

The Not Good, The Bad, and the Ugly: An Update on Melanoma and Non-melanoma Skin Cancer for Primary Care Clinicians

Skin, Bones, Hearts, and Private Parts 2020

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Learning Objectives

- Review the epidemiology of cutaneous neoplasms
- Discuss the risk factors
- Identify appropriate candidates for screening
- List the characteristics of a lesion that make it suspicious for melanoma or non-melanoma skin cancer
- Review the techniques for biopsy of a suspicious lesion
- Identify treatment and prognosis for different stages of melanoma and non-melanoma skin cancer
- Focus on prevention and screening

Skin Neoplasms: The Line-up

BENIGN

Seborrheic keratosis

Acrochordons

Hemangioma

Lentigines

Nevi

Lipoma

MALIGNANT

Actinic keratosis

Keratoacanthoma

Basal Cell CA

Squamous Cell CA

Malignant melanoma

Distinguishing Features (In General)

BENIGN vs. MALIGNANT



- Small Size (<5-6 mm)
- Slow Growth
- Distinct Borders
- Symmetrical
- Regular pigment



- Large Size
- Rapid Growth
- Indistinct Borders
- Not symmetrical
- Irregular pigment

Current data shows that the risk of developing skin cancer in a person's lifetime is:

1. 1 in 2 persons
2. 1 in 5 persons.
3. 1 in 10 persons.
4. 1 in 25 persons.
5. 1 in 80 persons.

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3. 1 in 10 persons.
4. 1 in 25 persons.
5. 1 in 80 persons.

ONE IN FIVE Americans will develop skin cancer in their lifetime.



SPOT Skin Cancer™

SpotSkinCancer.org

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Skin Cancer Stats

- **More** people are diagnosed with skin cancer each year in the **U.S. than all other cancers combined**
- The annual cost of treating skin cancers in the U.S. is estimated at **\$8.1 billion**
 - \$4.8 billion for non-melanoma skin cancers
 - \$3.3 billion for melanoma
- The diagnosis and treatment of non-melanoma skin cancers in the U.S. **increased by 77%** between 1994 and 2014 and melanoma rates have more than **doubled**
- Nearly **20 Americans die from melanoma every day**
- An estimated 6,850 people will die of melanoma in 2020
 - 4,610 will be men and 2,240 will be women
- 90% of non-melanoma skin cancers and 80% of melanoma skin cancers are associated with exposure to **UV radiation from the sun**
- UV radiation **is a human carcinogen**

Risk Factors: Things We Can't Control

- Age and biologic sex
- Caucasian
- Fair skin, blue eyes, blond, freckles, red hair
- Personal history of skin CA
- Family history of skin CA, familial dysplastic mole syndrome, large congenital nevi
- Dysplastic or atypical nevi, lots of nevi
- Xeroderma pigmentosum
- Immunosuppression

Risk Factors: Things We Can

- UVA and UVB exposure
 - Cumulative
 - Intermittent
 - Tanning bed use

Hmmm...How Many Sunburns Have You Had?

- A person's risk for melanoma doubles if he or she has had more than 5 sunburns (or just 1 blistering burn)
- One indoor tanning session increases SCC risk by 67%, BCC by 29%, and melanoma by 20%
 - More people develop skin cancer from indoor tanning than lung cancer from smoking
- Regular daily use of SPF 30 reduces your risk of melanoma and NMSC by 50%

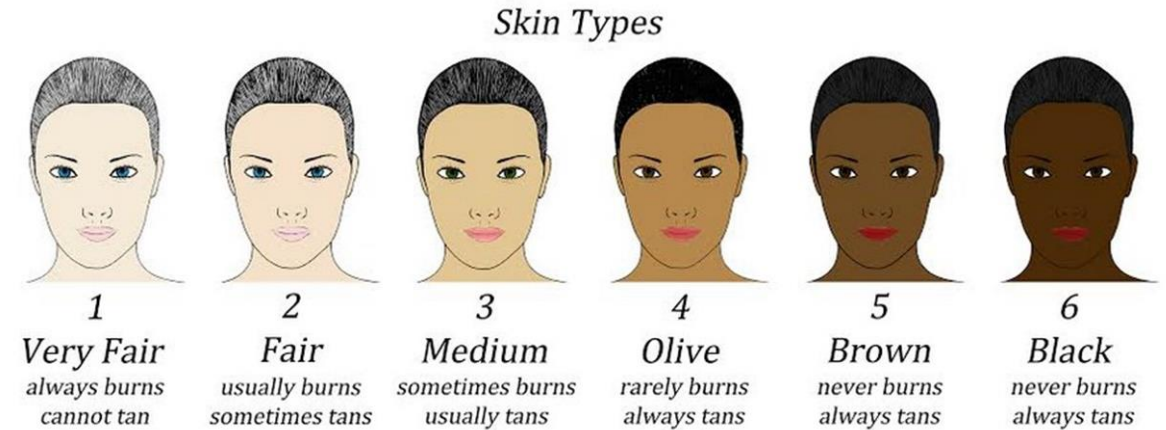


Non Melanoma Skin Cancers (NMSC)

- Basal Cell Carcinoma
 - Most common form of skin cancer
 - 4.3 million cases per year
- Squamous Cell Carcinoma
 - Second most common form of skin cancer
 - 1 million cases
 - 15,000 deaths
- Actinic Keratosis
- Keratoacanthoma

NMSC: Risk Factors

- UV exposure
- Radiation therapy
- Fitzpatrick skin types 1-4
- Prolonged immunosuppression
- HIV
- HPV
- Chronic inflammation
- Genetics
 - Basal cell nevus syndrome



Actinic Keratosis

Actinic Keratosis: Pathophysiology and Presentation

- Intraepidermal proliferation of atypical keratinocytes
- Low grade SCC, 5-15% progress to SCC

- Single or multiple erythematous plaques/papules
- Keratotic scale, crusted, ulcerated
- Better felt than seen – sandpaper and rough
- Skin adjacent to AKs usually shows signs of solar damage, such as a yellow or pale color, spotty hyperpigmentation, scattered telangiectasias, or xerosis



Actinic Keratosis: Management

- Destructive therapies
 - Surgery – shave, curettage, dermabrasion
 - Cryotherapy – most widely utilized
 - Photodynamic therapy – conventional and daylight
- Topical medications
 - 5-Fluorouracil
 - Imiquimod
 - Ingenol mebutate
 - Diclofenac
- Chemical peels
 - Trichloroacetic acid

Keratoacanthoma

Keratoacanthoma: Pathophysiology and Presentation

- Follicular-based squamous proliferation
- Low-grade squamous cell carcinoma, looks like SCC on pathology
- Associated with PUVA, trauma, chemical carcinogens, HPV

- Rapidly growing on hair bearing, sun-exposed skin
- Nodule, dome-shaped with a central keratotic plug, 1-2 cm
- Skin-colored, erythematous
- Proliferation, maturation, involution (4-9 months)

Keratoacanthoma



<https://www.dermnetnz.org/>

<http://www.dermatlas.com/derm/IndexDisplay.cfm?ImageID=-1486546221>

<http://www.atlasdermatologico.com.br/listar.asp?acao=mostrar&arquivo=Keratoacanthoma8.JPG>

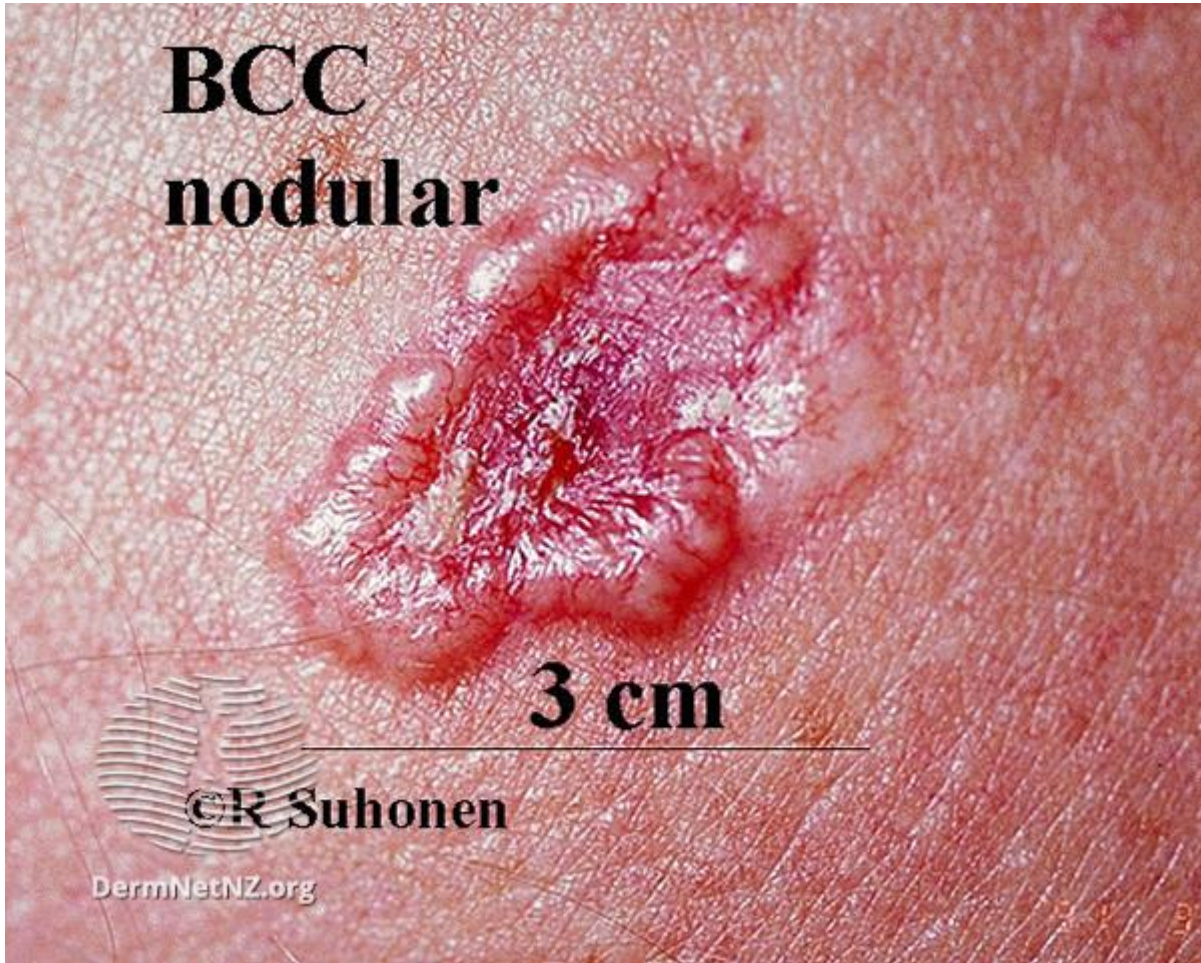
Keratoacanthoma: Management

- Conventional surgical excision – tissue to pathology
 - 4 mm margins, to subcutaneous fat
- Mohs for the face, ear, nose, instances when tissue sparing is important, lesions > 2 cm
- Intralesional therapy
 - 5-FU
 - Methotrexate
 - Bleomycin
 - Interferon alfa-2a/b

Basal Cell Carcinoma

BCC: Clinical Presentation

- 70% occur on the face (15% of the trunk)
- 3 types
 - Nodular (60%)
 - Most common on face
 - Pink or flesh-colored papule
 - Pearly or translucent
 - Telangiectasias
 - Rolled borders
 - Superficial (30%)
 - Morpheaform (5-10%)





Basal Cell Carcinoma: Low risk vs. High risk*

	LOW Risk	HIGH Risk
Location/size	Trunk and extremities < 20 mm (excludes pretibial, hands, feet, nails, ankles) Cheeks, forehead, scalp, neck, pretibial < 10 mm	> 20 mm > 10 mm Central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, pre and post auricular, temple, ear, genitalia, hands, feet
Borders	Well-defined	Poorly defined
Primary vs Recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of Prior RT	No	Yes
Pathology Subtype	Nodular or superficial	Aggressive growth pattern
Perineural Involvement	No	Yes

Squamous Cell Carcinoma

SCC: Clinical Presentation

- Erythematous scaly patch
 - Consider in the ddx of dermatitis that does not respond to tx
- Sun-exposed ears, lips, face (75%)
- Potential to metastasize
- Arsenic, insecticides, herbicides
- Smoking
- EtOH
- Immunocompromise





Cutaneous squamous cell carcinoma



Red papulo-nodule with scale on dorsal hand.

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UpToDate®

Squamous Cell Carcinoma: Low risk vs. High risk*

	LOW Risk	HIGH Risk
Location/size	Trunk and extremities < 20 mm (excludes pretibial, hands, feet, nails, ankles) Cheeks, forehead, scalp, neck, pretibial < 10 mm	> 20 mm > 10 mm Central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, pre and post auricular, temple, ear, genitalia, hands, feet
Borders	Well-defined	Poorly defined
Primary vs Recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of Prior RT or Inflammatory Process	No	Yes
Pathology Differentiation	Well or moderately	Poor
Perineural Involvement	No	Yes
Depth	< 2mm	≥ 2mm

NMSC: Treatment Options

Surgical

- Excision with margins
 - 4-6 mm low risk
- Mohs micrographic surgery
 - First line for high risk
- Curette and desiccation
 - Low risk only
- Cryosurgery
 - Low risk only

Non-Surgical

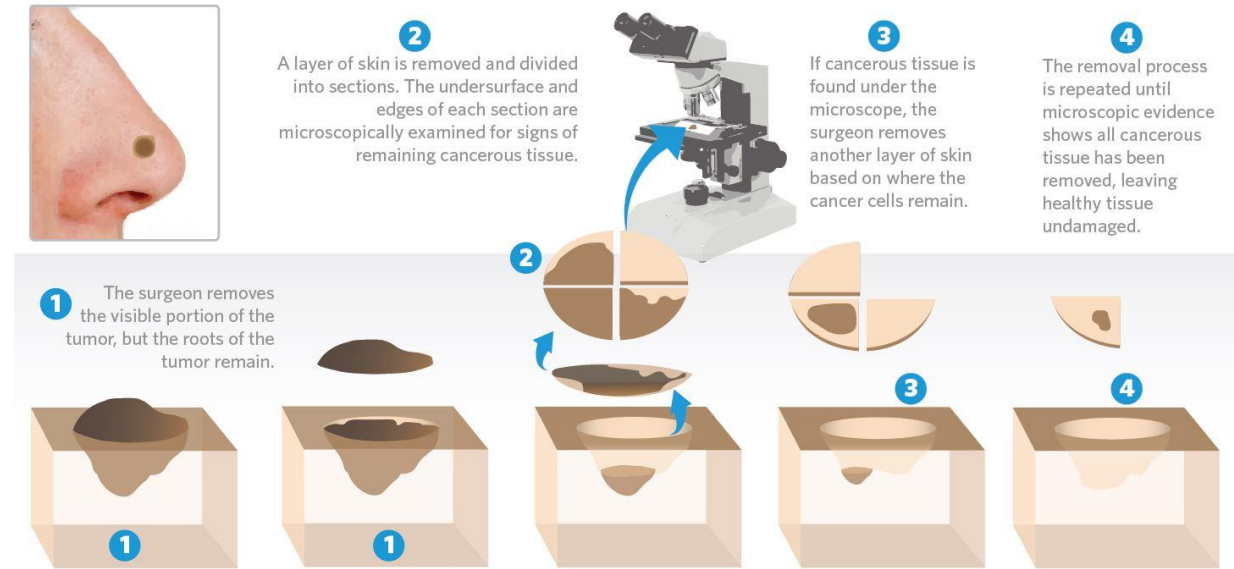
- Imiquimod cream (superficial BCC)
- 5% fluorouracil cream (sBCC)
- Photodynamic therapy (sBCC, SCCis)
- Laser
- Radiation
- Hedgehog pathway inhibitors
- Immunotherapy

Pathology: Key elements in addition to specimen

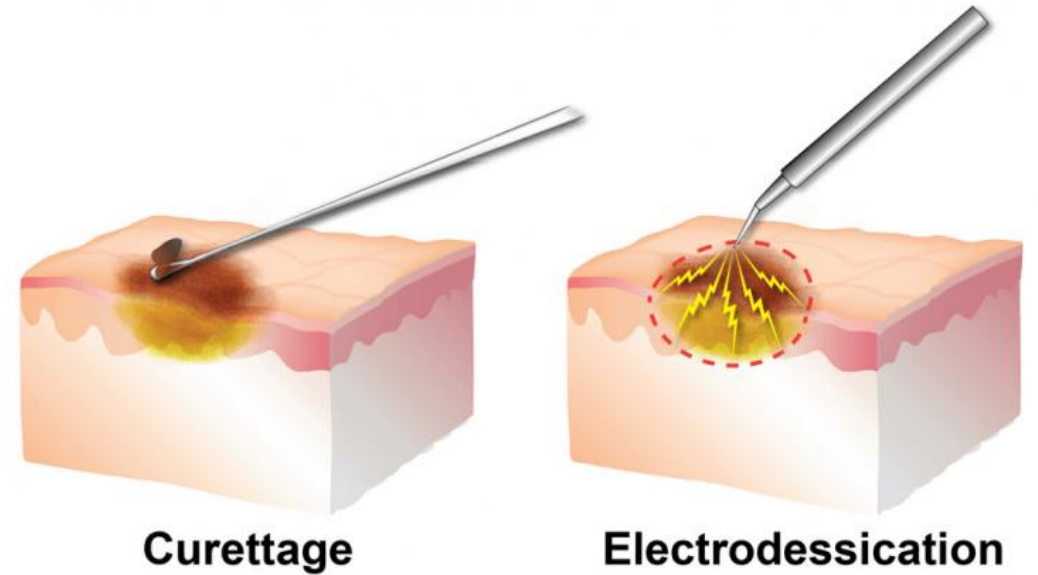
- Age
- Sex
- Anatomic location
- Recurrent lesion
- Size of lesion
- Immunosuppression
- History of radiation, organ transplant

Mohs Micrographic Surgery

- Gold Standard for high-risk NMSC
- Also useful for re-excisions when margins are positive after traditional excision
- 100% margin assessment
- Superior cure rates
- Low morbidity
 - 5-year disease free survival, 99% BCC, 97% SCC
- Significant tissue conservation



Curettage and Electrodesiccation



Topical Therapies

- Reserved for patients with small tumors in low-risk locations who are unable to tolerate more definitive therapies
- Imiquimod
 - Immunomodulator
 - sBCC on trunk, neck, extremities
 - Twice daily, once daily, every other day, for 6-16 weeks (typical once daily five times per week for 6 weeks)
 - AE – skin redness, swelling, erosions, crusts, vesicles, itching, tingling
- 5-FU
 - Antimetabolite
 - Twice-daily for 3-6 weeks
 - AE – Erythema, swelling, crust, erosions, ulcers, eschar

Photodynamic Therapy

- 2-part treatment
- Topical application of a photosensitizer (5-ALA or MAL) followed by incubation period
- Red, blue or broadband light irradiation
- Usually a single treatment cycle, but may be repeated
- Best evidence for use in small, well-demarcated nodular BCC

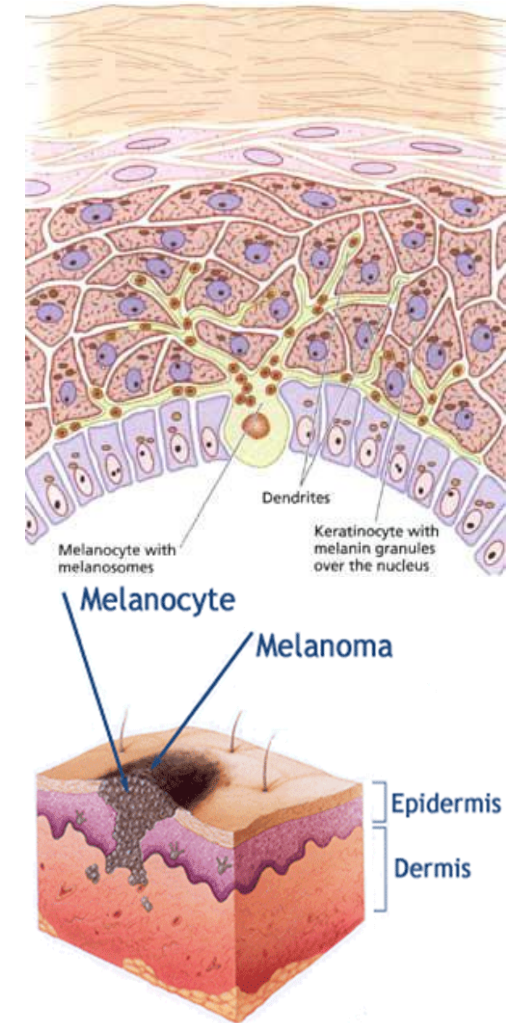
Preventative Measures: NMSC

- Sun protection
- Avoid tanning beds
- Regular F/U post diagnosis
 - New primary skin cancers
 - In-office
 - Self-screening
- Oral nicotinamide/vitamin B3 (500 mg BID, OTC)
 - Nazarali S, Kuzel P. Vitamin B Derivative (Nicotinamide) Appears to Reduce Skin Cancer Risk. *Skin Therapy Lett.* 2017;22(5):1–4.
 - Chen AC, Martin AJ, Choy B, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. *N Engl J Med.* 2015;373(17):1618–1626. doi:10.1056/NEJMoa1506197

Malignant Melanoma

What's Goes Wrong: Cancer of the Melanocytes

- Melanocytes originate from the neural crest cells in the fetus and then migrate to the skin at the dermal-epidermal junction
- Also migrate to the eyes (5%), meninges, upper esophagus, mucous membranes (1%)
- Melanocytes grow unchecked and abnormally
- Histologic findings
 - Cytologic atypia, mitotic figures, pagetoid or lentiginous growth pattern, positive immunohistochemical staining



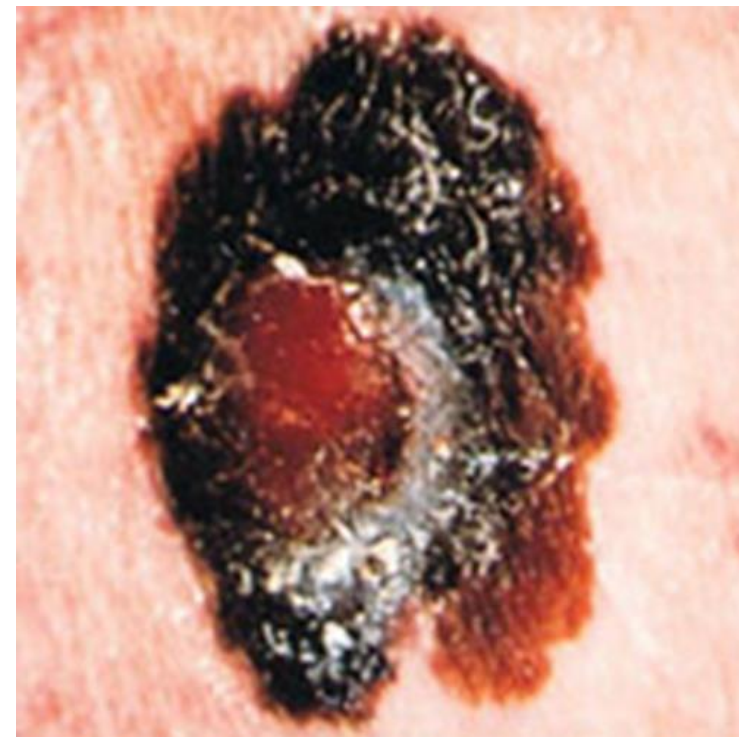
What is the most common site for the development of melanoma?

1. Head and neck
2. Nose and ears
3. Back and legs
4. Back of the hands

What is the most common site for the development of melanoma?

1. Head and neck
2. Nose and ears
- 3. Back and legs**
4. Back of the hands

Normal or Abnormal?



ABCDE (maybe F)

- A
- B
- C
- D
- E

F is coming...

The Seven-Point Checklist

- Major features
 - Change in size or obvious growth
 - Irregular shape
 - Variety of shades of brown and black
- Minor features
 - Diameter > 6mm
 - Inflammation
 - Oozing, crusting, bleeding
 - Change in sensation

Ugly Duckling Sign

- Recognition of a lesion that looks different from the rest

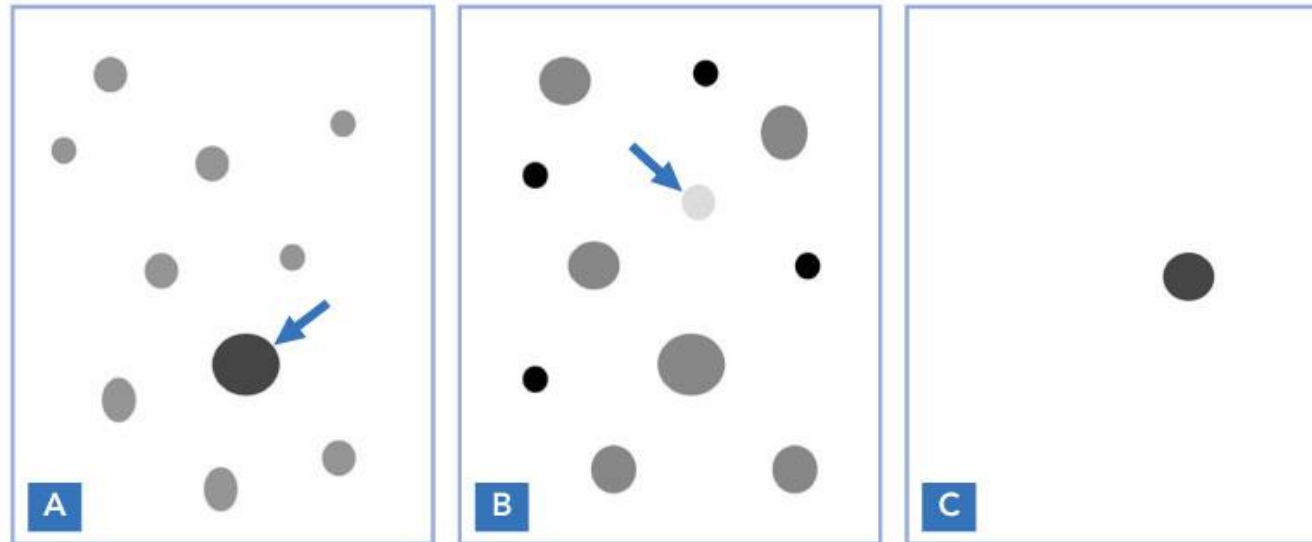
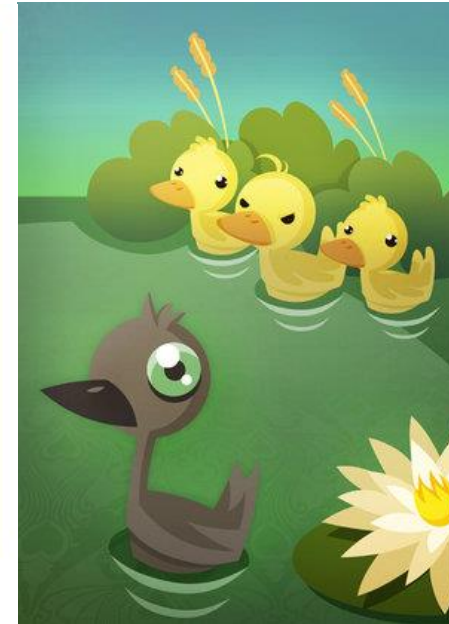


Figure 1. Three Examples of an Ugly Duckling



Dermoscopy

- Also called surface microscopy, oil epilluminescence microscopy
- Technique that uses incident light magnification, usually 10x, with the addition of a liquid at the skin-microscope interface
- Liquid eliminates the normal scattering of light at the level of the stratum corneum, allowing the epidermis to become transparent
- Utilized most often in the dermatologist office
- Requires training



Dermoscopy Findings in Melanoma



- Asymmetry of colors and shapes
- Areas of de-pigmentation
- Blue-gray dots
- Pseudo pods
- Blue-white veil

<http://dermoscopic.blogspot.com>



Typical Presentation

- Pigmented lesion that has recently changed
- New lesion that develops in adulthood or looks different than other nevi
- Lesion usually enlarges radially, then becomes raised
- Irregular borders
- Variegated color (pink-blue-black)
- Presence of ulceration or bleeding

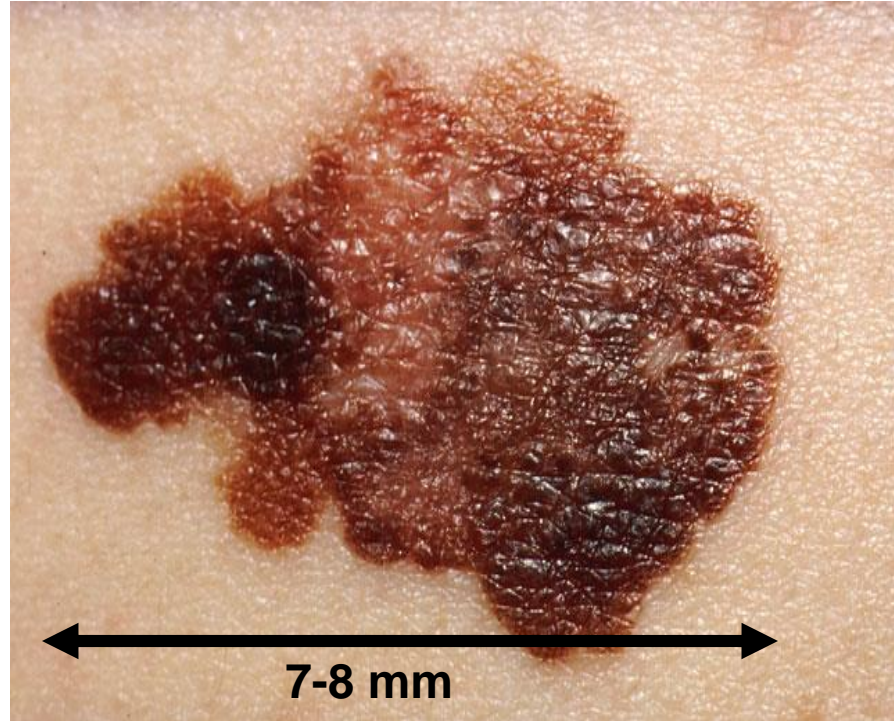
- Then...it looks like a good candidate for biopsy

Work-up of Suspicious Pigmented Lesion



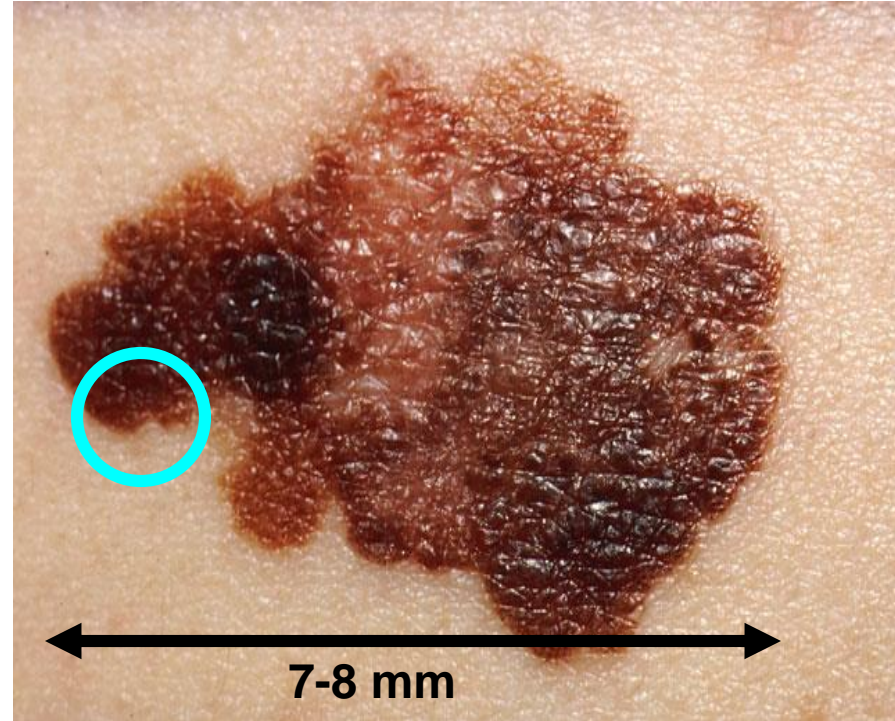
- Biopsy
- Review pathology and staging
- REFERRAL
- Lymph node evaluation (sentinel node mapping)
- Re-excision with 1-2 cm margins and/or lymph node removal
- Search for metastasis (lung, liver, brain), consider CXR, LDH, CT, brain imaging

So, where do I biopsy this thing?



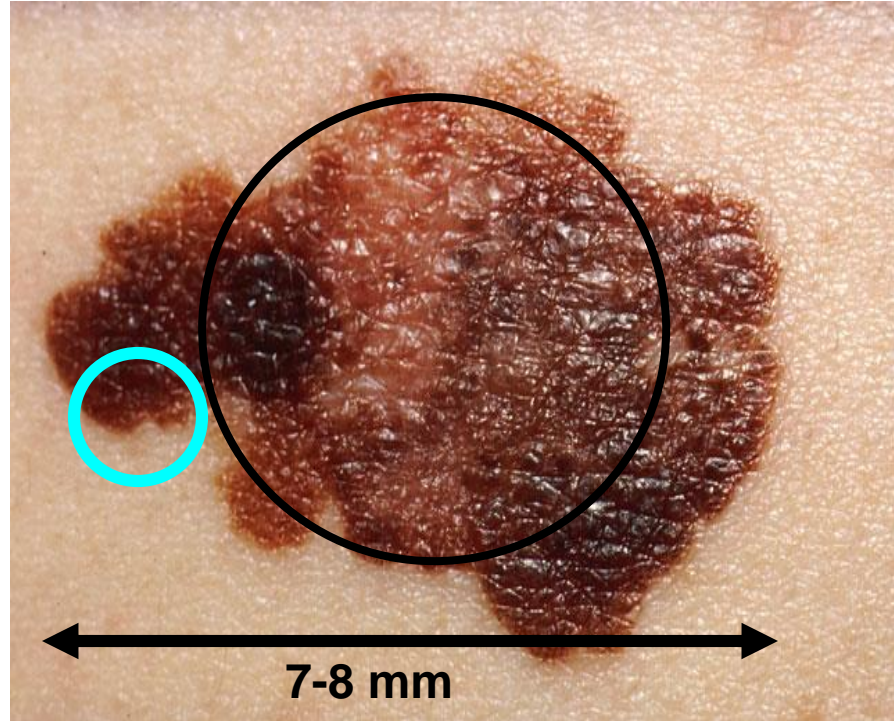
Where do I biopsy this thing?

Here



Where do I biopsy this thing?

Here
Here

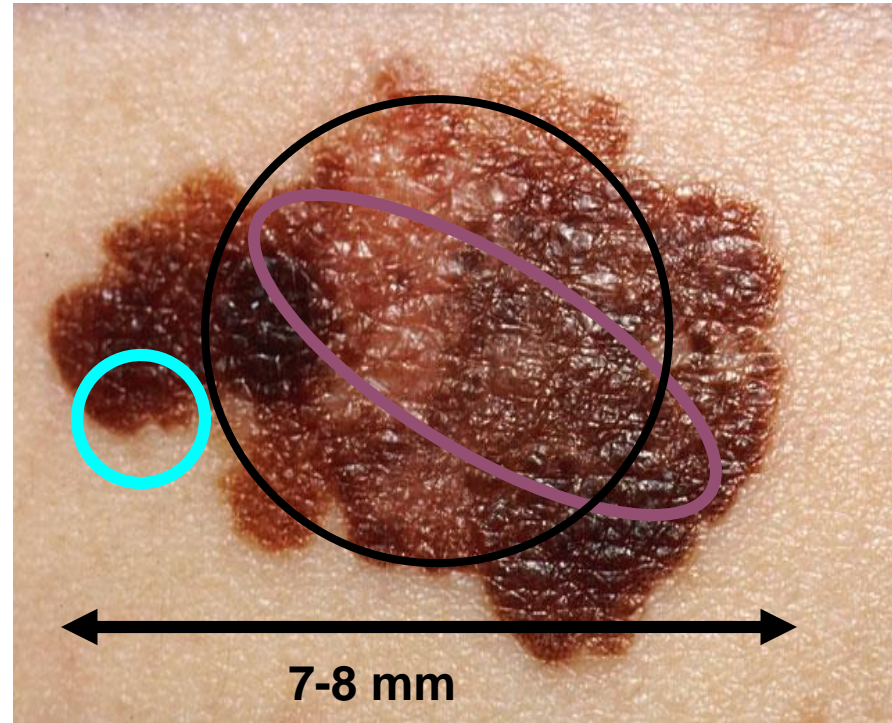


Where do I biopsy this thing?

Here

Here

Here



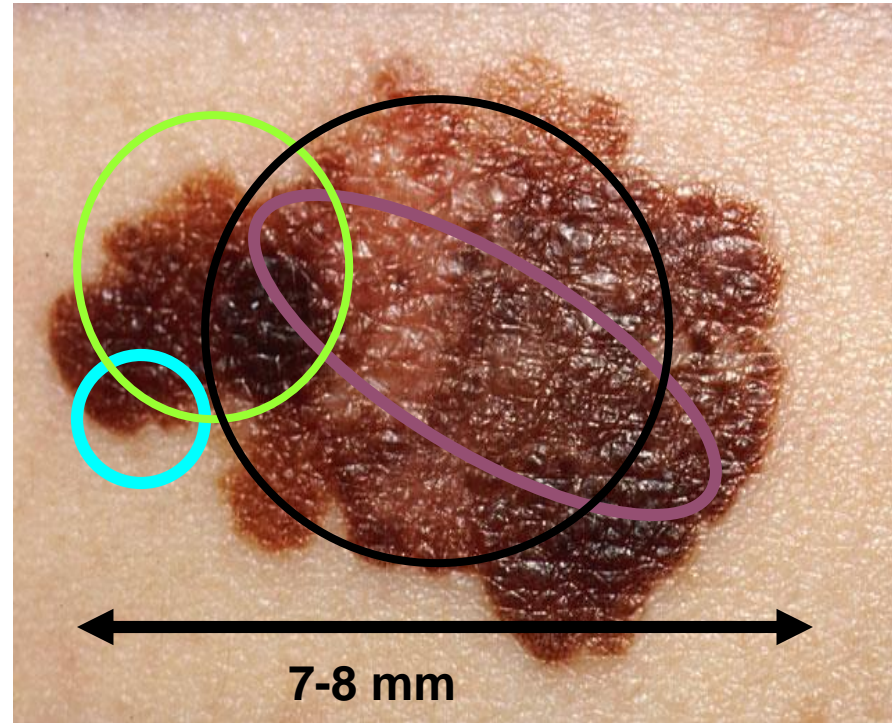
Where do I biopsy this thing?

Here

Here

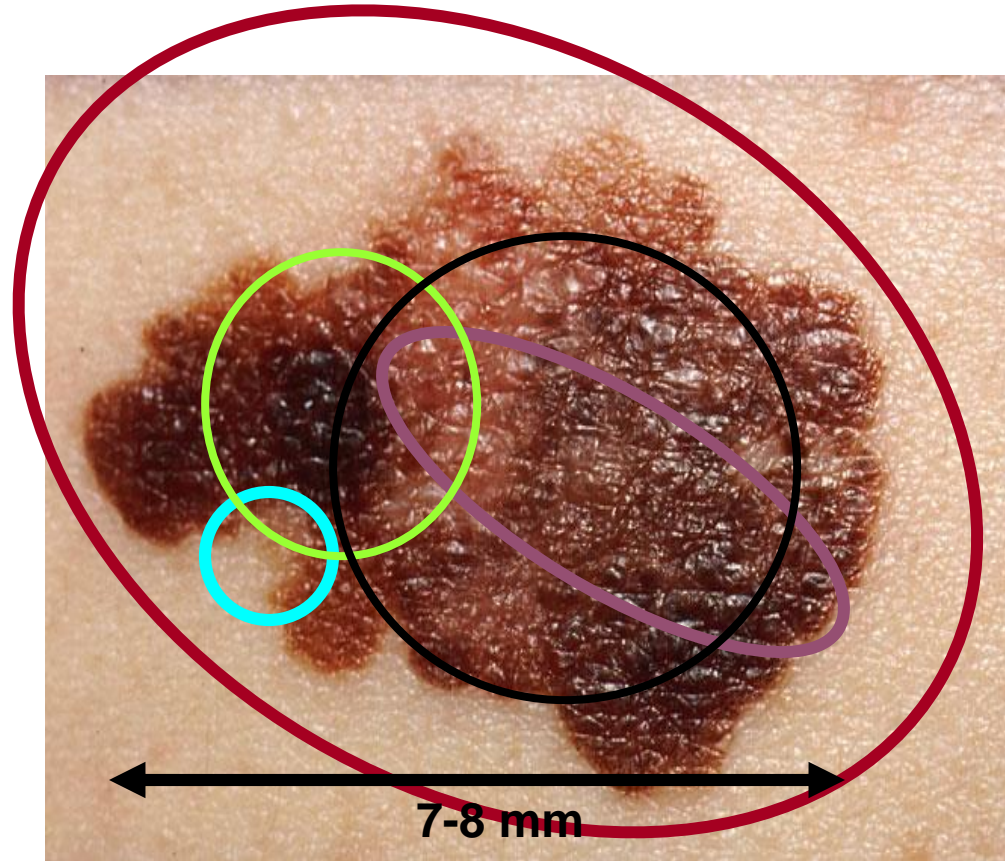
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Here

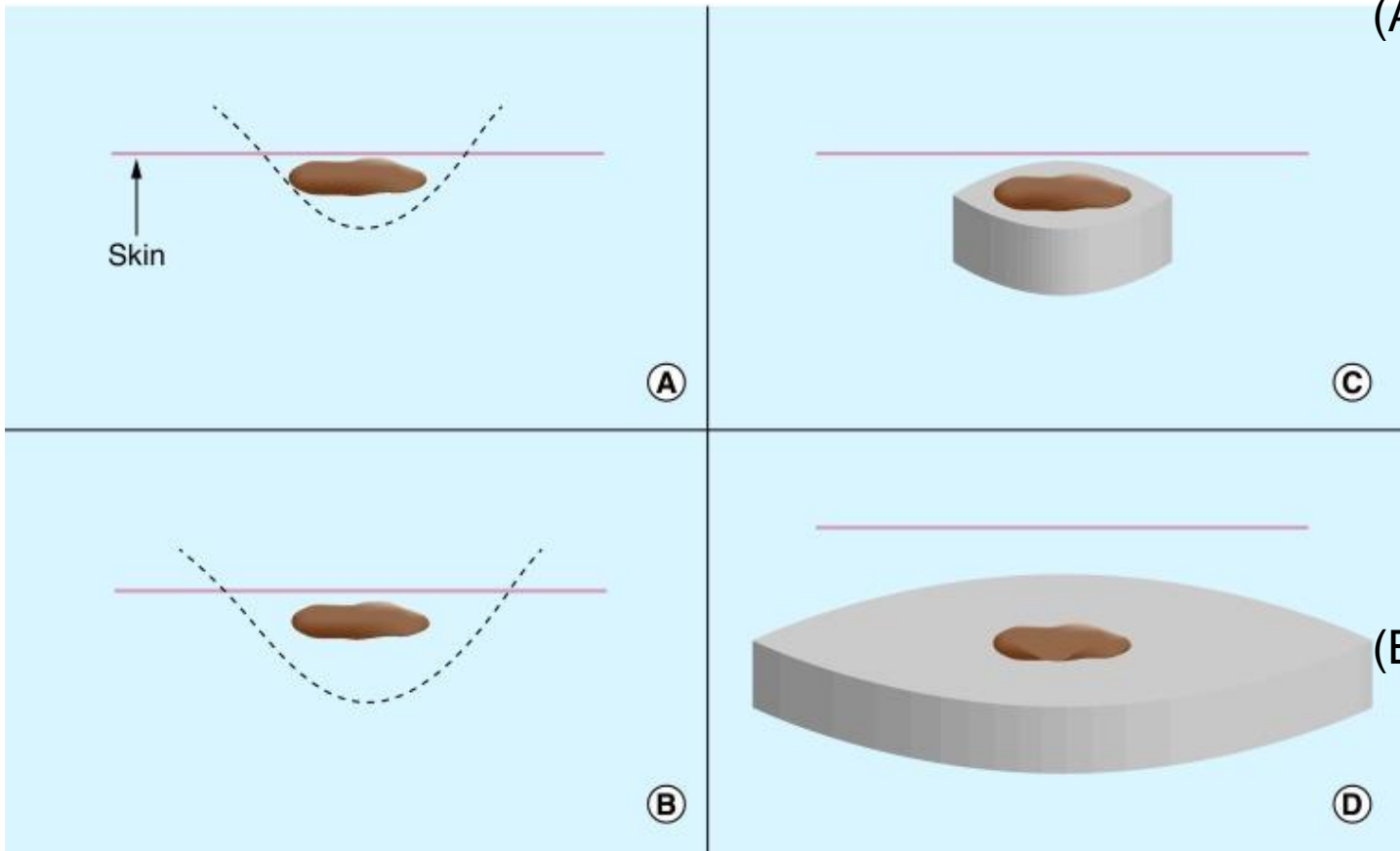


Where do I biopsy this thing?

Here
Here
Here
Here
Or Here



Excisional biopsy with 1-2 mm margins of healthy skin and to include all layers through subcutaneous fat



(A) Shave biopsies are the most superficial, with the fastest healing time, but run the risk of transecting the base of the tumor. The term 'shave biopsy' has variable meanings depending on the practitioner and can range from a superficial incisional biopsy to a complete excisional biopsy of a thin lesion. Shaves are appropriate for biopsying thin keratinocyte carcinomas but should not be utilized for biopsying suspicious pigmented lesions. The defect heals via secondary intention.

(B) The saucerization (i.e., deep shave or scoop) biopsy is similar to a shave biopsy but is wider and deeper (involving reticular dermis). Saucerizations may be used for biopsying suspicious pigmented lesions. The defect heals via secondary intention.

(C) The punch biopsy allows sampling of all skin layers and may be used for biopsying suspicious pigmented lesions or keratinocyte carcinomas. The defect is closed with sutures.

(D) The fusiform/elliptical excision is the largest type of biopsy and requires placement of sutures, leaving the largest scar.

Types of Melanoma

- Superficial spreading
- Nodular
- Acral lentiginous
- Lentigo maligna

Superficial Spreading Melanoma



- Most common type (70%)
- Peak incidence 40-50s
- Slowly growing, begins as pigmented macule or plaque
- Area of focal darkening
- Irregular margins with differing pigmentation (black, blue, gray, pink, white)
- Arises on intermittently sun-exposed areas with greatest nevus density

Superficial Spreading Melanoma



Nodular Melanoma



- Second most common type (15%)
- Onset 50s
- Vertical growth phase first
- Trunk, head, neck
- Rapid growth (0.5mm per month)
- Well-circumscribed borders, uniform pigment, bluish-black
- “EFG” = elevated, firm, and growing quickly

Acral Lentiginous Melanoma



- 10% of cases
- Very aggressive
- Poorest prognosis
- Palms, soles, subungual
- May also present on mucous membranes
- Brown-black macule with color variegation and irregular borders
- More common among darker skin types
- Not associated with sun-exposure



Lentigo Maligna Melanoma



- Least aggressive, least common subtype
- Sun-exposed areas (face)
- Elevated nodules
- Usually arises from large macular brown lesions that have been present for years
- Onset 50-70s
- Best prognosis

MM: Management

- American Joint Commission on Cancer (AJCC)
 - Revised system eliminating Clark level as prognostic for tumors > 1.0mm
- Based on **staging of the lesion**
 - Breslow vertical thickness of lesion (simplified thresholds 1.0, 2.0, 4.0mm)
 - Presence of ulceration
 - Mitotic rate
 - Sentinel node
 - Presence of regional or distant disease (nodal involvement or mets)
 - LDH level in regional or distant mets

Definitions

Primary Tumor (T)

- TX** Primary tumor cannot be assessed (for example, 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 1.1 - 2.0 mm
- T3** Melanomas 2.1 - 4.0 mm
- T4** Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and thickness as shown below:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Regional Lymph Nodes (N)

- NX** Patients in whom the regional nodes cannot be assessed (for example previously removed for another reason)
- N0** No regional metastases detected
- N1-3** Regional metastases based on the number of metastatic nodes, number of palpable metastatic nodes on clinical exam, and presence or absence of MSI²

NOTE: N1-3 and a-c subcategories assigned as shown below:

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult ¹ , no MSI ² b: clinically detected ¹ , no MSI ² c: 0 nodes, MSI present ²
N2	1-3 nodes	a: 2-3 nodes clinically occult ¹ , no MSI ² b: 2-3 nodes clinically detected ¹ , no MSI ² c: 1 node clinical or occult ¹ , MSI present ²
N3	>1 nodes	a: >3 nodes, all clinically occult ¹ , no MSI ² b: >3 nodes, ≥1 clinically detected ¹ or matted, no MSI ² c: >1 nodes clinical or occult ¹ , MSI present ²

Distant Metastasis (M)

- M0** No detectable evidence of distant metastases
- M1a** Metastases to skin, sub cutaneous, or distant lymph nodes
- M1b** Metastases to lung
- M1c** Metastases to all other visceral sites
- M1d** Metastases to brain

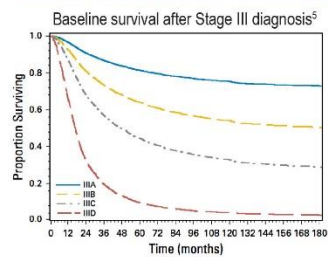
NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	Serum LDH
M1a-d	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Not assessed
M1a-d(0)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Normal
M1a-d(1)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging ³				Pathologic Staging ⁴			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	IB	T1b
	T2a		T2a
Stage IIA	T2b	N0	M0	IIA	T2b	M0	M0
	T3a		T2a
Stage IIB	T3b	IIB	T3b
	T4a		T4a
Stage IIC	T4b	IIC	T4b
Stage III	Any T	≥N1	M0	IIIA	T1-2a	N1a	M0
		T1-2a	N2a	..
	IIB	T0	N1b-c	M0
		T1-2a	N1b-c	..
		T1-2a	N2b	..
		T2b-3a	N1a-2b	..
	IIC	T0	N2b-c	M0
		T0	N3b-c	..
		T1a-3a	N2c-3c	..
		T3b-4a	Any N	..
		T4b	N1a-2c	..
	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

Notes

- ¹Nodes are designated as 'clinically detectable' if they can be palpated on physical exam and are confirmed melanoma by pathology following excision/biopsy.
- ²MSI comprise any satellite, locally recurrent, or in transit lesions.
- ³Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
- ⁴Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 and I patients are the exceptions; they do not necessarily require pathologic evaluation of their lymph nodes. Physicians should "discuss and consider" SLNB for patients with T1b Stage IA disease; physicians should "discuss and offer" SLNB for patients with Stage IB disease.
- ⁵From Haydu et al., Journal of Clinical Oncology, 2017.



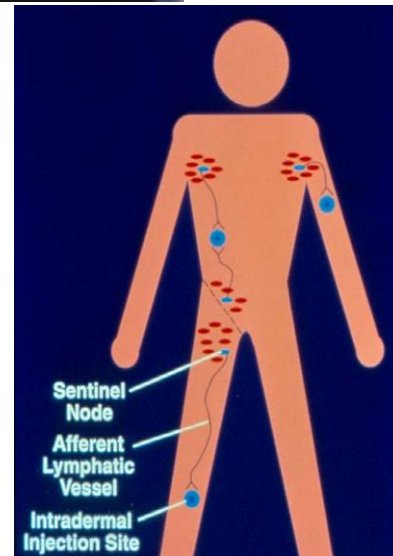
Stage	Baseline	3y survivors
IIIA	81.4	83.1
IIIB	64.0	76.0
IIIC	44.5	66.7
IIID	9.8	40.6

- <https://cancerstaging.org/references-tools/quickreferences/Documents/MelanomaMedium.pdf>

MM: Management

- Surgical excision (re-excision)
 - 1-2 cm margins are all that is needed
- Routine laboratory tests and imaging studies not required for asymptomatic patients with melanoma 4 mm or less (LDH, CXR)
- Sentinel node mapping and biopsy
 - For primary lesions > 1.0 mm
- Lymph node resection

Sentinel Node Mapping



- Status of SLN reflects that of the entire regional basin
- Dye and/or radiocolloid injected
- Identifies 20% of pts with occult met disease and allows early complete lymphadenectomy

MM: Management

- Adjuvant therapy based on risk of disease recurrence, stage, pt age, comorbidity, patient preference
 - Checkpoint inhibitor immunotherapy (anti-PD-1) – nivolumab, pembrolizumab, ipilimumab
 - Targeted therapy (BRAF/MEK inhibitors) – BRAF V600 driver mutation – dabrafenib plus trametinib, vemurafenib
 - Interferon alfa-2b
 - Chemotherapy- dacarbazine and other combinations
 - Radiation – mets
- Aggressive follow-up
- Focus on prevention

AJCC Melanoma of the Skin Staging – 8th Edition

- What does it mean for Primary Care?
- SLNB
- New treatment options for later stages

Surveillance

- Most recurrence occurs < 5 years
- Approximately 5% lifetime risk of second primary melanoma
- Justifies lifelong skin surveillance
- Stage 0: q 6 months indefinitely
- Stage I-II: q 3 months for 2 years, then q 6 months for 3 years, then yearly or continuing bi-annually

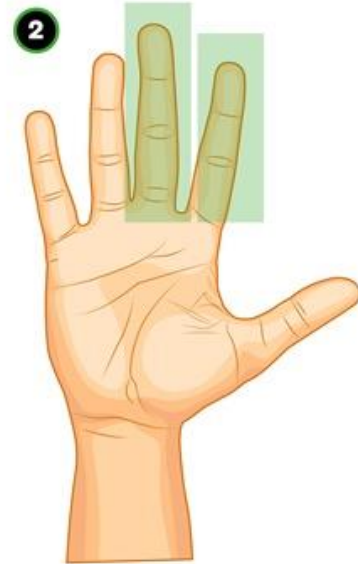
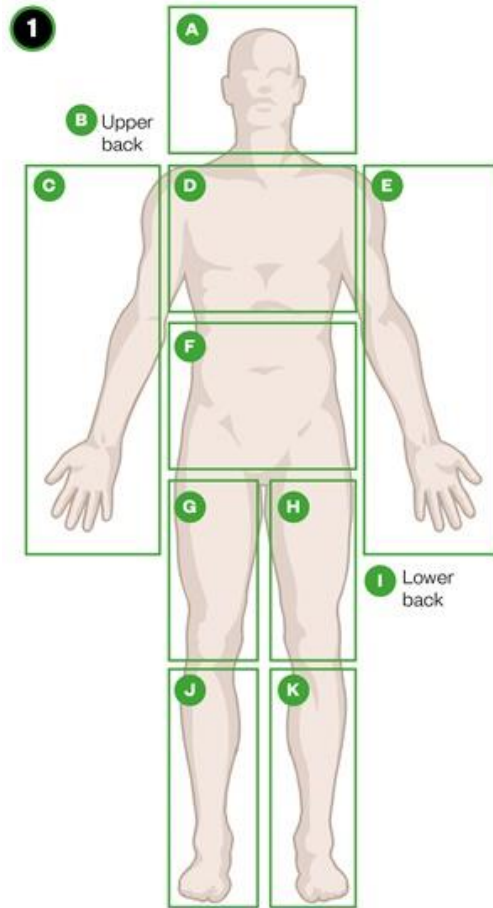
Refer Pts to Melanoma Care Centers in the US

- <http://www.melanomacare.org/centers.shtml>

Focus on Prevention

- Seek shade - cover up and stay inside
- Slather sunscreen
- Self-examination

Focus on Prevention: Sunscreen Application



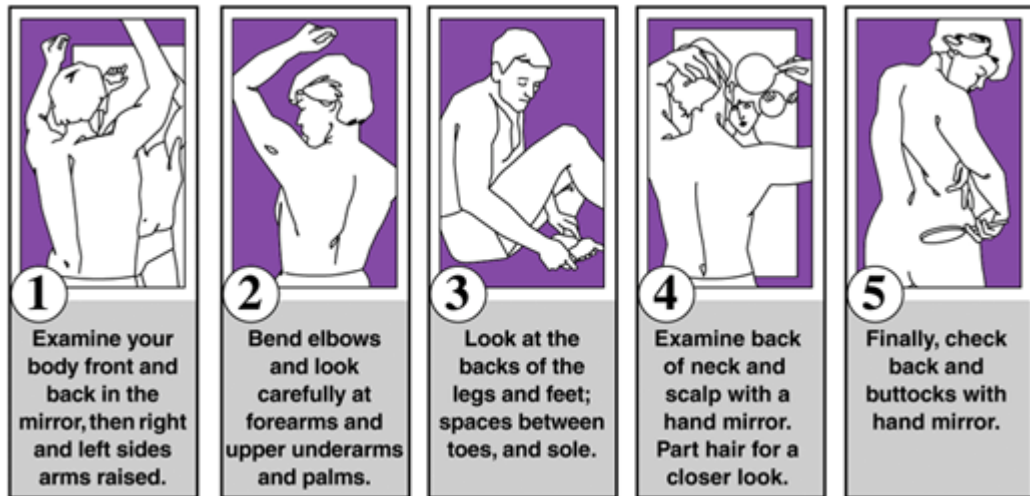
- 2 fingers worth
- Lasts 2 hours
- SPF 30 or greater
- UVB and UVA protection

Focus on Prevention: Skin Self-Exam

- Educate pts to perform skin self-exams on a regular basis
- Examine your “Birthday Suit” on your birthday
- Screen the ones you love on Valentine’s Day

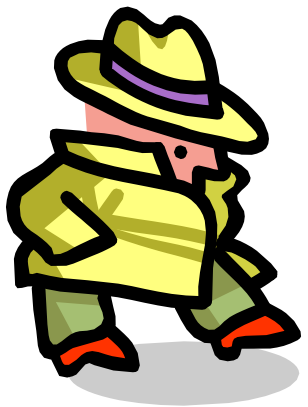
Skin Self-Exam

- <https://www.aad.org/public/spot-skin-cancer/learn-about-skin-cancer/detect/body-mole-map>
 - Melanoma Monday
 - AAD created skin cancer screening day
 - First Monday in May each year since 1985



Final Thoughts...

- See **Spot**
- See **Spot** change
- See PA
- “Dear 16-year-old me” https://www.youtube.com/watch?v=_4jgUcxMezM



Selected References/Resources

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