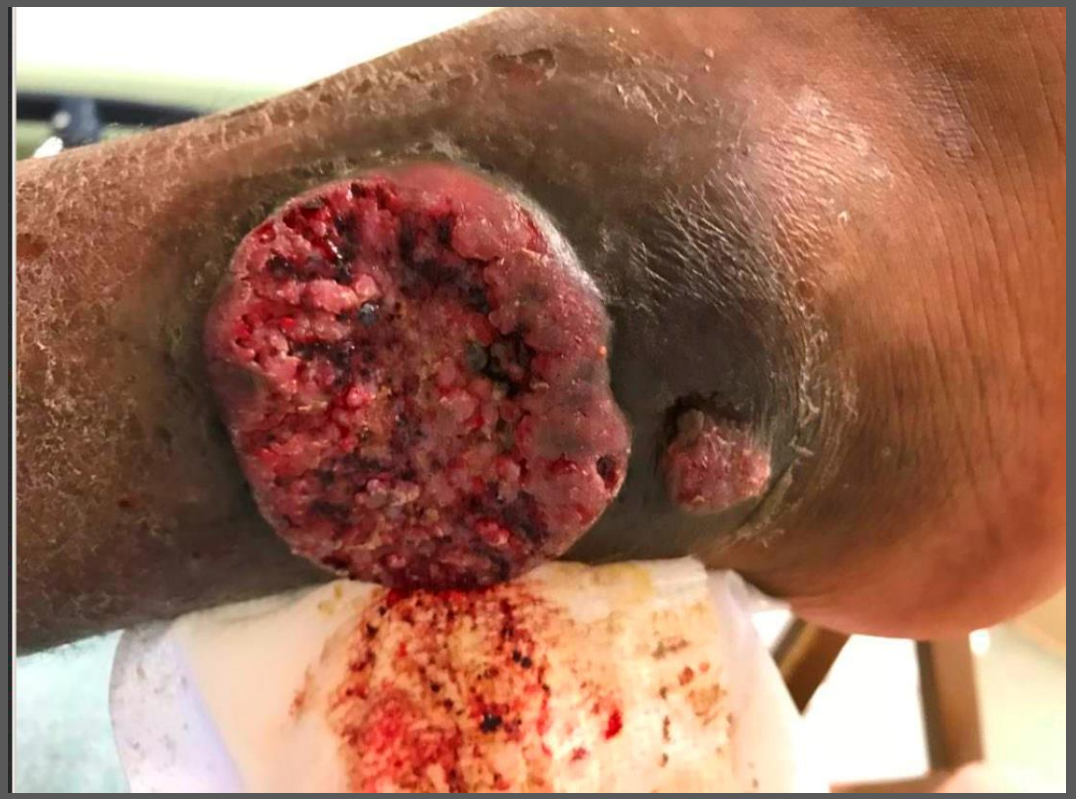
- **Non Melanoma skin Cancer types**
- **c) Sclerosing Basal Cell Carcinoma**
- Sclerosing basal cell carcinoma is often a significant diagnostic problem. The early lesion can look like a small white scar on the skin. This scar-like area slowly expands. Nodules of basal cell carcinoma can be apparent in late lesions but the sclerotic scarred area can expand to a very large size before it is clinically obvious as a skin cancer. It is most common on the face, and can produce quite significant morbidity because of its size at the time of diagnosis.
- Because the margins of sclerosing basal cell carcinoma are almost always very poorly defined, it is commonly recurrent after simple surgical excision. Micrographic surgery, if available, is the surgical treatment of choice or, in patients over 60, radiation therapy with generous margins. In all cases, the lesion must be examined carefully under very good light to ascertain the approximate margins.

- **Non Melanoma skin Cancer types**
- **d) Pigmented Basal Cell Carcinoma**
- Pigmented basal cell carcinoma occurs in dark skinned individuals, particularly Asians. Nodular basal cell carcinomas can be pigmented, as can superficial spreading basal cell carcinomas. Nodular basal cell carcinomas that are pigmented may be confused clinically with nodular melanoma. The differentiating feature, if completely pigmented, is that there are pigment flecks around the base of the nodule that are absent in melanoma. These flecks are the engorged melanocytes. In many cases the only way to clearly differentiate is a biopsy.

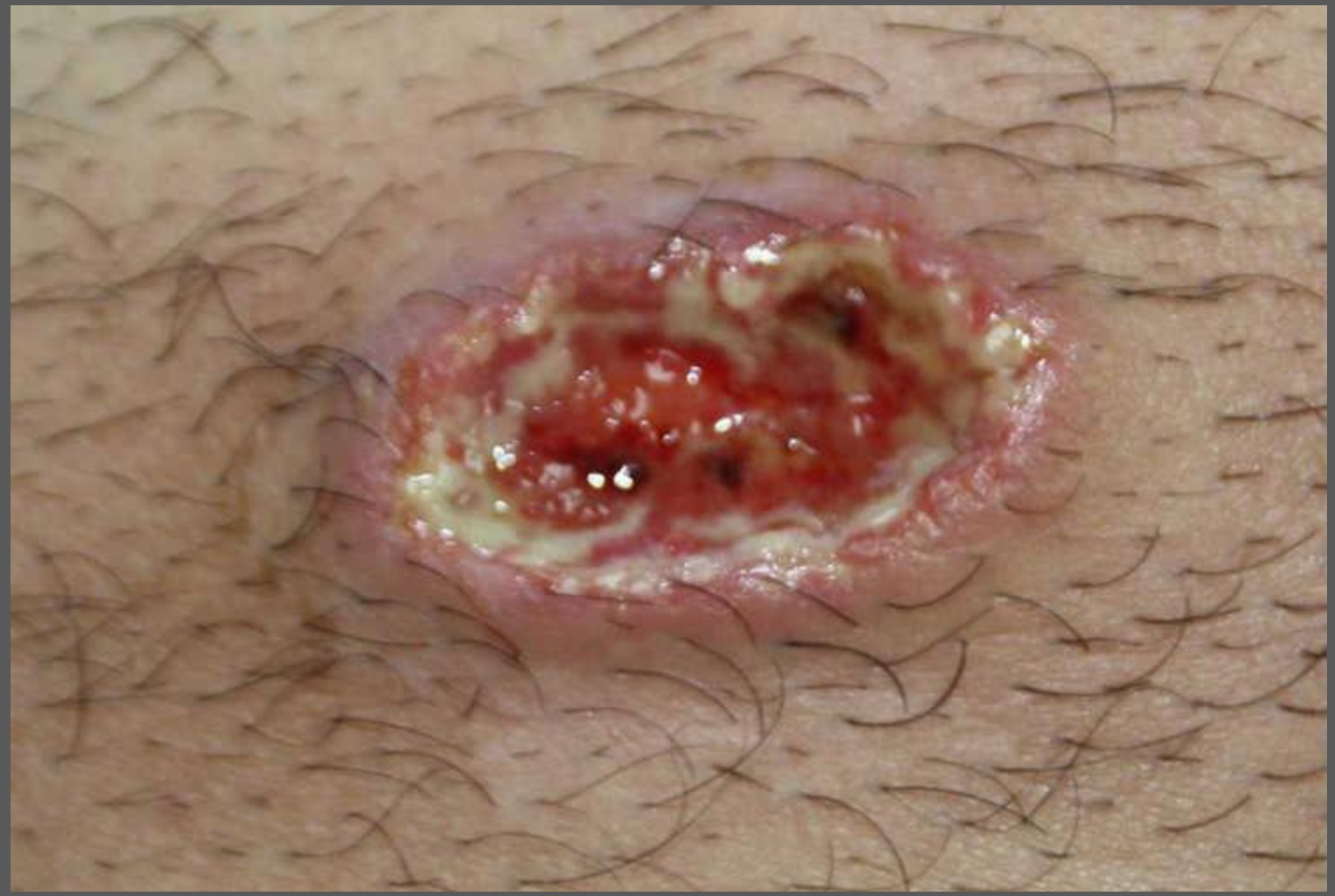
- **Non Melanoma skin Cancer types**



- **Non Melanoma skin Cancer types of squamous cell carcinoma**
- Fungating describes what the cancer might look like. They can grow in the shape of a fungus or cauliflower.
- Infiltrative squamous cell carcinoma (Ulcerating)



- **Non Melanoma skin Cancer types of squamous cell carcinoma**



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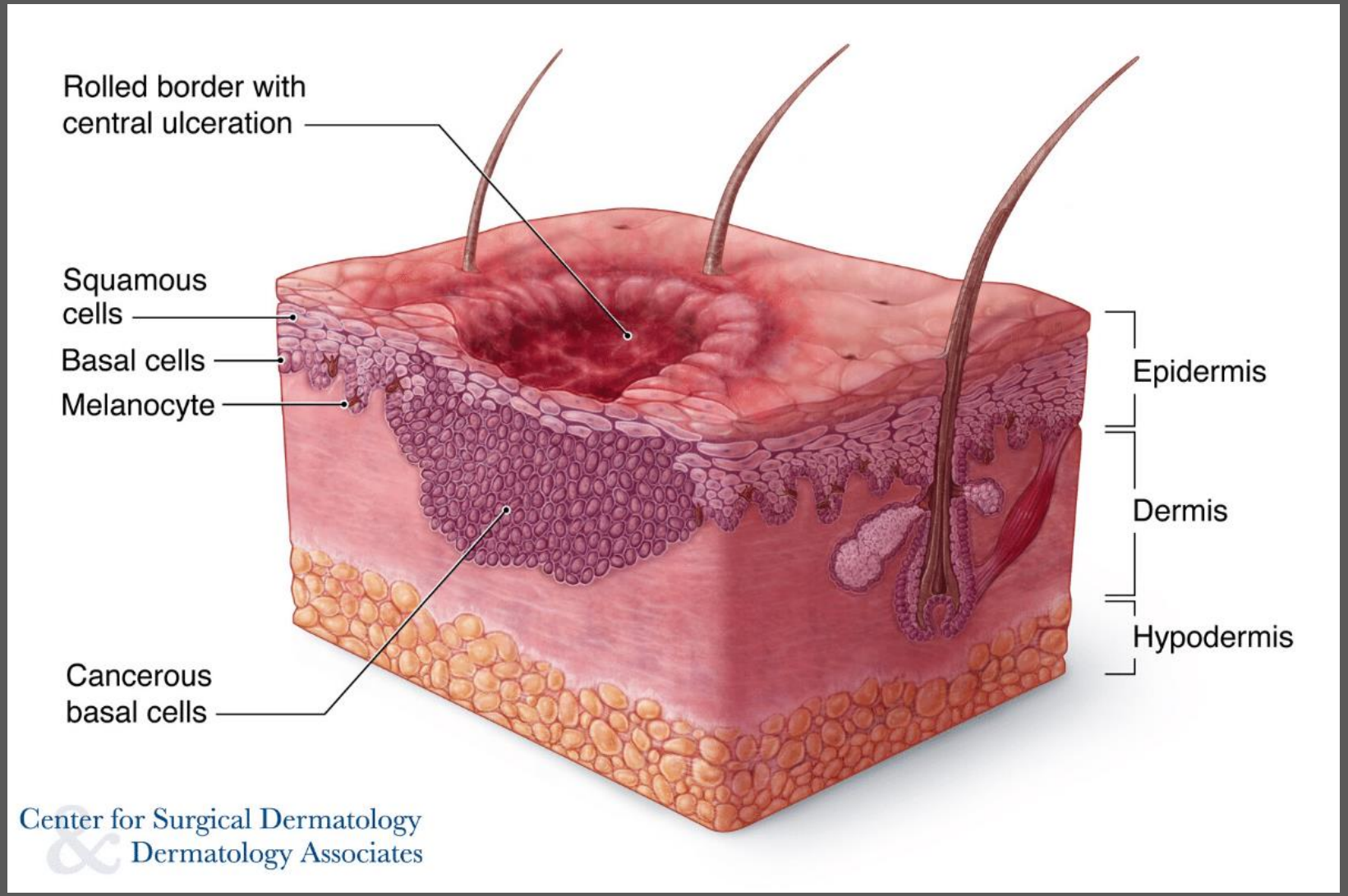

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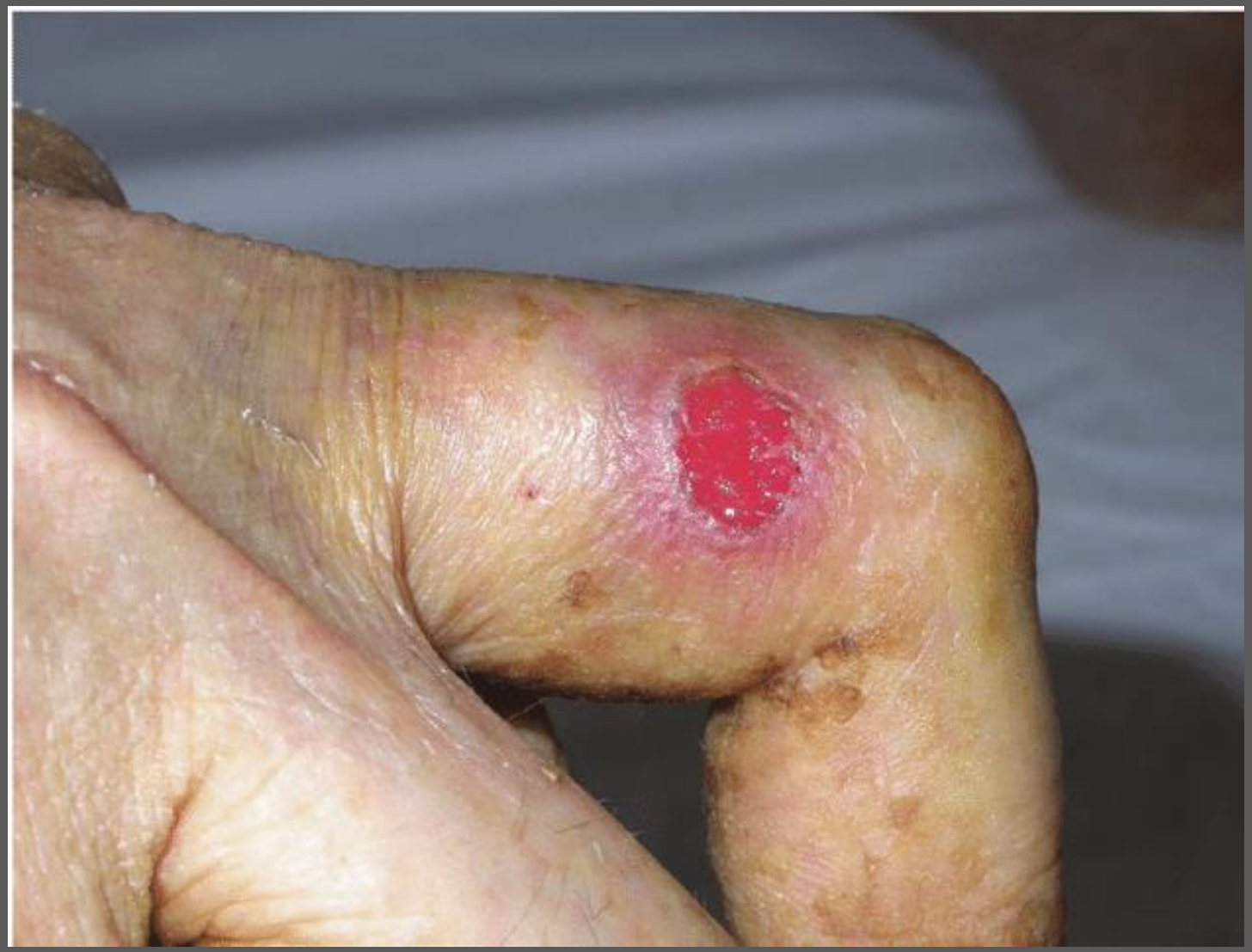

- **Non Melanoma skin Cancer treatment**

- Excisional surgery
- Mohs surgery
- Cryosurgery
- Curettage and electrodesiccation (electrosurgery)
- Laser surgery
- Radiation
- Photodynamic therapy (PDT)
- Topical medications

- **Non Melanoma skin Cancer prognosis**

Staging: TNM system for SCC			
Stage	**Primary tumour**	**Regional lymph nodes**	**Distant metastasis**
Stage 0	Tis= Carcinoma in situ	N0= no regional lymph node metastasis	M0
Stage I	T1= Tumour 2 cm or less	N0	M0
Stage II	T2= Tumour >2 cm but <5cm	N0	M0
	T3= Tumour >5cm	N0	M0
Stage III	T4= Tumour invading deeper extradermal structures	N0	M0
	Any T	N1= Regional lymph node spread	M0
Stage IV	Any T	Any N	M1= Distant metastasis


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