Skin Cancer

Tarek Afifi, MD FRCPC
Dermatologist & Mohs Surgeon

Faculty/Presenter Disclosure

- **Faculty:** Tarek Afifi

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** *Amgen, Bausch Health, AbbVie*
  - **Consulting Fees:** none
  - **Clinical trials:** LEO Pharma, AbbVie, Janzen Ortho, Amgen, Astellas, Galderma

Disclosure of Commercial Support

- **This program has received no financial or in-kind support from any outside organization.**

- **<u>Potential for conflict(s) of interest</u>:**
  - Tarek Afifi has received payment from Bausch Health and LEO Pharma whose product are being discussed in this program.

Mitigating Potential Bias

* This talk is based on a balanced review of the literature and personal patient experience.

SKIN CANCERS

- Melanoma
- Non-melanoma skin cancers (NMSC)
  - Basal Cell Carcinoma
  - Squamous Cell Carcinoma
  - Others
    - Merkel cell carcinoma
    - Cutaneous lymphomas
    - Sebaceous carcinoma
    - Dermatofibrosarcoma protuberans
- Metastatic cancer to the skin

SKIN CANCERS

- Melanoma
- Keratinocyte Carcinomas
  - Basal Cell Carcinoma
  - Squamous Cell Carcinoma
- Less common skin tumors
  - Merkel cell carcinoma
  - Cutaneous lymphomas
  - Sebaceous carcinoma
  - Dermatofibrosarcoma protuberans
- Metastatic cancer to the skin

OVERVIEW

1. Skin Cancer Epidemiology and Risk Factors
2. Clinical Presentation
3. Diagnosis
4. Management

LEARNING OBJECTIVES

1. Develop a concise approach to interviewing potential skin cancer patients
2. Refine our appreciation of skin cancer morphology
3. Develop a rational method for managing skin cancer
    - *Diagnostic investigations
    - *Treatment
    - *Referrals
    - *Follow-up and counselling

Why do we care about skin cancer?
(Skin Cancer Epidemiology)

	Skin Cancer	BCC	SCC	MM
Lifetime Incidence	1:5	1:5	1:20	1:50

Madan V et al. Nonmelanoma skin cancer. Lancet 2010;375:673-685.
Salasche SJ. J Am Acad Dermatol. 2000;42(1 Pt 2):4-7.

Skin Cancer: Major Risk Factors

Constitutional

- Skin Phototype
- Immune status
- Genetics/Personal & Family Hx
- Age

Environmental

- Radiation exposure
  - UV
  - Ionizing

Other

- SCC: HPV, tobacco, wounds
- Melanoma: numerous nevi, atypical nevi, congenital nevi

Skin Cancer: Major Risk Factors

Constitutional

- Skin Phototype
- **Immune status**
- Genetics/Personal & Family Hx
- Age

Environmental

- Radiation exposure
  - UV
  - Ionizing

Other

- SCC: HPV, tobacco, wounds
- Melanoma: numerous nevi, atypical nevi, congenital nevi

Immune dysfunction & skin cancer

Mechanisms

- Immunosurveillance
- Viral oncogenesis

Cancers (Incidence ratio in organ transplant recipients)

- Squamous cell carcinoma (65-250x)
- Basal cell carcinoma (10x)
- Kaposi sarcoma (80-200x)
- Merkel cell carcinoma (70x)
- Melanoma (4x)

Prognosis

- Increased: local aggression, local recurrence, distant metastases, mortality

A.P. Tufaro et al. Rising incidence and aggressive nature of cutaneous malignancies following transplation. Surgical Oncology 24 (2015) 345- 352

Doctor, do I have skin cancer?

Does this patient have skin cancer?

Relevant History Taking

- History of the lesion
  - Duration
  - Change
  - Bleeding
  - Pain
- Skin phototype and UV history
- Immune status
- Personal & family history of skin cancer
- Habits: smoking, tanning beds

Does this patient have skin cancer?

How do I assess the lesion?

Assessing the lesion

- **Important Morphology**
  - Site:
    - Sun exposed
  - Primary morphology
    - Papule
  - Secondary changes
    - Ulcerated
    - No scale
- Cancer specific pearls
  - Translucent / pearly
  - Telangiectatic

Does this patient have skin cancer?

How do I investigate a suspected BCC?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

Does this patient have skin cancer?

How do I investigate a suspected BCC?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

Does this patient have skin cancer?

Biopsy

- Incisional
  - Shave
  - Punch
- Excisional

Does this patient have skin cancer?

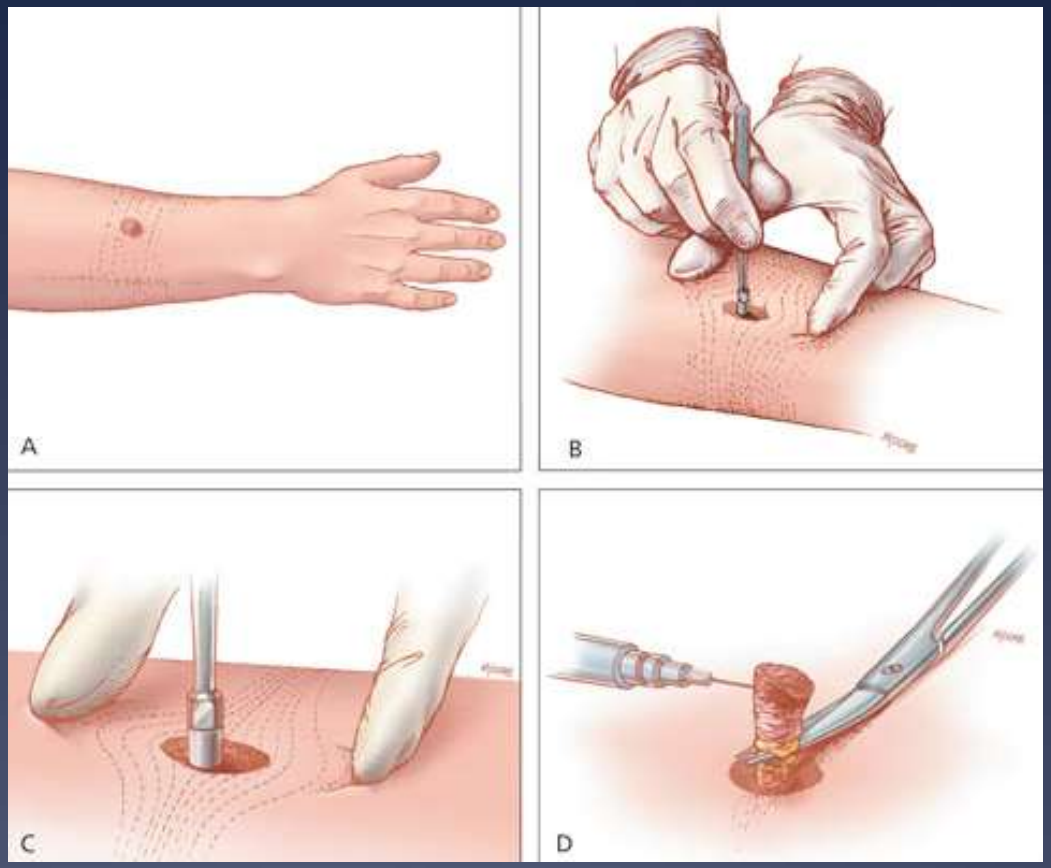
Biopsy

- Incisional
  - Shave
  - Punch
- Excisional

Does this patient have skin cancer?

Biopsy

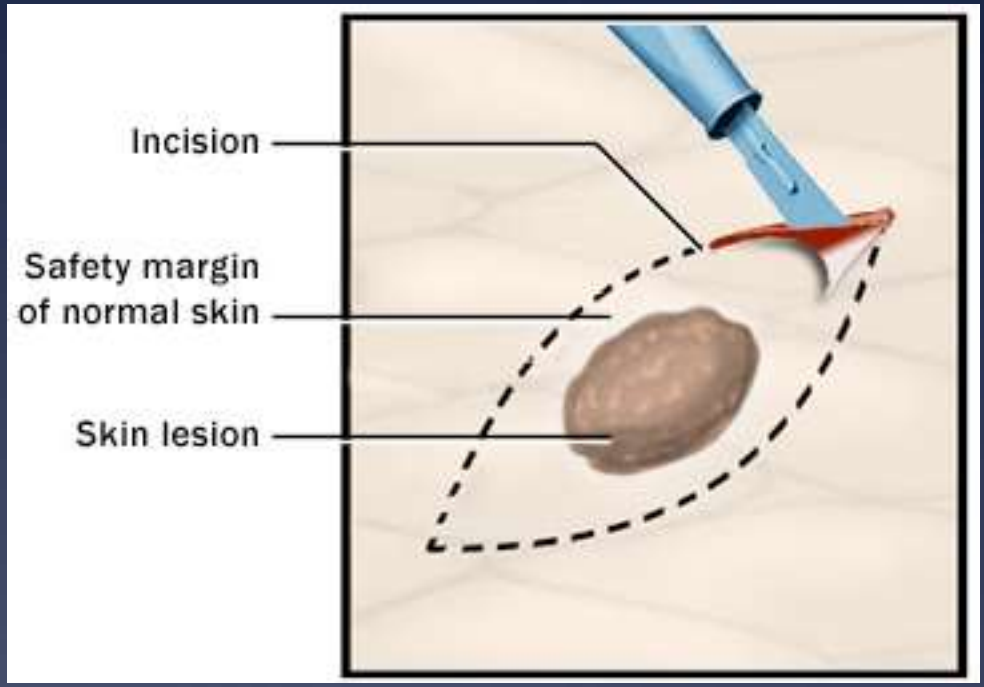
- Incisional
  - Shave
  - Punch
- Excisional



Does this patient have skin cancer?

Biopsy

- Incisional
  - Shave
  - Punch
- Excisional



Does this patient have skin cancer?

How do I investigate?

- Biopsy? What kind?
  - Depends on your suspected diagnosis
  - Nonmelanoma skin cancer: incisional
- Imaging?
  - Depends on your suspected diagnosis
  - Not necessary for most BCC
- Is observation ever okay?
  - Depends on your suspected diagnosis
  - Small non-morbid BCC + decreased life expectancy

Basal Cell Carcinoma

- Key Features
  - Photodistributed: 90% head and neck
  - Affects middle aged and elderly
  - Slow growing: 1 year doubling time

- Prognosis & Complications
  - Most small, low risk
  - Bleeding, ulceration, infection
  - Locally destructive without distant metastases

Basal Cell Carcinoma

Major Clinical Subtypes

Basal Cell Carcinoma

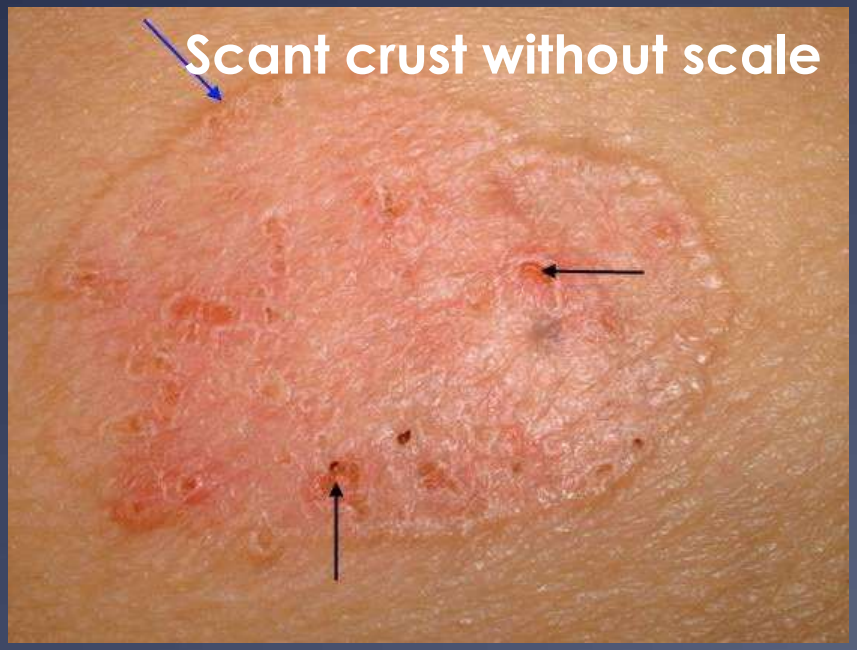
Major Clinical Subtypes

- Nodular (60%)

Basal Cell Carcinoma

Major Clinical Subtypes

- Nodular (60%)
- Superficial (15%)



Basal Cell Carcinoma

Major Clinical Subtypes

- Nodular (60%)
- Superficial (15%)
- Pigmented (4%)

Basal Cell Carcinoma

Major Clinical Subtypes

- Nodular (60%)
- Superficial (15%)
- Pigmented (4%)
- Sclerosing (3%)

When to suspect a BCC?

- ‘Pimple’ that doesn’t heal
- Persistent, pink, pearly crusted papule or nodule
- Bleeding, crusting, ulceration

Basal Cell Carcinoma

Major Pathologic Subtypes

- Superficial
- Nodular
- Sclerosing
- Infiltrative
- Micronodular

Basal Cell Carcinoma

Major Pathologic Subtypes (Recurrence Rate)

- Superficial (3%)
- Nodular (6.4%)
- Sclerosing (33%)
- Infiltrative (26%)
- Micronodular (18%)

HIGH RISK FOR RECURRENCE

Garcia et al. Mohs surgery comments and controversies. Int J Dermatol 2005;44:893-905

BCC Mimics

Doctor, do I have skin cancer?

Does this patient have skin cancer?

Relevant History Taking

- History of the lesion
  - Duration
  - Change
  - Bleeding
  - Pain
- Skin phototype and UV history
- Immune status
- Personal & family history of skin cancer
- Habits: smoking, tanning beds

Does this patient have skin cancer?

How do I assess the lesion?

Assessing the lesion

How do I assess the lesion?

- **Important Morphology**
  - Site:
    - Sun exposed
  - Primary morphology
    - Plaque
  - Secondary changes
    - Thick scale
- Cancer specific pearls
  - Hyperkeratotic plaque with indurated pink base
  - Dorsal hand (chronically sun exposed)

Does this patient have skin cancer?

How do I investigate a suspected SCC?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

Does this patient have skin cancer?

How do I investigate a suspected BCC?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

Does this patient have skin cancer?

How do I investigate?

- Biopsy? What kind?
  - Depends on your suspected diagnosis
  - Nonmelanoma skin cancer: incisional
- Imaging in SCC?
  - High risk tumors (CT)
    - For regional/lymphatic spread:
      - > 2cm diameter
      - Mucosal site
      - consider: perineural invasion, immunosuppressed, non UV initiated
    - Local site
      - Surgical planning: suspect bony invasion or deeply invasive

REFER

- Is observation ever okay for SCC?
  - Rarely

Squamous Cell Carcinoma

- Key Features
  - Photodistributed red, scaling/keratotic plaque
    - Variable morphology
  - Chronic sun
  - Mucosa AND cutaneous epithelia

- Prognosis
  - Metastatic rate: 4%
  - High Risk
    - Ear, Mucosa, Chronic ulcer

Squamous Cell Carcinoma

- SCC In Situ (Bowen's Disease)
  - No dermal invasion
  - Low risk of progression
    - Skin: 5%
    - Erythroplasia of Queryat: 10%


METRIC
1
2
3
4
5
6
7
8
9


Globalskinatlas.com

Squamous Cell Carcinoma

- Invasive SCC
  - Variable morphology
  - Red scaling keratotic plaque
  - Ulcer
  - Smooth nodule +/- crateriform keratinaceous core
  - Cutaneous horn
  - Verrucous (warty) plaque




Some common mimics

Does this patient have skin cancer?

What's what?

Suspected diagnosis?

Squamous Cell Carcinoma

Suspected diagnosis?

Chondrodermatis
Nodularis
Helicis

Suspected diagnosis?

Elastotic nodules of the ear

NMSC: Treatment

Categories

- Topical
- Locally Destructive
- Radiation
- Surgical
- Systemic

Topical Therapy

5 Fluorouracil
Imiquimod

- Useful for:
  - Superficial BCC (extrafacial, low risk)
  - SCC In Situ (off label)
- Regimen
  - 5 Fluorouracil: BID 5x/week x 6 weeks
  - Aldara: OD 5x/week x 6 weeks
  - Efficacy: 80%
- **Advantages**
  - At home treatment
  - Avoids surgery
- **DISADVANTAGES**
  - No histologic confirmation of cure
  - Lengthy treatment schedule
  - Significant morbidity

Locally Destructive Techniques

- **Cryotherapy (Liquid Nitrogen)**
  - Superficial BCC (select lesions only)
  - ? SCCIS
- **Curettage & Electrodessication**
  - Low risk nodular or superficial BCC
- Advantages
  - "quick and dirty"
- Disadvantages
  - No histologic confirmation of cure
  - Lengthy healing period
  - Suboptimal cosmetic outcome (poor scarring, PIH)

Surgery: Wide Local Excision

- Useful for:
  - BCC & SCC (all types)
- Margins
  - 4-6mm
- Advantages
  - Histologic confirmation of cure
  - High cure rates (90% primary, 80% recurrent)
- Disadvantages
  - Functional and cosmetic sequelae
  - Pain
  - Low efficacy for high risk lesions

Mohs Micrographic Surgery

- Staged removal of skin tumors with complete microscopic margin analysis

- 2 primary aims of Mohs surgery
  - Ensure histologically negative margins
  - Create smallest defect by sparing uninvolved tissue

- Indications
  - Tumors at high risk to recur
    - High risk pathology
    - Recurrent tumors
    - Large tumors
    - Scar tissue: Positive margins, Previously irradiated skin
  - Tumors on/near functionally or cosmetically important structures
    - Eyelids, lips, nose, ears, hands, genitals
    - Facial lesions >1cm

Radiation Therapy

- Useful for:
  - BCC
    - Primary or recurrent (90% cure)
  - SCC
    - Adjuvant for high risk tumors
- Advantages
  - Elderly/high surgical risk
  - Palliation
  - High cure rates for BCC
- Disadvantages
  - Lengthy and Costly
  - No histologic confirmation of clearance
  - Aggressive/extensive recurrence
  - Secondary carcinogenesis

Systemic Therapy

- Vismodegib
  - Hedgehog pathway inhibitor
  - Indications:
    - locally advanced or metastatic BCC
    - Not amenable to surgery/radiation
  - Efficacy
    - Response rate: 58%
    - Median duration of response: 12.8mths
    - Virtually all recur upon discontinuation

What about this guy?

Image used with permission from DermNetNZ.org

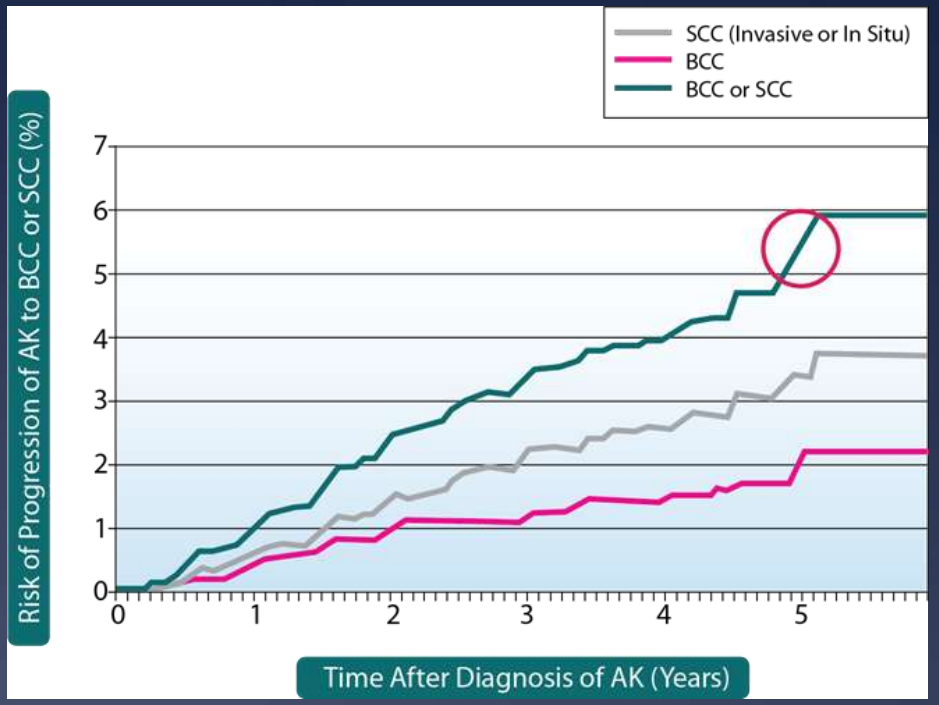
Actinic Keratosis & Cheilitis

- Why do they matter?
  - 80% of Caucasian's by 7th decade
  - SCC precursor
  - Risk marker for all types skin cancer

- What do they look like?
  - **Skin**: Ill-defined scaling/rough erythematous papule
  - **Lip**: confluent red, scaling, fissured lip
    - Indistinct vermillion border

Clinical Fate of Actinic Keratosis

- Natural course of individual AK lesions is unpredictable



Criscione VD, et al. *Cancer.* 2009;115:2523-2530.

- AK lesions can:
  - Persist[1]
  - Regress[2,3]
  - Progress[1]

→

- Hypertrophic AK
- SCC *in situ*
- Invasive SCC

1. Criscione AB et al. *Cancer*. 2009;115:2523-2530. 2. Marks R et al. *Br J Dermatol*. 1986;155:649-655.

AK and Field Cancerization

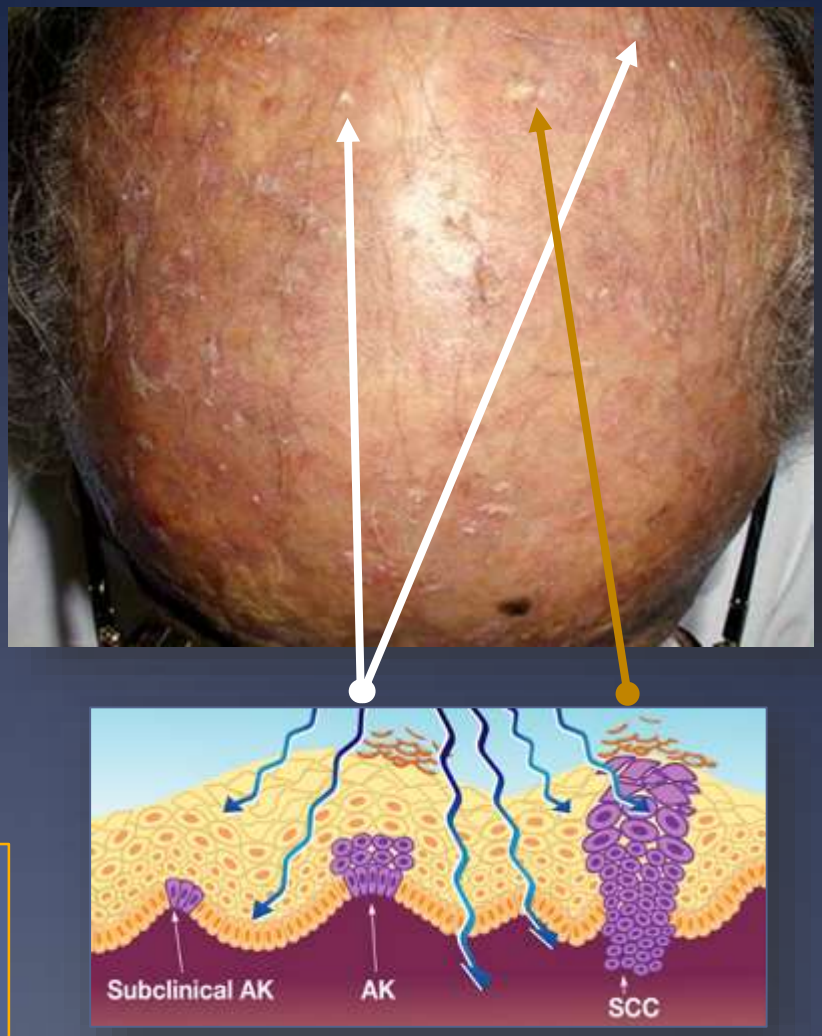
Photo courtesy Eggert Stockfleth, MD

- Photodamaged skin has:
  - Normal skin ->
  - Clinical AKs ->
  - Potentially SCC

1. Berman B et al. *Expert Opin. Pharmacother.* 2009;10(18):3015-3031

AK and Field Cancerization

Photo courtesy Eggert Stockfleth, MD



- Photodamaged skin has:
  - Normal skin
  - Subclinical AKs
    - Foci of mutant clones of keratinocytes
    - Up to 10x's as many as clinical AKs[1]
  - Clinical AKs
  - Potentially SCC

Multiple AKs in an area indicate that the entire area is photo-damaged

1. Berman B et al. *Expert Opin. Pharmacother.* 2009;10(18):3015-3031

Current Treatment Options for Actinic Keratosis

Lesion-directed treatments

- Physically destructive methods
  - Cryotherapy
  - C02 laser
- Surgical removal
  - Excision
  - Curettage
  - Electrodesiccation

Field-directed treatments

- 5-fluorouracil (5-FU)
- Imiquimod 5% or 3.75%
- Ingenol mebutate
- Photodynamic therapy (PDT)

Field Treatment: Mechanism

	Imiquimod[1] (n=26)	5-FU[2] (n=24)	LN2 (n=25)	Ingenol Mebutate
Clinical Clearance	TLR-7 agonist	cytotoxin	Cold	cytotoxin

1. 3x/week x 4 weeks. 4 weeks rest. May repeat x1
2. 5% 5FU BID x 4 weeks
3. 20-40 sec cryospray. May repeat in 1 week

Krawtchenko et al. *Br J Dermatol 2007*;157(suppl 2):34-40

Field Treatment: Regimen

	Imiquimod[1] (n=26)	5-FU[2] (n=24)	LN2 (n=25)	Ingenol Mebutate
Clinical Clearance	BID x 3 wks	TIW x 4wks	10s	OD x 3 days

1. 3x/week x 4 weeks. 4 weeks rest. May repeat x1
2. 5% 5FU BID x 4 weeks
3. 20-40 sec cryospray. May repeat in 1 week

Krawtchenko et al. *Br J Dermatol 2007*;157(suppl 2):34-40

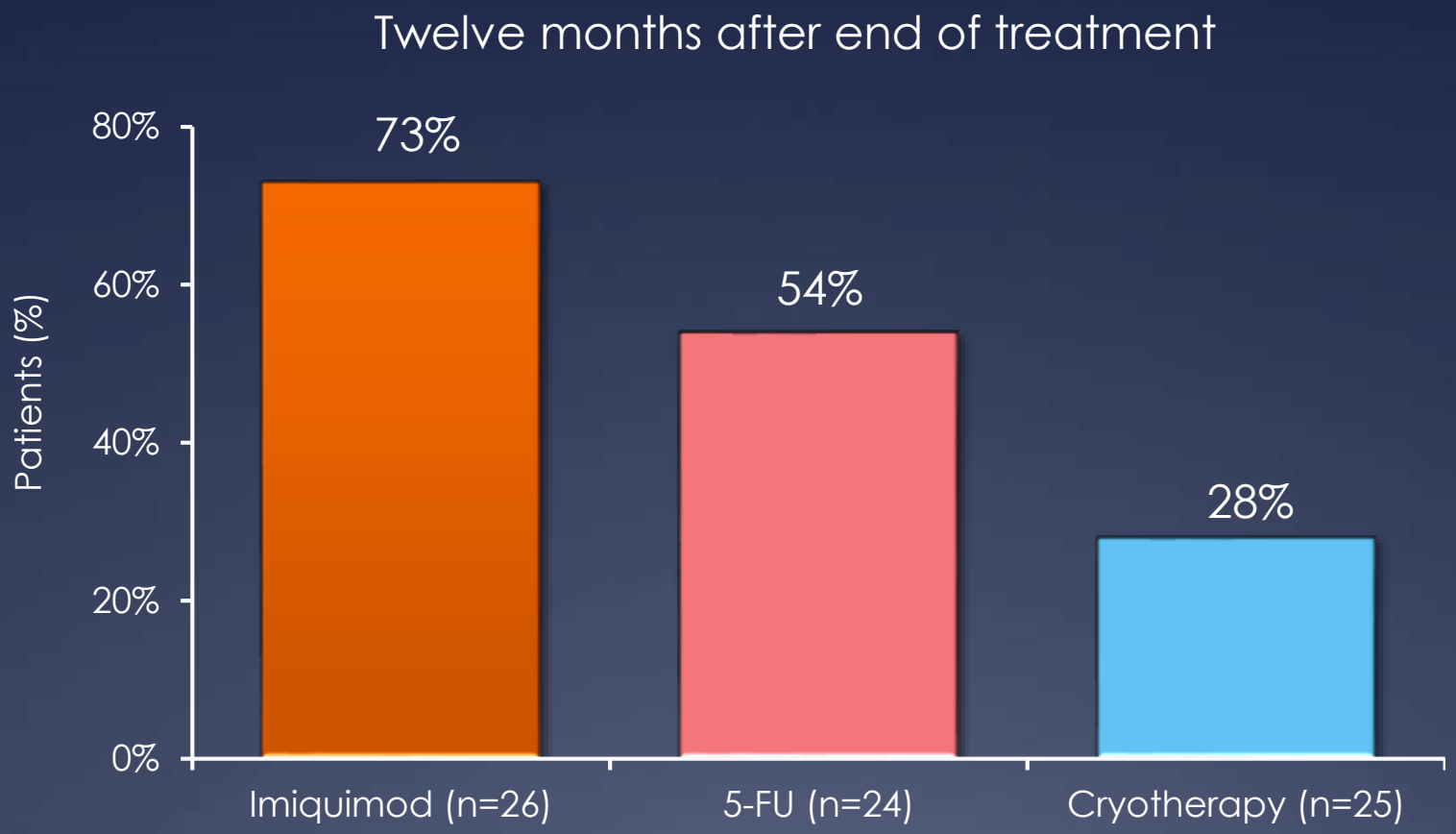
Field Treatment: Efficacy

	Imiquimod[1] (n=26)	5-FU[2] (n=24)	LN2 (n=25)	Ingenol Mebutate
Clinical Clearance	45-85%	48-96%	68-76%	42%

1. 3x/week x 4 weeks. 4 weeks rest. May repeat x1
2. 5% 5FU BID x 4 weeks
3. 20-40 sec cryospray. May repeat in 1 week

Krawtchenko et al. *Br J Dermatol 2007*;157(suppl 2):34-40

Sustained Clearance of Initially Cleared Lesions in All Patients



Out of all treated patients (including in the denominator also those not cleared at end of therapy)

Krawtchenko et al. *Br J Dermatol 2007*;157(suppl 2):34-40

Adverse Effects of Field Therapy

- Local reactions:
  - Erythema - Edema
  - Flaking/Scaling - Vesiculation/Pustulation
  - Crusting - Erosion/Ulceration

  *Ingenol mebutate: shorter duration of local side effects

- Systemic Symptoms
  - Flu-like (imiquimod)
  - Leukocytosis, thrombocytopenia (5FU)

- $$$
  - Aldara/Zyclara
  - Picato

Adverse Effects of Cryotherapy

- Acute
  - Pain or stinging during and after the procedure
  - Edema & Blister formation
- Delayed
  - Hypo- or hyper-pigmentation
  - +/- scarring

Management of AEs

- **Cryotherapy**
  - Minimize number of lesions treated per session
  - Emollients for ruptured bullae
- **Field Therapy**
  - Reduced frequency of application
  - Temporarily suspend therapy
  - Stop early
  - Sun avoidance and sunscreen
  - Post-treatment: emollients just as good as topical steroids

AK update: Daylight PDT

Photodynamic therapy

Photosensitizer (MAL)

Retained in tumor

Visible Light

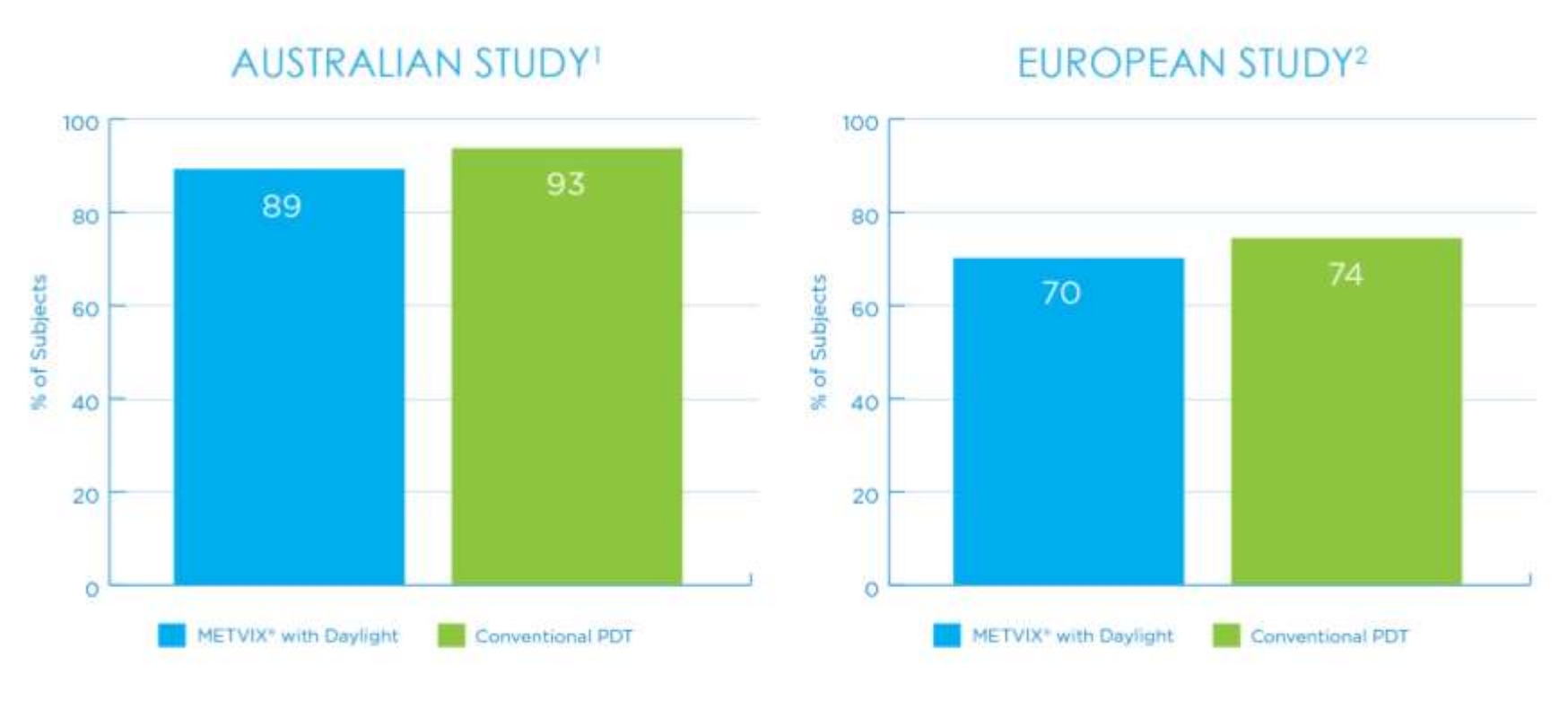
Activates PpIX

Singlet Oxygen / ROS

Tumor cell death

Necrosis + apoptosis

Photodynamic therapy



1. Rubel DM et al. Daylight photodynamic therapy with methyl aminolevulinate cream as convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol. 2014 Nov'171(5):1164-71.

2. Lacour JP et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomized, investigator-blinded, controlled, phase III study throughout Europe. J Eur Acad Dermatol Venreol. 2015 Oct5., available online

Actinic Keratosis & Cheilitis

When should you suspect SCC?

- Induration
- Size (>1cm)
- Ulceration or Bleeding
- Rapid growth
- Recalcitrant

Doctor, do I have skin cancer?

Does this patient have skin cancer?

Relevant History Taking

- History of the lesion
  - Duration
  - Change
  - Bleeding
  - Pain
- Skin phototype and UV history
- Immune status
- Personal & family history of skin cancer
- Habits: smoking, tanning beds

Does this patient have skin cancer?

How do I assess the lesion?

Assessing the lesion

How do I assess the lesion?

- **Important Morphology**
  - Site:
    - sun exposed?
  - Primary morphology
    - Thin plaque
  - Secondary changes
    - none
- Cancer specific pearls
  - Highly irregular shape
  - Colour variegation

Does this patient have skin cancer?

How do I investigate a suspected melanoma?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

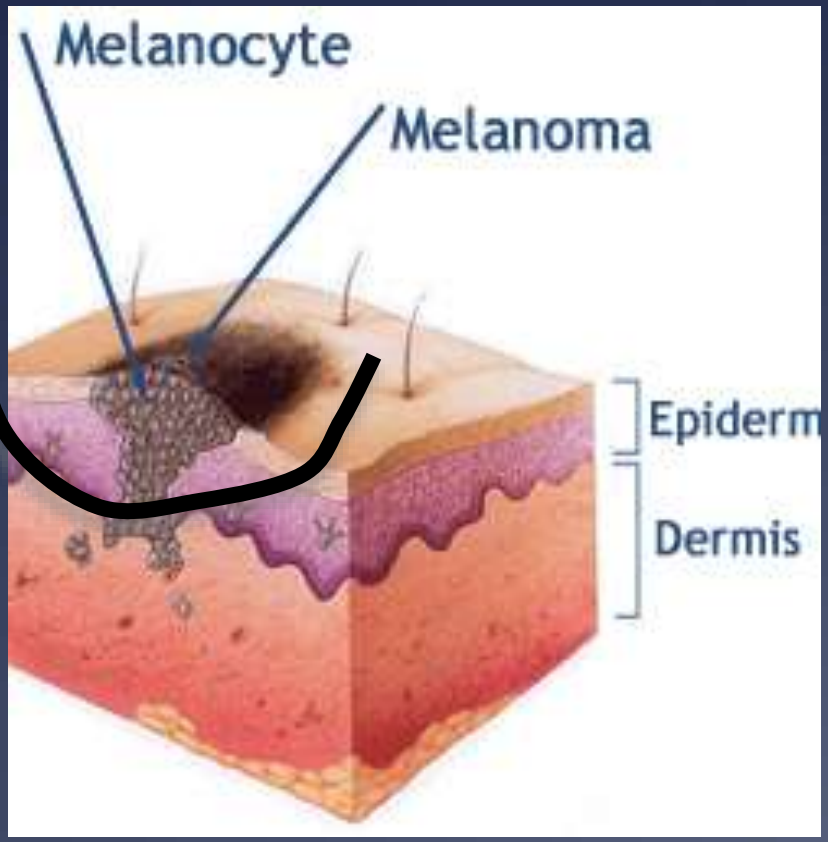
Does this patient have skin cancer?

How do I investigate a suspected melanoma?

- A. Biopsy
- B. Imaging
- C. No investigations (serial observation)

What type of biopsy?

Shave biopsy?



Punch biopsy?

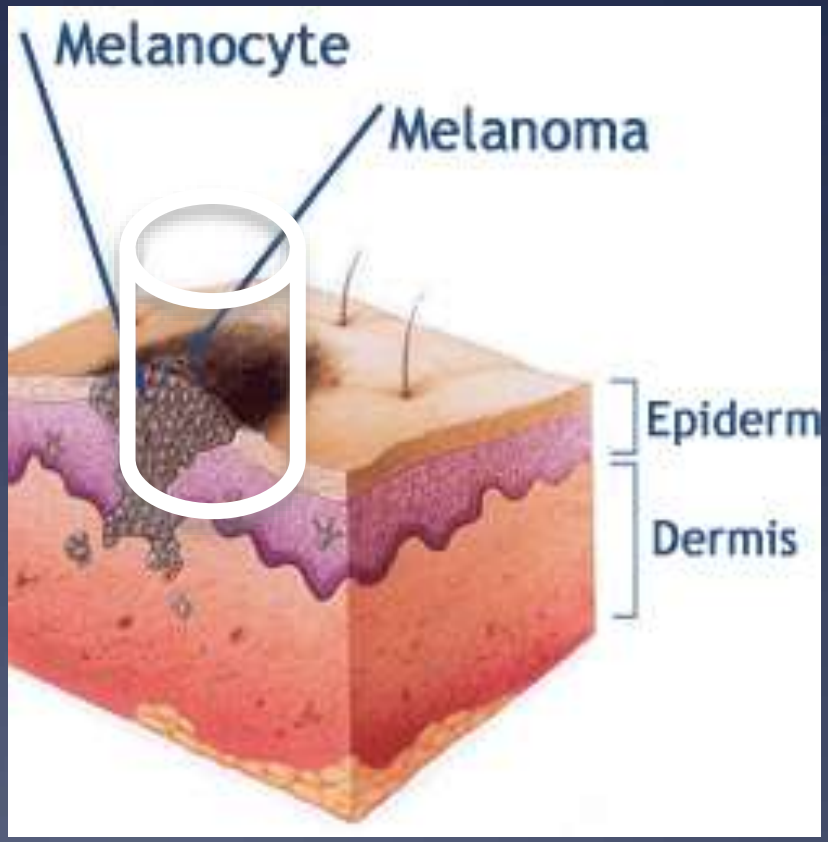


Photo source: http://emedical-help.com/melanoma-cancer-causes-and-risk-factors/melanoma/

What type of biopsy?

Excisional biopsy

NARROW

Photo source: http://emedical-help.com/melanoma-cancer-causes-and-risk-factors/melanoma/

Punch biopsy:

"atypical nevus with mild atypia"

Does this patient have skin cancer?

How do I investigate?

- Biopsy? What kind?
  - Depends on your suspected diagnosis
  - Melanoma: excisional
- Imaging in Melanoma?
  - High risk tumors (CT/PET)
- Sentinel lymph node biopsy
- Is observation ever okay for melanoma?
  - ?? Lentigo maligna (in situ) with advanced age

Melanoma

- Key Features
  - Evolving pigmented macule or papule
  - Areas of intermittent > chronic sun exposure
  - Affects old and young patients

- Prognosis
  - Stage dependent
  - Depth of invasion most powerful predictor of survival

Types of melanoma

* Superficial spreading

Types of melanoma

* Superficial spreading
* Nodular

Photo courtesy of www.orebroll.se

Types of melanoma

* Superficial spreading
* Nodular
* Lentigo maligna (melanoma)

Types of melanoma

* Superficial spreading
* Nodular
* Lentigo maligna
* Acral lentiginous

Types of melanoma

- Superficial spreading
- Nodular
- Acral lentiginous
- Lentigo maligna
- Amelanotic melanoma

Photo courtesy of www.orebroll.se

ABCDE

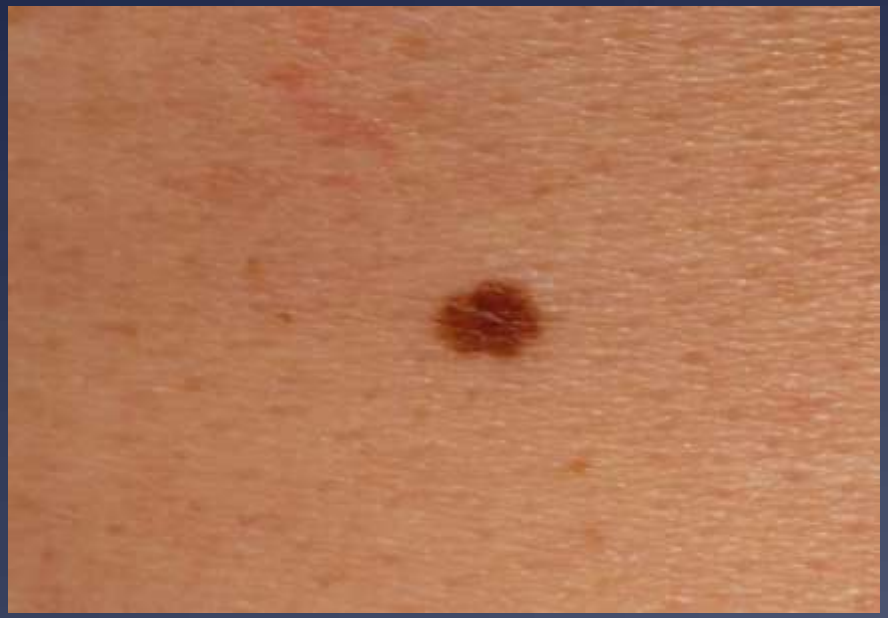
- **A**symmetry
- **B**order
- **C**olour
- **D**iameter
- **E**volution

Other clues

* Ugly duckling
* Symptoms

What's not a melanoma?

What's not a melanoma?



What's not a melanoma?

What's not a melanoma?

What's not a melanoma?

Practical Management of Melanoma

- Melanoma in situ
  - Excise with 5mm margins (or refer)
  - Skin surveillance with dermatology recommended
- Refer invasive melanoma
  - Sentinel lymph node biopsy and adjuvant therapy may be needed and indications are in flux

What about this guy?

Is there an AK equivalent for Melanoma?

- Atyical nevi
  - Relationship to melanoma is less clear cut
  - Risk marker, but not all "pre-melanomas"

- Mild – Moderate – Severe
  - Mild: pathologist in bad mood
  - Moderate: ??
  - Severe: treat like melanoma in situ (excise with 5mm margin)

Remove the ‘ugly duckling(s)’

PRACTICAL TIPS

Practical Tips

- Look at your patients skin
  - Annual physical
  - More frequently if history of skin cancer
- Don't ignore Actinic Keratoses
  - Treat the field when appropriate
  - Be alert for other skin cancers

Practical Tips

- Biopsy or refer worrisome lesions
  - Choose the appropriate biopsy!
- Refer for treatment
  - Complex, high risk and cosmetically important NMSC
  - All/Most melanomas
  - Make it clear when an urgent consult is requested
- Follow-up Skin Exams
  - BCC: q 6-12 mths
  - SCC: q 6 mths
  - MM: invasive q 4 mths, in situ q 6 mths

Practical Tips

- Sun Safety
  - Advise sun protection and tanning bed use
- Self aware
  - Advise skin self exam (q mthly)
- ? Nicotinamide
  - 500 mg PO BID
  - Buy on Amazon

The End