Skin Cancer Overview for the Primary Care Provider

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Disclosures

I have no financial interests to disclose.

Some treatments I will talk about will be "off-label." However, they are generally accepted as treatments in the dermatology community with supporting evidence-based research.

Objectives

- Identify the common clinical presentations of a BCC, SCC and melanoma skin cancer.
- Discuss the latest treatment guidelines for BCCs, SCCs and melanoma skin cancers.
- Describe the clinical presentation of actinic keratoses and evidence based management for the lesions.

Resources

https://dermnetnz.org/

https://www.aad.org/member/clinical-quality

Basal Cell Carcinoma (BCC)

Overview

- Most common malignancy in the United State.
- Over 3 million patients diagnosed every year.
- Rarely metastasizes: 0.0028% to 0.55%
- Risk factors: fair skin, blue eyes, sun exposure or sunburn history, immunosuppression, arsenic exposure
- Associated with a gene mutation in the hedgehog pathway
- About 50% of patients have a 2nd BCC within two years of initial BCC

Clinical Presentation

Based on subtype: Nodular, Superficial, Morpheaform

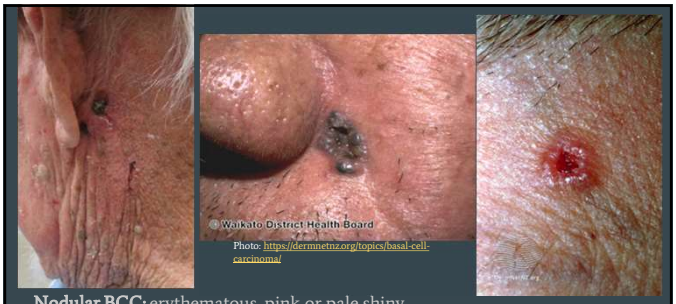
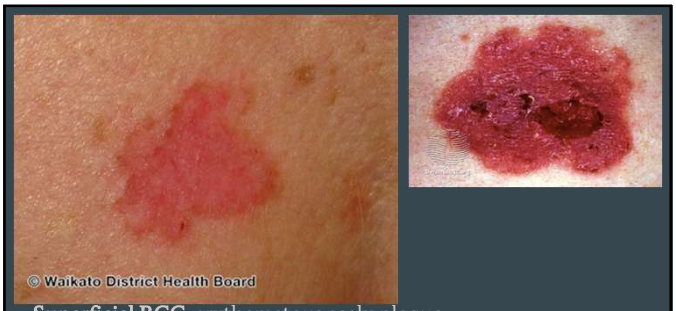


Photo: https://dermnetnz.org/topics/basal-cell-carcinoma/

Nodular BCC: erythematous, pink or pale shiny papule with "arborizing" vessels and sometimtimes grey speckles, sometimes ulcerated

Photo: https://dermnetnz.org/topics/basal-cell-carcinoma/



Superficial BCC: erythematous scaly plaque, can have erosions or a rolled border (subtle)

Photos: https://dermnetnz.org/topics/basal-cell-carcinoma/

Morpheaform: scared looking. Red, pink, white, atrophic plaques/papules

Photos: https://dermnetnz.org/topics/basal-cell-carcinoma/

Biopsy technique

All acceptable: Shave, Punch , Excisional biopsy

Pertinent information to provide the pathologist:

- Age, Sex, **Anatomic location** (be specific), Recurrent lesion
- Size of lesion, Immunosuppression, History (ie radiation burn, organ transplant)

The pathologist *should* provide the following in the the path report:

- **Histologic subtype**, Invasion beyond reticular dermis, Perineural involvement

Treatment

Risk Determination:

Low risk

- Less than 2 cm on trunk and extremities
- Less than 1 cm on cheeks, forehead, scalp, neck, and pretibia.
- Well defined borders
- Type: Nodular, superficial

High risk

- Greater than 2 cm on trunk and extremities
- Greater than 1 cm on cheeks, forehead, scalp
- Any size on central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular area, temple, ear, genitalia, hands, and feet.
- Poorly defined borders, recurrent BCC, Immunosuppressed patient, previous site of radiation
- Type: morpheaform, basosquamous, sclerosing, infiltrative, or micronodular
- Perineural involvement

Treatment Guidelines: Low Risk BCC

Standard of Care - **Excision** with 4mm margins is standard of care (94-98% cure rate)

Other options:

- **Electrodesiccation and curettage (ED&C)** - no specific guidelines provided by AAD.
  - Benefits: In-office, no mobility restrictions. Work well for low risk BCCs (nodular/superficial and less than 2 cm) on the trunk, arms, legs. Not for high risk locations.
  - Cons: Cannot "prove" the BCC is destroyed with pathology, lower cure rate, circular scarring
- **Cryosurgery** - double freeze/thaw cycle of 30-60 seconds
  - Utilize when excision is impractical or not indicated for low risk superficial BCCs only
  - Cure rate is variable: 95%-39%

Treatment Guidelines: Low Risk BCC

Superficial BCC treatment alternative to excision

- Topical modalities→ fluorouracil, imiquimod, PDT, superficial radiation therapy
  - Use if surgery is not feasible
  - Imiquimod and fluorouracil have a 60-80% cure rate
- Imiquimod (Aldara, Zyclara)
  - More available data for treating BCC and prefered by AAD over 5FU.
  - FDA approved for superficial BCC
  - Dosing: 5 times/week for 6 weeks
  - Potential systemic side effects, flu-like symptoms, etc. in addition to topical SE below.
- Fluorouracil (Efudex, AKA 5FU)
  - FDA approved for superficial BCC
  - Dosing: 5% BID for 3-6 weeks
  - Side effects: redness, swelling, erosions, crusts, vesicles, itching, tingling sensations, scarring, photosensitivity.

Treatment Guidelines: Low Risk BCC

Photodynamic Therapy (PDT)

- Apply a liquid photosensitizing agent: 5-aminolaevulinic acid or methyl-aminolaevulinic acid (5-ALA or MAL)
  - leave it on for one to several hours, then use blue or red light
- May need 2nd treatment
- Side Effects: erythema, erosions, sun avoidance is key, pain
- Cure rate: Mixed, 30-70%

Radiation Therapy

- For special situations only - surgery contraindicated or patient declines
- Perhaps a good option for BCCs less than 4 mm
- Types: superficial radiation therapy, brachytherapy, external beam radiation
- Delivered over several weeks, multiple session.

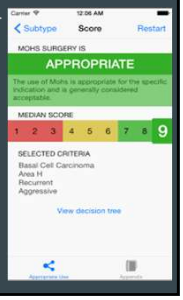
Mohs Micrographic Surgery

What is it?

- Smallest possible excision is made and tissue is prepped for slide readings at time of surgery.
- Mohs surgeon (trained in pathology via Mohs fellowship) reads the slide and ensures margins are clear.
- Second, third, etc stages taken until margins are clear.
- Once clear, patient's defect is closed.

Mohs Surgery

- High Risk BCCs: Mohs is standard of care
- Compared with excision, Mohs has a cure rate of 96% vs. 88% with excision for HIGH risk locations/aggressive BCCs.
- Benefit of tissue sparing, improved cosmetic outcomes and increased cure rate.
- Limitation: Uses paraffin blocks which can't undergo molecular testing for high risk features (such as melanoma)



Follow up and Education

- Annual or twice yearly full skin exams
  - 40-50% with one skin cancer will have another within 2 years
- Sunscreen, sun protection is paramount
  - Zinc and Titanium based sunscreens are best
- Nicotinamide: 500mg BID (not endorsed by AAD)
  - RCT of 386 patients over 12 months
  - Results: 23% decrease in NMSC
  - 11% reduction in Actinic Keratoses
  - Does not cause flushing, like niacin does.
  - Be careful if patient is on statins (can increase risk of muscle side effects)

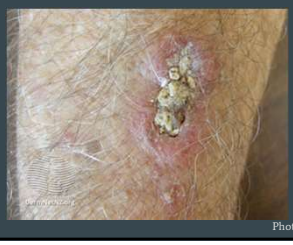
Cutaneous Squamous Cell Carcinoma

Squamous Cell Carcinoma

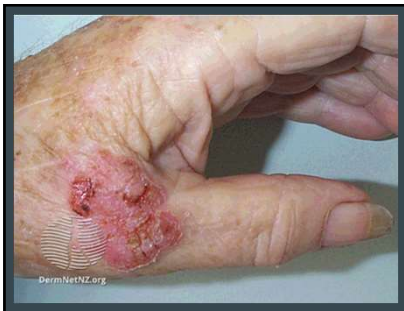
- Second most common form of skin cancer
- Male risk: 9-14%
- Female risk: 4-9%
- 200-400K new cases each year, resulting in about 3K deaths.
- Risk of mets is 4%
- Risk factors: sun exposure in youth, cumulative exposure over time, immunosuppressed (transplant patients), smoking, fair skin/blue eyes, presence of actinic keratosis
- Most common locations: Head, neck, arms hands

Presentation

Types: SCC in situ, Well differentiated SCCs, Keratoacanthoma type SCC, Moderately and poorly differentiated SCCs

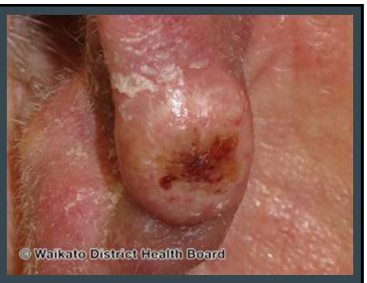


Photos: https://dermnetnz.org/topics/cutaneous-squamous-cell-carcinoma/



SCCIS or Bowen's

Photo: https://dermnetnz.org/topics/intraepidermal-squamous-cell-carcinoma/



Cutaneous horn and Keratoacanthoma types

Photos: https://dermnetnz.org/topics/cutaneous-squamous-cell-carcinoma/

Biopsy technique - same as BCC

All acceptable: Shave, Punch , Excisional biopsy

- More depth is often needed for SCC dx

Pertinent information to provide the pathologist:

- Age, Sex, Anatomic location (be specific), Recurrent lesion
- Size of lesion, Immunosuppression, History (ie radiation burn, organ transplant)

The pathologist *should* provide the following in the the path report:

- **Degree of differentiation, high risk histologic subtype**, Clark level/depth of invasion, Perineural involvement, **invasion of fascia, muscle, bone, margin status**

Treatment

Risk Determination

Low risk

- Less than 2 cm on trunk and extremities
- Less than 1 cm on cheeks, forehead, scalp, neck, and pretibia.
- Well defined borders
- Pathologic type: ***Well to moderately differentiated***
- ***Depth: <2mm***

Bold = difference from BCC risk stratification

***= I would argue Moderately should be considered high risk.**

High risk

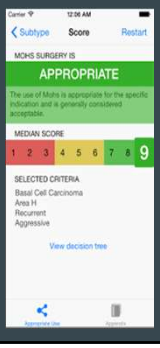
- Greater than 2 cm on trunk and extremities
- Greater than 1 cm on cheeks, forehead, scalp
- Any size on central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular area, temple, ear, genitalia, hands, and feet.
- Poorly defined borders, recurrent SCC, Immunosuppressed patient, previous site of radiation, ***rapidly growing, neurologic symptoms***
- Path Type: ***Poorly differentiated****
- ***Subtypes: Adenoid, adenosquamous, desmoplastic, or metaplastic***
- ***Depth: >2mm***
- Perineural involvement

Treatment Guidelines: Low Risk SCC

- **Standard of Care -** Excision with **4-6mm margins**
  - 94-98% cure rate

Treatment Guidelines: High Risk SCCs

- Mohs surgery is standard of care
- Benefit of tissue sparing, improved cosmetic outcomes and increased cure rate.



Low Risk: Other options (mainly for SCCIS)

- Electrodesiccation and curettage (ED&C)
  - Benefits: In-office, no mobility restrictions.
  - Works well for SCCIS (less than 2 cm) on the trunk, arms, legs.
  - **Per AAD: Non-hair bearing areas**
    - Cons: Cannot "prove" the SCC is destroyed with pathology, lower cure rate, circular scarring
- Cryosurgery - double freeze/thaw cycle of 30-60 seconds
  - Utilize when excision is impractical or not indicated for low risk only (SCCIS, less than 2cm)

Low Risk: Other options

- Topical chemotherapy - not recommended by AAD but used in practice quite frequently for SCC in situ
  - Imiquimod and 5FU are NOT FDA approved for SCCIS. However, there are case studies available supporting their use for SCCIS.
  - My experience: Both are a practical option for small SCCIS in patients wanting to avoid surgery.
- Radiation: superficial radiation therapy, isotope-based brachytherapy (interstitial or topical contact), or external electron beam radiation
  - Can be used for smaller, thinner tumors
  - Lower cure rates for primary lesions
  - Often used as an adjunct to surgical treatment in high risk SCCs with perinural or tissue involvement
- PDT - not recommended by AAD
  - PDT induced well differentiated SCC/keratoacanthoma is a reported phenomenon

Patients with mets

- Possible adjuvent radiation
- Chemoraditation for non-surgical lesions/candidates.
- Epidermal growth factor inhibitors and cisplatin can be used.
- These options are best handled with a specialized oncologist.

Follow up

- Annual or twice yearly full skin exams
- Counselling: Sun avoidance, sun protection, tanning bed avoidance

Transplant patients:

- Use of acitretin in transplant patients with multiple SCC history
- Work with transplant specialists for possible change to sirolimus
  - Less risk for SCC development

- Topical tretinoin and PO beta carotene is NOT recommended as a protective measure by AAD.

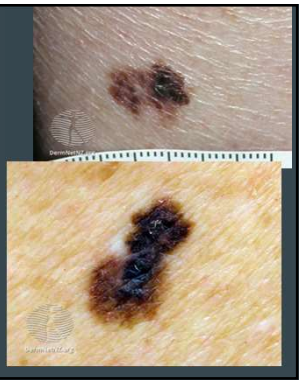
Melanoma

Malignant Cutaneous Melanoma (MM)

- Rates of melanoma doubled from 1982 to 2011.
- Most deadly form of skin cancer. About 7,000 patients died in 2019.
- Risk factors: sun exposure, tanning bed use (esp in women <45yo), caucasian, >50 moles or atypical moles, immediate family history, fair skin/blue eyes, previous non melanoma skin cancer or other cancers such as breast or thyroid CA.
- ~75% of MMs initiate from an existing nevus (mole)
- Common locations: Men = back, Women = legs
  - Less common to occur on genitals, lips, eyes, palms/soles, rarely starts in brain
- In situ = only within epidermis (MMIS)
- Invasive = spread to the dermis
- Metastatic = spread to other organs/tissue

Presentation

- Multi colored: Brown, grey, red, white.
- Follow the ABCDEs
  - Asymmetry
  - Border irregularity
  - Colour variation
  - Diameter over 6 mm
  - Evolving (enlarging, changing)
- Multiple types:
- **Superficial Spreading** (most common)

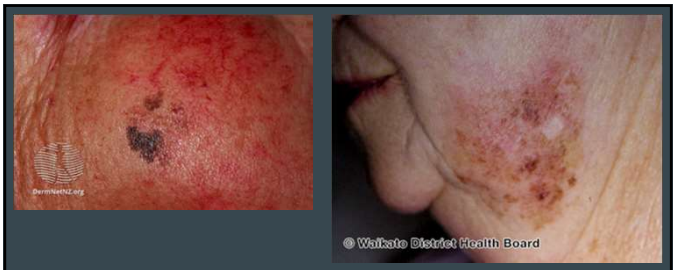


Photos: https://dermnetnz.org/topics/superficial-spreading-melanoma-images/

Nodular Melanoma - typically dome shaped or ulcerated

- Typically occurs de novo
- Less common, ~15%

Photos: https://dermnetnz.org/topics/nodular-melanoma-images/



Lentigo Maligna Melanoma - a form of MMIS

- Develops over 5-20 years. Occurs in sun exposed areas, normally the face.

Photos: https://dermnetnz.org/topics/lentigo-maligna-and-lentigo-maligna-melanoma/

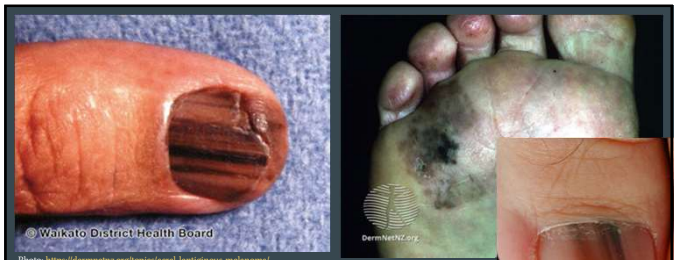
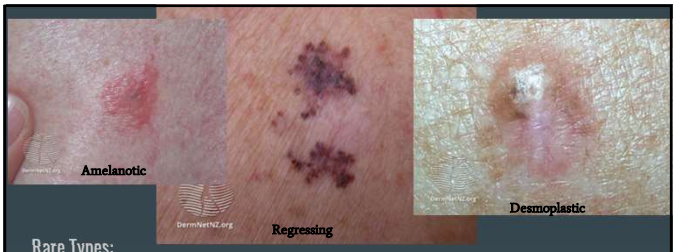


Photo: https://dermnetnz.org/topics/acral-lentiginous-melanoma/

Nail and acral melanomas

Photos: https://dermnetnz.org/topics/melanoma/



Rare Types:

- Amelanotic - lacks pigment, usually red or pink
- Regressing MM - white or scarred appearing
- Desmoplastic- appears fibrotic

Photos: https://dermnetnz.org/topics/desmoplastic-melanoma/, https://dermnetnz.org/topics/melanoma/

Biopsy technique

- Excisional biopsy is the standard of care: goal is to remove the entire lesion to fully evaluate the lesion, depth, type, etc.
- Acceptable methods:
  - elliptical excision
  - deep sauceration/scoop shave (most common)
  - punch excision.
- Narrow margins of 1-3mm are acceptable.
- Incomplete or partial sampling will prevent accurate staging of the lesion.
- Photos of the lesion are important to document for future surgical treatment.

Biopsy results

The pathologist *should* provide the following in the the path report:

- Size of specimen
- **Thickness - Breslow depth to the nearest 0.1mm**
- **Presence of ulceration +/-**
- **Mitotic rate:** No. of mitoses/mm2
- **Margins** - e.g. clear, MMIS at margins, transected, etc.
- Regression

Optional: subtype, lymphovascular or perineural invasion, regression, tumor category for staging, Clark level, vertical growth phase.

Understanding the Path Report

- Most important are Breslow depth (thickness) and ulceration.
  - mitotic rate - evidence that high mitoses = poorer outcome.
- Stage T1a → currently is less than 0.8mm Breslow Depth and no ulceration
- Stage T1b → 0.8mm to 1mm Breslow depth (no matter the ulceration)
- More on staging in next slides
- ***Take away:*** If >0.8mm or if less and ulcerated, patient needs a discussion of sentinel lymph node (SNL) biopsy and consult with surgical oncology or specialized melanoma surgeon.
  - If >1mm, more evidence in favor of SNL biopsy.

Staging

American Joint Committee on Cancer developed the staging system.

Reference: https://www.jaad.org/article/S0190-9622(18)32588-X/pdf, pg 213

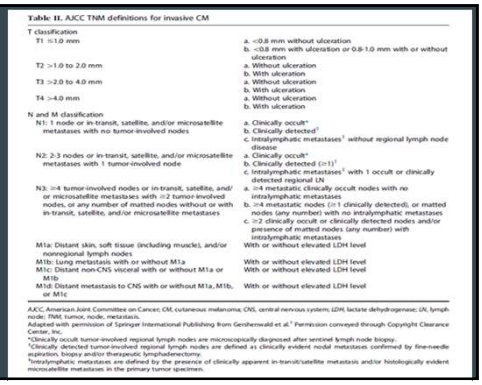


Table II. AJCC TNM definitions for invasive CM

T classification	
T1 ≤1.0 mm	a. <0.8 mm without ulceration b. <0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2 >1.0 to 2.0 mm	a. Without ulceration b. With ulceration
T3 >2.0 to 4.0 mm	a. Without ulceration b. With ulceration
T4 >4.0 mm	a. Without ulceration b. With ulceration
N and M classification	
N1: 1 node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	a. Clinically occult* b. Clinically detected† c. Intralymphatic metastases‡ without regional lymph node disease
N2: 2-3 nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	a. Clinically occult* b. Clinically detected (≥1)† c. Intralymphatic metastases‡ with 1 occult or clinically detected regional LN
N3: ≥4 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	a. ≥4 metastatic clinically occult nodes with no intralymphatic metastases b. ≥4 metastatic nodes (≥1 clinically detected), or matted nodes (any number) with no intralymphatic metastases c. ≥2 clinically occult or clinically detected nodes and/or presence of matted nodes (any number) with intralymphatic metastases
M1a: Distant skin, soft tissue (including muscle), and/or nonregional lymph nodes	With or without elevated LDH level
M1b: Lung metastasis with or without M1a	With or without elevated LDH level
M1c: Distant non-CNS visceral with or without M1a or M1b	With or without elevated LDH level
M1d: Distant metastasis to CNS with or without M1a, M1b, or M1c	With or without elevated LDH level

AJCC, American Joint Committee on Cancer; CM, cutaneous melanoma; CNS, central nervous system; LDH, lactate dehydrogenase; LN, lymph node; TNM, tumor, node, metastasis.
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*Clinically occult tumor-involved regional lymph nodes are microscopically diagnosed after sentinel lymph node biopsy.
†Clinically detected tumor-involved regional lymph nodes are defined as clinically evident nodal metastases confirmed by fine-needle aspiration, biopsy and/or therapeutic lymphadenectomy.
‡Intralymphatic metastases are defined by the presence of clinically apparent in-transit/satellite metastasis and/or histologically evident microsatellite metastases in the primary tumor specimen.

Staging Cont.

Groups of staging

Reference: https://www.jaad.org/article/S0190-9622(18)32588-X/pdf, pg 213

Table III. Pathologic stage groups according to the eight edition of the AJCC

Pathologic TNM stage groupings			
When T is	And N is	And M is	Pathologic stage
Tis*	N0	M0	0
T1a*	N0	M0	IA
T1b*	M0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0†	N1b, N1c	M0	IIIB
T0†	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Treatment: Surgical Margins

- Melanoma in situ (no Breslow depth) → 0.5cm to 1 cm surgical margins
  - Head and Neck: usually via staged excision for MMIS and Lentigo Maligna
  - Mohs maybe a recommendation in the future but need more research
- Breslow Depth ≤ 1mm → 1 cm surgical margins
- Breslow Depth > 1mm to 2mm → 1 to 2 cm surgical margins
- Breslow Depth > 2mm → 2 cm surgical margins
- SNL biopsy should be performed at the same time or prior to excision.
  - Allows the correct lymphatic channels to be identified → more accurate SNL biopsy

Sentinel Lymph Node Biopsy

- Blue dye is injected around the primary melanoma
- Surgeon uses a gamma probe to identify the afferent lymph node reservoirs that light up from the blue dye and sample those nodes.
- Positive SNL biopsy has an established poorer prognosis and negative SNL biopsies typically have better prognosis.
- Complete Lymph Node Dissections (CLND) after +SNL biopsy has been NOT shown to improve melanoma survival rate vs. monitoring with nodal based ultrasound monitoring.
  - AAD recommends collaboration of medical and surgical oncologist before performing a CLND.
- Patients with positive SNL biopsy will be offered immunotherapies by oncology.

Follow up

- Imaging and labs is NOT recommended for asymptomatic patients without nodal involvement.
  - CT/PET CT performed with positive SNL (usually by oncology)
- H&P: weight loss, night sweats, fatigue/malaise, SOB, new onset headaches, etc.
- Educate patient in performing self skin checks.
- Skin exams with derm per AAD:
  - MMIS: Q6-12 mos x 1-2 years, then annually
  - Stage IA-IIA: Q 6-12mos for 2-5 years, then annually
  - Stage IIB and higher: **Q 3-6mos for 2 years, then Q 6mos from year 3-5, then annually**
- Higher risk of 2nd MM in males, fair skin, multiple nevi, family history of MM and history of atypical nevi.

Second Line Treatments

- Immiquimod 5% has been shown to effectively treat LM or MMIS for non-surgical candidates
  - Range: 64-94% clearance from studies performed
  - Generally five times/weeks for at least 12 weeks.
  - This is OFF LABEL - is recommended as second line treatment by AAD for non-surgical candidates.
  - Take Away - Let a dermatology provider who has experience with this method use imiquimod.
- Non-surgical patients: also can use radiation but not common in US
- Radiation adjuvant therapy can be offered for high-risk desmoplastic type CM

Pregnancy and Melanoma

- Not enough evidence to support that pregnancy is a risk factor for MM.
- Women in general have a higher rate of MM
- Young women (in reproductive years) have a higher rate of MM
- MM is the most common cancer to occur during pregnancy.
- Several studies have found no causal link between MM and pregnancy.
  - One study found that women who had a pregnancy earlier in life and who had multiple children were less likely to develop MM.
  - Possibly more related to tanning bed use or sun exposure habits.
- No recommendation for a woman with a history of MM to postpone conception after treatment.
- No contraindication for biopsying a suspicious nevus in a pregnant woman.
- No contraindication for OCPs, HRT, IVF, etc in women with a history of MM.

Actinic Keratosis (AK)

Overview

Common in ages >50, fair skin

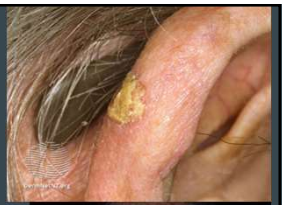
Affects 11-26% of US patients. Seen more in men.

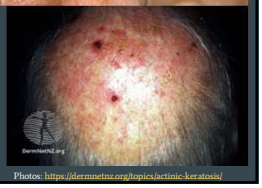
Caused by chronic, cumulative sun exposure

Occurs in sun exposed areas: Face, scalp, neck, arms

Risk to become squamous cell carcinoma - estimates vary

Presentation





- Hypertrophic AKs, pigmented AKs, actinic cheilitis (loss of vermilion border)
  - Thickening and tenderness are warning signs for SCC

Photos: https://dermnetnz.org/topics/actinic-keratosis/

Treatment

- Reduction and prevention: Daily to twice daily use of sunscreen
- Cryotherapy with liquid nitrogen - choice for few or distinct AKs
  - Clearance of 75% (compared to photodynamic therapy)
  - Treatment length: 5-40 seconds in studies
  - SE: pain, erythema, swelling, blistering, and hypopigmentation
- Photodynamic therapy (PDT)
  - blue or red light treatment with prior application of ALA or MAL (more frequently used)
  - About 70% clearance on first round and up to 90% on second round
  - Painful, photosensitivity- typically for 48 hours

Field Treatment

- Fluorouracil 0.5% (Carac), 5% (Efudex)
  - 0.5% - daily for 1 to 4 weeks
  - 5% - Twice daily for 2-6 weeks (cream or solution)
  - About 50% clearance
  - SE: erythema, scaling, tenderness, itching, swelling, blistering, scarring, flu like symptoms (rare).
- Imiquimod (Zyclara) 2.5 or 3.75% 2 weeks on, 2 weeks off, then repeat x 1
- Imiquimod (Aldara) 5% 2 times per week QHS for 16 weeks
  - Limit to 25 square cm on face/scalp, immunocompetent patients only
  - SE: erythema, itching, burning, etc.
    - Also HA, fatigue, nausea, influenza-like symptoms, and myalgia

Field Treatment cont.

- Ingenol mebutate (Picato)
  - 0.015% cream daily x 3 days for Face/scalp
  - 0.05% cream daily x 2 days for trunk/extremities
  - Limit treatment to 25 sq cm (5cmx5cm)
  - Clearance ~40%
  - Do not use on lips (HSV can occur). Avoid chest.
  - Often takes 2 courses.
  - Not for HAKs.
- Diclofenac 3% gel - BID for 90 days
  - limited efficacy of about 35% clearance (may get better results when combined with hyaluronic acid 2.5%).
  - SE: contact dermatitis, photosensitivity

Pearls

- Consider the patient's lifestyle and wishes:
  - Working, outdoor enthusiast, severe actinic damage, cosmetic concerns, motivated?
- Pick one field treatment and become comfortable with prescribing it.
- Cryotherapy - 10 to 20 seconds is likely optimal
- Refer for biopsy if tender, bleeding, growing, hyperkeratotic

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