

# Medical and Surgical Management of Basal Cell Carcinoma

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▶ I have no disclosures to reveal

# Goals

- ▶ Epidemiology, biology, pathology of Basal Cell Carcinoma (BCC)
- ▶ Treatment modalities and management options for patients
- ▶ Diagnosis and prevention strategies

# Definitions

Non-melanoma skin cancer (NMSC)

Basal Cell Carcinoma (BCC)

Squamous Cell Carcinoma (SCC)

Malignant Melanoma (MM)

Others: AFX, DFSP, Merkel Cell, MAC, etc

# Non-melanoma skin cancer (NMSC)

- ▶ 3.5 million people per year in the United States, BCCs comprise of 80% of these cancers
- ▶ Not regularly recorded in cancer registries, making it difficult to determine accurate incidence rates in large populations.
- ▶ 2006: total number of NMSC in US population estimated to be 3,507,693; total number of people treated estimated at 2,152,500

# Basal Cell Carcinoma (BCC)

- ▶ Most common malignancy in humans.
- ▶ Although occurs in all skin types and races, most likely: lightskinned individuals; incidence of BCC high in white populations of Celtic heritage, low in Hispanics, Asians, and Blacks.
- ▶ BCC development 19 times less common in dark-skinned populations than in white
- ▶ Low rates observed in dark-skinned populations attributed to increased melanin production, which provides a photoprotection factor of up to 13.4.

# Basal Cell Carcinoma (BCC)

- ▶ Male:female ratio 1.3 to 1.6:1
- ▶ Rare in children, increases in frequency with age, median age of diagnosis 68 years
- ▶ Anatomic distribution men:
  - ▶ head and neck (79.6%)
  - ▶ trunk (13.4%)
  - ▶ upper limbs (3.8%)
  - ▶ lower limbs (1.5%)
  - ▶ genitalia (0.1%)

# Basal Cell Carcinoma (BCC)

- ▶ Anatomic distribution women
  - ▶ head and neck (83.9%)
  - ▶ trunk (9.4%)
  - ▶ upper limbs (2.5%)
  - ▶ lower limbs (2.5%)
  - ▶ genitalia (0.2%)
- ▶ “Rain drop” pattern
- ▶ Great variability in incidence worldwide. People living in regions near equator or with a high ultraviolet-B (UVB) index are at great risk

# Basal Cell Carcinoma (BCC)

- ▶ Incidence of BCC steadily increasing
- ▶ Causes: greater UV exposure as a consequence of ozone depletion, greater sun-seeking behavior and exposure, increased longevity of the population
- ▶ Increased rates of BCC in younger patients likely due to environmental and behavioral influences, not simply greater lifespan

# Pathogenesis and Etiology

- ▶ Ultraviolet radiation exposure
  - ▶ Chronic sun exposure most common risk factor, typical latency period of 15 to 20 years
  - ▶ Both UVA and UVB exposure contribute, whether from sunlight, UV light therapy, or tanning booths
  - ▶ UV exposure not only risk factor: 20% of BCC arise on non-sun-exposed skin
  - ▶ In addition to cumulative UV dose and skin type, dysmorphic genes, duration and intensity of exposure, particularly in early childhood and adolescence, all play a role

# Pathogenesis and Etiology

- ▶ Direct DNA damage: UVB directly damages DNA and RNA with characteristic C / T or CC / TT transition.
- ▶ UVA is absorbed by melanin and damages DNA indirectly through free radicals.
- ▶ UV exposure also causes dose-dependent suppression of the cutaneous immune system, impairing immune surveillance of skin cancer

# Pathogenesis and Etiology

- ▶ Signaling Pathways
  - ▶ Hedgehog (Hh) molecular signaling pathway
  - ▶ patched (PTCH1) protein and smoothened (SMO) protein
  - ▶ tumor suppressor gene p53

# Pathogenesis and Etiology

- ▶ Immunosuppression
- ▶ Genodermatoses and syndromes
- ▶ Other exposures and associations
  - ▶ Ionizing radiation, x-ray, Grenz ray
  - ▶ Arsenic (Fowler solution)
  - ▶ Smoking and alcohol (?)
  - ▶ Photochemotherapy
  - ▶ Chronic scars
    - ▶ Thermal burns and vaccination scars

# BCC Histology

- ▶ Nodular



# BCC Histology

- ▶ Superficial



# BCC Histology

- ▶ Pigmented



# BCC Histology

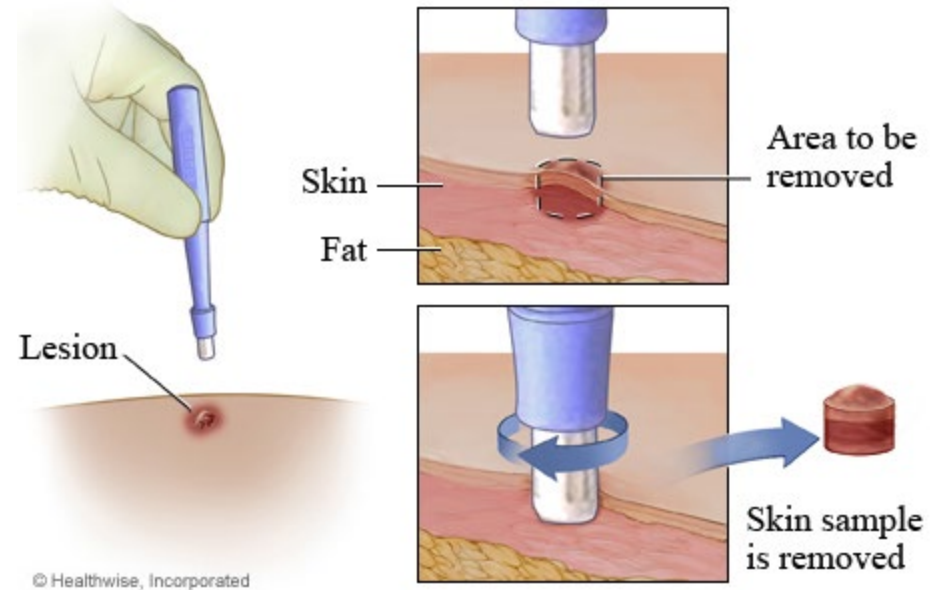
- ▶ Morpheaform/Infiltrative





# Diagnosis

- ▶ **Biopsy**
  - ▶ \*Shave
  - ▶ Punch

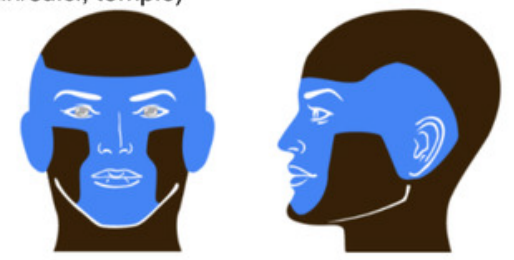


# Treatment options

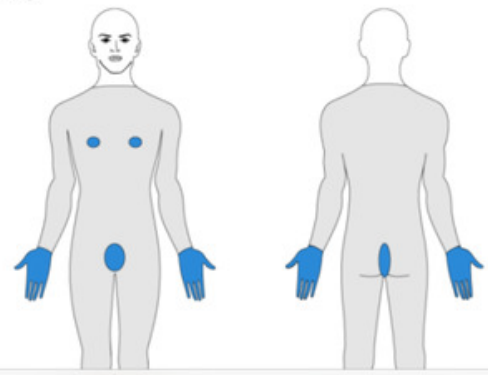
- ▶ Why treat? Mortality rare, but morbidity can be high: bleeding, functional, etc
- ▶ 10-fold increased incidence of second BCCs in patients with a BCC history compared with that in patients without a history of NMSC.
- ▶ This risk is reported to be 35% at 3 years and 50% at 5 years after initial diagnosis

### Area H ?

**Face** (central face, eyelids [including inner/outer canthi], eyebrows, nose, lips [cutaneous/mucosal/vermillion], chin, ear and periauricular skin/sulci, temple)

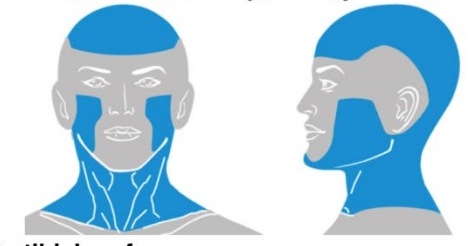


**Genitalia** (including perineal and perianal), **Nipples/areola**, **Hands**, **Feet**, **Ankles**, **Nail units**

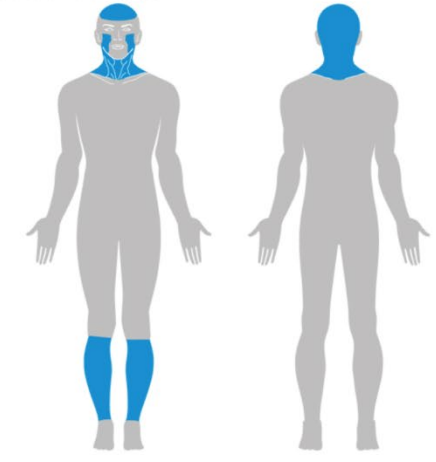


### Area M ?

**Cheeks**, **forehead**, **scalp**, **neck**, **jawline**,



**Pretibial surface**

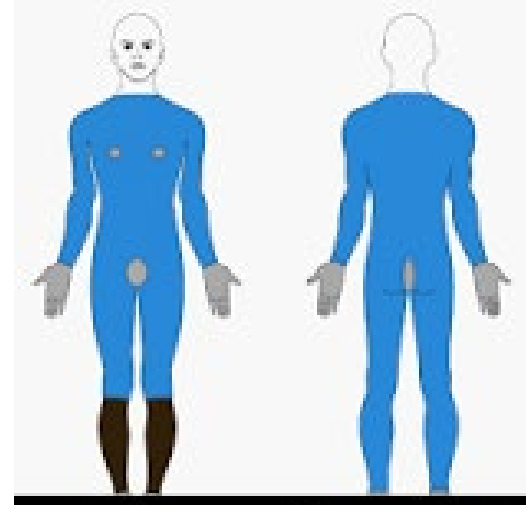


Area H ?

Area M ?

Area L -

**Trunk**, **Extremities** (excluding pretibial surface, hands, feet, nail units, and ankles)



**Table IV.** National Comprehensive Cancer Network stratification of low- versus high-risk BCC

Parameters	Low risk	High risk
Clinical		
Location <sup>*</sup> /size <sup>†</sup>	Area L <20 mm Area M <sup>‡</sup> <10 mm	Area L ≥20 mm Area M ≥10 mm Area H <sup>§</sup>
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiation therapy	No	Yes
Pathologic		
Growth pattern	Nodular, superficial <sup>  </sup>	Aggressive <sup>¶</sup>
Perineural involvement	No	Yes

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BCC, Basal cell carcinoma.

<sup>\*</sup>Area L consists of trunk and extremities (excluding hands, feet, nail units, pretibia, and ankles); area M consists of cheeks, forehead, scalp, neck, and pretibia; and area H consists of central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.

<sup>†</sup>Greatest tumor diameter.

# Clinical Risk Factors for Aggressive Tumor Behavior— “High-Risk” BCC

- ▶ Location - head and neck
- ▶ Size - e.g. 6 mm in high risk areas
- ▶ Border
- ▶ Pathologic subtype
- ▶ Perineural Involvement
- ▶ Primary versus Recurrent
- ▶ Site of Previous Radiation Therapy
- ▶ Young Age
- ▶ Immunosuppression

# Goals of BCC treatment (Surgical)

- ▶ (1) to remove the tumor completely so that no tumor persists and recurs at a later time
- ▶ (2) to avert or correct any functional impairment resulting from tumor removal
- ▶ (3) to provide the best possible cosmetic outcome, especially because most BCCs are on the face

**TABLE 2. Five-Year Recurrence Rates for Treatment of Primary and Recurrent BCC**

<i>Treatment Method</i>	<i>5-Year Recurrence Rate for Primary BCC (%)</i>	<i>5-Year Recurrence Rate for Recurrent BCC (%)</i>
Mohs surgery	1.0*	5.6†
All non-Mohs surgery methods	8.7*	19.9†
SSE	10.1*, 4.8‡	17.4†, 11.6‡
C&E	7.7*, 13.2§	40.0†, 18.1§
Radiation therapy	8.7*, 7.4	9.8†, 9.5
Cryotherapy	7.5*	13†¶

\*Rowe and colleagues<sup>64</sup> JDSO March 1989.

†Rowe and colleagues<sup>61</sup> JDSO April 1989.

‡Silvermann and colleagues<sup>65</sup> Part III.

§Silverman and colleagues<sup>65</sup> Part II.

||Silverman and colleagues<sup>66</sup> Part IV.

¶Data less than a 5-year follow-up.

# Treatment options

- ▶ Curettage and Electrodesiccation (C and D, ED & C)
  - ▶ Advantages: quick, relatively inexpensive, good for small low risk BCC
  - ▶ Disadvantages: risk of high recurrence, open wound to heal, pigmentary change, no histologic confirmation of clearance

# Treatment options

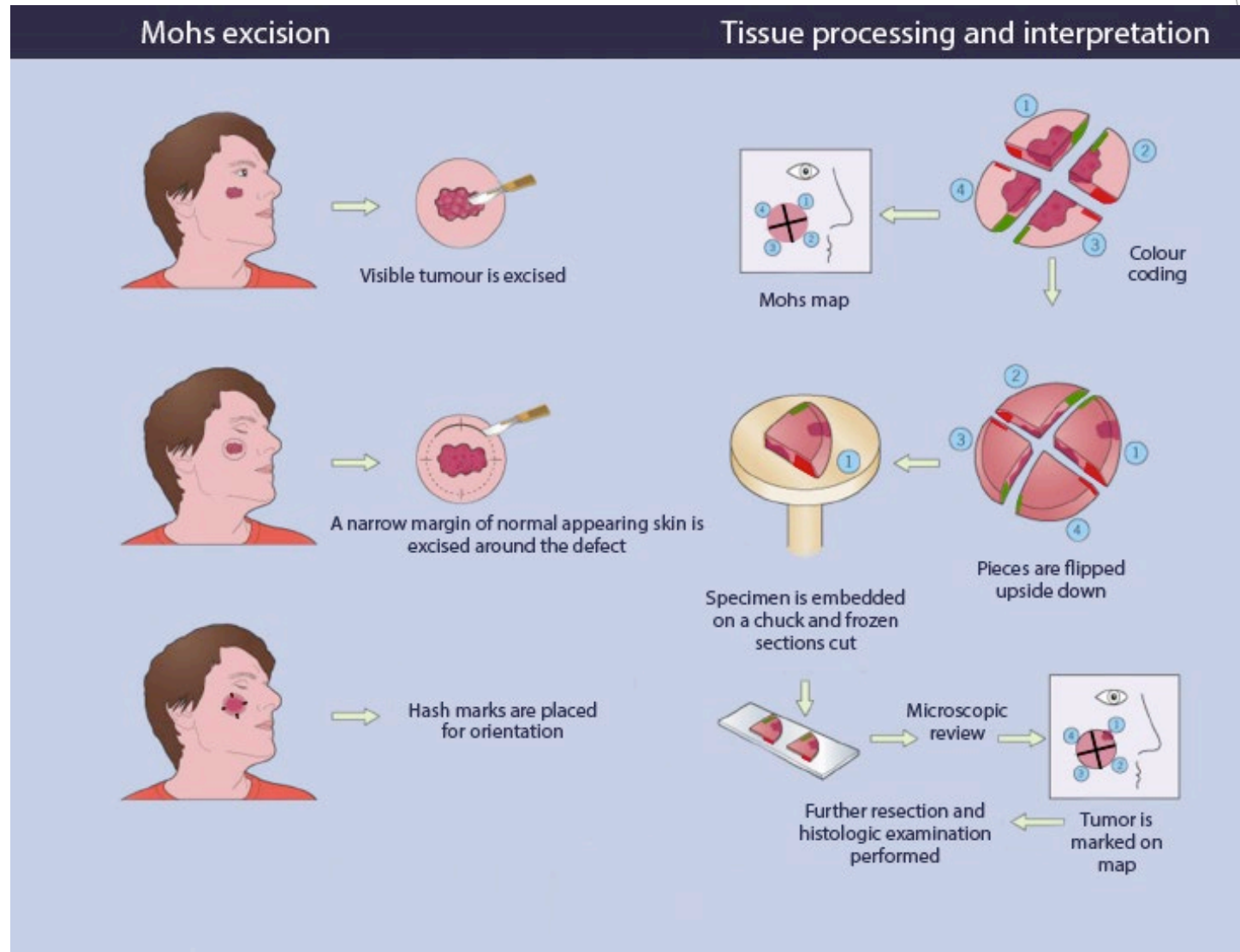
- ▶ Cryotherapy - controlled application of liquid nitrogen to treat tissue to at least  $-60^{\circ}\text{C}$ 
  - ▶ Similar Advantages and Disadvantages to C and D, scarring can be unpredictable and severe

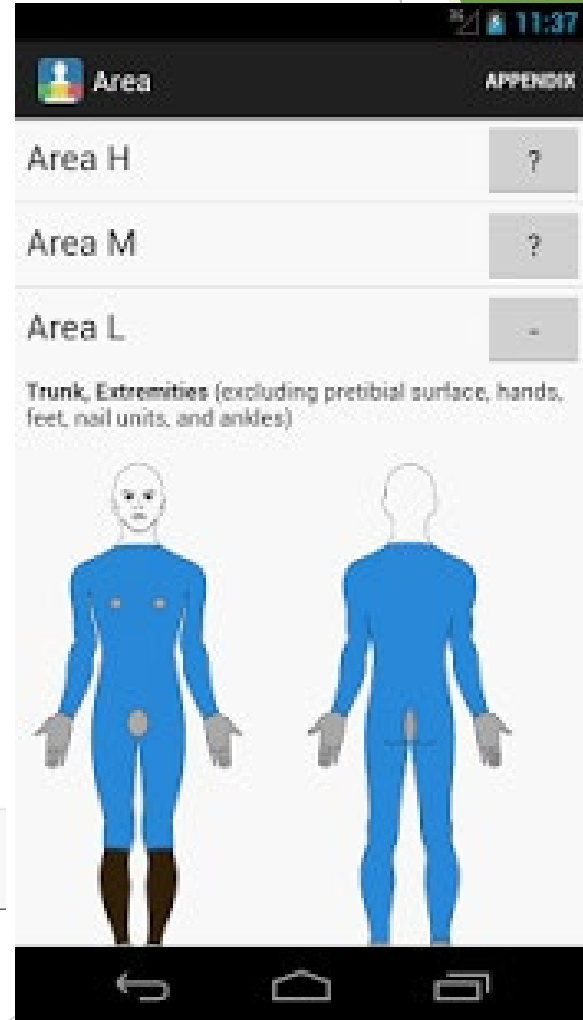
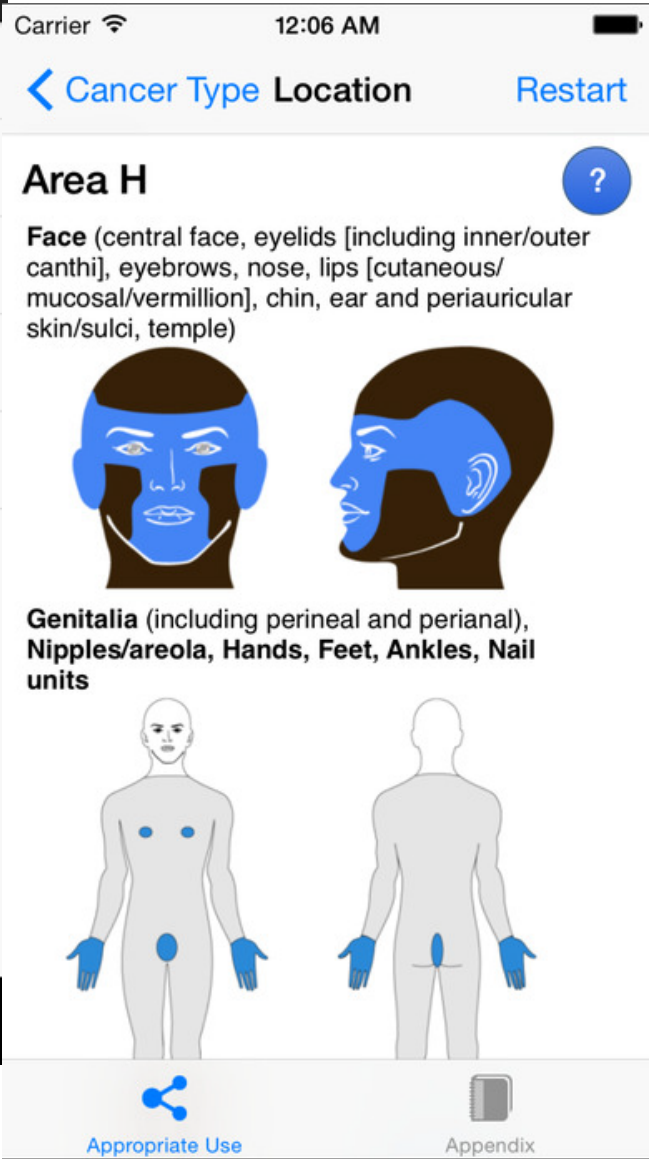
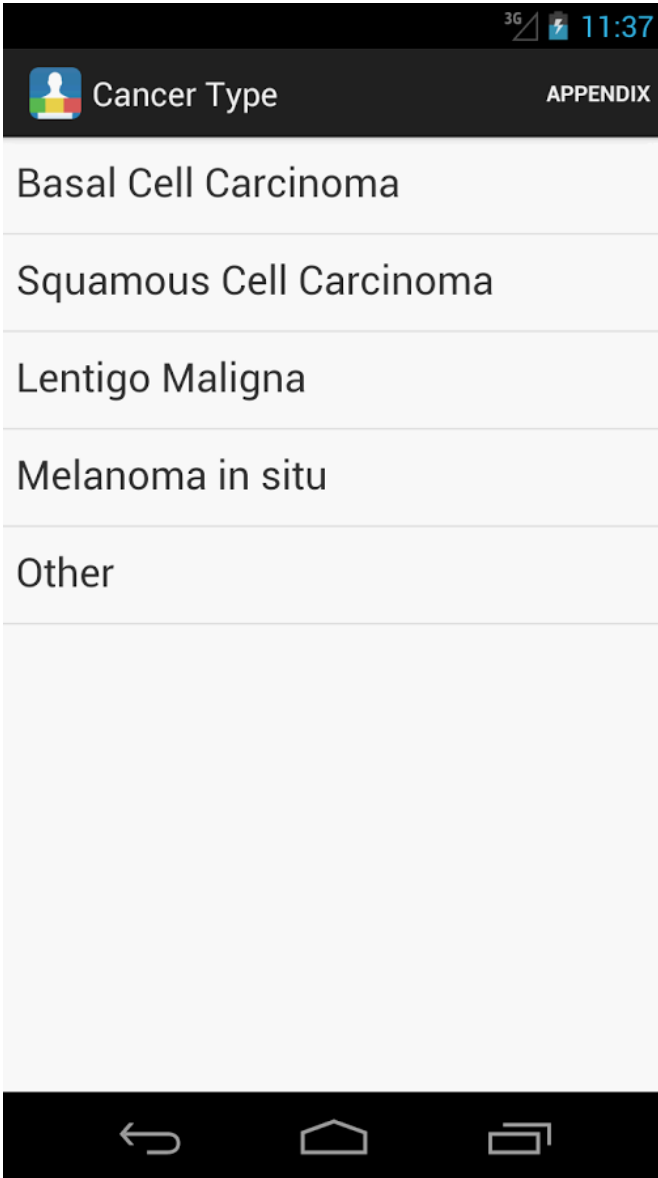
# Treatment options

- ▶ Standard Surgical Excision (SSE)
  - ▶ Well circumscribed tumors < 2 cm - 2-4 mm margins
  - ▶ >2 cm - as much as 6-10 mm margins
  - ▶ Advantages: histologic confirmation of clearance, sutured wounds have predictable healing time
  - ▶ Disadvantages: large wounds/scars, histologic confirmation may be unpredictable depending on tumor and location

# Treatment options

## ► Mohs Micrographic Surgery (MMS)





MOHS SURGERY IS

## APPROPRIATE

The use of Mohs is appropriate for the specific indication and is generally considered acceptable.

MEDIAN SCORE



SELECTED CRITERIA

Basal Cell Carcinoma  
Area H  
Recurrent  
Aggressive

[View decision tree](#)

**TABLE 3. Appropriate Use Criteria for Treatment of BCC by Mohs Surgery<sup>87</sup>**

<i>Tumor Type</i>	<i>Area H</i>	<i>Area M</i>	<i>Area L</i>
Primary superficial BCC	Mohs appropriate	Mohs appropriate (if $\geq 0.6$ cm) in nonimmunocompromised patient*; Mohs appropriate in immunocompromised patient (any size tumor)	—*
Primary nodular BCC	Mohs appropriate	Mohs appropriate	Mohs (if $>2.0$ cm) in nonimmunocompromised host; Mohs appropriate (if $>1.0$ cm) in immunocompromised patient*
Primary aggressive BCC	Mohs appropriate	Mohs appropriate	Mohs appropriate (if $>0.5$ cm)*
Recurrent BCC or other high-risk features	Mohs appropriate	Mohs appropriate	Mohs appropriate (if nonsuperficial)*

\*Mohs surgery is indicated for special patient features, regardless of lesion size or being superficial, including the following: radiation therapy, genetic syndromes, chronic ulcer or inflammation, osteomyelitis, traumatic scar.

# Treatment options

- ▶ Mohs Micrographic Surgery (MMS)
  - ▶ Advantages: tissue sparing, histologic confirmation of clearance at time of surgery, highest cure rate
  - ▶ Disadvantages: cost but might be mitigated by reduced recurrence rates, time consuming due to processing, surgical time, etc

**Table VIII.** Level of evidence and strength of recommendations for the surgical treatment of BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment plan	A	II	31,41
C&E for low-risk tumors	B	I, II	24,31,36,42-45 35-41,46-58
Standard excision with 4-mm margins	A	I	Expert opinion
• Low-risk BCC	C	III	
• High-risk BCC			
MMS for high-risk BCC	A	I, II	17,32,33,42,43,49,50

BCC, Basal cell carcinoma; C&E, curettage and electrodesiccation; MMS, Mohs micrographic surgery.

# Treatment options

## ▶ Radiation therapy

- ▶ Orthovoltage or superficial x-rays - range from 75 to 125 kV, lesions less than 5 mm in thickness.
- ▶ Megavoltage electron beam technology - more commonly used, penetrates tissue up to 6 cm, uses electron beams 6 to 20 MeV in strength.
- ▶ Brachytherapy - radioactive source applied on the surface of the tumor (as a mold) or is placed interstitially, produces less injury to the surrounding uninvolved tissue than electron beam radiation

# Treatment options

- ▶ Radiation therapy
  - ▶ Advantages: avoid surgery, medical comorbidities, adjuvant therapy
  - ▶ Disadvantages: cost and time (15-30 treatments), radiation dermatitis and other adverse effects, risk of subsequent sequelae from radiation

# Treatment options

- ▶ Topical therapies
  - ▶ 5-fluorouracil
  - ▶ Imiquimod
- ▶ Photodynamic therapy (PDT)
  - ▶ ALA, MAL, approved for AK's
- ▶ Recommended treatment regimen for imiquimod is once-daily 5 days per week for 6 weeks to 12 weeks and has been associated with up to 81% cure rates
- ▶ RCT comparing efficacy of imiquimod, fluorouracil, and MAL-PDT for treatment of superficial BCC: at 3 years, imiquimod (tumor-free survival: 79.7%; 95% CI, 71.6%-85.7%) superior to MAL-PDT (tumor free survival: 58.0%; 95% CI, 47.8%-66.9%) and fluorouracil (tumor free survival: 68.2%, 95% CI, 58.1%-76.3%)
- ▶ Topical therapies associated with adverse side effects: erythema, swelling, and erosions, which can limit compliance and decrease effectiveness.
- ▶ Use should be limited to superficial BCCs and small tumors in low-risk locations that cannot undergo treatment with more definitive therapies

**Table X.** Level of evidence and strength of recommendations for the nonsurgical treatment of BCC as alternatives to surgical therapy

Recommendation	Strength of recommendation	Level of evidence	References
Cryosurgery	A	I	36,41,46,60-63
Topical therapy			
• Imiquimod	A	I	39,64-77
• 5-FU	B	I, II	46,64,74-76,78,79
• Dose adjustments	A	I	39,68,70
PDT			
• ALA	A	I, II	38,47,61,74,76,77,80-85
• MAL	A	I, II	35,37,60,64,74,76,77,83,86,87
Radiation therapy			
• Traditional radiotherapies and modern superficial radiation therapy	B C	I, II II, III	23,34,42,43,46,62,88,89 90-92
• Electronic surface brachytherapy			
Laser therapy	C	II	74,93,94

ALA, Aminolevulinic acid; BCC, basal cell carcinoma; 5-FU, 5-fluorouracil; MAL, methylaminolevulinic acid.

# Treatment options - Systemic Therapies

- ▶ A subset of patients (e.g. BCNS and locally advanced or metastatic disease) require systemic treatment
- ▶ 2012: FDA approved Vismodegib (ERIVEDGE), first-in-class hedgehog pathway inhibitor, for treatment of locally advanced or metastatic BCCs
- ▶ Objective responses of 48% and 33% for patients with locally advanced and metastatic disease, respectively, were reported at 21-month follow-up
- ▶ Nearly all patients treated with vismodegib experienced at least 1 adverse effect, including muscle spasms, alopecia, dysgeusia, weight loss, fatigue, or diarrhea. Grade 3 or 4 adverse effects occurred in 25% of patients
- ▶ Double-blind randomized phase 2 study of patients with BCNS found that vismodegib significantly reduced incidence of new BCCs and size of existing tumors - only 17% of patients tolerated vismodegib continuously for full 36-month study
- ▶ Vismodegib can be taken with or without food and does not require laboratory work prior to or after initiation
- ▶ Reports of hepatotoxicity, so caution in patients with severe liver disease

# Treatment options - Systemic Therapies

- ▶ Sonidegib, the second hedgehog pathway inhibitor, is approved by FDA for treatment of locally advanced BCCs that recur after surgery or RT or who are not candidates for surgery or radiotherapy.
- ▶ Phase 2 Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT) trial found response rates of 44% to 58% for locally advanced BCC and 8% to 17% for metastatic BCC
- ▶ Nearly all patients experienced at least 1 adverse effect with elevated creatinine kinase and lipase most common grade 3 or grade 4 adverse effects
- ▶ Sonidegib should be taken on an empty stomach and should not be administered concomitantly with strong and moderate CYP3A inhibitors

# Treatment options - Systemic Therapies

- ▶ Two main limitations to hedgehog pathway inhibitor therapy are high frequency of adverse effects and development of tumor resistance
- ▶ Intermittent dosing regimens have been attempted as way to minimize side effects while not compromising efficacy
- ▶ Patients with BCNS respond to vismodegib and have a low acquired resistance
- ▶ Advanced and metastatic BCC patients, however, have lower overall response rates (approximately 48%) and an estimated 20% develop resistance during their first year

# Treatment options - Systemic Therapies

- ▶ Anti-programmed death-1 (PD-1) immunotherapy is another emerging treatment option for advanced BCC
- ▶ E.g. clinical trial investigating Cemiplimab, a fully human anti-PD-1 monoclonal antibody, in patients with locally advanced or metastatic BCC who experienced progression of disease or stable disease on or who cannot tolerate hedgehog pathway inhibitor therapy

**Table XII.** Level of evidence and strength of recommendations for the management of metastatic BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment with SMO inhibitors			
• Metastatic and Locally advanced BCC	A	I, II	<a href="#">107-111,113,114</a>
• Gorlin syndrome	B	I	<a href="#">115</a>
Platinum-based chemotherapy for metastatic BCC	C	III	<a href="#">106</a>
Palliative care	C	III	Expert opinion

BCC, Basal cell carcinoma; SMO, smoothed.

**Table XIII.** Recommendations for the follow-up of BCC and reduction of risk for future skin cancer

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After diagnosis of a first BCC, skin cancer screening for new keratinocyte cancers (BCC or cSCC) and for melanoma should be performed on at least an annual basis.

Patients with a history of BCC should be counseled on skin self-examination and sun protection.

The use of topical and oral retinoids (eg, tretinoin, retinol, acitretin, and isotretinoin) is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of BCC.

Dietary supplementation of selenium and  $\beta$ -carotene is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of BCC.

There is insufficient evidence to make a recommendation on the use of oral nicotinamide, DFMO, or celecoxib in the chemoprevention of BCC.

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*BCC*, Basal cell carcinoma; *DFMO*,  $\alpha$ -difluoromethylornithine; *cSCC*, cutaneous squamous cell carcinoma.

# Imaging

## ▶ Reflectance confocal microscopy (RCM)

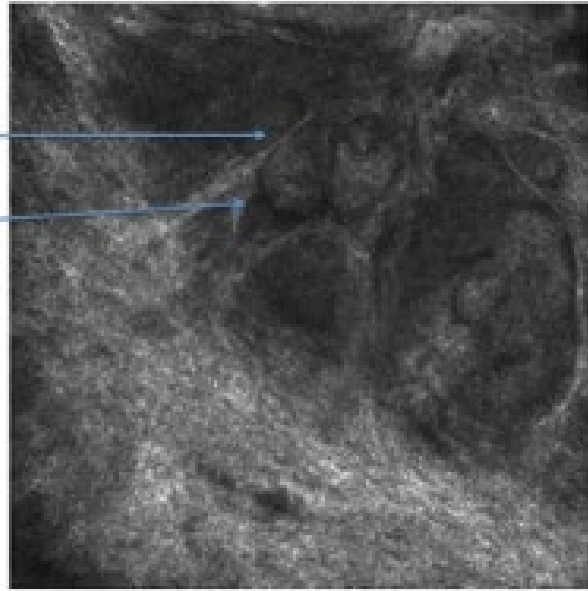
- ▶ allows for video rate imaging of thin sections of human skin in vivo, using near-infrared laser
- ▶ uses near-infrared laser light that is back-reflected from a desired focal point within the skin and allowed to pass back through a gating pinhole and enter the detector
- ▶ An algorithm for diagnosing BCCs based on RCM features was 100% sensitive and 88.5% specific when tested on nearly 800 lesions
- ▶ A meta-analysis of 3602 lesions found a pooled sensitivity and specificity of RCM for BCC of 91.7% and 91.3%, respectively
- ▶ RCM in conjunction with dermoscopy can assist in identifying BCC subtypes without skin biopsy
- ▶ Limitations include imaging depth and learning curve with interpreting images

**A**

**BCC Tumor Island**

RCM image of tumor islands  
(dark silhouette) seen in BCC

Areas of clefting also seen

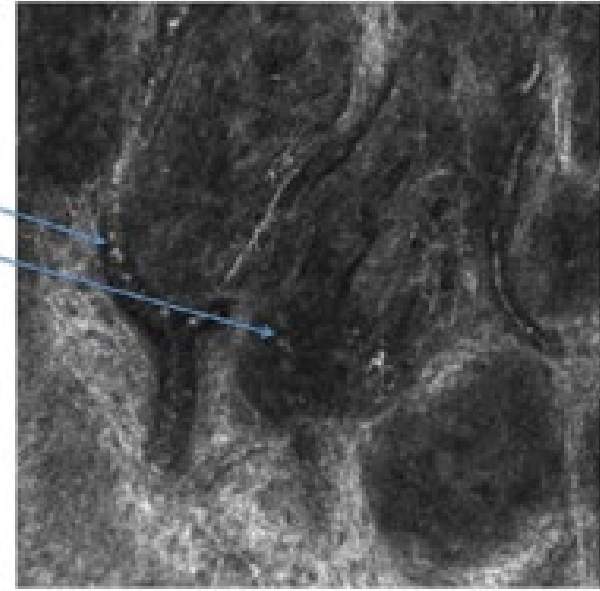


**B**

**BCC Tumor islands with  
plump vessels visible**

Horizontal vessel

Surrounding tumor islands



# Imaging

- ▶ Optical coherence tomography (OCT)
- ▶ allows for noninvasive, real-time diagnostic assessment of skin using infrared light projected onto the skin to produce an image based on the sum of light refractions of various skin structures with different optical properties
- ▶ In a cohort study, OCT had a sensitivity and specificity for sBCC diagnosis of 87% and 80%, respectively
- ▶ OCT had the highest accuracy (87.4%) when used in conjunction with dermoscopy

