

Skin Cancer

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Table of content

1. **MM**

2. NMSC

3. Adnexal skin cancer

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%.

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 II) (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

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.

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

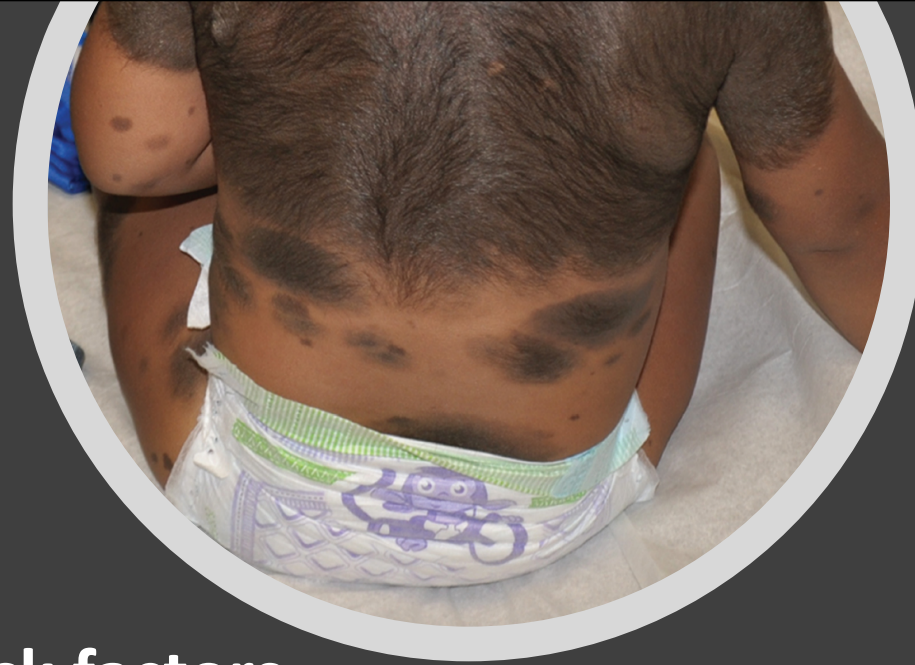
B. Demographic risk factors

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 transformation 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.

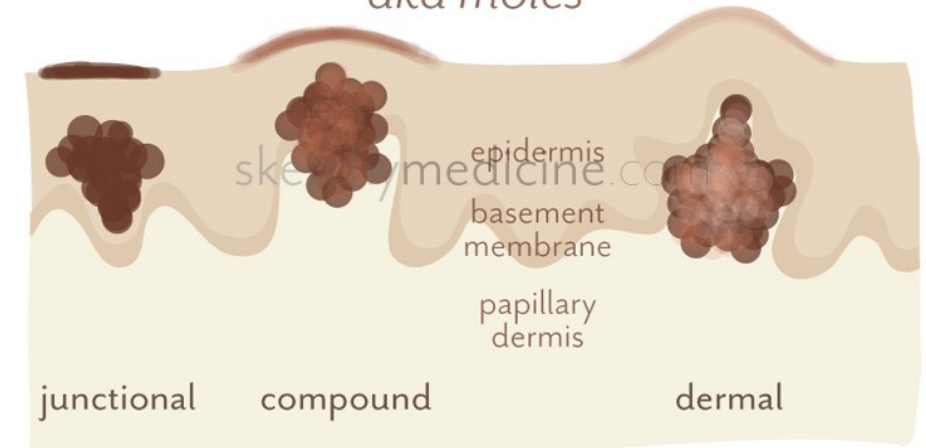


Melanoma

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.

Acquired Nevomelanocytic Nevi *aka moles*



Melanoma

5. Dysplastic or atypical nevus.

- 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



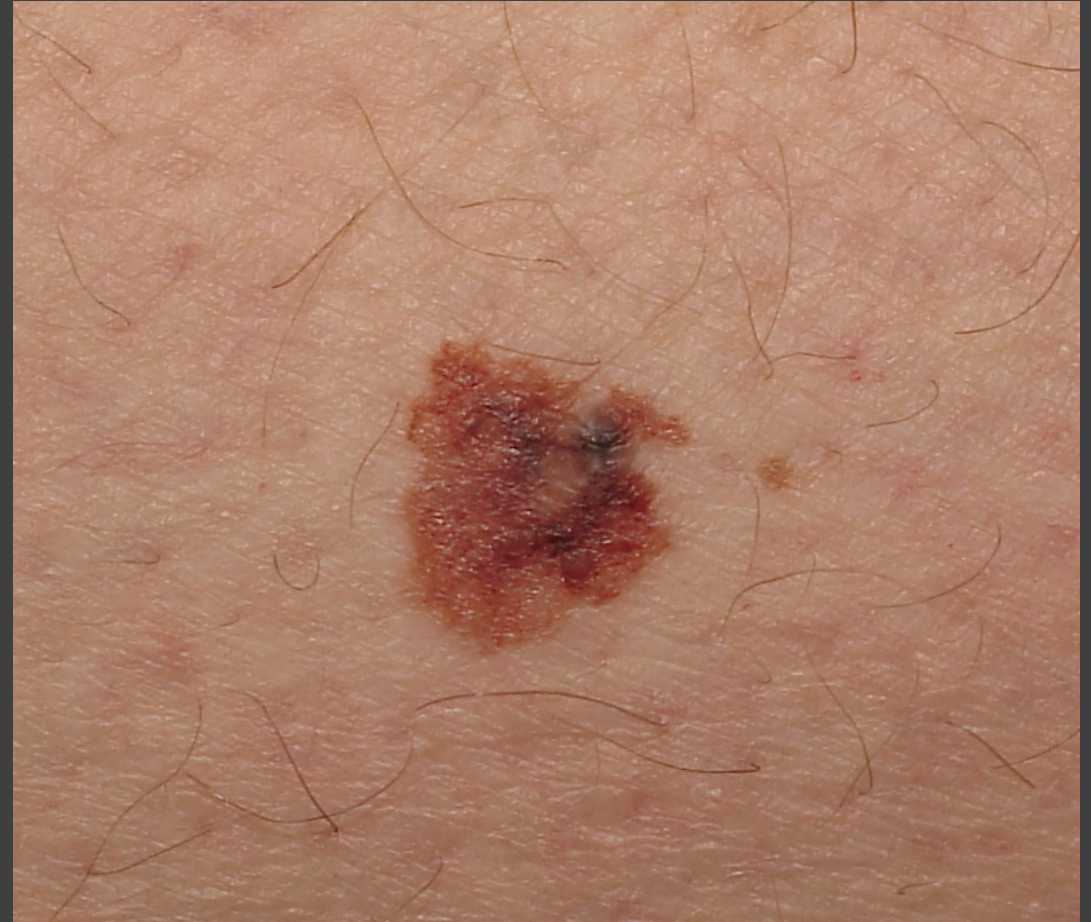
Common clinical features of melanoma (ABCDE mnemonic)

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 melanoma.

- 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 melanoma.

- 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 melanoma.

- 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 melanoma.

- Mucosal melanomas represent fewer than 2% of melanomas, usually presenting within the genital tract, anorectal region, and head and neck 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 melanoma)
- Interference with vision leads to earlier diagnosis.
- The eye has no lymphatic drainage; therefore, no nodal metastases are seen
- 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.

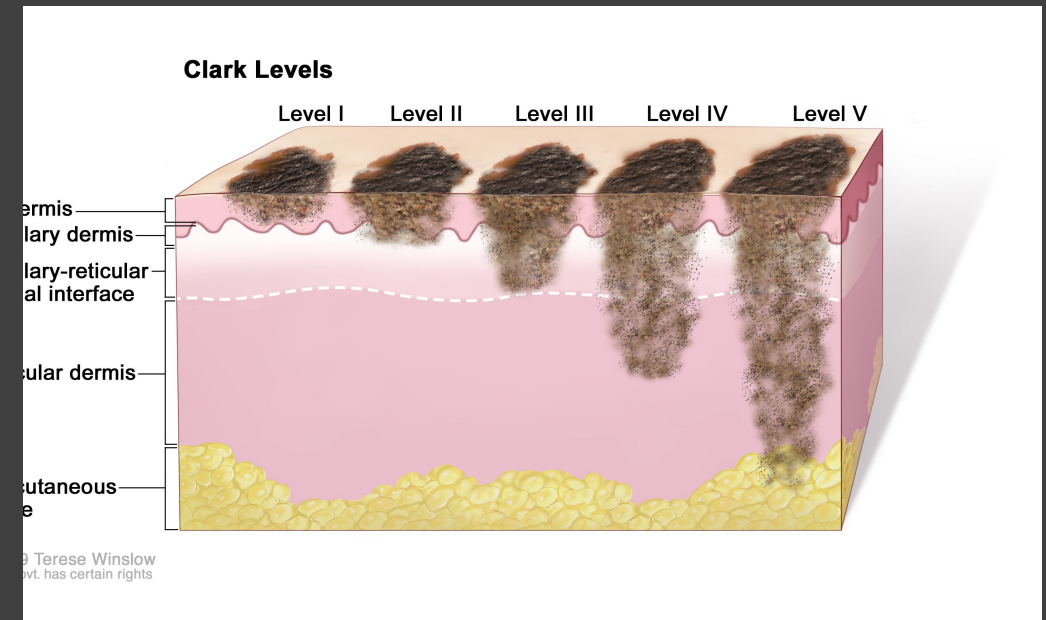
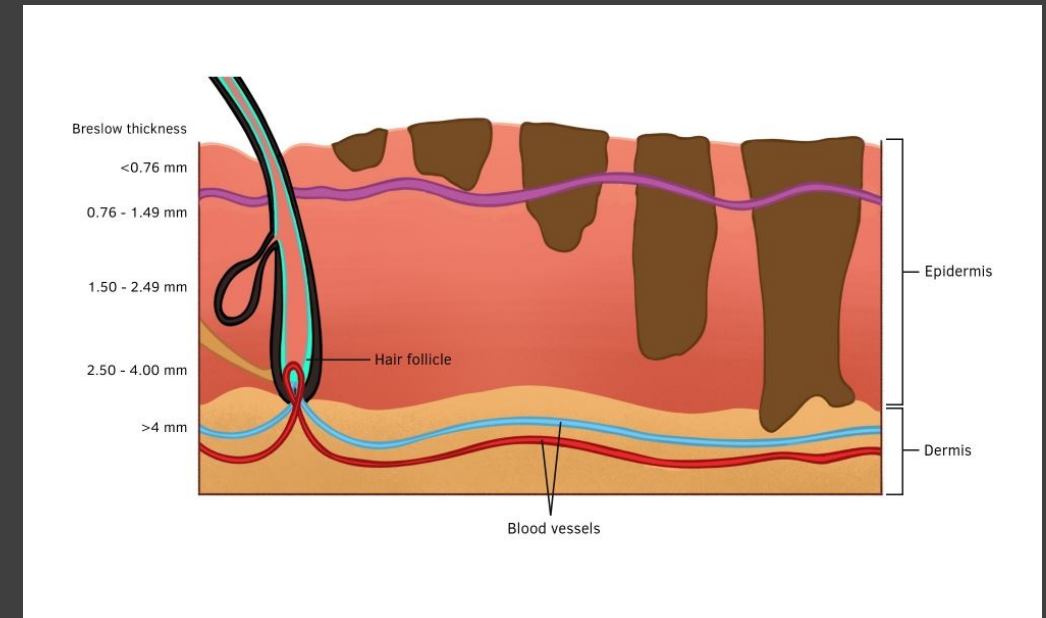
Melanoma staging and prognostic factors

- 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
<u>1.01-2.00</u>	77-89
<u>2.01-4.00</u>	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

Tis Melanoma in situ

T1 ≤1.0 mm

T2 1.01–2.0 mm

T3 2.01–4 mm

T4 >4.0 mm

Regional Lymph Node Involvement

N0 Negative

N1 1 node

N2 2–3 nodes

N3 4 or > metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic node(s)

Ulceration status

a: without ulceration and level II/III

b: with ulceration or level IV/V

a: without ulceration

b: with ulceration

a: without ulceration

b: with ulceration

a: without ulceration

b: with ulceration

Nodal Metastatic Mass

a: micrometastasis*

b: macrometastasis°

a: micrometastasis*

b: macrometastasis°

c: in-transit met(s)/satellite(s)

without metastatic nodes

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy

°Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension

Distant Metastasis

M0 No distinct metastasis
M1a Distant skin, subcutaneous,
or nodal mets
M1b Lung metastases
M1c All other visceral metastasis
Any distant metastasis

Serum Lactate Dehydrogenase

Normal

Normal
Normal
Elevated

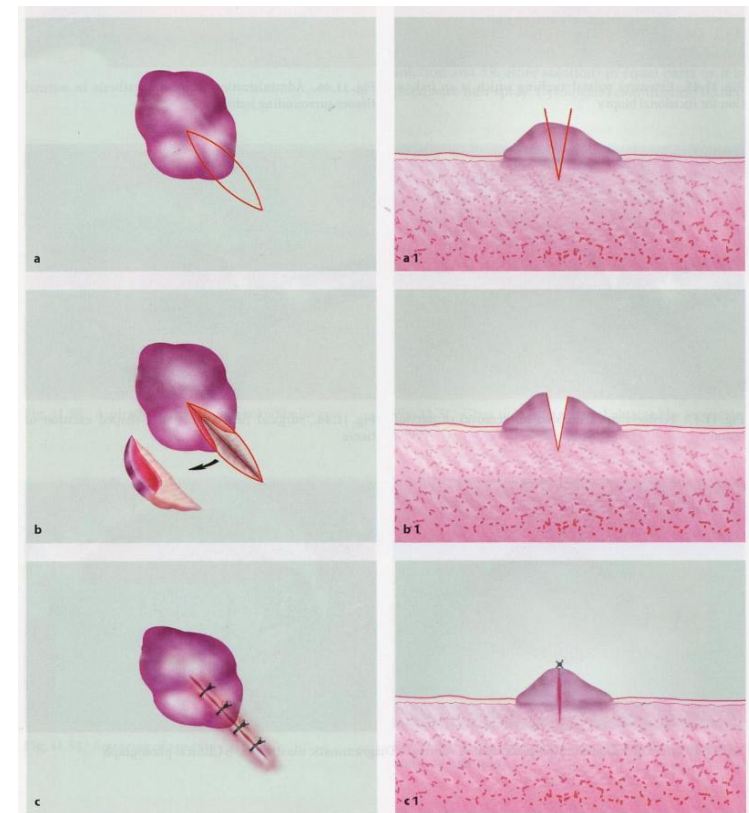
Staging

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

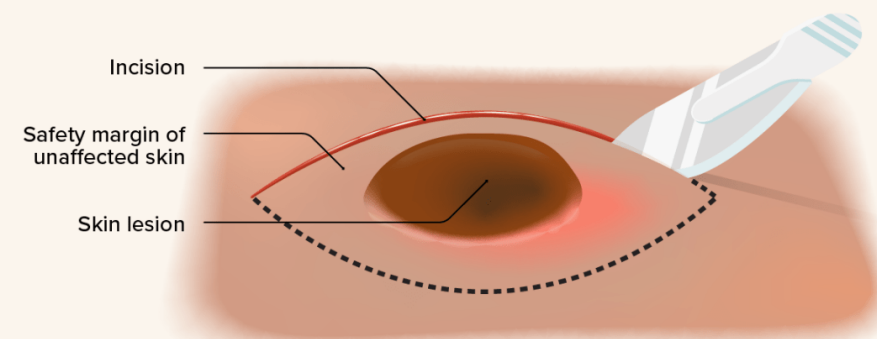
A. Diagnosis of primary melanoma is made by histologic analysis of full-thickness biopsy specimens.

- **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, b, c, Steps correspond to a, b, c, in vertical cross-sectional view

Excisional biopsy



- **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

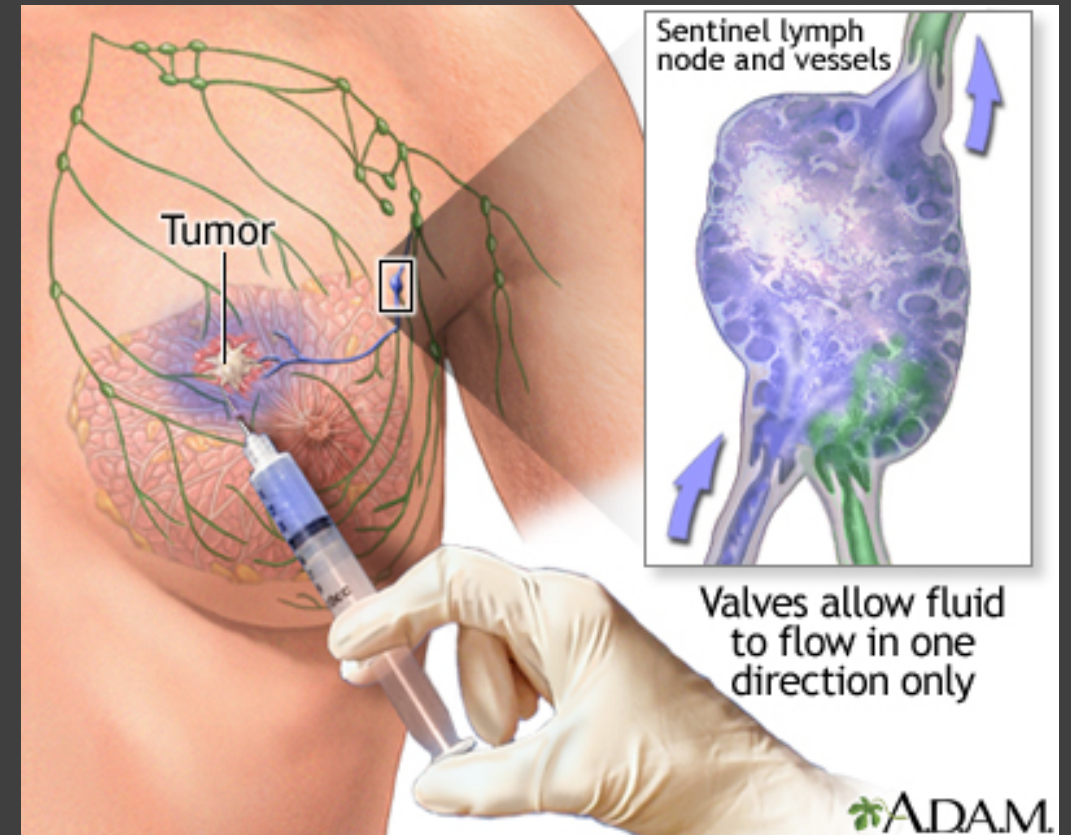
Melanoma Thickness (mm)	Margin (cm)
In situ	0.5
<1	1
1-4	2
>4	2-3
	(controversial)

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 1- to 2-mm (intermediate thickness) melanomas

2. Sentinel lymph node biopsy (SLNB)

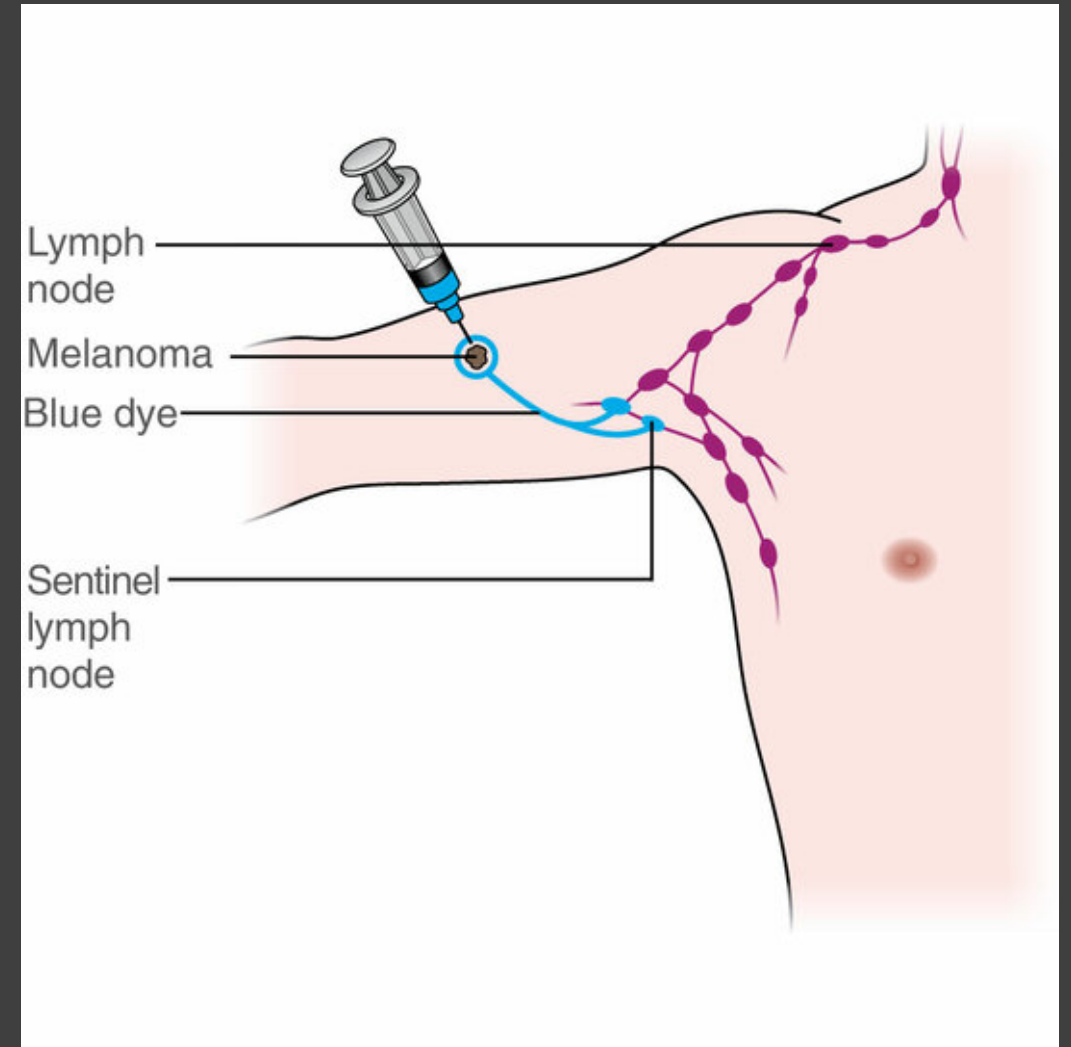
- a. In the sentinel node theory, a sentinel node will be the first lymph node seeded by tumor cells; therefore, excision of sentinel node(s) alone is adequate to determine nodal status. The morbidity of SLNB is considerably less than END. Sentinel node(s) can be detected in more than 20% to 95% of patients. 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 ^{99}Tc .
- (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)**

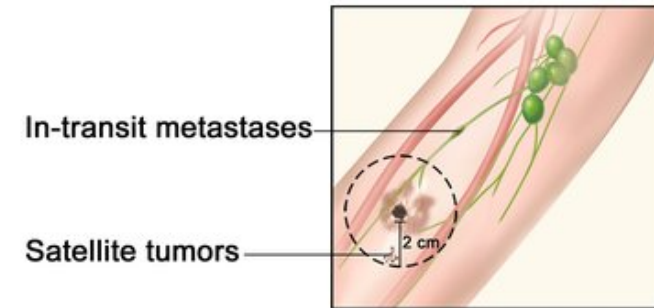
F. Following excision of the primary tumor, drapes, instruments, gowns, and gloves are changed and the regional lymph node basin(s) identified by lymphoscintigraphy are explored. All radioactive ("hot") and/or blue nodes are excised

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 tomographic (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.

Have cancer cells spread near the primary tumor?



Microsatellite tumors (only seen with a microscope)

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D. Surveillance and treatment of melanoma recurrence

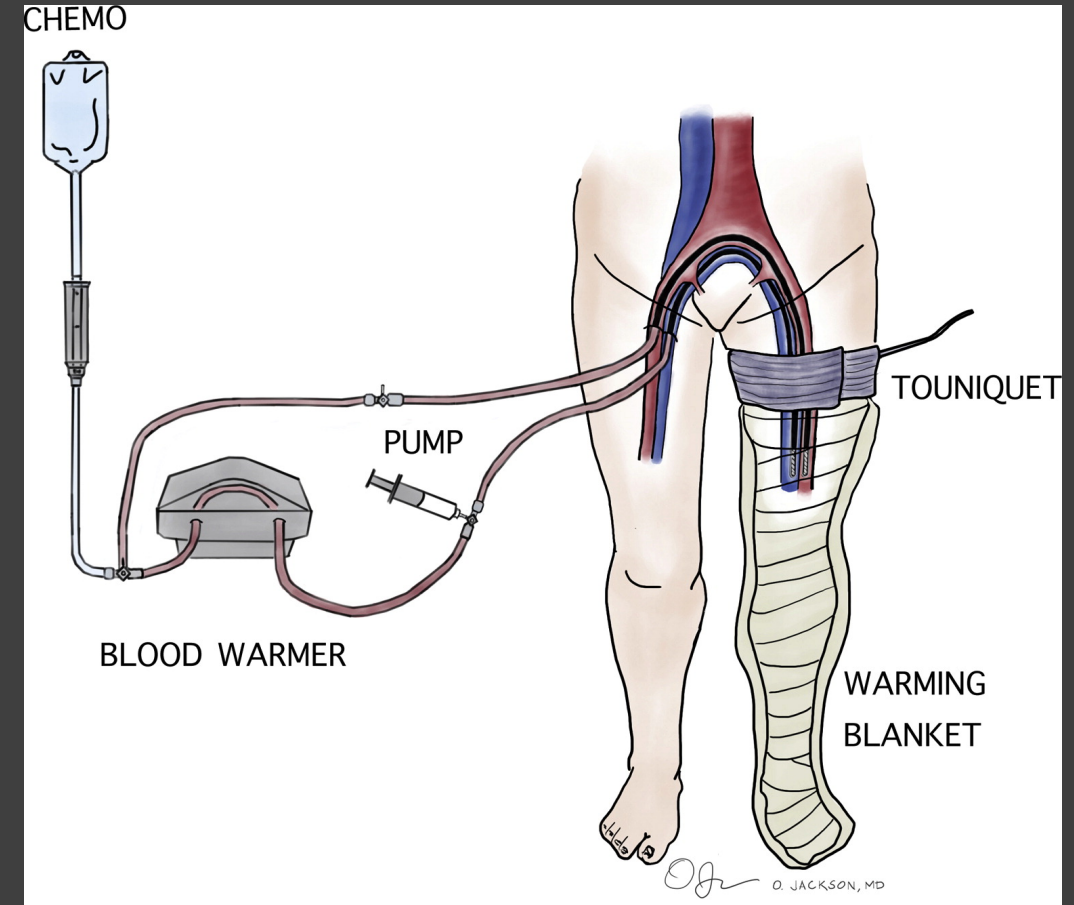
5. **The most common sites** of recurrence are the skin, subcutaneous tissues, distant lymph nodes, and then other sites (lung, liver, brain, bone, gastrointestinal tract).

6. **Reexcision** 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. 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.

